Protocol and Protocol Amendments

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113617 (HPV-062 EXT:015)
Administrative Change 1

Clinical Study Protocol
Sponsor:
GlaxoSmithKline Biologicals
Rue de l'Institut 89
B-1330 Rixensart, Belgium

Primary Study vaccine and number	No vaccines are administered in this study. GlaxoSmithKline Biologicals' candidate human papillomavirus (HPV) vaccine containing HPV-16/18 L1 VLP proteins and AS04 adjuvant (GSK 580299) was administered in the primary HPV-015 study.
Other Study vaccines	No vaccines are administered in this study.
eTrack study number and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
Investigational New Drug (IND) number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Date of protocol amendment 1	Amendment 1: 21 June 2010
Date of protocol administrative change 1	Administrative Change 1 Final: 18 August 2010
Title	Gynaecological follow-up of a subset of HPV-015 study subjects
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Co-ordinating author	PPD Scientific Writer
Contributing authors	PPD Clinical Development Manager PPD Director, Clinical Development PPD Project Statistician PPD Global Study Manager PPD Global Study Manager PPD Global Study Manager PPD Regulatory Affairs Representative PPD External Laboratory Coordinator PPD Clinical Safety Representative PPD Clinical Safety Representative PPD Clinical Data Coordinator

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113617 (HPV-062 EXT:015)
Administrative Change 1

Protocol Administrative Change 1 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	113617 (HPV-062 EXT:015)
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Date of protocol amendment 1	Amendment 1 Final: 21 June 2010
Date of protocol administrative change 1	Administrative Change 1 Final: 18 August 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Sponsor signatory	Dominique Descamps, MD, Director, Clinical Development GlaxoSmithKline Biologicals Rue de l'Institut 89 B-1330 Rixensart Belgium
Signature	_____
Date	_____

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Protocol Administrative Change 1 Rationale

Administrative Change number:	Administrative Change 1
Rationale/background for changes:	

Since the double-blind study HPV-015 will be extended by a maximum of three additional years, according to Protocol Amendment 4, dated 24 March 2010, it is important that central study staff involved in the studies remains blinded till the end of study HPV-015 for all subjects who have been participating in HPV-015 and will be participating in this study. Therefore, subjects enrolled in HPV-015 extension studies such as study HPV-062 cannot retain the HPV-015 subject number as is stated in the original protocol. Consequently, different identification numbers will be provided by an external statistician.

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Protocol Administrative Change 1 Investigator Agreement

I agree:

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

Hence I:

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

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eTrack study number(s) and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Date of protocol amendment 1	Amendment 1 Final: 21 June 2010
Date of protocol administrative change 1	Administrative Change 1 Final: 18 August 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Investigator name	
Signature	
Date	
Leiter der klinischen Prüfung' (LKP) name	
Signature	
Date	

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SYNOPSIS

Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects.
Indication	Cervarix is indicated in females from 10 years of age onwards for the prevention of persistent infection, premalignant cervical lesions and cervical cancer (squamous-cell carcinoma and adenocarcinoma) caused by oncogenic Human Papillomaviruses (HPV). This HPV-16/18 L1 VLP AS04 vaccine was administered to the HPV-015 study vaccine group. Cross-over vaccination will be offered to the subjects in the HPV-015 control group either by providing commercially available HPV-16/18 L1 VLP AS04 vaccine or, if the vaccine is not licensed in the considered country or not licensed for the respective age group, through a separate clinical trial protocol. No vaccine will be administered in the current study.
Rationale for the study and study design	This study will be conducted to allow for a safe exit from the HPV-015 study, ensuring that women who are at risk of developing a gynaecological lesion are medically monitored. Study subjects enrolled in the control arm of HPV-015 study may have been infected with the HPV types included in the vaccine during the study. All subjects may have been exposed to other high-risk HPV types. The current study will provide annual oncogenic HPV DNA testing and cervical cytology examination for a subset of HPV-015 subjects, who at their concluding HPV-015 study visit: • displayed normal cervical cytology but tested positive for oncogenic HPV infection • were pregnant so that no cervical sample could be collected For eligible subjects, the duration of this gynaecological follow-up will be up to a maximum of four years after the subjects' concluding visit of study HPV-015, since most cervical lesions develop within four years of infection and most oncogenic HPV infections are estimated to clear within two years [Trottier, 2008]. If very few subjects are eligible for this study at one HPV-015 study site and if adequate gynaelogical follow-up care is available through the local health care system, these subjects may be referred to the local health care system, provided that ethical committee approval is obtained by the responsible investigator. The initial protocol of the HPV-015 trial included a three-year

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efficacy follow-up. The HPV-015 protocol amendment 3 and 4 extended the HPV-015 trial by one and up to a maximum of three additional years, respectively. Subjects may however decide to conclude their participation in the HPV-015 study at Visit 9, Visit 11 or at the last study visit in HPV-015 planned under protocol amendment 4.

Note that subjects enrolled in this study can also concurrently participate in a GSK Biologicals study to receive cross-over vaccination.

This study is not intended to collect long-term efficacy, immunogenicity or safety follow-up data. Long-term data for GSK Biologicals' HPV vaccine will be obtained through other studies.

Study objectives

- To provide clinical management and, if required, treatment to subjects who at their concluding HPV-015 study visit displayed normal cervical cytology but tested positive for oncogenic HPV infection or who were pregnant at their concluding visit of the HPV-015 study so that no cervical sample could be collected.

Study design

- **Experimental design:** A phase IIIb, open, multi-centre study with one group.
- **Treatment allocation:** None.
- **Blinding**: Open.
- **HPV-015 concluding visit**: Subjects who participated in the HPV-015 study may decide to conclude their participation in the HPV-015 study at Visit 9, Visit 11 or at the last study visit in HPV-015 planned under protocol amendment 4.
- **Treatment groups:** One study group consisting of a subset of HPV-015 subjects who at their concluding HPV-015 study visit:
  - displayed normal cervical cytology but tested positive for oncogenic HPV infection
  - were pregnant so that no cervical sample could be collected at that visit
- **Vaccination schedule(s):** None.
- **Control:** None.
- **Type of study:** Gynaecological follow-up extension study of a subset of HPV-015 study subjects.
- **Data collection:** Remote Data Entry (RDE).
- **Duration of the study:** Maximum of four years for each

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subject.

- **Study visits per subject:** Up to four scheduled visits at approximately Months 12, 24, 36 and 48 after each subject's concluding HPV-015 study visit

  Subjects are eligible to join the study at any visit.

- **Study procedures:**

  Subjects will enter the study approximately one year after their HPV-015 concluding study visit. Annual visits will be scheduled for a maximum study duration of approximately four years

  At each visit, a gynaecological examination will be performed and cervical liquid-based cytology samples will be collected for cervical cytology examination and oncogenic HPV DNA testing, if the cytology reading is normal or ASCUS.

  The presence of oncogenic HPV infection will be determined by the Hybrid Capture® II (HCII) test, which detects HPV DNA types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 [Vernick 2003, Digene Corporation 2002]. Cervical cytology examination will be performed using the ThinPrep®Pap test.

  Continued study participation as well as further referral/treatment will be based on the test results from each visit, and will be aligned with the clinical management algorithm which is aligned with the 2009 American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines for use of HPV DNA testing as an adjunct to cytology for cervical cancer screening in women 30 years or older.

  The following clinical management algorithm will be applied:

  - Subjects with normal cervical cytology and who are oncogenic HPV DNA negative, will end their participation in the study.
  - Subjects with normal cervical cytology, but who are oncogenic HPV DNA positive in one single test, will be asked to return at the next study visit.
    This outcome will only be applicable to subjects who were pregnant at their concluding HPV-015 study visit so that no cervical sample could be collected at that visit.
  - Subjects with normal cervical cytology, but who are oncogenic HPV DNA positive in two subsequent tests, will be referred to colposcopy. The result of the

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subjects' concluding HPV-015 study visit will be taken into account at Visit 1.

- Subjects with a single cervical cytology reading of ≥ASC-US (atypical squamous cells of undetermined significance) positive for oncogenic HPV DNA will be referred to colposcopy.
- Subjects with a single cervical cytology reading of ≥LSIL (low grade squamous intraepithelial lesion) will be referred to colposcopy.

Please note that a missing result for HCII will be managed as oncogenic HPV positive.

In case of referral for colposcopy, the post-colposcopy follow-up strategies are:

- If no lesion is detected or the detected lesion does not require any treatment, subjects will be asked to return at the next study visit.
- If a lesion that requires treatment is detected, the subject should be referred to treatment according to local medical practice. Any further management following local cervical therapy for cervical lesions will be handled according to local medical practice within the local health care system. After treatment, the subject's participation in the study will end.

As management algorithms cannot define every clinical situation, it is the investigator's (or his/her designee's) responsibility to exercise appropriate clinical judgement in the medical management of each individual case.

Once their study participation ends, all subjects should be referred to their local health care system.

Subjects who have not developed cervical lesions by the end of the study, but who are still positive for oncogenic HPV infection, should be informed of the potential risks of being positive for oncogenic HPV DNA and the importance of continued follow-up.

- **Study visit activities and gynaecological follow-up reporting**
  - Gynaecological examination at Visit 1, Visit 2, Visit 3 and Visit 4.
  - Collection of cervical liquid-based cytology samples at Visit 1, Visit 2, Visit 3 and Visit 4 for cervical cytology examination and oncogenic HPV DNA testing, if the cytology reading is normal or ASCUS.

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- Referral to colposcopy according to protocol clinical management algorithm, if required.
- Conduct of colposcopy, colposcopy directed biopsies and local cervical therapy according to local medical practice, if required.
- Recording of colposcopic referral according to management algorithm, if required.
- Recording of treatment referrals according to local medical practice, if required.

- **Safety reporting:**
  - All fatal SAEs will be reported.
  - All SAEs assessed as being possibly related to study participation will be reported.
  - All SAEs assessed as being possibly related to a concurrent GSK medication will be reported.
  - Withdrawal from the study due to adverse events (AEs) or SAEs will be reported.

No other AEs or SAEs for HPV-015 study subjects will be reported in this study. AEs and SAEs related to the vaccine administrated in the HPV-015 trial should be reported as part of the HPV-015 study, as described in the HPV-015 study protocols.

Number of subjects

Approximately 1500 HPV-015 study subjects are expected to be eligible to participate in this study.

Study endpoints

- Occurrence of positive oncogenic HPV DNA results in cervical samples by HPV DNA testing (Hybrid Capture® II test [HCII]).
- Occurrence of cervical cytological abnormalities in cervical samples by ThinPrep® PapTest.
- Occurrence of referral to colposcopy.
- Occurrence of referral to treatment.

Study analysis

All study endpoints are descriptive, no inferential analyses will be performed.

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LIST OF ABBREVIATIONS

AE	Adverse event
AGC	Atypical glandular cells
AIS	Adenocarcinoma in-situ
ASC-US	Atypical squamous cells of undetermined significance
ASC-H	Atypical squamous cells cannot exclude HSIL
CIN	Cervical intraepithelial neoplasia
CIN1+	Cervical intraepithelial neoplasia as CIN1, CIN2,CIN3, adenocarcinoma in-situ and invasive cervical cancer
CIN2+	Cervical intraepithelial neoplasia as CIN2, CIN3, adenocarcinoma in-situ and invasive cervical cancer.
CRF/eCRF	Case Report Form/electronic Case Report Form
CRA	Clinical Research Associate
FDA	Food and Drug Administration, United States
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
GSM	Global Study Manager
HCII	Hybrid Capture II
HPV	Human papillomavirus
HR	High-risk
HR-HPV	High-risk (oncogenic) HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
HSIL	High grade squamous intraepithelial lesion
IB	Investigator Brochure.
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee

IND	Investigational New Drug
IRB	Institutional Review Board
LBC	Liquid Based Cytology
LEEP	Loop Electrosurgical Excision Procedure
LR	Low-risk
LSIL	Low grade squamous intraepithelial lesion
MedDRA	Medical Dictionary for Regulatory Activities
RDE	Remote data entry
SAE	Serious Adverse Event.
SPM	Study Procedures Manual.
SOP	Standard Operating Procedure
VAIN	Vaginal Intraepithelial Neoplasia
VIN	Vulval Intraepithelial Neoplasia
VLP	Virus-like particle

GLOSSARY OF TERMS

Adverse event:	Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.
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.
Conclusion Visit of Study HPV-015	Subjects who participated in the HPV-015 study may decide to conclude their participation in the HPV-015 study at Visit 9, Visit 11 or at the last study visit in HPV-015 planned under protocol amendment 4.
Eligible:	Qualified for enrolment 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:	GSK's tracking tool for clinical trials.
Global Study Manager	An individual assigned by GSK Biologicals Headquarters who is responsible for assuring the co-ordination of the operational aspects and proper conduct of a clinical study, including compliance with International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and GSK policies and standard operating procedures.
Investigational vaccine/product: **(Synonym of Investigational Medicinal**	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain

Product)	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 adverse events.
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.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical study, either as a recipient of the product(s) or as a control.
Subject number:	A unique number identifying a subject, assigned to each subject consenting to participate in the study.
Treatment:	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomisation or treatment allocation.
Treatment number:	A number identifying a treatment to a subject, according to the study randomisation or treatment allocation.

1. INTRODUCTION

1.1. Background

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

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

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

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

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

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

To date, more than 60 000 adolescent and adult females aged 10 years and above have received at least one dose of the HPV vaccine in clinical studies. A pooled safety analysis of data from almost 30 000 adolescent and adult females aged 10 years and above, of whom 16 142 received at least one dose of HPV vaccine, showed the vaccine to be generally well tolerated in women of all ages [Descamps , 2009].

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

A long-term efficacy follow-up study in women aged 15-25 years at the time of first vaccination demonstrated high vaccine efficacy against incident and persistent HPV-16/18 infections and their associated cytological cervical lesions up to 6.4 years of follow-up [Gall, 2007; Harper, 2004; Harper, 2006; Harper, 2008]. When tested in young female adolescents, the vaccine induced immune responses that were approximately 2-fold higher than those elicited in women 15-25 years of age [Pedersen, 2007]. In women up to 55 years of age, the vaccine induced sustained HPV antibody levels up to Month 24 after the first vaccine dose and these antibody levels remained significantly higher than those seen after natural infection [Schwarz, 2009].

The vaccine is marketed under the trade name Cervarix™. The first major market in which the vaccine was licensed, is Australia, where licensure was obtained in May 2007 for use in 10 to 45 year old females. In September 2007, the vaccine was licensed in the European Union for the prevention of high-grade cervical intraepithelial neoplasia (CIN grades 2 and 3) and cervical cancer causally related to HPV types 16 and 18. The present indication of the vaccine is for active immunization of girls and women from 10 years of age onwards for the prevention of persistent human papillomavirus (HPV) infections and related clinical outcomes (cytological abnormalities, pre-cancerous lesions and cervical cancer) caused by oncogenic HPV types 16 and 18. In October 2009, Cervarix was also approved by the United States Food and Drug Administration (US FDA) for use in females 10 through 25 years of age. The vaccine is currently licensed in over 100 countries worldwide.

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

1.2. Rationale for the study and study design

This study will be conducted to allow for a safe exit from the HPV-015 study, ensuring that women who are at risk of developing a gynaecological lesion are medically monitored.

Study subjects enrolled in the control arm of HPV-015 study may have been infected with the HPV types included in the vaccine during the study. All subjects may have been exposed to other high-risk HPV types.

The current study will provide annual oncogenic HPV DNA testing and cervical cytology examination for a subset of HPV-015 subjects, who at their concluding HPV-015 study visit:

- displayed normal cervical cytology but tested positive for oncogenic HPV infection
- were pregnant so that no cervical sample could be collected

For eligible subjects, the duration of this gynaecological follow-up will be up to a maximum of four years after the subjects' concluding HPV-015 study visit, since most cervical lesions develop within four years of infection and most oncogenic HPV infections are estimated to clear within two years [Trottier, 2008].

If very few subjects are eligible for this study at one HPV-015 study site and if adequate gynaecological follow-up care is available through the local health care system, these subjects may be referred to the local health care system, provided that ethical committee approval is obtained by the responsible investigator.

The initial protocol of the HPV-015 trial included a three year efficacy follow-up. The HPV-015 protocol amendment 3 and 4 extended the HPV-015 trial by one and up to a maximum of three additional years, respectively. Subjects may however decide to conclude their participation in the HPV-015 study at Visit 9, Visit 11 or at the last study visit in HPV-015 planned under protocol amendment 4.

Note that subjects enrolled in this study can also concurrently participate in a GSK Biologicals study to receive cross-over vaccination.

This study is not intended to collect long-term efficacy, immunogenicity or safety follow-up data. Long-term data for GSK Biologicals' HPV vaccine will be obtained through other studies.

1.2.1. Rationale for the use of placebo

Not applicable.

2. STUDY OBJECTIVES

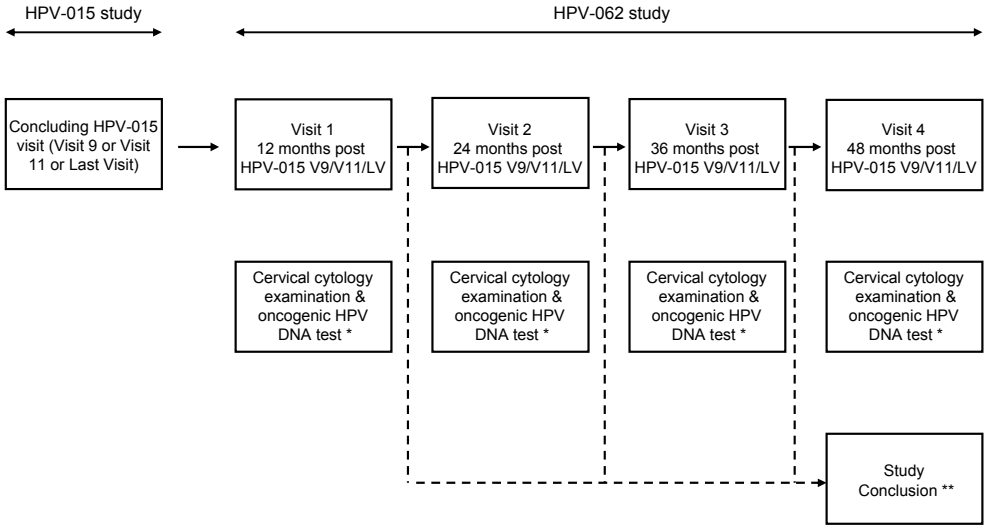
- To provide clinical management and, if required, treatment to subjects who at their concluding HPV-015 study visit displayed normal cervical cytology but tested positive for oncogenic HPV infection or who were pregnant at their concluding visit of the HPV-015 study so that no cervical sample could be collected

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

3. STUDY DESIGN OVERVIEW

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

Figure 1 Study visits and study procedures



*Subjects with two positive oncogenic HPV DNA tests or one cervical cytology reading ≥ASC-US (atypical squamous cells of undetermined significance) positive for oncogenic HPV DNA or one cervical cytology reading ≥LSIL (low grade squamous intraepithelial lesion) will be referred for colposcopy evaluation according to the clinical management algorithm. Oncogenic HPV tests (HCII) will only be performed on normal and ASCUS cytological samples.
** Study conclusion, see dotted line (--), will occur after any given visit that required treatment of cytological abnormality, any given visit with a negative oncogenic HPV DNA test and normal cervical cytology or the closing of study activities related to Visit 4.

- **Experimental design:** A phase IIIb, open, multi-centre study with one group.
- **Treatment allocation:** None.
- **Blinding:** Open.
- **HPV-015 concluding visit**: Subjects who participated in the HPV-015 study may decide to conclude their participation in the HPV-015 study at Visit 9, Visit 11 or at the last study visit in HPV-015 planned under protocol amendment 4.

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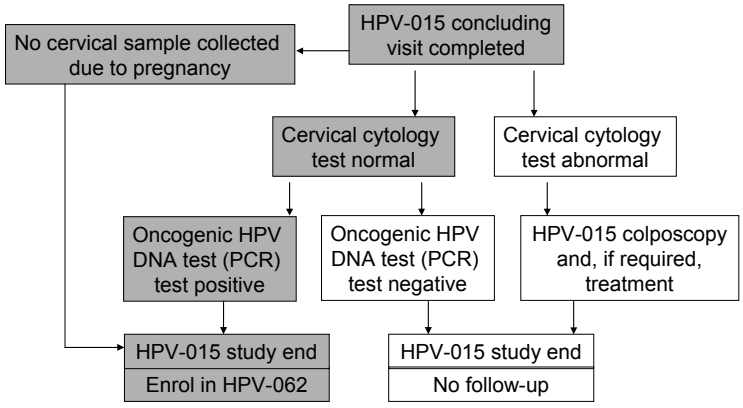
- **Treatment groups:** One study group consisting of a subset of HPV-015 subjects who at their concluding HPV-015 study visit:
  - displayed normal cervical cytology but tested positive for oncogenic HPV infection
  - were pregnant so that no cervical sample could be collected at that visit

The study eligibility algorithm is presented in Figure 2.

Figure 2 HPV-062 EXT:015 study eligibility algorithm



- **Vaccination schedule(s):** None.
- **Control:** None.
- **Type of study:** Gynaecological follow-up extension study of a subset of HPV-015 study subjects.
- **Data collection:** Remote Data Entry (RDE).
- **Duration of the study:** Maximum of four years for each subject.
- **Study visits per subject:** Up to four scheduled visits at approximately Months 12, 24, 36 and 48 after each subject's concluding HPV-015 study visit.

  Subjects are eligible to join the study at any visit.
- **Study procedures:**

  Subjects will enter the study approximately one year after their HPV-015 concluding visit. Annual visits will be scheduled for a maximum study duration of approximately four years.

  At each visit, a gynaecological examination will be performed and cervical liquid-based cytology samples will be collected for cervical cytology examination and oncogenic HPV DNA testing, if the cytology reading is normal or ASCUS.

  The presence of oncogenic HPV infection will be determined by the Hybrid Capture® II (HCII) test, which detects HPV DNA types 16, 18, 31, 33, 35, 39, 45,

51, 52, 56, 58, 59 and 68 [Vernick, 2003, Digene Corporation 2002]. Cervical cytology examination will be performed using the ThinPrep®Pap test.

Continued study participation as well as further referral/treatment will be based on the test results from each visit, and will be aligned with the clinical management algorithm which is aligned with the 2009 American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines for use of HPV DNA testing as an adjunct to cytology for cervical cancer screening in women 30 years or older.

The following clinical management algorithm will be applied, refer to Figure 3.

- Subjects with normal cervical cytology and who are oncogenic HPV DNA negative, will end their participation in the study.
- Subjects with normal cervical cytology, but who are oncogenic HPV DNA positive in one single test, will be asked to return at the next study visit.

  This outcome will only be applicable to subjects who were pregnant at their concluding HPV-015 study visit so that no cervical sample could be collected at that visit.
- Subjects with normal cervical cytology, but who are oncogenic HPV DNA positive in two subsequent tests, will be referred to colposcopy. The result of the subjects' last HPV-015 study visit will be taken into account at Visit 1.
- Subjects with a single cervical cytology reading of ≥ASC-US (atypical squamous cells of undetermined significance) positive for oncogenic HPV DNA will be referred to colposcopy.
- Subjects with a single cervical cytology reading of ≥LSIL (low grade squamous intraepithelial lesion) will be referred to colposcopy.

Please note that a missing result for HCII will be managed as oncogenic HPV positive.

In case of referral for colposcopy, the post-colposcopy follow-up strategies are:

- If no lesion is detected or the detected lesion does not require any treatment, subjects will be asked to return at the next study visit.
- If a lesion that requires treatment is detected, the subject should be referred to treatment according to local medical practice. Any further management following local cervical therapy for cervical lesions will be handled according to local medical practice within the local health care system. After treatment, the subject's participation in the study will end.

As management algorithms cannot define every clinical situation, it is the investigator's (or his/her designee's) responsibility to exercise appropriate clinical judgement in the medical management of each individual case.

Once their study participation ends, all subjects should be referred to their local health care system.

Subjects who have not developed cervical lesions by the end of the study, but who are still positive for oncogenic HPV infection, should be informed of the potential

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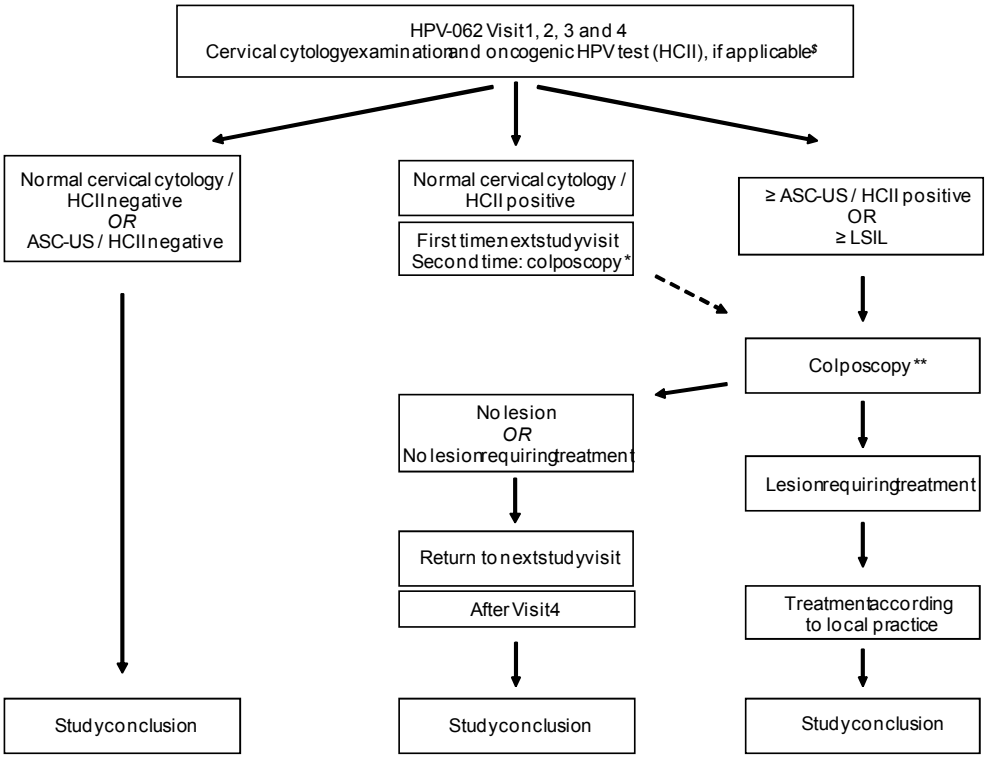
risks of being positive for oncogenic HPV DNA, and the importance of continued follow-up.

Figure 3 Clinical management algorithm



HPV DNA test (HCII) = Hybrid Capture® II test detecting HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68.
Specimens will be reported as "Quantity Not Sufficient" (QNS) in the case where there is an inadequate amount of cells for HCII and preferentially, a repeat sample will be collected. Missing HCII test results should be managed as oncogenic HPV positive
* = The result of the subject's concluding HPV-015 study visit will be taken into account. Subjects who were pregnant at that visit so that no cervical sample could be collected, and who display normal cytology but are positive for oncogenic HPV DNA at Visit 1, will return for the next study visit.
** = Colposcopy and/or colposcopy-directed biopsies will be performed according to local medical practice.
$ = Oncogenic HPV tests (HCII) will only be performed on normal and ASCUS cytological samples.

- **Study visit activities and gynaecological follow-up reporting**
  - Gynaecological examination at Visit 1, Visit 2, Visit 3 and Visit 4.
  - Collection of cervical liquid-based cytology samples at Visit 1, Visit 2, Visit 3 and Visit 4 for cervical cytology examination and oncogenic HPV DNA testing, if the cytology reading is normal or ASCUS.
  - Referral to colposcopy according to protocol clinical management algorithm, if required.
  - Conduct of colposcopy, colposcopy directed biopsies and local cervical therapy according to local medical practice, if required.
  - Recording of colposcopic referral according to management algorithm, if required.

- Recording of treatment referrals according to local medical practice, if required.

- **Safety reporting:**
  - All fatal SAEs will be reported.
  - All SAEs assessed as being possibly related to study participation will be reported.
  - All SAEs assessed as being possibly related to a concurrent GSK medication will be reported.
  - Withdrawal from the study due to adverse events (AEs) or SAEs will be reported.

No other AEs or SAEs for HPV-015 study subjects will be reported in this study. AEs and SAEs related to the vaccine administrated in the HPV-015 trial should be reported as part of the HPV-015 study, as described in the HPV-015 study protocol.

4. STUDY COHORT

4.1. Number of subjects

The study population will contain a subset of HPV-015 study subjects who displayed normal cervical cytology but tested positive for oncogenic HPV infection at their concluding HPV-015 study visit. Additionally, subjects who were pregnant at their concluding study visit were not able to provide a cervical sample and are therefore eligible for the study.

In total, approximately 1500 HPV-015 study subjects are expected to be eligible to participate in this study.

4.2. Inclusion criteria

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

- Written informed consent obtained from the subject prior to enrolment.
- Subjects who the investigator believes that they can and will comply with the requirements of the protocol.
- A subject previously enrolled in the study HPV-015 and who fulfils either of the following criteria:
  - displayed normal cervical cytology but tested positive for oncogenic HPV infection at her concluding HPV-015 study visit
  - was pregnant so that no cervical sample could be collected at her concluding HPV-015 study visit

4.3. Exclusion criteria for enrolment

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:

- A subject who at the HPV-015 concluding study visit displayed normal cervical cytology and who was negative for oncogenic HPV infection at that visit.
- A subject who at the HPV-015 concluding study visit had a cervical lesion at that visit or who had a cervical lesion that required treatment at her HPV-015 exit colposcopy.
- A subject for whom the cervical cytology results from the concluding HPV-015 study visit were unavailable for reasons other than pregnancy.

If at the time of enrolment the subject experiences heavy bleeding (menstruation or other) or heavy vaginal discharge, the pelvic exam cannot be performed. Enrolment will be deferred until condition is resolved according to investigator's medical judgment.

If the subject is pregnant at the time of enrolment, enrolment should be deferred until at least 3 months after the pregnancy has been completed. The subject should attend the next protocol scheduled visit (i.e. within the protocol windows). Subjects are eligible to enter the study at any visit.

5. CONDUCT OF THE STUDY

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

GSK will obtain favourable 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 be conducted in accordance with all applicable regulatory requirements, including a United States Investigational New Drug Application (US IND).

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

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

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- 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 prior to participation in the study.

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

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

5.2. Subject identification and randomisation of treatment

5.2.1. Subject identification (Administrative change 1)

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

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

5.2.2. Randomisation of treatment

Not applicable.

5.2.3. Randomisation of subjects to assay subsets

Not applicable.

5.3. Method of blinding

Not applicable.

5.4. General study aspects

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

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5.4.1. Cytology Report Terminology

Liquid-based cytology tests and oncogenic HPV tests (HCII) will be performed at Quest Diagnostics (Teterboro, NJ, US) or another GSK designated laboratory. Each cytopathological specimen will be reported according to the Bethesda 2001 Classification of cytological findings [Wright, 2002]. The terminology will include a statement as to whether a specimen is satisfactory or unsatisfactory.

The following categories for cytology reading will be specified:

- Negative for intraepithelial lesion or malignancy (negative).
  - Negative/HCII negative (Normal/oncogenic HPV negative)
  - Negative/HCII positive (Normal/oncogenic HPV positive).
  - Negative/HCII quantity not sufficient (Normal/QNS).
- Unsatisfactory.
- Atypical squamous cells of undetermined significance (ASC-US).
  - ASC-US/HCII negative (ASC-US/oncogenic HPV negative)
  - ASC-US/HCII positive (ASC-US/oncogenic HPV positive).
  - ASC-US/HCII quantity not sufficient (ASC-US/QNS).
- Atypical squamous cells cannot exclude HSIL (ASC-H).
- Low-grade squamous intraepithelial lesion (LSIL).
- High-grade squamous intraepithelial lesion (HSIL).
- Atypical glandular cells (AGC).
- Invasive malignancy.

Specimens will be reported as “Quantity Not Sufficient” (QNS) in the case where there is an inadequate amount of cells for HCII and preferentially, a repeat sample will be collected. Missing HCII test results should be managed as oncogenic HPV positive.

Oncogenic HPV tests (HCII) will only be performed on normal and ASCUS cytological samples.

The results of the cytology and HCII testing will be communicated to the investigator (or his/her designee) by Quest Diagnostics (Teterboro, NJ, US), or another GSK designated laboratory. The investigator (or his/her designee) will notify the subject of the test result and if applicable, it is recommended that the subject should receive colposcopy within 30 days after cytology and HCII results have been communicated by Quest Diagnostics (Teterboro, NJ, US), or another GSK designated laboratory.

5.4.2. Histopathology Report Terminology

Any histopathological lesions will be biopsied or excised locally according to local medical practice. Histopathological reports on biopsy and excision specimens will be written according to local medical practice.

5.4.3. Clinical Management Algorithm

The clinical management algorithm in Figure 3 describes the management of all cytology results obtained at study visits.

5.4.4. Unsatisfactory cytological findings

When the laboratory results deem a cervical liquid-based cytology specimen "unsatisfactory", study personnel are required to repeat the specimen as soon as possible after cytology results have been communicated and not wait until the next scheduled protocol visit. Only satisfactory results of a repeat cytology result will count as the final cytology result for that study visit.

In addition, cytological specimens reported as "satisfactory for evaluation-endocervical/ transformation zone component absent" should be managed according to the given cytological diagnosis. These smears should not be repeated but the information may be used for quality control monitoring.

Missing cytology results will be recorded as "missing results" (in the case of lost/ damaged sample) and preferentially a repeat cytology will be performed.

Specimens will be reported as "Quantity Not Sufficient" (QNS) in the case where there is an inadequate amount of cells for HCII and preferentially, a repeat sample will be collected. Missing HCII test results should be managed as oncogenic HPV positive according to the requirements specified in the clinical management algorithm (refer to Figure 3).

5.4.5. Abnormal cytology

Observation of abnormal cytology ≥ ASC-US (atypical squamous cells of undetermined significance) positive for oncogenic HPV DNA as determined by the HCII test will result in referral to colposcopic evaluation.

Observation of ≥ LSIL (low grade squamous intraepithelial lesion) will result in referral to colposcopic evaluation.

5.5. Colposcopic evaluation

The clinical management algorithm in Figure 3 describes the management of all cytology results obtained at study visits.

Colposcopy will be performed according to local medical practice. All colposcopies will be recorded in the eCRF and every attempt will be made to document colposcopy performed outside the study in the specific section on the eCRF.

Any cervical lesions will be biopsied or excised according to local medical practice. In addition, the vagina and vulva may be inspected with each colposcopy. All tissue will be processed locally.

5.6. Management of cervical lesions

Local cervical therapy for cervical lesions will be handled locally according to local medical practice.

Any further management following local cervical therapy for cervical lesions will be handled according to local medical practice within the local health care system. The treatment of cervical, lesions (or other lesions detected during the medical evaluation such as vaginal or vulval lesions) is to be handled according to local medical practice.

5.7. Outline of study procedures

Table 1 presents the outline of the study procedures to be followed by the investigator (at the study centre).

Subjects are eligible to enter the study at any visit.

The intervals between visits are outlined in Table 2. It is the investigator's responsibility to ensure that the intervals between visits are followed as closely as possible. If a subject misses a visit, the missed visit will not be performed, but the subject may return to the next scheduled visit.

If a subject becomes pregnant during the study, she will not undergo any gynaecological examination nor have a cervical cytology sample taken during her pregnancy. The missed visit will not be performed. Three months after delivery, the subject may return to the next scheduled visit. For subject that are pregnant at the last study visit, no conclusion visit will be performed. Women should be informed of the potential risks of being positive for oncogenic HPV DNA and of the importance of continued follow-up.

Investigators will follow-up subjects with SAEs assessed as being related to study procedures or SAEs assessed as being related to a concurrent GSK medication until the event has resolved, subsided, stabilised, disappeared, the event is otherwise explained, or the subject is lost to follow-up, or, in the case of non-serious AEs leading to study withdrawal, until they are lost to follow-up.

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Table 1 List of study procedures

Visit	VISIT 1	VISIT 2	VISIT 3	VISIT 4
Timing (Months post concluding HPV-015 visit (Visit 9, Visit 11 or last HPV-015 study visit as planned in the HPV-015 protocol amendment 4))	**Month 12**	**Month 24**	**Month 36**	**Month 48**
Informed consent	●	●*	●*	●*
Check inclusion criteria	●	●*	●*	●*
Check exclusion criteria	●	●*	●*	●*
Collect demographic data	●	●*	●*	●*
Gynaecological examination	●	●	●	●
Collect cervical liquid-based cytology sample	●	●	●	●
Review oncogenic HPV infection status, if applicable	○	○	○	○
Review cervical cytology status	○	○	○	○
Record referral to colposcopy, if applicable	●	●	●	●
Record treatment referral, if applicable	●	●	●	●
Record concomitant medication/vaccination, if applicable	●	●	●	●
Review continued study participation and counsel subjects for gynaecological follow-up if study conclusion[$]	○	○	○	
Reporting of fatal SAEs	●	●	●	●
Reporting of SAEs related to study participation	●	●	●	●
Reporting of SAEs related to a concurrent GSK medication	●	●	●	●
Reporting of AEs and SAEs leading to study withdrawal	●	●	●	●
Study Conclusion	● $	● $	● $	●

● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not requires documentation in the individual eCRF.
*Subjects are eligible to join the study at any visit
$ A subject who has been referred to local treatment or who displays normal cervical cytology and who tests negative for oncogenic HPV DNA will exit the study.

Table 2 Intervals between study visits

Interval (Months after HPV-015 concluding visit (Visit 9, Visit 11 or last HPV-015 study visit as planned in the HPV-015 protocol amendment 4))	Length of interval (days)	Recommended interval between scheduled visits (days)*
Concluding visit HPV-015 → Visit 1 HPV-062 (Month 12)	183-547	365
Concluding visit HPV-015 → Visit 2 HPV-062 (Month 24)	548-912	730
Concluding visit HPV-015 → Visit 3 HPV-062 (Month 36)	913-1277	1095
Concluding visit HPV-015 → Visit 4 HPV-062 (Month 48)	1278-1642	1460

*There should be a minimum of 183 days between two consecutive study visits.

5.8. Detailed description of study procedures

Subjects are eligible to join the study at any visit.

5.8.1. Procedures prior to study participation

5.8.1.1. Informed consent

Before performing any other study procedure, the signed informed consent of the subject needs to be obtained. Refer to Section 5.1 for information on how to obtain informed consent.

5.8.2. Procedures during study participation

5.8.2.1. Check inclusion and exclusion criteria

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

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.

5.8.2.2. Collect demographic data

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

5.8.2.3. Gynaecological examination

Perform gynaecological examination according to local medical practice. This may include breast exam. Treatment of any abnormality observed during this examination will be performed according to local medical practice or by referral to an appropriate health care provider. Study related pelvic exams for collection of cervical specimens will be suspended in women known to be pregnant and will resume 3 months after resolution. Missing procedures will not be rescheduled.

5.8.2.4. Cervical sampling

- Collect sample for cervical liquid-based cytology examination (ThinPrep® PapTest). Oncogenic HPV DNA (HCII) testing will be performed, if applicable.

  Sexual intercourse should be avoided for the 24 hours before collection of a cervical specimen. Cervical specimen collection must be performed a minimum of one day after menstrual flow has ceased. Female subjects who will be menstruating during planned visits will be invited to reschedule cervical specimen collection and/or their pelvic examination according to the medical judgement of the investigator. Pelvic examinations for collection of cervical specimens will be suspended in female subjects known to be pregnant until 3 months after resolution.

In case of abnormal cytological findings and if contact cannot be confirmed by phone, a certified/registered letter requiring the signature of the subject will be sent by the study site personnel.

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5.8.2.5. Review oncogenic HPV infection status and cervical cytology status

- Review oncogenic HPV infection status, if applicable.
- Review cervical cytology status.

5.8.2.6. Recording of referral to colposcopy and treatment (if applicable)

- Record referral for colposcopy according to clinical management algorithm, if applicable. The result of the subjects' last HPV-015 study visit will be taken into account. It is recommended that colposcopy is performed within 30 days of referral.
- Record treatment referral, if applicable.

5.8.2.7. Recording of concomitant medication

- Record concomitant medication, if applicable.

5.8.2.8. Review of continued study participation

- Review continued participation in study according to clinical management algorithm and counsel the subject for appropriate continuous gynaecological follow up if study conclusion.

5.8.2.9. Reporting of non-serious AEs and SAEs

- Report all fatal SAEs (refer to Section 8.1.3 for the definition of SAEs).
- Report all SAEs assessed as being possibly related to study participation.
- Report all SAEs assessed as being possibly related to a concurrent GSK medication.
- Report all AEs/SAEs (refer to Section 8.1 for the definition of AEs) leading to withdrawal from the study.

Refer to Section 8.3 for procedures for the Investigator to record 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 will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious.

5.8.2.10. Study conclusion

At study conclusion, the subject will be counselled for appropriate continuous gynaecological follow up. No other post-study treatment will be provided.

5.9. Biological Sample handling and analysis

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

Samples will not be labelled 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. Any anti-HIV testing will also require specific consent and 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).

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.

5.9.1. Use of specified study materials

When materials are provided by GSK Biologicals or Quest Diagnostics, it is MANDATORY that all clinical samples be collected and stored exclusively using those materials in the appropriate manner. The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals or Quest Diagnostics 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 of clinical trial supplies in the SPM.

5.9.2. Biological samples

Table 3 Biological samples

Sample type	Quantity	Unit	Timepoint	Subset /Sub-cohort Name
Cervical sample	N/A	N/A	scheduled	N/A

5.9.3. Laboratory assays

Please refer to Section 5.9.4 for a detailed description of the assays performed in the study.

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The following sections describe laboratory assays to be used for all biological samples collected throughout the entire study period. Detailed instructions for all laboratory assays will be provided in a separate manual to the investigator.

Cytology samples will be shipped to Quest Diagnostics (Teterboro, NJ, US), or another GSK designated laboratory (refer to Appendix A) prior to any laboratory assay/testing being performed.

Biopsy samples will be processed locally, if applicable.

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.

Sample analysis will be performed in the specific laboratories described in Table 4.

Table 4 Laboratory assays

Laboratory Discipline	Component	Scale	Method	Test kit/ Manufacturer	Unit	Cut-off	Laboratory*
Qualitative cervical cytology	Bethesda 2001 System for reporting cervical Cytology diagnoses	Qualitative	Microscopy of cervical cytology	ThinPrep®PapTest™/ Cytyc Corp.	N/A	N/A	Quest Diagnostics (Teterboro, NJ US) or another GSK designated laboratory
Qualitative DNA hybridisation	HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 (Oncogenic probe [cocktail B])	Qualitative	Nucleic acid hybridisation	Hybrid Capture® II HPV DNA Test/Digene Corporation	N/A	N/A	Quest Diagnostics (Teterboro, NJ USA) or another GSK designated laboratory

*GSK Biologicals laboratory or validated laboratory designated by GSK Biologicals.
N/A: Not Applicable

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.

5.9.4. Biological samples evaluation

5.9.4.1. Cytology

Cervical cytology will be performed using the ThinPrep® PapTest (Cytyc Corporation, Boxborough, MA, USA), by Quest Diagnostics (Teterboro, NJ, US), or another GSK designated laboratory. Cervical cells for ThinPrep® cytology will be collected using the sampling device provided and rinsed into a collection vial containing PreservCyt® medium (provided by GSK Biologicals or Quest Diagnostics).

Note that collection of cytological specimens at colposcopy will be performed according to local medical practice.

5.9.4.2. HPV DNA Testing by Hybrid Capture II (HCII)

After ThinPrep® cytology slides have been prepared, residual PreservCyt® specimens on slides read as normal or ASCUS will be tested for HPV DNA. Testing will be done by Quest Diagnostics (Teterboro, NJ, US), or another GSK designated laboratory using the Hybrid Capture® II test (HCII; Digene Corp., Gaithersburg, MD, USA). Probe B will be used and is designed to detect infections with one of 13 oncogenic HPV types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) [Vernick 2003, Digene Corporation 2002]. This test does not provide type-specific data.

5.9.5. Immunological correlates of protection

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

6. STUDY VACCINE AND ADMINISTRATION

No investigational product will be administered in the current study.

GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine was administered to the HPV-015 study vaccine group. Cross-over vaccination will be offered to the subjects in the HPV-015 control group either by providing commercially available HPV-16/18 L1 VLP AS04 vaccine or, if the vaccine is not licensed for the respective age group in the considered country, through a separate clinical trial protocol. No vaccine will be administered in the current study.

6.1. Concomitant medication/vaccination

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

All concomitant medication administered for the treatment of an AE that leads to study withdrawal must be recorded in the eCRF with generic name of the medication (trade names are allowed for combination drugs only), medical indication (including which AE), total daily dose, route of administration, start and end dates of treatment.

Similarly, concomitant medication administered for the treatment of an ultimately fatal SAE, an SAE leading to study withdrawal, an SAE related to study participation or an SAE related to GSK products at any time, must be recorded on the SAE screens in the eCRF, as applicable. Refer to Section 8.1.3 for the definition of a SAE.

Any investigational medication or vaccine must be recorded in the eCRF.

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

Concomitant medication/vaccination as defined in Section 6.1 as well as investigational medication or vaccine administered from the concluding visit of HPV-015 to the HPV-062 EXT:015 study conclusion must be recorded in the eCRF throughout the study period.

7. HEALTH ECONOMICS

Not applicable.

8. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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

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

8.1. Safety definitions

NOTE: The term AE denotes both non-serious and serious adverse events. In this study, only fatal SAEs, SAEs related to study participation, SAEs related to a concurrent GSK medication and AEs or SAEs leading to withdrawal from the study will be reported.

8.1.1. Definition of an adverse event

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

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

Examples of an AE include:

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

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- 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 product or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with vaccine administration.
- Significant failure of expected pharmacological or biological action.

8.1.2. 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).

8.1.3. Definition of a serious adverse event

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

a. Results in death.

b. Is life-threatening.

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

c. Requires hospitalisation or prolongation of existing hospitalisation.

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

Hospitalisation 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, diarrhoea, 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 judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

8.1.4. Solicited adverse events

Not applicable.

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

Abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments that are judged by the investigator to be clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE, as defined in Section 8.1.1 or of a SAE, as defined in Section 8.1.3. 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 judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

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

8.2.1. Pregnancy

Pregnancies and pregnancy outcomes during the current study will not be followed-up, if they are not fatal SAEs, SAEs related to study participation, SAEs related to a concurrent GSK medication or AEs/SAEs leading to withdrawal from the study.

While pregnancy itself is not considered an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or a SAE, as described in Sections 8.1.1 and 8.1.3, and will be followed as described in Section 8.4.4, if it is a fatal SAE, an SAE related to study participation, an SAE related to a concurrent GSK medication or an AE/SAE leading to withdrawal from the study.

A spontaneous abortion is always considered to be a SAE and will be reported as described in Section 8.4, if it is a fatal SAE, an SAE related to study participation, an SAE related to a concurrent GSK medication or an AE/SAE leading to withdrawal from the study. Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered by the investigator to be reasonably related in time to a study procedure will be reported to GSK Biologicals as described in Section 8.4, if it is a fatal SAE, an SAE related to study participation, an SAE related to a concurrent GSK medication or an AE/SAE leading to withdrawal from the study. 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.

Serious pregnancy outcomes that are reported as related to the study vaccine administered in HPV-015 have to be reported under the HPV-015 protocol.

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

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

All AEs leading to study withdrawal that are either observed by the investigator or one of his clinical collaborators or reported by the subject spontaneously or in response to a direct question will be evaluated by the investigator. AEs leading to study withdrawal that are not previously documented in the study will be recorded in the Adverse Event screen within the subject's eCRF. The nature of each event, date and time (where

appropriate) of onset, outcome and intensity should be established. Details of any corrective treatment should be recorded on the appropriate page of the eCRF.

An overview of the protocol-required reporting periods for adverse events and serious adverse events is given in Table 5.

Table 5 Reporting periods for adverse events and serious adverse events

Study activity	Visit 1. Month 12	Visit 2 Month 24	Visit 3 Month 36	Visit 4 Month 48
Reporting of SAEs related to study participation, SAEs related to a concurrent GSK medication or any fatal SAEs,				
Reporting of AEs or SAE leading to study withdrawal				

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 5. 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 HPV-015 study, and he/she considers the event reasonably related to the investigational product, the investigator will promptly notify the Study Contact for Reporting SAEs. Any post-study SAEs for HPV-015 subjects are to be recorded in the HPV-015 study.

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 should be asked a non-leading question such as:

'Have you felt different in any way 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.

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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:

The investigator will assess 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 judgement.

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 a SAE. Grade 3 is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 8.1.3.

8.3.2.2.2. Assessment of causality

The investigator should assess the causality of each AE/SAE. The investigator will use clinical judgement to determine the relationship of AEs/SAEs to study procedures or to GSK concomitant medication. Alternative causes, such as natural history of the underlying diseases, concomitant therapy and other risk factors will be considered and investigated.

There may be situations when an AE/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 AE/SAE to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE information accordingly.

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If an event meets the criteria to be determined 'serious' (refer to Section 8.1.3), it will be examined by the investigator to the extent to enable determination of all contributing factors applicable to each SAE.

Possible contributing factors include:

- Medical history.
- Concomitant medication.
- Protocol required procedure.
- Other procedure not required by the protocol.
- Other cause (specify).

8.3.2.3. Assessment of outcomes

Outcome of any non-serious AE leading to study withdrawal 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).

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

8.4.1. Prompt reporting of serious adverse events to GSK Biologicals

SAEs will be reported promptly to GSK as described in Table 6 once the investigator determines that the event meets the protocol definition of an SAE.

Table 6 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**
All SAEs	24 hours*	SAE report/SAE screen	24 hours*	SAE report/SAE screen

* Time frame allowed after receipt or awareness of the information.

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.

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Back-up Study Contact for Reporting SAEs
GSK Biologicals Clinical Safety & Pharmacovigilance
Fax: PPD or PPD
24/24 hour and 7/7 day availability

8.4.2. Regulatory reporting requirements for serious adverse events

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

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

8.4.3. Completion and transmission of SAEs reports to GSK Biologicals

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

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

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

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

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

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

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

When additional information is received on a SAE after freezing of the subject's eCRF, new or updated information is to be recorded on the paper SAE Report Form, with all changes signed and dated by the investigator. The updated SAE Report Form should be 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. 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 the end of the study.

Investigators will follow-up subjects:

- With SAEs or subjects withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilised, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.

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

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

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GSK Biologicals will be provided with a copy of any available post-mortem findings, including histopathology.

8.5. Treatment of adverse events

Treatment of any adverse event is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of an AE should be recorded in the subject's eCRF. Refer to Section 6.1.

8.6. Unblinding

For subjects who conclude the HPV-015 study at Visit 9 or Visit 11, but agree to remain blinded until the final analysis of study HPV-015, the following applies:

GSK Biologicals' policy (incorporating ICH E2A guidance, EU Clinical Trial Directive and Federal Regulations) is to unblind any serious adverse event (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

For subjects who conclude the HPV-015 study at Visit 9 or Visit 11, but agree to remain blinded until the final analysis of study HPV-015, the following applies:

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

For subjects concluding the HPV-015 study at the last study visit planned under protocol amendment 4, the HPV-062 EXT:015 study will be open label, i.e. both the investigator and the subject will be aware of the vaccine being administered to the subjects. Therefore, the information given hereunder is limited to the unblinding of SAEs to any third parties (e.g. any doctor other than the study investigator), in accordance with GSK Biologicals' standard operating procedures.

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) For US/Canada only: PPD (GSK Biologicals Central Safety Physician on-call) **Back-up phone contact**: Outside US/Canada: PPD For US/Canada only: PPD

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

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 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/is available for the concluding contact foreseen in the protocol or who was discharged from the study, either due to treatment referral or due to having cleared the oncogenic HPV infection is considered to have completed the study.

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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 is any subject who did not come back for the concluding visit and who was not discharged from the study, either due to treatment referral or due to having cleared the oncogenic HPV infection.

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

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

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

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

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

9.2.2. Subject withdrawal from investigational vaccine/product

Not applicable.

9.3. Extension study

Not applicable.

10. DATA EVALUATION: CRITERIA FOR EVALUATION OF OBJECTIVES

10.1. Study endpoints

- Occurrence of positive oncogenic HPV DNA results in cervical samples by HPV DNA testing (Hybrid Capture® II test [HCII]).
- Occurrence of cervical cytological abnormalities in cervical samples by ThinPrep® PapTest.
- Occurrence of referral to colposcopy.
- Occurrence of referral to treatment.

10.2. Estimated sample size

This study is descriptive and no power evaluations will be performed.

Approximately 1500 HPV-015 study subjects are expected to be invited to participate in this study.

10.3. Study cohorts to be evaluated

The study cohort will include all subjects who attended at least one visit in the study and for whom data are available. No according-to-protocol cohort has been defined.

10.4. Derived and transformed data

Not applicable.

10.5. Conduct of analyses

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

10.5.1. Sequence of analyses

Not applicable.

10.5.2. Statistical considerations for interim analyses

No interim analysis is planned for this study.

10.6. Statistical methods

10.6.1. Analysis of demographics/baseline characteristics

Demographic characteristics (age and gender), withdrawal status will be summarised using descriptive statistics:

- Frequency tables will be generated for categorical variable such as race.
- Mean, median, standard error will be provided for continuous data such as age.

10.6.2. Analysis of efficacy

Not applicable.

10.6.3. Analysis of immunogenicity

Not applicable.

10.6.4. Descriptive analysis of safety

For each subject and overall:

- Results of oncogenic HPV DNA tests.
- Results of cervical cytology tests.
- Referrals to colposcopy according to management algorithm, if required.
- Referrals to treatment according to local medical practice, if required.
- All fatal SAEs occurring throughout the study period.
- All SAEs assessed as being possibly related to study participation occurring throughout the study period.
- All SAEs assessed as being possibly related to GSK products occurring throughout the study period.
- Withdrawal from the study due to AEs or SAEs.

11. ADMINISTRATIVE MATTERS

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

11.1. Remote Data Entry instructions

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

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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 Good Clinical practice (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 an 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.

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

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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.

12. COUNTRY SPECIFIC REQUIREMENTS

Not applicable.

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Appendix A Laboratory assays

Cytology

Cervical cytology will be performed using the ThinPrep® PapTest (Cytyc Corporation, Boxborough, MA, USA), by Quest Diagnostics (Teterboro, NJ, US) or another GSK designated laboratory. Cervical cells for ThinPrep® cytology at scheduled 12-month interval visits will be collected using the sampling device provided rinsed into a collection vial containing PreservCyt® medium (provided by GSK Biologicals or Quest Diagnostics).

Note that collection of cytological specimens at colposcopy will be performed according to local medical practice.

HPV DNA Testing by Hybrid Capture II (HCII)

After ThinPrep® cytology slides have been prepared, residual PreservCyt® specimens on slides read as normal or ASCUS will be tested for HPV DNA. Testing will be done by Quest Diagnostics (Teterboro, NJ, US), or another GSK designated laboratory using the Hybrid Capture® II test (HCII; Digene Corp., Gaithersburg, MD, USA). Probe B will be used and is designed to detect infections with one of 13 oncogenic HPV types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) [Vernick 2003, Digene Corporation 2002]. This test does not provide type-specific data.

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Appendix B Amendments and Administrative Changes to the Protocol

GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Amendment 1**	
eTrack study number and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Amendment number:	Amendment 1
Amendment date:	Amendment 1 Final: 21 June 2010
Co-ordinating author:	PPD Scientific Writer

Rationale/background for changes:

- Redundant text concerning oncogenic HPV DNA test results classification was deleted from Section 5.4.1.
- According to the protocol, histopathological reports will be performed locally and do not require reporting in the eCRF. This has been corrected in Section 5.4.2.
- According to the protocol, colposcopy should be performed on women with two positive oncogenic HPV DNA tests or one cervical cytology reading ≥ASC-US positive for oncogenic HPV DNA or one cervical cytology reading ≥LSIL (missing HCII test results should be managed as oncogenic HPV positive). This has been corrected in Section 5.5.
- Oncogenic HPV testing (HCII) will only be performed on normal and ASCUS cytological samples. This has been corrected throughout the protocol.
- It has been clarified throughout the protocol that oncogenic HPV infection status and cervical cytology status do not have to be recorded in the eCRF, as these data will automatically be transferred into the database.
- The list of contributing authors has been updated.
- The indication for Cervarix has been updated to be in line with the current Global Data Sheet.
- Throughout the document, some minor corrections (including typographical and formatting errors) and clarifications have been performed.

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113617 (HPV-062 EXT:015)
Administrative Change 1

Amended text has been indicated in *bold italics*, deletions are indicated by ~~strikethrough~~ in the following sections:

Title page

Contributing authors	PPD Regulatory Affairs Representative PPD ***Regulatory Affairs Representative*** PPD External Laboratory Coordinator PPD ***External Laboratory Coordinator*** PPD Clinical Data Coordinator PPD ***Clinical Data Coordinator***

Synopsis

Indication	~~GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine is indicated in females from 10 years of age onwards for the prevention of pre-malignant cervical lesions and cervical cancer causally related to Human Papillomavirus (HPV) types 16 and 18.~~ ***Cervarix is indicated in females from 10 years of age onwards for the prevention of persistent infection, premalignant cervical lesions and cervical cancer (squamous-cell carcinoma and adenocarcinoma) caused by oncogenic Human Papillomaviruses (HPV).***
Rationale for the study and study design	If very few subjects are eligible for this study at one HPV-015 study site and if adequate gynaelogical follow-up care is available through the local health care system, these subjects may be referred to the local health care system***, provided that ethical committee approval is obtained by the responsible investigator***. **(Note, also amended in Section 1.2)**
Study design	• **Study procedures:** At each visit, a gynaecological examination will be performed and cervical liquid-based cytology samples will be collected for ~~oncogenic HPV DNA testing and~~ cervical cytology examination ***and oncogenic HPV DNA testing, if the cytology reading is normal or ASCUS***. The presence of oncogenic HPV infection will be determined by the Hybrid Capture® ~~2~~***II*** (~~HC2~~***HCII***) test, which detects HPV DNA types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 [Vernick 2003, Digene Corporation 2002]. Cervical cytology examination will be performed using the ThinPrep®Pap test. Continued study participation as well as further referral/treatment will be based on the test results from each visit, and ~~will be performed according to a~~***will be***

aligned with the clinical management algorithm which is aligned with the 2009 American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines for use of HPV DNA testing as an adjunct to cytology for cervical cancer screening in women 30 years or older.

The following clinical management algorithm will be applied:

- Subjects with normal cervical cytology and who are oncogenic HPV DNA negative, will end their participation in the study.
- Subjects with normal cervical cytology, but who are oncogenic HPV DNA positive in one single test, will be asked to return at the next study visit.

  This outcome will only be applicable to subjects who were pregnant at their concluding HPV-015 study visit so that no cervical sample could be collected at that visit.
- Subjects with normal cervical cytology, but who are oncogenic HPV DNA positive in two subsequent tests, will be referred to colposcopy. The result of the subjects' concluding HPV-015 study visit will be taken into account at Visit 1.
- Subjects with a single cervical cytology reading of ≥ASC-US (atypical squamous cells of undetermined significance) positive for oncogenic HPV DNA will be referred to colposcopy.
- Subjects with a single cervical cytology reading of ≥LSIL (low grade squamous intraepithelial lesion) will be referred to colposcopy~~, irrespective of their oncogenic HPV DNA test result~~.

Please note that a missing result for HCII will be managed as oncogenic HPV positive.

In case of referral for colposcopy, the post-colposcopy follow-up strategies are:

- If no lesion is detected or the detected lesion does not require any treatment, subjects will be asked to return at the next study visit.
- If a ~~high-grade~~ lesion ***that requires treatment*** is detected, the subject should be referred to treatment according to local medical practice. Any further management following local cervical therapy for cervical lesions will be handled according to local medical practice within the local health care system. After treatment, the subject's participation in the study will end.

- **Study visit activities and gynaecological follow-up reporting**
  - Collection of cervical liquid-based cytology samples at Visit 1, Visit 2, Visit 3 and Visit 4 for cervical cytology examination and oncogenic HPV DNA testing***, if the cytology reading is normal or ASCUS*** ~~and recording of the results~~.

(Note, also amended in Section 3)

LIST OF ABBREVIATIONS

~~HC2~~HCII	***Hybrid Capture ~~2~~II***

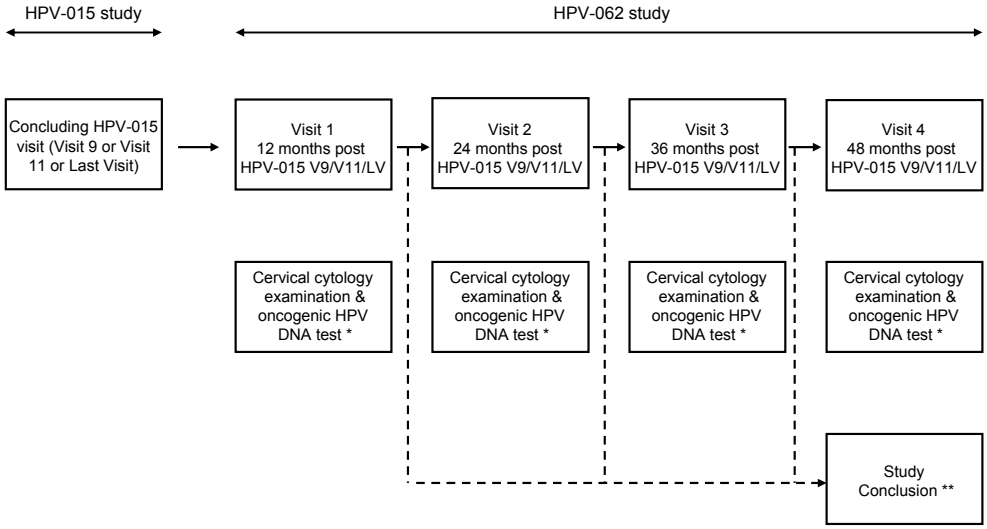
(Note, this has been updated throughout the protocol)

GLOSSARY OF TERMS

Conclusion Visit of Study HPV-015	***Subjects who participated in the HPV-015 study may decide to conclude their participation in the HPV-015 study at Visit 9, Visit 11 or at the last study visit in HPV-015 planned under protocol amendment 4.***

3. STUDY DESIGN OVERVIEW

Figure 1 Study visits and study procedures



*Subjects with two positive oncogenic HPV DNA tests or one cervical cytology reading ≥ASC-US (atypical squamous cells of undetermined significance) positive for oncogenic HPV DNA or one cervical cytology reading ≥LSIL (low grade squamous intraepithelial lesion) will be referred for colposcopy evaluation according to the clinical management algorithm. ***Oncogenic HPV tests (HCII) will only be performed on normal and ASCUS cytological samples.***

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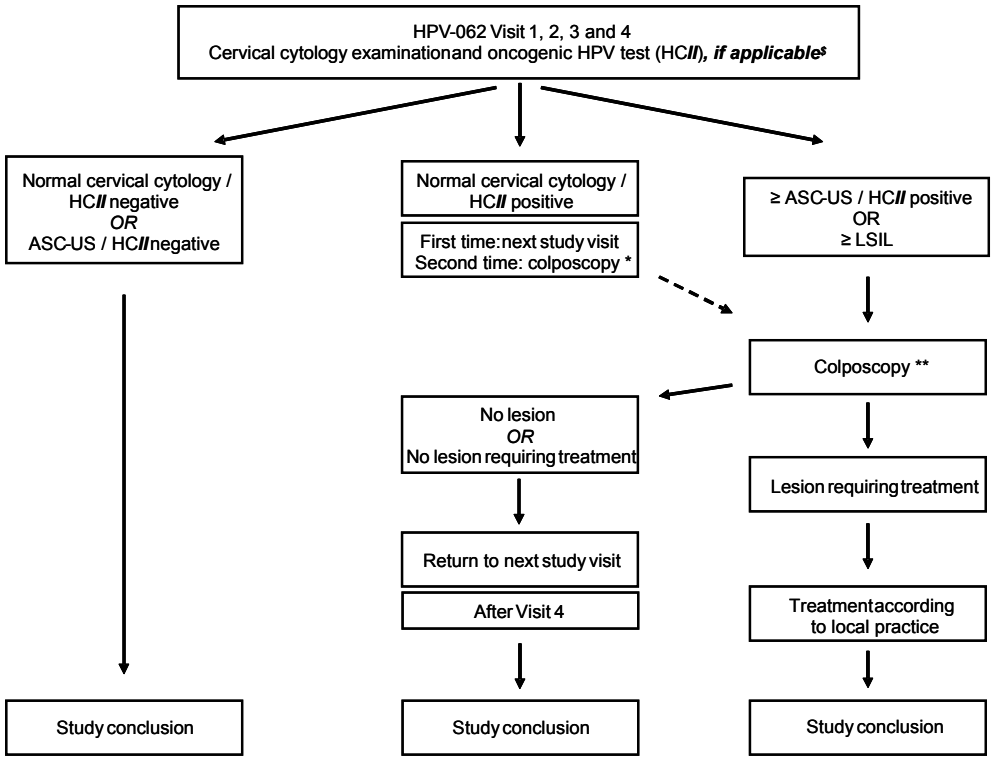
Figure 3 Clinical management algorithm



HPV DNA test (~~HC2~~*HCII*) = Hybrid Capture® ~~2~~*II* test detecting HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68. Specimens will be reported as "Quantity Not Sufficient" (QNS) in the case where there is an inadequate amount of cells for ~~HC2~~*HCII* and preferentially, a repeat sample will be collected. Missing ~~HC2~~*HCII* test results should be managed as oncogenic HPV positive
$ = Oncogenic HPV tests (HCII) will only be performed on normal and ASCUS cytological samples.

5.4.1. Cytology Report Terminology

Liquid-based cytology tests and oncogenic HPV ~~DNA~~ tests ***(HCII)*** will be performed at Quest Diagnostics (Teterboro, NJ, US) or another GSK designated laboratory. Each cytopathological specimen will be reported according to the Bethesda 2001 Classification of cytological findings [Wright, 2002].

The following categories for cytology reading will be specified:

- Negative for intraepithelial lesion or malignancy (negative).
  - ***Negative/HCII negative (Normal/oncogenic HPV negative)***
  - ***Negative/HCII positive (Normal/oncogenic HPV positive).***
  - ***Negative/HCII quantity not sufficient (Normal/QNS).***
- Unsatisfactory.

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- Atypical squamous cells of undetermined significance (ASC-US).
  - ASC-US/HC~~2~~***II*** negative (ASC-US/oncogenic HPV negative)
  - ASC-US/HC~~2~~***II*** positive (ASC-US/oncogenic HPV positive).
  - ASC-US/HC~~2~~***II*** quantity not sufficient (ASC-US/QNS).
- Atypical squamous cells cannot exclude HSIL (ASC-H).
- Low-grade squamous intraepithelial lesion (LSIL).
- High-grade squamous intraepithelial lesion (HSIL).
- Atypical glandular cells (AGC).
- Invasive malignancy.

~~The following categories for oncogenic HPV test (HC2) outcome will be specified:~~

- ~~Oncogenic HPV negative.~~
- ~~Oncogenic HPV positive.~~
- ~~Quantity Not Sufficient (QNS).~~

Oncogenic HPV tests (HCII) will only be performed on normal and ASCUS cytological samples.

The results of the cytology and ~~HC2~~***HCII*** testing will be communicated to the investigator (or his/her designee) by Quest Diagnostics (Teterboro, NJ, US), or another GSK designated laboratory. The investigator (or his/her designee) will notify the subject of the test result and if applicable, it is recommended that the subject should receive colposcopy within 30 days after cytology ***and HCII*** results have been communicated by Quest Diagnostics (Teterboro, NJ, US), or another GSK designated laboratory.

5.4.2. Histopathology Report Terminology

Any histopathological lesions will be biopsied or excised locally according to local medical practice. Histopathological reports on biopsy and excision specimens will be ~~performed locally and~~ ***written*** according to local medical practice. ~~All histopathological reports will be recorded in the eCRF.~~

~~The following categories could be classified:~~

- ~~Negative.~~
- ~~Low grade squamous intraepithelial lesion (condyloma / cervical intraepithelial neoplasia grade 1 (CIN1) / vaginal intraepithelial neoplasia grade 1 (VAIN 1) / vulval intraepithelial neoplasia grade 1 (VIN 1)).~~
- ~~High grade squamous intraepithelial lesion (cervical intraepithelial neoplasia grade 2 (CIN2) / vaginal intraepithelial neoplasia grade 2 (VAIN 2) / vulval intraepithelial neoplasia grade 2 (VIN 2)).~~

- ~~High grade squamous intraepithelial lesion (cervical intraepithelial neoplasia grade 3 (CIN3) / vaginal intraepithelial neoplasia grade 3 (VAIN 3) / vulval intraepithelial neoplasia grade 3 (VIN 3)).~~
- ~~Adenocarcinoma *in-situ* (AIS).~~

~~Invasive malignancy.~~

5.4.5. Abnormal cytology

Observation of ≥ LSIL (low grade squamous intraepithelial lesion) will result in referral to colposcopic evaluation~~, irrespective of the oncogenic HPV DNA test result~~.

5.5. Colposcopic evaluation

Colposcopy will be performed according to local medical practice ~~on women with abnormal cytological findings~~. All colposcopies will be recorded in the eCRF and every attempt will be made to document colposcopy performed outside the study in the specific section on the eCRF.

Any cervical lesions will be biopsied or excised according to local medical practice. In addition, the vagina and vulva may be inspected with each colposcopy ~~and any vaginal or vulval lesions possibly associated with HPV (other than condylomas) may be biopsied or excised according to local medical practice~~. All tissue will be processed locally.

5.6. Management of cervical lesions

Any further management following local cervical therapy for cervical lesions will be handled according to local medical practice within the local health care system. The treatment of cervical~~, vaginal or vulval~~ lesions ***(or other lesions detected during the medical evaluation such as vaginal or vulval lesions)*** ~~possibly associated with HPV~~ is to be handled according to local medical practice.

5.7. Outline of study procedures

Table 1 List of study procedures

Visit	VISIT 1	VISIT 2	VISIT 3	VISIT 4
Timing (Months post concluding HPV-015 visit (Visit 9, ~~or~~ Visit 11 *or last HPV-015 study visit as planned in the HPV-015 protocol amendment 4*))	**Month 12**	**Month 24**	**Month 36**	**Month 48**
Review ~~and record~~ oncogenic HPV infection status***, if applicable***	○**	○**	○**	○**
Review ~~and record~~ cervical cytology status	○**	○**	○**	○**
Record concomitant medication/***vaccination***, if applicable	●	●	●	●

***** Amended 21 June 2010***

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5.8.2.4. Cervical sampling

- Collect sample for cervical liquid-based cytology examination (ThinPrep® PapTest)**.** ~~and o~~***O***ncogenic HPV DNA (~~HC2~~***HCII***) test***ing will be performed, if applicable***.

5.8.2.5. Review ~~and record~~ oncogenic HPV infection status and cervical cytology status

- Review ~~and record~~ oncogenic HPV infection status***, if applicable***.
- Review ~~and record~~ cervical cytology status.

5.8.2.6. Recording of referral *to colposcopy* and treatment (if applicable)

5.9.1. Use of specified study materials

When materials are provided by GSK Biologicals ***or Quest Diagnostics***, it is MANDATORY that all clinical samples be collected and stored exclusively using those materials in the appropriate manner. The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals ***or Quest Diagnostics*** 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 of clinical trial supplies in the SPM.

5.9.4.1. Cytology

Cervical cytology will be performed using the ThinPrep® PapTest (Cytyc Corporation, Boxborough, MA, USA), by Quest Diagnostics (Teterboro, NJ, US), or another GSK designated laboratory. Cervical cells for ThinPrep® cytology ~~at scheduled 12-month interval visits~~ will be collected using the sampling device provided ***and*** rinsed into a collection vial containing PreservCyt® medium (provided by ~~sponsor~~ ***GSK Biologicals or Quest Diagnostics***).

(Note, also amended in Appendix A)

5.9.4.2. HPV DNA Testing by Hybrid Capture ~~2~~*II* (~~HC2~~*HCII*)

After ThinPrep® cytology slides have been prepared, residual PreservCyt® specimens on slides ~~for all samples~~ ***read as normal or ASCUS*** will be tested for HPV DNA. Testing will be done by Quest Diagnostics (Teterboro, NJ, US), or another GSK designated laboratory using the Hybrid Capture® ~~2~~***II*** test (~~HC2~~***HCII***; Digene Corp., Gaithersburg, MD, USA). Probe B will be used and is designed to detect infections with one of 13 oncogenic HPV types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) [Vernick 2003, Digene Corporation 2002]. This test does not provide type-specific data.

(Note, also amended in Appendix A)

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8.4.1. Prompt reporting of serious adverse events to GSK Biologicals

Back-up Study Contact for Reporting SAEs
GSK Biologicals Clinical Safety ~~Physician~~& *Pharmacovigilance*
Fax: PPD or PPD
24/24 hour and 7/7 day availability

8.6. Unblinding

For subjects who conclude the HPV-015 study at Visit 9 or Visit 11, but agree to remain blinded until the final analysis ***of study HPV-015***, the following applies:

8.7. Emergency unblinding

For subjects who conclude the HPV-015 study at Visit 9 or Visit 11, but agree to remain blinded until the final analysis ***of study HPV-015***, the following applies:

GSK Biologicals Central Safety Physician (Study Contact for Emergency Code Break)
~~Mobile p~~*P*hones for 7/7 day availability: **Outside US/Canada**: PPD (GSK Biologicals Central Safety Physician ***on-call)*** **For US/Canada only:** PPD (~~Head Safety Evaluation and Risk Management North America~~ ***GSK Biologicals Central Safety Physician on-call***) **Back-up ~~mobile~~ phone contact:** PPD ***Outside US/Canada:*** PPD ***For US/Canada only:*** PPD

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GlaxoSmithKline Biologicals Clinical Research & Development **Protocol Administrative Change 1**	
eTrack study number and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Administrative change number:	Administrative change 1
Administrative change date:	Administrative change 1 Final: 18 August 2010
Co-ordinating author:	PPD Scientific Writer
Rationale/background for changes: Since the double-blind study HPV-015 will be extended by a maximum of three additional years, according to Protocol Amendment 4, dated 24 March 2010, it is important that central study staff involved in the studies remains blinded till the end of study HPV-015 for all subjects who have been participating in HPV-015 and will be participating in this study. Therefore, subjects enrolled in HPV-015 extension studies such as study HPV-062 cannot retain the HPV-015 subject number as is stated in the original protocol. Consequently, different identification numbers will be provided by an external statistician.	

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

Section 5.2.1. Subject identification

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

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

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113617 (HPV-062 EXT:015)
Final

Protocol Sponsor Signatory Approval

eTrack study number and Abb²reviated Title	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Sponsor signatory	Dominique Descamps, MD, Director, Clinical Development GlaxoSmithKline Biologicals Rue de l'Institut 89 B-1330 Rixensart Belgium
Signature	PPD pp PPD
Date	15 avril 2010

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Protocol Investigator Agreement

I agree:

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

Hence I:

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

GlaxoSmithKline

File Note

Alias / Abbreviated Study Title	E-Track Study #
HPV-062 EXT:015	113617

Date: 15-May-2012

Concerns: Investigator Agreement Pages for Final Protocol

Details:

This NTF serves to clarify the Investigator Agreement Pages that are considered not applicable for the above noted study. Each of the Canadian sites listed below received initial ethics approval incorporating Amendment 1, version dated 21-Jun-2010. Thus, the investigator agreement pages for the Final Protocol, version dated 03-Mar-2010 are not applicable and have not been signed by the investigators.

This NTF is applicable to the following Principal Investigators:

- PPD (centre PPD
- (centre
- PPD centre PPD
- (centre
- (centre
- PPD (centre PPD
- PPD (centre PPD – note that initial ethics approval included protocol administrative change 1 dated 18Aug2010.

Made by: PPD

Signature: PPD

Function: Associate Study Manager

Signature Date: 15 May 2012

GlaxoSmithKline

NOTE TO FILE

Alias / Abreviated Study Title (if applicable)	HPV - 062 EXT: 015 (113617)
E-Track Study Number (if applicable)	113617
Site ID (if applicable)	All impacted site numbers

Please use the form below to describe the Issue / incident. Please refer to the instructions for authors when completing. The use of this Form is optional and may be adapted as required.

	Details
Initial Incident/Issue	Upon Reconciliation/QC of Investigator Agreement/signature pages in CARS (documentum) for study 113617 Portugal, it has been notice that all sites signed administrative change 1. This is true for all impacted sites as described below: PI – Dr. PPD Site number PPD PI – PPD : Site number - PPD PI- PPD : Site number PPD PI- PPD ; Site number-PPD PI- PPD Site number -PPD No signature pages were signed by Principal Investigator from the Final protocol dated, 03 March 2010 as well Amendment 1 dated from 21 June 2010, because the study started under Administrative change 1 , from 18 August 2010.
Not all of the following sections may apply to all Note to Files. Please complete the ones that do apply.	
Cause of Incident/Issue	No signature pages were signed for the Final protocol (03 March 2010) and Amendment 1 (21 June 2010) because the study started under Administrative change 1 (18 Aug 2010).
Consequence(s) of Issue/incident	
Corrective Action(s) with justification and timeline(s) for completion	
Outcome of Corrective Action(s)	File note reporting the issue, so that signed administrative changes 1 can be indexed in CARS under HPV062- EXT 015 (113617) under each of the impacted sites.
Reference document(s)	
Additional Information appended to this Note To File	

Please complete the signature panel below and include all stakeholders involved

GlaxoSmithKline

NOTE TO FILE

	Full Name and job function	Signature	Date
Author	PPD CRA	PPD	29 –JUNE-2012
Co-Author (if applicable)			
Reviewed by (if applicable)	PPD		29-JUNE -2012
Approved by (if applicable)			

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113617 (HPV-062 EXT:015)
Final

eTrack study number(s) and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Investigator name	HENRY KITCHENER
Signature	PPD
Date	18/1/11, PPD
Leiter der klinischen Prüfung' (LKP) name	
Signature	
Date	

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NOTE TO FILE

Alias / Abreviated Study Title (if applicable)	HPV-062 Ext 015
E-Track Study Number (if applicable)	113617
Site ID (if applicable)	N/A

Please use the form below to describe the Issue / incident. Please refer to the instructions for authors when completing. The use of this Form is optional and may be adapted as required.

	Details
Initial Incident/Issue	No signature pages were signed and received from sites for the original/final HPV-062 protocol dated 03Mar2010 or Protocol Amendment 1 dated 21Jun2010.
Not all of the following sections may apply to all Note to Files. Please complete the ones that do apply.	
Cause of Incident/Issue	The HPV-062 study started under Protocol Administrative Change 1 dated 18Aug2010. Therefore, these signature pages were the first to be signed by sites and collected by GSK.
Consequence(s) of Issue/incident	None
Corrective Action(s) with justification and timeline(s) for completion	This NTF will be uploaded into CARS (Documentum) for clarification purposes.
Outcome of Corrective Action(s)	N/A
Reference document(s)	N/A
Additional Information appended to this Note To File	N/A

Please complete the signature panel below and include all stakeholders involved

	Full Name and job function	**Signature**	**Date**
Author	PPD US Study Manager	PPD	07Dec2012
Co-Author (if applicable)	N/A		

GlaxoSmithKline

NOTE TO FILE

Reviewed by (if applicable)	N/A		
Approved by (if applicable)	N/A		

GlaxoSmithKline

NOTE TO FILE

CONFIDENTIAL

113617 (HPV-062 EXT:015)
Amendment 1

Protocol Amendment 1 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Date of protocol amendment 1	Amendment 1 Final: 21 June 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Sponsor signatory	Dominique Descamps, MD, Director, Clinical Development GlaxoSmithKline Biologicals Rue de l'Institut 89 B-1330 Rixensart Belgium
Signature	PPD
Date	7 Jul 2010

For internal use only

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CONFIDENTIAL

Protocol Amendment 1 Investigator Agreement

I agree:

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

Hence I:

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

CONFIDENTIAL

113617 (HPV-062 EXT:015)
Amendment 1

eTrack study number(s) and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Date of protocol amendment 1	Amendment 1 Final: 21 June 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Investigator name	MURDO FERGUSON
Signature	PPD
Date	10 AUG PPD 1ST 2010
Leiter der klinischen Prüfung' (LKP) name	
Signature	_____
Date	_____

For internal use only

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CONFIDENTIAL

113617 (HPV-062 EXT:015)
Amendment 1

eTrack study number(s) and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Date of protocol amendment 1	Amendment 1 Final: 21 June 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Investigator name	GINETTE GIRARD, MD
Signature	PPD
Date	07 Sept 2010
Leiter der klinischen Prüfung' (LKP) name	
Signature	
Date	

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CONFIDENTIAL

113617 (HPV-062 EXT:015)
Amendment 1

eTrack study number(s) and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Date of protocol amendment 1	Amendment 1 Final: 21 June 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Investigator name	Shelly McNeil
Signature	PPD
Date	PPD 2010/09/28
Leiter der klinischen Prüfung' (LKP) name	
Signature	
Date	

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eTrack study number(s) and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Date of protocol amendment 1	Amendment 1 Final: 21 June 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Investigator name	DR. DEBORAH MONEY
Signature	PPD
Date	Dec. 2, PPD 0
Leiter der klinischen Prüfung' (LKP) name	
Signature	
Date	

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CONFIDENTIAL

113617 (HPV-062 EXT:015)
Amendment 1

eTrack study number(s) and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Date of protocol amendment 1	Amendment 1 Final: 21 June 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Investigator name	BARBARA ROMANOWSKI
Signature	PPD
Date	9 Aug 10
Leiter der klinischen Prüfung' (LKP) name	
Signature	
Date	

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GlaxoSmithKline

NOTE TO FILE

Alias / Abreviated Study Title (if applicable)	HPV - 062 EXT: 015 (113617)
E-Track Study Number (if applicable)	113617
Site ID (if applicable)	All impacted site numbers

Please use the form below to describe the Issue / incident. Please refer to the instructions for authors when completing. The use of this Form is optional and may be adapted as required.

	Details
Initial Incident/Issue	Upon Reconciliation/QC of Investigator Agreement/signature pages in CARS (documentum) for study 113617 Portugal, it has been notice that all sites signed administrative change 1. This is true for all impacted sites as described below: PI – Dr. PPD Site number PPD PI – PPD : Site number - PPD PI- PPD : Site number PPD PI- PPD ; Site number-PPD PI- PPD Site number -PPD No signature pages were signed by Principal Investigator from the Final protocol dated, 03 March 2010 as well Amendment 1 dated from 21 June 2010, because the study started under Administrative change 1 , from 18 August 2010.
Not all of the following sections may apply to all Note to Files. Please complete the ones that do apply.	
Cause of Incident/Issue	No signature pages were signed for the Final protocol (03 March 2010) and Amendment 1 (21 June 2010) because the study started under Administrative change 1 (18 Aug 2010).
Consequence(s) of Issue/incident	
Corrective Action(s) with justification and timeline(s) for completion	
Outcome of Corrective Action(s)	File note reporting the issue, so that signed administrative changes 1 can be indexed in CARS under HPV062- EXT 015 (113617) under each of the impacted sites.
Reference document(s)	
Additional Information appended to this Note To File	

Please complete the signature panel below and include all stakeholders involved

GlaxoSmithKline

NOTE TO FILE

	Full Name and job function	Signature	Date
Author	PPD CRA	PPD	29 –JUNE-2012
Co-Author (if applicable)			
Reviewed by (if applicable)	PPD		29-JUNE -2012
Approved by (if applicable)			

CONFIDENTIAL

113617 (HPV-062 EXT:015)
Amendment 1

eTrack study number(s) and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Date of protocol amendment 1	Amendment 1 Final: 21 June 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Investigator name	HENRY KITCHENER
Signature	PPD
Date	18/1/11
Leiter der klinischen Prüfung' (LKP) name	
Signature	
Date	

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GlaxoSmithKline

NOTE TO FILE

Alias / Abreviated Study Title (if applicable)	HPV-062 Ext 015
E-Track Study Number (if applicable)	113617
Site ID (if applicable)	N/A

Please use the form below to describe the Issue / incident. Please refer to the instructions for authors when completing. The use of this Form is optional and may be adapted as required.

	Details
Initial Incident/Issue	No signature pages were signed and received from sites for the original/final HPV-062 protocol dated 03Mar2010 or Protocol Amendment 1 dated 21Jun2010.
Not all of the following sections may apply to all Note to Files. Please complete the ones that do apply.	
Cause of Incident/Issue	The HPV-062 study started under Protocol Administrative Change 1 dated 18Aug2010. Therefore, these signature pages were the first to be signed by sites and collected by GSK.
Consequence(s) of Issue/incident	None
Corrective Action(s) with justification and timeline(s) for completion	This NTF will be uploaded into CARS (Documentum) for clarification purposes.
Outcome of Corrective Action(s)	N/A
Reference document(s)	N/A
Additional Information appended to this Note To File	N/A

Please complete the signature panel below and include all stakeholders involved

	Full Name and job function	**Signature**	**Date**
Author	PPD US Study Manager	PPD	07Dec2012
Co-Author (if applicable)	N/A		

GlaxoSmithKline

NOTE TO FILE

Reviewed by (if applicable)	N/A		
Approved by (if applicable)	N/A		

GlaxoSmithKline

NOTE TO FILE

CONFIDENTIAL

Protocol Administrative Change 1 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Date of protocol amendment 1	Amendment 1 Final: 21 June 2010
Date of protocol administrative change 1	Administrative Change 1 Final: 18 August 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Sponsor signatory	Dominique Descamps, MD, Director, Clinical Development GlaxoSmithKline Biologicals Rue de l'Institut 89 B-1330 Rixensart Belgium
Signature	PPD
Date	1 - SEP. 2010

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CONFIDENTIAL

Protocol Administrative Change 1 Investigator Agreement

I agree:

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

Hence I:

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

CONFIDENTIAL

113617 (HPV-062 EXT:015)
Administrative Change 1

eTrack study number(s) and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Date of protocol amendment 1	Amendment 1 Final: 21 June 2010
Date of protocol administrative change 1	Administrative Change 1 Final: 18 August 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Investigator name	MURDO FERGUSON.
Signature	PPD
Date	31 AUG PPD 11
Leiter der klinischen Prüfung' (LKP) name	
Signature	
Date	

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113617 (HPV-062 EXT:015)
Administrative Change 1

eTrack study number(s) and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Date of protocol amendment 1	Amendment 1 Final: 21 June 2010
Date of protocol administrative change 1	Administrative Change 1 Final: 18 August 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Investigator name	GINETTE GIRARD, M.D.
Signature	PPD
Date	27 JUN 2011
Leiter der klinischen Prüfung' (LKP) name	
Signature	
Date	

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CONFIDENTIAL

113617 (HPV-062 EXT:015)
Administrative Change 1

eTrack study number(s) and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Date of protocol amendment 1	Amendment 1 Final: 21 June 2010
Date of protocol administrative change 1	Administrative Change 1 Final: 18 August 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Investigator name	Shelly McNeil
Signature	PPD
Date	09 SEP 11
Leiter der klinischen Prüfung' (LKP) name	
Signature	
Date	

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CONFIDENTIAL

113617 (HPV-062 EXT:015)
Administrative Change 1

eTrack study number(s) and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Date of protocol amendment 1	Amendment 1 Final: 21 June 2010
Date of protocol administrative change 1	Administrative Change 1 Final: 18 August 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Investigator name	Deborah Money
Signature	PPD
Date	Sept. 7 2011 PPD
Leiter der klinischen Prüfung' (LKP) name	
Signature	_____
Date	_____

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CONFIDENTIAL

113617 (HPV-062 EXT:015)
Administrative Change 1

eTrack study number(s) and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Date of protocol amendment 1	Amendment 1 Final: 21 June 2010
Date of protocol administrative change 1	Administrative Change 1 Final: 18 August 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Investigator name	PPD
Signature	
Date	6 June 11
Leiter der klinischen Prüfung' (LKP) name	R. Romanowski
Signature	
Date	

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CONFIDENTIAL

113617 (HPV-062 EXT:015)
Administrative Change 1

eTrack study number(s) and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Date of protocol amendment 1	Amendment 1 Final: 21 June 2010
Date of protocol administrative change 1	Administrative Change 1 Final: 18 August 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extens PPD dy for the follow-up of a subset of HPV-015 st jects
Investigator name	h.J.M. Helmerhorst maecoloog
Signature	
Date	2 NOV. 2010
Leiter der klinischen Prüfung' (LKP) name	PPD
Signature	
Date	

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CONFIDENTIAL

113617 (HPV-062 EXT:015)
Administrative Change 1

eTrack study number(s) and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Date of protocol amendment 1	Amendment 1 Final: 21 June 2010
Date of protocol administrative change 1	Administrative Change 1 Final: 18 August 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Investigator name	G. Kenter
Signature	PPD
Date	PPD 6/6/2011
Leiter der klinischen Prüfung' (LKP) name	
Signature	_____
Date	_____

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GlaxoSmithKline

File Note

Alias / Abbreviated Study Title	CPMS / E-Track #
113617	HPV-062

Date: 27/MAY/2011

Concerns: HPV-062 Protocol Administrative change 01. Investigator´s agreement pages. PORTUGAL

Details:

The original pages of investigator´s agreements (Protocol HPV062 Administrative Change 01) had not a checksum printed on them because of a printing error. However, by their signatures, the Portuguese investigators participating in the study confirmed that they had received, read and approved that protocol version (Protocol HPV062 Administrative Change 01).

The investigators agreed to sign with the date pre-printed on the pages of the investigator´s agreements.

In order to clarify these facts this file note is written and signed.

CRA: PPD
PORTUGAL

Signature: PPD

Signature Date: 27/MAY/2011

PPD

From: PPD
Sent: PPD 12 augustus 2016 18:08
To: PPD
Subject: Fwd:

---------- Forwarded message ----------
From: PPD
Date: 2016-08-12 17:07 GMT+01:00
Subject:
To: PPD

Dear Gentlemen,

As requested please find attached the following documentas that where required:- 1.- Administrative Change 1(HPV-062) 03-03 2010 final: 21 June 2010.
- 2.- Amendment 2 (HPV_066)
They are acessable at this point because of library vacation I re signed these originals.

Thank You, Best Regards

PPD

Protocol Administrative Change 1 signature page for the HPV062 study was signed already at the time of release.
At the time of requesting a copy of this signed signature page, it was not accessable by the PI. Therefore she signed a new signature page. The PI accidentally signed as "Leiter der klinischen Prüfung" (LKP) where she should have signed as Investigator.

PPD

PPD

linical Lead

Quintiles

CONFIDENTIAL

113617 (HPV-062 EXT:015)
Administrative Change 1

eTrack study number(s) and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Date of protocol amendment 1	Amendment 1 Final: 21 June 2010
Date of protocol administrative change 1	Administrative Change 1 Final: 18 August 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Investigator name	Dr. Margarida Anes
Signature	PPD
Date	18 AUGUST 201(PPD
Leiter der klinischen Prüfung' (LKP) name	
Signature	_____
Date	_____

CONFIDENTIAL

113617 (HPV-062 EXT:015)
Administrative Change 1

eTrack study number(s) and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Date of protocol amendment 1	Amendment 1 Final: 21 June 2010
Date of protocol administrative change 1	Administrative Change 1 Final: 18 August 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Investigator name	Dr. Elvira Bártolo
Signature	PPD
Date	18 AUG
Leiter der klinischen Prüfung' (LKP) name	
Signature	_____
Date	_____

CONFIDENTIAL

113617 (HPV-062 EXT:015)
Administrative Change 1

eTrack study number(s) and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Date of protocol amendment 1	Amendment 1 Final: 21 June 2010
Date of protocol administrative change 1	Administrative Change 1 Final: 18 August 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Investigator name	
Signature	
Date	_____
Leiter der klinischen Prüfung' (LKP) name	
Signature	PPD
Date	2016/08/12

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CONFIDENTIAL

113617 (HPV-062 EXT:015)
Administrative Change 1

eTrack study number(s) and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Date of protocol amendment 1	Amendment 1 Final: 21 June 2010
Date of protocol administrative change 1	Administrative Change 1 Final: 18 August 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Investigator name	Dr. Irene Santo
Signature	PPD
Date	18 AUGUST 2010
Leiter der klinischen Prüfung' (LKP) name	
Signature	_____
Date	_____

18-AUG-2010

CONFIDENTIAL

113617 (HPV-062 EXT:015)
Administrative Change 1

eTrack study number(s) and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Date of protocol amendment 1	Amendment 1 Final: 21 June 2010
Date of protocol administrative change 1	Administrative Change 1 Final: 18 August 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Investigator name	Minkina
Signature	PPD
Date	30 Oct 2014
Leiter der klinischen Prüfung' (LKP) name	
Signature	_____
Date	_____

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CONFIDENTIAL

113617 (HPV-062 EXT:015)
Administrative Change 1

eTrack study number(s) and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Date of protocol amendment 1	Amendment 1 Final: 21 June 2010
Date of protocol administrative change 1	Administrative Change 1 Final: 18 August 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Investigator name	PPD
Signature	
Date	2 P P D. 01. 2012
Leiter der klinischen Prüfung' (LKP) name	
Signature	
Date	

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113617 (HPV-062 EXT:015)
Administrative Change 1

eTrack study number(s) and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Date of protocol amendment 1	Amendment 1 Final: 21 June 2010
Date of protocol administrative change 1	Administrative Change 1 Final: 18 August 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Investigator name	CHEW GHEE KHENG
Signature	PPD
Date	23/2/12 PPD
Leiter der klinischen Prüfung' (LKP) name	
Signature	
Date	

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113617 (HPV-062 EXT:015)
Administrative Change 1

eTrack study number(s) and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Date of protocol amendment 1	Amendment 1 Final: 21 June 2010
Date of protocol administrative change 1	Administrative Change 1 Final: 18 August 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Investigator name	PPD
Signature	
Date	7/8/2011
Leiter der klinischen Prüfung' (LKP) name	
Signature	
Date	

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113617 (HPV-062 EXT:015)
Administrative Change 1

eTrack study number(s) and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Date of protocol amendment 1	Amendment 1 Final: 21 June 2010
Date of protocol administrative change 1	Administrative Change 1 Final: 18 August 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Investigator name	Antony Hollingworth
Signature	PPD
Date	PPD 22/7/14
Leiter der klinischen Prüfung' (LKP) name	
Signature	_____
Date	_____

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113617 (HPV-062 EXT:015)
Administrative Change 1

eTrack study number(s) and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Date of protocol amendment 1	Amendment 1 Final: 21 June 2010
Date of protocol administrative change 1	Administrative Change 1 Final: 18 August 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Investigator name	HENRIK KITCHENER
Signature	PPD
Date	21/4/11.
Leiter der klinischen Prüfung' (LKP) name	
Signature	
Date	

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113617 (HPV-062 EXT:015)
Administrative Change 1

eTrack study number(s) and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Date of protocol amendment 1	Amendment 1 Final: 21 June 2010
Date of protocol administrative change 1	Administrative Change 1 Final: 18 August 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Investigator name	Kevin S PPD #5, MD
Signature	PPD
Date	PPD 10/19/11
Leiter der klinischen Prüfung' (LKP) name	
Signature	
Date	

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113617 (HPV-062 EXT:015)
Administrative Change 1

eTrack study number(s) and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Date of protocol amendment 1	Amendment 1 Final: 21 June 2010
Date of protocol administrative change 1	Administrative Change 1 Final: 18 August 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Investigator name	Terry L. Poling, MD
Signature	PPD
Date	PPD PPD 8/12/12
Leiter der klinischen Prüfung' (LKP) name	
Signature	
Date	

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eTrack study number(s) and Abbreviated Title(s)	113617 (HPV-062 EXT:015)
IND number	BB-IND 7920
EudraCT number	2009-017282-35
Date of protocol	Final: 03 March 2010
Date of protocol amendment 1	Amendment 1 Final: 21 June 2010
Date of protocol administrative change 1	Administrative Change 1 Final: 18 August 2010
Detailed Title	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
Investigator name	PPD Jack Stapleton, MD
Signature	
Date	10/5/11
Leiter der klinischen Prüfung' (LKP) name	
Signature	
Date	

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