Clinical Study Protocol

Sponsor:

GlaxoSmithKline Biologicals

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Primary Study vaccine and number	GlaxoSmithKline (GSK) Biologicals' human papillomavirus (HPV) vaccine containing HPV-16/18 L1 virus-like particles (VLPs) and AS04 adjuvant (GSK580299)
eTrack study number and Abbreviated Title	113621(HPV-067 EXT 015)
Investigational New Drug (IND) number	BB-IND7920
Date of protocol	Final: 18 May 2010
Date of protocol amendments/ administrative change	Administrative Change 1 Final: 18 Aug 2010 Amendment 1 Final: 9 Dec 2010 Amendment 2 Final: 13 Jan 2011
Title	Safety study of GSK Biologicals' human papillomavirus vaccine (GSK-580299) in healthy female control subjects from the GSK HPV-015 study
Detailed Title	A phase IIIb, open-label, multi-centre immunization study to evaluate the safety of GlaxoSmithKline (GSK) Biologicals' HPV-16/18 L1 VLP AS04 vaccine administered intramuscularly according to a 0, 1, 6-month schedule in healthy female subjects who received the placebo control in the GSK HPV-015 study
Co-ordinating author	PPD, Scientific Writer
Contributing authors *(Amended 13 Jan 2011)*	• PPD, Manager, Clinical Development, HPV vaccines • PPD, Global Study Manager, HPV vaccines • PPD and PPD, Biostatisticians • PPD, Senior Manager, Epidemiology and Safety • PPD, Expert Scientist, Clinical Regulatory Affairs, Clinical Registration and Labelling • PPD, Clinical Data Coordinators, Clinical Data Management • PPD, Director, HPV Vaccines, Global Clinical Research and Development • PPD, ***Director, HPV Vaccines, Global Clinical Research and Development***

GSK Biologicals' Protocol DS v 13.1

Protocol Amendment 2 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	113621(HPV-067 EXT 015)
IND number	BB-IND7920
Date of protocol amendment	Amendment 2 Final: 13 Jan 2011
Detailed Title	A phase IIIb, open-label, multi-centre immunization study to evaluate the safety of GlaxoSmithKline (GSK) Biologicals' HPV-16/18 L1 VLP AS04 vaccine administered intramuscularly according to a 0, 1, 6-month schedule in healthy female subjects who received the placebo control in the GSK HPV-015 study
Sponsor signatory	Dominique Descamps MD, Director, Clinical Development, HPV Vaccines, GlaxoSmithKline Biologicals
Signature	_____
Date	_____

Protocol Amendment 2 Rationale

Administrative Change number:	Amendment 2
Rationale/background for changes:	

The exclusion criterion "*Administration of any chronic drug therapy to be continued during the study period*" has been removed to be in line with the original HPV-015 study protocol.

Upon request of regulatory authorities, the list of pIMDs has been updated to include the term "*undifferentiated spondyloarthritides*".

In addition, the list of contributing authors has been updated. Cross-referencing to the first amendment has been removed for clarity.

Protocol Amendment 2 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments or protocol administrative changes, and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals' investigational product(s) and other study-related duties and functions as described in the protocol.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject's legally authorised representative.
- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor or the investigational product, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

eTrack study number and Abbreviated Title	113621(HPV-067 EXT 015)
IND number	BB-IND7920
Date of protocol amendment	Amendment 2 Final: 13 Jan 2011
Detailed Title	A phase IIIb, open-label, multi-centre immunization study to evaluate the safety of GlaxoSmithKline (GSK) Biologicals' HPV-16/18 L1 VLP AS04 vaccine administered intramuscularly according to a 0, 1, 6-month schedule in healthy female subjects who received the placebo control in the GSK HPV-015 study
Investigator name	
Signature	
Date	

SYNOPSIS

Detailed Title	A phase IIIb, open-label, multi-centre immunization study to evaluate the safety of GlaxoSmithKline (GSK) Biologicals' HPV-16/18 L1 VLP AS04 vaccine administered intramuscularly according to a 0, 1, 6-month schedule in healthy female subjects who received the placebo control in the GSK HPV-015 study
Indication	*Cervarix* is indicated in females from 10 years of age onwards for the prevention of persistent infection, premalignant cervical lesions and cervical cancer (squamous-cell carcinoma and adenocarcinoma) caused by oncogenic Human Papillomavirus (HPV) types.
Rationale for the study and study design	Subjects in the HPV-015 study either received the HPV-16/18 L1 VLP AS04 vaccine or placebo control [$Al(OH)_3$], following a 0, 1, 6-month vaccination schedule. According to the HPV-015 protocol, once the HPV-015 study was concluded, the control placebo group would be offered the HPV-16/18 L1 VLP AS04 vaccine as well. As recommended by the study Independent Data Monitoring Committee (IDMC), unblinding and cross-over immunization of control recipients with the HPV vaccine will be provided after completion of their end of study activities as follows: • For subjects who complete study activities after the database is frozen for final analysis, unblinding will occur within 4-6 months after last subject last visit (LSLV) of the final study visit. • Subjects who will not participate in any of the extensions will be given the option of unblinding before the database is frozen for final analysis upon individual request. The HPV-16/18 L1 VLP AS04 vaccine is licensed in the participating countries, but it is not indicated for the age group (26 years and above) involved in the HPV-015 study and this study. Approximately 600 subjects from the control placebo group are expected to enrol in this study. This study is thus being conducted to enable all women, who received the control placebo in the HPV-015 study, to also receive HPV-16/18 L1 VLP AS04 vaccine. Safety data in terms of SAEs, medically significant conditions and pregnancy (and their outcomes) will be collected during the study period.
Objective(s)	• To assess the safety of the HPV-16/18 L1 VLP AS04 vaccine throughout the study period.

Study design

- **Experimental design**: Phase IIIB, multi-centric, single-group: HPV vaccine group (HPV-16/18 L1 VLP AS04).
- **Treatment allocation**: sequential allocation of subjects to receive the HPV-16/18 L1 VLP AS04 vaccine
- **Blinding**: open-label
- **Treatment group**: HPV vaccine group (HPV-16/18 L1 VLP AS04)
- **Vaccination schedule**: Three doses of HPV-16/18 L1 VLP AS04 vaccine (20 µg HPV-16, 20 µg HPV-18) administered intramuscularly according to a 0, 1, 6-month schedule.
- **Control**: uncontrolled
- **Type of study**: e.g. self-contained, extension of study HPV-015
- **Data collection**: eCRF
- **Duration of the study**: Approximately 12 months per subject.
- **Study visits per subject**: Three scheduled visits are planned at Months 0, 1, 6. There will be a telephone contact with the subject at Month 12 (i.e. six months after the third dose of the HPV-16/18 L1 VLP AS04 vaccine).
- **Safety monitoring:**
  - All serious adverse events (SAEs) occurring throughout the study period (i.e. from Day 0 up to the telephone contact at Month 12) will be reported for all subjects.
  - Medically significant conditions (including potential immune-mediated diseases [pIMDs]) will be reported for all subjects throughout the study period.
  - Pregnancies and pregnancy outcomes will be reported for all subjects throughout the study period.

Number of subjects

Approximately 600 subjects are planned to participate to this cross-over vaccination study.

Endpoints

Safety

- Serious adverse events (SAEs)
  - Occurrence, intensity and causal relationship to vaccination of SAEs throughout the study
- Medically significant conditions(including pIMDs)

- Occurrence, intensity and causal relationship to vaccination of medically significant conditions (including pIMDs) throughout the study

- Pregnancies and pregnancy outcomes
  - Occurrence of pregnancies and pregnancy outcomes throughout the study

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LIST OF ABBREVIATIONS

AE	Adverse event
$Al(OH)_3$	Aluminium hydroxide
AS04	GlaxoSmithKline's proprietary adjuvant system consisting of aluminium salt plus 3-*O*-desacyl-*4'*-monophosphoryl lipid A (MPL)
CIN	Cervical Intraepithelial Neoplasia
CIN2+	CIN2, CIN3, AIS or invasive cervical cancer
eCRF	electronic Case Report Form
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HIV	Human Immunodeficiency Virus
HPV	Human papillomavirus
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
LSLV	Last Subject Last Visit
µg	microgram
mg	milligram
ml	millilitre
MPL	3-*O*-desacyl-*4'*-monophosphoryl lipid A
pIMD	potential Immune-Mediated Disease
RDE	Remote Data Entry
SAE	Serious Adverse Event
SPM	Study Procedures Manual
VLP	Virus-like particles

GLOSSARY OF TERMS

Adequate contraception:	Adequate contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly (when applicable, as mentioned in the product label) for example abstinence, combined or progestogen oral contraceptives, injectable progestogen, implants of levonorgestrel, oestrogenic vaginal ring, percutaneous contraceptive patches or intrauterine device (IUD) or intrauterine system (IUS), vasectomy with documented azoospermia of the sole male partner or male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository) or male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository). For azoospermia, 'documented' refers to the laboratory report of azoospermia, required for acceptable documentation of successful vasectomy in the subject's male partner.
Adverse event:	Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
eTrack:	GSK's tracking tool for clinical trials.
Global Study Manager	An individual assigned by GSK Biologicals Headquarters who is responsible for assuring the co-ordination of the operational aspects and proper conduct of a clinical study, including compliance with International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and GSK policies and standard operating procedures.

Investigational vaccine/product: **(Synonym of Investigational Medicinal Product)**	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Medically Significant Condition:	Medically significant conditions are defined as AEs prompting emergency room or physician visits that are not (1) related to common diseases or (2) routine visits for physical examination or vaccination, or SAEs that are not related to common diseases. Common diseases include: upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, cervicovaginal yeast infections, menstrual cycle abnormalities and injury. Medically significant conditions include potential immune-mediated diseases (pIMDs).
Menopause:	Menopause is the age associated with complete cessation of menstrual cycles, menses, and implies the loss of reproductive potential by ovarian failure. A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile at the appropriate age e.g. > 45 years.
pIMD	Potential immune-mediated diseases (pIMDs) are a subset of Medically Significant Conditions that include autoimmune diseases and other inflammatory and/or neurological disorders of interest which may or may not have an autoimmune aetiology.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the product(s) or as a control.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomisation or treatment allocation.

TRADEMARKS

The following trademarks are used in the present protocol.

Note: In the body of the Protocol (including the synopsis), the names of the vaccines/products and/or medications will be written without the subscript symbol ™ or ®.

Trademarks of the GlaxoSmithKline group of companies	generic description
Cervarix™	Human papillomavirus vaccine types 16 and 18 (Recombinant, AS04 adjuvanted, adsorbed)

1. INTRODUCTION

1.1. Background

Cervical cancer is the most important manifestation of genital human papillomavirus (HPV) infection and is one of the leading causes of cancer mortality in women worldwide [Parkin, 2001a; Parkin, 2001b]. Papillomaviruses, members of the papovaviridae family, are non-enveloped deoxyribonucleic acid (DNA) viruses which can cause a variety of proliferative epithelial lesions in humans, including benign papillomas (warts) and invasive cancer [Lowy, 2001; Zur Hausen , 2002].

Currently, over 200 different types of HPVs have been recognized. Based on whether they infect basal epithelial cells of the skin or the inner lining of tissues, they are categorized as cutaneous or mucosal types [Burd, 2003]. At least 30 HPV types have been identified that infect the genital mucosa [Bosch, 1995]. HPV types are also classified by their relative malignant potential into low-risk (LR) types (e.g. HPV-6, -11, -42, -43, and -44) and high-risk (HR) or oncogenic types (e.g. HPV-16, -18, -31, -33, -34, -35, -39, -45, -51, -52, -56, -58, -59, -66, -68 and -70) [Burd, 2003]. Persistent infection with an oncogenic HPV type has been clearly associated with the development of cervical cancer [Schiffman, 2005] and the association between cervical cancer and infection with a HR HPV type is supported both by strong epidemiological evidence and the detection of HPV DNA in up to 99.7% of cervical cancers worldwide [Schiffman 2005; Burd 2003].

The distribution of HPV types varies within countries and between regions. HPV-16 and HPV-18 are the first and second most common types in all regions, with some variation in their distribution. HPV-16 is the most prevalent oncogenic HPV type and is present in approximately 54% of cervical tumor specimens worldwide. HPV-18 is associated with approximately 17% of cervical cancers, with the remaining tumors containing DNA from other oncogenic HPV types such as HPV-45 and -31. In combination, these two HPV types (HPV-16 and HPV-18) account for approximately 70% of cervical cancer cases globally [Clifford 2003].

In the general population, the estimated worldwide prevalence of HPV among women is between 5% and 40% [Baseman, 2005; Franco, 1999]. This wide variation reflects underlying population characteristics (i.e. age range, geographic area, risk behaviours), the use of different HPV DNA test methods, and also differences in the sexual activity of the individuals studied. Assuming a conservative prevalence of 10% in developed countries and 15% in developing countries, one author estimated 270 million HPV infections amongst women globally [Bosch, 2002].

1.2. GlaxoSmithKline Biologicals' HPV Vaccine

GlaxoSmithKline (GSK) Biologicals has developed a candidate prophylactic HPV vaccine based on L1 proteins of HPV-16 and HPV-18 formulated with AS04 (comprised of aluminium hydroxide [$Al(OH)_3$] and 3-*O*-desacyl-*4'*-monophosphoryl lipid A [MPL]). The vaccine contains HPV-16 and HPV-18 L1 VLP proteins produced using an

expression system based on the use of insect cells and recombinant Baculoviruses encoding L1 proteins of HPV-16 and HPV-18. The recombinant expressed proteins undergo self-assembly to form empty viral capsids referred to as virus-like particles (VLPs) [Kirnbauer, 1992]. A study comparing different vaccine formulations demonstrated that the highest antibody titres were induced by AS04-adjuvanted vaccine formulations [Giannini, 2006]. The AS04 adjuvant system is comprised of aluminium salts ($Al(OH)_3$) and 3-O-desacyl-4'-monophosphoryl lipid A (MPL) and is also used in other vaccines, including a hepatitis B vaccine licensed in Europe for use in haemodialysis patients from the age of 15 years and above under the name Fendrix as well as in an investigational HSV vaccine.

To date, more than 60 000 adolescent and adult females aged 9 years and above have received at least one dose of the HPV vaccine in clinical studies. A pooled safety analysis of data from almost 30 000 adolescent and adult females aged 10 years and above, of whom 16 142 received at least one dose of HPV vaccine, showed the vaccine to be generally well tolerated in women of all ages [Descamps, 2009]. In this publication , subjects from the HPV-015 trial were included and the safety profile in women aged 26 and above was similar to the one in 15-25 year olds who received the vaccine.

Results of a large multinational phase III trial in women aged 15-25 years demonstrated high vaccine efficacy against cervical intraepithelial neoplasia grade 2 and above (CIN2+), CIN1+ and persistent infection (6-month and 12-month definition) associated with HPV-16 and/or HPV-18, significant vaccine efficacy against CIN2+ and CIN3+ irrespective of HPV type in the lesion as well as evidence of protection against HPV types 31, 33 and 45 [Paavonen, 2009]. This study also demonstrated the vaccine to be generally well tolerated in a broad range of women including those of different nationalities and ethnicities [Paavonen, 2007].

A long-term efficacy follow-up study in women aged 15-25 years at the time of first vaccination demonstrated high vaccine efficacy against incident and persistent HPV-16/18 infections and their associated cervical lesions up to 6.4 years of follow-up [Gall, 2007; Harper, 2004; Harper, 2006; The GlaxoSmithKline Vaccine HPV-007 Study Group, 2009].

When tested in young female adolescents, the vaccine induced immune responses that were approximately 2-fold higher than those elicited in women 15-25 years of age [Pedersen, 2007]. In women up to 55 years of age, the vaccine induced sustained HPV antibody levels up to Month 24 after the first vaccine dose and these antibody levels remained significantly higher than those seen after natural infection [Schwarz, 2009].

The first major market in which the vaccine under evaluation in this study was licensed is Australia, where licensure was obtained in May 2007 for use in 10 to 45 year old females. The vaccine is marketed under the trade name *Cervarix*. In September 2007, the vaccine was licensed in the European Union for the prevention of high-grade cervical intraepithelial neoplasia (CIN grades 2 and 3) and cervical cancer causally related to HPV types 16 and 18. In October 2009, *Cervarix* has also been approved by the United States Food and Drug Administration (US FDA) for use in females 10 through 25 years of age. The vaccine is currently licensed in over 100 countries worldwide.

Please refer to the current Investigator Brochure for a review of pre-clinical and clinical studies, and the potential risks and benefits of the candidate prophylactic HPV-16/18 vaccine formulated with AS04.

1.3. Rationale for the study and study design

Subjects in the HPV-015 study either received the HPV-16/18 L1 VLP AS04 vaccine or placebo control [$Al(OH)_3$], following a 0, 1, 6-month vaccination schedule. According to the HPV-015 protocol, once the HPV-015 study was concluded, the control placebo group would be offered the HPV-16/18 L1 VLP AS04 vaccine as well.

As recommended by the study Independent Data Monitoring Committee (IDMC), unblinding and cross-over immunization of control recipients with the HPV vaccine will be provided after completion of their end of study activities as follows:

- For subjects who complete study activities after the database is frozen for final analysis, unblinding will occur within 4-6 months after last subject last visit (LSLV) of the final study visit.
- Subjects who will not participate in any of the extensions will be given the option of unblinding before the database is frozen for final analysis upon individual request.

The HPV-16/18 L1 VLP AS04 vaccine is licensed in the participating countries, but it is not indicated for the age group (26 years and above) involved in the HPV-015 study and this study. Approximately 600 subjects from the control placebo group are expected to enrol in this study.

This study is thus being conducted to enable all women, who received the control placebo in the HPV-015 study, to also receive HPV-16/18 L1 VLP AS04 vaccine. Safety data in terms of SAEs, medically significant conditions and pregnancy (and their outcomes) will be collected during the study period.

2. STUDY OBJECTIVE

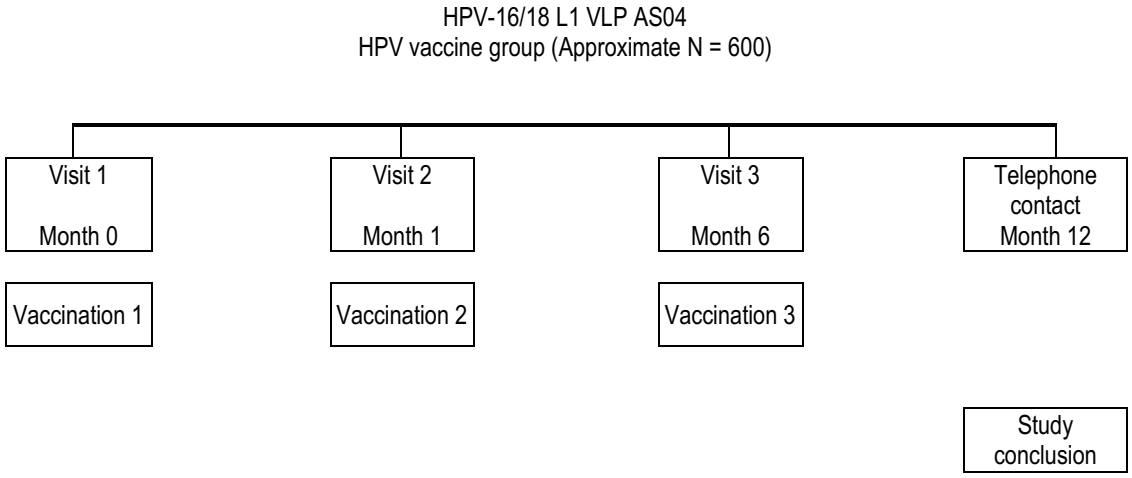
- To assess the safety of the HPV-16/18 L1 VLP AS04 vaccine throughout the study period.

Refer to Section 10.1 for the definition of the study endpoint.

3. STUDY DESIGN OVERVIEW

An overview of the study design is presented in Figure 1.

Figure 1 Study visits and study procedures



- **Experimental design**: Phase IIIB multi-centric, single-group: HPV vaccine group (HPV-16/18 L1 VLP AS04).
- **Treatment allocation**: sequential allocation of subjects to receive the HPV-16/18 L1 VLP AS04 vaccine
- **Blinding**: open-label
- **Treatment group**: HPV vaccine group (HPV-16/18 L1 VLP AS04)
- **Vaccination schedule**: Three doses of HPV-16/18 L1 VLP AS04 vaccine (20 µg HPV-16, 20 µg HPV-18) administered intramuscularly according to a 0, 1, 6-month schedule.
- **Control**: uncontrolled .
- **Type of study**: e.g. self-contained, extension of study HPV-015
- **Data collection**: eCRF
- **Duration of the study**: Approximately 12 months per subject.
- **Study visits per subject**: Three scheduled visits are planned at Months 0, 1, 6. There will be a telephone contact with the subject at Month 12 (i.e. six months after the third dose of the HPV-16/18 L1 VLP AS04 vaccine).
- **Safety monitoring:**
  - All serious adverse events (SAEs) occurring throughout the study period (i.e. from Day 0 up to the telephone contact at Month 12) will be reported for all subjects.
  - Medically significant conditions (including pIMDs) will be reported for all subjects throughout the study period.
  - Pregnancies and pregnancy outcomes will be reported for all subjects throughout the study

4. STUDY COHORT

4.1. Number of subjects/centres

Overview of the recruitment plan:

Of all subjects participating in the HPV-015 conclusion visits who received the control placebo in the HPV-015 study, approximately 600 subjects are expected to enrol in this study. Subjects who participated in the HPV-015 study may decide to conclude their participation in the HPV-015 study at Visit 9, Visit 11 or at the last study visit in HPV-015 planned under protocol amendment 4.

These subjects will be contacted and invited to participate in this cross-over vaccination study with GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine. Enrolment should take place within two years after the subject has completed the HPV-015 study.

4.2. Inclusion criteria for enrolment

All subjects must satisfy **ALL** the following criteria at study entry:

- Subjects who the investigator believes can and will comply with the requirements of the protocol
- A subject previously enrolled in the HPV-015 study, who received the control vaccine, and who cannot receive the commercially available HPV-16/18 L1 VLP AS04 vaccine because the subject is above the age for which the vaccine is licensed.
- Written informed consent obtained from the subject
- Free of obvious health problems as established by medical history and clinical examination before entering into the study.
- Female subjects of non-childbearing potential may be enrolled in the study.
    - Non-childbearing potential is defined as current tubal ligation, hysterectomy, ovariectomy or post-menopause.

  Refer to the Glossary Of Terms for the definition of menopause.
- Female subjects of childbearing potential may be enrolled in the study, if the subject:
    - has practiced adequate contraception for 30 days prior to vaccination, and
    - has a negative pregnancy test on the day of vaccination, and
    - has agreed to continue adequate contraception during the entire treatment period and for 2 months after completion of the vaccination series.

  Refer to the Glossary Of Terms for the definition of adequate contraception.

4.3. Exclusion criteria for enrolment *(Amended 13 Jan 2011)*

The following criteria should be checked at the time of study entry. If ANY exclusion criterion applies, the subject must not be included in the study:

- Pregnant or breastfeeding (women must be at least three months post-pregnancy and not breastfeeding to enter the study).
- A woman planning to become pregnant, likely to become pregnant (as determined by the investigator) or planning to discontinue contraceptive precautions during the vaccination phase of the study, i.e. up to two months after the last vaccine dose.
- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the first dose of study vaccine, or planned use during the study period.
- Previous vaccination against HPV or planned administration of another HPV vaccine during the study other than that foreseen in the protocol.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs within six months prior to the first vaccine dose. For corticosteroids, this will mean prednisone greater than or equal to 20 mg/day, or equivalent. Inhaled and topical steroids are allowed
- Planned administration/administration of a vaccine not foreseen by the study protocol within 30 days (i.e., Day 0-29) of each dose of vaccine, with the exception of administration of routine meningococcal, hepatitis B, hepatitis A, inactivated influenza, diphtheria/tetanus and/or diphtheria/tetanus-containing vaccine up to 8 days before each dose of study vaccine. Enrolment will be deferred until the subject is outside of specified window.
- Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational product (pharmaceutical product or device).

  NOTE: Subjects enrolled in this study may also be eligible for a four-year gynaecological follow-up of the HPV-015 study (HPV-062), in which no investigational product will be administered. Subjects may participate to both studies at the same time.
- Previous administration of MPL or AS04 adjuvant.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Cancer or autoimmune disease under treatment.
- Administration of immunoglobulins and/or any blood products within the 3 months preceding the first dose of study vaccine or planned administration during the study period.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine including latex.

- History of any neurological disorders or seizures.
- Acute disease and/or fever at the time of enrolment.

  Fever is defined as temperature ≥ 37.5°C (99.5°F) on oral, axillary or tympanic setting, or ≥ 38.0°C (100.4°F) on rectal setting.

  Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may be enrolled at the discretion of the investigator.

  Enrolment will be deferred until condition is resolved.
- Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening tests.

5. CONDUCT OF THE STUDY

5.1. Regulatory and ethical considerations, including the informed consent process

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with the ICH Guideline for Good Clinical Practice (GCP), all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

GSK will obtain favourable opinion/approval to conduct the study from the appropriate regulatory agency, in accordance with applicable regulatory requirements, prior to a site initiating the study in that country.

Conduct of the study includes, but is not limited to, the following:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent as appropriate.
- Investigator reporting requirements as stated in the protocol.

GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.

Freely given and written informed consent must be obtained from each subject as appropriate, prior to participation in the study.

GSK Biologicals will prepare a model Informed Consent Form (ICF) which will embody the ICH GCP and GSK Biologicals required elements. While it is strongly recommended that this model ICF is to be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally

effective. Clinical judgement, local regulations and requirements should guide the final structure and content of the local version of the ICF.

The investigator has the final responsibility for the final presentation of the ICF, respecting the mandatory requirements of local regulations. The ICF generated by the investigator with the assistance of the sponsor's representative must be acceptable to GSK Biologicals and be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC.

5.2. Subject identification and randomisation of treatment

The target will be to enrol approximately 600 eligible subjects to receive the HPV-16/18 L1 VLP AS04 vaccine in this study .

5.2.1. Subject identification

A new identification number will be assigned to the subject to preserve the blind for HPV-015 data during this HPV-015 extension study.

5.2.2. Randomisation of treatment

A sequential numbering of the vaccine doses will be performed at GSK Biologicals, Rixensart, using a standard SAS® (Statistical Analysis System) program. The vaccine doses labeled with those treatment numbers will be distributed to the study centres. No randomization will be performed: at each vaccination, the treatment number must be recorded by the investigator/co-investigator or delegate in the eCRF (Vaccine Administration Section).

5.2.3. Randomisation of subjects to assay subsets

Not applicable.

5.3. Method of blinding

Since this is an open-label study with a single treatment group, no blinding will be applied.

5.4. General study aspects

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM provides the investigator and the site personnel with administrative and detailed technical information that does not impact the safety of the subjects.

5.5. Outline of study procedures

Table 1 List of study procedures

Type of contact	visit 1	visit 2	visit 3	phone contact 12
Timepoint (s)	**months 0**	**months 1**	**months 6**	**months 12**
Informed consent	●			
Check inclusion/exclusion criteria	●			
Check contraindications		●	●	
Medical history	●			
Record administration of any HPV vaccine other than that foreseen by the study protocol	●	●	●	●
Collect demographic data	●			
History-directed physical examination	●			
Urine sample for pre-vaccination pregnancy test	●	●	●	
Pre-vaccination body temperature	●	●	●	
Vaccination	●	●	●	
Record administration of any concomitant medication, vaccination or medical treatment	●	●	●	●
Reporting of medically significant conditions (including pIMDs)	●	●	●	●
Reporting of serious adverse events	●	●	●	●
Reporting of pregnancies (and outcomes)	●	●	●	●
Safety follow-up contact				●
Study Conclusion				●

The investigator or his/her designee will contact the subjects by telephone approximately six months after the third vaccine dose to obtain information on the occurrence of any of the safety endpoints.

● is used to indicate a study procedure that requires documentation in the individual eCRF

It is the investigator's responsibility to ensure that the intervals between visits/contacts are followed. The intervals between vaccination visits, and the interval between the last vaccination visit and the telephone contact at Month 12 are provided in Table 2. It is preferable to follow these intervals as closely as possible.

Table 2 Intervals between study visits

Interval	Optimal length of interval (months)	Recommended interval between scheduled visits/contact (months)
1 (visit 1→ visit 2)	1 – 2.5	1
2 (visit 1→ visit 3)	5 - 12	6
3 (visit 3→ phone contact)	6 - 7	6

5.6. Detailed description of study procedures

5.6.1. Procedures prior to study participation

5.6.1.1. Informed consent

Before performing any other study procedure, the signed/thumb printed informed consent of the subject needs to be obtained. Refer to Section 5.1 for the requirements on how to obtain informed consent as appropriate.

5.6.2. Procedures prior to the first vaccination

5.6.2.1. Check inclusion and exclusion criteria

Check all applicable inclusion and exclusion criteria as described in Sections 4.2 and 4.3 before enrolment.

5.6.2.2. Collect demographic data

Record demographic data such as age, gender and ethnicity in the subject's eCRF.

5.6.2.3. Medical history and history-directed physical examination

Perform a history-directed medical and physical examination and record any pre-existing or concurrent conditions or signs and/or symptoms present in a subject prior to the start of the study in the eCRF. Treatment of any abnormality observed during this examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

5.6.3. Procedures at each vaccination visit

5.6.3.1. Urine pregnancy test

Female subjects of childbearing potential are to have a urine pregnancy test prior to any study vaccine administration. The study vaccine may only be administered if the pregnancy test is negative.

5.6.3.2. Check contraindications to vaccination (only prior to second and third vaccine dose)

Contraindications to vaccination are to be checked at the beginning of each vaccination visit. Refer to Section 6.5.

5.6.3.3. Check and record concomitant medication/vaccination

Concomitant medication/vaccination must be recorded in the eCRF as described in Section 6.6. Refer also to Section 6.6 for details on the medication/vaccination forbidden and/or allowed during the study.

5.6.3.4. Assess pre-vaccination body temperature

The axillary, rectal, oral or tympanic body temperature of all subjects needs to be measured prior to any study vaccine administration. The preferred route for recording temperature in this study will be oral or axillary. If the subject has fever [fever is defined as temperature ≥ 37.5°C (99.5°F) on oral or, axillary or tympanic setting, or ≥ 38.0°C (100.4°F) on rectal setting] on the day of vaccination, the vaccination visit will be rescheduled within the interval for this visit (see Table 2).

5.6.3.5. Vaccination

- After completing the prerequisite procedures prior to vaccination, one dose of study vaccine will be administered intramuscularly (IM) in the deltoid of the non-dominant arm (refer to Section 6.3 for detailed description of the vaccine administration procedure). If the investigator or delegate determines that the subject's health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled within the interval for this visit.
- The vaccinees will be observed closely for at least 30 minutes, with appropriate medical treatment readily available in case of anaphylaxis following the administration of vaccine.

5.6.3.6. Recording of medically significant conditions and SAEs

- Refer to Section 8.3 for procedures for the Investigator to record AEs (medically significant conditions only) and SAEs that are related to study participation or GSK concomitant medication/vaccination and to Section 8.4 for guidelines on how to report these AEs/SAEs to GSK Biologicals.
- The subjects will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.
- Refer to the Refer to the Glossary Of Terms for the definition of medically significant conditions

5.6.4. Procedures during follow-up phone contact

- The investigator or his/her designee will contact the subjects by telephone approximately six months after the third vaccine dose to obtain information on the occurrence of any of the safety endpoints.
- The procedures to be performed during the follow-up telephone contact such as recording of any concomitant medication/vaccination or medical treatment and recording of medically significant conditions and SAEs are also performed during

this phone contact and are described in Section 5.6.3.3 and Section 5.6.3.6, respectively.

5.6.4.1. Study conclusion

The investigator will review safety data collected during the entire cross-vaccination study to ensure accuracy and completeness and will complete the Study Conclusion screen in the eCRF.

5.7. Biological sample handling and analysis

Not applicable.

5.7.1. Immunological correlates of protection

No correlate of protection has been demonstrated for the HPV-16 and HPV-18 antigens used as part of the HPV-16/18 L1 VLP AS04 vaccine.

6. STUDY VACCINE AND ADMINISTRATION

6.1. Description of study vaccine

The candidate vaccine to be used has been developed and manufactured by GSK Biologicals.

The Quality Control Standards and Requirements for the candidate vaccine are described in separate Quality Assurance documents (e.g. release protocols, certificate of analysis) and the required approvals have been obtained.

The vaccine is labelled and packed according to applicable regulatory requirements.

The composition of the HPV-16/18 L1 VLP AS04 vaccine is presented in Table 3.

Table 3 Study vaccine

Vaccine name	Formulation	Presentation	Volume	Number of doses
HPV-16/18 L1 VLP AS04	Each 0.5 ml dose contains: - 20 µg HPV-16 L1 VLP - 20 µg HPV-18 L1 VLP - 50 µg MPL - 0.5 mg aluminium as Al(OH)3 - 8 mM sodium dihydrogen phosphate dihydrate - 150 mM sodium chloride - water for injection	Liquid in pre-filled syringes	0.6 ml	3

MPL = 3-*O*-desacyl-*4'*-monophosphoryl lipid A; $Al(OH)_3$ = aluminium hydroxide; L1 = structural protein of HPV
ml = millilitre; µg = microgram

6.2. Storage and handling of study vaccine

The study vaccine to be administered to the subjects must be stored in a safe and locked place with no access by unauthorised personnel.

The study vaccine must be stored at the defined temperature range (i.e. +2 to +8°C/36°F to 46°F). Please refer to the Module on Clinical Trial Supplies in the SPM for more details on storage of the study vaccine. The storage temperature of the vaccine will be monitored daily with temperature monitoring device(s) (at the minimum calibrated) and will be recorded as specified in the SPM.

The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact.

Any temperature deviation outside the range 0 to +8°C/32 to 46°F must be reported to the sponsor as soon as detected. Following an exposure to a temperature deviation, vaccine will not be used until written approval has been given by the Sponsor.

In case of temperature deviation between 0 and +2°C/32 and 36°F, the impacted study vaccine can still be administered, but the site must take adequate actions to go back to the defined range +2 to +8°C/36 to 46°F and avoid re-occurrence of such a temperature deviation.

Please refer to the Module on Clinical Trial Supplies in the SPM for details and instructions on the Temperature deviation process, packaging and accountability of the study vaccine.

6.3. Dosage and administration of study vaccine

GSK Biologicals will supply the HPV-16/18 L1 VLP AS04 vaccine as 0.6 ml liquid in pre-filled syringes to be administered (0.5ml) into the deltoid of the non-dominant arm on a 0, 1, 6 month schedule (refer to Table 4). Additional syringes will be provided to each site to replace broken, lost or damaged syringes as needed.

The HPV-16/18 L1 VLP AS04 vaccine is provided as individual pre-filled syringes for single use. Each syringe must be brought to room temperature and resuspended (by inversion) prior to injection by standard aseptic technique. The study vaccine must be used as soon as possible after preparation of the syringe.

Table 4 Dosage and administration

Type of contact and timepoint	Dose	Vaccine/Product	Route [1]	Site [2]	Side [3]
visit 1 ((months 0)	1	HPV-16/18 L1 VLP AS04	IM	D	N-D
visit 2 (months 1)	1	HPV-16/18 L1 VLP AS04	IM	D	N-D
visit 3 (months 6)	1	HPV-16/18 L1 VLP AS04	IM	D	N-D

[1] Intramuscular (IM)
[2] Deltoid (D)
[3] Non-dominant (N-D)

6.4. Replacement of unusable vaccine doses

Additional vaccine doses will be provided to replace those that are unusable (see the Module on Clinical Trial Supplies in the SPM for details).

In addition to the vaccine doses provided for the planned number of subjects (including over-randomisation when applicable), at least 5% additional doses will be supplied to replace those that are unusable.

6.5. Contraindications to subsequent vaccination

The following events constitute absolute contraindications to further administration of the HPV-16/18 L1 VLP AS04 vaccine. If any of these events occur during the study, the subject must not receive additional doses of vaccine but may continue other study procedures at the discretion of the investigator (see Section 8.4.5).

- Anaphylaxis following the administration of the vaccine.
- Pregnancy (see Section 8.2)
- Any serious adverse event (SAE) judged to be related to study vaccine.
- Administration of another HPV vaccine during the study other than that foreseen by protocol.
- Any acute or newly acquired chronic condition at the time of scheduled vaccination, which in the opinion of the investigator precludes further administration of the study vaccine.
- Other significant reactions which in the opinion of the investigator (or designate) preclude further administration of the study vaccine (may include severe pain, severe swelling, severe limitation of motion, persistent high fever, severe headache or other systemic or local reactions).
- Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection.

The following events constitute contraindications to administration of the HPV-16/18 L1 VLP AS04 vaccine at that point in time; if any of these events occur at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol (see Section 5.5), or withdrawn at the discretion of the investigator (see Section 8.4.5).

- Acute disease and/or fever at the time of vaccination.
    - Fever is defined as temperature ≥ 37.5°C (99.5°F) on oral, axillary or tympanic setting, or ≥ 38.0°C (100.4°F) on rectal setting. The preferred route for recording temperature in this study will be oral or axillary.
    - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever can be administered the HPV-16/18 L1 VLP AS04 vaccine.

6.6. Concomitant medication/vaccination

At each study visit/contact, the investigator should question the subject if she received any HPV vaccine other than that foreseen in the study protocol at any time during the study period. The trade name of the vaccine, route of administration and date(s) of administration should be recorded in the eCRF. Refer to Sections 4.3 and 6.5.

At each study visit/contact, the investigator should question the subject about any medication taken and vaccination received by the subject.

All concomitant medication/vaccination, with the exception of vitamins and/or dietary supplements, are to be recorded in the eCRF. This also applies to concomitant medication administered prophylactically in anticipation of reaction to the vaccination and any medication intended to treat an AE.

A prophylactic medication is a medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination (e.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring [fever is defined as temperature ≥ 37.5°C (99.5°F) on oral, axillary or tympanic setting, or ≥ 38.0°C (100.4°F) on rectal setting]).

Any treatments and/or medications specifically contraindicated, administered at any time during the study period are to be recorded with generic name of the medication (trade names are allowed for combination drugs only), medical indication, total daily dose, route of administration, start and end dates of treatment. Refer to Sections 4.3 and 6.5.

Similarly, concomitant medication administered for the treatment of a SAE, at any time, must be recorded on the SAE Report / SAE screens in the eCRF, as applicable. Refer to Section 8.1.2 for the definition of a SAE.

6.6.1. Time window for recording concomitant medication/vaccination in the eCRF

All concomitant medications, with the exception of vitamins and/or dietary supplements, administered at ANY time during the period starting with the administration of each dose of study vaccine and ending 30 days after each dose of study vaccine must be recorded in the eCRF.

Any vaccine not foreseen in the study protocol administered in the period beginning 30 days preceding each dose of study vaccine and ending 30 days after each dose of study vaccine must be recorded in the eCRF.

Any investigational medication or vaccine administered throughout the study (i.e. from Day 0 through Month 12) must be recorded in the eCRF.

7. HEALTH ECONOMICS

Not applicable.

8. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The investigator or site staff is/are responsible during the study for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE) as provided in this protocol.

Each subject will be instructed to contact the investigator immediately should they/the subject manifest any signs or symptoms they perceive as serious.

NOTE: The term AE denotes both non-serious and serious adverse events. In this study, only SAEs and non-serious AEs that are medically significant conditions will be reported.

8.1. Safety definitions

8.1.1. Definition of an adverse event

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Examples of an AE include:

- Medically significant conditions (please refer to Section 8.1.4 for the definition of medically significant condition).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with vaccine administration.

Examples of an AE DO NOT include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

AEs may include pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject's previous therapeutic regimen).

Example of events to be recorded in the medical history section of the eCRF:

- Pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study (i.e. prior to the first study vaccination).

NOTE: In this study, only SAEs and non-serious AEs that are medically significant conditions will be reported.

8.1.2. Definition of a serious adverse event

A serious adverse event (SAE) is any untoward medical occurrence that:

a. Results in death.

b. Is life-threatening.

   NB: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

c. Requires hospitalisation or prolongation of existing hospitalisation.

   NB: In general, hospitalisation signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are also considered AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

d. Results in disability/incapacity, or

   NB: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect in the offspring of a study subject.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.

Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

8.1.3. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events

Abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g. ECGs, X-rays, vital signs, etc) that are judged by the investigator to be clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE, as defined in Section 8.1.1 or of a SAE, as defined in Section 8.1.2. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as medically significant conditions or SAEs, if applicable.

The investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

8.1.4. Medically significant conditions

Medically significant conditions are defined as:

- AEs prompting emergency room or physician visits that are:
  1. not related to common diseases, or
  2. not related to routine visits for physical examination or vaccination
- SAEs that are not related to common diseases.

Common diseases include: upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, cervicovaginal yeast infections, menstrual cycle abnormalities and injury.

Medically significant conditions include pIMDs.

8.1.4.1. Potential immune-mediated diseases

Potential immune-mediated diseases (pIMDs) are a subset of medically significant conditions that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. AEs that need to be recorded and reported as pIMDs include those listed in the table below.

However, the investigator will exercise his/her medical and scientific judgement in deciding whether other immune-mediated diseases have an autoimmune origin (i.e. pathophysiology involving systemic or organ-specific pathogenic autoantibodies) and should also be recorded as a pIMD.

Onset of a new pIMD or exacerbation of a pre-existing pIMD (serious or non-serious) will be recorded in the SAE screen of the subject's eCRF.

Table 5 List of potential immune-mediated diseases *(Amended 13 Jan 2011)*

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
• Cranial nerve disorders, including paralyses/paresis (e.g. Bell's palsy), and neuritis (e.g. optic neuritis) • Multiple sclerosis (including variants) • Transverse myelitis • Guillain-Barré syndrome, (including Miller Fisher syndrome and other variants) • Other demyelinating diseases (including acute disseminated encephalomyelitis) • Myasthenia gravis (including Lambert-Eaton myasthenic syndrome) • Non-infectious encephalitis/ encephalomyelitis • Neuritis (including peripheral neuropathies)	• Systemic lupus erythematosus • Scleroderma (including, CREST syndrome and morphoea) • Systemic sclerosis • Dermatomyositis • Polymyositis • Antisynthetase syndrome • Rheumatoid arthritis, • Juvenile chronic arthritis, (including Still's disease) • Polymyalgia rheumatica • Reactive arthritis • Psoriatic arthropathy • Ankylosing spondylitis ***(including undifferentiated spondyloarthritides)*** • Relapsing polychondritis • Mixed connective tissue disorder	• Psoriasis • Vitiligo • Raynaud's phenomenon • Erythema nodosum • Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis) • Cutaneous lupus erythematosus • Alopecia areata • Lichen planus • Sweet's syndrome
Liver disorders	**Gastrointestinal disorders**	**Metabolic diseases**
• Autoimmune hepatitis • Primary biliary cirrhosis • Primary sclerosing cholangitis • Autoimmune cholangitis.	• Crohn's disease • Ulcerative colitis • Ulcerative proctitis • Celiac disease	• Autoimmune thyroiditis (including Hashimoto thyroiditis) • Grave's or Basedow's disease • Diabetes mellitus type I • Addison's disease

Vasculitides	Others
• Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis. • Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome, thromboangiitis obliterans (Buerger's disease), necrotizing vasculitis, allergic granulomatous angiitis, Henoch-Schonlein purpura, anti-neutrophil cytoplasmic antibody positive vasculitis, Behcet's syndrome, leukocytoclastic vasculitis. • Vasculitides secondary to other immune mediated diseases such as lupus vasculitis and rheumatoid vasculitis.	• Autoimmune hemolytic anemia • Autoimmune thrombocytopenias • Antiphospholipid syndrome • Pernicious anemia • Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis) • Uveitis • Autoimmune myocarditis/cardiomyopathy • Sarcoidosis • Stevens-johnson syndrome • Sjögren's syndrome • Idiopathic pulmonary fibrosis • Goodpasture syndrome

When there is enough evidence to make any of the above diagnoses, the AE must be reported as a pIMD. Symptoms, signs or conditions which might (or might not) represent the above diagnoses, should be recorded and reported as AEs but not as pIMDs until the final or definitive diagnosis has been determined, and alternative diagnoses have been eliminated or shown to be less likely.

In order to facilitate the documentation of pIMDs in the eCRF, a pIMD standard questionnaire and a list of preferred terms (PTs) and PT codes corresponding to the above diagnoses will be available to investigators at study start.

8.2. Pregnancy

Any female subjects that are pregnant or lactating at the time of vaccination must not receive additional doses of study vaccine but may continue other study procedures at the discretion of the investigator.

While pregnancy itself is not considered an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or a SAE, as described in Section 8.1.1 and 8.1.2, and will be followed as described in Section 8.4.5.

A spontaneous abortion is always considered to be a SAE and will be reported as described in Section 8.4. Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered by the investigator to be reasonably related in time to the receipt of the investigational product will be reported to GSK Biologicals as described in Section 8.4. While the investigator is not obligated to actively seek this information from former study participants, he/she may learn of a pregnancy through spontaneous reporting.

Information on pregnancies identified during screening/prior to vaccine administration is not required to be collected and communicated to safety.

8.3. Detecting and recording adverse events, serious adverse events and pregnancies

8.3.1. Time period for detecting and recording adverse events, serious adverse events and pregnancies

The standard time period for collecting and recording medically significant conditions will begin at the first receipt of study vaccine and will end 6 months following the administration of the last dose of study vaccine (i.e. at study conclusion) for each subject. Medically significant conditions should be recorded in the AE screen of the subjects eCRF if they are non-serious and in the SAE screen of the subject's eCRF if they are serious. When the medically significant condition is considered as a pIMD, it always has to be reported in the SAE screen of the subject's eCRF. See also Section 8.4 for instructions on reporting of pIMDs.

The standard time period for collecting and recording pregnancies will begin at the first receipt of study vaccine and will end 6 months following administration of the last dose of study vaccine (i.e. at study conclusion). See section 8.4 for instructions on reporting of pregnancies.

The standard time period for collecting and recording SAEs will begin at the first receipt of study vaccine and will end 6 months following administration of the last dose of study vaccine (i.e. at study conclusion). See section 8.4 for instructions on reporting of SAEs.

Any conditions or signs and/or symptoms present in a subject prior to study HPV-06*7* need not be recorded. ***(Amended 13 Jan 2011)***

In addition to the above-mentioned reporting requirements and in order to fulfil international reporting obligations, SAEs that are related to study participation (e.g. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine or any fatal SAE will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged.

An overview of the protocol-required reporting periods for adverse events and serious adverse events is given in Table 6.

Table 6 Reporting periods for adverse events, serious adverse events and pregnancies

Study activity	Pre-vacc. (Consent obtained)	Visit 1 Day 0 1st vacc.		Visit 2 Month 1 2nd vacc.		Visit 3 Month 6 3rd vacc.	Telephone contact Month 12 Study Conclusion 6 months post 3rd vaccination
Reporting of SAEs, medically significant conditions (including pIMDs), pregnancies and pregnancy outcomes							
Reporting of fatal SAEs and SAEs related to study participation or concurrent GSK vaccine/drugs							

Pre-vacc: pre-vaccination; Vacc: vaccination.

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 6. Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the investigator will promptly notify the Study Contact for Reporting SAEs.

8.3.2. Evaluation of adverse events and serious adverse events

8.3.2.1. Active questioning to detect adverse events and serious adverse events

The investigator will inquire about the occurrence of SAEs and medically significant conditions, pregnancies and pregnancy outcomes at each visit during the study and at the telephone contact at Month 12.

All AEs either observed by the investigator or one of his clinical collaborators or reported by the subject spontaneously or in response to a direct question will be evaluated by the investigator for the detection and documentation of events meeting the criteria and definition of SAEs and/or medically significant conditions. AEs not previously documented in the study will be recorded on the Adverse Event screen within the subject's eCRF, if applicable. The nature of each event, date and time (where appropriate) of onset, outcome, intensity and relationship to the HPV vaccine should be entered. Details of any corrective treatment should be recorded on the appropriate page of the eCRF. Refer to Section 6.6.

As a consistent method of soliciting AEs, the subject should be asked a non-leading question such as:

'*Have you felt different in any way since receiving the vaccine or since the previous visit?*'

AEs already documented in the eCRF, i.e. at a previous assessment, and designated as "not recovered/not resolved" or "recovering/resolving" should be reviewed at subsequent visits, as necessary. If these have resolved, the documentation in the eCRF should be completed.

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE on the eCRF or SAE screens as applicable. It is not acceptable for the investigator to send photocopies of the subject's medical records to GSK Biologicals instead of the appropriate completed AE/SAE screens in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

The investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

The electronic system using SAE screens in the eCRF will be the primary mode for reporting SAEs to GSK Biologicals during the study period. In case this electronic system for reporting SAEs does not work or after freezing of the subject's eCRF, paper SAE Report Forms and the facsimile (Fax) system should be used to report SAEs. Refer to Section 8.4.3.1 for details of the back-up reporting system.

8.3.2.2. Assessment of adverse events

8.3.2.2.1. Assessment of intensity

The investigator will assess the maximum intensity that occurred over the duration of the event for all other AEs, including SAEs reported during the study. The assessment will be based on the investigator's clinical judgement.

The intensity of each AE and SAE recorded in the eCRF or SAE screens, as applicable, should be assigned to one of the following categories:

1 (mild)	=	An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AE which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AE which prevents normal, everyday activities (In adults/adolescents, such an AE would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy.)

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 8.1.2.

8.3.2.2.2. Assessment of causality

The investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. The investigator will use clinical judgement to determine the relationship. Alternative plausible causes, based on natural history of the underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the investigational product will be considered and investigated. The investigator will also consult the Investigator Brochure and/or Product Information for marketed products, in the determination of his/her assessment.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the SAE to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Causality of all other AEs than local (injection site) reactions should be assessed by the investigator using the following question:

Is there a reasonable possibility that the AE may have been caused by the investigational product?

NO	:	The AE is not causally related to administration of the study vaccine(s). There are other, more likely causes and administration of the study vaccine(s) is not suspected to have contributed to the AE.
YES	:	There is a reasonable possibility that the vaccine(s) contributed to the AE.

Non-serious and serious AEs will be evaluated as two distinct events. If an event meets criteria to be determined 'serious' (see Section 8.1.2 for definition of serious adverse event), additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors applicable to each SAE.

Possible contributing factors include:

- Medical history
- Other medication
- Protocol required procedure
- Other procedure not required by the protocol
- Lack of efficacy of the vaccine, if applicable
- Erroneous administration
- Other cause (specify).

8.3.2.3. Assessment of outcomes

Outcome of any non-serious AE or SAE reported during the entire study will be assessed as:

- Recovered/resolved
- Not recovered/not resolved
- Recovering/resolving
- Recovered with sequelae/resolved with sequelae
- Fatal (SAEs only).

8.3.2.4. Medically attended visits

For each symptom the subject experiences, the subject will be asked if she received medical attention defined as hospitalisation, an emergency room visit or a visit to or from medical personnel (medical doctor) for any reason and this information will be recorded in the eCRF.

8.4. Reporting and follow-up of adverse events, serious adverse events and pregnancies

8.4.1. Prompt reporting of serious adverse events and other events to GSK Biologicals

SAEs will be reported promptly to GSK as described in Table 7 once the investigator determines that the event meets the protocol definition of an SAE.

Pregnancies will be reported promptly to GSK as described in Table 7 once the investigator becomes aware of a pregnancy in the time period defined in Section 8.3. The subject will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether that be full-term or premature, information on the status of the mother and child will be forwarded to GSK. Generally, follow-up should be no longer than 6 to 8 weeks following the estimated delivery date.

Any pIMDs that occur in the time period defined in Section 8.3.1will be reported promptly to GSK within the timeframes described in Table 7, once the investigator becomes aware of the pIMD.

Table 7 Time frames for submitting SAEs and other events reports to GSK Biologicals

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hours*	SAE report/SAE screen	24 hours*	SAE report/SAE screen
Pregnancy	24 hours*	Pregnancy Report Form	24 hours*	Pregnancy Report Form
pIMDs	24 hours**	SAE report/SAE screen	24 hours*	SAE report/SAE screen

* Time frame allowed after receipt or awareness of the information.
** Time frame allowed after the diagnosis is established and known to the investigator.

In case the electronic reporting system is temporarily unavailable, a back-up system is in place. Please refer to Section 8.4.3 for a detailed description.

Study Contact for Reporting SAEs
Please see the Sponsor Information Sheet for contact details.
Back-up Study Contact for Reporting SAEs
GSK Biologicals Clinical Safety & Pharmacovigilance Fax: PPD or PPD **24/24 hour and 7/7 day availability**

8.4.2. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.4.1. GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the Study Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

Investigator safety reports are prepared according to the current GSK policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to the investigational product and unexpected. The purpose of the report is to fulfil specific regulatory and GCP requirements, regarding the product under investigation.

8.4.3. Completion and transmission of SAEs reports to GSK Biologicals

Once an investigator becomes aware that a SAE has occurred in a study subject, the investigator will complete and submit the information in the SAE screens in eCRF within 24 hours. The SAE screens in eCRF will always be completed as thoroughly as possible with all available details of the event and will be submitted by the investigator. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the SAE screens in eCRF. The SAE screens in eCRF should be updated when additional relevant information is received WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report.

8.4.3.1. Back-up system in case the electronic SAE reporting system does not work

If the SAE reporting system has been down for 24 hours, the investigator or his/her delegate should fax an SAE report form directly to the GSK Central Safety department (please refer to Section 8.4.1) within 24 hours. The maximum timeline for reporting SAEs to central safety is therefore 48 hours.

NB. This back-up system should only be used if the electronic reporting system is not working and NOT if the system is slow.

As soon as the electronic reporting system is working again, the investigator or delegate must update the SAE screens in the eCRF within 24 hours.

The final valid information for regulatory reporting will be the information reported through the electronic system.

When additional information is received on a SAE after freezing of the subject's eCRF, new or updated information is to be recorded on the paper SAE Report Form, with all

changes signed and dated by the investigator. The updated SAE Report Form should be sent to GSK Biologicals WITHIN 24 HOURS of receipt of the follow-up information.

In rare circumstances, if the electronic system for reporting SAEs does not work and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE Report Form sent by email or by mail. Initial notification via the telephone does not replace the need for the investigator to complete and submit SAE screens in the eCRF (or complete and sign the SAE Report Form if back-up system need to be used).

In the event of a death determined by the investigator to be related to vaccination, completion of SAE screens in the eCRF/sending of the fax (if electronic SAE reporting system does not work or after freezing of the subject's eCRF) must be accompanied by telephone call to the Study Contact for Reporting SAEs.

8.4.3.2. Updating of SAE information after freezing of the subject's eCRF

When additional information is received on a SAE after freezing of the subject's eCRF, new or updated information should be recorded on a SAE Report Form, with all changes signed and dated by the investigator. The updated form should be faxed to the GSK Biologicals Clinical Safety and Pharmacovigilance department or to the Study Contact for Reporting SAEs (refer to the Sponsor Information Sheet) WITHIN 24 HOURS of receipt of the follow-up information.

8.4.4. Reporting of pIMDs to GSK Biologicals

Once onset of a new pIMD or exacerbation of a pre-existing pIMD is diagnosed (serious or non-serious) in a study subject, the investigator (or designate) must complete the information in the SAE screens of the eCRF WITHIN 24 HOURS after the he/she becomes aware of the diagnosis. A field on the SAE screen allows to specify that the event is a pIMD and whether it is serious or non serious. The SAE screens will always be completed as thoroughly as possible with all available details of the event, in accordance with the pIMD standard questionnaire provided. Even if the investigator does not have all information regarding a pIMD, the SAE screens should still be completed within 24 hours. Once additional relevant information is received, the SAE screens in the eCRF should be updated WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report.

Refer to Sections 8.4.3.1 and 8.4.3.2 for back-up system and updating of SAE information after freezing of the subject's eCRF.

8.4.5. Follow-up of adverse events and serious adverse events

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide further information to GSK Biologicals on the subject's condition.

All AEs (medically significant conditions only) and SAEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the end of the study.

Investigators will follow-up subjects:

- With SAEs or subjects withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilised, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.
- Or, in the case of other non-serious AEs (medically significant conditions only), until they complete the study or they are lost to follow-up.

Clinically significant laboratory abnormalities will be followed up until they have returned to normal, or a satisfactory explanation has been provided. Additional information (including but not limited to laboratory results) relative to the subsequent course of such abnormalities noted for any subject must be made available to the Site Monitor.

GSK Biologicals may request that the investigator perform or arrange for the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obliged to assist. If a subject dies during participation in the study or during a recognised follow-up period, GSK Biologicals will be provided with a copy of any available post-mortem findings, including histopathology.

8.5. Treatment of adverse events

Treatment of any adverse event is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of an AE should be recorded in the subject's eCRF. Refer to Section 6.6.

8.6. Unblinding

Not applicable.

8.7. Emergency unblinding

This study will be open label, i.e. both the investigator and the subject will be aware of the vaccine being administered to the subjects. Therefore, the information given hereunder is limited to the unblinding of SAEs to any third parties (e.g. any doctor other than the study investigator), in accordance with GSK Biologicals' standard operating procedures.

The investigator, or other physician managing the subject, should contact GSK Biologicals' Central Safety Physician to discuss the need for emergency unblinding. Alternatively the investigator may contact the local contact who will contact the GSK Central Safety Physician.

The investigator, or person designated by the investigator, should contact GSK Biologicals' Central Safety physician directly or via the local safety contact (see below and Study Contact for Emergency Code Break in Sponsor Information page) to discuss the need for emergency unblinding.

An investigator should request for unblinding of the subject's treatment code only in the case of a medical emergency, or in the event of a serious medical condition, when knowledge of the investigational study vaccine(s)/product(s) is essential for the clinical management or welfare of the subject.

The GSK Biologicals' Central Safety Office will be allowed to access the individual randomisation code. The code will be broken by the GSK Biologicals' Central Safety physician (see below and Study Contact for Emergency Code Break in Sponsor Information) only in the case of medical events that the investigator/physician in charge of the subject feels cannot be treated without knowing the identity of the study vaccine.

GSK Biologicals Central Safety Physician (Study Contact for Emergency Code Break)
Phones for 7/7 day availability: +PPD (GSK Biologicals Central Safety Physician on-call) Back-up phone contact: +PPD

8.8. Subject card

Study subjects must be provided with the address and telephone number of the main contact for information about the trial.

Investigator/delegate should therefore provide a "subject card" to each subject. The aim of this card is to inform any physician having to deal with a subject in an emergency situation that the subject is in a clinical trial and that he/she can contact the trial investigator for more relevant information.

Subjects must be instructed to keep these cards in their possession at all times.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject completion

A subject who is available for the concluding contact foreseen in the protocol is considered to have completed the study.

9.2. Subject withdrawal

Subjects who are withdrawn because of SAEs/AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn as result of a SAE/AE until resolution of the event (see Section 8.4).

Withdrawals will not be replaced.

9.2.1. Subject withdrawal from the study

From an analysis perspective, a 'withdrawal' from the study refers to any subject who was not available for the concluding contact foreseen in the protocol.

All data collected until the date of withdrawal/last contact of the subject will be used for the analysis.

A subject is considered a 'withdrawal' from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this subject from the date of withdrawal/last contact.

Investigators will make an attempt to contact those subjects who do not return for scheduled visits or follow-up.

Information relative to the withdrawal will be documented in the eCRF. The investigator will document whether the decision to withdraw a subject from the study was made by the subject herself, or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event
- Non-serious adverse event
- Protocol violation (specify)
- Consent withdrawal, not due to an adverse event
- Moved from the study area
- Lost to follow-up
- Death
- Other (specify).

9.2.2. Subject withdrawal from investigational vaccine

A 'withdrawal' from the investigational vaccine refers to any subject who does not receive the complete treatment, i.e. when no further planned dose is administered from the date of withdrawal. A subject withdrawn from the investigational vaccine may not necessarily be withdrawn from the study as further study procedures or follow-up may be performed (safety or immunogenicity) if planned in the study protocol.

Information relative to premature discontinuation of the investigational vaccine will be documented on the Vaccine Administration screen of the eCRF. The investigator will document whether the decision to discontinue further vaccination/treatment was made by the subject herself or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event
- Non-serious adverse event
- Other (specify).

10. DATA EVALUATION: CRITERIA FOR EVALUATION OF OBJECTIVES

10.1. Study endpoints

- Occurrence, intensity and causal relationship to vaccination of medically significant conditions (including pIMDs) throughout the study
- Occurrence, intensity and causal relationship to vaccination of SAEs throughout the study
- Occurrence of pregnancies and pregnancy outcomes throughout the study

10.2. Estimated sample size

No sample size is calculated for this study. Approximately 600 subjects who received the control placebo in the HPV-015 study, will be invited to participate in this study for cross-over vaccination with GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine.

10.3. Study cohorts to be evaluated

10.3.1. Total Vaccinated Cohort

The Total Vaccinated Cohort will include all vaccinated subjects (i.e. subjects who received at least one dose of HPV-16/18 L1 VLP AS04 vaccine in this study) for whom safety data are available.

10.4. Derived and transformed data

Not applicable.

10.5. Conduct of analyses

SAEs, other medically significant conditions, pregnancies and pregnancy outcomes will be described in detail. These safety data will be presented in a clinical study report.

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

10.6. Statistical methods

10.6.1. Analysis of demographics/baseline characteristics

Demographic characteristics (age, region, race) of each study cohort will be tabulated.

The mean age (plus range and standard deviation) of the enrolled subjects will be calculated.

The distribution of subjects enrolled among the study sites will be tabulated.

10.6.2. Analysis of safety

The analysis will be performed on the Total vaccinated cohort.

No inferential analysis will be performed. Analyses of safety endpoints will only be descriptive.

The proportion of subjects with at least one report of an SAE and/or at least one medically significant condition (including pIMDs) will be tabulated with exact 95% confidence interval (CI) throughout the study period.

SAEs and other medically significant conditions (including pIMDs) will be described in detail. SAEs and other medically significant conditions (including pIMDs) will be further evaluated for their clinical relevance and relationship to vaccination.

Pregnancies and pregnancy outcomes will be described in detail.

11. ADMINISTRATIVE MATTERS

To comply with ICH GCP administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality and publications must be fulfilled.

11.1. Remote Data Entry instructions

Remote Data Entry (RDE), a validated computer application, will be used as the method for data collection.

In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs are reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

The investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site once the database is archived and the study report is complete and approved by all parties.

11.2. Monitoring by GSK Biologicals

Monitoring visits by a GSK Site Monitor are for the purpose of confirming that GSK Biologicals' sponsored studies are being conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and that are consistent with GCP and the applicable regulatory requirement(s) (verifying continuing compliance with the protocol, amendment(s), reviewing the investigational product accountability records, verifying that the site staff and facilities continue to be adequate to conduct the study).

The investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits.

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform a RDE review and a Source Document Verification (SDV). By SDV we understand verifying RDE entries by comparing them with the source data that will be made available by the investigator for this purpose.

The Source Documentation Agreement Form describes the source data for the different data in the RDE. This document should be completed and signed by the site monitor and investigator and should be filed in the monitor's and investigator's study file. Any data item for which the RDE will serve as the source must be identified, agreed and documented in the source documentation agreement form.

For RDE, the monitor will mark completed and approved screens at each visit.

In accordance with applicable regulations, GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the eCRF entries will serve as the source document.

GSK will monitor the study to verify that, amongst others, the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.

- Study is conducted in accordance with the currently approved protocol and any amendments, any other study agreements, GCP and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

11.3. Archiving of data at study sites

Following closure of the study, the investigator must maintain all site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g. audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g. microfiche, scanned, electronic for studies with an eCRF); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

GSK will inform the investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by ICH GCP, any institutional requirements or applicable laws or regulations, or GSK standards/procedures; otherwise, the minimum retention period will default to 15 years.

The investigator/institution must notify GSK of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

11.4. Audits

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

11.5. Posting of information on Clinicaltrials.gov

Study information from this protocol will be posted on clinicaltrials.gov before enrolment of subjects begins.

11.6. Ownership, confidentiality and publication

11.6.1. Ownership

All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) are the sole property of GSK.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by site staff during the course of or as a result of the study are the sole property of GSK, and are hereby assigned to GSK.

If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed between GSK and the study site, that contract's ownership provisions shall apply rather than this statement.

11.6.2. Confidentiality

Documented evidence that a potential investigator is aware and agrees to the confidential nature of the information related to the study must be obtained by means of a confidentiality agreement.

All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) will be kept confidential by the investigator and other site staff. This information and data will not be used by the investigator or other site personnel for any purpose other than conducting the study. These restrictions do not apply to: (i) information which becomes publicly available through no fault of the investigator or site staff; (ii) information which it is necessary to disclose in confidence to an IEC or IRB solely for the evaluation of the study; (iii) information which it is necessary to disclose in order to provide appropriate medical care to a study subject; or (iv) study results which may be published as described in the next paragraph. If a written contract for the conduct of the study which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

11.6.3. Publication

For multicentre studies, the first publication or disclosure of study results shall be a complete, joint multicentre publication or disclosure coordinated by GSK. Thereafter, any secondary publications will reference the original publication(s).

Prior to submitting for publication, presentation, use for instructional purposes, or otherwise disclosing the study results generated by the site (collectively, a 'Publication'), the investigator shall provide GSK with a copy of the proposed Publication and allow GSK a period to review the proposed Publication (at least twenty-one working days, or at least fifteen working days for abstracts/posters/presentations). Proposed Publications shall not include either GSK confidential information other than the study results or personal data on any subject, such as name or initials.

At GSK's request, the submission or other disclosure of a proposed Publication will be delayed a sufficient time to allow GSK to seek patent or similar protection of any inventions, know-how or other intellectual or industrial property rights disclosed in the proposed Publication.

If a written contract for the conduct of the study, which includes publication provisions inconsistent with this statement is executed, that contract's publication provisions shall apply rather than this statement.

11.6.4. Provision of study results to investigators, posting to the clinical trials registers and publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

The results summary will be posted to the GSK Clinical Study Register no later than 12 months after the LSLV or sooner if required by legal agreement, local law or regulation. In addition, a manuscript will be submitted to a peer-reviewed journal for publication within 18 months of LSLV. When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.

12. COUNTRY SPECIFIC REQUIREMENTS

Not applicable.

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Appendix A Amendments and Administrative Changes to the Protocol

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Administrative Change 1**	
eTrack study number and Abbreviated Title(s)	113621 HPV-067 EXT 015
IND number	BB-IND7920
Administrative change number:	Administrative change 1
Administrative change date:	Administrative change 1 Final: 18 May 2010
Co-ordinating author:	PPD Scientific Writer
Rationale/background for changes: Since the double-blind study HPV-015 will be extended by a maximum of three additional years, according to Protocol Amendment 4, dated 24 March 2010, it is important that central study staff involved in the studies remains blinded till the end of study HPV-015 for all subjects who have been participating in HPV-015 and will be participating in this study. Therefore, subjects enrolled in HPV-015 extension studies such as study HPV-067 cannot retain the HPV-015 subject number as is stated in the original protocol. Consequently, different identification numbers will be provided by an external statistician.	

Amended text has been indicated in *bold italics* and deleted text has been indicated in ~~strikethrough~~ in the following sections:

Section 5.2.1. Subject identification

~~Subjects will retain their identification numbers from study HPV-015.~~

A new identification number will be assigned to the subject to preserve the blind for HPV-015 data during this HPV-015 extension study.

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment 1**	
eTrack study number and Abbreviated Title(s)	113621 HPV-067 EXT 015
IND number	BB-IND7920
Amendment number	Amendment 1
Amendment date:	Amendment 1 Final: 9 Dec 2010
Co-ordinating author:	PPD, Scientific Writer
Rationale/background for changes: Due to their potent immune stimulating effect, there are theoretical concerns that modern adjuvants like GSK Biologicals' novel adjuvant systems might result in undesirable effects on the body's immune system, which could include onset of new or exacerbation of underlying autoimmune diseases in particular. Accordingly, a heightened surveillance on the occurrence of any such conditions in recipients of novel adjuvant containing vaccines in clinical trials has been put in place by GSK. Protocol amendment 1 was hence developed to implement reporting of potential immune-mediated diseases (pIMDs). In addition, the contributing authors, the contact information for Emergency Code Break and the formulation of the HPV-16/18 L1 VLP AS04 vaccine were updated.	

Amended text has been indicated in *bold italics* and deleted text has been indicated in ~~strikethrough~~ in the following sections:

Title page

Contributing authors

- PPD ~~*and*~~ PPD, Manager, Clinical Development, HPV vaccines
- PPD ~~, Senior Specialist, Biostatistician, Clinical Biometrics~~
- PPD ***and*** PPD***, Biostatisticians***
- PPD ~~*and*~~ PPD, Clinical Data Coordinator, Clinical Data Management

Synopsis

Study design

- **Safety monitoring:**
- Medically significant conditions ***(including potential immune-mediated diseases [pIMDs])*** will be reported for all subjects throughout the study period.

Endpoints

- Medically significant conditions ***(including pIMDs)***
  - Occurrence, intensity and causal relationship to vaccination of medically significant conditions ***(including pIMDs)*** throughout the study

List of abbreviations

pIMD	***potential Immune-Mediated Disease***

Glossary of terms

Medically Significant Condition:	Medically significant conditions are defined as AEs prompting emergency room or physician visits that are not (1) related to common diseases or (2) routine visits for physical examination or vaccination, or SAEs that are not related to common diseases. Common diseases include: upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, cervicovaginal yeast infections, menstrual cycle abnormalities and injury. ***Medically significant conditions include potential immune-mediated diseases (pIMDs).***
pIMD	***Potential immune-mediated diseases (pIMDs) are a subset of Medically Significant Conditions that include autoimmune diseases and other inflammatory and/or neurological disorders of interest which may or may not have an autoimmune aetiology.***

Section 3: Study design overview

- **Safety monitoring:**
  - Medically significant conditions ***(including pIMDs)*** will be reported for all subjects throughout the study period.

Section 5.5: Outline of study procedures

Table 1 List of study procedures

Type of contact	visit 1	visit 2	visit 3	phone contact
Timepoint (s)	months 0	months 1	months 6	months 12
Reporting of ~~non-serious adverse events that are~~ medically significant ***conditions (including plMDs)***	•	•	•	•

Section 6.1: Description of study vaccine

Table 3 Study vaccine

Vaccine name	Formulation	Presentation	Volume	Number of doses
HPV-16/18 L1 VLP AS04	Each 0.5 ml dose contains: - 20 µg HPV-16 L1 VLP - 20 µg HPV-18 L1 VLP - 50 µg MPL - 0.5 mg aluminium as Al(OH)3 - ***8 mM sodium dihydrogen phosphate dihydrate*** - ~~*4.4 mg*~~ ***150 mM*** sodium chloride - water for injection	Liquid in pre-filled syringes	0.6 ml	3

MPL = 3-O-desacyl-4'-monophosphoryl lipid A; Al(OH)3 = aluminium hydroxide; L1 = structural protein of HPV
ml = millilitre; µg = microgram

Section 8.1.1: Definition of an adverse event

~~Medically significant conditions are AEs prompting emergency room or physician visits that are not (1) related to common diseases or (2) routine visits for physical examination or vaccination, or SAEs that are not related to common diseases. (SAEs related to common diseases will be reported, but are not classified as medically significant conditions for analysis purposes.) Common diseases include: upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, cervicovaginal yeast infections, menstrual cycle abnormalities and injury.~~

Examples of an AE include:

- Medically significant conditions ***(please refer to Section 8.1.4 for the definition of medically significant condition).***

Section 8.1.4: Medically significant conditions

Medically significant conditions are defined as:

- ***AEs prompting emergency room or physician visits that are:***
  1. ***not related to common diseases, or***
  2. ***not related to routine visits for physical examination or vaccination***
- ***SAEs that are not related to common diseases.***

Common diseases include: upper respiratory infections, sinusitis, pharyngitis, gastroenteritis, urinary tract infections, cervicovaginal yeast infections, menstrual cycle abnormalities and injury.

Medically significant conditions include pIMDs.

Section 8.1.4.1: Potential immune-mediated diseases

Potential immune-mediated diseases (pIMDs) are a subset of medically significant conditions that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. AEs that need to be recorded and reported as pIMDs include those listed in the table below.

However, the investigator will exercise his/her medical and scientific judgement in deciding whether other immune-mediated diseases have an autoimmune origin (i.e. pathophysiology involving systemic or organ-specific pathogenic autoantibodies) and should also be recorded as a pIMD.

Onset of a new pIMD or exacerbation of a pre-existing pIMD (serious or non-serious) will be recorded in the SAE screen of the subject's eCRF.

Table 5 List of potential immune-mediated diseases

Neuroinflammatory disorders	*Musculoskeletal disorders*	*Skin disorders*
• ***Cranial nerve disorders, including paralyses/paresis (e.g. Bell's palsy), and neuritis (e.g. optic neuritis)*** • ***Multiple sclerosis (including variants)*** • ***Transverse myelitis*** • ***Guillain-Barré syndrome, (including Miller Fisher syndrome and other variants)*** • ***Other demyelinating diseases (including acute disseminated encephalomyelitis)*** • ***Myasthenia gravis (including Lambert-Eaton myasthenic syndrome)*** • ***Non-infectious encephalitis/ encephalomyelitis*** • ***Neuritis (including peripheral neuropathies)***	• ***Systemic lupus erythematosus*** • ***Scleroderma (including, CREST syndrome and morphoea)*** • ***Systemic sclerosis*** • ***Dermatomyositis*** • ***Polymyositis*** • ***Antisynthetase syndrome*** • ***Rheumatoid arthritis,*** • ***Juvenile chronic arthritis, (including Still's disease)*** • ***Polymyalgia rheumatica*** • ***Reactive arthritis*** • ***Psoriatic arthropathy*** • ***Ankylosing spondylitis*** • ***Relapsing polychondritis*** • ***Mixed connective tissue disorder***	• ***Psoriasis*** • ***Vitiligo*** • ***Raynaud's phenomenon*** • ***Erythema nodosum*** • ***Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis)*** • ***Cutaneous lupus erythematosus*** • ***Alopecia areata*** • ***Lichen planus*** • ***Sweet's syndrome***
Liver disorders	*Gastrointestinal disorders*	*Metabolic diseases*
• ***Autoimmune hepatitis*** • ***Primary biliary cirrhosis*** • ***Primary sclerosing cholangitis*** • ***Autoimmune cholangitis.***	• ***Crohn's disease*** • ***Ulcerative colitis*** • ***Ulcerative proctitis*** • ***Celiac disease***	• ***Autoimmune thyroiditis (including Hashimoto thyroiditis)*** • ***Grave's or Basedow's disease*** • ***Diabetes mellitus type I*** • ***Addison's disease***

Vasculitides	*Others*
• ***Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis.*** • ***Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome, thromboangiitis obliterans (Buerger's disease), necrotizing vasculitis, allergic granulomatous angiitis, Henoch-Schonlein purpura, anti-neutrophil cytoplasmic antibody positive vasculitis, Behcet's syndrome, leukocytoclastic vasculitis.*** • ***Vasculitides secondary to other immune mediated diseases such as lupus vasculitis and rheumatoid vasculitis.***	• ***Autoimmune hemolytic anemia*** • ***Autoimmune thrombocytopenias*** • ***Antiphospholipid syndrome*** • ***Pernicious anemia*** • ***Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis)*** • ***Uveitis*** • ***Autoimmune myocarditis/cardiomyopathy*** • ***Sarcoidosis*** • ***Stevens-johnson syndrome*** • ***Sjögren's syndrome*** • ***Idiopathic pulmonary fibrosis*** • ***Goodpasture syndrome***

When there is enough evidence to make any of the above diagnoses, the AE must be reported as a pIMD. Symptoms, signs or conditions which might (or might not) represent the above diagnoses, should be recorded and reported as AEs but not as pIMDs until the final or definitive diagnosis has been determined, and alternative diagnoses have been eliminated or shown to be less likely.

In order to facilitate the documentation of pIMDs in the eCRF, a pIMD standard questionnaire and a list of preferred terms (PTs) and PT codes corresponding to the above diagnoses will be available to investigators at study start.

Section 8.3.1: Time period for detecting and recording adverse events, serious adverse events and pregnancies

The standard time period for collecting and recording medically significant conditions will begin at the first receipt of study vaccine and will end 6 months following the administration of the last dose of study vaccine (*i.e. *at study conclusion) for each subject. Medically significant conditions should be recorded in the AE screen of the subjects eCRF if they are non-serious and in the SAE screen of the subject's eCRF if they are serious. When the medically significant condition is considered as a pIMD, it always has to be reported in the SAE screen of the subject's eCRF. See also Section 8.4 for instructions on reporting of pIMDs.

The standard time period for collecting and recording pregnancies will begin at the first receipt of study vaccine and will end 6 months following administration of the last dose of study vaccine (*i.e. *at study conclusion). See section 8.4 for instructions on reporting of pregnancies.

The standard time period for collecting and recording SAEs will begin at the first receipt of study vaccine and will end 6 months following administration of the last dose of study vaccine (*i.e. *at study conclusion). See section 8.4 for instructions on reporting of SAEs.

Table 6 Reporting periods for adverse events, serious adverse events and pregnancies

Study activity	Pre-vacc. (Consent obtained)	Visit 1 Day 0 1st vacc.		Visit 2 Month 1 2nd vacc.		Visit 3 Month 6 3rd vacc.	Telephone contact Month 12 Study Conclusion 6 months post 3rd vaccination
Reporting of SAEs, medically significant conditions ***(including pIMDs)***, pregnancies and pregnancy outcomes							

Section 8.4.1: Prompt reporting of serious adverse events and other events to GSK Biologicals

Any pIMDs that occur in the time period defined in Section 8.3.1 will be reported promptly to GSK within the timeframes described in Table 7, once the investigator becomes aware of the pIMD.

Table 7 Time frames for submitting SAEs and other events reports to GSK Biologicals

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Time Frame	Documents	Time Frame	Documents
pIMDs	*24 hours***	*SAE report/SAE screen*	*24 hours**	*SAE report/ SAE screen*

Time frame allowed after receipt or awareness of the information.

*** Time frame allowed after the diagnosis is established and known to the investigator.***

Section 8.4.3.2: Updating of SAE information after freezing of the subject's eCRF

When additional information is received on a SAE after freezing of the subject's eCRF, new or updated information should be recorded on a SAE Report Form, with all changes signed and dated by the investigator. The updated form should be faxed to the GSK Biologicals Clinical Safety and Pharmacovigilance department or to the Study Contact for Reporting SAEs (refer to the Sponsor Information Sheet) WITHIN 24 HOURS of receipt of the follow-up information.

Section 8.4.4: Reporting of pIMDs to GSK Biologicals

Once onset of a new pIMD or exacerbation of a pre-existing pIMD is diagnosed (serious or non-serious) in a study subject, the investigator (or designate) must complete the information in the SAE screens of the eCRF WITHIN 24 HOURS after the he/she becomes aware of the diagnosis. A field on the SAE screen allows to specify that the event is a pIMD and whether it is serious or non serious. The SAE screens will always be completed as thoroughly as possible with all available details of the event, in accordance with the pIMD standard questionnaire provided. Even if the investigator does not have all information regarding a pIMD, the SAE screens should still be completed within 24 hours. Once additional relevant information is received, the SAE screens in the eCRF should be updated WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report.

Refer to Sections 8.4.3.1 and 8.4.3.2 for back-up system and updating of SAE information after freezing of the subject's eCRF.

Section 8.7: Emergency unblinding

GSK Biologicals Central Safety Physician (Study Contact for Emergency Code Break)
~~Mobile p~~***P***hones for 7/7 day availability: ~~+~~PPD ~~+~~PPD (GSK Biologicals Central Safety Physician ***on-call***) Back-up ~~mobile~~ phone contact ~~(all countries)~~: ~~+~~PPD ~~+~~PPD

Section 10.1: Study endpoints

- Occurrence, intensity and causal relationship to vaccination of medically significant conditions ***(including pIMDs)*** throughout the study

Section 10.6.2: Analysis of safety

The proportion of subjects with at least one report of an SAE and/or at least one medically significant condition ***(including pIMDs)*** will be tabulated with exact 95% confidence interval (CI) throughout the study period.

SAEs and other medically significant conditions ***(including pIMDs)*** will be described in detail. SAEs and other medically significant conditions ***(including pIMDs)*** will be further evaluated for their clinical relevance and relationship to vaccination.

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment 2**	
eTrack study number and Abbreviated Title(s)	113621 HPV-067 EXT 015
IND number	BB-IND7920
Amendment number	Amendment 2
Amendment date:	13 Jan 2011
Co-ordinating author:	PPD, Project Manager, Scientific Writing
Rationale/background for changes: The exclusion criterion "*Administration of any chronic drug therapy to be continued during the study period*" has been removed to be in line with the original HPV-015 study protocol. Upon request of regulatory authorities, the list of pIMDs has been updated to include the term "*undifferentiated spondyloarthritides*". In addition, the list of contributing authors has been updated. Cross-referencing to the first amendment has been removed for clarity.	

Amended text has been indicated in *bold italics* in the following sections:

Title page

Contributing authors

- PPD***, Director, HPV Vaccines, Global Clinical Research and Development***

Section 4.3.: Exclusion criteria for enrolment:

The following criterion has been deleted:

- ~~Administration of any chronic drug therapy to be continued during the study period.~~

Section 8.1.4.1.: Potential immune-mediated diseases

Table 5 List of potential immune-mediated diseases

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
• Cranial nerve disorders, including paralyses/paresis (e.g. Bell's palsy), and neuritis (e.g. optic neuritis) • Multiple sclerosis (including variants) • Transverse myelitis • Guillain-Barré syndrome, (including Miller Fisher syndrome and other variants) • Other demyelinating diseases (including acute disseminated encephalomyelitis) • Myasthenia gravis (including Lambert-Eaton myasthenic syndrome) • Non-infectious encephalitis/ encephalomyelitis • Neuritis (including peripheral neuropathies)	• Systemic lupus erythematosus • Scleroderma (including, CREST syndrome and morphoea) • Systemic sclerosis • Dermatomyositis • Polymyositis • Antisynthetase syndrome • Rheumatoid arthritis, • Juvenile chronic arthritis, (including Still's disease) • Polymyalgia rheumatica • Reactive arthritis • Psoriatic arthropathy • Ankylosing spondylitis ***(including undifferentiated spondyloarthritides)*** • Relapsing polychondritis • Mixed connective tissue disorder	• Psoriasis • Vitiligo • Raynaud's phenomenon • Erythema nodosum • Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis) • Cutaneous lupus erythematosus • Alopecia areata • Lichen planus • Sweet's syndrome

Section 8.3.1.: Time period for detecting and recording adverse events, serious adverse events and pregnancies

Any conditions or signs and/or symptoms present in a subject prior to study HPV-06~~6~~*7* need not be recorded.

Protocol Amendment 2 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	113621(HPV-067 EXT 015)
IND number	BB-IND7920
Date of protocol amendment	Amendment 2 Final: 13 Jan 2011
Detailed Title	A phase IIIb, open-label, multi-centre immunization study to evaluate the safety of GlaxoSmithKline (GSK) Biologicals' HPV-16/18 L1 VLP AS04 vaccine administered intramuscularly according to a 0, 1, 6-month schedule in healthy female subjects who received the placebo control in the GSK HPV-015 study
Sponsor signatory	Dominique Descamps MD, Director, Clinical Development, HPV Vaccines, GlaxoSmithKline Biologicals
Signature	PPD
Date	18 FEB 2011

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