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

Primary Study vaccine and number	GlaxoSmithKline (GSK) Biologicals' human papillomavirus (HPV) vaccine containing HPV-16/18 L1 virus-like particles (VLPs) and AS04 adjuvant (GSK 580299)
eTrack study number and Abbreviated Title	207347 (HPV-093 EXT 058)
Date of protocol	Final Version 1: 19 May 2017
Title	Persistence of immune response to GSK Biologicals' HPV vaccine in healthy Chinese female subjects from the HPV-058 study.
Detailed Title	A phase III, open-label, mono-centre, follow-up extension study to evaluate the persistence of immune response to GSK Biologicals' HPV vaccine in healthy Chinese female subjects who received three doses of the vaccine in the HPV-058 study.
Co-ordinating author	PPD, Scientific Writer
Contributing authors	• PPD, Clinical and Epidemiology R&D Project Lead • PPD, Clinical Research and Development Lead • PPD, Project Statistician • PPD Lead Statistician • PPD, Study Delivery Lead • PPD and PPD, Clinical Safety representative • PPD, Study Data Manager • PPD, Oversight Data Manager • PPD, Clinical Read Out Team Leader • PPD, Clinical Laboratory Sciences Study Manager • PPD, Global Patents representative • PPD, Clinical Trial Supply Manager • PPD, Regulatory Affairs representative • PPD, Head of Clinical Research and Development, China/Hong Kong

eTrack study number and Abbreviated Title	207347 (HPV-093 EXT 058)
Detailed Title	A phase III, open-label, mono-centre, follow-up extension study to evaluate the persistence of immune response to GSK Biologicals' HPV vaccine in healthy Chinese female subjects who received three doses of the vaccine in the HPV-058 study.
Contributing authors	• PPD, Local Delivery Lead Clinical Operations Senior Manager, China • PPD, Local Medical Lead, China • PPD Local Delivery Lead, China

GSK Biologicals' Protocol DS v 15.0

Protocol Sponsor Signatory Approval

eTrack study number and Abbreviated Title	207347 (HPV-093 EXT 058)
Date of protocol	Final Version 1: 19 May 2017
Detailed Title	A phase III, open-label, mono-centre, follow-up extension study to evaluate the persistence of immune response to GSK Biologicals' HPV vaccine in healthy Chinese female subjects who received three doses of the vaccine in the HPV-058 study
Sponsor signatory	Frank Struyf, M.D., Ph.D., Director, Clinical and Epidemiology R&D Project Lead, HPV and Hepatitis vaccines, GlaxoSmithKline Biologicals SA.
Signature	_____
Date	_____

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Protocol Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline (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' study vaccine 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 acceptable 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 vaccine, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

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

eTrack study number and Abbreviated Title	207347 (HPV-093 EXT 058)
Date of protocol	Final Version 1: 19 May 2017
Detailed Title	A phase III, open-label, mono-centre, follow-up extension study to evaluate the persistence of immune response to GSK Biologicals' HPV vaccine in healthy Chinese female subjects who received three doses of the vaccine in the HPV-058 study
Investigator name	_____
Signature	_____
Date	_____

For internal use only

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Sponsor Information

1. Sponsor

GlaxoSmithKline Biologicals
Rue de l'Institut 89
B-1330 Rixensart, Belgium

2. Sponsor Medical Expert for the Study

Refer to the local study contact information document.

3. Sponsor Study Monitor

Refer to the local study contact information document.

4. Sponsor Study Contact for Reporting of a Serious Adverse Event

GSK Biologicals Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 8.3.2.

SYNOPSIS

Detailed Title	A phase III, open-label, mono-centre, follow-up extension study to evaluate the persistence of immune response to GSK Biologicals' HPV vaccine in healthy Chinese female subjects who received three doses of the vaccine in the HPV-058 study
Indication	In China, *Cervarix* is approved for use in females 9 through 25 years of age for the prevention of cervical cancer, cervical intraepithelial neoplasia grade 2, grade 3 (CIN 2/3) and adenocarcinoma *in situ* and cervical intraepithelial neoplasia grade 1 (CIN 1) caused by high risk human papillomavirus (HPV) types 16 and 18.
Rationale for the study and study design	• **Rationale for the study** In China, the burden of cervical cancer is most likely underestimated with over 61,000 new cases of cervical cancer being diagnosed annually, responsible for more than 29,000 deaths [HPV Information Centre, 2016]. In the last decade, the mortality rates of cervical cancer have significantly slowed down, presumably due to the implementation of screening programs, development of cervical cancer treatments and prevention strategies like vaccination. However, the incidence of cervical cancer among younger women is increasing, and the mortality rates in rural China are still high [Yang, 2003; Shi, 2012]. HPV prophylactic vaccination would efficiently reduce the incidence of cervical cancer in China, where it is difficult to implement effective and regular screening programs due to the size of the population [Zhu, 2014a; Zhu, 2014b; Zhao, 2014]. The safety, immunogenicity and efficacy of the HPV-16/18 vaccine were assessed in four clinical trials, involving over 8000 Chinese females between 9 through 45 years of age [Zhu, 2011; *Cervarix* Product Information, 2016]. The HPV-058 study was designed to evaluate the safety and immunogenicity of the HPV-16/18 vaccine in Chinese female subjects aged 9 through 17 years. Similarly, the HPV-039 study was designed to assess the vaccine efficacy, immunogenicity and safety in healthy Chinese female subjects aged 18 through 25 years. The primary objective of the HPV-058 study was to demonstrate the non inferiority of the immune response to the HPV-16/18 vaccine in subjects from the HPV-058 study compared to the immune response in subjects from the HPV-039 study, one month after the last dose.

This extension study (HPV-093 EXT 058) is being conducted to evaluate the persistence of immune response in subjects who received the HPV-16/18 vaccine, seven to eight years after the last dose of primary vaccination in the HPV-058 study. In addition, the study will describe the immune responses in subjects who received the HPV-16/18 vaccine in the HPV-058 study to the responses observed at a comparable time-point (Year 6) in subjects who belonged to the immunogenicity subset in the HPV-039 study.

- **Rationale for the study design**

All subjects who received three doses of the HPV-16/18 vaccine administered according to 0, 1 and 6 months schedule in the HPV-058 study will be invited to participate in this study. In order to assess the persistence of immune responses seven to eight years after the last vaccine dose against HPV-16/18, a blood sample will be taken from all the subjects.

The study will be open-label, uncontrolled and non-randomised as no vaccine will be administered during the study. In order to fulfil international reporting obligations, serious adverse events (SAEs) that are related to study participation (i.e. protocol-mandated procedures) or are related to a concurrent GSK medication/vaccine will be collected and recorded from the time the subject consents to participate in the study until she is discharged from the study.

Objectives

Primary

- To assess the immune response against HPV types 16 and 18 [as determined by Enzyme Linked Immunosorbent Assay (ELISA)] seven to eight years after completion of the vaccination schedule in the HPV-058 study.

Secondary

- To describe the immune response against HPV types 16 and 18 (as determined by ELISA) observed seven to eight years after completion of the vaccination schedule in the HPV-058 study to the response observed (at Year 6) in subjects aged 18-25 years at vaccination in the HPV-039 study.

Study design

- **Experimental design**: Phase III, open-label, mono-centric, single country study with a single group.
- **Duration of the study**: One day
  - Epoch 001: starting at Visit 1 (Day 1) and ending at Visit 1 (Day 1)

- **Primary completion Date (PCD)**: Visit 1 (Day 1).
- **End of Study (EoS)**: Last testing results released for samples collected at Visit 1.
- **Study group**: The study group is as follows**:**
  - HPV group: Subjects from HPV-058 study who received all three doses of the HPV-16/18 vaccine will be eligible to take part in this extension study.

Synopsis Table 1 Study group and epoch foreseen in the study

Study group	Number of subjects	Age (Min/Max)	Epoch
			Epoch 001
HPV group	Up to 369	17 years and above (i.e., 9-17 years old at the time of first vaccination in HPV-058 study)	x

- **Control**: none, i.e. uncontrolled.
- **Vaccination schedule and Treatment allocation**: No vaccine will be administered in this extension study.
- **Blinding**: Open-label

Synopsis Table 2 Blinding of study epoch

Study Epoch	Blinding
Epoch 001	open-label

- **Sampling schedule**: One blood sample (approximately 5 ml) will be drawn from all subjects at the study visit (Visit 1) for HPV-16/18 antibody concentrations determination by ELISA.
- **Type of study**: self-contained and extension of HPV-058 study.
- **Data collection**: electronic Case Report Form (eCRF).

Number of subjects

Up to 369 healthy Chinese female subjects of age 17 years and above at the time of enrolment are expected to participate in this extension study. Subjects from HPV-058 study who completed the vaccination schedule (0, 1 and 6 months) will be eligible to take part in this study.

Endpoints

Primary

- Anti-HPV-16/18 seropositivity rates and antibody concentrations assessed by ELISA at Visit 1 (Day 1).

Secondary

- Anti-HPV-16/18 seropositivity rates and antibody concentrations assessed by ELISA at Visit 1 (Day 1) compared with anti-HPV-16/18 seropositivity rates and antibody concentrations at Year 6 in subjects from the immunogenicity subset in study HPV-039.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ATP	According to Protocol
CI	Confidence Interval
CIN	Cervical Intraepithelial Neoplasia
eCRF	electronic Case Report Form
ELISA	Enzyme Linked Immunosorbent Assay
EoS	End of Study
ES	Exposed Set
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GSK	GlaxoSmithKline
HPV	Human Papillomavirus
ICF	Informed Consent Form
IAF	Informed Assent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LAR	Legally Acceptable Representative
LSLV	Last Subject Last Visit
MPL	3-*O*-desacyl-4'-monophosphoryl lipid A
NIFDC	National Institutes for Food and Drug Control
PCD	Primary Completion Date
PPS	Per Protocol Set
SAE	Serious Adverse Event

SDV	Source Document Verification
SPM	Study Procedures Manual
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 adverse event (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. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a serious adverse event. In an open-label study, no blind is used. Both the investigator and the subject know the identity of the treatment assigned.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
End of Study **(Synonym of End of Trial)**	For studies without collection of human biologicals samples or imaging data EoS is the Last Subject Last Visit (LSLV). For studies with collection of Human Biologicals Samples or imaging data, EoS is defined as the date of the last testing/reading released of the Human Biological Samples or imaging data, related to primary and secondary endpoints. EoS must be achieved no later than 8 months after LSLV
Epoch:	An epoch is a set of consecutive time-points or a single time-point from a single protocol. Epochs are defined to support a main purpose which is either to draw conclusions on subject participation or to draw a complete conclusion to define or precise the targeted label of the product. Supporting means that data collected at the time-points included in an epoch must be sufficient to fulfil the purpose of the epoch.

	Typical examples of epochs are screening, immunogenicity follow-ups, safety follow-up.
eTrack:	GSK's tracking tool for clinical trials.
Immunological correlate of protection:	The defined immune response above which there is a high likelihood of protection in the absence of any host factors that might increase susceptibility to the infectious agent.
Investigational vaccine/product: **(Synonym of Investigational Medicinal Product)**	A pharmaceutical form of an active ingredient being tested in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Legally acceptable representative **(The terms legal representative or legally authorised representative are used in some settings.)**	An individual or juridical or other body authorised under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.
Primary completion date:	The date that the final subject was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated.
Protocol amendment:	The International Conference on Harmonisation (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.
Self-contained study:	Study with objectives not linked to the data of another study.
Site Monitor:	An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.

Study vaccine:	Any investigational vaccine being tested and/or any authorised use of a vaccine as a reference or administered concomitantly, in a clinical trial that evaluates the use of an investigational vaccine.
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 vaccine 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.
Treatment number:	A number identifying a treatment to a subject, according to treatment allocation.

TRADEMARK

The following trademark is used in the present protocol.

Note: In the body of the protocol (including the synopsis), the name of the vaccine will be written without the superscript symbol ™ and in *italics*.

Trademark of the GlaxoSmithKline group of companies	Generic description
Cervarix™	Human papillomavirus vaccine types 16 and 18 (recombinant, AS04-adjuvanted)

1. INTRODUCTION

1.1. Background

Cervical cancer is the fourth most common cancer among women worldwide [International Agency for Research on Cancer, 2012].A total of 4.5% of all cancers (with nearly 630,000 new cancer cases per year) are attributable to HPV [De Martel , 2017]. Infection with HPV has been clearly established as the central cause of cervical cancer [Walboomers, 1999]. Up to 71% of the cervical cancer cases are attributable to the high--risk HPV types (HR-HPV) 16 and 18 [de Sanjose, 2010]. Consequently, a vaccine which could prevent infection with HR-HPV types, or decrease their consequences, would be of great value.

GlaxoSmithKline (GSK) Biologicals has therefore developed a prophylactic HPV vaccine, *Cervarix,* based on L1 proteins of HPV-16 and HPV-18 formulated with AS04 (comprising aluminium hydroxide [$Al(OH)_3$] and 3-*O*-desacyl-4'-monophosphoryl lipid A [MPL]).

Cervarix was first licensed in Australia in May 2007 and in the European Union in September 2007. The vaccine is currently licensed in 136 countries and regions worldwide. In July 2016, *Cervarix* (hereafter referred to as the HPV-16/18 vaccine) was approved for use as a three-dose schedule at 0, 1, 6 months in females from 9 to 25 years in China.

To date, more than 60,000 adolescent and adult females aged nine years and above have received at least one dose of the HPV 16/18 vaccine in clinical studies. The vaccine is known to be immunogenic and generally well tolerated. Pooled safety analyses of girls and women aged nine years and above who received HPV vaccine have shown that the vaccine was generally well tolerated in women of all ages [Descamps, 2009; Angelo, 2014].

1.2. Rationale for the study and study design

1.2.1. Rationale for the study

In China, the burden of cervical cancer is most likely underestimated with over 61,000 new cases of cervical cancer being diagnosed annually, responsible for more than 29,000 deaths [HPV Information Centre, 2016]. In the last decade, the mortality rates of cervical cancer have significantly slowed down, presumably due to the implementation of screening programs, development of cervical cancer treatments and prevention strategies like vaccination. However, the incidence of cervical cancer among younger women is increasing, and the mortality rates in rural China are still high [Yang, 2003; Shi, 2012]. . HPV prophylactic vaccination would efficiently reduce the incidence of cervical cancer in China, where it is difficult to implement effective and regular screening programs due to the size of the population [Zhu, 2014a; Zhu, 2014b; Zhao, 2014].

The safety, immunogenicity and efficacy of the HPV-16/18 vaccine were assessed in four clinical trials, involving over 8000 Chinese females between 9 through 45 years of age [Zhu, 2011; *Cervarix* Product Information, 2016]. The HPV-058 study was designed to evaluate the safety and immunogenicity of the HPV-16/18 vaccine in Chinese female subjects aged 9 through 17 years. Similarly, the HPV-039 study was designed to assess the vaccine efficacy, immunogenicity and safety in healthy Chinese female subjects aged 18 through 25 years. The primary objective of the HPV-058 study was to demonstrate the non inferiority of the immune response to the HPV-16/18 vaccine in subjects from the HPV-058 study compared to the immune response in subjects from the HPV-039 study, one month after the last dose.

This extension study (HPV-093 EXT 058) is being conducted to evaluate the persistence of immune response in subjects who received the HPV-16/18 vaccine, seven to eight years after the last dose of primary vaccination in the HPV-058 study. In addition, the study will describe the immune responses in subjects who received the HPV-16/18 vaccine in the HPV-058 study to the responses observed at a comparable time-point (Year 6) in subjects who belonged to the immunogenicity subset in the HPV-039 study.

1.2.2. Rationale for the study design

All subjects who received three doses of the HPV-16/18 vaccine administered according to 0, 1 and 6 months schedule in the HPV-058 study will be invited to participate in this study. In order to assess the persistence of immune responses seven to eight years after the last vaccine dose against HPV-16/18, a blood sample will be taken from all the subjects.

The study will be open-label, uncontrolled and non-randomised as no vaccine will be administered during the study. In order to fulfil international reporting obligations, serious adverse events (SAEs) that are related to study participation (i.e. protocol-mandated procedures) or are related to a concurrent GSK medication/vaccine will be collected and recorded from the time the subject consents to participate in the study until she is discharged from the study.

1.3. Benefit : Risk Assessment

Please refer to the Prescribing Information for information regarding the summary potential risks and benefits of HPV-16/18 vaccine.

2. OBJECTIVES

2.1. Primary objective

- To assess the immune response against HPV types 16 and 18 [as determined by Enzyme Linked Immunosorbent Assay (ELISA)] seven to eight years after completion of the vaccination schedule in the HPV-058 study.

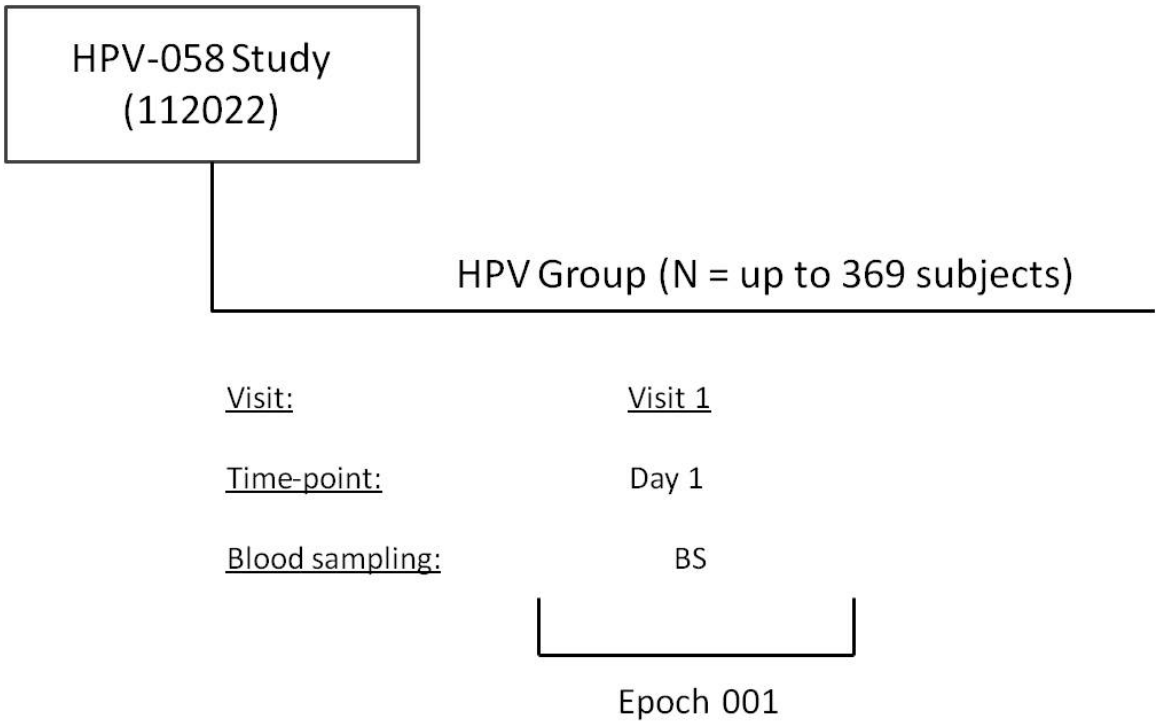
Refer to Section 10.1 for the definition of the primary endpoint.

2.2. Secondary objective

- To describe the immune response against HPV types 16 and 18 (as determined by ELISA) observed seven to eight years after completion of the vaccination schedule in the HPV-058 study to the response observed (at Year 6) in subjects aged 18-25 years at vaccination in the HPV-039 study.

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

3. STUDY DESIGN OVERVIEW



N = Number of subjects
BS = Blood sample

Protocol waivers or exemptions are not allowed unless necessary for the management of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 5.5), are essential and required for study conduct.

- **Experimental design:** Phase III, open-label, mono-centric, single country study with a single group.
- **Duration of the study:** One day.
  - Epoch 001: starting at Visit 1 (Day 1) and ending at Visit 1 (Day 1).
- **Primary completion date (PCD):** Visit 1 (Day 1).

  Refer to glossary of terms for the definition of PCD.

- **End of study (EoS):** Last testing results released for samples collected at Visit 1.

  Refer to glossary of terms for the definition of EoS.

- **Study group:** The study group is as follows**:**
  - HPV group: Subjects from HPV-058 study who received all three doses of the HPV-16/18 vaccine will be eligible to take part in this extension study.

The study group and epoch foreseen in the study are presented in Table 1

Table 1 Study group and epoch foreseen in the study

Study group	Number of subjects	Age (Min/Max)	Epoch
			Epoch 001
HPV group	Up to 369	17 years and above (i.e., 9-17 years old at the time of first vaccination in HPV-058 study)	x

- **Control**: none, i.e. uncontrolled.
- **Vaccination schedule and treatment allocation:** No vaccine will be administered in this extension study.
- **Blinding:** Open-label.

Table 2 Blinding of study epoch

Study Epoch	Blinding
Epoch 001	Open-label

- **Sampling schedule:** One blood sample (approximately 5 ml) will be drawn from all subjects at the study visit (Visit 1) for HPV-16/18 antibody concentrations determination by ELISA.
- **Type of study:** self-contained and extension of HPV-058 study.
- **Data collection:** electronic Case Report Form (eCRF).

4. STUDY COHORT

4.1. Number of subjects/centres

Up to 369 healthy Chinese female subjects of age 17 years and above at the time of enrolment are expected to participate in this extension study.

Overview of the recruitment plan

- This study will be conducted in China.
- The study will be monitored by the study monitor.
- At the time of initiation of the extension study, the investigator will contact all subjects from the HPV group who completed the primary vaccination study (HPV-058). The reason for non-participation in the extension study will be documented in the site's screening log.

- Enrolment will be terminated when all eligible subjects either have been enrolled, or have refused participation or have been lost to follow-up. The reasons for subjects who have been lost to follow up will be documented.

4.2. Inclusion criteria for enrolment

Deviations from inclusion criteria are not allowed because they can potentially jeopardise the scientific integrity, regulatory acceptability of the study or subject's safety. Therefore, adherence to the criteria as specified in the protocol is essential.

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

- Subjects/subject's parents/legally acceptable representative(s) [LAR(s)] who, in the opinion of the investigator, can and will comply with the requirements of the protocol.
- Written informed consent obtained from the subject or subject's parents/LAR(s) prior to performing any study specific procedure.
- Written informed assent obtained from the subjects below the legal age of consent.
- Subjects who received all three doses of the HPV-16/18 vaccine in the HPV-058 study.
- Healthy subjects as established by medical history and clinical examination before entering into the study.

4.3. Exclusion criteria for enrolment

Deviations from exclusion criteria are not allowed because they can potentially jeopardise the scientific integrity, regulatory acceptability of the study or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

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:

- Use of any investigational or non-registered product (drug or vaccine which may have an impact on the study objectives) during the period starting 30 days (Day 29 to Day 1) before the study visit.
- Concurrently participating in another clinical study, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).
- Previous vaccination against HPV outside the HPV-058 study.
- Subjects with contraindications related to blood draw such as blood disorders and anticoagulants use.

5. CONDUCT OF THE STUDY

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

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

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

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

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

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

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

Freely given and written or witnessed/ thumb printed informed consent must be obtained from each subject and/or each subject's parent(s)/LAR(s) and subject informed assent , as appropriate, prior to participation in the study.

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

In accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice, those subjects who can only be enrolled in the study with the consent of the subject's legally acceptable representative (e.g. minors), should be informed about the study to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date a written informed assent form (IAF). It is required that the assent be signed by each subject, if capable, in addition to the informed consent that is to be signed by her legal representative. It should be assessed whether an assent is required depending of the age of the study population and the local requirements.

GSK Biologicals strongly recommends that if the subject reaches the age of consent during the study they will be asked to provide consent at the next study visit (if applicable). This procedure should be applied according to local laws and regulations.

The investigator has the final responsibility for the final presentation of the ICF and IAF, respecting the mandatory requirements of local regulations. The ICF and IAF 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

5.2.1. Subject identification

The subject number will be aligned with the subject unique identification numbers of the parent study (HPV-058).

5.3. Method of blinding

This is an open-label study, and no vaccine will be administered during the study.

The laboratory in charge of the laboratory testing will not be blinded to the treatment, and codes will be used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.

5.4. General study aspects

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

5.5. Outline of study procedures

The list of study procedures is presented in Table 3

Table 3 List of study procedures

Age	17 years and above
Epoch	**Epoch 001**
Type of contact	**Visit 1**
Time-point	**Day 1**
Sampling time-point	**Day 1**
Informed consent / Informed assent*	●
Check inclusion/exclusion criteria	●
Collect demographic data	●
Medical history including vaccination history	●
Compare the subject information between parent study (HPV-058) and current study (HPV-093)	O
Subject number allocation	●
Laboratory Assays	
Blood sampling for antibody determination (~5 mL)	●
Safety assessments	
Record any concomitant medication/vaccination	●
Recording of SAEs related to study procedures or concomitant GSK medications/vaccine and events with a fatal outcomes	●
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 require documentation in the individual eCRF
* Written informed assent will be obtained from the subjects below the legal age of consent.

5.6. Detailed description of study procedures

5.6.1. Informed consent and Informed assent

The signed/witnessed/thumb printed informed consent of the subject/subject's parent(s)/LAR(s) must be obtained before study participation. The signed informed assent of the subject below the age of consent (i.e. minor) should be obtained in addition to the signed informed consent by her parent(s)/LAR(s) according to local rules and regulations. Refer to Section 5.1 for the requirements on how to obtain informed consent and assent, as appropriate.

5.6.2. Check inclusion and exclusion criteria

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

5.6.3. Collect demographic data

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

5.6.4. Medical history

Obtain the subject's medical history by interview and/or review of the subject's medical records and record any pre-existing conditions or signs and/or symptoms present in a subject at the time of enrolment in the eCRF.

5.6.5. Compare subject information

The subject information between the parent study (HPV-058) and the current study (HPV-093) will be compared in order to avoid collection of any inconsistent information.

5.6.6. Study group and subject number allocation

Subject number allocation will be performed as described in Section 5.2.1 and aligned with the parent study (HPV-058).

5.6.7. Sampling

Refer to the Module on Biospecimen Management in the Study Procedure Manual (SPM) for detailed instructions for the collection, handling and processing of the samples.

5.6.7.1. Blood sampling for antibody determination

Blood samples will be taken during Visit 1 (Day 1) as specified in Section 5.5.

- A volume of at least approximately 5 mL of whole blood (to provide at least 1.8 mL of serum) should be drawn from all subjects for analysis of humoral immune response at Visit 1 (Day 1). After centrifugation, serum samples should be kept at –20°C/ –4°F or below until shipment. Refer to the SPM for more details on sample storage conditions.

5.6.8. Check and record concomitant medication/vaccination

Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section 6.1.

5.6.9. Recording of SAEs

Refer to Section 8.2 for procedures for the investigator to record SAEs. Refer to Section 8.3 for guidelines and how to report SAE reports to GSK Biologicals.

5.6.10. Study conclusion

The investigator will:

- review data collected to ensure accuracy and completeness
- complete the Study Conclusion screen in the eCRF.

5.7. Biological sample handling and analysis

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

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

- Collected samples will be used for protocol mandated research and purposes related to the improvement, development and quality assurance of the laboratory tests described in this protocol. This may include the management of the quality of these tests, the maintenance or improvement of these tests, the development of new test methods, as well as making sure that new tests are comparable to previous methods and work reliably.
- It is also possible that future findings may make it desirable to use the samples acquired in this study for future research, not described in this protocol. Therefore, all subjects will be asked to give a specific consent to allow GSK or a contracted partner to use the samples for future research. Future research will be subject to the laws and regulations in China and will only be performed once an independent Ethics Committee or Review Board has approved this research.

Information on further investigations and their rationale can be obtained from GSK Biologicals.

Any sample testing will be done in line with the consent of the individual subject/subject's parent(s)/LAR(s).

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

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

Collected samples will be stored for a maximum of 20 years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK Biologicals.

5.7.1. Use of specified study materials

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

5.7.2. Biological samples

The type and quantity of biological samples that will be collected for analysis has been provided in Table 4.

Table 4 Biological samples

Sample type	Quantity	Unit	Time-point
Blood	At least 5	mL	Visit 1 (Day 1)

5.7.3. Laboratory assays

Please refer to APPENDIX A for a detailed description of the assays performed in the study. Please refer to APPENDIX B for the address of the clinical laboratories used for sample analysis.

One aliquot will be prepared for all serological samples, which will then be shipped to the National Institutes for Food and Drug Control (NIFDC) in China. The NIFDC will perform all serological assays.

Table 5 presents the laboratory assays for humoral immunity (antibody determination).

Table 5 Humoral Immunity (Antibody determination)

System	Component	Method	Kit / Manufacturer	Unit*	Cut-off*	Laboratory
Serum	Human Papilloma Virus Genotype 16.Virus Like Particle Ab.IgG	ELI**	NA	EU/ml	19	NIFDC***
	Human Papilloma Virus Genotype 18.Virus Like Particle Ab.IgG				18	

*Assay cut-off and unit might be subject to change during the course of the study (e.g. in case of requalification, revalidation or standardisation). In this case, this will be documented in the clinical report.
**ELI: GSK validated Enzyme Linked Immuno Sorbent Assay (ELISA).
***NIFDC: National Institutes for Food and Drug Control, China.

Additional exploratory testing on the vaccine and/or on the disease under study may be performed within the framework of the study if deemed necessary for accurate interpretation of the data or should such assay(s) become available at GSK. These assays may not be represented in the objectives/endpoints of the study protocol.

5.7.4. Biological samples evaluation

5.7.4.1. Immunological read-outs

The immunological read-outs are presented in Table 6.

Table 6 Immunological read-outs

Blood sampling time-point		No. subjects	Component	Components priority rank
Type of contact and time-point	Sampling time-point			
Visit 1 (Day 1)	Day 1	All	anti-HPV-16	1
			anti-HPV-18	2

In case of insufficient blood sample volume to perform assays for all antibodies, the samples will be analysed according to priority ranking provided in Table 6.

5.7.5. Immunological correlates of protection

There are currently no correlates of protection defined for the HPV-16 and HPV-18 antigens used as part of the HPV-16/18 vaccine.

6. STUDY VACCINE AND ADMINISTRATION

No vaccine will be administered in this extension study. The HPV-16/18 vaccine was administered as a three dose schedule in the primary vaccination study HPV-058.

Please refer to the HPV-058 study protocol for a detailed description of the study vaccine and administration.

6.1. Concomitant medications/products and concomitant vaccinations

At each study visit, the investigator or delegate should question the subject and/or the subject's parent(s)/LAR(s) about any medications/products taken and vaccinations received by the subject.

6.1.1. Recording of concomitant medications/products and concomitant vaccinations

The following concomitant medication(s)/product(s)/vaccine(s) must be recorded in the eCRF.

- All concomitant medications/products, except vitamins and dietary supplements, administered during the period starting 30 days before the study visit.
- Any concomitant vaccination administered in the period starting 30 days before the study visit.
- Prophylactic medication (i.e. medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).

  E.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring [fever is defined as temperature ≥ 37.0°C regardless the location of measurement per local guidance]. The preferred location for measuring temperature in this study will be the axilla.
- Any concomitant medications/products/vaccines relevant to a SAE to be reported as per protocol or administered for the treatment of a SAE. In addition, concomitant medications relevant to SAEs need to be recorded on the expedited Adverse Event report.

6.1.2. Concomitant medications/products/vaccines that may lead to the elimination of a subject from per-protocol analyses

The use of the following concomitant medications/products/vaccines will not require withdrawal of the subject from the study but may determine a subject's evaluability in the per-protocol analysis.

- Drug and/or alcohol abuse.

7. HEALTH ECONOMICS

Not applicable.

8. SAFETY

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

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

8.1. Safety definitions

8.1.1. Definition of an adverse event

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

An AE can therefore be any 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.
- New conditions detected or diagnosed after study vaccine 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 study vaccine or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with study vaccine(s) administration.
- 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).

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/SAE.
- 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.
- Pre-existing conditions or signs and/or symptoms present in a subject prior to the study vaccination. These events will be recorded in the medical history section of the eCRF.

8.1.2. Definition of a serious adverse event

A SAE is any untoward medical occurrence that:

a. Results in death,

b. Is life-threatening,

   Note: 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,

   Note: 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 in an 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 or diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an AE.

d. Results in disability/incapacity, OR

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

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

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

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

In absence of diagnosis, abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g. ECGs, X-rays, vital signs, etc) that are judged by the investigator to be clinically significant will be recorded as AE or SAE if they meet the definition of an AE or SAE (refer to Sections 8.1.1 and 8.1.2). Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also 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.

8.2. Detecting and recording serious adverse events

8.2.1. Time period for detecting and recording serious adverse events

The time period for collecting and recording SAEs will begin and end at Visit 1 (Day1) for each subject. See Section 8.3 for instructions on reporting of SAEs.

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

An overview of the protocol-required reporting periods for SAEs is given in Table 7.

Table 7 Reporting periods for collecting safety information

Event	V1 D1
SAEs related to study participation or concurrent GSK medication/vaccine and events with a fatal outcome	

V1: Visit 1, D1: Day 1.

8.2.2. Post-Study serious adverse events

A post-study SAE is defined as any event that occurs outside of the SAE reporting period defined in Table 7. Investigators are not obligated to actively seek SAEs in former study participants. However, if the investigator learns of any SAE at any time after a subject has been discharged from the study, and she considers the event reasonably related to the study vaccine, the investigator will promptly notify the Study Contact for Reporting SAEs.

8.2.3. Evaluation of serious adverse events

When a 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 a SAE in the eCRF. The investigator is not allowed to send photocopies of the subject's medical records to GSK Biologicals instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.

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

8.2.3.1. Assessment of outcomes

The investigator will assess the outcome of all SAEs recorded during the study as:

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

8.3. Reporting of serious adverse events

8.3.1. Prompt reporting of serious adverse events

SAEs that occur in the time period defined in Section 8.2, and considered related to study participation or concurrent GSK medication/vaccine, will be reported promptly to GSK within the timeframes described in Table 8, once the investigator determines that the event meets the protocol definition of a SAE.

Table 8 Timeframes for submitting serious adverse events

Type of Event	Initial Reports		Follow-up of Relevant Information on a Previous Report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report

* Timeframe allowed after receipt or awareness of the information.
‡ The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.

8.3.2. Contact information for reporting serious adverse events

Study Contact for Reporting SAEs
Refer to the local study contact information document.
Back-up Study Contact for Reporting SAEs
24/24 hour and 7/7 day availability: **GSK Biologicals Clinical Safety & Pharmacovigilance** Outside US & Canada sites: Fax: +PPD or +PPD Email address: PPD

8.3.3. Completion and transmission of SAE reports to GSK Biologicals

Once an investigator becomes aware that a SAE has occurred in a study subject, the investigator (or designate) must complete the information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS. The report will always be completed as thoroughly as possible with all available details of the event. Even if the investigator does not have all information regarding a SAE, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report. The investigator will be required to confirm the review of the SAE causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE.

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

If the electronic reporting system does not work, the investigator (or designate) must complete, then date and sign a paper Expedited Adverse Events Report and fax it to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within 24 hours.

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 designate) must complete the electronic Expedited Adverse Events Report within 24 hours. The final valid information for regulatory reporting will be the information reported through the electronic SAE reporting system.

8.3.4. Updating of SAE information after removal of write access to the subject's eCRF

When additional SAE information is received after removal of the write access to the subject's eCRF, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the Study Contact for Reporting SAEs (refer to the Sponsor Information) or to GSK Biologicals Clinical Safety and Pharmacovigilance department within the designated reporting time frames specified in Table 8.

8.3.5. Regulatory reporting requirements for serious adverse events

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.3.1. 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 study vaccine and unexpected. The purpose of the report is to fulfil specific regulatory and GCP requirements, regarding the product under investigation.

8.4. Follow-up of serious adverse events

8.4.1. Follow-up of serious adverse events

8.4.1.1. Follow-up during the study

After the initial SAE report, the investigator is required to proactively follow each subject and provide additional relevant information on the subject's condition to GSK Biologicals (within 24 hours for SAEs; refer to Table 8).

8.4.1.2. Follow-up after the subject is discharged from the study

The investigator will follow subjects:

- with SAEs, until the event has resolved, subsided, stabilised, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.

If the investigator receives additional relevant information on a previously reported SAE, he/she will provide this information to GSK Biologicals using a electronic Expedited Adverse Events Report.

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

8.5. Treatment of serious adverse events

Treatment of any SAE is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of a SAE should be recorded in Expedited Adverse Event Report of the subject's eCRF (refer to Section 6.1).

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject completion

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

9.2. Subject withdrawal

Withdrawals will not be replaced.

9.2.1. Subject withdrawal from the study

From an analysis perspective, a 'withdrawal' from the study refers to any subject who signs the consent form but refuses blood sampling and hence withdraws from the study.

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

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

*In case a subject is withdrawn from the study because she/the subject's parent(s)/LAR(s) has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject/subject's parent(s)/LAR(s), in the eCRF.

Subjects who are withdrawn from the study because of SAEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will follow subjects who are withdrawn from the study as result of a SAE until resolution of the event (see Section 8.4.1.2).

10. STATISTICAL METHODS

10.1. Primary endpoint

- Anti-HPV-16/18 seropositivity rates and antibody concentrations assessed by ELISA at Visit 1 (Day 1).

10.2. Secondary endpoint

- Anti-HPV-16/18 seropositivity rates and antibody concentrations assessed by ELISA at Visit 1 (Day 1) compared with anti-HPV-16/18 seropositivity rates and antibody concentrations at Year 6 in subjects from the immunogenicity subset in study HPV-039.

10.3. Determination of sample size

No sample size is calculated for this study. Up to 369 healthy Chinese female subjects of age 17 years and above at the time of enrolment are expected to participate in this extension study. Subjects from HPV-058 study who completed the vaccination schedule (0, 1 and 6 months) will be eligible to take part in this study.

10.4. Cohorts for Analyses

10.4.1. Exposed Set

- The Exposed Set (ES) will include all subjects who participate in this study, and
- Analysis of immunogenicity on this cohort will include subjects for whom serology results are available.

10.4.2. Per-protocol cohort for analysis of immunogenicity

The Per-Protocol Set (PPS) for analysis of immunogenicity will include all evaluable subjects who were included in the according to protocol (ATP) immunogenicity analysis in the primary vaccination study (HPV-058), met all eligibility criteria, complied with the procedures defined in the protocol, with no elimination criteria during the study, and with serology results available at this blood sampling time-point.

10.5. Derived and transformed data

- The cut-off value of anti-HPV-16/18 antibodies is defined by the laboratory before the analysis.
- A seronegative subject is a subject whose antibody concentration is below the cut-off value.
- A seropositive subject is a subject whose antibody concentration is greater than or equal to the cut-off value.
- The Geometric Mean Concentration (GMC) calculations are performed by taking the anti-log of the mean of the log concentration transformations. Antibody concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMC calculation.
- For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements

10.6. Analysis of demographics

- Demographic characteristics (age and race) of each study cohort will be tabulated.
- The mean age (plus range and standard deviation) of the enrolled subjects, will be calculated.

10.7. Analysis of immunogenicity

The primary analysis will be based on the PPS for analysis of immunogenicity.

- For all subjects, for whom blood sample results are available:
  - Seropositivity rates with exact 95% confidence interval (CI) will be calculated for anti-HPV-16 and anti-HPV-18 antibodies.
  - GMCs (with 95% CI and range) will be tabulated for anti-HPV-16 and anti-HPV-18 antibodies.
- The distribution of antibody concentrations for anti-HPV-16 and anti-HPV-18 will be displayed using reverse cumulative curves.
- An analysis of the anti-HPV-16 and anti-HPV-18 seropositivity rates and antibody concentrations at Year 6 in subjects from the HPV-039 study and blood sampling time-point of this study will be presented.

10.8. Interpretation of analyses

All analyses will be descriptive with the aim to assess the persistence of anti-HPV-16/18 antibodies.

10.9. 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.

10.9.1. Sequence of analyses

The analysis of all immunogenicity data collected in the study will be conducted.

An integrated clinical study report containing all data will be written and made available to the investigators.

10.9.2. Statistical considerations for interim analyses

All analyses will be conducted on final data and therefore no statistical adjustment for interim analyses is required.

11. ADMINISTRATIVE MATTERS

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

11.1. electronic Case Report Form instructions

A validated GSK defined electronic data collection tool will be used as the method for data collection.

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

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

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

11.2. Study Monitoring by GSK Biologicals

GSK will monitor the study to verify that, amongst other items, 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, 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.

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

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform a eCRF review and a Source Document Verification (SDV). By SDV we understand verifying eCRF 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 eCRF. This document should be completed and signed by the site monitor and investigator and should be filed in the investigator's study file. Any data item for which the eCRF will serve as the source must be identified, agreed and documented in the source documentation agreement form.

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. Record retention

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible, when needed (e.g. audit or inspection), and must be available for review 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); however, caution needs to be exercised before such action is taken. The investigator must ensure 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 that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place 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. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by ICH GCP, any institutional requirements, applicable laws or regulations, or GSK standards/procedures, otherwise, the minimum retention period will default to 25 years after completion of the study report.

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

11.4. Quality assurance

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

11.5. Posting of information on publicly available clinical trial registers and publication policy

GSK assures that the key design elements of this protocol will be posted on the GSK website and in publicly accessible database(s) such as clinicaltrials.gov, in compliance with the current regulations.

GSK also assures that results of this study will be posted on the GSK website and in publicly accessible regulatory registry(ies) within the required time-frame, in compliance with the current regulations. The minimal requirement is to have primary endpoint summary results disclosed at latest 12 months post primary completion date (PCD) and to have secondary endpoint disclosed at latest 12 months after the last subject last visit (LSLV) as described in the protocol.

GSK also aims to publish the results of these studies in searchable, peer reviewed scientific literature and follows the guidance from the International Committee of Medical Journal Editors.

11.6. Provision of study results to investigators

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

GSK Biologicals will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

11.7. Data Sharing

Under the framework of the SHARE initiative, results of GSK studies may be combined with non- GSK studies, to investigate further about the study product(s) and other product(s), and /or the disease/condition under investigation and related diseases and conditions.

12. COUNTRY SPECIFIC REQUIREMENTS

Not applicable.

13. REFERENCES

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APPENDIX A LABORATORY ASSAYS

Anti-HPV-16 and anti-HPV-18 enzyme-linked immunosorbent assay (ELISA)

Antibody responses against HPV-16 and HPV-18 VLPs will be quantified by ELISA. These immunoassays are based on the direct test principle. Purified VLPs from *Cervarix* are coated onto a 96-well microtitration plate. After a washing and saturation step, serial dilutions of sera, control sera and standards are distributed and incubated in the coated wells to allow the specific antibody present in the sample to react with the corresponding antigen. Non-specific reactants are removed by washing, and a peroxidase-conjugated anti human IgG polyclonal antibody is added to react with the specific antibody. Excess conjugate is removed by washing. Enzyme substrate and chromogen are added and the colour is allowed to develop. After adding the Stop Reagent, the resultant colour change is quantified and expressed in EU/mL. The intensity of the resultant yellow colour is directly proportional to the concentration of anti-VLP antibodies present in the sample.

Titres are calculated by reference to a standard serum using the 4-parameters equation for each serum dilution, and the final titre of a serum is the average of all titres falling in the proportional part of the reference curve. The cut-off of the assay for HPV-16 is 19 ELISA units per millilitre (EU/mL) and for HPV-18 is 18 EU/mL.

APPENDIX B CLINICAL LABORATORIES

Table 9 Outsourced laboratories

Laboratory	Address
National Institute for Food and Drug Control (NIFDC), China.	No 2 Tiantan Xili, Beijing, 100050, China.

Protocol Sponsor Signatory Approval

eTrack study number and Abbreviated Title	207347 (HPV-093 EXT 058)
Date of protocol	Final Version 1: 19 May 2017
Detailed Title	A phase III, open-label, mono-centre, follow-up extension study to evaluate the persistence of immune response to GSK Biologicals' HPV vaccine in healthy Chinese female subjects who received three doses of the vaccine in the HPV-058 study
Sponsor signatory	Frank Struyf, M.D., Ph.D., Director, Clinical and Epidemiology R&D Project Lead, HPV and Hepatitis vaccines, GlaxoSmithKline Biologicals SA.
Signature	PPD
Date	29 MAY 2017

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