Clinical Study Protocol

Sponsor:

GlaxoSmithKline Biologicals

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1330, Rixensart, Belgium

Primary Study vaccine and number	GlaxoSmithKline (GSK) Biologicals' human papillomavirus (HPV) vaccine containing HPV-16 and HPV-18 L1 VLP proteins and AS04 adjuvant (GSK-580299).
Other Study vaccine	Merck's quadrivalent HPV vaccine (Types 6, 11, 16, and 18), recombinant (Gardasil®).
eTrack study number and Abbreviated Title	109823 (HPV-019 PRI)
EudraCT number	2013-003429-28
Date of protocol	30 July 2009
Date of protocol amendment/ administrative change	Amendment 1: Final 20 April 2010 Administrative change 1: Final 20 July 2010 Amendment 2: Final 23 December 2010 Amendment 3: Final 23 May 2011 Amendment 4: Final 04 October 2011 Amendment 5: Final 20 March 2012 Amendment 6:Final: 06 June 2012 Amendment 7 Final: 19 December 2013 Amendment 8 Final: 26 April 2016
Title	Safety and immunogenicity of Cervarix™ in human immunodeficiency-virus infected females.
Detailed Title	A phase IV, observer-blind, randomized, controlled, multicentric study to assess the safety and immunogenicity of GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine (Cervarix™) administered intramuscularly according to a three-dose schedule (Day 0, Week 6, Month 6) in human immunodeficiency virus-infected (HIV+) female subjects aged 15 - 25 years, as compared to Merck's HPV-6/11/16/18 vaccine (Gardasil®).
Coordinating authors	• PPD / PPD / PPD, Scientific Writers
Contributing authors (Amended: 26 April 2016)	• PPD, Clinical Development Director • PPD, Clinical Development Director • PPD ***and*** PPD, Clinical Research & Development Leads • PPD, Clinical Development Manager • PPD, Global Study Manager • PPD, Global Study Manager • PPD, Senior Specialist, Biostatistics • PPD, Project Statistician • PPD, Clinical Immunology • PPD, Clinical Immunology • PPD, Clinical Immunology

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Protocol Amendment 8 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	109823 (HPV-019 PRI)
EudraCT number	2013-003429-28
Date of protocol amendment	Amendment 8 Final: 26 April 2016
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Sponsor signatory	Frank Struyf, MD, Project Level Clinical Research & Development Lead, Clinical Development, HPV vaccines, Vaccines Discovery and Development, GlaxoSmithKline Biologicals
Signature	_____
Date	_____

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Protocol Amendment 8 Rationale

Amendment number: Amendment 8
Rationale/background for changes: • The protocol was amended to align the section of the protocol on management of HIV+ subjects with the recently revised WHO guidelines on when to start antiretroviral therapy (ART) in HIV+ subjects. The revision of the WHO guidelines presented evidence that earlier use of ART results in better long-term clinical outcomes for people living with HIV compared with delayed treatment, including pregnant and breastfeeding women. This guideline advises to start ART in all adults with HIV regardless of their clinical stage and at any CD4 cell count. At the time of implementation of the protocol amendment, the vaccination phase had already completed, and therefore the exclusion criterion for subsequent vaccination after initiation of ART during the course of the study was not revised.

Protocol Amendment 8 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 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 authorized 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 one 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	109823 (HPV-019 PRI)
EudraCT number	2013-003429-28
Date of protocol amendment	Amendment 8 Final: 26 April 2016
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Investigator name	_____
Signature	_____
Date	_____

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SYNOPSIS

Detailed Title

A phase IV, observer-blind, randomized, controlled, multicentric study to assess the safety and immunogenicity of GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine (Cervarix™) administered intramuscularly according to a three-dose schedule (Day 0, Week 6, Month 6) in human immunodeficiency virus-infected (HIV+) female subjects aged 15 - 25 years, as compared to Merck's HPV-6/11/16/18 vaccine (Gardasil®).

Indication

For active immunization of women from the age of 10 years onwards to prevent cervical cancer (squamous-cell carcinoma and adenocarcinoma) by protecting against incident and persistent infections, cytological abnormalities including atypical squamous cells of undetermined significance (ASC-US) and cervical intraepithelial neoplasia (CIN), CIN 1 and pre-cancerous lesions (CIN 2 and CIN 3), caused by oncogenic HPV types 16 and 18.

Rationale for the study and study design

- Rationale for the study

HIV+ females are known to be predisposed to a higher risk of HPV infection and subsequent CIN lesions. HPV vaccination of this high-risk group is therefore likely to be beneficial.

Two HPV vaccines are currently licensed in numerous countries: Merck's quadrivalent HPV-6/11/16/18 vaccine (Gardasil®) and GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine (Cervarix™). GSK's HPV vaccine is based on the L1 capsid protein of HPV-16 and HPV-18. L1 proteins are produced by recombinant deoxyribonucleic acid (DNA) technology and auto assemble as non-infectious virus-like particles (VLPs). The vaccine is formulated with the GSK proprietary AS04 adjuvant system, composed of aluminium hydroxide ($Al[OH]_3$) and 3-*O*-desacyl-*4*'- monophosphoryl lipid A (MPL). Merck's HPV vaccine is comprised of purified VLPs adsorbed on preformed aluminium-containing adjuvant (amorphous aluminium hydroxyphosphate sulfate).

To date, there are limited data available on the use of the two available HPV vaccines in HIV+ subjects, although several trials are ongoing or planned. It is known that HIV+ women can mount a humoral response to HPV antigen [Palefsky, 2006].

Recently, preliminary data with *Gardasil* in HIV+ children were presented [Moscicki, 2009], showing the vaccine to be generally safe and to induce seroconversion for HPV-6, -11, -16 and -18 (using competitive Luminex immunoassay) in

nearly 100% of those initially seronegative by Week 28 (i.e., four weeks after receiving the last dose of the three-dose vaccination schedule). Antibody titers against HPV-16 and HPV-18 were lower compared to results previously reported for healthy children. Some children were seropositive at baseline or became positive during the trial, underscoring the importance of immunizing children before sexual activity. A majority of HIV+ children developed cell-mediated immunity.

In phase II trials, the AS04-adjuvanted vaccine has been shown to induce significantly higher antibody responses to both antigens when compared to the same antigens formulated with $Al(OH)_3$ [Giannini, 2006]. Recently, results from a large-scale comparative trial between the two licensed HPV vaccines show that immune responses, one month after following the full vaccination course, were significantly higher with *Cervarix* compared to *Gardasil*, as indicated by HPV-16 and HPV-18 neutralizing antibody levels in serum, positivity rates in cervicovaginal secretions (CVS) and HPV-16 and HPV-18 specific B cell frequencies [Einstein, 2009]. These properties may prove important for HIV+ individuals to mount a good immunogenic response to HPV vaccination.

Although inactivated vaccines can be administered safely to persons with altered immunocompetence, the effectiveness of such vaccinations might be suboptimal [ACIP, 2006]. The fact that *Cervarix* and *Gardasil* do not contain live infectious agents greatly reduces concerns about potential harmful effects.

The current study is designed to assess the safety and immunogenicity of *Cervarix* in HIV+ subjects aged 15 - 25 years, as compared to *Gardasil*. For comparative purposes, a group of HIV- subjects will also be evaluated.

- Rationale for the study design

As both *Cervarix* and *Gardasil* target prevention of HPV-16 and HPV-18 genital tract cancers and pre-cancerous lesions, a comparison of these vaccines in terms of immunogenicity and safety is warranted.

A group of HIV- female subjects will be used as control. These subjects will be randomized to receive either *Cervarix* or *Gardasil* and compared to the HIV+ cohort to evaluate the effect of the HIV+ immunocompromised state on the immunogenicity and safety of both vaccines.

Objectives

Co-Primary

Safety:

- To evaluate the safety and reactogenicity of both vaccines in HIV+ subjects for up to one month after the third dose of vaccine.

Immunogenicity:

The following objectives will be assessed sequentially:

- To demonstrate non-inferiority of *Cervarix* versus (vs.) *Gardasil* in terms of geometric mean titers (GMTs) against HPV-16 and HPV-18 measured by Pseudovirion-based neutralization assay (PBNA) one month after administration of the third dose of vaccine in HIV+ subjects.

  Criterion: Non-inferiority will be demonstrated if the lower limit of the 95% confidence interval (CI) for the ratio of GMTs (Cervarix over Gardasil) is above 0.5 for both HPV types.

- If the first primary objective for immunogenicity is demonstrated, superiority of *Cervarix* over *Gardasil* in terms of GMTs against HPV-16 and HPV-18 measured by PBNA in HIV+ subjects will be assessed following a sequential approach.

  – First, superiority for HPV-18 will be assessed.

    Criterion: Superiority will be demonstrated if the lower limit of the 95% CI for the ratio of GMTs (Cervarix over Gardasil) is above 1 for HPV-18 type with a statistically significant p-value.

  – Second, if superiority for HPV-18 is shown, superiority for HPV-16 will be assessed.

    Criterion: Superiority will be demonstrated if the lower limit of the 95% CI for the ratio of GMTs (Cervarix over Gardasil) is above 1 for HPV-16 type with a statistically significant p-value.

Secondary

Immunogenicity:

- To demonstrate superiority of *Cervarix* vs. *Gardasil* in terms of GMTs against HPV-16 or HPV-18 measured by PBNA one month after the administration of the third dose of vaccine in HIV- subjects.

  Criterion: Superiority of Cervarix vs. Gardasil will be demonstrated if the lower limit of the 97.5% CI for the

ratio of GMTs (Cervarix over Gardasil) is above 1 for the antigen considered with a statistically significant p-value.

- To evaluate the antibody response of both vaccines with respect to HPV-16 and HPV-18 antibody levels by Enzyme-Linked Immunosorbent Assay (ELISA) at Day 0, Week 6, Week 10, Months 7, 12, 18 and 24 in all (HIV+ and HIV-) subjects.
- To evaluate the antibody response, by ELISA, against HPV-16 and HPV-18 in CVS at Day 0, Week 6, Week 10, Months 7, 12 and 24 in post-menarcheal subjects who volunteer for this procedure.
- To evaluate the memory B and T cell-mediated immune (CMI) response against HPV-16 and HPV-18 at Day 0, Week 6, Week 10, Months 7 and 12 in a subset of approximately 100 subjects (50 HIV+ and 50 HIV-).

Safety:

- To evaluate the safety and reactogenicity of both vaccines in HIV- subjects for up to one month after the third dose of vaccine.
- To evaluate the safety and reactogenicity of both vaccines in all subjects for up to 24 months after the first vaccine dose.

Exploratory

Immunogenicity:

- To demonstrate non-inferiority of *Cervarix* in HIV+ subjects vs. *Gardasil* in HIV- subjects in terms of GMTs against HPV-16 or HPV-18 measured by PBNA one month after the administration of the third dose of vaccine.

  Criterion: Non-inferiority will be demonstrated for if the lower limit of the 95% CI for the ratio of GMTs (Cervarix over Gardasil) is above 0.5 for the antigen considered.
- To evaluate the antibody response of both vaccines with respect to HPV-16 and HPV-18 by ELISA at Day 0, Months 7, 12, 18 and 24 in HIV+ subjects stratified by HIV mode of transmission, if sufficient data are available.
- To evaluate the antibody response of both vaccines with respect to HPV-16 and HPV-18 by ELISA at Day 0, Months 7, 12, 18 and 24 in HIV+ subjects by nadir CD4 cell count category, if sufficient data are available.

Study design

- Experimental design: A multicentric, observer-blind, controlled trial with two vaccine groups (*Cervarix* and *Gardasil*) and a staggered enrollment (Part A and Part B).
- Treatment allocation: randomized 1:1 with central randomization call-in system on internet (SBIR).
- Blinding: observer-blind.
- Vaccination schedule: at Day 0, Week 6, and Month 6.
- Active Control: *Gardasil.*
- The enrollment will be stratified by HIV infection status and by age as follows:
  - HIV+ subjects 18 - 25 years;
  - HIV- subjects 18 - 25 years;
  - HIV+ subjects 15 - 17 years;
  - HIV- subjects 15 - 17 years.
- In **Part A**, a subset of 60 subjects aged 18 - 25 years (30 HIV+ and 30 HIV- subjects) will be vaccinated (Dose 1) and evaluated for safety before proceeding with the enrollment and vaccination of the remaining subjects (**Part B**;). Administration of Dose 2 to the subjects in Part A will not depend on the outcome of the safety evaluation unless there are specific safety concerns for an individual subject or if requested by the Independent Data Monitoring Committee (IDMC) or Vaccine Safety Monitoring Board (VSMB).

  A safety interim analysis will be performed on the 6-week post-dose 1 vaccination data from the subjects in Part A to evaluate the following parameters:
  - solicited symptoms during the 7-day follow-up period (Days 0 – 6);
  - unsolicited symptoms, medically significant conditions (including potential immune-mediated diseases [pIMDs]), new onset chronic diseases (NOCDs), new onset autoimmune diseases (NOADs) and serious adverse events (SAEs) up to Day 30 after administration of the first dose (Days 0 – 29);
  - hematological and biochemical parameters;
  - CD4 cell counts, HIV viral load, the HIV clinical stage of each individual subject (for HIV+ subjects only).

The results of this safety interim analysis will be reviewed by the GSK Safety Review Team and the IDMC. The IDMC will provide recommendation to the sponsor via the GSK Safety Review Team prior to proceeding with the enrollment of the remaining study subjects in Part B of the study.

- In case of any safety concern, the GSK Safety Review Team (including, as core members, the GSK Biologicals' Central Safety Physician, Clinical Research & Development Lead (CRDL) and Biostatistician of the project) will inform the GSK VSMB who will provide recommendations on the study continuation to the safety review team and investigators.
- The study will be supervised by an IDMC consisting of clinical experts and a biostatistician that will oversee safety and ethical aspects of the trial.
- Type of study: self-contained. Data from this study may subsequently be pooled with data from other studies.
- Data collection: Remote Data Entry System (RDE).
- Duration of the study: The study will last approximately 24 months for each subject, including an active phase from Day 0 to Month 7 and a subsequent extended safety and immunogenicity follow-up phase from Month 7 to Month 24.

Number of subjects

- Approximately 300 HIV+ subjects aged 15 - 25 years will be enrolled, stratified into two age strata (15 - 17 years and 18 - 25 years).
- Approximately 300 HIV- subjects aged 15 - 25 years will be enrolled, stratified into two age strata (15 - 17 years and 18 - 25 years).
- The subjects will be enrolled in two parts: the first part (Part A) will include 60 subjects (30 HIV+ and 30 HIV-) aged 18 – 25 years and the second part (Part B) will include the remaining subjects.

Endpoints

Co-Primary:

Safety in HIV+ subjects up to Month 7:

- Occurrence and intensity of solicited local symptoms within seven days (Days 0 - 6) after each and any vaccination in HIV+ subjects.
- Occurrence, intensity and relationship to vaccination of solicited general symptoms within seven days (Days 0 - 6) after each and any vaccination in HIV+ subjects.
- Occurrence, intensity and relationship to vaccination of

unsolicited symptoms within 30 days (Days 0 - 29) after any vaccination in HIV+ subjects.

- Occurrence of SAEs up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.
- Occurrence of medically significant conditions (including pIMDs) up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.
- Occurrence and outcome of pregnancies up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.
- Occurrence of clinically relevant abnormalities in hematological and biochemical parameters up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.
- CD4 cell count up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.
- HIV viral load up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.
- HIV clinical staging up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.

Immunogenicity:

- HPV-16 and HPV-18 antibody titers by PBNA 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.

Secondary:

Safety:

- Occurrence and intensity of solicited local symptoms within seven days (Days 0 - 6) after each and any vaccination in HIV- subjects.
- Occurrence, intensity and relationship to vaccination of solicited general symptoms within seven days (Days 0 - 6) after each and any vaccination in HIV- subjects.
- Occurrence, intensity and relationship to vaccination of unsolicited symptoms within 30 days (Days 0 - 29) after any vaccination in HIV- subjects.
- Occurrence of SAEs up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV- subjects.
- Occurrence of medically significant conditions (including pIMDs) up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV- subjects.

- Occurrence and outcome of pregnancies throughout the study (i.e., up to Month 24) in all subjects.
- Occurrence of clinically relevant abnormalities in hematological and biochemical parameters assessed at all study visits in all subjects.
- Occurrence of SAEs during the entire study period (i.e., up to Month 24) in all subjects.
- Occurrence of medically significant conditions (including pIMDs) up to 12 months after the last dose of vaccine (i.e., Month 18) in all subjects.
- CD4 cell count, HIV viral load and HIV clinical staging at Months 12, 18 and 24 in HIV+ subjects.

Immunogenicity:

- HPV-16 and HPV-18 antibody titers by PBNA one month after the last dose of vaccine (i.e., Month 7) in HIV- subjects.
- HPV-16 and HPV-18 antibody titers and total Immunoglobulin G (IgG) titers by ELISA in serum at Day 0, Week 6, Week 10, Months 7, 12, 18 and 24 in all (HIV+ and HIV-) subjects.
- HPV-16 and HPV-18 antibody titers and total IgG titers by ELISA in CVS at Day 0, Week 6, Week 10, Months 7, 12 and 24 in post-menarcheal subjects who volunteer for this procedure.
- Frequencies of HPV-16 and HPV-18 specific B cells and T cells at Day 0, Week 6, Week 10, Months 7 and 12 in a subset of approximately 100 subjects (50 HIV+ and 50 HIV-).

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
$Al(OH)_3$	Aluminium salt
ART	AntiRetroviral Therapy
ARV	Antiretroviral
AS04	GlaxoSmithKline's proprietary adjuvant system consisting of aluminium salt [$Al(OH)_3$] plus 3-*O*-desacyl-*4'*-monophosphoryl lipid A (MPL)
ASC-US	Atypical Squamous Cells of Undetermined Significance
ATP	According-to-Protocol
CRDL	Clinical Research & Development Lead
CI	Confidence Interval
CIN	Cervical Intraepithelial Neoplasia
CMI	Cell-Mediated Immunity
CVS	Cervicovaginal Secretion
DNA	DeoxyriboNucleic Acid
eCRF	Electronic Case Report Form
ELISA	Enzyme-Linked Immunosorbent Assay
EL.U	ELISA unit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMT	Geometric Mean Titer
GSK	GlaxoSmithKline
HAART	Highly Active AntiRetroviral Therapy
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IRB	Institutional Review Board
LAR	Legally Acceptable Representative

MedDRA	Medical Dictionary for Regulatory Activities
MPL	3-*O*-desacyl-*4'*- monophosphoryl lipid A
NOAD	New Onset Autoimmune Disease
NOCD	New Onset Chronic Diseases
PBMC	Peripheral Blood Mononuclear Cells
PBNA	Pseudovirion-Based Neutralization Assay
pIMD	potential immune-mediated disease
RDE	Remote Data Entry
SAE	Serious Adverse Event
SBIR	Internet Randomization
SD	Standard Deviation
SOP	Standard Operating Procedures
SPM	Study Procedures Manual
STD	Sexually Transmitted Disease
STI	Sexually Transmitted Infection
TB	Tuberculosis
ULN	Upper Limit of Normal
VLP	Virus-Like Particle
vs.	Versus
VSMB	Vaccine Safety Monitoring Board
WHO	World Health Organization

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 or intrauterine system, vasectomy with documented azoospermia of the sole male partner or double barrier method (condom or occlusive cap plus spermicidal agent).

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 (AE): 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 unfavorable 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.

Blinding: A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. In a single-blind trial, the investigator and/or his staff are aware of the treatment assignment but the subject is not. In an observer-blind study, the subject and the site and Sponsor personnel involved in the clinical evaluation of the subjects are blinded while other study personnel may be aware of the treatment allocation (see Section 5.3 for details on observer-blinded studies). When the investigator and Sponsor staff who are involved in the treatment or clinical evaluation of the subjects and review/analysis of data are also unaware of the treatment assignments, the study is double-blind. Partially-blind is to be used for study designs with different blinding levels between different groups, e.g., double-blinded

	consistency lots which are open with respect to the control group. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event (SAE).
Child in care:	A child who has been placed under the control or protection of an agency, organization, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legal guardian.
Eligible:	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Epoch:	An epoch is a well defined part of a protocol that covers a set of consecutive time points. Generally, an epoch is self-contained and allows to perform a data analysis to address some of the trial objectives (e.g., primary, booster, yearly follow-ups,…).
eTrack:	GlaxoSmithKline's (GSK) tracking tool for clinical trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis (see Sections 6.6.1 and 10.4 for details on criteria for evaluability).
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 authorization 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.
Medical Monitor:	An individual medically qualified to assume the responsibilities of the Sponsor (GSK Biologicals) especially in regards to the ethics, clinical safety of a study and the assessment of AEs.
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 potential immune-mediated diseases (pIMDs).

Menarche: Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1 - 2 years of breast development, thelarche. However, a young female can become pregnant before her first menses. Thus, a conservative definition of non-childbearing potential in a pre-menarcheal female is a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue).

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 one year without menses with an appropriate clinical profile at the appropriate age e.g., > 45 years.

pIMDs Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology.

Protocol amendment:	ICH defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.
Protocol administrative change:	A protocol administrative change addresses changes to only logistical or administrative aspects of the study. NB: Any change that falls under the definition of a protocol amendment (e.g., a change that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study) MUST be prepared as an amendment to the protocol.
Randomization:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Site Monitor:	An individual assigned by the Sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Solicited AE:	AEs to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.
Sub-cohort:	A group of subjects for whom specific data are collected compared to other subjects.
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 randomization or treatment allocation.
Treatment number:	A number identifying a treatment to a subject, according to the study randomization or treatment allocation.

Unsolicited AE:	Any AE reported in addition to those solicited during the clinical study. Also any 'solicited' symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited AE.

1. INTRODUCTION

1.1. Background

Papillomaviruses are members of the papovaviridae family of non-enveloped deoxyribonucleic acid (DNA) viruses, which can cause a variety of proliferative epithelial lesions in humans, including papillomas (warts) and neoplasia [Shah, 1990]. Currently, over 200 different types of human papillomaviruses (HPVs) have been recognized [Burd, 2003].

Each HPV type is targeted to either cutaneous or mucosal epithelium. At least 30 HPV types have been identified that infect the genital mucosa [Bosch, 1995]. Fifteen of these HPV types are known to cause cervical cancer and high-grade, pre-cancerous, intraepithelial lesions. These types are identified as oncogenic or high-risk (e.g., HPV-16, 18, 31, 33, and 45). Low-risk HPV types which infect genital mucosa (e.g., HPV-6, 11, 42, 43 and 44) are responsible for most benign genital warts, produce low-grade intraepithelial lesions of the cervix, and are rarely associated with invasive malignancies [Eiben, 2002; Munoz, 2003].

The association of cervical cancer and infection with an oncogenic HPV type is based on strong epidemiological evidence and by the detection of HPV DNA in up to 99.7% of cervical cancers from all geographic areas [Walboomers, 1999]. Meta-analysis of a wide range of studies revealed that HPV-16 is the most prevalent high-risk HPV type and is present in over 50% of cervical tumor specimens worldwide. HPV-18 is the second most prevalent type and is associated with approximately 16% of cervical cancers, with the remaining tumors containing DNA from other high-risk types such as HPV-45, 31 and 33 [Clifford, 2003]. Nearly 500,000 new cases of cervical cancer are diagnosed each year worldwide, and approximately 270,000 deaths are attributable to the disease [Parkin, 2005]. Consequently, the social and economic costs of HPV-induced diseases of the genital tract are enormous, and development of prophylactic vaccines, which would prevent HPV infection or decrease their consequences, would be of great value.

Much of the work carried out to date on HPV immunoprophylactic vaccines has focused on the viral capsid proteins L1 and L2, and has been driven by genetic engineering techniques that can be used to express these proteins. Recombinant expressed L1, the major capsid protein of HPV, self assembles to form empty viral capsids referred to as viral-like particles (VLPs) [Kirnbauer, 1992]. VLPs formed from the L1 protein are both morphologically and antigenically similar to authentic papillomavirions [Hagensee, 1994; Rose, 1994; Christensen, 1994]. Data from animal models indicate that L1 VLPs are non-infectious and generate protection against viral challenge [Kirnbauer, 1996; Lowe, , 1997; Breitburd, 1995; Suzich, 1995]. An optimal L1 protein-based vaccine designed to prevent cervical cancer will require at least HPV-16 and HPV-18 L1 protein components.

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]). To date, more than 30,000 adolescent and adult females aged 10 years and above have

received at least one dose of the vaccine. The results of a pooled safety analysis of approximately 30,000 girls and women aged 10 years and above, of whom 16,142 received at least one dose of HPV vaccine, have shown that the vaccine is generally safe and well tolerated [Descamps, 2009].

The first major market in which the HPV vaccine under evaluation in this study was licensed is Australia for use in females aged 10 - 45 years. The vaccine is marketed under the name Cervarix™. In September 2007, the vaccine was licensed in the European Union and is indicated for the prevention of persistent infection, premalignant cervical lesions and cervical cancer caused by oncogenic HPV types. To date, the vaccine is licensed in more than 110 countries worldwide. The recommended vaccination schedule is 0, 1, 6 months.

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.

In 2006, Merck's vaccine *Gardasil* was approved by the Food and Drug Administration (FDA) for the prevention of cervical cancer. The vaccine is comprised of purified VLPs adsorbed on preformed aluminium-containing adjuvant (amorphous aluminium hydroxyphosphate sulfate). In the United States, *Gardasil* is indicated for use in girls and women 9 to 26 years of age for prevention of diseases caused by HPV types 6, 11, 16, and 18: cervical, vulvar, vaginal and anal cancer, genital warts and pre-cancerous or dysplastic lesions of cervical adenocarcinoma in situ, cervical intraepithelial neoplasia (CIN) grades 1, 2 & 3, vulvar- and vaginal-intraepithelial neoplasia grades 2 & 3 and anal intraepithelial neoplasia grades 1, 2 & 3, respectively. The recommended dosing schedule for *Gardasil* is administration in three doses according to a 0, 2, 6-month schedule [GARDASIL, Prescribing Information, 2011]. If an alternate vaccination schedule is necessary, the second dose should be administered at least one month after the first dose and the third dose should be administered at least three months after the second dose. All three doses should be given within a one-year period.

1.2. Rationale for the study and study design

1.2.1. Rationale for the study

Human immunodeficiency virus-infected (HIV+) females are known to be predisposed to a higher risk of HPV infection and subsequent CIN lesions. HPV vaccination of this high-risk group is therefore likely to be beneficial.

Two HPV vaccines are currently licensed in numerous countries: Merck's quadrivalent HPV-6/11/16/18 vaccine (Gardasil®) and GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine (Cervarix™). GSK's HPV vaccine is based on the L1 capsid protein of HPV-16 and HPV-18. L1 proteins are produced by recombinant DNA technology and auto assemble as non-infectious VLPs. The vaccine is formulated with the GSK proprietary AS04 adjuvant system, composed of $Al(OH)_3$ and MPL. Merck's HPV vaccine is comprised of purified VLPs adsorbed on preformed aluminium-containing adjuvant (amorphous aluminium hydroxyphosphate sulfate).

To date, there are limited data available on the use of the two available HPV vaccines in HIV+ subjects, although several trials are ongoing or planned. It is known that HIV+ women can mount a humoral response to HPV antigen [Palefsky, 2006].

Recently, preliminary data with *Gardasil* in HIV+ children were presented [Moscicki, 2009], showing the vaccine to be generally safe and to induce seroconversion for HPV-6, -11, -16 and -18 (using competitive Luminex immunoassay) in nearly 100% of those initially seronegative by Week 28 (i.e., four weeks after receiving the last dose of the three-dose vaccination schedule). Antibody titers against HPV-6 and HPV-18 were lower compared to results previously reported for healthy children. Some children were seropositive at baseline or became positive during the trial, underscoring the importance of immunizing children before sexual activity. A majority of HIV+ children developed cell-mediated immunity.

In phase II trials, the AS04-adjuvanted vaccine has been shown to induce significantly higher antibody responses to both antigens when compared to the same antigens formulated with $Al(OH)_3$ [Giannini, 2006]. Recently, results from a large-scale comparative trial between the two licensed HPV vaccines show that immune responses, one month after following the full vaccination course, were significantly higher with *Cervarix* compared to *Gardasil*, as indicated by HPV-16 and HPV-18 neutralizing antibody levels in serum, positivity rates in cervicovaginal secretions (CVS) and HPV-16 and HPV-18 specific B cell frequencies [Einstein, 2009]. These properties may prove important for HIV+ individuals to mount a good immunogenic response to HPV vaccination.

Although inactivated vaccines can be administered safely to persons with altered immunocompetence, the effectiveness of such vaccinations might be suboptimal [ACIP, 2006]. The fact that *Cervarix* and *Gardasil* do not contain live infectious agents greatly reduces concerns about potential harmful effects.

The current study is designed to assess the safety and immunogenicity of *Cervarix* in HIV+ subjects aged 15 - 25 years, as compared to *Gardasil*. For comparative purposes, a group of HIV- subjects will also be evaluated.

1.2.2. Rationale for the study design

As both *Cervarix* and *Gardasil* target prevention of HPV-16 and HPV-18 genital tract cancers and pre-cancerous lesions, a comparison of these vaccines in terms of immunogenicity and safety is warranted.

A group of HIV- female subjects will be used as control. These subjects will be randomized to receive either *Cervarix* or *Gardasil* and compared to the HIV+ cohort to evaluate the effect of the HIV+ immunocompromised state on the immunogenicity and safety of both vaccines.

2. OBJECTIVES

2.1. Co-Primary objectives

Safety:

- To evaluate the safety and reactogenicity of both vaccines in HIV+ subjects for up to one month after the third dose of vaccine.

Immunogenicity:

The following objectives will be assessed sequentially:

- To demonstrate non-inferiority of *Cervarix* versus (vs.) *Gardasil* in terms of geometric mean titers (GMTs) against HPV-16 and HPV-18 measured by Pseudovirion-based neutralization assay (PBNA) one month after administration of the third dose of vaccine in HIV+ subjects.

  Criterion: Non-inferiority will be demonstrated if the lower limit of the 95% confidence interval (CI) for the ratio of GMTs (Cervarix over Gardasil) is above 0.5 for both HPV types.

- If the first primary objective for immunogenicity is demonstrated, superiority of *Cervarix* over *Gardasil* in terms of GMTs against HPV-16 and HPV-18 measured by PBNA in HIV+ subjects will be assessed following a sequential approach.
  - First, superiority for HPV-18 type will be assessed.

    Criterion: Superiority will be demonstrated if the lower limit of the 95% CI for the ratio of GMTs (Cervarix over Gardasil) is above 1 for HPV-18 type with a statistically significant p-value.
  - Second, if superiority for HPV-18 is shown, superiority for HPV-16 will be assessed.

    Criterion: Superiority will be demonstrated if the lower limit of the 95% CI for the ratio of GMTs (Cervarix over Gardasil) is above 1 for HPV-16 type with a statistically significant p-value.

Refer to Section 10.1 for the definition of the primary endpoints.

2.2. Secondary objectives

Immunogenicity:

- To demonstrate superiority of *Cervarix* vs. *Gardasil* in terms of GMTs against HPV-16 or HPV-18 measured by PBNA one month after the administration of the third dose of vaccine in HIV- subjects.

  Criterion: Superiority of Cervarix vs. Gardasil will be demonstrated if the lower limit of the 97.5% CI for the ratio of GMTs (Cervarix over Gardasil) is above 1 for the antigen considered with a statistically significant p-value.

- To evaluate the antibody response of both vaccines with respect to HPV-16 and HPV-18 antibody levels by Enzyme-Linked Immunosorbent Assay (ELISA) at Day 0, Week 6, Week 10, Months 7, 12, 18 and 24 in all (HIV+ and HIV-) subjects.
- To evaluate the antibody response, by ELISA, against HPV-16 and HPV-18 in CVS at Day 0, Week 6, Week 10, Months 7, 12 and 24 in post-menarcheal subjects who volunteer for this procedure.
- To evaluate the memory B and T cell-mediated immune (CMI) response against HPV-16 and HPV-18 at Day 0, Week 6, Week 10, Months 7 and 12 in a subset of approximately 100 subjects (50 HIV+ and 50 HIV-).

Safety:

- To evaluate the safety and reactogenicity of both vaccines in HIV- subjects for up to one month after the third dose of vaccine.
- To evaluate the safety and reactogenicity of both vaccines in all subjects for up to 24 months after the first vaccine dose.

Refer to Section 10.2 for the definition of the secondary endpoints.

2.3. Exploratory objectives

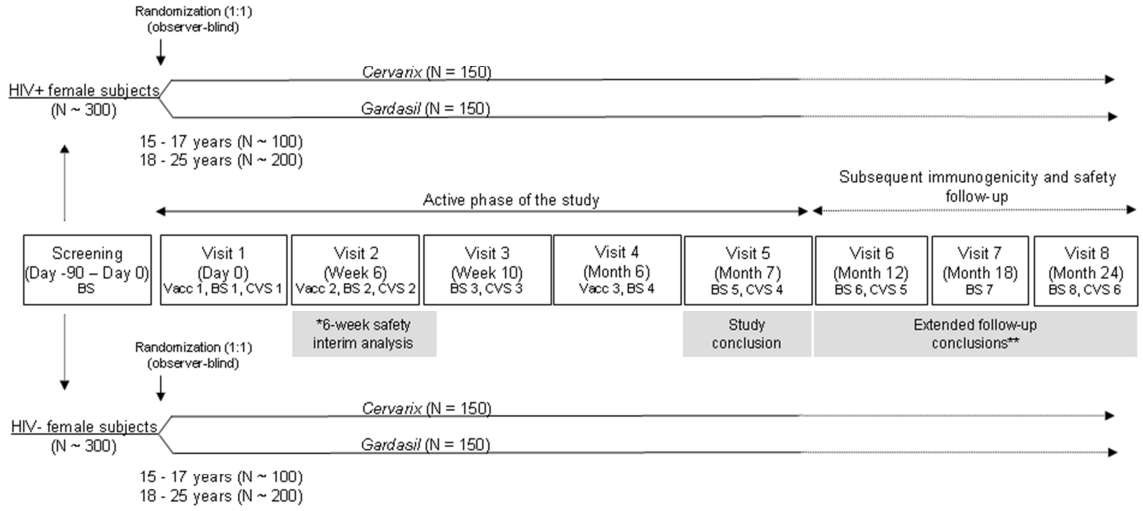
Immunogenicity:

- To demonstrate non-inferiority of *Cervarix* in HIV+ subjects vs. *Gardasil* in HIV- subjects in terms of GMTs against HPV-16 or HPV-18 measured by PBNA one month after the administration of the third dose of vaccine.

  Criterion: Non-inferiority will be demonstrated if the lower limit of the 95% CI for the ratio of GMTs (Cervarix over Gardasil) is above 0.5 for the antigen considered.
- To evaluate the antibody response of both vaccines with respect to HPV-16 and HPV-18 by ELISA at Day 0, Months 7, 12, 18 and 24 in HIV+ subjects stratified by HIV mode of transmission, if sufficient data are available.
- To evaluate the antibody response of both vaccines with respect to HPV-16 and HPV-18 by ELISA at Day 0, Months 7, 12, 18 and 24 in HIV+ subjects by nadir CD4 cell count category, if sufficient data are available.

3. STUDY DESIGN OVERVIEW

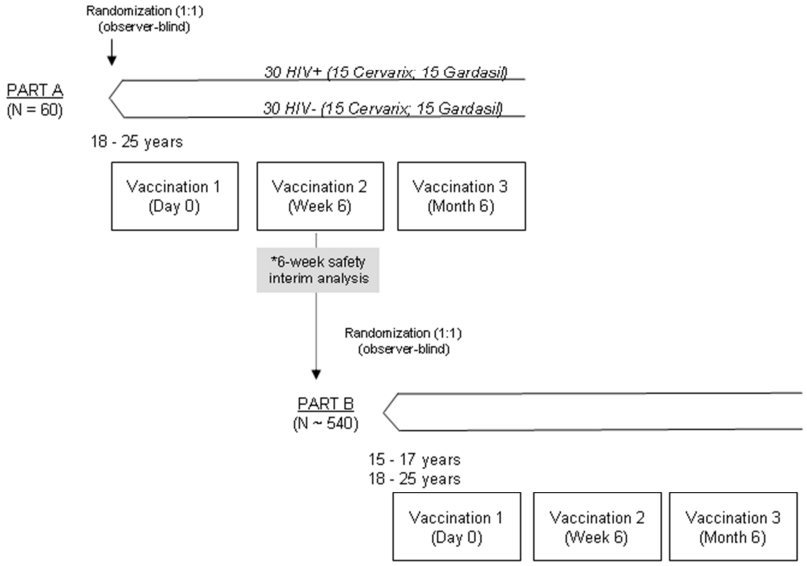
Figure 1 Study design



Vacc: Vaccination; BS: Blood sample; CVS: Cervicovaginal secretions

* The 6-week safety evaluation will be assessed in a subset of approximately 60 subjects aged 18 - 25 years (30 HIV+ and 30 HIV- subjects) [PART A].
** The results of the analyses conducted on the data collected up to Month 12, 18 and 24 will be written in annex reports.

Figure 2 Overview of staggered vaccination progress and safety evaluation



* If the safety evaluation does not indicate any safety concern, the remainder of the subjects will be enrolled.

- Experimental design: A multicentric, observer-blind, controlled trial with two vaccine groups (*Cervarix* and *Gardasil*) and a staggered enrollment (Part A and Part B).
- Treatment allocation: randomized 1:1 with central randomization call-in system on internet (SBIR). Refer to Section 5.2 for a detailed description of the randomization method.
- Blinding: observer-blind. Refer to Section 5.3 for details of blinding procedure.
- Vaccination schedule: at Day 0, Week 6, and Month 6.
- Active Control: *Gardasil.*
- The enrollment will be stratified by HIV infection status and by age as follows:
  - HIV+ subjects 18 - 25 years;
  - HIV- subjects 18 - 25 years;
  - HIV+ subjects 15 - 17 years;
  - HIV- subjects 15 - 17 years.
- In **Part A**, a subset of 60 subjects aged 18 - 25 years (30 HIV+ and 30 HIV- subjects) will be vaccinated (Dose 1) and evaluated for safety before proceeding with the enrollment and vaccination of the remaining subjects (**Part B**) (see Figure 2). The results of this safety interim analysis will be reviewed by the GSK Safety Review Team and the Independent Data Monitoring Committee (IDMC). The IDMC will provide recommendation to the sponsor via the GSK Safety Review Team prior to proceeding with the enrollment of the remaining study subjects in Part B of the study (see Section 5.4.2 for details).
- The study will be supervised by an IDMC consisting of clinical experts and a biostatistician that will oversee safety and ethical aspects of the trial.
- Type of study: self-contained. Data from this study may subsequently be pooled with data from other studies.
- Data collection: Remote Data Entry System (RDE).
- Duration of the study: The study will last approximately 24 months for each subject, including an active phase from Day 0 to Month 7 and a subsequent extended safety and immunogenicity follow-up phase from Month 7 to Month 24.

4. STUDY COHORT

4.1. Number of subjects/centers

Approximately 600 subjects aged between 15 and 25 years were planned to be enrolled in order to reach 480 evaluable subjects for the analysis at Month 7. Due to high rate of non evaluable subjects, additional subjects will be enrolled in this study in order to maintain the statistical power for analysis. Thus , approximately 700 subjects will be enrolled in this study to obtain 480 evaluable subjects:

- Approximately 300 HIV+ subjects, stratified into two age strata (15 - 17 years and 18 - 25 years).
- Approximately 300 HIV- subjects, stratified into two age strata (15 - 17 years and 18 - 25 years).

The subjects will be enrolled in two parts: the first part (Part A) will include 60 subjects (30 HIV+ and 30 HIV-) aged 18 – 25 years and the second part (Part B) will include the remaining subjects.

Please refer to Section 10.3 for a detailed description of the criteria used in the estimation of the sample size.

An overview of the sub-cohorts is provided in Table 1.

Table 1 Sub-cohorts

Sub-cohort name	Description	Estimated number of subjects
HIV+ sub-cohort (safety)	Assessment of CD4 cell count, HIV viral load, antiretroviral (ARV) treatment and HIV clinical stage	300
CMI sub-cohort* (immunogenicity)	Assessment of B cells and T cells response	100
CVS sub-cohort (immunogenicity)	Measure of Immunoglobulin G (IgG) titers	Post-menarcheal subjects who volunteer for this procedure

*CMI will be done in selected countries.

- Overview of the recruitment plan

The study will be performed in multiple centers located in multiple countries. A center is defined as a single recruiting site or multiple recruiting sites under one principal investigator.

While every effort will be made to reach the planned recruitment target of 300 HIV+ and 300 HIV- subjects, for operational reasons (i.e., difficulty in finding sufficient eligible subjects), it may be necessary to stop recruitment of HIV+ subjects prior to reaching the target. The impact on the power of a potentially smaller sample size and the uncertain variability is tabulated in Section 10.3.

To allow GSK Biologicals to take advantage of greater rates of recruitment than anticipated at individual centers in this multicenter study and to thus reduce the overall study recruitment period, an over-randomization of supplies will be prepared.

To encourage participation in the study and to achieve recruitment targets on time, the center will be encouraged to manage the recruitment plan using methods that are acceptable within local regulations, such as advertisements in news media and use of posters and flyers. All such recruitment material will be approved by the local ethics committee.

The specific terms for the achievement of recruitment targets and criteria for the termination of enrollment will be addressed in the investigator's financial agreement.

GSK Biologicals Site Monitors will be responsible for monitoring and direct implementation of the recruitment plan.

4.2. Inclusion criteria

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

- Subjects who the investigator believes that they and/or their parent(s)/legally acceptable representative(s) (LAR) can and will comply with the requirements of the protocol (e.g., completion of the diary cards, return for follow-up visits) should be enrolled in the study.
- A female between, and including, 15 and 25 years of age at the time of the first vaccination.
- Written informed consent obtained from the subject and/or from the subject's parent or LAR.
- Subjects willing to undergo HIV Voluntary Counseling and Testing (VCT) and willing to be informed of their HIV infection status.
- For HIV seropositive subjects:
  - Subjects must be HIV seropositive according to World Health Organization (WHO) case definition, i.e., positive HIV antibody testing (rapid or laboratory-based enzyme immunoassay, confirmed by a second HIV antibody test relying on different antigens or of different operating characteristics and/or positive virological test for HIV or its components such as HIV-ribonucleic acid [RNA], HIV-DNA or ultrasensitive HIV P24 antigen). [WHO, 2006]
  - Regardless of their prior clinical stage, subject must be asymptomatic (or only have persistent generalized lymphadenopathy).
  - If not on triple therapy (highly active antiretroviral therapy [HAART]), subjects should have a CD4 cell count > 350 cells/mm^3.
  - If currently taking antiretrovirals (ARVs), subjects must be on HAART for at least one year, have undetectable viral load (i.e., viral load ≤ 400 copies/mm^3) for at least six months, and have a CD4 cell count > 350 cells/mm^3 at study entry.
- For HIV seronegative subjects:
  - Subjects confirmed as HIV seronegative at the screening visit are eligible to participate in the HIV- group of the study.
- For non-virgin female subjects:
  - Subjects must have no history of abnormal cytology or CIN 1/2/3.
  - Subjects must have had no more than six life-time sexual partners prior to enrollment.
- Subjects must have no history of congenital malformations of the uterine cervix, or history of cauterization or surgical procedures involving damage to the transformation zone of the cervix or stenosis.

- Female subjects of non-childbearing potential may be enrolled in the study.
  - Non-childbearing potential is defined as pre-menarche, current tubal ligation, hysterectomy, ovariectomy or post-menopause.

Please refer to the GLOSSARY OF TERMS for the definition of menarche and 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 at screening and on the day of vaccination, and
  - has agreed to continue adequate contraception during the entire treatment period and for two months after completion of the vaccination series.

Please refer to the GLOSSARY OF TERMS for the definition of adequate contraception.

4.3. Exclusion criteria for enrollment

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:

- Previous vaccination against HPV, or planned administration of any HPV vaccine other than that foreseen by the study protocol during the study period (Day 0 to Month 24).
- Active tuberculosis (TB) diagnosed by AF B sputum test and/or chest X-ray at the screening visit (criteria mandatory only for HIV+ subjects).
- Current TB therapy.
- Hemoglobin < 8.0 g/dL at the screening visit.
- Creatinine > 1.5-fold the upper limit of normal (ULN) at the screening visit.
- Alanine aminotransferase (ALT) > 2.5-fold ULN at the screening visit.
- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) within 30 days preceding the first dose of study vaccine, or planned use during the study period (Day 0 to Month 24).
- Chronic administration (defined as more than 14 consecutive days) of immunosuppressants or other immune-modifying drugs (with the exception of ART) within six months prior to the first vaccine dose. For corticosteroids, this will mean prednisone ≥ 0.5 mg/kg/day, or equivalent. Inhaled and topical steroids are allowed.
- Administration of a vaccine not foreseen by the study protocol within 30 days (Days 0 - 29) before the first dose of study vaccine/control. Enrollment will be postponed until the subject is outside the specified window.
- Planned administration of a vaccine not foreseen by the study protocol within 30 days before or 30 days after (i.e., Days 0 - 29) any dose of study vaccine.

- Previous administration of MPL or AS04 adjuvant (see APPENDIX B for a list of GSK vaccines containing MPL).
- Cancer or autoimmune disease under treatment.
- Hypersensitivity to latex (found in syringe-tip cap and plunger).
- History of allergic disease or reactions likely to be exacerbated by any component of the vaccine/control (e.g., aluminium, MPL).
- Acute disease and/or fever at the time of enrollment.
  - Fever is defined as temperature ≥ 37.5°C on oral, axillary or tympanic setting.
  - Subjects with a minor illness (such as mild diarrhea, mild upper respiratory infection) without fever may be enrolled at the discretion of the investigator.
- Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory testing performed at the screening visit.
- History of any neurological disorders or seizures.
- Pregnant or breastfeeding female.
- A subject planning to become pregnant, likely to become pregnant (as determined by the investigator) or planning to discontinue contraceptive precautions during the study period, up to two months after the last vaccine dose (i.e., up to Month 8).
- Concurrently participating in another clinical study, at any time during the study period (Day 0 to Month 24), in which the subject has been or will be exposed to an investigational or a non-investigational product (pharmaceutical product or device).
- Any medically diagnosed or suspected immunodeficient condition (other than HIV for HIV seropositive subjects), based on medical history, physical examination and/or laboratory tests results.
- Administration of immunoglobulins and/or any blood products within the three months preceding the first dose of study vaccine/control or planned administration during the study period. Enrollment will be postponed until the subject is outside the specified window.
- Administration of trimethoprim/sulphamethoxazole within seven days before the first dose of study vaccine/control, or planned administration of trimethoprim/sulphamethoxazole within seven days after the first dose of study vaccine/control.

Note: Trimethoprim/sulphamethoxazole is extensively prescribed in HIV-infected patients and can interfere with the assessment and interpretation of the reactogenicity of the vaccine in the study.

- Current drugs or alcohol abuse.
- Child in care (Please refer to the GLOSSARY OF TERMS for the definition of child in care).

A list of criteria that will eliminate subjects from According-to-Protocol (ATP) analyses can be found in Sections 6.6.1, 6.7 and 10.4.

5. CONDUCT OF THE STUDY

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

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

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

The study has been designed and will be conducted in accordance with the ICH Harmonised Tripartite Guideline for clinical investigation of medicinal products in the paediatric population (ICH E11) and all other applicable ethical guidelines.

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

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favorable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- 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 and/or each subject's parent(s)/LAR(s) 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 judgment, local regulations and requirements should guide the final structure and content of the local version of the ICF.

In accordance with the ICH Harmonized Tripartite Guidelines for GCP, those subjects who can only be enrolled in the study with the consent of the subject's LAR(s) (e.g., minors), should be informed about the study to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date a written informed assent. It is required that the assent be signed by each subject, if capable, in addition to the informed consent that is to be signed by her legal

representative. It should be assessed whether an assent is required depending of the age of the study population and the local requirements.

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 randomization of treatment

5.2.1. Subject identification

Subject numbers will be assigned sequentially to subjects consenting to participate or to subjects whose parent(s)/LAR(s) have consented their participation in the study, according to the range of subject numbers allocated to each study center.

5.2.2. Randomization of treatment

5.2.2.1. Randomization of supplies

The randomization will be performed at GSK Biologicals, Rixensart, using MATEX, a program developed for use in SAS® (Cary, NC, USA) by GSK Biologicals. A randomization blocking scheme (1:1 ratio) will be used to ensure that balance between treatments is maintained: a treatment number will be allocated at each dose for each subject.

To allow GSK Biologicals to take advantage of greater rates of recruitment than anticipated at individual centers in this multicenter study, and thus to reduce the overall study recruitment period, a 30% over-randomization of supplies will be prepared.

The vaccine doses will be distributed to the study center while respecting the randomization block size.

5.2.2.2. Treatment allocation to the subject

The treatment allocation at the investigator site will be performed using a central randomization system on internet (SBIR). Subjects will be stratified according to their country, to their HIV infection status at baseline and their age.

In addition, HIV+ subjects will be randomized according to their baseline CD4 cell count (350 cells/mm^3 ≤ CD4 count ≤ 500 cells/mm^3 or CD4 count > 500 cells/mm^3) and the fact they are on HAART or not (HAART/non-HAART). The randomization algorithm for HIV+ subjects will use a minimization procedure accounting for CD4 cell count and HAART.

When a subject has provided informed consent and is confirmed as eligible, the person in charge of the vaccination will access SBIR. Upon providing the subject's identification number, the dose, the country, her HIV infection status and age, the randomization system will either allocate a treatment number for HIV- subjects or ask for the baseline CD4 cell count and HAART/non-HAART of the HIV+ subjects and then allocate a treatment number. The allocation of the treatment number (Gardasil or Cervarix) will follow a ratio 1:1.

The first 60 subjects (30 HIV- and 30 HIV+ subjects) to be enrolled in the study will have to be between 18 and 25 years old. Treatment numbers will be allocated by SBIR accounting for country, HIV infection status and, for HIV+ subjects, baseline CD4 cell count and HAART/non-HAART. Once 30 HIV+ subjects and 30 HIV- subjects have been enrolled, SBIR will be locked and enrolment suspended until results from the Week 6 interim safety analysis on these subjects are available. Once the results have been reviewed by the GSK safety review team and the IDMC, enrollment will be initiated for the remaining subjects (within six weeks after availability of the safety results).

Each treatment number must be recorded in the electronic case report form (eCRF) on the Vaccine Administration screen (Randomization/Treatment Allocation Section).

When SBIR is not available, please refer to SBIR user guide or Study Procedures Manual (SPM) for specific instructions.

5.2.3. Randomization of subjects to assay subsets

A randomized subset of 100 subjects from selected countries will have sera tested for CMI response. These subjects will be randomized according to their HIV infection status at baseline. The subset will therefore be composed of 50 HIV+ subjects (25 on *Cervarix* and 25 on *Gardasil*) and 50 HIV- subjects (25 on *Cervarix* and 25 on *Gardasil*).

5.3. Method of blinding

Data will be collected in an observer-blind manner. Due to differences in the visual appearance of the two HPV vaccines, syringes will be prepared and administered by qualified medical personnel not otherwise involved in the conduct of the study or in the assessment of symptoms. The vaccine recipient and those responsible for the evaluation of any study endpoint (e.g., safety, reactogenicity) will all be unaware of which vaccine was administered during the entire study period. Refer to the Study Procedures Manual (SPM) for specific instructions on observer blind stratergy.

Study and GSK personnel directly involved in the conduct of the study will be blinded to the individual subject treatment. In order to preserve the blind, the interim analysis will be performed by an external statistician, therefore only a non-GSK statistician will be unblinded to the treatment allocation. Similarly, when all subjects will complete their Month 7 visit and the database will be frozen, the primary analysis will also be performed by an external statistician. The subjects, investigator, study personnel and GSK staff will remain blinded until completion of study follow-up. All analysis, until completion of study follow-up, will be performed by an external statistician to preserve blinding of study.

The serological data, which will lead to the unblinding of the treatment groups, will not be available during the course of the trial to the investigator or any person involved in the clinical conduct of the study (including data cleaning).

5.4. General study aspects

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying 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.

5.4.1. Independent Data Monitoring Committee

An IDMC established by GSK will advise GSK and the study investigator with respect to the study. This IDMC includes independent experts in the fields of papillomaviruses, gynecology, infectious diseases, vaccinology, and biostatistics who will periodically review and evaluate the accumulated study safety data for participant safety, study contact and progress, and make recommendations to the Sponsor concerning the continuation, modification, or termination of the trial. The IDMC will meet approximately four times per year to review study methods and results and make recommendations to GSK concerning study continuation. Ad hoc meetings can be convened based on requests from GSK or any of the reviewing IRBs. The IDMC will develop triggers for nonscheduled meetings. The IDMC will be responsible for unblinded analyses, if required. The operating rules of the IDMC will be established by GSK and will be documented by a charter.

5.4.2. Staggered vaccination process

In Part A, a subset of 60 subjects aged 18 – 25 years (30 HIV+ and 30 HIV- subjects) will be vaccinated (Dose 1) and evaluated for safety before proceeding with the enrollment and vaccination of the remaining subjects (Part B) (see Figure 2). Administration of Dose 2 to these subjects in Part A will not depend on the outcome of the safety evaluation unless there are specific safety concerns for an individual subject or if requested by the IDMC or Vaccine Safety Monitoring Board (VSMB).

A safety interim analysis will be performed on the 6-week post-dose 1 vaccination data from the subjects in Part A to evaluate the following parameters:

- solicited symptoms during the 7-day follow-up period (Days 0-6);
- unsolicited symptoms, medically significant conditions (including potential immune-mediated diseases [pIMDs]), new onset chronic diseases (NOCDs), new onset autoimmune diseases (NOADs), and serious adverse events (SAEs) up to Day 30 after administration of the first dose (Days 0-29);
- hematological and biochemical parameters;
- CD4 cell count, HIV viral load, ART status and the HIV clinical stage of each individual subject (for HIV+ subjects only).

The subjects in this subset could have a home visit by the study nurse to collect their diary cards.

5.4.3. Review of safety data

A Safety Review Team, including as core members the GSK Biologicals' Central Safety Physician, the Clinical Research & Development Lead (CRDL) and Biostatistician of the project, and the IDMC will be responsible for reviewing the 6-week safety data of Part A. The IDMC will provide recommendation to the sponsor via the GSK Safety Review Team prior to proceeding with the enrollment of the remaining study subjects in Part B of the study.

In case of any safety concern, the CRDL is responsible for urgent communication and escalation to the GSK VSMB, who will provide recommendations on the study continuation at an *ad hoc* meeting.

5.4.4. Counseling for HIV, sexual transmitted infection and disease prevention and birth control

At the screening visit, prior to HIV testing, counseling will be provided to the potential participant by trained study personnel. Counseling will also be provided by a trained counselor once results of HIV testing are available, regardless of the test result. Subjects will be informed of their HIV results as soon as they are available. Participants in HIV negative group will be provided with additional HIV testing and counselling at Month 7 and Month 24.

At each visit during the study, individual, age-appropriate counseling on types of birth control and pregnancy prevention (including abstinence) and on methods to reduce risk of sexually transmitted infections and diseases (STIs and STDs) will be provided to subjects by study site personnel, if appropriate. This counseling will be conducted in private, according to local law/regulations.

5.4.5. Follow-up of HIV positive subjects in the study (Amended: 26 April 2016)

Subjects who are HIV+ will be managed throughout the study and after completion of the study by their local physician as per local treatment guidelines.

Previous WHO recommendations advised to start ART in subjects with a CD4 cell count ≤350 cells/mm^3 irrespective of their clinical stage [WHO, 2009]. A revision in late 2015 of the WHO guideline on when to start ART presented evidence showing that earlier use of ART results in better, long term clinical outcomes for people living with HIV compared with delayed treatment, including pregnant and breastfeeding women. This guideline advises to start ART in all adults with HIV regardless of their clinical stage and at any CD4 cell count [WHO, 2015].

Subjects eligible for ART at any time at Screening or after enrollment will be referred to the local Primary Health Care HIV Clinic which will give them access to medical care according to the local standard of care. A referral letter to ARV Center will be provided to each subject who needs to be referred and assurance will be taken that each subject has been properly referred (appointment, transportation, follow-up).

Subjects who are HIV seronegative at study entry but who seroconvert to HIV seropositive during the study will be referred to the local HIV Services/Primary Health Care HIV Clinic for counselling and follow-up.

The referral processes and subject management will be described in a study site internal operating procedure.

5.5. Outline of study procedures

The study procedures are detailed in Table 2.

Table 2 List of study procedures

Epoch	Screening	Active Phase of the Study					Immunogenicity and Safety Follow-up		
Visit Timing Sampling time point	Screening visit Up to 90 days Screening	Visit 1 Day 0 Pre-vacc	Visit 2 Week 6 Post-vacc I	Visit 3 Week 10 Post-vacc II	Visit 4 Month 6 Post-vacc II	Visit 5 Month 7 Post-vacc III	Visit 6 Month 12 Post-vacc III	Visit 7 Month 18 Post-vacc III	Visit 8 Month 24 Post-vacc III
Informed consent	●								
Check in- and exclusion criteria	●	●							
Randomization (SBIR)		●							
Check elimination criteria			●	●	●	●	●	●	●
Check contraindications		●	●		●				
Collect demographic data age, race, height weight	 ● ●	 ●	 ●	 ●	 ●	 ●	 ●	 ●	 ●
Medical history	●								
History-directed physical examination	●	●	●	●	●	●	●	●	●
Pre-vaccination body temperature		●	●		●				
Urine sample for pregnancy test	●	●	●		●				
Counseling for HIV[&], STD and STI prevention and birth control	●	●	●	●	●	●	●	●	●
Distribution of subject card	●								
Blood sampling									
for anti-HPV-16/18 determination (5 mL)		●	●	●		●	●	●	●
for CMI response in a subset of 100 subjects (36 mL)[§]		●	●	●		●	●		
for hematology/biochemistry parameters determination (10 mL)	●	●	●	●	●	●	●	●	●
for HIV testing (Rapid test, 5 mL)[†]	●[‡]					●[Ω]			●[Ω]
Collection of CVS in post-menarcheal subjects who volunteer for the procedures		●	●	●		●	●		●
Vaccination		●	●		●				
Daily post-vaccination recording of solicited (Days 0 – 6) and unsolicited symptoms (Days 0 – 29) by subjects/parents/LARs		●	●		●				
Recording of non-serious AEs within 30 days post-vaccination, by investigator		●	●		●				

Epoch	SCREENING	ACTIVE PHASE OF THE STUDY					IMMUNOGENICITY AND SAFETY FOLLOW-UP		
Visit **Timing** **Sampling time point**	**SCREENING VISIT** **Up to 90 days** **Screening**	**VISIT 1** **Day 0** **Pre-vacc**	**VISIT 2** **Week 6** **Post-vacc I**	**VISIT 3** **Week 10** **Post-vacc II**	**VISIT 4** **Month 6** **Post-vacc II**	**VISIT 5** **Month 7** **Post-vacc III**	**VISIT 6** **Month 12** **Post-vacc III**	**VISIT 7** **Month 18** **Post-vacc III**	**VISIT 8** **Month 24** **Post-vacc III**
Distribution of diary cards		○	○		○				
Return and verification of diary cards			○	○		○			
Diary card transcription by investigator			●	●		●			
Record any concomitant medication/ vaccination	●	●	●	●	●	●	●	●	●
Reporting of SAEs	●	●	●	●	●	●	●	●	●
Reporting of medically significant conditions (including pIMDs)		●	●	●	●	●	●	●	
Reporting of pregnancies and outcomes		●	●	●	●	●	●	●	●
Study conclusion						●			
Extended follow-up conclusion							●	●	●
Specific procedures for HIV+ subjects									
Medical history, incl. gynecological history and review of medical records of HIV history	●								
AF B / Chest X-ray	●								
HIV / AIDS WHO clinical staging	●	●	●	●	●	●	●	●	●
Record Nadir CD4 (if applicable)	●								
Record ARV therapy (if applicable)	●	●	●	●	●	●	●	●	●
Blood sampling for HIV confirmatory test (5 mL)	●								
Blood sampling for CD4 cell counting (4 mL)	●	●	●	●	●	●	●	●	●
Blood sampling for HIV viral load (3 mL)	●	●	●	●	●	●	●	●	●

The double-line border following Visit 1 indicates the interim analysis which will be performed on the 6-week post-vaccination 1 data collected in a subset of approximately 60 subjects (30 HIV+ and 30 HIV- subjects). The triple-line border following Month 7 indicates the analysis which will be performed on all data obtained after all subjects have completed Visit 5 (Month 7). A final report will be written after all results are available. The dotted-line border following Months 12, 18 and 24 indicate analyses which will be performed on all data obtained after all subjects have completed Visit 6 (Month 12), Visit 7(Month 18) and Visit 8 (Month 24), respectively; these results will be reported in annex reports.

§: Subset of subjects from selected countries.

†: HIV Rapid tests used locally according to National Guideline (e.g., Determine®; First response®). If rapid test is positive, HIV confirmatory test will be performed.

‡: For HIV+ subjects only, if the medical records of the subjects already have results documented for HIV testing, the HIV Rapid test should not be repeated at screening; however, HIV confirmatory test and testing for CD4 cell count and viral load should be performed.

Ω: HIV Rapid tests for HIV negative subjects only.

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

○ is used to indicate a study procedure that does not require documentation in the individual eCRF.

&: Participants in HIV negative group will be provided with additional HIV testing and counselling at Month 7 and Month 24.

It is the investigator's responsibility to ensure that the intervals between visits/contacts are strictly followed.

Follow-up for the occurrence of SAEs will continue for 18 months after administration of the last dose of study vaccine/control to each subject (i.e., up to Month 24 [Visit 8]).

Table 3 Intervals between study visits

Interval	Length of interval (days)	Recommended interval between scheduled visits (days)
Screening visit → Visit 1, Day 0	up to 90 days	90
Visit 1, Day 0 → Visit 2, Week 6	40 - 62	42
Visit 2, Week 6 → Visit 3, Week 10	30 - 48	30
Visit 3, Week 10 → Visit 4, Month 6	98 - 140	106
Visit 4, Month 6 → Visit 5, Month 7	21 - 60	30
Visit 1, Day 0 → Visit 6, Month 12	335 - 395	365
Visit 1, Day 0 → Visit 7, Month 18	515 - 575	545
Visit 1, Day 0 → Visit 8, Month 24	700 - 760	730

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 informed consent of the subject or subject's parent(s)/LAR(s) needs to be obtained. In addition, a written informed assent must be obtained from the subjects below the legal age of consent. Refer to Section 5.1 for information on how to obtain informed consent.

5.6.2. Procedures during screening epoch

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 at the time of informed consent and randomization (i.e., at Screening and Visit 1).

If a subject is enrolled while not meeting all inclusion criteria or while meeting any of the exclusion criteria, this must be reported in the eCRF.

5.6.2.2. Collect demographic data

Record demographic data such as age, race, height and weight in the subject's eCRF.

5.6.2.3. History-directed physical examination

Perform a history-directed physical examination and record any pre-existing 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.

Record the age at which the subjects had their first menstruation. Pre-menarcheal subjects will be instructed to inform the study personnel if their first menstruation occurs during the study (up to two months after the last dose of the vaccine).

For HIV+ subjects only, question subjects about their medical history, including gynecological history and medical records of HIV history (date of diagnosis of HIV infection and mode of contamination). An HIV/AIDS WHO clinical staging will be performed. If applicable, nadir CD4 cells/mm^3 and the subject's ARV therapy will be recorded.

5.6.2.4. AF B sputum test and/or chest X-ray

HIV+ subjects will have an AF B sputum test and/or chest X-ray. Subjects with active TB are not eligible for the study.

5.6.2.5. Urine pregnancy test

All subjects are to have a urine pregnancy test prior to any study vaccine administration. The study vaccines may only be administered if the pregnancy test is negative.

5.6.2.6. Blood sampling for HIV testing and safety

All subjects will have blood samples collected for:

- HIV testing (5 mL, Rapid test);
- Evaluation of hematology and biochemistry parameters (10 mL).

HIV+ subjects will have blood samples collected for:

- HIV confirmatory test (5 mL)
- Determination of CD4 cell count (4 mL);
- Determination of HIV viral load (3 mL);

For HIV+ subjects, if the subject's medical records already have the HIV tests documented/confirmed, the HIV Rapid test should not be repeated, but the other tests (HIV confirmatory test, determination of CD4 cell count and determination of HIV viral load) must be performed.

5.6.2.7. Birth control and counseling for HIV, STI and STD prevention

Provide age-appropriate individual counseling on birth control, pregnancy prevention (including abstinence), and on methods to reduce risk of STIs and STDs to all subjects at each visit.

Provide pre- and post-HIV test counseling. Post-HIV test counseling can be provided as soon as HIV test result (by Rapid test) is available. Make record of this procedure in the eCRF section of the visit during which the HIV test was performed. All subjects found to be HIV-infected will be referred to the national program for medical management according to local guidelines (see Section 5.4.5).

5.6.2.8. Check and record concomitant medication/vaccination and intercurrent medical conditions

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. The use of disallowed medication/vaccination could lead to the elimination of a subject from the ATP analyses.

At each study visit subsequent to the first vaccination visit it must be verified if the subject has experienced or is experiencing any intercurrent medical condition listed in Section 6.7. If this is the case, the condition(s) must be recorded in the eCRF.

5.6.2.9. Distribution of subject card

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 (see Section 8.8).

5.6.3. Procedures during active phase of the study (Visit 1 – Visit 5)

Note that some of the procedures to be performed during the active phase of the study (such as a history-directed physical examination, counseling for STD and STI prevention and birth control, blood sampling for determination of CD4 cell count and HIV viral load in HIV+ subjects, HIV/AIDS clinical staging in HIV+ subjects, urine pregnancy test, check and record concomitant medication/vaccination, ARV therapy (if applicable) and weight, and check of in/exclusion criteria) are also performed at screening and are described in Section 5.6.2.

5.6.3.1. Check contraindications to vaccination

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

5.6.3.2. Assess pre-vaccination body temperature

The oral or axillary body temperature of all subjects needs to be measured prior to any study vaccine administration. A temperature ≥ 37.5°C warrants deferral of the vaccination pending recovery of the subject.

5.6.3.3. Randomization

At the first vaccination visit, randomization will occur as explained in Section 5.2.

5.6.3.4. Blood sampling for safety or immune response assessments

As specified in the List of Study Procedures in Section 5.5 (Table 2), blood samples are taken during certain study visits. Refer to the Module on Biospecimen Management in the SPM for general handling of blood samples.

- A volume of at least 5 mL of whole blood should be drawn from all subjects for evaluation of antibodies against HPV-16 and HPV-18. After centrifugation, serum samples should be kept at –20°C until shipment.
- A volume of at least 36 mL of whole blood should be drawn from a subset of 100 subjects from selected countries for analysis of CMI response at each predefined time point. The blood should be stored at the investigator's site at room temperature and it must not be centrifuged. Samples will be shipped at room temperature (20 to 25°C) to the designated validated laboratory for cell separation to be performed within 24 hours.
- A volume of at least 10 mL of whole blood should be drawn from all subjects for evaluation of hematological and biochemical parameters.
- A volume of at least 5 mL of whole blood should be drawn from HIV negative subjects for HIV testing (Rapid test).

  A confirmatory test (5 mL of whole blood)will be performed on all subjects found to be HIV positive. All subjects found to be HIV-infected will be referred to the national program for medical management according to local guidelines (see Section 5.4.5).

5.6.3.5. Sampling of cervico-vaginal secretions for immune response assessment

As specified in the List of Study Procedures in Section 5.5 (Table 2), two CVS samples will be taken during certain study visits. Full details for taking CVS samples are provided in the Module on Biospecimen Management in the SPM accompanying this protocol.

CVS samples for evaluation of antibodies against HPV-16 and HPV-18 will be collected in post-menarcheal subjects who volunteer for this procedure. The investigator will ensure that the CVS samples are taken within the interval of study visit.

- Sexual intercourse and the use of intravaginal medications (including intravaginal contraceptives) should be avoided for the 24 - 48 hours before collection of a CVS sample. CVS sample collection must be performed a minimum of one day after menstrual flow has ceased. Subjects who will be menstruating during planned visits will be invited to reschedule cervical specimen collection at least 2 - 3 days after their menses. Recording of the date of the last menstrual period will be carried out for subjects selected for CVS assessment.

5.6.3.6. Treatment number assignment

At each vaccination visit, the subject will be assigned a treatment number defining the treatment she will be receiving. The treatment number must be recorded in the eCRF at each vaccination visit.

5.6.3.7. Vaccination

- After completing the prerequisite procedures prior to vaccination, one dose of study vaccine/control (*Cervarix*/*Gardasil*) will be administered intramuscularly (IM) in the deltoid muscle 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. The investigator will record the presence/absence of urticaria/rash within 30 minutes of vaccination.

5.6.3.8. Recording of non-serious AEs and SAEs

- Refer to Section 8.3 for procedures for the Investigator to record adverse events (AEs) 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/subjects' parent(s)/LAR(s) will be instructed to contact the investigator immediately should they/the subject manifest any signs or symptoms they perceive as serious.
- After each vaccination, diary cards will be provided to the subjects/subjects' parent(s)/LAR(s) to record body (axillary) temperature and any solicited local/general (Days 0 - 6) or unsolicited AEs (Days 0 – 29) occurring after vaccination. The subjects will be instructed to bring the completed diary card to the next visit.
- Collection and verification of completed diary cards will be performed during discussion with the subject/subject's parent(s)/LAR(s). Any unreturned diary cards will be sought from the subjects through telephone call(s) or any other convenient procedure. The investigator will transcribe the collected information into the eCRF in English.
- The investigator will record any SAE, medically significant conditions (including pIMDs), pregnancy and pregnancy outcome that may have occurred since the previous visit.

5.6.3.9. Conclusion of the active phase of the study

An interim safety evaluation will be performed on the 6-week post-vaccination 1 data collected in a subset of approximately 60 subjects (30 HIV+ and 30 HIV- subjects) before proceeding with the vaccination of the remaining subjects (see Section 5.4.2).

The final analysis will be performed at Month 7, based on all data obtained up to the study conclusion visit (Visit 5).

5.6.4. Procedures during immunogenicity and safety follow-up (Visit 6 – Visit 8)

The immunogenicity and safety follow-up period includes Visit 6, 7 and 8. Note that all of the procedures to be performed during the follow-up period (such as blood sampling, checking elimination criteria, a history-directed physical examination, counseling for HIV, STD and STI prevention and birth control, recording of concomitant medication/vaccination, ARV therapy (if applicable), weight, SAEs, medically significant conditions (including pIMDs) and pregnancies) are also performed during the active phase of the study and are described in Section 5.6.3.

5.6.4.1. Extended follow-up conclusion

Blinded annex analyses will be performed at Month 12 and Month 18; and an unblinded annex analysis at Month 24, based on all data obtained up to extended follow-up conclusion visits (Visit 6, Visit 7 and Visit 8, respectively).

5.7. Biological Sample handling and analysis

Please refer to the SPM for details of biospecimen management (handling, storage and shipment).

Samples will not be labeled with information that directly identifies the subjects but will be coded with the identification number for the subject (subject number).

Collected samples may be used in other assays, for test improvement or test development of analytical methods related to the study vaccine and its constituents or the disease under study to allow to achieve a more reliable measurement of the vaccine response. Under these circumstances, additional testing on the samples may be performed by GSK Biologicals outside the scope of this protocol.

Refer to the GSK Biologicals Research & Development Position Paper which describes the rationale for and some examples of what further investigations may include.

Any sample testing will be done in line with the consent of the individual subject.

Any human pharmacogenetic testing will require specific consent from the individual subjects and the ethics committee approval.

Refer also to the Investigator Agreement, where it is noted that the Investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

If additional testing is performed, the marker priority ranking given in Section 5.7.4 may be changed.

Collected samples will be stored for up to 15 years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK Biologicals.

5.7.1. Use of specified study materials

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples (including serum samples) be collected and stored exclusively using those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for the definition of study cohorts to be evaluated). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, then appropriate materials from the investigator's site are to be used. Refer to the Module on Clinical Trial Supplies in the SPM.

5.7.2. Biological samples

Table 4 Biological samples

Sample type	Quantity	Unit	Time point	Subset /Sub-cohort Name*
Blood for humoral immunology	5	mL	Day 0, Week 6, Week 10, Months 7, 12, 18 and 24	All
Blood for CMI	36	mL	Day 0, Week 6, Week 10, Months 7 and 12	CMI sub-cohort
Blood for hematology/biochemistry parameters	10	mL	Screening, Day 0, Weeks 6 and 10, Months 6, 7, 12, 18 and 24	All
CVS	NS	NS	Day 0, Week 6, Week 10, Months 7, 12 and 24	CVS sub-cohort
Blood for HIV testing (Rapid test)	5	mL	Screening**	All
			Month 7, Month 24	HIV- sub-cohort
Blood for HIV confirmatory test	5	mL	Screening	HIV+ sub-cohort
Blood for determination CD4 cell counts	4	mL	Screening, Day 0, Weeks 6 and 10, Months 6, 7, 12, 18 and 24	HIV+ sub-cohort
Blood for determination HIV viral load	3	mL	Screening, Day 0, Weeks 6 and 10, Months 6, 7, 12, 18 and 24	HIV+ sub-cohort

NS = not specified
* Refer to Section 4.1 for sub-cohort description / Refer to Section 5.2.3 for subset description.
** For HIV+ subjects only, if the medical records of the subjects already have results documented for HIV testing, the HIV Rapid test should not be repeated at screening; however, HIV confirmatory test and testing for CD4 cell count and viral load should be performed.

5.7.3. Laboratory assays

Please refer to APPENDIX A for a detailed description of the assays performed in the study.

Anti-HPV-16 and anti-HPV-18 ELISA testing will be performed at GSK or in a validated laboratory designated by GSK on all serological and CVS samples collected. In order to account for the variation of the immunoglobulin G (IgG) levels during the menstrual cycle, total IgG will also be measured in the CVS samples by an ELISA. CVS samples showing 200 erythrocytes or more per µL will be excluded for antibody assessment.

Assays for the determination of antibodies and CMI response will be performed at GSK Biologicals' laboratory or in a validated laboratory designated by GSK Biologicals using standardized and validated procedures.

HIV Rapid test, HIV confirmatory test by ELISA, CD4 cell count and HIV viral load determination will be performed by a local laboratory. Blood samples will be drawn from all HIV+ subjects at all scheduled visits (including screening) to determine CD4 cell count (4 mL) and HIV viral load (3 mL). A blood sample of 5 mL will be drawn from all documented HIV+ subjects during screening to confirm their HIV seropositivity. A blood sample of 5 mL will be drawn from all HIV negative subjects during screening, at Month 7 and at Month 24 to assess their HIV serostatus.

Please refer to Table 5 for an overview of all laboratory assays to be performed during the study.

Table 5 Laboratory assays

Laboratory Discipline	Component	Scale	Method	Test kit/ Manufacturer	Unit	Cut-off	Laboratory
Humoral Immunology	HPV 16.PsV Ab	Quantitative	PBNA$^{\Delta,\dagger}$	NCI methodology adapted by GSK	ED_{50}	40	GSK Biologicals*
	HPV 18.PsV Ab						
	HPV 16.VLP IgG	Quantitative	ELISA†	In house assay	EL.U/mL	19	GSK Biologicals*
	HPV 18.VLP IgG					18	
	HPV 16.VLP IgG	Quantitative	ELISA‡	In house assay	EL.U/mL	NA	GSK Biologicals*
	HPV 18.VLP IgG						
	IgG	Quantitative	Immunonephel-ometry assay†	IgG on the BN II◦	µg/ml	100	GSK Biologicals*
	IgG	Quantitative	ELISA‡	In house assay	µg/mL	NA	GSK Biologicals*
	Anti-HIV	Qualitative	Rapid test§	NR**	NA	NA	Local Laboratory
Cell Mediated Immunology	Specific CD4 or CD8 T cells	Quantitative	IntraCellular cytokine assay	NA	Events/10^6	NA	GSK Biologicals*
	Specific Memory B cells	Quantitative	B cell ELISPOT	NA	Events/10^6	NA	GSK Biologicals*
Hematology chemistry	White blood cells (total + differential), red blood cells, platelets, hematocrit, hemoglobin	Quantitative	NR**	NR**	NR**	NR**	Local Laboratory
Blood chemistry	Creatinine, ALT	Quantitative	NR**	NR**	NR**	NR**	Local Laboratory
HIV+ subjects only							
HIV viral load (copies/mL) CD4 cell count (cell/mm^3)		Quantitative	NR**	NR**	NR**	NR**	Local Laboratory
HIV confirmatory testing		Qualitative	ELISA	NR**	EL.U/mL	NR**	Local laboratory

*GSK Biologicals laboratory or validated laboratory designated by GSK Biologicals
**NR: not required
ED_{50}: Estimated Dose: serum dilution giving a 50% reduction of the signal compared to a control without serum
ALT: alanine aminotransferase; ELISA: Enzyme-linked Immunosorbent Assay; EL.U: ELISA unit; NCI: National Cancer Institute
Δ The pseudovirion-based neutralization (PBNA) assay is based on a method developed by Pastrana *et al*. [Pastrana, 2004] at the NCI.
† Assays performed on blood samples.
‡ Assays performed on CVS samples.
NA Not applicable
◦ BNII fully automated system from Siemens at Bio Analytical Research Corporation (BARC)
§ HIV Rapid test will be used locally according to National Guidelines.

Collected samples will be used for purposes related to the quality assurance of data generated within the scope of this protocol, such as for maintenance of assays described in this protocol and comparison between analytical methods and/or laboratories.

The GSK Biologicals' clinical laboratories have established a Quality System supported by procedures. The activities of GSK Biologicals' clinical laboratories are audited regularly for quality assessment by an internal (Sponsor-dependent) but laboratory-independent Quality Department.

5.7.4. Biological samples evaluation

5.7.4.1. Immunological read-outs

The timings for the immunological read-outs are outlined in Table 6.

Table 6 Immunological read-outs

Timing	Week/ Month	Visit no.	Marker	Assay Method	No. subjects
Blood Sampling					
Pre-vaccination	Day 0	1	anti-HPV-16	PBNA and ELISA	All
			anti-HPV-18	PBNA and ELISA	
			Total IgG	Immunonephelometry	CVS sub-cohort*
Post-vaccination I	Week 6	2	anti-HPV-16	ELISA	All
			anti-HPV-18	ELISA	
			Total IgG	Immunonephelometry	CVS sub-cohort*
Post-vaccination II	Week 10	3	anti-HPV-16	ELISA	All
			anti-HPV-18	ELISA	
			Total IgG	Immunonephelometry	CVS sub-cohort*
Post-vaccination III	Month 7	5	anti-HPV-16	PBNA and ELISA	All
			anti-HPV-18	PBNA and ELISA	
			Total IgG	Immunonephelometry	CVS sub-cohort*
Post-vaccination III	Month 12	6	anti-HPV-16	ELISA	All
			anti-HPV-18	ELISA	
			Total IgG	Immunonephelometry	CVS sub-cohort*
Post-vaccination III	Month 18	7	anti-HPV-16	ELISA	All
			anti-HPV-18	ELISA	
Post-vaccination III	Month 24	8	anti-HPV-16	ELISA	All
			anti-HPV-18	ELISA	
			Total IgG	Immunonephelometry	CVS sub-cohort*
CVS Sampling					
Pre-vaccination	Day 0	1	anti-HPV-16	ELISA	CVS sub-cohort*
			anti-HPV-18		
			Total IgG		
Post-vaccination I	Week 6	2	anti-HPV-16	ELISA	CVS sub-cohort*
			anti-HPV-18		
			Total IgG		
Post-vaccination II	Week 10	3	anti-HPV-16	ELISA	CVS sub-cohort*
			anti-HPV-18		
			Total IgG		
Post-vaccination III	Month 7	5	anti-HPV-16	ELISA	CVS sub-cohort*
			anti-HPV-18		
			Total IgG		
Post-vaccination III	Month 12	6	anti-HPV-16	ELISA	CVS sub-cohort*
			anti-HPV-18		
			Total IgG		
Post-vaccination III	Month 24	8	anti-HPV-16	ELISA	CVS sub-cohort*
			anti-HPV-18		
			Total IgG		

* Post-menarcheal subjects who volunteer for the CVS sampling procedure.
ELISA: Enzyme-Linked Immunosorbent Assay; CVS: cervicovaginal secretion; IgG: immunoglobulin G;
PBNA: Pseudovirion-Based Neutralization Assay

At the discretion of GSK, if findings in the present study or in other studies justify it, PBNA testing could also be performed on serum or CVS samples taken at Week 10 or at Months 12, 18 or 24. Similarly, testing for antibodies directed against other non-vaccine types, including HPV-6, -11, -31, -33, -45, -52, and -58, could be performed.

In case of insufficient blood sample volume to perform assays for all antibodies, the samples will be analyzed according to the following priority ranking:

1. PBNA, anti-HPV-18
2. PBNA, anti-HPV-16
3. ELISA, anti-HPV-16
4. Nephelometry, total IgG
5. ELISA, anti-HPV-18

In case of insufficient CVS sample volume to perform assays for all antibodies, the samples will be analyzed according to the following priority ranking:

1. ELISA, anti-HPV-16
2. ELISA, total IgG
3. ELISA, anti-HPV-18

Samples will not be labeled with information that directly identifies the subjects but will be coded with the identification number for the subject.

5.7.4.2. Hematology/Blood Chemistry

Hematological and biochemical parameters testing will be performed by a local laboratory. Samples of 10 mL of whole blood will be drawn from all study subjects at all scheduled visits to assess these parameters.

5.7.4.3. Cell-mediated immune response

The timings for cell-mediated immune response (CMI) measurement are outlined in Table 7.

Table 7 CMI Sampling

Timing	Week/ Month	Visit no.	Marker	Assay Method	No. subjects
CMI Sampling					
Pre-vaccination	Day 0	1	HPV-16/18 specific CD4/CD8 T cells	IntraCellular cytokine assay	CMI sub-cohort
			HPV-16, -18 specific memory B cells	B cell ELISPOT	
Post-vaccination I	Week 6	2	HPV-16/18 specific CD4/CD8 T cells	IntraCellular cytokine assay	CMI sub-cohort
			HPV-16, -18 specific memory B cells	B cell ELISPOT	
Post-vaccination II	Week 10	3	HPV-16/18 specific CD4/CD8 T cells	IntraCellular cytokine assay	CMI sub-cohort
			HPV-16, -18 specific memory B cells	B cell ELISPOT	
Post-vaccination III	Month 7	5	HPV-16/18 specific CD4/CD8 T cells	IntraCellular cytokine assay	CMI sub-cohort
			HPV-16, -18 specific memory B cells	B cell ELISPOT	
Post-vaccination III	Month 12	6	HPV-16/18 specific CD4/CD8 T cells	IntraCellular cytokine assay	CMI sub-cohort
			HPV-16, -18 specific memory B cells	B cell ELISPOT	

5.7.5. Immunological correlates of protection

No correlate of protection has been demonstrated so far for the HPV-16 and HPV-18 antigens used as part of *Cervarix*.

6. STUDY VACCINES AND ADMINISTRATION

6.1. Description of study vaccines

The candidate GSK HPV vaccine 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 vaccines are labeled and packed according to applicable regulatory requirements and have been locally licensed in each of the participating countries.

The commercial vaccine, *Gardasil*, is assumed to comply with the specifications given in the manufacturer's Summary of Product Characteristics. *Gardasil* is licensed by Merck & Co in all countries participating in this study and indicated for use at the age the female subjects will be vaccinated in this study. Note that *Gardasil* will be administered at Day 0, Week 6, and Month 6 in this study, which is slightly different from the vaccination schedule recommended in the manufacturer's prescribing information (0, 2, 6-month); however, flexibility around the second dose is allowed: 'if an alternate vaccination schedule is necessary, the second dose should be administered at least one month after the first dose and the third dose should be administered at least three months after the second dose. All three doses should be given within a one-year period'.

Table 8 describes the formulation and presentation of the vaccines used in this study.

Table 8 Vaccine components

Vaccine	Formulation	Presentation	Volume	N° doses
Cervarix (GSK Biologicals)	20 μg HPV-16 L1 VLP 20 μg HPV-18 L1 VLP 50 μg MPL 500 μg aluminium in the form of $Al(OH)_3$ 8 mM sodium dihydrogen phosphate dihydrate 150 mM sodium chloride water for injection	Liquid in pre-filled syringes	0.5 mL	3
Gardasil (Merck)	20 μg HPV-6 L1 protein 40 μg HPV-11 L1 protein 40 μg HPV-16 L1 protein 20 μg HPV-18 L1 protein 225 μg aluminium hydroxyphosphate	Liquid in pre-filled syringes	0.5 mL	3

MPL: 3-*O*-desacyl-*4'*-monophosphoryl lipid A; Al(OH)3: aluminium hydroxide; VLP: virus-like particle
mL: milliliter; μg: microgram

6.2. Storage and handling of study vaccines

All study vaccines to be administered to the subjects must be stored in a safe and locked place with no access by unauthorized personnel.

Study vaccines will be stored at the defined temperature range (i.e., +2 to +8°C). Please refer to the Module on Clinical Trial Supplies in the SPM for more details on storage of the study vaccines. The storage temperature of the vaccines will be monitored daily with validated temperature monitoring devices 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, i.e., temperature outside the range (0°C - 8°C or above - 15°C), must be reported to the Sponsor as soon as detected. Following an exposure to a temperature deviation, vaccines will not be used until written approval has been given by the Sponsor.

Adequate actions must be taken in case of temperature deviation between 0 and +2°C to go back to the defined range +2 to +8°C. The impacted study vaccines can still be administered, but the site should avoid re-occurrence of temperature deviation.

Refer to the Module on Clinical Trial Supplies in the SPM for details and instructions on the packaging and accountability of the study vaccines.

6.3. Dosage and administration of study vaccines

Cervarix and *Gardasil* will be supplied as a liquid in individual pre-filled syringes to be administered intramuscularly according to a three-dose schedule (Day 0, Week 6, Month 6). Additional syringes will be provided to each site to replace broken, lost or damaged vials as needed. Due to the difference in the visual appearance of the two HPV

vaccines, study vaccines will be administered in an observer-blinded manner (see Section 5.3).

The study vaccine should be injected intramuscularly in the deltoid muscle of the non-dominant upper arm. The vaccine should not be injected in the gluteal area or areas where there may be a major nerve trunk and/or a blood vessel. Before injection, the skin at the injection site should be cleansed and prepared with a suitable germicide. After insertion of the needle, aspirate and wait to see if any blood appears in the syringe, which will help avoid inadvertent injection into a blood vessel.

The vaccinees will be observed closely for at least 30 minutes following the administration of vaccines, with appropriate medical treatment readily available in case of a rare anaphylactic reaction. Epinephrine injection (1:1000) must be immediately available should an acute anaphylactic reaction occur due to any component of the study vaccines.

See Table 9 for details on vaccines' dosages and administration.

Table 9 Dosage and administration

Group	Dose	Vaccine	Route	Site	Side	Location
Cervarix	0.5 mL	*Cervarix*	IM	D	Non-dominant	U
Gardasil	0.5 mL	*Gardasil*	IM	D	Non-dominant	U

D: deltoid; IM: intramuscularly; U: upper

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-randomization), at least 5% additional doses will be supplied to replace those that are unusable. In case a vaccine dose is broken or unusable, the investigator should replace it with another vaccine dose. Although the Sponsor needs not be notified immediately in these cases (except in the case of cold-chain failure), documentation of the use of another vaccine dose must be recorded by the investigator on the vaccine administration page of the eCRF and on the vaccine accountability form.

The investigator will use the central randomization system (SBIR) to obtain the vial number. The system will ensure, in a blinded manner, that the vial is of the same formulation as the randomized vaccine.

6.5. Contraindications to subsequent vaccination

The following events constitute absolute contraindications to further administration of the study vaccine (*Cervarix*) or active control (*Gardasil*). 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 vaccine.
- 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 that in the opinion of the investigator (or designee) 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).
- Pregnancy (see Section 8.2.1).
- Any SAE judged to be related to study vaccine.
- Hypersensitivity reaction following vaccine administration (including urticaria within 30 minutes of vaccine administration).
- Evolution to worst WHO Clinical Stage 2, 3 or 4 of the HIV-associated disease during the study.
- Initiation of ART during the study.

The following events constitute contraindications to administration of study vaccine or active control 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). The subject must be followed until resolution of the event, as with any AE.

- Acute disease at the time of vaccination.

  Acute disease is defined as the presence of a moderate or severe illness with or without fever. All vaccines can be administered to persons with a minor illness such as diarrhea, mild upper respiratory infection without fever.

  (Fever is defined as temperature ≥ 37.5°C on oral or axillary setting.)
- Fever at the time of vaccination.

  (Fever is defined as temperature ≥ 37.5°C on oral or axillary setting).

6.6. Concomitant medication/vaccination

At each study visit/contact, the investigator should question the subject and/or the subject's parent(s)/LAR(s) 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 antipyretic 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 on oral or axillary setting]).

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

6.6.1. Medications/products that may lead to the elimination of a subject from ATP analyses

The following criteria should be checked at each visit subsequent to the first vaccination visit. If any become applicable during the study, it will not require withdrawal of the subject from the study but may determine a subject's evaluability in the ATP analysis. See Section 10.4 for definition of study cohorts to be evaluated.

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccines during the study period (up to Month 24).
- Chronic administration (defined as more than 14 consecutive days) of immunosuppressants or other immune-modifying drugs (with the exception of ART) during the study period. For corticosteroids, this will mean prednisone, or equivalent, ≥ 0.5 mg/kg/day. Inhaled and topical steroids are allowed.
- Administration of a vaccine not foreseen by the study protocol during the period starting from 30 days before each dose of vaccine and ending 30 days after (i.e., Days 0 - 29).
- Administration of any HPV vaccine other than that foreseen by the study protocol during the study period (up to Month 24). Administration of any HPV vaccine other than that foreseen by the study protocol will also result in withdrawal from the study.
- Administration of immunoglobulins and/or any blood products during the study period (up to Month 24).
- Switch in ART due to treatment failure.
- Administration of trimethoprim/sulphamethoxazole within seven days before any dose of study vaccine/control, or planned administration of trimethoprim/sulphamethoxazole within seven days after any dose of study vaccine/control.

  Note: trimethoprim/sulphamethoxazole is extensively prescribed in HIV-infected patients and can interfere with the assessment and interpretation of the reactogenicity of the vaccine in the study.
- Drug and/or alcohol abuse.

A detailed, comprehensive list of reasons for elimination from ATP analyses will be established at the time of data cleaning.

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

All concomitant medications, with the exception of vitamins and/or dietary supplements, administered at ANY time during the period starting from the first (screening) until the last contact (Visit 8) in this study are to 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 (i.e., Days 0 - 29) after any dose of study vaccine is to be recorded in the eCRF.

Any investigational medication or vaccine administered throughout the study (i.e., from screening up to Month 24) must be recorded in the eCRF.

6.7. Intercurrent medical conditions leading to elimination from an ATP cohort

The following should be checked at each visit subsequent to the first vaccination visit. If any become applicable during the study, it will not require withdrawal of the subject from the study but may determine a subject's evaluability in the ATP analysis.

- Pregnancy after administration of first vaccine dose and within two months after completion of vaccination series.
- For HIV+ subjects: any newly diagnosed immuno-suppressive conditions other than HIV, and/or HIV/AIDS treatment failure.
- For HIV- subjects: any newly diagnosed immuno-suppressive conditions including HIV.

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 AE or SAE as provided in this protocol.

Each subject/subject's parent(s)/LAR(s) will be instructed to contact the investigator immediately should they/the subject manifest any signs or symptoms they perceive as serious.

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 unfavorable 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:

- 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 they 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 vaccine 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 procedures (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital, admission for routine examination).
- 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.
- For therapeutic studies, the disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

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).

NB: AEs to be recorded as endpoints (solicited AEs) are described in Section 8.1.3. All other AEs will be recorded as unsolicited AEs.

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).

8.1.2. Definition of a serious adverse event

An 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 hospitalization or prolongation of existing hospitalization.

   NB: In general, hospitalization 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 hospitalization are also considered AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

   Hospitalization for elective treatment of a pre-existing condition (known/diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an AE.

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, diarrhea, influenza, 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 judgment 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 hospitalization but may jeopardize 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 hospitalization.

8.1.3. Solicited adverse events

Solicited AEs occurring within seven days (Days 0 – 6) after each vaccination will be collected by the subject/subject's parent(s)/LAR(s) and recorded on the diary card (see Table 10 and Table 11). The completed diary card will be returned to the investigator at the next visit (Visits 2, 3 and 5).

In addition, the presence or absence of urticaria/rash within 30 minutes of vaccine administration following each vaccine dose will be documented by the investigator.

The following local (injection-site) AEs will be solicited:

Table 10 Solicited local adverse events

Pain at injection site
Redness at injection site
Swelling at injection site

The following general AEs will be solicited:

Table 11 Solicited general adverse events

Fatigue
Fever*
Gastrointestinal symptoms †
Headache
Arthralgia‡
Myalgia
Rash
Urticaria

* Fever is defined as: axillary/oral temperature ≥ 37.5°C.
† Gastrointestinal symptoms include nausea, vomiting, diarrhea and/ or abdominal pain.
‡ Arthralgia (joint pain): only joints that are distal from the injection site.

NB: Temperature will be recorded in the evening. Should additional temperature measurements be performed at other times of day, the highest temperature will be recorded in the eCRF.

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

Abnormal laboratory findings (e.g., clinical chemistry, hematology, urinalysis) or other abnormal assessments (e.g., physical examination) 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 an 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 AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the

subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

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

8.1.5. 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.

8.1.5.1. Potential immune-mediated diseases

Potential immune-mediated diseases (pIMDs) are a subset of AEs 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 12 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.

The standard time period for collecting and recording of pIMDs will begin at the first receipt of study vaccine and will end 6 months following administration of the last vaccine dose.

8.2. Events or outcomes not qualifying as adverse events or serious adverse events

8.2.1. Pregnancy

Any female subjects that are pregnant or lactating at the time of vaccination must not receive additional doses of study vaccine/comparator 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 an 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 an 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

All AEs starting within 30 days following administration of each dose of study vaccine/comparator must be recorded into the Adverse Event screen in the subject's eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

The time period for collecting and recording of medically significant conditions will begin at the first receipt of study vaccine and will end approximately 12 months following administration of the last vaccine dose (i.e., up to Month 18). Medically significant conditions that are not considered as a pIMD must be recorded on the Adverse

Event Form, or Serious Adverse Event form as appropriate, in the subject's eCRF, irrespective of severity or whether or not they are considered vaccination related. pIMDs must be recorded into the SAE screen in the subject's eCRF. See Section 8.4 for instructions on reporting and recording of pIMDs.

The standard time period for collecting and recording SAEs and pregnancies will begin at the first receipt of study vaccine/comparator and will continue throughout the study period (up to Month 24) for each subject. See Section 8.4 for instructions on reporting and recording SAEs and pregnancies.

In addition to the above-mentioned reporting requirements and in order to fulfill 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 is discharged.

An overview of the protocol-required reporting periods for AEs and SAEs is given in Table 13.

Table 13 Reporting periods for adverse events, serious adverse events and pregnancies

Study activity	Pre-V1*	V1 D0	30 d post-V1 D30	V2 W6	30 d post-V2 W10	V3 M6	30 d post-V3 M7	*12 m post-V3* *M18*	Study conclusion M24
Reporting of AEs**									
Reporting of medically significant conditions (including pIMDs)									
Reporting of SAEs and pregnancies									
Reporting SAEs related to study participation or GSK concomitant products or any fatal SAE									

* i.e. consent obtained. Pre-V: pre-vaccination; V: vaccination; Post-V: post-vaccination; D: day; W: week; M: month
** Solicited AEs within 7 days after each vaccination; unsolicited AEs within 30 days after each vaccination.

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 13. 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

As a consistent method of soliciting AEs, the subject or the subject's parent(s)/LAR(s) should be asked a non-leading question such as:

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

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 Report 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.

8.3.2.2. Assessment of adverse events

8.3.2.2.1. Assessment of intensity

Intensity of the following AEs will be assessed as described in Table 14.

Table 14 Intensity scales for solicited symptoms in adults and children of 6 years of age or more

AE	Intensity grade	Parameter
Solicited local AEs		
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Redness at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Solicited general AEs		
Fever*		Record temperature in °C
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Fatigue	0	Normal
	1	Mild: Fatigue that is easily tolerated
	2	Moderate: Fatigue that interferes with normal activity
	3	Severe: Fatigue that prevents normal activity
Gastrointestinal symptoms (nausea, vomiting, diarrhea and/or abdominal pain)	0	Gastrointestinal symptoms normal
	1	Mild: Gastrointestinal symptoms that are easily tolerated
	2	Moderate: Gastrointestinal symptoms that interfere with normal activity
	3	Severe: Gastrointestinal symptoms that prevent normal activity
Arthralgia**	0	None
	1	Arthralgia that is easily tolerated
	2	Arthralgia that interferes with normal activity
	3	Arthralgia that prevents normal activity
Myalgia	0	None
	1	Myalgia that is easily tolerated
	2	Myalgia that interferes with normal activity
	3	Myalgia that prevents normal activity
Rash	0	None
	1	Rash that is easily tolerated
	2	Rash that interferes with normal activity
	3	Rash that prevents normal activity
Urticaria	0	None
	1	Urticaria distributed on a single body area only
	2	Urticaria distributed on 2 or 3 body areas but no more
	3	Urticaria distributed on at least 4 body areas

*Fever is defined as: axillary/oral temperature ≥37.5°C.
**Arthralgia (joint pain): only joints that are distal from the injection site.

The maximum intensity of local injection site redness/swelling will be scored at GSK Biologicals as follows:

Grade 0	:	0 mm
Grade 1	:	> 0 mm to ≤ 20 mm
Grade 2	:	> 20 mm to ≤ 50 mm
Grade 3	:	> 50 mm

The maximum intensity of fever will be scored at GSK Biologicals as follows:

Grade 0	:	< 37.5 °C
Grade 1	:	≥ 37.5 °C to ≤ 38.0 °C
Grade 2	:	> 38.0 °C to ≤ 39.0 °C
Grade 3	:	> 39.0 °C

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

The intensity of each AE and SAE recorded in the eCRF or SAE Report 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 an SAE. Grade 3 is a category utilized 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 judgment 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 an 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.

In case of concomitant administration of multiple vaccines, it may not be possible to determine the causal relationship of general AEs to the individual vaccines administered. The investigator should, therefore, assess whether the AE could be causally related to vaccination rather than to the individual vaccines.

All solicited local (injection site) reactions will be considered causally related to vaccination. Causality of all other AEs 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 SAE), 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(s), if applicable.
- Erroneous administration.
- Other cause (specify).

8.3.2.3. Assessment of outcomes

Outcome of any non-serious AE occurring within 30 days post-vaccination (i.e., unsolicited AE) or any 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 solicited and unsolicited symptom the subject experiences, the subject/subject's parent(s)/LAR(s) will be asked if they received medical attention defined as hospitalization, 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 15 once the investigator determines that the event meets the protocol definition of an SAE.

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 15, once the investigator becomes aware of the pIMD.

Pregnancies will be reported promptly to GSK as described in Table 15 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 six to eight weeks following the estimated delivery date.

Table 15 Time frames for submitting SAEs and other events reports to GSK Biologicals

Type of Event	Initial Reports		Follow-up 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 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.

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 an SAE(s) that is both attributable to the investigational product and unexpected. The purpose of the report is to fulfill 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 an 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 an 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 resent 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 needs 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.

8.4.4. 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 (i.e. after the diagnosis is established and known to the investigator.). 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 Section 8.4.3.1 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 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.

All AEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until 30 days after the last vaccination.

All medically significant conditions (including pIMDs) 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, stabilized, 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 (e.g., non-serious medically significant conditions [including pIMDs]), 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 recognized 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 AE 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

GSK Biologicals' policy (incorporating ICH E2A guidance, EU Clinical Trial Directive and Federal Regulations) is to unblind any SAE report associated with the use of the investigational product, which is unexpected and attributable/suspected, prior to regulatory reporting. The GSK Biologicals' Central Safety physician is responsible for unblinding the treatment assignment in accordance with specified time frames for expedited reporting of SAEs (refer to Section 8.4.1).

8.7. Emergency unblinding

Unblinding of a subject's individual treatment code should occur only in the case of a medical emergency, or in the event of a serious medical condition, when knowledge of the study treatment is essential for the clinical management or welfare of the subject, as judged by the investigator.

The emergency unblinding process consists of the automated system SBIR that allows the investigator to have unrestricted, immediate and direct access to the subject's individual study treatment.

The investigator has the option of contacting a GSK Biologicals' On-call Central Safety Physician (or Backup) if he/she needs medical advice.

Any emergency unblinding must be fully documented by using the Emergency Unblinding Documentation Form, which must be appropriately completed by the investigator and sent within 24 hours to GSK Biologicals.

GSK Biologicals' Contact information for Emergency Unblinding 24/24 hour and 7/7 day availability
GSK Biologicals' Central Safety Physician: Outside US/Canada: +PPD (GSK Biologicals Central Safety Physician on-call) GSK Biologicals' Central Safety Physician Back-up: Outside US/Canada: +PPD Emergency Unblinding Documentation Form transmission: Outside US & Canada: Fax: +PPD or +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 returns for the concluding visit (Visit 5 at Month 7) foreseen in the protocol is considered to have completed the active phase of the study. A subject who returns for the final follow-up visit (Visit 8 at Month 24) is considered to have completed the extended immunogenicity/safety follow-up of the study.

9.2. Subject withdrawal

Subjects who are withdrawn because of AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn as result of an 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 did not come back for the concluding visit/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, by the subject's parent(s) or LAR(s), or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- SAE.
- Non-SAE.
- Protocol violation (specify).
- Consent withdrawal, not due to an AE.
- 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 was made by the subject herself, by the subject's parent(s) or LAR(s, by or the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- SAE.

- Non-SAE.
- Other (specify).

10. DATA EVALUATION: CRITERIA FOR EVALUATION OF OBJECTIVES

10.1. Co-Primary endpoints

Safety in HIV+ subjects up to Month 7:

- Occurrence and intensity of solicited local symptoms within seven days (Days 0 - 6) after each and any vaccination in HIV+ subjects.
- Occurrence, intensity and relationship to vaccination of solicited general symptoms within seven days (Days 0 - 6) after each and any vaccination in HIV+ subjects.
- Occurrence, intensity and relationship to vaccination of unsolicited symptoms within 30 days (Days 0 - 29) after any vaccination in HIV+ subjects.
- Occurrence of SAEs up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.
- Occurrence of medically significant conditions (including pIMDs) up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.
- Occurrence and outcome of pregnancies up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.
- Occurrence of clinically relevant abnormalities in hematological and biochemical parameters up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.
- CD4 cell count up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.
- HIV viral load up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.
- HIV clinical staging up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.

Immunogenicity:

- HPV-16 and HPV-18 antibody titers by PBNA 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.

10.2. Secondary endpoints

Safety:

- Occurrence and intensity of solicited local symptoms within seven days (Days 0 - 6) after each and any vaccination in HIV- subjects.

- Occurrence, intensity and relationship to vaccination of solicited general symptoms within seven days (Days 0 - 6) after each and any vaccination in HIV- subjects.
- Occurrence, intensity and relationship to vaccination of unsolicited symptoms within 30 days (Days 0 - 29) after any vaccination in HIV- subjects.
- Occurrence of SAEs up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV- subjects.
- Occurrence of medically significant conditions (including pIMDs) up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV- subjects.
- Occurrence and outcome of pregnancies throughout the study (i.e., up to Month 24) in all subjects.
- Occurrence of clinically relevant abnormalities in hematological and biochemical parameters assessed at all study visits in all subjects.
- Occurrence of SAEs during the entire study period (i.e., up to Month 24) in all subjects.
- Occurrence of medically significant conditions (including pIMDs) up to 12 months after the last dose of vaccine (i.e., Month 18) in all subjects.
- CD4 cell count, HIV viral load and HIV clinical staging at Months 12, 18 and 24 in HIV+ subjects.

Immunogenicity:

- HPV-16 and HPV-18 antibody titers by PBNA one month after the last dose of vaccine (i.e., Month 7) in HIV- subjects.
- HPV-16 and HPV-18 antibody titers and total IgG titers by ELISA in serum at Day 0, Week 6, Week 10, Months 7, 12, 18 and 24 in all (HIV+ and HIV-) subjects.
- HPV-16 and HPV-18 antibody titers and total IgG titers by ELISA in CVS at Day 0, Week 6, Week 10, Months 7, 12 and 24 in post-menarcheal subjects who volunteer for this procedure.
- Frequencies of HPV-16 and HPV-18 specific B cells and T cells at Day 0, Week 6, Week 10, Months 7 and 12 in a subset of 100 subjects (50 HIV+ and 50 HIV-).

10.3. Estimated sample size

A total of 600 subjects, 300 in HIV+ group and 300 in HIV-ve group were planned to be enrolled in this study.

Due to high rate of non evaluable subjects, (data integrity issue at one site; protocol non compliance; high drop out rate) additional subjects will be enrolled in this study in order to maintain the statistical power for analysis. Thus , approximately 700 subjects will be enrolled in this study to obtain 480 evaluable subjects.

Primary Objective

The primary objective for immunogenicity is to demonstrate non-inferiority of *Cervarix* vs. *Gardasil* in terms of GMTs against HPV-16 and HPV-18 measured by PBNA one month after the third vaccination (i.e., Month 7) in HIV+ subjects aged 15 - 25 years.

Criterion:

Non-inferiority will be demonstrated if the lower limit of the 95% CI for the ratio of GMTs (*Cervarix* over *Gardasil*) is above 0.5 for both HPV types.

95% CIs of anti HPV-16 and anti HPV-18 GMT ratios at Month 7 will be computed using an ANOVA model of the $\log_{10}$ transformation of the titers. The vaccine group will be included in the model as covariate. The interaction effect between vaccine group and CD4 cell count will be explored in a second model, including vaccine group, CD4 cell count and the interaction as covariates.

Assumptions:

Based on the HPV-010 study in HIV- subjects aged 18 - 26 years, standard deviation (SD) of the logarithm (base 10) of titers (measured by PBNA at Month 7) is assumed to be 0.6 for both HPV types (HPV-16 and HPV-18) and for both *Cervarix* and *Gardasil* groups. SD in HIV+ subjects is unknown.

As the non-inferiority has to be demonstrated for both HPV-16 and HPV-18 types, type II error will be adjusted using Bonferroni's method (the overall type II error is equal to the sum of the individual type II error).

Power:

A sample size of 120 HIV+ evaluable subjects per vaccine group will allow to demonstrate non-inferiority of both HPV types with an overall power of 94% (calculated with *PASS2005, Power analysis of a non-inferiority test of the difference of two means*) and with the following assumptions:

- SD = 0.6 ($\log_{10}$ titers)
- alpha one-sided = 2.5%
- non-inferiority margin = 0.301 ($\log_{10}$ titers) corresponding to a 2-fold
- true difference = 0

Considering a drop-out rate of 20%, approximately 150 HIV+ subjects will be enrolled in each vaccine group.

As the SD is unknown in HIV+ subjects, the table below shows the impact of a SD increase on overall power. Several power calculations are presented to know the impact of ending the study recruitment early (see Section 4.1 of this document).

SD	Evaluable N = 150	Evaluable N = 120	Evaluable N = 105	Evaluable N = 90
0.6	98%	94%	90%	83%
0.7	92%	83%	75%	64%
0.8	80%	66%	55%	42%

Note: target will be 120 evaluable subjects.

The target sample size may also be revised once new data and information are available (especially from study HPV-020) on the observed SD in HIV+ subjects with different CD4 counts, and initial HPV seropositivity in HIV+ subjects.

Superiority tests

If non-inferiority of *Cervarix* vs. *Gardasil* in terms of GMTs for HPV-16 and HPV-18 is shown, superiority of *Cervarix* over *Gardasil* in HIV+ subjects aged 15 - 25 years will be assessed following a sequential approach.

Superiority for HPV-18 type will be assessed first. If the lower limit of the 95% CI for the ratio of GMTs (*Cervarix* over *Gardasil*) is above 1 for HPV-18 type, superiority will be demonstrated and the p-value associated with a test of superiority will be calculated.

If superiority for HPV-18 is shown, superiority for HPV-16 will be then assessed. If the lower limit of the 95% CI for the ratio of GMTs (*Cervarix* over *Gardasil*) is above 1 for HPV-16 type, superiority will be demonstrated and the p-value associated with a test of superiority for HPV-16 will be calculated.

There will be no adjustment of type I error since the tests are performed sequentially.

A sample size of 120 evaluable HIV+ subjects per vaccine group will allow to demonstrate superiority for HPV-18 (and similarly for HPV-16) with a power of 97% (calculated with *PASS2005*) and with the following assumptions:

- SD = 0.6 (log_{10} titers)
- alpha two-sided = 5%
- difference between groups = 0.301 (log_{10} titers) corresponding to a 2-fold

The table below shows the impact of the SD on the power for the test of superiority.

SD	Enrolled N = 150 Evaluable N = 120
0.6	97%
0.7	91%
0.8	83%

Secondary Objective

The first secondary immunogenicity objective is to demonstrate superiority of *Cervarix* vs. *Gardasil* in terms of GMTs against HPV-16 or HPV-18 measured by PBNA one month after the third vaccination in HIV- subjects aged 15 - 25 years.

Criterion: Superiority for HPV-16 (or HPV-18) will be demonstrated if the lower limit of the 97.5% CI for the ratio of GMTs (*Cervarix* over *Gardasil*) is above 1 for HPV-16 (HPV-18, respectively) with a statistically significant p-value.

A sample size of 120 evaluable HIV- subjects per vaccine group will allow demonstrating superiority of at least one HPV type with a power of 95% (calculated with *PASS2005*) with the following assumptions:

- SD = 0.6 (log_{10} titers)
- alpha two-sided = 2.5%
- difference between groups = 0.301 (log_{10} titers) corresponding to a 2-fold

10.4. Study cohorts to be evaluated

10.4.1. Total Vaccinated cohort

The Total Vaccinated cohort will include all vaccinated subjects for whom data are available.

- The Total Vaccinated cohort for analysis of safety will include all subjects with at least one vaccine administration documented for unsolicited AEs and concomitant medication and will include subjects with documented doses for solicited symptoms. For hematological and biochemical parameters, CD4 cell count and HIV viral load, the Total Vaccinated cohort of safety will include all subjects with available data for whom at least one vaccine administration is documented.
- The Total Vaccinated cohort for analysis of immunogenicity will include vaccinated subjects for whom data concerning immunogenicity endpoint measures are available.

The Total Vaccinated cohort analysis will be performed per treatment actually administered.

10.4.2. According-To-Protocol (ATP) cohort for analysis of safety

The ATP cohort for analysis of safety will include subjects:

- who have received three doses of study vaccine/comparator;
- with sufficient data to perform an analysis of safety (at least one dose with safety follow-up);
- for whom administration site of study vaccine/comparator is known;
- who have not received a vaccine not specified or forbidden in the protocol.

- for whom the randomization code has not been broken.

10.4.3. According-to-protocol (ATP) cohort for analysis of immunogenicity

The ATP cohort for analysis of immunogenicity will include all evaluable subjects from the ATP cohort of safety:

- who meet all eligibility criteria;
- who comply with the procedures and intervals defined in the protocol;
- who do not meet the elimination criteria (refer to Section 6.6.1);
- who do not present with a medical condition as listed Section 6.7;
- for whom data concerning immunogenicity endpoint measures are available. This will include subjects for whom assay results are available for antibodies against at least one study vaccine antigen component after vaccination.

10.5. Derived and transformed data

Immunogenicity:

- The cut-off value is defined by the laboratory before the analysis and is described in Section 5.7.3.
- A seronegative subject is a subject whose titer is below the cut-off value.
- A seropositive subject is a subject whose titer is greater than or equal to the cut-off value.
- Seroconversion is defined as the appearance of antibodies (i.e., antibody titer greater than or equal to the cut-off value) in the serum of subjects seronegative before vaccination.
- The GMT calculations are performed by taking the anti-log of the mean of the log titer transformations. Antibody titers below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMT calculation.
- The CIs are 95% CIs. The 95% CIs for GMTs are obtained within each group separately. The 95% CI for the mean of the log-transformed titer was first obtained assuming that log-transformed titers are normally distributed with unknown variance. The 95% CI for the GMT is then obtained by exponential-transformation of the 95% CI for the mean of log-transformed titer.
- Conversion for CVS analyses is defined as the appearance of antibodies (i.e., titer greater than or equal to the limit of quantification [LOQ]) in the CVS of subjects negative before vaccination.
- The GMT calculations for CVS samples are calculated on positive CVS samples only.
- The Pearson coefficient of correlation between serum (ELISA) and CVS standardized for total IgG will be calculated.

- In the CMI analysis, zero values will be given an arbitrary value of 1 for the purpose of the geometric mean calculations.
- Handling of missing data: for a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis excludes subjects with missing or non-evaluable measurements.

Safety:

- For the analysis of solicited symptom, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the Total Vaccinated cohort will include only subjects/doses with documented safety data (i.e., symptom screen completed).
- For the analysis of unsolicited AEs/SAEs/concomitant medication, all vaccinated subjects will be considered and subjects who did not report an event will be considered as subjects without an event.
- For the analysis of medically significant conditions, the database will be searched for any code that matched the pre-established list of common diseases, and matching events will not retained for the analysis. The list of common diseases with their corresponding medical dictionary for regulatory activities (MedDRA) codes will be established by GSK before the analysis.
- GSK assessment of NOCDs (only for the interim analysis): All AEs reported during the trial will be compared with a GSK pre-defined list of potential chronic diseases derived from the MedDRA codes. This list is approved by the IDMC supervising the HPV project. The determination of whether a potential chronic disease (identified by the pre-defined list or by the investigator) is considered to be a NOCD will be based on review by a GSK physician of the whole symptoms reported by the subject including subject's medical history.
- GSK assessment of NOADs (only for the interim analysis): Within the AEs that will be considered as NOCDs (GSK assessment) using a separate pre-defined list, AEs of potential autoimmune etiology will be identified.

10.6. Conduct of analyses

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

10.6.1. Sequence of analyses

An interim analysis will be performed on the 6-week post-dose 1 vaccination data in a subset of approximately 60 subjects (30 HIV+ and 30 HIV- subjects). No clinical study report will be written at this stage.

The final analysis will be performed on all safety and immunogenicity data obtained after all subjects have completed Visit 5 (Month 7), and will be presented in a clinical study report.

The results of the analyses conducted on the safety and immunogenicity data collected up to Months 12, 18 and 24 will be reported in annex reports.

10.6.2. Statistical considerations for interim analyses

A descriptive blinded interim analysis will be performed on the 6-week post-dose 1 vaccination safety data from the first 30 HIV+ (15 on *Cervarix*, 15 on *Gardasil*) and 30 HIV- (15 on *Cervarix*, 15 on *Gardasil*) subjects enrolled. The results of this safety interim analysis will be reviewed by GSK Safety Review Team and the IDMC. The IDMC will provide recommendations to the Sponsor via the GSK Safety Review Team prior to proceeding with the enrollment of the remaining study subjects. The administration of vaccine Dose 2 will be put on hold if the review of the safety data raises any safety concern. In case of any safety concern the CRDL is responsible for the urgent communication and escalation to the GSK VSMB, who will provide recommendations on the study continuation at an *ad hoc* meeting.

In order to maintain the study blind, the interim analysis will be performed by an external statistician. Outputs will be presented by HIV infection status and treatment group without treatment unblinding (A/B) and with no individual unblinding.

The following endpoints will be analyzed for the interim analysis:

- Occurrence and intensity of solicited local symptoms within seven days (Days 0 - 6).
- Occurrence, intensity and relationship to vaccination of solicited general symptoms within seven days (Days 0 - 6).
- Occurrence, intensity and relationship to vaccination of unsolicited symptoms within 30 days (Days 0 - 29).
- Occurrence of SAEs.
- Occurrence of medically significant conditions (including pIMDs).
- Occurrence of NOCD and NOAD.
- Occurrence of clinically relevant abnormalities in hematological and biochemical parameters.
- CD4 cell count.
- HIV viral load.
- HIV clinical staging.

10.7. Statistical methods

10.7.1. Analysis of demographics/baseline characteristics

Demographic characteristics (age, race, height and weight) of each study cohort will be tabulated. They will be presented for all subjects enrolled as a whole and by treatment group.

The distribution of subjects enrolled among the study sites will be tabulated as a whole and per treatment group.

Cohorts for analysis and withdrawal status will be summarized per treatment group.

The HIV mode of transmission, WHO clinical staging, HIV viral load, CD4 cell count and ARV use of the subjects at baseline will be presented as a whole and by treatment group.

10.7.2. Analysis of safety

The primary analysis will be performed on the Total Vaccinated cohort. A second analysis based on the ATP cohort for safety will be performed to complement the Total Vaccinated cohort analysis.

The following analyses will be done on HIV+ subjects (primary objectives) and on HIV- subjects (secondary objectives).

The percentage of subjects with at least one local solicited AE, with at least one general solicited AE and with any solicited AE during the solicited follow-up period (Days 0 – 6) will be tabulated with exact 95% CI after each vaccine dose and overall. The percentage of doses followed by at least one local solicited AE, by at least one general solicited AE and by any solicited AE will be tabulated, over the whole vaccination course, with exact 95% CI. The same calculations will be performed for grade 3 solicited AEs, solicited AEs related to vaccination and grade 3 solicited AEs related to vaccination.

The percentage of subjects with at least one local (solicited or unsolicited) AE, with at least one general (solicited or unsolicited) AE and with any (solicited or unsolicited) AE during the 30-day follow-up period (Days 0 - 29) will be tabulated with exact 95% CI after each vaccine dose and overall. The percentage of doses followed by at least one local (solicited or unsolicited) AE, by at least one general (solicited or unsolicited) AE and by any (solicited or unsolicited) AE will be tabulated, over the whole vaccination course, with exact 95% CI. The same calculations will be performed for grade 3 solicited and unsolicited AEs, solicited and unsolicited AEs related to vaccination and grade 3 solicited and unsolicited AEs related to vaccination.

The percentage of subjects reporting each individual solicited local and general AE during the solicited follow-up period will be tabulated with exact 95% CI. The percentage of doses followed by each individual solicited local and general AE will be tabulated, per dose and over the whole vaccination course, with exact 95% CI. For all solicited symptoms, the same calculations will be performed for grade 3 AEs and for AEs with relationship to vaccination (general symptoms only) and for grade 3 AEs related to vaccination (general symptoms only).

The median duration of solicited local and general symptoms during the solicited follow-up period will be tabulated. The same tabulation will be performed for grade 3 solicited symptoms. The number of solicited local and general symptoms ongoing beyond the 7-day follow-up period, together with the time to resolution will be described in detail.

The proportion of subjects with at least one report of a medically significant condition classified by MedDRA, whenever available, and reported from first vaccination up to 12 months after the last vaccine dose (i.e., Month 18) will be tabulated with exact 95% CI.

The proportion of subjects with at least one report of a pIMDs reported up to 12 months after the last vaccine dose (i.e., Month 18) will be tabulated with exact 95% CI.

SAEs, withdrawal due to AE(s) and pregnancy outcomes will be described in detail.

The proportion of subjects who started to receive at least one concomitant medication (as defined in Section 6.6) during the entire study period will be calculated with 95% CI. The use of antipyretics will also be reported.

Hematology and biochemistry analysis will include any abnormal values of creatinine, ALT, hematocrit, hemoglobin, white and red blood cells and differential platelets. The percentage of subjects outside the normal ranges for each relevant time point will be calculated.

In HIV+ subjects, CD4 cell counts, HIV viral load, WHO HIV clinical staging and the use of ARVs will be tabulated for each time point when data is available. Variation of CD4 cell counts, HIV viral load and use of ARVs at each time point with respect to the baseline value (Day 0) will also be described.

The safety analysis will also be performed according to CD4 cell counts at baseline, and for HIV+ subjects, by HAART/non-HAART category.

10.7.2.1. Planned safety interim analysis

Once safety data collected on the first 60 subjects (30 HIV+ and 30 HIV-), an interim analysis of safety data will be performed per blinded group (AxBxC tables) on data as clean as possible.

The percentage of subjects reporting each individual solicited local and general AEs during the solicited follow-up period (Days 0 – 6) following Dose 1 will be tabulated with exact 95% CI.

The same tabulation will be performed for Grade 3 AEs, for AEs with relationship to vaccination (general symptoms only) and for Grade 3 AEs related to vaccination (general symptoms only).

The proportion of subjects with at least one report of unsolicited AE classified by MedDRA, whenever available, and reported up to 30 days (Days 0 – 29) after vaccination will be tabulated with exact 95% CI. The same tabulation will be performed for Grade 3 unsolicited AEs and for unsolicited AEs with a relationship to vaccination.

The proportion of subjects with at least one report of a medically significant condition classified by MedDRA, whenever available, and reported up to Visit 2 (Week 6) will be tabulated with exact 95% CI.

The proportion of subjects with at least one report of a pIMD will be reported up to Visit 2 (Week 6) and will be tabulated with exact 95% CI.

The proportion of subjects with at least one report of NOCD (investigator assessment and GSK assessment) classified by MedDRA, whenever available, and reported up to Visit 2 (Week 6) will be tabulated with exact 95% CI.

The proportion of subjects with at least one report of NOAD (GSK assessment) classified by MedDRA, whenever available, and reported up to Visit 2 (Week 6) will be tabulated with exact 95% CI.

SAEs and withdrawal due to AE(s) will be described in detail.

Hematology and biochemistry analysis will include any abnormal values of creatinine, ALT, hematocrit, hemoglobin, red blood cells, platelets and white blood cells. The percentage of subjects outside the normal ranges will be calculated.

In HIV+ subjects, CD4 counts, HIV viral load, WHO HIV Clinical Stage and use of ARVs will be tabulated (descriptive statistics) when data is available. Variation of CD4 counts and HIV viral load with respect to baseline value (Day 0) will also be described. Variation of the use of ARVs with respect to baseline value (Day 0) will also be described.

10.7.3. Analysis of immunogenicity

10.7.3.1. Between-group assessment

Primary and secondary between-group comparisons to assess non-inferiority will be done on the ATP cohort for immunogenicity (by PBNA, regardless of HPV serostatus at baseline) for the antigen under analysis. A second analysis on Total Vaccinated cohort will be performed to support the primary analysis.

Primary and secondary between-group comparisons to assess superiority will be performed on the Total Vaccinated cohort (by PBNA; regardless of HPV serostatus at baseline). A second analysis on ATP cohort for immunogenicity will be performed to support the primary analysis.

Two-sided 95% CIs of anti-HPV-16 and anti-HPV-18 GMT ratios (*Cervarix* over *Gardasil*), at Month 7, will be computed using an ANOVA model on the $\log_{10}$ transformation of the titers for HIV+ subjects (primary objective) and for HIV- subjects (secondary objectives). The ANOVA model will include the vaccine group as fixed effect. A second model will be fitted with the CD4 cell count and the interaction vaccine group by CD4 cell count as covariates. The objective of this second model will be to explore the interaction effect between the vaccine group and the CD4 cell count.

If the lower limits of the two-sided 95% for both ratios of GMTs (*Cervarix* over *Gardasil*, type 16 and 18 antigens) are above 0.5, non-inferiority of *Cervarix* to *Gardasil* will be shown.

If the lower limit of the two-sided 95% for the ratio of GMTs (*Cervarix* over *Gardasil*) is above 1 for one antigen, superiority will be shown and the p-value associated with a test of superiority will be calculated.

10.7.3.2. Within-group assessment

The within-group comparisons will be performed on the ATP cohort for analysis of immunogenicity. A second analysis based on the Total Vaccinated cohort will be performed to complement the ATP analysis.

PBNA and ELISA

For each group, at each time point with a blood sample result available (Months 0 and 7 for PBNA; Day 0, Week 6, Week 10, Months 7, 12, 18 and 24 for ELISA), the following analyses will be conducted:

- Seroconversion and seropositivity rates for each antigen (with exact 95% CI) per pre-vaccination status.
- GMTs with 95% CI and range for antibodies for each antigen per pre-vaccination status.
- The distribution of antibody titers for each antigen using reverse cumulative distribution curves.

The following analyses will be performed as exploratory objectives in HIV+ subjects for each time point with a blood sample result available (Day 0, Week 6, Week 10, Months 7, 12, 18 and 24; ELISA):

- Seroconversion and seropositivity rates along with GMTs with 95% CI stratified by HIV mode of transmission, if sufficient data are available;
- Seroconversion and seropositivity rates along with GMTs with 95% CI stratified by nadir CD4 cell count category, if sufficient data are available. The categories for nadir CD4 cell count will be defined in the Report Analysis Plan.

CVS

In addition, in a subset of volunteers that provided cervical samples (Day 0, Week 6, Week 10, Months 7, 12 and 24; ELISA), the following analyses will be performed:

- Seropositivity rates for each antigen (with exact 95% CI) per pre-vaccination status.
- GMTs with 95% CI and range for antibodies for each antigen per pre-vaccination status.
- Correlation with serum antibody titers.

Note: These analyses will be performed on samples where the Hemastix test showed less than 200 erythrocytes per μL (ery/μL).

CMI

In addition, in a subset of approximately 100 subjects from selected countries (Day 0, Week 6, Week 10, Months 7 and 12; T cell by intracellular cytokine staining [ICS]; B cell by ELISPOT), the following analyses will be performed:

CD4/CD8 T cell response by ICS (IntraCellular Cytokine Staining)

Frequency of cytokines-positive (d-CD40L, d-IL2, d-TNFα, d-IFNγ or all doubles) CD4 or CD8 T cells, for each stimulant (HPV-16 and HPV-18) at each time point (Day 0, Week 6, Week 10, Months 7 and 12) will be summarized for each group by the number of values (N), the number of missing values, minimum, 1st quartile, median, 3rd quartile, maximum and geometric mean (Gmean).

Further, for each test and for each stimulant (HPV-16 and HPV-18) at each time point, the number and percentage of subjects above a defined threshold will be calculated.

This threshold will be determined on the basis of 95^{th} percentile of frequency of CD4 or CD8 all doubles stimulated by HPV-16 or HPV-18 antigen at Day 0 for HPV-negative subjects. In addition, threshold will be checked separately for HIV- and HIV+ subjects.

For CD4 T cell response, the same tabulations will be performed according to the type specific HPV serological status before vaccination.

The same tabulations will be performed on HIV+ subjects for each time point according to CD4 count (level/mm^3), HIV viral load (copies/mL), and ARV use.

B cell response by ELISPOT

The results of each stimulant (HPV-16 and HPV-18) at each time point (Day 0, Week 6, Week 10, Months 7 and 12) will be summarized for each group by the number of values (N), the number of missing values, minimum, 1st quartile, median, 3rd quartile, maximum and geometric mean (Gmean). Values of 0 will be given an arbitrary value of 1 for the purpose of geometric mean calculation.

Further, for each stimulant (HPV-16 and HPV-18) the number and percentage of subjects above 0 will be calculated.

The same tabulations will be performed on subjects according to the type specific HPV serological status before vaccination.

The same tabulations will be performed on HIV+ subjects for each time point according to CD4 count (level/mm^3), HIV viral load (copies/mL), ARV use.

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

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 clinical 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. Ownership, confidentiality and publication

11.5.1. 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.

11.5.2. 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.

11.5.3. Publication

For multicenter studies, the first publication or disclosure of study results shall be a complete, joint multicenter 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.

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WHO Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/. Accessed on 26 April 2016.

APPENDIX A LABORATORY ASSAYS

Pseudovirion-based neutralization assay

The pseudo-neutralization assay was developed by Pastrana *et al* [Pastrana, 2004]. Briefly, pseudovirions are produced by co-transfecting human embryonic kidney cells expressing SV40 T antigen (293TT) with plasmids coding for HPV-16 or -18 L1 gene, HPV-16 or -18 L2 gene and a secreted alkaline phosphatase gene (SeAP). Two days post transfection, cells are lysed and the pseudovirions containing the SeAP reporter gene are purified by ultracentrifugation on iodixanol (OptiPrep) gradient.

To measure neutralizing titers, serial 4-fold serum dilutions are incubated with a fixed amount of purified HPV pseudovirions. The mixture is then added to a monolayer of 293TT cells and incubated for 3 days. The expression level of the SeAP is measured in the culture medium and is proportional to the amount of pseudovirions able to infect cells and so, inversely proportional to the amount of neutralizing antibody present in the serum. Neutralizing titers are expressed as the serum dilution leading to 50% reduction of the SeAP activity.

Antibody extraction from CVS samples

Briefly, each spear is weighed to estimate the volume of secretions absorbed by the sponge by subtracting the weight of the dry spear. CVS samples weighing less than 10 mg are excluded. The spear is placed in a centrifugation tube containing a filter unit (Spin-x centrifuge filter unit, Costar, Cambridge, Mass.) and the sample is extracted by washing the spear twice with 300 µl of extraction buffer.

The concentration of erythrocytes is measured by the Hemastix® test (Siemens Medical Solutions Diagnostics Europe Ltd., Dublin, Ireland) which is based on the peroxidase activity of hemoglobin. An aliquot of extracted sample is dispensed onto the Hemastix® strip test end. After 1 minute, the colour of the test pad is matched to the colour chart on the bottle label. Results are expressed as 0, 10, 25, 80 or 200 erythrocytes per µL. CVS samples showing 200 erythrocytes per µL are excluded for antibody assessment. Then 4 µL of foetal bovine serum are added in the sample to stabilize the proteins and the final volume of CVS extracted sample is measured. A dilution factor is calculated based on the estimated volume and dry weight of the spear as $[(x\text{-}y)+v]/(x\text{-}y)$, where x equals the weight of the spear after collection, y is the mean weight of 20 dry spears weighed separately and v is the final volume of sample measured after extraction.

Anti-HPV-16 and anti-HPV-18 for serum and CVS samples (ELISA)

Quantitation of antibodies to HPV-16 and HPV-18 VLPs will be performed by ELISA. These immunoassays are based on the direct test principle. Purified VLPs are coated onto a 96-well microtitration plate. After a washing and saturation step, serial dilutions of samples, control sera and standards are distributed and incubated in the coated wells to allow the specific antibody present in the sample to react with the corresponding antigen. Non-specific reactants are removed by washing and a peroxidase-conjugated anti-human polyclonal antibody is added to react with the specific antibody. Excess conjugate is

removed by washing. Enzyme substrate and chromogen (trimethyl benzindine and hydrogen peroxide) are added and the colour is allowed to develop. After adding the Stop Reagent, the resultant colour change is quantified and expressed in ELISA units per milliliter (EL.U/mL). The intensity of the resultant yellow colour is directly proportional to the concentration of anti-VLP antibody present in the sample. For CVS samples, the final antibody titer is multiplied by the dilution factor obtained during the antibody extraction step of the CVS.

Titers are calculated by reference to a standard serum using the 4-parameters equation for each sample dilution, and the final titer of a sample is the average of all titers falling in the proportional part of the reference curve.

Total Human IgG ELISA

The hIgG assay is a two-site immunoenzymetric assay. Affinity purified anti-hIgG antibodies are coated onto a 96-wells microplate. After a washing and a blocking step, dilutions of CVS samples, control and standard are incubated on the plate. The microplate is washed and HRP (HorseRadishPeroxidase)-conjugated anti-human IgG polyclonal antibodies are added. After incubation, unbound antibodies are removed by washing and TMB (TetraMethylBenzidine) is incubated to reveal the enzyme activity. Colour reaction is stopped by addition of sulphuric acid and the resulting yellow colour is measured spectrophotometrically.

The intensity of the colour is directly proportional to the concentration of the hIgG present in the sample.

Titers are calculated from a reference standard curve using a 4 parameters logistic fitting algorithm and expressed in µg/mL.

Total Human IgG by nephelometry assay in serum

Total human IgG in serum will be measured by the nephelometric method using the BNII fully automated system from Siemens. This test is used in medical laboratories and considered as being the gold standard for plasma protein analysis.

Polystyrene particles coated with antibodies directed against human IgG will agglutinate when mixed with diluted human samples containing human IgG. The intensity of the scattered light in the nephelometer will depend on the concentration of the IgG in the sample and consequently its concentration will be determined by comparison with dilutions of a standard of known concentration

Cell mediated immune (CMI) response assays

IntraCellular cytokine assay

The CMI response is assessed by GSK Biologicals, or a designated laboratory, on thawed peripheral blood mononuclear cells (PBMCs) by intracellular cytokine staining. This assay provides information on the frequency of CD4 and CD8 T cells responding to the

antigen and producing secreted molecules involved in immunity; such as IFN-γ, IL-2, TNF-α, and CD40-L.

Briefly, the subjects PBMCs are stimulated for 2 hours with a pool of overlapping peptides covering the entire sequence of the vaccine antigen or the protein antigen. An intracellular block (Brefeldin A) is then added to inhibit cytokine secretion for a subsequent overnight stimulation. Cells are then harvested, stained for surface markers (CD4 and CD8) and fixed. Fixed cells are permeabilized and stained with anti-cytokine-specific antibodies, washed and analyzed by flow cytometry.

Results will be expressed as frequency of cytokine(s)-positive CD4 or CD8 T cells within the CD4 or CD8 T cell subpopulation.

Extra analyses, not described in the protocol, related to the immune response to HPV vaccination might be performed if deemed necessary.

B cell ELISPOT assay

The B Cell ELISPOT technology allows the quantification of memory B cells specific to a given antigen.

The method is adapted from the assay developed by Crotty and collaborators [Crotty, 2004]. PBMC are differentiated into antibody secreting cells and incubated into nitro-plates coated with either the antigen of interest (for the detection of antigen-specific memory B cells) or anti-human Ig (for the detection of total memory B cells). A conventional immuno-enzymatic procedure [Crotty, 2004] is applied to detect antibody/antigen spots enumerating memory B cells. The results are expressed as the frequencies of antigen-specific memory B cells within the total memory B cell population.

Biochemistry and Hematology

These measurements will be performed using standard laboratory methods. The protocols and normal values of these tests will be recorded by each laboratory before the study center can start.

The description of the methodologies used as well as the normal laboratory values will be provided to GSK Biologicals before the study starts for appropriate documentation into the study files.

APPENDIX B GSK VACCINES CONTAINING MPL

- Human Papillomavirus vaccine
  - HPV-16/18 L1 VLP AS04 vaccine
  - HPV-31/45 L1 VLP AS04 vaccine
  - HPV-16/18/31/45 L1 VLP AS04 vaccine
- Herpes Simplex 2 Virus vaccine
- Hepatitis B Adjuvanted vaccine (Fendrix™)
- Malaria vaccine
  - RTS, S MPL
  - RTS, S AS02A
  - RTS, S AS01B
- Influenza adjuvanted vaccine
- Henogen adjuvanted hepatitis B vaccine (HB-AS02V)
- Hepatitis A and B MPL adjuvanted vaccine
- Varicella Zoster vaccine
- Human Immunodeficiency Virus vaccine
- Streptococcal pneumonia for elderly vaccine
- Tuberculosis vaccine
- Epstein Barr virus vaccine
- Cytomegalovirus vaccine
- Respiratory Syncytial Virus vaccine
- Human Papillomavirus vaccine Next Generation (4 or more HPV types including HPV-16/18/33/58)
- Therapeutic vaccines (HBV, GW, HIV and HSV)
- ASCI cancer vaccines (MAGE-A3, dHER2, CPC-P501)
- MPL- containing biologicals developed by Corixa (including studies with Detox)

Note: Apart from Fendrix™, all the products listed are in development and not licensed anywhere. Fendrix™ is not licensed in the countries where the study will take place.

APPENDIX C AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment 1**	
eTrack study number(s) and Abbreviated Title(s)	109823 (HPV-019 PRI)
Amendment number:	Amendment 1
Amendment date:	20 April 2010
Co-ordinating author:	PPD

Rationale/background for changes:
The main reason for amending this protocol is that, since the last revision of the WHO guidelines in 2006, new and compelling evidence has become available concerning the start of antiretroviral therapy (ART) in HIV-infected adults and adolescents. Subjects who have a CD4 count ≤ 350 cells/mm^3 should now be treated irrespective of their clinical stage [WHO, 2009].

Some clarifications have been made to the flowchart, weight and ARV therapy (if applicable) will be recorded at each visit. Also, a history-directed physical examination will be performed at each visit.

Section 6.2 (Storage and handling of study vaccines) has been modified in order to align the wording with the new version of SOP-BIO-CLIN-7055 v04 entitled "Management of the Cold Chain for GlaxoSmithKline Biologicals investigational human subject research" effective since 31 March 2010.

Facsimile numbers for prompting SAEs to GSK Biologicals have been updated as well as the phone numbers in case of emergency unblinding.

Minor corrections such as inconsistencies, formatting and typos have been made.

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

Title page (Coordinating author):

The following coordinating author has been added:

PPD **, *Scientific Writer***

Title page (Contributing authors):

The following contributing authors have been added:

PPD ***, Clinical Development Director***

PPD ***, Clinical Development Manager***

PPD ***, Clinical Data Coordinator***

PPD ***Regulatory Affairs***

Synopsis: Study design:

In **Part A**, a subset of 60 subjects aged 18 - 25 years (30 HIV+ and 30 HIV- subjects) ~~in one country~~ will be vaccinated (Dose 1) and evaluated for safety before proceeding with the enrollment and vaccination of the remaining subjects (**Part B**; 540 subjects).

List of abbreviations:

HAART: Highly Active AntiRetroviral Therapy

Section 1. Introduction

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]). To date, more than 30,000 adolescent and adult females aged 10 years and above have received at least one dose of the vaccine. The results of a pooled safety analysis of approximately ***30,000*** ~~39,000~~ girls and women aged 10 years and above, of whom 16,142 received at least one dose of HPV vaccine, have shown that the vaccine is generally safe and well tolerated [Descamps, 2009].

Section 3. Study design overview

In **Part A**, a subset of 60 subjects aged 18 - 25 years (30 HIV+ and 30 HIV- subjects) ~~in one country~~ will be vaccinated (Dose 1) and evaluated for safety before proceeding with the enrollment and vaccination of the remaining subjects (**Part B**; 540 subjects) (see Figure 2).

Section 4.1. Number of subjects/centers

Table 1 Sub-cohorts

Sub-cohort name	Description	Estimated number of subjects
HIV+ sub-cohort (safety)	Assessment of CD4 cell count, HIV viral load, antiretroviral (ARV) treatment and HIV clinical stage	300
CMI sub-cohort* (immunogenicity)	Assessment of B cells and T cells response	100
CVS sub-cohort (immunogenicity)	Measure of Immunoglobulin G (IgG) titers	Post-menarcheal subjects who volunteer for this procedure

*CMI will be done in selected countries.

Section 4.2. Inclusion criteria

- For HIV seropositive subjects:
  - Subjects must be HIV seropositive according to World Health Organization (WHO) case definition, i.e., positive HIV antibody testing (rapid or laboratory-based enzyme immunoassay, confirmed by a second HIV antibody test relying on different antigens or of different operating characteristics and/or positive virological test for HIV or its components such as HIV-ribonucleic acid [RNA], HIV-DNA or ultrasensitive HIV P24 antigen). [WHO, 2006]
  - ~~Subjects with WHO Clinical Stage 1 HIV-associated disease (i.e., asymptomatic and/or persistent generalized lymphadenopathy) are eligible to participate in the study. Subjects with WHO Clinical Stage 2 or worse HIV-associated disease are not eligible to participate to the study.~~
  - ***Regardless of their prior clinical stage, subject must be asymptomatic (or only have persistent generalized lymphadenopathy).***
  - ***If not on triple therapy (highly active antiretroviral therapy [HAART]), subjects should have a CD4 cell count > 350 cells/mm^3.***
  - ***If currently taking antiretrovirals (ARVs), subjects must be on HAART for at least one year, have undetectable viral load (i.e., viral load ≤ 400 copies/mm^3) for at least six months, and have a CD4 cell count > 350 cells/mm^3 at study entry.*** ~~Subjects currently on antiretroviral therapy (ART) must be compliant to ART and have undetectable viral load (i.e., viral load ≤ 400 copies/mm^3 during the last six months). However, it is not necessary for subjects to be on treatment if clinically they do not reach the local criteria to indicate treatment, i.e., the subjects should be compliant to the local standard of care.~~

Section 4.3. Exclusion criteria for enrollment

- Current TB ~~prophylaxis or~~ therapy.

Section 5.2.2.2. Treatment allocation to the subject

In addition, HIV+ subjects will be randomized according to their baseline CD4 cell count (***350 cells/mm^3 ≤ CD4 count ≤ 500 cells/mm^3 or CD4 count > 500 cells/mm^3*** ~~> 500 cells/mm^3; 500 cells/mm^3 ≤ CD4 count ≥ 200 cells/mm^3; < 200 cells/mm^3~~) and ***the fact they are on HAART or not (HAART/non-HAART).*** The randomization algorithm for HIV+ subjects will use a minimization procedure accounting for CD4 cell count ***and HAART***.

When a subject has provided informed consent and is confirmed as eligible, the person in charge of the vaccination will access SBIR. Upon providing the subject's identification number, the dose, the country, her HIV infection status and age, the randomization system will either allocate a treatment number for HIV- subjects or ask for the baseline CD4 cell count ***and HAART/non-HAART*** of the HIV+ subjects and then allocate a treatment number. The allocation of the treatment number (*Gardasil* or *Cervarix*) will follow a ratio 1:1.

The first 60 subjects (30 HIV- and 30 HIV+ subjects) to be enrolled in the study will have to be between 18 and 25 years old. Treatment numbers will be allocated by SBIR accounting for country, HIV infection status and, for HIV+ subjects, baseline CD4 cell count ***and HAART/non-HAART***. Once 30 HIV+ subjects and 30 HIV- subjects have been enrolled, SBIR will be locked and enrolment suspended until results from the Week 6 interim safety analysis on these subjects are available. Once the results have been reviewed by the GSK safety review team and the IDMC, enrollment will be initiated for the remaining subjects (within six weeks after availability of the safety results).

Section 5.4.2. Staggered vaccination process

In Part A, a subset of 60 subjects aged 18 – 25 years (30 HIV+ and 30 HIV- subjects) ~~in one country~~ will be vaccinated (Dose 1) and evaluated for safety before proceeding with the enrollment and vaccination of the remaining subjects (**Part B**; 540 subjects) (see Figure 2). Administration of Dose 2 to these subjects in Part A will not depend on the outcome of the safety evaluation unless there are specific safety concerns for an individual subject or if requested by the IDMC or Vaccine Safety Monitoring Board (VSMB).

- CD4 cell count, HIV viral load, ***ARV status and*** the HIV clinical stage of each individual subject (for HIV+ subjects only).

Section 5.4.4. Counseling for HIV, sexual transmitted infection and disease prevention and birth control

At the screening visit, prior to HIV testing, counseling will be provided to the potential participant by trained study personnel. Counseling will also be provided by a trained counselor once results of HIV testing are available, regardless of the test result. Subjects will be informed of their HIV results ***as soon as they are available*** ~~at the next visit (Visit 1)~~.

Section 5.4.5. Follow-up of HIV positive subjects in the study

Since the WHO last guideline revision in 2006, new and compelling evidence has become available, particularly concerning the earlier start of ART. Subjects who have a CD4 cell count ≤ 350 cells/mm^3 should be treated irrespective of their clinical stage [WHO, 2009].

Subjects eligible for ART at any time ***at Screening or*** after enrollment will be referred to the local Primary Health Care HIV Clinic which will give them access to medical care according to the local standard of care. A referral letter to ARV Center will be provided to each subject who needs to be referred and assurance will be taken that each subject has been properly referred (appointment, transportation, follow-up).

Section 5.5. Outline of study procedures

Epoch	SCREENING	ACTIVE PHASE OF THE STUDY					IMMUNOGENICITY AND SAFETY FOLLOW-UP		
Visit	SCREENING VISIT	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7	VISIT 8
Timing	Up to 90 days	Day 0	Week 6	Week 10	Month 6	Month 7	Month 12	Month 18	Month 24
Sampling time point	Screening	Pre-vacc	Post-vacc I	Post-vacc II	Post-vacc II	Post-vacc III	Post-vacc III	Post-vacc III	Post-vacc III
Collect demographic data									
age, race, height	●								
weight	●	●	●	●	●	●	●	●	●
History-directed physical examination	●	●	●	●	●	●	●	●	●
Specific procedures for HIV+ subjects									
Record Nadir CD4 (if applicable)	●								
Record ARV therapy (if applicable)	●	●	●	●	●	●	●	●	●

The double-line border following Visit 1 indicates the interim analysis which will be performed on the 6-week post-vaccination 1 data collected in a subset of approximately 60 subjects (30 HIV+ and 30 HIV- subjects) ~~in one country~~. The triple-line border following Month 7 indicates the analysis which will be performed on all data obtained after all subjects have completed Visit 5 (Month 7). A final report will be written after all results are available. ***The dotted-line border following Months 12, 18 and 24 indicate analyses which will be performed on all data obtained after all subjects have completed Visit 6 (Month 12), Visit 7(Month 18) and Visit 8 (Month 24), respectively; these results will be reported in annex reports.*** ~~The results of the analyses conducted on the data collected up to Month 12, 18 and 24 will be reported in annex reports.~~

Section 5.6.2.3. History-directed physical examination

For HIV+ subjects only, question subjects about their medical history, including gynecological history and medical records of HIV history (date of diagnosis of HIV infection and mode of contamination). ***An HIV/AIDS WHO clinical staging will be performed. If applicable, nadir CD4 cells/mm^3 and the subject's ARV therapy will be recorded.***

Section 5.6.2.6. Blood sampling for HIV testing and safety

- ~~An HIV/AIDS WHO clinical staging will be performed.~~

Section 5.6.3. Procedures during active phase of the study (Visit 1 – Visit 5)

Note that some of the procedures to be performed during the active phase of the study (such as ***a history-directed physical examination,*** counseling for STD and STI prevention and birth control, blood sampling for determination of CD4 cell count and HIV viral load in HIV+ subjects, HIV/AIDS clinical staging in HIV+ subjects, urine pregnancy test, check and record concomitant medication/vaccination, ***ARV therapy (if applicable) and weight***, and check of in/exclusion criteria) are also performed at screening and are described in Section 5.6.2.

Section 5.6.3.4. Blood sampling for safety or immune response assessments

- A volume of at least 10 mL of whole blood should be drawn from all subjects for evaluation of hematological and biochemical parameters. ~~After centrifugation, serum samples should be kept at - 20°C until shipment.~~

Section 5.6.3.9. Conclusion of the active phase of the study

An interim safety evaluation will be performed on the 6-week post-vaccination 1 data collected in a subset of approximately 60 subjects (30 HIV+ and 30 HIV- subjects) ~~in one country~~ before proceeding with the vaccination of the remaining subjects (see Section 5.4.2).

Section 5.6.4. Procedures during immunogenicity and safety follow-up (Visit 6 – Visit 8)

The immunogenicity and safety follow-up period includes Visit 6, 7 and 8. Note that all of the procedures to be performed during the follow-up period (such as ***a history-directed physical examination,*** blood sampling, checking elimination criteria, counseling for HIV, STD and STI prevention and birth control, recording of concomitant medication/vaccination, ***ARV therapy (if applicable), weight***, SAEs, medically significant conditions, NOCDs, NOADs and pregnancies) are also performed during the active phase of the study and are described in Section 5.6.3.

Section 6.2 Storage and handling of study vaccines

Any temperature deviation, i.e., temperature outside the ~~defined~~ range (~~2~~ ***0***°C - 8°C or ***above*** ~~-20~~ ***-15***°C ~~of storage~~), must be reported to the Sponsor as soon as detected. Following an exposure to a temperature deviation, vaccines will not be used until written approval has been given by the Sponsor.

Adequate actions must be taken in case of temperature deviation between 0 and +2°C to go back to the defined range +2 to +8°C. The impacted study vaccines can still be administered, but the site should avoid re-occurrence of temperature deviation.

Section 6.4. Replacement of unusable vaccine doses

In addition to the vaccine doses provided for the planned number of subjects (including over-randomization), at least 5% additional doses will be supplied to replace those that are unusable. In case a vaccine dose is broken or unusable, the investigator should replace it with ~~a replacement~~ ***another*** vaccine dose. Although the Sponsor needs not be notified immediately in these cases (except in the case of cold-chain failure), documentation of the use of ~~the replacement~~ ***another*** vaccine ***dose*** must be recorded by the investigator on the vaccine administration page of the eCRF and on the vaccine accountability form.

The investigator will use the central randomization system (SBIR) to obtain the ~~replacement~~ vial number. The system will ensure, in a blinded manner, that the ~~replacement~~ vial is of the same formulation as the randomized vaccine.

Section 6.5. Contraindications to subsequent vaccination

- Evolution to ***worst*** WHO Clinical Stage 2, 3 or 4 of the HIV-associated disease during the study.

Section 6.6.1. Medications/products that may lead to the elimination of a subject from ATP analyses

- ***Switch in ART due to treatment failure.*** ~~ARV therapy that is not stable during the study (i.e., subjects not compliant with ARV or with HIV viral load > 400 copies/mm^3 at any time during the study before Month 7).~~

Section 6.7. Intercurrent medical conditions leading to elimination from an ATP cohort

- For HIV+ subjects: any newly diagnosed immuno-suppressive conditions other than HIV, ***and/or HIV/AIDS treatment failure***.

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

Table 15 Reporting periods for adverse events, serious adverse events and pregnancies

Study activity	Pre-V1*	V1 D0	30 d post-V1 D30	V2 W6	30 d post-V2 W10	V3 M6	30 d post-V3 M7	Study conclusion
Reporting of AEs**								
Reporting of medically significant conditions, NOCDs and NOADs								
Reporting of SAEs and pregnancies								
Reporting SAEs related to study participation or GSK concomitant products or any fatal SAE								

* i.e. consent obtained. Pre-V: pre-vaccination; V: vaccination; Post-V: post-vaccination; D: day; W: week; M: month

***** Solicited AEs within 7 days after each vaccination; unsolicited AEs within 30 days after each vaccination.***

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

Back-up Study Contact for Reporting SAEs
GSK Biologicals Clinical Safety ~~Physician~~ & Pharmacovigilance ***Fax:*** +PPD ***or*** +PPD ~~Tel: +PPD~~ ~~Fax: +PPD or +PPD~~ ~~Mobile phones for 7/7 day availability:~~ ~~+PPD (Head Safety Evaluation and Risk Management Adult/Adolescent/Emerging Diseases)~~ ~~Back-up mobile phone contact:~~ ~~+PPD~~ **~~24/24 hour and 7/7 day availability~~**

Section 8.7. Emergency unblinding

~~The investigator/delegate must instruct study subjects to carry a card (or equivalent) at all times during the study in order to facilitate unblinding in the event of a medical emergency managed by a physician other than the investigator/investigational site staff.~~

GSK Biologicals Central Safety Physician (Study Contact for Emergency Code Break)
Mobile phones for 7/7 day availability: ***Outside US/Canada:*** +PPD ***(GSK Biologicals Central Safety Physician)*** ***Back-up mobile phone contact (all countries):*** +PPD
~~Tel: +PPD~~ ~~Fax: +PPD or +PPD~~ ~~Mobile phones for 7/7 day availability:~~ ~~+PPD (Head Safety Evaluation and Risk Management Adult/Adolescent/Emerging Diseases)~~ ~~Back-up mobile phone contact:~~ ~~+PPD~~

Section 10.5 Derived and transformed data

- ***The GMT calculations for CVS samples are calculated on positive CVS samples only.***

Section 10.6.1. Sequence of analyses

An interim analysis will be performed on the 6-week post-dose 1 vaccination data in a subset of approximately 60 subjects (30 HIV+ and 30 HIV- subjects) ~~in one country~~. No clinical study report will be written at this stage.

Section 10.7.2. Analysis of safety

Hematology and biochemistry analysis will include any abnormal values of creatinine, ALT, hematocrit, ***hemoglobin,*** white and red blood cells and differential platelets. The percentage of subjects outside the normal ranges for each relevant time point will be calculated.

The safety analysis will also be performed according to CD4 cell counts at baseline***, and for HIV+ subjects, by HAART/non-HAART category.***

Section 10.7.2.1 Planned safety interim analysis

Hematology and biochemistry analysis will include any abnormal values of creatinine, ALT, hematocrit, ***hemoglobin,*** red blood cells, platelets and white blood cells. The percentage of subjects outside the normal ranges will be calculated.

Section 12. References

WHO Rapid Advice - Antiretroviral therapy for HIV infection in adults and adolescents. World Health Organization 2009. November 2009.

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Administrative Change 1**	
eTrack study number and Abbreviated Title	109823 (HPV-019)
Administrative change number:	Administrative Change 1
Administrative change date:	20 July 2010
Co-ordinating author:	PPD

Rationale/background for changes:

- Update of the list of co-ordinating authors for this administrative change
- The contact details for reporting of the emergency code break have been clarified. As of now new phone numbers (two for the US /Canada & two for the rest of the world) will be used for the safety contact for code break (emergency unblinding) depending on the region the study is conducted.

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

Cover page

Coordinating author PPD, Scientific Writer

Section 8.7: Emergency unblinding

GSK Biologicals Central Safety Physician **(Study Contact for Emergency Code Break)(**
~~Mobile phones~~ ***Phones*** for 7/7 day availability: Outside US/Canada: ~~+~~PPD + F F(GSK Biologicals Central Safety Physician ***on-call***) Back-up ~~mobile~~ phone contact (~~all countries~~): ~~+~~PPD ***Outside US/Canada:*** PPD

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment 2**	
eTrack study number(s) and Abbreviated Title(s)	109823 (HPV-019 PRI)
Amendment number:	Amendment 2
Amendment date:	23 December 2010
Co-ordinating authors:	PPD

Rationale/background for changes:

Protocol Amendment 2 was developed to:

- Implement reporting of potential immune-mediated diseases (pIMDs). 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.
- Add two additional HIV tests at Month 7 and Month 24 for HIV negative subjects.
- Update the formulation of the HPV-16/18 L1 VLP AS04 vaccine.
- Update the list of contributing authors.
- Make minor modifications/ clarifications to the protocol.

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

Title page

Contributing authors

- PPD, PPD, Clinical Development Manager***s***
- PPD**,** PPD, Clinical Safety

Synopsis

Study design

- A safety interim analysis will be performed on the 6-week post-dose 1 vaccination data from the subjects in Part A to evaluate the following parameters:
  - unsolicited symptoms, medically significant conditions (***including potential immune-mediated diseases [pIMDs]),*** new onset chronic diseases (NOCDs), new onset autoimmune diseases (NOADs) and serious adverse events (SAEs) up to Day 30 after administration of the first dose (Days 0 - 29);

Endpoints

Co-Primary:

- Occurrence of medically significant conditions (***including pIMDs)*** up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.
- ~~Occurrence of NOCDs up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.~~
- ~~Occurrence of NOADs up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.~~

Secondary

- Occurrence of medically significant conditions (***including pIMDs)*** up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV- subjects.
- ~~Occurrence of NOCDs up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV- subjects.~~
- ~~Occurrence of NOADs up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV- subjects.~~
- Occurrence of medically significant conditions ***(including pIMDs)*** ~~during the entire study period (i.e., up to Month 24)~~ ***up to 12 months after the last dose of vaccine (i.e., Month 18)*** in all subjects.
- ~~Occurrence of NOCDs during the entire study period (i.e., up to Month 24) in all subjects.~~
- ~~Occurrence of NOADs during the entire study period (i.e., up to Month 24) in all subjects.~~

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: 1. not ~~(1)~~ related to common diseases***,*** or 2. ***not related to*** ~~(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 5.4.2: Staggered vaccination process

A safety interim analysis will be performed on the 6-week post-dose 1 vaccination data from the subjects in Part A to evaluate the following parameters:

- unsolicited symptoms, medically significant conditions ***(including potential immune-mediated diseases [pIMDs]),*** new onset chronic diseases (NOCDs), new onset autoimmune diseases (NOADs) and serious adverse events (SAEs) up to Day 30 after administration of the first dose (Days 0-29); ***(***hematological and biochemical parameters;

Section 5.4. 4: Counseling for HIV, sexual transmitted infection and disease prevention and birth control

At the screening visit, prior to HIV testing, counseling will be provided to the potential participant by trained study personnel. Counseling will also be provided by a trained counselor once results of HIV testing are available, regardless of the test result. Subjects will be informed of their HIV results as soon as they are available. ***Participants in HIV negative group will be provided with additional HIV testing and counselling at month 7 and month 24.***

Section 5.5: Outline of study procedures

Table 2 List of study procedures

Epoch	SCREENING	ACTIVE PHASE OF THE STUDY					IMMUNOGENICITY AND SAFETY FOLLOW-UP		
Visit	SCREENING VISIT	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7	VISIT 8
Timing	Up to 90 days	Day 0	Week 6	Week 10	Month 6	Month 7	Month 12	Month 18	Month 24
Sampling time point	Screening	Pre-vacc	Post-vacc I	Post-vacc II	Post-vacc II	Post-vacc III	Post-vacc III	Post-vacc III	Post-vacc III
Blood sampling									
Counseling for HIV[&], STD and STI prevention and birth control	●	●	●	●	●	●	●	●	●
for HIV testing (Rapid test, 5 mL)[†]	●					●[Ω]			●[Ω]
Reporting of medically significant conditions, ***(including pIMDs)***		●	●	●	●	●	●	●	●
~~Reporting of NOCDs and NOADs~~	●	●	●	●	●	●	●	●	●

†: HIV Rapid tests used locally according to National Guideline (e.g., Determine®; First response®). If rapid test is positive, HIV confirmatory test will be performed.
Ω: HIV Rapid tests for HIV negative subjects only.
● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
&Participants in HIV negative group will be provided with additional HIV testing and counselling at month 7 and month 24.

Section 5.6.2.3: History-directed physical examination

Record the age at which the subjects had their first menstruation. Pre-menarcheal subjects will be instructed to inform ***the study personnel*** if their first menstruation occurs during the study (up to two months after the last dose of the vaccine).

Section 5.6.3.4: Blood sampling for safety or immune response assessments

- ***A volume of at least 5 mL of whole blood should be drawn from HIV negative subjects for HIV testing (Rapid test).***

  Provide pre- and post-HIV test counseling. Post-HIV test counseling can be provided as soon as HIV test result (by Rapid test) is available. Make record of this procedure in the eCRF section of the visit during which the HIV test was performed. All subjects found to be HIV-infected will be referred to the national program for medical management according to local guidelines (see Section5.4.5)

Section 5.6.3.8: Recording of non-serious AEs and SAEs

- The investigator will record any SAE, medically significant conditions (***including pIMDs),*** ~~NOCD, NOAD,~~ pregnancy and pregnancy outcome that may have occurred since the previous visit.

Section 5.6.4: Procedures during immunogenicity and safety follow-up (Visit 6 – Visit 8)

The immunogenicity and safety follow-up period includes Visit 6, 7 and 8. Note that all of the procedures to be performed during the follow-up period (such as blood sampling, checking elimination criteria, a history-directed physical examination, counseling for HIV, STD and STI prevention and birth control, recording of concomitant medication/vaccination, ARV therapy (if applicable), weight, SAEs, medically significant conditions (***including pIMDs)*** ~~NOCDs, NOADs~~ and pregnancies) are also performed during the active phase of the study and are described in Section 5.6.3 .

Section 5.7.2: Biological samples

Table 4 Biological samples

Sample type	Quantity	Unit	Time point	Subset /Sub-cohort Name*
Blood for HIV testing (Rapid test)	5	mL	Screening	All
			Month 7, Month 24	HIV- sub-cohort

Section 5.7.3: Laboratory assays

HIV Rapid test, HIV confirmatory test by ELISA, CD4 cell count and HIV viral load determination will be performed by a local laboratory. Blood samples will be drawn from all HIV+ subjects at all scheduled visits (including screening) to determine CD4 cell count (4 mL) and HIV viral load (3 mL). A blood sample of 5 mL will be drawn from all documented HIV+ subjects during screening to confirm their HIV seropositivity. ***A blood sample of 5 mL will be drawn from all HIV negative subjects during screening, at Month 7 and at Month 24 to assess their HIV serostatus.***

Section 5.7.4.1: Immunological read-outs

Table 6 Immunological read-outs

Timing	Week/ Month	Visit no.	Marker	Assay Method	No. subjects
Blood Sampling					
Post-vaccination I	Week 6	2	anti-HPV-16	ELISA	All
			anti-HPV-18	ELISA	
			Total IgG	***ELISA***	***CVS sub-cohort****

Section 5.7.4.3: Cell-mediated immune response ~~Cytology~~

The timings for ~~cytological read-outs~~ ***cell-mediated immune response (CMI) measurement*** are outlined in Table 7.

Section 6.1: Description of study vaccines

Table 8 Vaccine components

Vaccine	Formulation	Presentation	Volume	N° doses
Cervarix (GSK Biologicals)	20 µg HPV-16 L1 VLP 20 µg HPV-18 L1 VLP 50 µg MPL 500 µg aluminium in the form of $Al(OH)_3$ ***8 mM sodium dihydrogen phosphate dihydrate*** ***150 mM sodium chloride*** ***water for injection***	Liquid in pre-filled syringes	0.5 mL	3

Section 8.1.5: 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 8.1.5.1: Potential immune-mediated diseases

Potential immune-mediated diseases (pIMDs) are a subset of AEs 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 12 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.

The standard time period for collecting and recording of pIMDs will begin at the first receipt of study vaccine and will end 6 months following administration of the last vaccine dose.

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

The time period for collecting and recording of ~~***Mm***~~***edically*** significant conditions ~~occurring throughout the entire study period (up to Month 24)~~ ***will begin at the first receipt of study vaccine and will end approximately 12 months following administration of the last vaccine dose (i.e., up to Month 18). Medically significant conditions that are not considered as a pIMD*** must be recorded on the Adverse Event Form, or Serious Adverse Event form as appropriate, in the subject's eCRF, irrespective of severity or whether or not they are considered vaccination related. ~~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.~~ ***pIMDs must be recorded into the SAE screen in the subject's eCRF. See Section 8.4 for instructions on reporting and recording of pIMDs.***

Table 13 Reporting periods for adverse events, serious adverse events and pregnancies

Study activity	Pre-V1*	V1 D0	30 d post-V1 D30	V2 W6	30 d post-V2 W10	V3 M6	30 d post-V3 M7	*12 m post-V3* *M18*	Study conclusion M24
Reporting of medically significant conditions ***(including pIMDs)***									

Section 8.3.2.5: AEs of specific interest

~~AEs of specific interest for safety monitoring include NOCDs and NOADs.~~

~~Occurrences of NOCDs and NOADs will be reported during the entire study period, whether or not they are considered to be possibly related to the treatment administration. Medical documentation of the events will be reported in appropriate targeted follow-up~~

~~forms included in the eCRF. These events have also to be reported as AE or SAE as appropriate in the eCRF.~~

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

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 15, once the investigator becomes aware of the pIMD.

Table 15 Time frames for submitting SAEs and other events reports to GSK Biologicals

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

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

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 Section8.4.3.1 for back-up system and updating of SAE information after freezing of the subject's eCRF.

Section 8.4.5: Follow-up of adverse events and serious adverse events

All medically significant conditions (***including pIMDs)*** ~~NOCDs/NOADs~~ 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, stabilized, 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 (e.g., ***non-serious*** medically significant conditions [***including pIMDs]*** ~~and NOCDs/NOADs~~), until they complete the study or they are lost to follow-up.

Section 10.1 Co-Primary endpoints

Safety in HIV+ subjects up to Month 7:

- Occurrence of medically significant conditions (***including pIMDs)*** up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.
- ~~Occurrence of NOCDs up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.~~
- ~~Occurrence of NOADs up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV+ subjects.~~

Section 10. 2: Secondary endpoints

- Occurrence of medically significant conditions ***(including pIMDs)*** up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV- subjects.
- ~~Occurrence of NOCDs up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV- subjects.~~
- ~~Occurrence of NOADs up to 30 days after the last dose of vaccine (i.e., Month 7) in HIV- subjects.~~
- Occurrence of medically significant conditions ***(including pIMDs)*** ~~during the entire study period (i.e., up to Month 24)~~ ***up to 12 months after the last dose of vaccine (i.e., Month 18)*** in all subjects.
- ~~Occurrence of NOCDs during the entire study period (i.e., up to Month 24) in all subjects.~~
- ~~Occurrence of NOADs during the entire study period (i.e., up to Month 24) in all subjects.~~

Section 10.5: Derived and transformed data

- GSK assessment of NOCDs ***(only for the interim analysis)***: All AEs reported during the trial will be compared with a GSK pre-defined list of potential chronic diseases derived from the MedDRA codes. This list is approved by the IDMC supervising the HPV project. The determination of whether a potential chronic disease (identified by the pre-defined list or by the investigator) is considered to be a NOCD will be based on review by a GSK physician of the whole symptoms reported by the subject including subject's medical history.
- GSK assessment of NOADs ***(only for the interim analysis)***: Within the AEs that will be considered as NOCDs (GSK assessment) using a separate pre-defined list, AEs of potential autoimmune etiology will be identified.

Section 10.6.2: Statistical considerations for interim analyses

The following endpoints will be analyzed ***for the interim analysis***:

- Occurrence of medically significant conditions ***(including pIMDs).***

Section 10.7.2: Analysis of safety

The proportion of subjects with at least one report of a medically significant condition classified by MedDRA, whenever available, and reported ***from first vaccination up to 12 months after the last vaccine dose (i.e., Month 18)*** ~~during the entire study period~~ will be tabulated with exact 95% CI.

The proportion of subjects with at least one report of a pIMDs reported up to 12 months after the last vaccine dose (i.e., Month 18) will be tabulated with exact 95% CI.

~~The proportion of subjects with at least one report of NOCD (GSK assessment and investigator assessment) classified by MedDRA, whenever available, and reported during the entire study period will be tabulated with exact 95% CI.~~

~~The proportion of subjects with at least one report of NOAD (GSK assessment) classified by MedDRA, whenever available, and reported during the entire study period will be tabulated with exact 95% CI.~~

Section 10.7.2.1: Planned safety interim analysis

The proportion of subjects with at least one report of a pIMD will be reported up to Visit 2 (Week 6) and will be tabulated with exact 95% CI.

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment 3**	
eTrack study number(s) and Abbreviated Title(s)	109823 (HPV-019 PRI)
Amendment number:	Amendment 3
Amendment date:	23 May 2011
Co-ordinating author:	PPD

Rationale/background for changes:

- This amendment was issued to clarify that for HIV+ subjects whose HIV status is documented, the HIV Rapid test does not need to be repeated.
- As recommended by the study IDMC, exploratory analyses have been included to evaluate the immunogenicity of the study vaccines in HIV+ subjects stratified by HIV mode of transmission and by nadir CD4 cell count category.
- The introduction has been updated with the current licensure status and indication of Cervarix™ and Gardasil®.
- Minor corrections such as formatting and typos have been made.

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

Synopsis

Objectives

Exploratory

Immunogenicity:

- ***To evaluate the antibody response of both vaccines with respect to HPV-16 and HPV-18 by ELISA at Day 0, Months 7, 12, 18 and 24 in HIV+ subjects stratified by HIV mode of transmission, if sufficient data are available.***
- ***To evaluate the antibody response of both vaccines with respect to HPV-16 and HPV-18 by ELISA at Day 0, Months 7, 12, 18 and 24 in HIV+ subjects by nadir CD4 cell count category, if sufficient data are available.***

Section 1.1. Background

The first major market in which the HPV vaccine under evaluation in this study was licensed is Australia for use in females aged 10 - 45 years. The vaccine is marketed under the name Cervarix™. In September 2007, the vaccine was licensed in the European Union and is indicated for the prevention of ***persistent infection,*** premalignant cervical lesions and cervical cancer ~~causally related to HPV types 16 and 18~~***caused by oncogenic HPV types***. To date, the vaccine is licensed in more than ~~90~~***110*** countries worldwide.

In the United States, *Gardasil* is indicated for use in girls and women 9 to 26 years of age for prevention of diseases caused by HPV types 6, 11, 16, and 18: cervical***, vulvar, vaginal and anal*** cancer, genital warts and pre-cancerous or dysplastic lesions of cervical adenocarcinoma *in situ*, cervical intraepithelial neoplasia (CIN) grades 1, 2 & 3, vulvar- and vaginal-intraepithelial neoplasia grades 2 & 3 ***and anal intraepithelial neoplasia grades 1, 2 & 3***, respectively. The recommended dosing schedule for *Gardasil* is administration in three doses according to a 0, 2, 6-month schedule [*GARDASIL*, ~~European Public Assessment Report, 2009~~***Prescribing Information, 2011***].

Section 2.3. Exploratory objectives

2.3. Exploratory objectives

Immunogenicity:

- ***To evaluate the antibody response of both vaccines with respect to HPV-16 and HPV-18 by ELISA at Day 0, Months 7, 12, 18 and 24 in HIV+ subjects stratified by HIV mode of transmission, if sufficient data are available.***

- ***To evaluate the antibody response of both vaccines with respect to HPV-16 and HPV-18 by ELISA at Day 0, Months 7, 12, 18 and 24 in HIV+ subjects by nadir CD4 cell count category, if sufficient data are available.***

Section 5.5. Outline of study procedures

The following footnote has been added in Table 5 to the procedure "*Blood sampling for HIV testing (Rapid test, 5 mL)*" at the screening timepoint:

‡: For HIV+ subjects only, if the medical records of the subjects already have results documented for HIV testing, the HIV Rapid test should not be repeated at screening; however, HIV confirmatory test and testing for CD4 cell count and viral load should be performed.

Section 5.6.2.6. Blood sampling for HIV testing and safety

~~Note that, f~~***F***or HIV+ subjects, if the subject's medical records already have the HIV tests documented/confirmed, the~~se~~ HIV ***Rapid*** test should not be repeated***, but the other tests (HIV confirmatory test, determination of CD4 cell count and determination of HIV viral load) must be performed***.

Section 5.7.2. Biological samples

Table 4 Biological samples

Sample type	Quantity	Unit	Time point	Subset /Sub-cohort Name*
Blood for HIV testing (Rapid test)	5	mL	Screening**	All
			Month 7, Month 24	HIV- sub-cohort

NS = not specified

* Refer to Section 4.1 for sub-cohort description / Refer to Section 5.2.3 for subset description.

***** For HIV+ subjects only, if the medical records of the subjects already have results documented for HIV testing, the HIV Rapid test should not be repeated at screening; however, HIV confirmatory test and testing for CD4 cell count and viral load should be performed.***

Section 10.7.3.2. Within-group assessment

PBNA and ELISA

The following analyses will be performed as exploratory objectives in HIV+ subjects for each time point with a blood sample result available (Day 0, Week 6, Week 10, Months 7, 12, 18 and 24; ELISA):

- ***Seroconversion and seropositivity rates along with GMTs with 95% CI stratified by HIV mode of transmission, if sufficient data are available;***
- ***Seroconversion and seropositivity rates along with GMTs with 95% CI stratified by nadir CD4 cell count category, if sufficient data are available. The categories for nadir CD4 cell count will be defined in the Report Analysis Plan.***

Section 12. References

GARDASIL ~~(Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine) European Public Assessment Report. Revision 11. Published June 2009. http://www.emea.europa.eu/humandocs/Humans/EPAR/gardasil/gardasil.htm. Accessed: 22 June 2009~~***(Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant) Prescribing Information. April, 2011***.

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment 4**	
eTrack study number(s) and Abbreviated Title(s)	109823 (HPV-019 PRI)
Amendment number:	Amendment 4
Amendment date:	04 October 2011
Co-ordinating author:	PPD

Rationale/background for changes:

- Per protocol, assessment of primary objectives for non-inferiority/superiority were planned to be performed on the ATP cohort for immunogenicity in initially seronegative (S-) subjects. In the HPV-020 study, there was a high baseline seropositivity (S+) rate in both HIV + and HIV – subjects (50-80%). As this can also be expected in the HPV-019 study, many subjects will be eliminated from the primary endpoint analysis and this objective might not be met due to a low sample size. Therefore, the HPV-019 protocol was amended to analyse the primary endpoints regardless of initial HPV serostatus.
- The text in Section 10.3 (sample size estimation) was reworded accordingly.

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

Title page

Sponsor Signatory

Frank Struyf ~~Dominique Descamps~~, MD, Director Clinical Development HPV Vaccines

Section 10.3 Estimated sample size

Primary Objective

Considering a drop-out rate of ~~10% (withdrawal and elimination criteria) at Month 7 and a HPV positive rate of 10%~~ ***20%***, approximately 150 HIV+ subjects will be enrolled in each vaccine group.

As the SD is unknown in HIV+ subjects, the table below shows the impact of a SD increase on overall power. Several power calculations are presented to know the impact of ending the study recruitment early (see Section 4.1 of this document) ~~or of having more than 10% of subjects enrolled being HPV-16/18 seropositive at baseline~~.

Section 10.7.3.1 Between-group assessment

Primary and secondary between-group comparisons to assess non-inferiority will be done on the ATP cohort for immunogenicity ~~on seronegative subjects~~ (by PBNA, ***regardless of HPV serostatus at baseline***) ~~at baseline~~ for the antigen under analysis ~~(subjects seropositive for only one antigen will be eliminated for the analysis of that antigen but~~

~~will remain evaluable for the analysis of the other antigen)~~. A second analysis on Total Vaccinated cohort ~~(regardless of serostatus at baseline)~~ will be performed to support the primary analysis.

Primary and secondary between-group comparisons to assess superiority will be performed on the Total Vaccinated cohort ~~on all subjects~~ ***(by PBNA;*** ~~(~~regardless of ***HPV*** serostatus at baseline). A second analysis on ATP cohort for immunogenicity ~~on seronegative subjects (by PBNA~~) at baseline will be performed to support the primary analysis.

Section 10.7.3.2 Within-group assessment

PBNA and ELISA

For each group, at each time point with a blood sample result available (Months 0 and 7 for PBNA; Day 0, Week 6, Week 10, Months 7, 12, 18 and 24 for ELISA), the following analyses will be conducted:

- Seroconversion and seropositivity rates for each antigen (with exact 95% CI) per pre-vaccination status.
- GMTs with 95% CI and range for antibodies for each antigen per pre-vaccination status.
- The distribution of antibody titers for each antigen using reverse cumulative distribution curves ~~in the sub-cohort of subjects initially seronegative~~.

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment 5**	
eTrack study number(s) and Abbreviated Title(s)	109823 (HPV-019 PRI)
Amendment number:	Amendment 5
Amendment date:	20 March 2012
Co-ordinating author:	PPD, Scientific Writer

Rationale/background for changes:

Amendment 5 for the HPV-019 PRI protocol was developed in order to:

- Revise the length of interval between the study visits 4 and 5, by allowing subjects to be considered for ATP analyses even if the first four visits occur at the maximum permissible interval for each visit.
- Furthermore, since the primary endpoint is evaluated 1 month after administration of the third dose of vaccine, the recommended interval between Visit 4 and Visit 5 has been modified to 30 days.
- Update the list of contributing authors.

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

Title page

Contributing authors

The following contributing authors have been added:

- PPD, ***Global Study Manager***
- PPD, ***Senior Specialist, Biostatistics***

Section 5.5 Outline of study procedures

Table 3 Intervals between study visits

Interval	Length of interval (days)	Recommended interval between scheduled visits (days)
Screening visit → Visit 1, Day 0	up to 90 days	90
Visit 1, Day 0 → Visit 2, Week 6	40 – 62	42
Visit 2, Week 6 → Visit 3, Week 10	30 – 48	30
Visit 3, Week 10 → Visit 4, Month 6	98 – 140	106
Visit 4, Month 6 ~~Visit 1, Day 0 →~~ Visit 5, Month 7	~~190 – 230~~ ***21 – 60***	~~210~~ ***30***
Visit 1, Day 0 → Visit 6, Month 12	335 – 395	365
Visit 1, Day 0 → Visit 7, Month 18	515 – 575	545
Visit 1, Day 0 → Visit 8, Month 24	700 – 760	730

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment 6

eTrack study number(s) and Abbreviated Title(s)	109823 (HPV-019 PRI)
Amendment number:	Amendment 6
Amendment date:	Final: 06 June 2012
Co-ordinating author:	PPD, Emtex, contractor for GSK Biologicals, Scientific Writer

Rationale/background for changes:
The protocol is being amended for the following reason:

At the European Medicines Agency's (EMA) request, GSK Biologicals has updated its procedure for emergency unblinding during the conduct of a clinical study. According to the revised procedure, the responsibility and the decision to break the treatment code in emergency situations resides solely with the investigator and consequently, the investigator will have full authority to break the treatment code.

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

Section 8.7. Emergency unblinding

~~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 product is essential for the clinical management or welfare of the subject.~~

~~The GSK Biologicals' Central Safety Office will be allowed to access the individual randomization 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(s).~~

~~**GSK Biologicals Central Safety Physician**~~
~~**(Study Contact for Emergency Code Break)**~~

~~Phones for 7/7 day availability:~~
~~Outside US/Canada:~~
~~+~~PPD ~~(GSK Biologicals Central Safety Physician on-call)~~
~~Back-up phone contact:~~
~~Outside US/Canada:~~
~~+~~PPD

Unblinding of a subject's individual treatment code should occur only in the case of a medical emergency, or in the event of a serious medical condition, when knowledge of the study treatment is essential for the clinical management or welfare of the subject, as judged by the investigator.

The emergency unblinding process consists of the automated system SBIR that allows the investigator to have unrestricted, immediate and direct access to the subject's individual study treatment.

The investigator has the option of contacting a GSK Biologicals' On-call Central Safety Physician (or Backup) if he/she needs medical advice.

Any emergency unblinding must be fully documented by using the Emergency Unblinding Documentation Form, which must be appropriately completed by the investigator and sent within 24 hours to GSK Biologicals.

GSK Biologicals' Contact information for Emergency Unblinding 24/24 hour and 7/7 day availability
GSK Biologicals' Central Safety Physician: ***Outside US/Canada:*** +PPD ***(GSK Biologicals Central Safety Physician on-call)*** ***GSK Biologicals' Central Safety Physician Back-up:*** ***Outside US/Canada:*** +PPD ***Emergency Unblinding Documentation Form transmission:*** ***Outside US & Canada:*** ***Fax:*** +PPD ***or*** +PPD

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment 7

eTrack study number(s) and Abbreviated Title(s)	109823 (HPV-019 PRI)
Amendment number:	Amendment 7
Amendment date:	Final: 19 December 2013
Co-ordinating author:	PPD , Scientific Writer

Rationale/background for changes:
The HPV-019 protocol is being amended for the following reasons:

- Due to high rate of non evaluable subjects, (data integrity issue at one site; protocol non compliance; high drop out rate) additional subjects will be enrolled in this study, in order to maintain the statistical power for analysis.
- The IgG ELISA assay will be replaced by IgG nephelometry assay to measure total IgG in the serum matrix, because the assay output of nephelometry was proven less variable than that of ELISA. This change in the assay will be implemented for the testing of serum samples for all time points.
- The assay used to measure anti-HPV-16/-18 antibody concentrations at the designated laboratory was improved to increase the assay precision by changing the assay cut-off value from 8 EL.U/mL to 19 EL.U/mL for HPV-16 and from 7 EL.U/mL to 18 EL.U/mL for HPV-18. This change in the assay will be implemented for the testing of samples for all time points.
- Other small changes were made in order to accommodate the recruitment of subjects from another country, to clarify that some activities in the protocol are mandatory only for HIV+ subjects (this reflects what is actually done in the study procedures and is in line with the study procedures manual) and to clarify the blinding strategy for analysis..

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

Contributing authors

- PPD , ***Clinical Research & Development Lead***~~Clinical Development Manager~~
- PPD , ***Study Data Manager***
- PPD , ***Project statistician***
- PPD , ***Study Delivery Manager***
- PPD , ***Study Delivery Lead***
- PPD , ***Global Vaccines Clinical Laboratories representative (GVCL), (External consultant for GlaxoSmithKline Vaccines)***
- PPD , ***Project manager GVCL***
- PPD , ***Regulatory Affairs Representative***

- PPD ***Project level Clinical Research & Development Lead***

Sponsor signatory approval page:

Sponsor signatory	Frank Struyf, MD, ***Project Level Clinical Research & Development Lead, Clinical Development, HPV vaccines, Vaccines Discovery and Development,*** GlaxoSmithKline Biologicals ~~Director Clinical Development HPV Vaccines GlaxoSmithKline Biologicals~~

List of abbreviations:

~~**CDM**~~	~~Clinical Development Manager~~
CRDL	***Clinical Research & Development Lead***

The term Clinical Development Manager (CDM) has been replaced by ***Clinical Research & Development Lead (CRDL)*** throughout the document. This is reflected in the synopsis (study design), in Section 5.4.3 and in Section 10.6.2.

Synopsis:

Study design	• In **Part A**, a subset of 60 subjects aged 18 - 25 years (30 HIV+ and 30 HIV- subjects) will be vaccinated (Dose 1) and evaluated for safety before proceeding with the enrollment and vaccination of the remaining subjects (**Part B**; ~~540 subjects~~). Administration of Dose 2 to the subjects in Part A will not depend on the outcome of the safety evaluation unless there are specific safety concerns for an individual subject or if requested by the Independent Data Monitoring Committee (IDMC) or Vaccine Safety Monitoring Board (VSMB).

Glossary of terms:

~~**Global Study Manager:**~~	~~An individual assigned by GSK Biologicals Headquarters who is responsible for assuring the coordination of the operational aspects and proper conduct of a clinical study, including compliance with International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP) and GSK policies and standard operating procedures (SOPs).~~

Section 3 Study design overview

Figure 2 Overview of staggered vaccination progress and safety evaluation

In **Part A**, a subset of 60 subjects aged 18 - 25 years (30 HIV+ and 30 HIV- subjects) will be vaccinated (Dose 1) and evaluated for safety before proceeding with the enrollment and vaccination of the remaining subjects (**Part B**~~; 540 subjects~~) (see Figure 2). The results of this safety interim analysis will be reviewed by the GSK Safety Review Team and the Independent Data Monitoring Committee (IDMC). The IDMC will provide recommendation to the sponsor via the GSK Safety Review Team prior to proceeding with the enrollment of the remaining study subjects in Part B of the study (see Section 5.4.2 for details)

Section 4.1 Number of subjects/centers

Approximately 600 subjects aged between 15 and 25 years ***were planned to be*** ~~will be~~ enrolled in order to reach 480 evaluable subjects for the analysis at Month 7. ***Due to high rate of non evaluable subjects, additional subjects will be enrolled in this study in order to maintain the statistical power for analysis. Thus , approximately 700 subjects will be enrolled in this study to obtain 480 evaluable subjects***:

- Overview of the recruitment plan

The study will be performed in multiple centers located in ***multiple countries***~~India, Thailand and Brazil~~. A center is defined as a single recruiting site or multiple recruiting sites under one principal investigator. ~~The enrollment period is anticipated to occur over approximately three months and will be competitive across the centers in each country~~.

~~Actual numbers of subjects enrolled vs. target numbers of subjects enrolled will be assessed on a continuous basis using internet randomization (SBIR). Monitoring of actual enrollment against target enrollment will be performed; the frequency of monitoring visits will be adapted to the study site.~~

Section 4.3 Exclusion criteria for enrolment

- Active tuberculosis (TB) diagnosed by AF B sputum test and/or chest X-ray at the screening visit ***(criteria mandatory only for HIV+ subjects)***.

Section 5.2.2.2 Treatment allocation to the subject

~~Approximately ***691*** subjects aged 15 – 25 years will be enrolled, of whom approximately 300 HIV+ subjects and 300HIV- subjects.~~

Section 5.3 Method of blinding

Data will be collected in an observer-blind manner. Due to differences in the visual appearance of the two HPV vaccines, syringes will be prepared and administered by qualified medical personnel not otherwise involved in the conduct of the study or in the assessment of symptoms. The vaccine recipient and those responsible for the evaluation

of any study endpoint (e.g., safety, reactogenicity) will all be unaware of which vaccine was administered during the entire study period. ***Refer to the Study Procedures Manual (SPM) for specific instructions on observer blind stratergy.***

Study and GSK personnel directly involved in the conduct of the study will be blinded to the individual subject treatment. In order to preserve the blind, the interim analysis will be performed by an external statistician, therefore only a non-GSK statistician will be unblinded to the treatment allocation. Similarly, when all subjects will complete their Month 7 visit and the database will be frozen, the primary analysis will also be performed by an external statistician. The subjects, investigator, study personnel and GSK staff will remain blinded until completion of study follow-up. ***All analysis, until completion of study follow-up, will be performed by an external statistician to preserve blinding of study.***.

Section 5.4.2 Staggered vaccination process

In Part A, a subset of 60 subjects aged 18 – 25 years (30 HIV+ and 30 HIV- subjects) will be vaccinated (Dose 1) and evaluated for safety before proceeding with the enrollment and vaccination of the remaining subjects (Part B~~; 540 subjects~~) (see Figure 2). Administration of Dose 2 to these subjects in Part A will not depend on the outcome of the safety evaluation unless there are specific safety concerns for an individual subject or if requested by the IDMC or Vaccine Safety Monitoring Board (VSMB).

Section 5.6.3.4 Blood sampling for safety or immune response assessments

- A volume of at least 5 mL of whole blood should be drawn from HIV negative subjects for HIV testing (Rapid test).

  ~~Provide pre- and post-HIV test counseling. Post-HIV test counseling can be provided as soon as HIV test result (by Rapid test) is available. Make record of this procedure in the eCRF section of the visit during which the HIV test was performed~~. A confirmatory test (5 mL of whole blood)will be performed on all subjects found to be HIV positive. All subjects found to be HIV-infected will be referred to the national program for medical management according to local guidelines (see Section 5.4.5).

Section 5.6.4.1 Extended follow-up conclusion

Blinded annex analyses will be performed at Month 12 and Month 18; and ***an unblinded annex analysis at*** Month 24, based on all data obtained up to extended follow-up conclusion visits (Visit 6, Visit 7 and Visit 8, respectively).

Section 5.7.3 Laboratory assays

Table 5 Laboratory assays

Laboratory Discipline	Component	Scale	Method	Test kit/ Manufacturer	Unit	Cut-off	Laboratory
Humoral Immunology	HPV 16.PsV Ab	Quantitative	PBNA$^{\Delta,\dagger}$	NCI methodology adapted by GSK	ED_{50}	40	GSK Biologicals*
	HPV 18.PsV Ab						
	HPV 16.VLP IgG	Quantitative	ELISA†	In house assay	EL.U/mL	~~8~~ ***19***	GSK Biologicals*
	HPV 18.VLP IgG					~~7~~ ***18***	
	HPV 16.VLP IgG	Quantitative	ELISA‡	In house assay	EL.U/mL	NA	GSK Biologicals*
	HPV 18.VLP IgG						
	IgG	***Quantitative***	***Immunonephel-ometry assay***†	***IgG on the BN II***$^{\circ}$	***µg/ml***	***100***	***GSK Biologicals****
	IgG	Quantitative	ELISA†,‡	In house assay	µg/mL	NA	GSK Biologicals*
	Anti-HIV	Qualitative	Rapid test§	NR**	NA	NA	Local Laboratory
Cell Mediated Immunology	Specific CD4 or CD8 T cells	Quantitative	IntraCellular cytokine assay	NA	Events/10^6	NA	GSK Biologicals*
	Specific Memory B cells	Quantitative	B cell ELISPOT	NA	Events/10^6	NA	GSK Biologicals*
Hematology chemistry	White blood cells (total + differential), red blood cells, platelets, hematocrit, hemoglobin	Quantitative	NR**	NR**	NR**	NR**	Local Laboratory
Blood chemistry	Creatinine, ALT	Quantitative	NR**	NR**	NR**	NR**	Local Laboratory
HIV+ subjects only							
HIV viral load (copies/mL) CD4 cell count (cell/mm^3)		Quantitative	NR**	NR**	NR**	NR**	Local Laboratory
HIV confirmatory testing		Qualitative	ELISA	NR**	EL.U/mL	NR**	Local laboratory

*GSK Biologicals laboratory or validated laboratory designated by GSK Biologicals

**NR: not required

ED_{50}: Estimated Dose: serum dilution giving a 50% reduction of the signal compared to a control without serum

ALT: alanine aminotransferase; ELISA: Enzyme-linked Immunosorbent Assay; EL.U: ELISA unit; NCI: National Cancer Institute

Δ The pseudovirion-based neutralization (PBNA) assay is based on a method developed by Pastrana *et al*. [Pastrana, 2004] at the NCI.

† Assays performed on blood samples.

‡ Assays performed on CVS samples.

NA Not applicable

$^{\circ}$ ***BNII fully automated system from Siemens at Bio Analytical Research Corporation (BARC)***

§ HIV Rapid test will be used locally according to National Guidelines.

Section 5.7.4.1 Immunological read-outs

Table 6 Immunoligical read-outs

Timing	Week/ Month	Visit no.	Marker	Assay Method	No. subjects
Blood Sampling					
Pre-vaccination	Day 0	1	anti-HPV-16	PBNA and ELISA	All
			anti-HPV-18	PBNA and ELISA	
			Total IgG	***Immunonephelometry*** ~~ELISA~~	CVS sub-cohort*
Post-vaccination I	Week 6	2	anti-HPV-16	ELISA	All
			anti-HPV-18	ELISA	
			Total IgG	***Immunonephelometry*** ~~ELISA~~	CVS sub-cohort*
Post-vaccination II	Week 10	3	anti-HPV-16	ELISA	All
			anti-HPV-18	ELISA	
			Total IgG	***Immunonephelometry*** ~~ELISA~~	CVS sub-cohort*
Post-vaccination III	Month 7	5	anti-HPV-16	PBNA and ELISA	All
			anti-HPV-18	PBNA and ELISA	
			Total IgG	***Immunonephelometry*** ~~ELISA~~	CVS sub-cohort*
Post-vaccination III	Month 12	6	anti-HPV-16	ELISA	All
			anti-HPV-18	ELISA	
			Total IgG	***Immunonephelometry*** ~~ELISA~~	CVS sub-cohort*
Post-vaccination III	Month 18	7	anti-HPV-16	ELISA	All
			anti-HPV-18	ELISA	
Post-vaccination III	Month 24	8	anti-HPV-16	ELISA	All
			anti-HPV-18	ELISA	
			Total IgG	***Immunonephelometry*** ~~ELISA~~	CVS sub-cohort*

In case of insufficient blood sample volume to perform assays for all antibodies, the samples will be analyzed according to the following priority ranking:

3. ***Nephelometry*** ~~ELISA~~, total IgG

Section 10.3 Estimated sample size

A total of 600 subjects, 300 in HIV+ group and 300 in HIV-ve group were planned to be enrolled in this study.

Due to high rate of non evaluable subjects, (data integrity issue at one site; protocol non compliance; high drop out rate) additional subjects will be enrolled in this study, in order to maintain the statistical power for analysis. Thus, approximately 700 subjects will be enrolled in this study to obtain 480 evaluable subjects.

Appendix A Laboratory assays

Total Human IgG ELISA

The hIgG assay is a two-site immunoenzymetric assay. Affinity purified anti-hIgG antibodies are coated onto a 96-wells microplate. After a washing and a blocking step, dilutions of ~~serum or~~ CVS samples, control and standard are incubated on the plate. The microplate is washed and HRP (HorseRadishPeroxidase)-conjugated anti-human IgG polyclonal antibodies are added. After incubation, unbound antibodies are removed by washing and TMB (TetraMethylBenzidine) is incubated to reveal the enzyme activity. Colour reaction is stopped by addition of sulphuric acid and the resulting yellow colour is measured spectrophotometrically.

Total Human IgG by nephelometry assay in serum

Total human IgG in serum will be measured by the nephelometric method using the BNII fully automated system from Siemens. This test is used in medical laboratories and considered as being the gold standard for plasma protein analysis.

Polystyrene particles coated with antibodies directed against human IgG will agglutinate when mixed with diluted human samples containing human IgG. The intensity of the scattered light in the nephelometer will depend on the concentration of the IgG in the sample and consequently its concentration will be determined by comparison with dilutions of a standard of known concentration

GlaxoSmithKline Biologicals

Clinical Research & Development

Protocol Amendment 8

eTrack study number(s) and Abbreviated Title(s)	109823 (HPV-019 PRI)
Amendment number:	Amendment 8
Amendment date:	26 April 2016
Co-ordinating author:	PPD, Scientific Writer

Rationale/background for changes:

- The protocol was amended to align the section of the protocol on management of HIV+ subjects with the recently revised WHO guidelines on when to start antiretroviral therapy (ART) in HIV+ subjects. The revision of the WHO guidelines presented evidence that earlier use of ART results in better long-term clinical outcomes for people living with HIV compared with delayed treatment, including pregnant and breastfeeding women. This guideline advises to start ART in all adults with HIV regardless of their clinical stage and at any CD4 cell count. At the time of implementation of the protocol amendment, the vaccination phase had already completed, and therefore the exclusion criterion for subsequent vaccination after initiation of ART during the course of the study was not revised.

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

Contributing authors

- PPD ***and*** PPD, Clinical Research & Development Leads
- PPD ***and*** PPD, Study Data Managers
- PPD ***, Project Data Manager***
- PPD ***, Lead Statistician***
- PPD, ~~Global Vaccines Clinical Laboratories representative~~ ***Laboratory Study Manager,-Clinical Laboratory Sciences(~~GVCL~~CLS), (***External consultant for GlaxoSmithKline ~~Vaccines~~***Biologicals)***
- PPD ~~, Project manager~~ ***Clinical Research Team Lead, ~~GVCL~~CLS***
- PPD ***and*** PPD, Regulatory Affairs Representatives

Section 5.4.5: Follow-up of HPV positive subjects in the study

Previous WHO recommendations advised to start ART in subjects with a CD4 cell count ≤350 cells/mm^3 irrespective of their clinical stage [WHO, 2009]. A revision in late 2015 of the WHO guideline on when to start ART presented evidence showing that earlier use of ART results in better long-term clinical outcomes for people living with HIV compared with delayed treatment, including pregnant and breastfeeding women. This guideline advises to start ART in all adults with HIV regardless of their clinical

stage and at any CD4 cell count [WHO, 2015]. ~~Since the WHO last guideline revision in 2006, new and compelling evidence has become available, particularly concerning the earlier start of ART. Subjects who have a CD4 cell count ≤ 350 cells/mm^3 should be treated irrespective of their clinical stage [WHO, 2009].~~

Section 12: References:

WHO Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/. Accessed on 26 April 2016.

Protocol Amendment 8 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	109823 (HPV-019 PRI)
EudraCT number	2013-003429-28
Date of protocol amendment	Amendment 8 Final: 26 April 2016
Detailed Title	A phase IV, observer-blind, randomized, controlled, multicentric study to assess the safety and immunogenicity of GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine (Cervarix™) administered intramuscularly according to a three-dose schedule (Day 0, Week 6, Month 6) in human immunodeficiency virus-infected (HIV+) female subjects aged 15 - 25 years, as compared to Merck's HPV-6/11/16/18 vaccine (Gardasil®).
Sponsor signatory	Frank Struyf, MD, Project Level Clinical Research & Development Lead, Clinical Development, HPV vaccines, Vaccines Discovery and Development, GlaxoSmithKline Biologicals
Signature	PPD
Date	30 MAY 2016

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