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 (Types 16, 18) Vaccine, Adsorbed*** (GSK580299)
eTrack study number and Abbreviated Title	205779 (HPV-092 EXT 039)
Date of protocol	Final: 31 March 2017
Date of protocol amendment	Amendment 1 Final: 21 June 2018
Title (Amended: 21 Jun 2018)	Safety ***and protective effect*** study of GSK Biologicals' Human Papillomavirus ***(Types 16, 18)*** Vaccine, ***Adsorbed*** (GSK580299) in healthy female subjects from ***the*** HPV-039 ***study***.
Detailed Title (Amended: 21 Jun 2018)	A phase III/***IV*** open-label, multi-centre study to evaluate the safety of ***GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed***, administered intramuscularly according to a 0,1,6-month schedule, in healthy Chinese female subjects above 26 years of age ***who received the control vaccine in study HPV-039 and to evaluate the protective effect of GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed, up to approximately 10 years after vaccination, in reducing HPV-associated cervical infection in subjects who participated in the HPV-039 study***.
Co-ordinating author	PPD, Scientific Writer

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Contributing authors (Amended: 21 Jun 2018)	• PPD, Clinical and Epidemiology R&D Project Leads • PPD, Clinical Research and Development Leads • PPD, Associate Scientist, Research and Development • PPD, Project Statistician • PPD, Lead Statistician • PPD, Study Delivery Leads • PPD, Clinical Safety representatives • PPD, Study Data Manager • PPD, Oversight Data Manager • PPD, Global Patents representative • PPD, Clinical Trial Supply Manager • PPD ***, Clinical Read-out Team Leader*** • PPD ***, CLS Study Manager*** • PPD, Regulatory Affairs representatives • PPD, Local Delivery Lead, China

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Contributing authors (continued) (Amended: 21 Jun 2018)	• PPD ***, Local Medical Lead, China*** • PPD , Head of Clinical Research and Development, China/Hong Kong • PPD ***, Regulatory Affairs, China*** • PPD ***, Local Delivery Lead, China***

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Protocol Amendment 1 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	205779 (HPV-092 EXT 039)
Date of protocol	Amendment 1 Final: 21 June 2018
Detailed Title (Amended: 21 Jun 2018)	A phase III/***IV*** open-label, multi-centre study to evaluate the safety of ***GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed,*** administered intramuscularly according to a 0,1,6-month schedule, in healthy Chinese female subjects above 26 years of age ***who received the control vaccine in study HPV-039 and to evaluate the protective effect of GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed, up to approximately 10 years after vaccination, in reducing HPV-associated cervical infection in subjects who participated in the HPV-039 study***.
Sponsor signatory	Dorota Borys, M.D., Director, Clinical and Epidemiology R&D Project Lead, HPV, Hepatitis and Pneumococcal vaccines, GlaxoSmithKline Biologicals SA.
Signature	
Date	

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Protocol Amendment 1 Rationale

Amendment number: Amendment 1
Rationale/background for changes: The protocol has been amended to support the post-licensure commitment to the Center for Drug Evaluation (CDE) of National Drug Administration of China (CNDA) with regard to the assessment of long term protective effect of GSK Biologicals' HPV vaccine, Adsorbed in subjects who participated in the HPV-039 study. To address this, the following changes have been made: • The study design has been modified to include the HPV-vaccinated subjects from the HPV-039 study. The number of subjects for the study has been updated from up to 3025 to up to 6051. • Assessment of rates of HPV-16/18 incident infection up to approximately 10 years after vaccination in the study HPV-039 has been added as a secondary objective. Long term efficacy against virological, cytological, histopathological endpoints will be assessed as a tertiary objective. • Procedures namely; gynaecological examination, cervical sampling, follow-up colposcopy and biopsy in subjects with abnormal cytology have been added at Visit 1. • The assay section has been updated to include testing related to cervical samples and biopsy. • The statistical section has been updated to describe "Analysis of long term protective effect" on HPV infection. • Additionally, regulatory approval of Gardasil and Gardasil 9 and approval of *Cervarix* age indication extension up to 45 years in China has been mentioned. • Owing to the extension of age indication of *Cervarix* up to 45 years, it is specified in the protocol that subjects also have the opportunity to receive *Cervarix* free of charge outside of the current study, when commercially available.

Protocol Amendment 1 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	205779 (HPV-092 EXT 039)
Date of protocol	Amendment 1 Final: 21 June 2018
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Investigator name	_____
Signature	_____
Date	_____

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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 8.4.2.

SYNOPSIS

Detailed Title (Amended: 21 Jun 2018)

A phase III/*IV* open-label, multi-centre study to evaluate the safety of ***GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed,*** administered intramuscularly according to a 0,1,6-month schedule, in healthy Chinese female subjects above 26 years of age ***who received the control vaccine in study HPV-039 and to evaluate the protective effect of GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed, up to approximately 10 years after vaccination, in reducing HPV-associated cervical infection in subjects who participated in the HPV-039 study***.

Indication (Amended: 21 Jun 2018)

Cervarix is approved for use in females 9 through ***45*** years of age for the prevention of cervical cancer, cervical intraepithelial neoplasia grade 2, grade 3 (CIN 2/3) and adenocarcinoma *in situ* ***(AIS)*** and cervical intraepithelial neoplasia grade 1 (CIN1) caused by high risk human papillomavirus (HPV) types 16 and 18***.***

Rationale for the study and study design (Amended: 21 Jun 2018)

- **Rationale for the study**

The burden of cervical cancer in China is most likely underestimated. In China, over 61,000 new cases of cervical cancer are diagnosed annually, responsible for more than 29,000 deaths [HPV Information Centre, 2016]. A meta-analysis of 18 studies on the distribution of HPV types in cervical lesions estimated the proportional impact of HPV-16 and HPV-18 on invasive cervical cancer to be as high as 69.6% in Chinese women [Bao, 2007]. A recent assessment in Chinese women revealed high-risk (HR)-HPV infection prevalence of 21.07%, where infection with the HPV-16 sub-type was the most common (4.82%) [Wang, 2015]. Prophylactic vaccination with a HPV vaccine would efficiently reduce the incidence of cervical cancer and may be particularly useful 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 ***GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed*** were assessed in a total of four clinical trials, involving over 8000 Chinese females between 9 and 45 years of age, of whom over 4000 subjects received the vaccine [Zhu, 2011; *Cervarix* Product Information, 2016]. The results of the phase II/III efficacy study (HPV-039) showed high and sustained vaccine efficacy against all virological, cytological and histopathological efficacy endpoints associated with HPV-

16/18. There was no sign of waning efficacy at the end of the study (up to Month 72). The ***Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed*** was generally well tolerated in Chinese women aged 18-25 years [GlaxoSmithKline Biologicals Clinical Report 107638 (HPV-039)].

This study has been ***designed*** following ethical considerations, to enable all subjects who received placebo in the HPV-039 study, to also receive GSK Biologicals' ***Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed***. Safety data in terms of serious adverse events (SAEs), any adverse events (AEs)/SAEs leading to premature discontinuation of the study, potential immune mediated diseases (pIMDs) and pregnancies (and their outcomes) will be collected during the study period. ***In addition, this study aims to assess the long term protective effect of the vaccine, in an exploratory manner, in terms of rates of HPV-related (vaccine type) incident cervical infection (secondary objective), cytological abnormalities and CIN2+ lesions (tertiary objective)up to approximately 10 years after vaccination in subjects who participated in HPV-039 study, to support the post-licensure commitments to the Center for Drug Evaluation (CDE) of National Drug Administration of China (CNDA).***
At the availability of the commercial vaccine for use in individuals above 25 years, subjects will be offered the opportunity to receive Cervarix free of charge either by participating to this study or without participating to this study.

- **Rationale for the study design**

This study will be conducted in an open-label and non-randomised manner, ***since the subjects who had participated in study HPV-039 already know the treatment they received and only those in the control group will receive Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in the current study***. Safety data will be collected from Dose 1 until the end of the study ***in subjects vaccinated in this study***. ***Cervical samples will be collected at Visit 1 from all subjects to test for HPV incident infection and cytological abnormalities. Subjects with abnormal cytology will be called back for colposcopy follow-up and biopsy to examine for the presence of CIN lesions***.

Limitations:

In the HPV-039 study, the efficacy of GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed against virological, cytological and histopathological endpoints associated with HPV types 16 and 18, was demonstrated up to 6 years after vaccination and subjects were screened every 6 months. The study was unblinded after completion and since the Year 6, 3-4 years have elapsed with no regular follow-up of the subjects. As a consequence, at Year 10, there might be high subject attrition, leading to a potential imbalance in the numbers of subjects from the vaccinated versus control group returning for the current study. This as well as a lack of regular gynaecological follow-up between Year 6 and Year 10 may compromise assessments of vaccine efficacy in this study. Therefore, vaccine efficacy analyses will be exploratory.

Objectives (Amended: 21 Jun 2018)

Primary objective:

- To assess the safety of ***GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in subjects above 26 years of age, who previously received placebo in the HPV-039 study, in terms of related SAEs.***

Secondary objectives:

- ***To assess the safety of GSK Biologicals Human Papillomavirus (Types 16, 18) Vaccine in terms of occurrence of unsolicited AEs in subjects above 26 years of age, who previously received placebo in the HPV-039 study.***
- ***To assess the protective effect of GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in all subjects who participated in the HPV-039 study in terms of the rates of HPV 16/18 incident infection up to approximately 10 years after vaccination.***
- ***To assess the protective effect of GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in all subjects who participated in the HPV-039 study in terms of the rates of incident infection associated with any or combination of oncogenic HPV types, up to approximately 10 years after vaccination.***

Tertiary objectives:

- ***To assess the long term efficacy of GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in the prevention of incident infection associated with HPV-16 and/or HPV-18 or with any or combination of oncogenic HPV types.***

- ***To assess the long term efficacy of GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in the prevention of cytological abnormalities associated with HPV-16 and/or HPV-18.***
- ***To assess the long term efficacy of GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in the prevention of cytological abnormalities associated with any or combination of oncogenic HPV types.***
- ***To assess the long term efficacy of the GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in the prevention of histopathologically-confirmed CIN1+ associated with HPV-16 and/or HPV-18.***
- ***To assess the long term efficacy of the GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in the prevention of histopathologically-confirmed CIN1+ associated with any or combination of oncogenic HPV types.***
- ***To assess the long term efficacy of the GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in the prevention of histopathologically-confirmed CIN2+ associated with HPV-16 and/or HPV-18.***
- ***To assess the long term efficacy of the GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in the prevention of histopathologically-confirmed CIN2+ associated with any or combination of oncogenic HPV types.***
- ***To assess the long term efficacy of the GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in the prevention of other histopathologically-confirmed endpoints associated with HPV-16 and/or HPV-18 or any or combination of oncogenic HPV types.***

Study design (Amended: 21 Jun 2018)

- **Experimental design:** Phase III/***IV***, open-label, ***partially-controlled***, multi-centric, single-country study ***with two parallel groups***.

- **Duration of the study**:

  Subjects who previously received HPV vaccination in study HPV-039 (Vacc-HPV-039 group)*:

  – ***The study duration is one day (Visit 1) i.e., when a subject comes for cervical sample collection.***

  Subjects who previously received the control vaccine in study HPV-039 and will receive HPV vaccination in this study (HPV Group)*:

  – Approximately 12 months per subject ***(approximately 6 months for 3-dose vaccination followed by 6-month extended safety follow-up after last dose).***

  o Epoch 001: starting at Visit 1 (Day 1) and ending at Call 2 (Month 12)

  ****Subjects who have abnormal cytology findings in the cervical sample collected at Visit 1 will be called back for a follow-up visit for colposcopy examination and biopsy (when needed).***

- **Primary completion Date (PCD):** Call 2 (Month 12)
- **End of Study (EoS):** Last subject's last visit/contact (Call 2 [Month 12]) or ***last testing results released for samples collected at Visit 1 and related call-back visit, whatever comes later.***
- **Study groups: *Two groups***

  – ***Vacc-HPV-039 group i.e. subjects who received HPV vaccine in HPV-039 study who will undergo cervical sample collection only.***

  – ***HPV group (Ctrl-HPV-039 group) i.e. subjects who received control vaccine in HPV-039 study will receive HPV vaccine in the current study and undergo cervical sample collection before HPV vaccination..***

Synopsis Table 1 Study groups and epoch foreseen in the study

Study Groups	Number of subjects	Age	Epoch
			Epoch 001
Vacc-HPV-039 group	***Up to 3026***	From 26 years	x
HPV group	***Up to 3025***	***From 26 years***	***x***

Synopsis Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine name	Study Groups	
		Vacc-HPV-039 group	*HPV group*
HPV-16/18	***Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed*** (HPV16-18 AS04D)	***No treatment***	***x***

- **Control:** ***none for safety objectives; HPV group (Ctrl-HPV-039 group) for long term protective effect objectives.***
- **Vaccination schedule:** Three doses of ***Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed*** (20 µg HPV-16, 20 µg HPV-18) administered intramuscularly according to a 0, 1, 6-month schedule.
- **Treatment allocation:** ***Treatment allocation depends on the randomization in the previous study i.e. only the subjects from the control group of HPV-039 study will receive HPV vaccination in the current study. Subjects who previously received the Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in HPV-039 study will not receive vaccination in this study***.
- **Blinding:** open-label

Synopsis Table 3 Blinding of study epoch

Study Epoch	Blinding
Epoch 001	open-label

- ***Sampling schedule: A cervical sample will be taken at Visit 1 before vaccine administration.***

  For subjects who have abnormal cytology findings in the cervical sample collected at Visit 1, there will be a call-back follow-up visit for colposcopy examination. A cervical biopsy will be taken depending on the results of the colposcopy examination.

- **Type of study:** self-contained.
- **Data collection:** Electronic Case Report Form (eCRF).
- **Safety monitoring:**
  - ***All subjects: SAEs related to study participation.***
  - HPV group ***(Ctrl-HPV-039 group)***:
    - All SAEs, and any AE/SAE leading to premature discontinuation of the study will be reported throughout the study.
    - pIMDs will be reported throughout the study.
    - Pregnancies and pregnancy outcomes will be reported throughout the study.

Number of subjects (Amended: 21 Jun 2018)

Up to 6051 subjects who ***participated*** in the HPV-039 study will be invited to participate in this study.

The study recruitment period is expected to last approximately 6 months and the recruitment period will be communicated to all study investigators. Investigators will make all efforts to invite and enrol subjects during this period.

Women who are pregnant during the recruitment period will be offered participation in the study or free of charge vaccination outside the study using commercial vaccine three months after the pregnancy ends.

Hence, the study end may change depending on study progress.

Endpoints (Amended: 21 Jun 2018)

Primary Endpoint:

- ***Safety endpoint***
  - ***HPV group (Ctrl-HPV-039 group)***
    - ***Occurrence of SAEs related to study vaccine.***

Secondary endpoints:

- ***Safety endpoints***
  - ***HPV group (Ctrl-HPV-039 group)***
    - Occurrence of pIMDs throughout the study.
    - Occurrence of pregnancies and pregnancy outcomes throughout the study.
    - Any AE/SAE leading to premature discontinuation from the study.
    - Occurrence of SAEs.
  - ***All subjects***
    - ***Occurrence of SAEs related to study participation.***
- ***Virological endpoints***
  - ***Incident cervical infection associated with HPV-16 and/or HPV-18 (by PCR).***
  - ***Incident cervical infection associated with any oncogenic HPV type (e.g. HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68 or combination of oncogenic HPV types; by PCR).***

Tertiary endpoints

- ***Virological endpoint***
  - ***Incident infection associated with HPV-16/18, any other oncogenic type, irrespective of HPV type.***
- ***Cytological endpoints***
  - ***Any cytological abnormality (i.e., [ASC-US] associated with HPV-16 and/or HPV-18 cervical infection (by PCR).***
  - ***Any cytological abnormality associated with any oncogenic HPV type (e.g. HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68 or combination of oncogenic HPV types; by PCR).***
  - ***Any cytological abnormality irrespective of the HPV type.***
- ***Histopathological endpoints***
  - ***Histopathologically-confirmed CIN1+ associated with HPV-16 and/or HPV-18 (by PCR).***
  - ***Histopathologically-confirmed CIN2+ associated with HPV-16 and/or HPV-18 (by PCR).***

    CIN2+ is defined as CIN2, CIN3, LCGIN, HCGIN, adenocarcinoma in-situ (AIS) or invasive cervical cancer.
  - ***Histopathologically-confirmed CIN1+ associated with cervical infection with any oncogenic HPV type (e.g. HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68 or combination of oncogenic HPV types; by PCR).***
  - ***Histopathologically-confirmed CIN2+ associated with cervical infection with any oncogenic HPV type (e.g. HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68 or combination of oncogenic HPV types; by PCR).***
  - ***Histopathologically-confirmed CIN1+ lesions irrespective of HPV type***
  - ***Histopathologically-confirmed CIN2+ lesions irrespective of HPV type***
  - ***Histopathologically-confirmed VIN1+ associated with HPV-16 and/or HPV-18 infection (by PCR).***
  - ***Histopathologically-confirmed VaIN1+ associated with HPV-16 and/or HPV-18 infection (by PCR).***
  - ***Histopathologically-confirmed VIN1+ associated with any oncogenic HPV type (e.g. HPV-16, -18, -31, -33, -35, -39,***

-45, -51, -52, -56, -58, -59, -66 and -68 or combination of oncogenic HPV types; by PCR).

- ***Histopathologically-confirmed VaIN1+ associated with any oncogenic HPV type (e.g. HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68 or combination of oncogenic HPV types; by PCR).***
- ***Histopathologically-confirmed VIN1+ irrespective of HPV type.***
- ***Histopathologically-confirmed VaIN1+ irrespective of HPV type.***

For the above mentioned tertiary endpoints, VIN (Vulvar Intraepithelial Neoplasia) is defined as VIN1+ or VIN2+, and VaIN (Vaginal Intraepithelial Neoplasia) is defined as VaIN1+ or VaIN2+.

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LIST OF ABBREVIATIONS (AMENDED: 21 Jun 2018)

AE:	Adverse Event
AIS:	***Adenocarcinoma in situ***
CDE:	***Center for Drug Evaluation***
CICAMS/CFC:	***Cancer Institute/Hospital, Chinese Academy of Medical Sciences and Cancer Foundation of China***
CNDA:	***National Drug Administration of China***
eCRF:	electronic Case Report Form
EDD:	Estimated Date of Delivery
EGA:	Estimated Gestational Age
EoS:	End of Study
eTDF:	Electronic Temperature Excursion Decision Form
GCP:	Good Clinical Practice
GSK:	GlaxoSmithKline
IB:	Investigator Brochure
ICF:	Informed Consent Form
ICH:	International Conference on Harmonisation
IEC:	Independent Ethics Committee
IRB:	Institutional Review Board
LBC:	***Liquid-Based Cytology***
LMP:	Last Menstrual Period
LSLV:	Last Subject Last Visit
MedDRA:	Medical Dictionary for Regulatory Activities
PCD:	Primary Completion Date
pIMD:	Potential Immune-Mediated Disease
SAE:	Serious Adverse Event
SBIR:	Randomisation System on Internet
SDV:	Source Document Verification
SPM:	Study Procedures Manual
TVC	***Total Vaccinated Cohort***

GLOSSARY OF TERMS

Adequate contraception: Adequate contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label for example:

- abstinence from penile-vaginal intercourse, when this is their preferred and usual lifestyle,
- Combined estrogen and progesterone oral contraceptives,
- injectable progestogen,
- implants of etenogestrel or levonorgestrel,
- Contraceptive vaginal ring,
- percutaneous contraceptive patches,
- intrauterine device or intrauterine system,
- male partner sterilisation prior to the female subject's entry into the study, and this male is the sole partner for that subject,

  The information on the male sterility can come from the site personnel's review of the subject's medical records; or interview with the subject on her medical history.
- male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository), and/or progesterone alone oral contraceptive.

Adequate contraception does not apply to subjects of child bearing potential with same sex partners, or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle.

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 timepoints or a single timepoint 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 timepoints included in an epoch must be sufficient to fulfil the purpose of the epoch. Typical examples of epochs are screening, primary vaccinations, boosters, yearly immunogenicity follow-ups, and surveillance periods for efficacy or safety.
eTrack:	GSK's tracking tool for clinical trials.
Investigational vaccine: **(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.

Menarche:	Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1-2 years of breast development, thelarche. However, a young female can become pregnant before her first menses. Thus, a conservative definition of non-childbearing potential in a pre-menarcheal female is a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue).
Menopause:	Menopause is the age associated with complete cessation of menstrual cycles, menses, and implies the loss of reproductive potential by ovarian failure. A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile at the appropriate age e.g. > 45 years.
Potential Immune-Mediated Disease:	Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology.
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/product:	Any investigational vaccine/product being tested and/or any authorised use of a vaccine/ product/placebo as a reference or administered concomitantly, in a clinical trial that evaluates the use of an investigational vaccine/product.
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 ™ or ® and in *italics*.

Trademark of the GSK group of companies	Generic description
Cervarix	Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed

Trademarks not owned by the GSK group of companies	Generic description
GARDASIL (Merck & CO., Inc.)	Quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine
GARDASIL 9 (Merck & CO., Inc.)	Human Papillomavirus 9-valent Vaccine, Recombinant

1. INTRODUCTION

1.1. Background (Amended: 21 Jun 2018)

Cervical cancer is the fourth most common cancer among women worldwide, with nearly 528,000 new cases and nearly 266,000 deaths each year [International Agency for Research on Cancer, 2012]. 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.

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

Cervarix was first licensed in ***May 2007*** in Australia, for use in 10 to 45 year old females. In September 2007, the vaccine was licensed in Europe ***for use from the age of 9 years*** for the ***prevention of persistent infection, premalignant ano-genital lesions (cervical, vulvar, vaginal and anal) and cervical, vulvar, vaginal and anal cancers (squamous-cell carcinoma and adenocarcinoma) caused by oncogenic Human Papillomaviruses (HPVs).*** The vaccine has been licensed in over 133 countries and regions worldwide. In July 2016, *Cervarix* (hereafter referred to as the ***Human Papillomavirus [Types 16, 18] Vaccine, Adsorbed***) was approved for use as a 3-dose schedule at 0, 1, 6 months in females from 9 to 25 years in China. ***The extension of the vaccine indication up to 45 years of age was approved by the Chinese authorities on 10-May-2018.***

In May 2017, Merck's recombinant quadrivalent HPV vaccine, Gardasil, also received approval in China. In April 2018, Gardasil 9 was granted conditional approval by National Drug Administration of China (CNDA)with additional requirements in China.

To date, ***safety and immunogenicity data were evaluated in*** more than 60,000 adolescents and adults aged 9 years and above in clinical studies. The vaccine is known to be immunogenic and generally well tolerated. Pooled safety analyses of girls and women aged 9 years and above 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 (Amended: 21 Jun 2018)

The burden of cervical cancer in China is most likely underestimated. In China, over 61,000 new cases of cervical cancer are diagnosed annually, responsible for more than 29,000 deaths [HPV Information Centre, 2016]. A meta-analysis of 18 studies on the distribution of HPV types in cervical lesions estimated the proportional impact of HPV-16 and HPV-18 on invasive cervical cancer to be as high as 69.6% in Chinese women [Bao, 2007]. A recent assessment in Chinese women revealed HR-HPV infection prevalence of 21.07%, where infection with the HPV-16 sub-type was the most common (4.82%) [Wang, 2015]. Prophylactic vaccination with a HPV vaccine would efficiently reduce the incidence of cervical cancer and may be particularly useful 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 ***GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed*** were assessed in a total of four clinical trials ***conducted in China***, involving over 8000 Chinese females between 9 and 45 years of age, of whom over 4000 subjects received the ***vaccine*** [Zhu, 2011; *Cervarix* Product Information, 2016]. The results of the phase II/III efficacy study (HPV-039) showed high and sustained vaccine efficacy against all virological, cytological and histopathological efficacy endpoints associated with HPV-16/18. There was no sign of waning efficacy at the end of the study (up to Month 72). The ***Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed*** was generally well tolerated in Chinese women aged 18-25 years [GlaxoSmithKline Biologicals Clinical Report 107638 (HPV-039)].

This study ***has been designed*** following ethical considerations, to enable all subjects who received placebo in the HPV-039 study, to also receive ***GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed.*** Safety data in terms of serious adverse events (SAEs), any adverse events (AEs)/SAEs leading to premature discontinuation of the study, potential immune mediated diseases (pIMDs) and pregnancies (and their outcomes) will be collected during the study period. ***In addition, this study aims to assess the long term protective effect of the vaccine, in an exploratory manner, in terms of rates of HPV related (vaccine type) incident cervical infection (secondary objective), cytological abnormalities and CIN2+ lesions (tertiary objective) up to approximately 10 years after vaccination in subjects who participated in HPV-039 study, to support the post-licensure commitments to the Center for Drug Evaluation (CDE) of CNDA.***

At the availability of the commercial vaccine for use in individuals above 25 years, subjects will be offered the opportunity to receive Cervarix free of charge either by participating to this study or without participating to this study.

1.2.2. Rationale for the study design

This study will be conducted in an open-label and non-randomised manner ***since the subjects who had participated in study HPV-039 already know the treatment they received and only those in the control group will receive Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in the current study***. Safety data will be collected from Dose 1 until the end of the study ***in subjects vaccinated in this study***. ***Cervical samples will be collected at Visit 1 from all subjects to test for HPV incident infection and cytological abnormalities***. ***Subjects with abnormal cytology will be called back for colposcopy follow-up and biopsy to examine for the presence of CIN lesions***.

Limitations:

In the HPV-039 study, the efficacy of GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed against virological, cytological and histopathological endpoints associated with HPV types 16 and 18, was demonstrated up to 6 years after vaccination and subjects were screened every 6 months. The study was unblinded after completion and since the Year 6, 3-4 years have elapsed with no regular follow-up of the subjects. As a consequence, at Year 10, there might be high subject attrition, leading to a potential imbalance in the numbers of subjects from the vaccinated versus control group returning for the current study. This as well as a lack of regular gynaecological follow-up between Year 6 and Year 10 may compromise assessment of vaccine efficacy in this study. Therefore, vaccine efficacy analyses will be exploratory.

1.3. Benefit : Risk Assessment (Amended: 21 Jun 2018)

Please refer to the Prescribing Information for information regarding the summary potential risks and benefits of ***Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed.***

The following section outlines the risk assessment and mitigation strategy for this study protocol:

1.3.1. Risk Assessment

Important Potential Risk	Data/Rationale for Risk	Mitigation Strategy
Investigational vaccine		
Theoretical potential risk of inducing or exacerbating an autoimmune disease following vaccination.*	Potential concern that ***Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed***, and adjuvanted vaccines in general, might be associated with an increased risk of new onset of autoimmune diseases. Analysis of cumulative data so far remains inconclusive with respect to any potential pathogenic link between ***Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed*** and autoimmune diseases.	Naturally occurring autoimmune diseases are multi-aetiological conditions with multiple risk factors, including genetic predisposition. Relative risks for autoimmune diseases following ***Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed*** administration are derived from the most recent pooled analysis of clinical trial data, which showed no difference between groups. The incidence of autoimmune diseases is being monitored closely in the ongoing clinical trials, post-marketing spontaneous reports, literature and observational epidemiological studies specifically designed to evaluate the risk of autoimmune diseases following vaccination with ***Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed***.
Study Procedures		
Allergic reactions (including anaphylactic and anaphylactoid reactions), ***angioedema***, or other immediate reactions such as syncope or vasovagal response following vaccination.	Spontaneous data	Subjects will be observed for at least 30 minutes after vaccine administration, with medical attention available in case of anaphylactic reactions.
Colposcopy with targeted biopsies may involve rare events such as lower abdominal pain, vaginal bleeding, fever, chills and yellow colored vaginal discharge.	***Spontaneous data*** ***In general, the colposcopy and biopsy procedures are relatively simple and safe***	***Colposcopy and biopsy will be conducted by experts from the Cancer Institute/Hospital, Chinese Academy of Medical Sciences and Cancer Foundation of China***

Only for subjects being vaccinated in this study.

1.3.2. Benefit Assessment (Amended: 21 Jun 2018)

Cervical cancer is one of the most common cancers in women, and is often fatal. Vaccination with ***Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed*** is likely to prevent the occurrence of HPV infection, premalignant genital lesions and cervical cancers associated with HPV types 16 and 18. All study participants ***who belonged to the control group in the HPV-039 study*** will ***be invited to*** receive ***Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed***. ***In addition, subjects from HPV-039 study will also be invited to take part in gynaecological examination and cervical sampling during the study. In case of abnormal cytology results of cervical samples, the subjects will be called back for a follow-up colposcopy examination. Colposcopy is an important routine procedure in the initial evaluation of cervical abnormalities for cancer screening in many countries. Colposcopy with targeted biopsies provides accurate***

identification of cervical diseases when present, as well as reassurance of the absence of disease in the subjects. Since cervical screening in this age group is not the standard of care in China at present, the study provides an opportunity for the enrolled subjects to have a cervical cancer screening.

1.3.3. Overall Benefit : Risk Conclusion

Taking into account the measures taken to minimise risk to subjects participating in this study, the potential or identified risks identified in association with ***Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed or in association with the study procedures*** are justified by the potential benefits (prevention of HPV infection, ***screening of HPV-related diseases***) that may be afforded to subjects.

2. OBJECTIVES (AMENDED: 21 JUN 2018)

2.1. Primary objective

To assess the safety of ***GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in subjects above 26 years of age, who previously received placebo in the HPV-039 study, in terms of related SAEs***.

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

2.2. Secondary objectives

- ***To assess the safety of GSK Biologicals Human Papillomavirus (Types 16, 18) Vaccine in terms of occurrence of unsolicited AEs in subjects above 26 years of age, who previously received placebo in the HPV-039 study.***
- ***To assess the protective effect of GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in all subjects who participated in the HPV-039 study in terms of the rates of HPV 16/18 incident infection up to approximately 10 years after vaccination.***
- ***To assess the protective effect of GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in all subjects who participated in the HPV-039 study in terms of the rates of incident infection associated with any or combination of oncogenic HPV types, up to approximately 10 years after vaccination.***

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

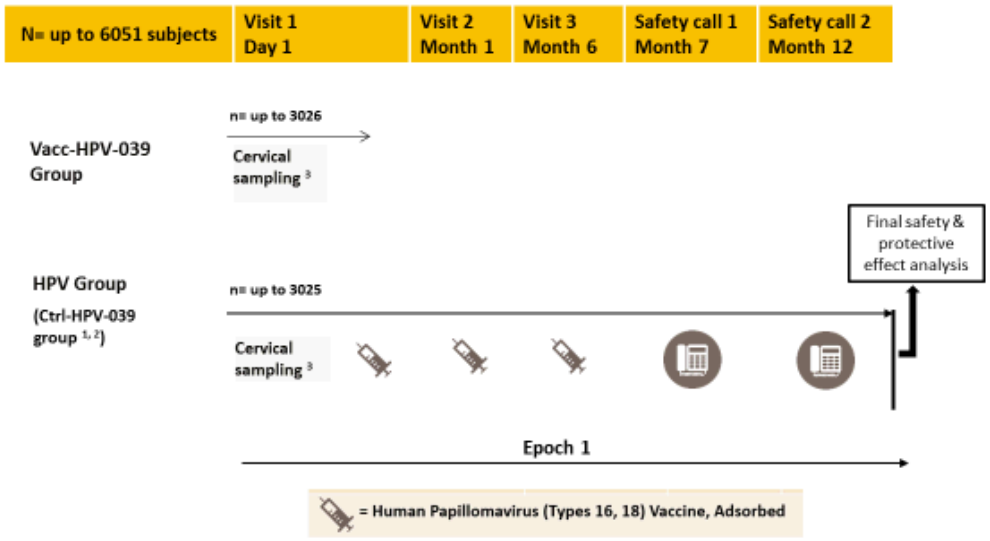
2.3. Tertiary objectives

- ***To assess the long term efficacy of GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in the prevention of incident infection associated with HPV-16 and/or HPV-18 or with any or combination of oncogenic HPV types.***
- ***To assess the long term efficacy of GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in the prevention of cytological abnormalities associated with HPV-16 and/or HPV-18.***
- ***To assess the long term efficacy of GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in the prevention of cytological abnormalities associated with any or combination of oncogenic HPV types.***
- ***To assess the long term efficacy of the GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in the prevention of histopathologically-confirmed CIN1+ associated with HPV-16 and/or HPV-18.***
- ***To assess the long term efficacy of the GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in the prevention of histopathologically-confirmed CIN1+ associated with any or combination of oncogenic HPV types.***
- ***To assess the long term efficacy of the GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in the prevention of histopathologically-confirmed CIN2+ associated with HPV-16 and/or HPV-18.***
- ***To assess the long term efficacy of the GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in the prevention of histopathologically-confirmed CIN2+ associated with any or combination of oncogenic HPV types.***
- ***To assess the long term efficacy of the GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in the prevention of other histopathologically-confirmed endpoints associated with HPV-16 and/or HPV-18 or any or combination of oncogenic HPV types.***

Refer to Section 10.3 for the definition of the tertiary endpoint(s) and to section 10.12.1 for the reporting of tertiary endpoint results.

3. STUDY DESIGN OVERVIEW (AMENDED: 21 JUN 2018)

Figure 1 Study design diagram



N: Number of subjects

[1] Sampling from the subjects of Ctrl-HPV-039 group will be done before vaccination.

[2] Subjects can choose to consent to both cervical sampling and vaccination procedures or one of the two procedures during the informed consent process.

[3] Call back visit for colposcopy and follow-up of subjects with abnormal cytology. Medical care of subjects with abnormal cervical lesions will be outside of the study, according to the local medical practice.

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/***IV***, open-label, ***partially-controlled***, multi-centric, single-country study ***with two parallel groups***.
- **Duration of the study:**

  Subjects who previously received HPV vaccination in study HPV-039 (Vacc-HPV-039 group)*:

  – ***The study duration is one day (Visit 1) i.e., when a subject comes for cervical sample collection.***

  Subjects who previously received the control vaccine in study HPV-039 and will receive HPV vaccination in this study (HPV Group)*:

  – Approximately 12 months per subject ***(approximately 6 months for 3-dose vaccination followed by 6-month extended safety follow-up after last dose)***

    o Epoch 001: starting at Visit 1 (Day 1) and ending at Call 2 (Month 12)

  ****Subjects who have abnormal cytology findings in the cervical sample collected at Visit 1 will be called back for a follow-up visit for colposcopy examination and biopsy (when needed).***

- **Primary completion Date (PCD):** Call 2 (Month 12)

Refer to glossary of terms for the definition of PCD.

- **End of Study (EoS):** Last subject's last visit/contact (Call 2 [Month 12]) or ***last testing results released for samples collected at Visit 1 and related call back visits, whatever comes later.***

Refer to glossary of terms for the definition of EoS.

- **Study groups:** ***Two groups:***
  - ***Vacc-HPV-039 group i.e. subjects who received HPV vaccine in HPV-039 study who will undergo cervical sample collection only.***
  - ***HPV group (Ctrl-HPV-039 group) i.e. subjects who received control vaccine in HPV-039 study will receive HPV vaccine in the current study and undergo cervical sample collection before HPV vaccination.***

Table 1 Study groups and epoch foreseen in the study

Study Groups	Number of subjects	Age	Epoch
			Epoch 001
Vacc-HPV-039 group	***up to 3026***	From 26 years	x
HPV group	***up to 3025***	***From 26 years***	***x***

Table 2 Study groups and treatment foreseen in the study

Treatment name	Vaccine name	Study Groups	
		Vacc-HPV-039 group	***HPV group***
HPV-16/18	***Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed*** (HPV16-18 AS04D)	***No treatment***	***x***

- **Control:** ***none for safety objectives; HPV group (Ctrl-HPV-039 group) for long term protective effect objectives.***
- **Vaccination schedule:** Three doses of ***Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed*** (20 µg HPV-16, 20 µg HPV-18) administered intramuscularly according to a 0, 1, 6-month schedule.
- **Treatment allocation:** ***Treatment allocation depends on the randomization in the previous study i.e. only the subjects from the control group of HPV-039 study will receive HPV vaccination in the current study. Subjects who previously received the Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in HPV-039 will not receive vaccination in this study.***
- **Blinding:** open-label

Table 3 Blinding of study epochs

Study Epoch	Blinding
Epoch 001	open-label

- ***Sampling schedule: A cervical sample will be taken at Visit 1 before vaccine administration.***

  For subjects who have abnormal cytology findings in the cervical sample collected at Visit 1, there will be a call-back follow-up visit for colposcopy examination. A cervical biopsy will be taken depending on the results of the colposcopy examination.

- **Type of study:** self-contained.
- **Data collection:** Electronic Case Report Form (eCRF).
- ***Safety*** **monitoring:**
  - ***All subjects:***
    - ***SAEs related to study participation.***
  - ***HPV group (Ctrl-HPV-039 group):***
    - All SAEs, and any AE/SAE leading to premature discontinuation of the study will be reported throughout the study.
    - pIMDs will be reported throughout the study.
    - Pregnancies and pregnancy outcomes will be reported throughout the study.

4. STUDY COHORT (AMENDED: 21 JUN 2018)

4.1. Number of subjects/centres

Overview of the recruitment plan

Up to 6051 subjects who ***participated*** in the HPV-039 study will be invited to participate in this study.

The study recruitment period is expected to last approximately 6 months and the recruitment period will be communicated to all study investigators. Investigators will make all efforts to invite and enrol subjects during this period.

Women who are pregnant during the recruitment period will be offered participation in the study or free of charge vaccination outside the study using commercial vaccine three months after the pregnancy ends.

Hence, the study end may change depending on study progress.

4.2. Inclusion criteria for enrolment (Amended: 21 Jun 2018)

Deviations from inclusion 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.

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

- Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. return for study visits, available for follow-up telephone contacts).
- Written informed consent obtained from the subject prior to performing any study specific procedure.
- Subjects previously enrolled in the HPV-039 study.
- ***Subjects with negative pregnancy test at Visit 1.***

Additional inclusion criteria for subjects of HPV group undergoing vaccination ONLY:

- Healthy subjects as established by medical history and clinical examination before entering into the study.
- Female subjects of non-childbearing potential may be enrolled in the study.
  - Non-childbearing potential is defined as pre-menarche, current bilateral tubal ligation or occlusion, hysterectomy, bilateral ovariectomy or post-menopause.

Please refer to the glossary of terms for the definition of menarche and menopause.

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

Please refer to the glossary of terms for the definition of adequate contraception.

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:

- Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).
- Previous vaccination against HPV ***outside of study HPV-039***.

Additional exclusion criteria for subjects of HPV group undergoing vaccination ONLY:

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine during the period starting 30 days before the first dose of study vaccine (Day -29 to Day 1), or planned use during the study period.
- Any medical condition that in the judgment of the investigator would make intramuscular injection unsafe.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting six months prior to the first vaccine dose. For corticosteroids, this will mean prednisone (≥20 mg/day, or equivalent). Inhaled and topical steroids are allowed.
- Planned administration/administration of a vaccine/product not foreseen by the study protocol in the period starting 30 days before and after each dose of vaccine administration, with the exception of administration of routine vaccines e.g. meningococcal, hepatitis B, hepatitis A, inactivated influenza up to eight days before and after each dose of study vaccine. Enrolment will be deferred until the subject is outside of the specified window.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine.
- Previous administration of MPL or AS04 adjuvant.
- Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening tests.
- Cancer or autoimmune disease under treatment.
- Hypersensitivity to latex.
- Acute disease and/or fever at the time of enrolment.
  - Fever is defined as temperature ≥37.0°C. The preferred location for measuring temperature in this study will be the axilla.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may, be enrolled at the discretion of the investigator.

- Pregnant or ***breastfeeding. Subjects must be at least three months post-pregnancy and not breastfeeding to enter the study. For pregnant or lactating women, also please refer to Section 4.1.***
- Females planning to become pregnant or planning to discontinue contraceptive precautions during the vaccination phase of the study, i.e. up to two months after the last vaccine dose.

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 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 or witnessed/ thumb printed informed consent must be obtained from each subject, as appropriate, prior to participation in the study.

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

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

5.2. Subject identification and randomisation (Amended: 21 Jun 2018)

5.2.1. Subject identification

Subjects will be allocated the same identification numbers as in study HPV-039.

5.2.1.1. Treatment allocation to the subject

The treatment numbers will be allocated by dose.

A sequential list of treatment numbers will be generated by MATerial EXcellence (MATEX). The Randomisation and Treatment Allocation System on Internet (SBIR) will be used to allocate treatment numbers to the subjects.

After obtaining the signed and dated ICF from the subject and having checked the eligibility of the subject, the site staff in charge of the vaccine administration will access SBIR. Upon providing the subject identification number, the system will provide the treatment number to be used for the first dose.

When SBIR is not available, please refer to the SBIR user guide for specific instructions.

For each dose subsequent to the first dose, the study staff in charge of the vaccine administration will access SBIR, provide the subject identification number, and the system will provide a treatment number.

The number of each administered treatment must be recorded in the eCRF on the Vaccine Administration screen.

5.3. Method of blinding (Amended: 21 Jun 2018)

Not applicable since this is an open-label study. However the laboratory in charge of the laboratory testing will 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.

The laboratory testing mentioned above refers to the cytology, histopathology and PCR and HPV DNA testing described in Table 7.

5.4. General study aspects (15 May 2018)

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

5.4.1. HPV DNA testing

All assessments of cervical samples for this study will be done by the Cancer Institute/Hospital, Chinese Academy of Medical Sciences and Cancer Foundation of China (CICAMS/CFC).

"Reflex" testing by the US FDA and China FDA-approved hybridization assay (Hybrid Capture® 2 test [HCII]) will be used to guide a subject's management in case of atypical squamous cells of undetermined significance (ASC-US, see Section 5.6.8.2). CICAMS/CFC will automatically perform HPV DNA Hybrid Capture II (HCII) testing on the liquid-based cytology specimen. Study personnel do not need to request the HCII testing.

Currently available data do not support the use of HPV DNA PCR testing in the routine management of subjects diagnosed with abnormal cervical cytology. The HPV DNA PCR testing, which will be used in this study, has been developed for investigational use only. For this reason, clinical management will not be driven by the results of this testing. A number of procedures will be followed to ensure that HPV DNA PCR test results do not bias either the conduct of the trial, or the clinical management of the study subjects.

These procedures include:

1. ***Study sites and study personnel will be blinded to HPV DNA PCR test results throughout the study to ensure that these results do not bias either the conduct of the trial, or the clinical management of study subjects. This includes bias that might result from deviations from regular study interval visits for cervical cytological follow-up and/or colposcopic procedures.***
2. ***HPV DNA PCR test results will NOT be provided to the investigators or study subjects until the end of the study. A summary report on results will be distributed to the investigators after study completion. It will be the responsibility of the investigators to inform study subjects of their results. The clinical management of subjects should follow the recommended guidelines outlined below and should be based solely on cervical cytology or biopsy results and HCII testing (not HPV DNA PCR test results).***

5.4.2. Management of subjects with abnormal cytology

Cervical cytology specimens will be collected using the sampling device provided. Cytological examination will be performed using the ThinPrep® PapTest (Cytyc Corporation, Boxborough, MA, USA). HPV DNA PCR testing will be performed on the cervical cytology specimens collected on Day 1 (Visit 1). In case of abnormal cytology results, the subjects will be called back for a follow-up visit for colposcopy examination. The following algorithms (see Figure 2, Figure 3, Figure 4 and Figure 5) describe clinical management guidelines to be followed by the investigator (and/or designee). Treatment of subjects with abnormal findings is not within the scope of this study; however, the subjects will be referred to local healthcare centres to follow local medical practices. The algorithms are based on the guidelines of the American Society

for Colposcopy and Cervical Pathology and European guidelines, and are designed to provide a consistent method of detection, clinical management and reporting for cervical lesions. The clinical management algorithms cannot define every clinical situation and, therefore, it is the investigator's (or designee's) responsibility to exercise appropriate clinical judgment in the medical management of exceptional cases. Compliance with the algorithm will be monitored.

5.4.2.1. *Cytology and histology report terminology*

Each cytopathology specimen will be reported according to the Bethesda 2001 Classification of cytological findings. The terminology will include a statement as to whether a specimen is satisfactory or unsatisfactory. In addition, specimens that are satisfactory but show no endocervical component will be identified for quality control of cytological sampling.

For the purposes of the trial, management is specified for the categories:

- ***Unsatisfactory***
- ***Negative for intraepithelial lesion or malignancy (negative)***
- ***Atypical squamous cells of undetermined significance (ASC-US):***
  - ***ASC-US / Hybrid Capture II negative (ASC-US/oncogenic HPV negative)***
  - ***ASC-US / Hybrid Capture II positive (ASC-US/oncogenic HPV positive)***
  - ***ASC-US / Hybrid Capture 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***

Specimens will be reported as "Quantity Not Sufficient" when there is an inadequate amount of cells for HCII testing. In case of ASC-US/QNS or missing HCII test results, subjects will be informed and encouraged to follow regular gynaecological examination according to local practice.

Histopathological reports on biopsy and excision specimens will classify the findings as:

- ***Negative***
- ***Condyloma***
- ***Cervical intraepithelial neoplasia grade 1 [CIN1]***

  Vaginal intraepithelial neoplasia grade 1 [VaIN1]

  Vulvar intraepithelial neoplasia grade 1 [VIN1])

- ***Cervical intraepithelial neoplasia grade 2 [CIN2]***

  Vaginal intraepithelial neoplasia grade 2 [VaIN2]

  Vulvar intraepithelial neoplasia grade 2 [VIN2])
- ***Cervical intraepithelial neoplasia grade 3 [CIN3]***

  Vaginal intraepithelial neoplasia grade 3 [VaIN3]

  Vulvar intraepithelial neoplasia grade 3 [VIN3])
- ***Low grade cervical glandular intraepithelial neoplasia (LCGIN)***
- ***High grade cervical glandular intraepithelial neoplasia (HCGIN)***
- ***Adenocarcinoma in-situ (AIS)***
- ***Invasive malignancy***

5.4.2.2. *Cytology and colposcopy management algorithms*

The algorithm in Figure 2 describes the clinical management of all cytology results obtained at Day 1 (Visit 1). Subjects with cytology reported as negative or as ASC-US/ oncogenic HPV negative will not be called back for a follow-up biopsy sample. Subjects with abnormal cytological findings (except ASC-US/oncogenic HPV negative) should be managed according to the recommendations for follow-up in Figure 2 and the colposcopy algorithms in Figure 3, Figure 4 and Figure 5. The results of the cytology will be communicated to the investigator (or designee) by CICAMS/CFC. The investigator (or designee) will notify the subject of the test result and, when appropriate, the subject should receive colposcopy within approximately 30 days after cytology results have been communicated by CICAMS/CFC.

5.4.2.3. *Unsatisfactory cytological findings and missing cytology results*

When the laboratory results deem a cervical liquid-based cytology (cervical-LBC) specimen unsatisfactory, study personnel are required to repeat the cervical-LBC specimen as soon as possible after cytology results have been communicated. Only satisfactory results of a repeat cytology result will count as the final cytology result. Likewise, HPV DNA PCR testing will not be performed on unsatisfactory cytology specimens.

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 will be used for quality control monitoring. Abnormal cytology should be managed according to the appropriate protocol-specified algorithm. Missing cytology results will be recorded as missing results (in the case of lost damaged sample).

5.5. Outline of study procedures (Amended: 21 Jun 2018)

Table 4 *List of study procedures – Vacc-HPV-039 group*

Epoch	*Epoch 001*
Type of contact	*Visit 1*
Time points	*Day 1*
Informed consent	●
Check inclusion/exclusion criteria	●
Collect demographic data	●
Medical and vaccination history†	●
Physical examination	●
Pregnancy test	●
Gynaecological Examination	●
Cervical sampling	●
*Referral for colposcopy (if applicable)***	*O*
*Report colposcopy results (if applicable)***	●
Safety assessments	
*Record any concomitant medications/vaccinations**	●
Recording of SAEs (related to study participation)	●
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.
† Medical history since the last visit in study HPV- 039 will be recorded. The subjects should also provide their history of any HPV related infection/disease with all available information.
**Including only medications/vaccinations which may lead to elimination from per-protocol analysis*
*** Subjects with abnormal cervical cytology will be evaluated according to the cytology and colposcopy clinical management algorithms (see Section 5.4.2 and Section 5.6.9) at unscheduled visits following Visit 1.*

Table 5 ***List of study procedures – HPV Group (Ctrl-HPV-039 group)***

Epoch	Epoch 001				
Type of contact	**Visit 1**	**Visit 2**	**Visit 3**	**Call 1**	**Call 2**
Time points	**Day 1**	**Month 1**	**Month 6**	**Month 7**	**Month 12**
Informed consent	●				
Check inclusion/exclusion criteria	●				
Collect demographic data	●				
Medical and vaccination history †	●				
Physical examination	●				
Pregnancy test	●	●	●		
Check contraindications and warnings and precautions to vaccination	●	●	●		
Gynaecological Examination	●				
Cervical sampling	●				
Referral for colposcopy (if applicable)*	***O***				
Report colposcopy results (if applicable)*	●				
Pre-vaccination body temperature	●	●	●		
Vaccine					
Treatment number allocation	O				
Treatment number allocation for subsequent doses		O	O		
Recording of administered treatment number	●	●	●		
Vaccine administration	●	●	●		
Safety assessments					
Record any concomitant medications/vaccinations	●	●	●	●	●
Recording of pregnancies and outcomes	●	●	●	●	●
Recording of SAEs	●	●	●	●	●
Recording of AEs/SAEs leading to premature withdrawal from the study	●	●	●	●	●
Recording of pIMDs	●	●	●	●	●
Safety follow-up contact				●	●
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.

† Medical history since the last visit in study HPV- 039 must be recorded. The subjects should also provide their history of any HPV related infection/disease with all available information.
***** Subjects with abnormal cervical cytology will be evaluated according to the cytology and colposcopy clinical management algorithms (see Section 5.4.2 and Section 5.6.9) at unscheduled visits following Visit 1.***

Whenever possible, the investigator should arrange study visits within the interval described in Table 6.

Table 6 **Intervals between study visits (*for the HPV Group*)**

Interval	Length of interval	Optimal length of interval
Visit 1 → Visit 2	21 - 62 days	30 days
Visit 1 → Visit 3	161 - 216 days	180 days
Visit 3 → Call 1	21 - 62 days	30 days
Visit 3 → Call 2	150 - 210 days	180 days

5.6. Detailed description of study procedures (Amended: 21 Jun 2018)

Note: Each study procedure is detailed in subsequent subsections only once, even if some of them need to be performed during more than one visit.

5.6.1. Informed consent

The signed/witnessed/thumb printed informed consent of the subject must be obtained before study participation. Refer to Section 5.1 for the requirements on how to obtain informed consent, as appropriate.

Subjects in the HPV group (Ctrl-HPV-039 group) will be given the choice to consent to either sampling or vaccination or both procedures during the informed consent process.

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 prior to ***cervical sample collection or*** the first study vaccination in the eCRF.

The subjects should also provide their history of any HPV related infection/disease with all available information since their last visit in study HPV-039.

5.6.5. Physical examination

Perform a physical examination of the subject, including assessment of axillary body temperature and resting vital signs: systolic/diastolic blood pressure, heart rate and respiratory rate after at least 10 minutes of rest. Collected information needs to be recorded in the eCRF.

Physical examination at each study visit subsequent to the first vaccination visit will be performed only if the subject indicates during questioning that there might be some underlying pathology(ies) or if deemed necessary by the Investigator or delegate.

If the investigator determines that the subject's health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled.

For subjects in the Vacc-HPV-039 group, the investigator must use her medical judgement to decide if a subject can undergo cervical sampling procedure. Subjects may be rescheduled or excluded from the study on the basis of medical history.

Treatment of any abnormality observed during physical examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

5.6.6. Pregnancy test

Female subjects of childbearing potential are to have a ***negative*** urine pregnancy test prior to any ***gynaecological examination, cervical sample collection or*** vaccine administration.

Note: Pregnancy test must be performed even if the subject is menstruating at the time of the study visit.

In case of a positive urine pregnancy test result, the subjects would not be allowed to receive vaccination or undergo cervical sampling until 3 months after the end of pregnancy.

5.6.7. Check contraindications, warnings and precautions to vaccination

Contraindications, warnings and precautions to vaccination must be checked at the beginning of each vaccination visit. Refer to Sections 6.5 and 6.6 for more details.

5.6.8. *Gynaecological examination and cervical sampling* (Amended: 21 Jun 2018)

5.6.8.1. *Gynaecological examination*

Gynaecological examination will be performed on Day 1 (Visit 1). At gynaecological examination, according to local medical practice, the vagina and vulva will be inspected using the unaided eye or the colposcope or a magnifying glass. If needed, acetic acid may be applied.

Any vaginal or vulvar lesions possibly associated with HPV (other than condylomas) will be biopsied and excised according to local medical practice. This may include referral to the study colposcopists. All tissues will be shipped to CICAMS/CFC. After completion of the gynaecological examination, women should be encouraged to continue follow-up in the context of local medical practice.

5.6.8.1.1. Requirements for cervical specimen collection

Sexual intercourse must 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 are menstruating during planned visits will be invited to reschedule cervical specimen collection 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 delivery.

5.6.8.1.2. Cervical Sampling

All subjects should undergo pelvic examination during which a cervical-LBC sample will be collected for HPV DNA testing by PCR and cytological examination (refer to Sections 5.4.2 and 5.6.9 for details on gynaecological examination and follow-up algorithms [colposcopy and biopsy procedures]).

5.6.8.2. *ASC-US or LSIL*

An observation of ASC-US will result in reflex testing by CICAMS/CFC for high-risk HPV types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) using HCII. Results will be communicated to the investigator (or designee) as "ASC-US/oncogenic HPV negative" or "ASC-US/oncogenic HPV positive".

Subjects with ASC-US/oncogenic HPV negative results will not be called back for a follow-up biopsy procedure; however, will be encouraged to continue follow-up in the context of local medical practice.

Subjects with ASC-US/oncogenic HPV positive results or LSIL will be referred for colposcopic evaluation (see Figure 3 for the low-grade colposcopy management algorithm).

Specimens will be reported as "Quantity Not Sufficient" (QNS) when there is an inadequate amount of cells for HCII testing. In case of ASC-US/QNS or missing HCII test results, subjects will be informed and encouraged to follow regular gynaecological examination according to local practice.

To ensure active follow-up with subjects missing a follow-up visit or a colposcopy visit, study personnel will contact the subject by using established local communication methods. The site will make at least three attempts to contact the subject. If contact cannot be achieved after three attempts, a certified/registered letter will be sent by the site.

5.6.8.3. *AGC*

Observation of AGC will result in an immediate referral for colposcopic evaluation (see Figure 4 for the AGC colposcopy management algorithm).

5.6.8.4. *ASC-H / greater than or equal to HSIL*

Observation of ASC-H or ≥HSIL will result in an immediate referral for colposcopic evaluation (see Figure 5 for the high-grade colposcopy management algorithm).

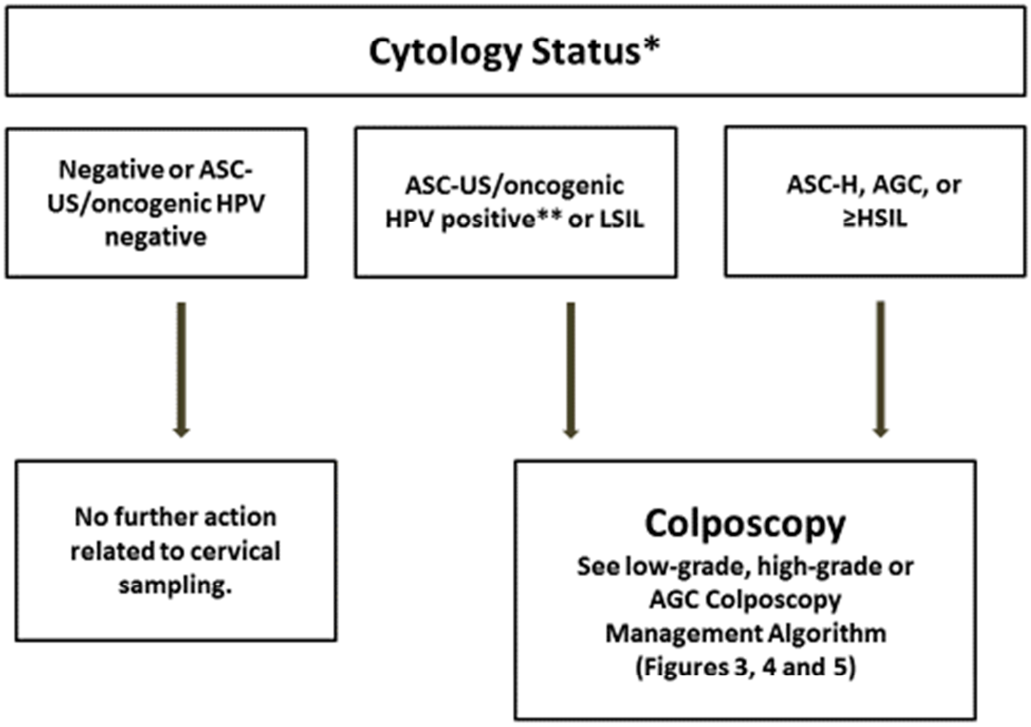
5.6.9. Colposcopic evaluations of abnormal cytologies

Colposcopy provides the link between cytology and biopsy. Colposcopy will be performed by a trained and experienced colposcopist. Colposcopy will be performed on subjects with abnormal cytological findings (except ASC-US/oncogenic HPV negative, see Figure 2).

Given that the expertise of the clinical site teams varies in the field of cervical disease management and colposcopy, the qualifications and experience of the participating colposcopists will be reviewed.

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.

Figure 2 Cytology Management Algorithm



** If a cervical liquid-based cytology (LBC) specimen is deemed "unsatisfactory" by the laboratory, the subject must be informed to arrange for another cervical sampling visit.*

*** Oncogenic HPV positive means that the cytology specimen is positive for an oncogenic HPV type by Hybrid Capture II (HCII) testing. This test will automatically be performed on specimens with an ASC-US result (reflex testing). Specimens will be reported as "Quantity Not Sufficient" (QNS) when there is an inadequate amount of cells for HCII testing. In case of ASC-US/QNS or missing HCII test results, subjects will be informed and encouraged to follow regular gynaecological examination according to local practice.*

5.6.9.1. *Colposcopic procedures*

If the transformation zone is not fully visualized, the colposcopy is to be considered as not satisfactory. In these cases, an endocervical specimen by endocervical curettage will have to be collected during the colposcopy and the vagina carefully inspected.

- ***A normal colposcopy impression may result in taking an endocervical specimen by endocervical curettage according to the appropriate algorithm and local medical practices.***
- ***A colposcopy impression of LSIL or equivocal will result in biopsy. A colposcopy impression of ≥HSIL will also result in a biopsy.***

If the biopsy result/endocervical specimen is negative or ≤CIN1, no further action is required; however, the subjects can continue with protocol-specified procedures if applicable and will be encouraged to have a follow-up according to local medical practice. If the biopsy result or the endocervical specimen is ≥CIN2 or AIS, the subject will be referred for treatment according to local medical practice.

A biopsy specimen that cannot be adequately evaluated by the histopathologist will be reported as non-diagnostic. If the biopsy is reported as non-diagnostic, the subjects will be offered a repeat colposcopy as soon as possible and a further biopsy would be taken from any abnormal or equivocal area.

Any cervical lesions will be biopsied according to colposcopy management algorithms. In addition, the vagina and vulva will be inspected with each colposcopy and any vaginal or vulvar lesions possibly associated with HPV (other than condylomas) will be biopsied or excised according to local medical practice.

All tissues will be shipped to CICAMS/CFC. All tissues will be examined in CICAMS/CFC and the report from CICAMS/CFC will be used for clinical management.

Every effort should be made to encourage subjects to have the colposcopic examination within this study. Should a subject have a colposcopy performed outside of the study, she will be asked to consent to allow study staff to access her medical records and to obtain slides and tissue for evaluation if possible.

5.6.9.2. *Colposcopy management for low-grade cytology*

The management algorithm shown in Figure 3 should be used for any subject who has cytological abnormalities graded as ASC-US/oncogenic HPV positive or LSIL.

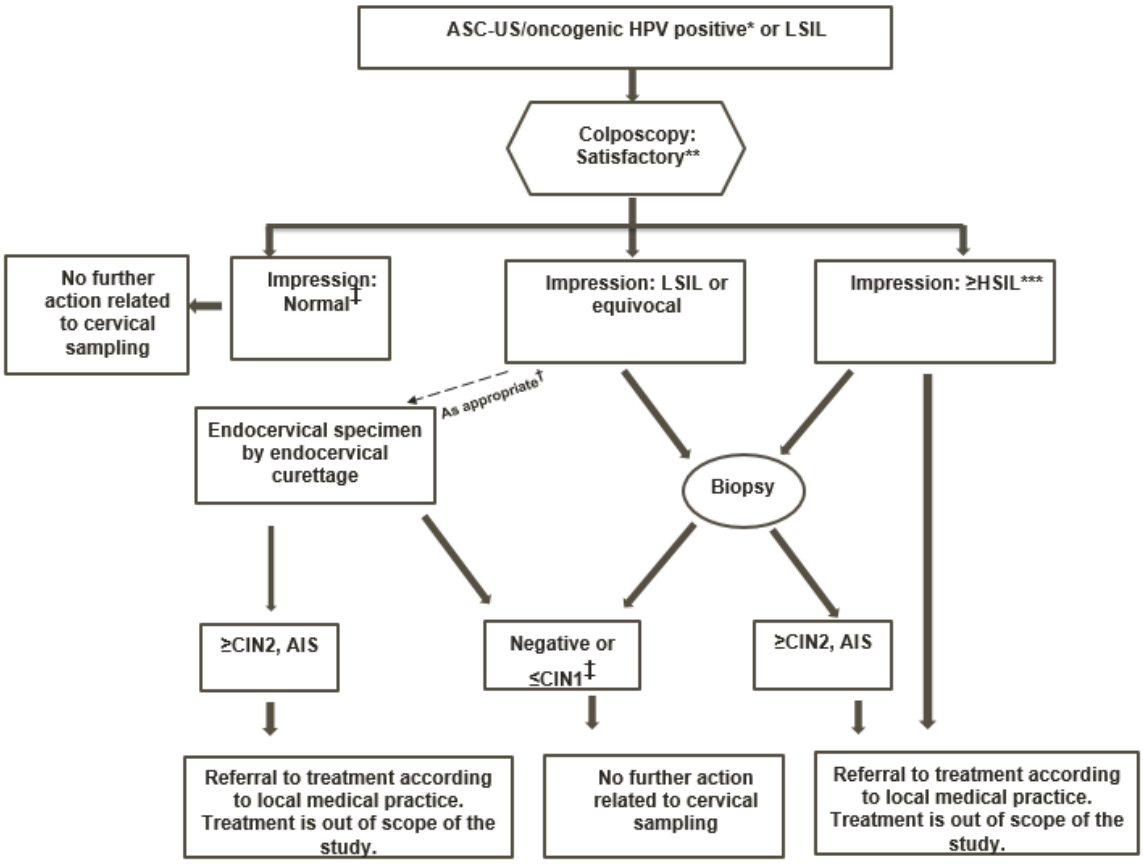
An unsatisfactory colposcopy indicates that the transformation zone is unable to be fully visualized. In these cases, an endocervical specimen must be taken by endocervical curettage and the vagina carefully inspected. If any abnormality is seen, this should be managed according to the algorithm.

If it is a normal colposcopy impression no further action is required and the subjects can continue with protocol-specified procedures, if applicable and will be encouraged to continue follow-up in the context of local medical practice.

A colposcopy impression of LSIL will result in biopsy - collection of an endocervical specimen by endocervical curettage is optional. If the biopsy result is negative or ≤CIN1, no further action is required and the subjects can continue with protocol-specified procedures, if applicable and is encouraged to be followed up according to the local medical practice. If biopsy or endocervical curettage show ≥CIN2 or AIS, subjects will be referred for treatment according to local medical practice.

For colposcopic impression of ≥HSIL, a biopsy will be performed. If the biopsy result is ≥CIN2 or AIS, the subject will be referred for treatment according to local medical practice. Subjects with ≥HSIL may also be referred to treatment without biopsy.

Figure 3 Colposcopy Management Algorithm for subjects with ASC-US/oncogenic HPV positive results or LSIL



Note: Specimens will be reported as "Quantity Not Sufficient" (QNS) when there is an inadequate amount of cells for HCII testing. In case of ASC-US/QNS or missing HCII test results, subjects will be informed and encouraged to follow regular gynaecological examination according to local practice

*** An unsatisfactory colposcopy indicates that the transformation zone is unable to be fully visualized. In these cases an endocervical specimen must be taken and the vagina inspected.*

****If invasive cancer is suspected, management should be according to accepted standard medical practice. Subjects who do not have a biopsy in the study will be asked to consent to allow study staff to obtain their tissue for evaluation if possible.*

† Collection of endocervical specimen will depend on local practice and clinical judgement.

‡ subjects will be encouraged to have gynaecological follow-up as per local practice.

5.6.9.3. *Colposcopy management algorithm for AGC*

This management algorithm (Figure 4) should be used for any subject who has a single cytological abnormality graded as AGC.

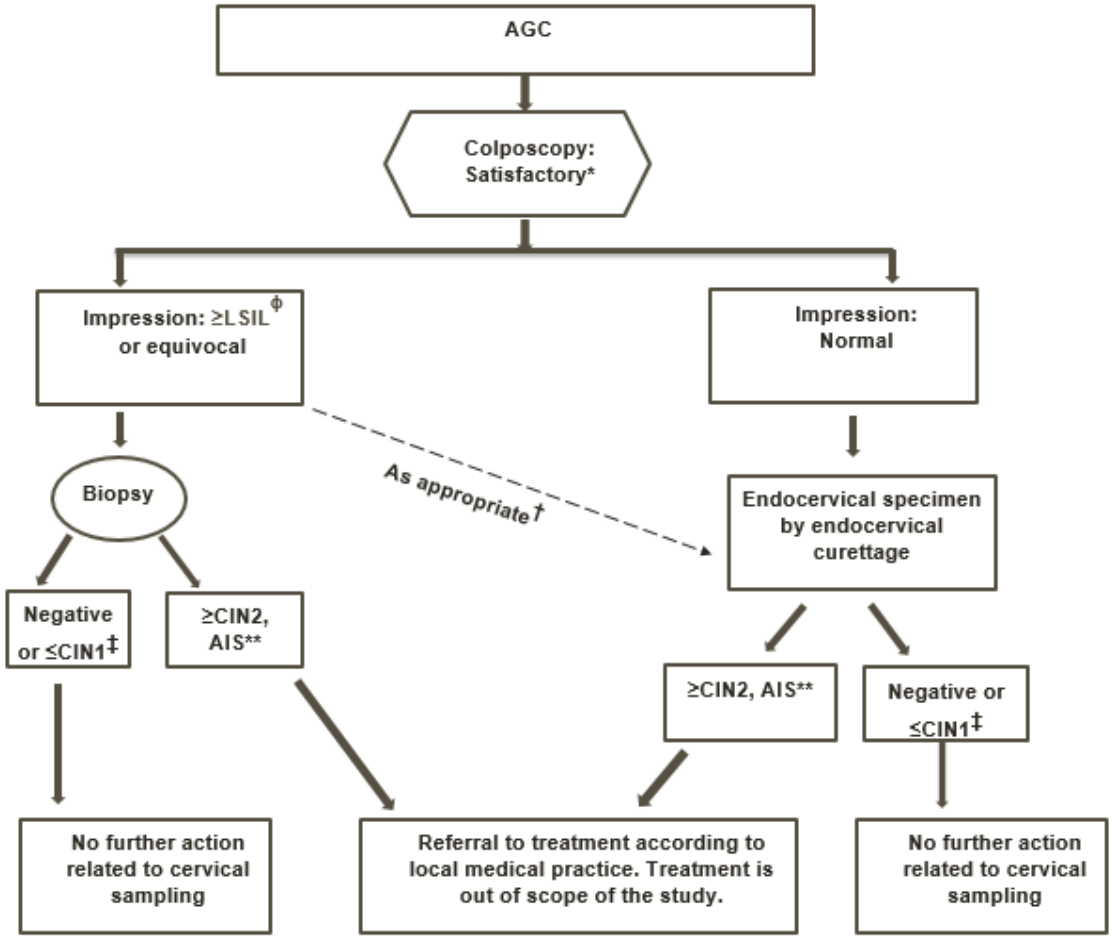
An unsatisfactory colposcopy indicates that the transformation zone is unable to be fully visualized. In these cases, an endocervical specimen must be taken and the vagina carefully inspected. If any abnormality is seen, this should be managed according to the algorithm.

If the colposcopic impression is normal, an endocervical specimen by endocervical curettage will be collected, cytology will be reviewed and the vagina should also be carefully inspected. If endocervical and cytological review results are negative or ≤LSIL or≤CIN1 or negative, no further action is required and the subjects can continue with protocol-specified procedures, if applicable and will be encouraged to continue follow-up in the context of local medical practice. If cytology result (except ASC-US/oncogenic HPV negative) or colposcopy is abnormal, please refer to appropriate colposcopy management algorithm.

If endocervical and cytological review results are ≥HSIL, AGC or AIS, the subjects will be referred for treatment as per local medical practice.

If the colposcopic impression is ≥LSIL or equivocal, a biopsy should be performed depending on the colposcopic impression and local medical practice. An endocervical specimen by endocervical curettage may be collected. If a biopsy confirms ≥CIN2 or AIS, the subjects will be referred for treatment as per local medical practice. If the biopsy result is negative or ≤CIN1, no further action is required and the subjects can continue with protocol-specified procedures, if applicable and will be encouraged to continue follow-up in the context of local medical practice. If cytology result (except ASC-US/oncogenic HPV negative) or colposcopy is abnormal, please refer to appropriate colposcopy management algorithm.

Figure 4 Colposcopy Management Algorithm for subjects with AGC



** An unsatisfactory colposcopy indicates that the transformation zone is unable to be fully visualized. In these cases, an endocervical specimen must be taken and the vagina inspected.*

† Collection of endocervical specimen and cytological review will depend on local practice and clinical judgement of discrepancy between findings. A high grade AGC should lead to excision biopsy.

ϕ If invasive cancer is suspected, management should be according to accepted standard medical practice.

‡ subjects will be encouraged to have gynaecological follow-up as per local practice

5.6.9.4. *Colposcopy management algorithm for high-grade cytology*

This management algorithm (Figure 5) should be used for any subject who has a single cytological abnormality graded as ASC-H or ≥HSIL.

An unsatisfactory colposcopy indicates that the transformation zone is unable to be fully visualized. In these cases, an endocervical specimen must be taken and the vagina carefully inspected. If any abnormality is seen, this should be managed according to the algorithm.

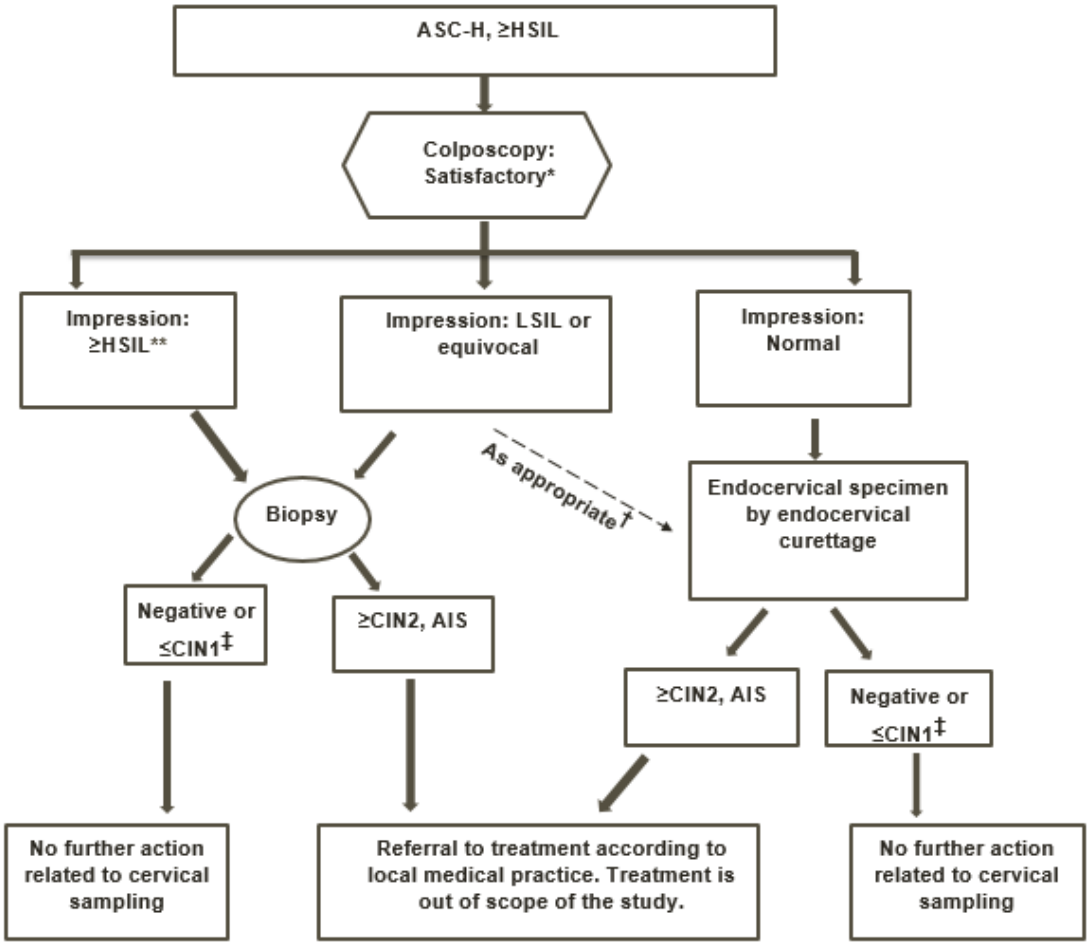
If the colposcopic impression is normal, an endocervical specimen by endocervical curettage will be collected, cytology will be reviewed and the vagina should also be carefully inspected. If the endocervical sampling and cytological review results are negative or ≤LSIL, ≤CIN1 no further action is required and the subjects can continue with protocol-specified procedures, if applicable. If cytological review or endocervical sampling confirms HSIL, ASC-H, AGC or AIS, the subjects will be referred for treatment as per local medical practice.

If the colposcopic impression is LSIL or equivocal, a biopsy should be performed. An endocervical specimen by endocervical curettage may be collected and cytology reviewed depending on local medical practice. If the biopsy result is negative or ≤CIN1, no further action is required and the subjects can continue with protocol-specified procedures, if applicable. If the biopsy result is ≥CIN2 or AIS, the subjects will be referred for treatment as per local medical practice.

For colposcopic impression of ≥HSIL, a biopsy will be performed. If the biopsy result is negative or ≤CIN1, no further action is required and the subjects can continue with protocol-specified procedures, if applicable. If the biopsy result is ≥CIN2 or AIS, the subjects will be referred for treatment as per local medical practice.

For any colposcopy/biopsy/endocervical specimen results ≤LSIL or ≤CIN1, subjects will be encouraged to continue follow-up in the context of local medical practice.

Figure 5 Coloposcopy Management Algorithm for subjects with ASC-H or HSIL



** An unsatisfactory colposcopy indicates that the transformation zone is unable to be fully visualized. In these cases, an endocervical specimen must be taken and the vagina inspected.*
*** If invasive cancer is suspected, management should be according to accepted standard medical practice.*
† Collection of endocervical specimen will depend on local practice and clinical judgement.
‡ subjects will be encouraged to have gynaecological follow-up as per local practice.

5.6.10. Sampling (Amended: 21 Jun 2018)

Refer to the Module on Biospecimen Management in the SPM for detailed instructions for the collection, handling and processing of the samples. Refer to section 5.6.8 for cervical sample collection.

The procedures listed in sections 5.6.11 to 5.6.13 are only applicable for subjects undergoing vaccination in this study.

5.6.11. Assess pre-vaccination body temperature

The ***axillary*** temperature of each subject needs to be measured prior to any study vaccine administration. If the subject has fever [fever is defined as temperature ≥37.0°C regardless the location of measurement] on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see Table 7).

5.6.12. Treatment number allocation

Treatment number allocation will be performed as described in Section 5.2.1.1. The number of each administered treatment must be recorded in the eCRF.

5.6.13. Study Vaccine administration

- After completing all prerequisite procedures prior to vaccination, one dose of study vaccine will be administered intramuscularly (IM) in the deltoid of the non-dominant arm (refer to Section 6.3 for detailed description of the vaccine administration procedure). If the investigator or delegate determines that the subject's health on the day of administration temporarily precludes vaccine administration, the visit will be rescheduled within the allowed interval for this visit (refer to Table 7).
- The subjects will be observed closely for at least 30 minutes following the administration of the vaccine, with appropriate medical treatment readily available in case of anaphylaxis.

5.6.14. Check and record concomitant medication/vaccination

Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section 6.7.

5.6.15. Recording of AEs, SAEs, pregnancies and its outcome and pIMDs

- Refer to Section 8.3 for procedures for the investigator to record SAEs, pregnancies and pIMDs. Refer to Section 8.4 for guidelines and how to report SAE, pregnancy and pIMD reports to GSK Biologicals.

5.6.16. Safety follow-up contact

- The investigator or his/her designee will contact the subjects ***who have been vaccinated,*** by telephone approximately one and six months after the third vaccine dose to obtain information on the occurrence of any of the safety endpoints.
- The procedures to be performed during the follow-up telephone contact such as recording of any concomitant medication/vaccination or medical treatment and recording of SAEs, pregnancies ***and its outcome (as applicable)*** and pIMDs are also performed during this phone contact and are described in Section 5.6.14 and Section 5.6.15, respectively.

5.6.17. 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 (Amended: 21 Jun 2018)

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.

- ***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.

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.

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 10.5 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

Cervical samples will be collected at Visit 1 from all the subjects to check for HPV infection. Subjects who have abnormal cytology findings in the cervical sample collected at Visit 1 will be called back for a follow-up colposcopy visit. A cervical biopsy may be taken depending on the colposcopy findings. No blood samples will be taken during the study.

5.7.3. Laboratory assays

The assays to be performed are summarized in Table 7.

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.

5.7.3.1. Cervical Cytology

All original cervical samples collected will be prepared by trained laboratory personnel using the ThinPrep® 2000 Processor to transfer and fix the cells onto glass slides. All cytology specimens will be processed and then evaluated according to the Bethesda 2001 classification system for reporting cervical cytology diagnoses.

Cervical cytology will be performed using the ThinPrep® PapTest. (Cytyc Corporation, Boxborough, MA, USA). Cervical cells for ThinPrep® cytology will be collected using the sampling device provided rinsed into a collection vial containing PreservCyt® medium. Specimens will be stored according to the CICAMS/CFC procedure until shipment to CICAMS/CFC. Cytological specimens must be shipped at ambient temperature within one month of collection.

From the PreservCyt® specimen (original sample), one 1 mL aliquot will be prepared and withdrawn prior to ThinPrep® slide preparation (to avoid possible specimen-to-specimen contamination) for HPV DNA testing. The remaining sample will be used for cytological analysis at CICAMS/CFC.

In case a commercialized test/equipment is not available, an equivalent test/equipment may be used after approval by GSK.

5.7.3.2. *Polymerase chain reaction (PCR) typing of HPV DNA from PreservCyt specimens*

To test for HPV DNA, SPF10 primers which amplify a 65 nucleotide region of the HPV L1 gene for most of the known HPV isolates are used; the generic amplification products are detected by hybridization on a microtitre plate (DEIA). HPV-positive specimens will be typed by reverse hybridization line probe assay (LiPA), using 25 HPV-specific hybridization probes enabling detection of 14 oncogenic HPV types [HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68] and 11 non-oncogenic HPV types [HPV-6, -11, -34, -40, -42, -43, -44, -53, -54, -70 and -74]. All HPV positive samples will also be tested by HPV-16 specific PCR and HPV-18 specific PCR. Redundant testing using generic SPF10 PCR with LiPA, followed by HPV-16/18 type-specific PCR (TS-PCR) affords maximum test sensitivity. The results of this testing algorithm will be considered definitive for all HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68 and HPV-6, -11, -34, -40, -42, -43, -44, -53, -54, -70 and -74 related study endpoints using HPV DNA testing from PreservCyt® specimens.

5.7.3.3. *Hybrid Capture II testing*

Clinical management will be guided by Hybrid Capture II testing (see Section 5.4.2). After ThinPrep® cytology slides have been prepared, residual PreservCyt® specimens on slides read as ASC-US will be tested for HPV DNA. Testing will be done by CICAMS/CFC using the HCII test (Digene Corp., Gaithersburg, MD, USA). Probe B will be used and is designed to detect infections with 13 oncogenic HPV types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) [Vernick, 2003]. This test is fast, reliable and accurate, but does not provide type-specific data. Therefore, additional HPV DNA testing by PCR will be required to define trial endpoints, as discussed above.

Vaginal and vulvar biopsies will be handled according to the same procedures as cervical biopsies.

5.7.3.4. *Histopathology*

Biopsy specimens obtained during the trial will be fixed in buffered formalin (provided by the sponsor) and shipped to CICAMS/CFC for histopathological evaluation and PCR examination.

Vaginal and vulvar biopsies will be handled according to the same procedures as cervical biopsies.

5.7.3.4.1. Histopathological analysis

Histopathological analysis will be performed by CICAMS/CFC. All biopsies will be reported independently by two designated, expert pathologists. In case of disagreement in diagnosis between the two pathologists, a third expert panel member will examine the specimen and a consensus diagnosis will be reached. These diagnoses will be placed in the results reporting system and made available electronically at each site within a designated timeframe (e.g. 7 days) of receipt at CICAMS/CFC. These results will be used for patient management. CICAMS/CFC will expedite reports on specimens marked urgent, engage in telephone consultation with clinicians and send slides to sites for review by local pathologists on request. Tissue blocks will be retained by CICAMS/CFC and, at the discretion of the sponsor, may be evaluated by additional techniques to assess the presence of HPV, expression of HPV genes, host responses elicited by HPV or other mechanisms involved in cervical carcinogenesis.

Specimens from subjects having biopsies performed outside the study (e.g. very urgent clinical need such as suspected invasive cancer) can be examined and entered into the study.

5.7.3.5. *HPV DNA PCR testing in tissue*

The formalin fixed and paraffin embedded tissue blocks used for histopathological analysis will be sectioned for PCR examination at CICAMS/CFC using an appropriate clean technique. Sections will be tested for HPV DNA using PCR methodology. Samples of lesions will be selected for further analysis using micro-dissection as appropriate. To test for HPV DNA, SPF10 primers which amplify a 65 nucleotide region of the HPV L1 gene for most of the known HPV isolates are used; the generic amplification products are detected by hybridization on a microtitre plate (DEIA). HPV-positive specimens will be typed by reverse hybridization line probe assay (LiPA), using 25 type-specific hybridization probes. This typing process enables detection of 14 oncogenic HPV types [HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68] and 11 non-oncogenic HPV types [HPV-6, -11, -34, -40, -42, -43, -44, -53, -54, -70 and -74]. All HPV positive samples will also be tested by HPV-16 specific PCR and HPV-18 specific PCR. Redundant testing using generic SPF10 PCR with LiPA, followed by HPV-16/18 type-specific PCR (TS-PCR) affords maximum test sensitivity. The results of this testing algorithm will be considered definitive for all HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68 and HPV-6, -11, -34, -40, -42, -43, -44, -53, -54, -70 and -74 related study endpoints using HPV DNA testing from histopathology.

Any remaining histopathological sample may be used to further characterize HPV infections and associated molecular changes. Histopathological samples may also be used for the purpose of validating HPV assays.

Because the proper role of HPV DNA PCR testing in clinical management is undefined, the results of this testing will be released to investigators and subjects only at the end of the study.

In cases where multiple HPV types are detected in the samples, additional exploratory assays, such as laser microdissection may be performed to investigate the causal role of individual HPV types.

Please refer to APPENDIX A for more details on the laboratory assays. Any remaining cytological sample may be used to further characterize HPV infections and associated molecular changes. This may include sequencing, determination of viral load using quantitative HPV PCR or subtyping of HPV detected.

Table 7 ***Laboratory Assays***

Assay type	*Marker*	*Assay method*	*Test kit/ Manufacturer*	*Assay unit*	*Assay cut-off*	*Laboratory*
Qualitative cervical cytology	*Bethesda 2001 System for reporting cervical cytology diagnoses*	*MICRLI (Microscopy of cervical cytology)*	*ThinPrep® PapTest™*	*No unit*	*N/A*	*CICAMS/CFC*
Qualitative Histopathology	*CIN classification*	*MICRLI (Microscopy of tissue sections)*	*Not applicable*	*Qualitative*	*Qualitative*	*CICAMS/CFC*
Qualitative ("generic") PCR for HPV DNA (using SPF10 primers) + LiPA on cervical swab	*HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 6, 11, 34, 40, 42, 43, 44, 53, 54, 70 and 74*	*PCR*	*HPV SPF10 PCR DEIA*	*No unit*	*N/A*	*CICAMS/CFC*
		nucleic acid hybridization	*HPV SPF10 PCR LIPA*	*No unit*	*N/A*	*CICAMS/CFC*
Qualitative ("generic") PCR for HPV DNA (using SPF10 primers) + LiPA on cervical tissue	*HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 6, 11, 34, 40, 42, 43, 44, 53, 54, 70 and 74*	*PCR*	*HPV SPF10 PCR DEIA*	*No unit Qualitative*	*N/A Qualitative*	*CICAMS/CFC*
		nucleic acid hybridization	*HPV SPF10 PCR LIPA*	*No unit*	*N/A*	*CICAMS/CFC*
Qualitative ("type-specific") PCR for HPV DNA on cervical swab	*HPV-16*	*PCR*	*HPV TS16 PCR/DEIA*	*No unit*	*N/A*	*CICAMS/CFC*
	HPV-18	*PCR*	*HPV TS18 PCR/DEIA*	*No unit*	*N/A*	*CICAMS/CFC*
Qualitative ("type-specific") PCR for HPV DNA on cervical tissue	*HPV-16*	*PCR*	*HPV TS16 PCR/DEIA*	*No unit*	*N/A*	*CICAMS/CFC*
	HPV-18	*PCR*	*HPV TS18 PCR/DEIA*	*No unit*	*N/A*	*CICAMS/CFC*
Qualitative	*HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 (Oncogenic probe [cocktail B])*	*NAH (Nucleic acid hybridization)*	*Hybrid Capture® 2 HPV DNA Test/Digene Corporation*	*No unit Qualitative*	*N/A Qualitative*	*CICAMS/CFC*

CICAMS/CFC: Cancer Institute/Hospital Chinese Academy Medical Sciences and Cancer Foundation of China; DEIA: DNA enzyme immunoassay; PCR: Polymerase Chain Reaction

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.

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.

6. STUDY VACCINE AND ADMINISTRATION (AMENDED: 21 JUN 2018)

6.1. Description of study vaccine

The ***Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed*** has been developed and manufactured by GSK Biologicals.

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

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

Table 8 Study vaccine

Treatment name	Vaccine name	Formulation	Presentation	Volume to be administered*	Number of doses
HPV-16/18	***Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed*** (HPV16-18 AS04D)	Each 0.5 mL dose contains: HPV16 L1 VLP=20µg; HPV18 L1 VLP=20µg; $Al(OH)_3$=325/175µg Al3+; MPL=50µg	Liquid in pre-filled syringes	0.5 ml	3

MPL = 3-O-desacyl-4'-monophosphoryl lipid A; Al(OH)3 = aluminium hydroxide; L1 = structural protein of HPV; VLP = Virus-like Particle; mL = millilitre; µg = microgram; ***mg=milligram***

6.2. Storage and handling of study vaccine

The study vaccine must be stored at the respective label storage temperature conditions in a safe and locked place. Access to the storage space should be limited to authorised study personnel. The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded. Refer to the Module on Clinical Trial Supplies in the SPM for more details on storage of the study vaccine.

Temperature excursions must be reported in degree Celsius.

Any temperature excursion outside the range of 0.0 to +8.0°C (for +2 to +8°C/+36 to +46°F label storage condition) impacting investigational medicinal products (IMPs) must be reported in the appropriate temperature excursion ***application***. The impacted IMPs must not be used and must be stored in quarantine at label temperature conditions until usage approval has been obtained from the sponsor.

In case of temperature excursion below +2.0°C down to 0.0°C impacting IMP(s), there is no need to report in ***the temperature excursion application***, but adequate actions must be taken to restore the +2 to +8°C/+36 to +46°F label storage temperature conditions. The impacted IMP(s) may still be administered, but the site should avoid re-occurrence of such temperature excursion. Refer to the Module on Clinical Trial Supplies in the SPM for more details on actions to take.

Refer to the Module on Clinical Trial Supplies in the SPM for details and instructions on the temperature excursion reporting and usage decision process, packaging and accountability of the study vaccine.

6.3. Dosage and administration of study vaccine

Table 9 Dosage and administration

Type of contact and time point	Study groups	Treatment name	Volume to be administered	Route[1]	Site	
					Location	Laterality[2]
Visit 1 (Day 1)	HPV group	HPV-16/18	0.5 ml	IM	Deltoid	Non-dominant
Visit 2 (Month 1)			0.5 ml	IM	Deltoid	Non-dominant
Visit 3 (Month 6)			0.5 ml	IM	Deltoid	Non-dominant

1Intramuscular (IM)

2The non-dominant arm is the preferred arm of injection. In case it is not possible to administer the vaccine in the non-dominant arm, an injection in the dominant arm may be performed.

6.4. Replacement of unusable vaccine

In addition to the vaccine doses provided for the planned number of subjects (including over-randomisation when applicable), at least 10% additional vaccine doses will be supplied to replace those that are unusable.

6.5. Contraindications to subsequent vaccination

The following events constitute absolute contraindications to further administration of the ***Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed.*** If any of these events occur during the study, the subject must not receive additional doses of vaccine but may continue other study procedures at the discretion of the investigator (see Section 8.5).

- Anaphylaxis following the administration of vaccine.
- Pregnancy (see Section 8.2.1).
- Any confirmed or suspected immunosuppressive or immunodeficient condition, including HIV infection.
- Any condition that in the judgment of the investigator would make intramuscular injection unsafe.
- Hypersensitivity to the active substances or to any of the excipients.
- Any SAE judged ***by Investigator*** to be related to ***the*** study vaccine.
- Administration of another HPV vaccine during the study other than that foreseen by protocol.
- Any acute or newly acquired chronic condition at the time of scheduled vaccination, which in the opinion of the investigator precludes further administration of the study vaccine.
- Other significant reactions which in the opinion of the investigator (or designate) preclude further administration of the study vaccine (may include severe pain, severe swelling, severe limitation of motion, persistent high fever, severe headache or other systemic or local reactions).
- Occurrence of a new pIMD or the exacerbation of an existing pIMD that, in the opinion of the investigator, expose the subject to unacceptable risk from subsequent vaccination. In such cases, the investigator should use his/her clinical judgement prior to administering the next dose of the vaccine. Refer to Section 8.1.4.1 for the definition of pIMDs.

The following events constitute contraindications to administration of the ***Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed*** at that point in time; if any of these events occur at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol (see Section 5.5), or the subject may be withdrawn at the discretion of the investigator (see Section 8.5).

- Acute disease and/or fever at the time of vaccination.
  - Fever is defined as temperature ≥ 37.0°C. The preferred location for measuring temperature in this study will be the axilla.
  - ***Subjects*** with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever can be administered the ***Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed***.

6.6. Warnings and precautions

Refer to the approved product label/package insert.

6.7. Concomitant medications/products and concomitant vaccinations

At each study visit/contact, the investigator or delegate should question the subject about any medications/products taken and vaccinations received by the subject.

6.7.1. 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 and following each dose of study vaccine (Day 1 to Day 31).
- Any concomitant vaccination administered in the period starting 30 days before the first dose of study vaccine and ***last contact for each subject***.
- 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]. The preferred location for measuring temperature in this study will be the axilla.
- ***Any concomitant medications/products/vaccines listed in Section 6.7.2.***
- Any concomitant medications/products/vaccines relevant to a SAE/pIMD to be reported as per protocol or administered at any time during the study period for the treatment of a SAE /pIMD. In addition, concomitant medications relevant to SAEs and pIMD need to be recorded on the expedited Adverse Event report.

6.7.2. 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. See Section 10.5 for cohorts to be analysed.

- ***Previous vaccination against HPV outside of study HPV-039.***
- ***History of long-acting immune-modifying drugs administered at any time (e.g. infliximab).***
- ***Drug and/or alcohol abuse.***

7. HEALTH ECONOMICS

Not applicable.

8. SAFETY (AMENDED: 21 JUN 2018)

The investigator or site staff is/are responsible for the detection, documentation and reporting of events meeting the criteria and definition of an AE or 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

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 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).

Collection of solicited AEs is not planned in this study. All other AEs will be recorded as UNSOLICITED AEs.

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 first 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.

8.1.4. Adverse events of specific interest

8.1.4.1. Potential immune-mediated diseases (Amended: 21 Jun 2018)

pIMDs are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. AEs that need to be recorded and reported as pIMDs include those listed in Table 10.

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

Table 10 List of potential immune-mediated diseases (Amended: 21 Jun 2018)

Neuroinflammatory disorders	*Musculoskeletal disorders*	*Skin disorders*
• *Cranial nerve neuropathy, including paralysis and paresis (e.g. Bell's palsy).* • *Optic neuritis.* • *Multiple sclerosis.* • *Transverse myelitis.* • *Guillain-Barré syndrome, including Miller Fisher syndrome and other variants.* • *Acute disseminated encephalomyelitis, including site specific variants e.g.: non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis.* • *Myasthenia gravis, including Lambert-Eaton myasthenic syndrome.* • *Demyelinating peripheral neuropathies including:* - *Chronic inflammatory demyelinating polyneuropathy,* - *Multifocal motor neuropathy* - *Polyneuropathies associated with monoclonal gammopathy.* • *Narcolepsy.*	• *Systemic lupus erythematosus and associated conditions* • *Systemic scleroderma (Systemic sclerosis), including:* - *Diffuse Scleroderma* - *CREST syndrome* • *Idiopathic inflammatory myopathies, including:* - *Dermatomyositis* - *Polymyositis* • *Anti-synthetase syndrome.* • *Rheumatoid Arthritis and associated conditions including:* - *Juvenile Idiopathic Arthritis* - *Still's disease.* • *Polymyalgia rheumatica.* • *Spondyloarthropathies, including:* - *Ankylosing Spondylitis,* - *Reactive Arthritis (Reiter's Syndrome),* - *Undifferentiated Spondyloarthritis,* - *Psoriatic Arthritis,* - *Enteropathic arthritis.* • *Relapsing Polychondritis.* • *Mixed Connective Tissue disorder.* • *Gout*	• *Psoriasis.* • *Vitiligo.* • *Erythema nodosum.* • *Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis).* • *Lichen planus.* • *Sweet's syndrome.* • *Localised Scleroderma (Morphoea).*

Vasculitis	*Blood disorders*	*Others*
• *Large vessels vasculitis including:* - *Giant Cell Arteritis (Temporal Arteritis),* - *Takayasu's Arteritis.* • *Medium sized and/or small vessels vasculitis including:* - *Polyarteritis nodosa,* - *Kawasaki's disease,* - *Microscopic Polyangiitis,* - *Wegener's Granulomatosis (granulomatosis with polyangiitis),* - *Churg–Strauss syndrome (allergic granulomatous angiitis or eosinophilic granulomatosis with polyangiitis),* - *Buerger's disease (thromboangiitis obliterans),* - *Necrotizing vasculitis (cutaneous or systemic),* - *anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified),* - *Henoch-Schonlein purpura (IgA vasculitis),* - *Behcet's syndrome,* - *Leukocytoclastic vasculitis.*	• *Autoimmune hemolytic anemia.* • *Autoimmune thrombocytopenia.* • *Antiphospholipid syndrome.* • *Pernicious anemia.* • *Autoimmune aplastic anemia.* • *Autoimmune neutropenia.* • *Autoimmune pancytopenia.*	• *Autoimmune glomerulonephritis including:* - *IgA nephropathy,* - *Glomerulonephritis rapidly progressive,* - *Membranous glomerulonephritis,* - *Membranoproliferative glomerulonephritis,* - *Mesangioproliferative glomerulonephritis.* - *Tubulointerstitial nephritis and uveitis syndrome.* • *Ocular autoimmune diseases including:* - *Autoimmune uveitis* - *Autoimmune retinitis.* • *Autoimmune myocarditis.* • *Sarcoidosis.* • *Stevens-Johnson syndrome.* • *Sjögren's syndrome.* • *Alopecia areata.* • *Idiopathic pulmonary fibrosis.* • *Goodpasture syndrome.* • *Raynaud's phenomenon.*
Liver disorders	*Gastrointestinal disorders*	*Endocrine disorders*
• *Autoimmune hepatitis.* • *Primary biliary cirrhosis.* • *Primary sclerosing cholangitis.* • *Autoimmune cholangitis.*	• *Inflammatory Bowel disease, including:* - *Crohn's disease,* - *Ulcerative colitis,* - *Microscopic colitis,* - *Ulcerative proctitis.* • *Celiac disease.* • *Autoimmune pancreatitis.*	• *Autoimmune thyroiditis (Hashimoto thyroiditis).* • *Grave's or Basedow's disease.* • *Diabetes mellitus type I.* • *Addison's disease.* • *Polyglandular autoimmune syndrome.* • *Autoimmune hypophysitis.*

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

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

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

8.2.1. Pregnancy

Subjects from HPV group (Ctrl-HPV-039 group) who are pregnant or lactating at the time of vaccination must not receive additional doses of study vaccine but may continue other study procedures at the discretion of the investigator.

While pregnancy itself is not considered an AE or SAE, any adverse pregnancy outcome or complication or elective termination of a pregnancy for medical reasons will be recorded and reported as an AE or a SAE.

Note: The pregnancy itself should always be recorded on an electronic pregnancy report.

The following should always be considered as SAE and will be reported as described in Sections 8.4.1 and 8.4.3:

- Spontaneous pregnancy loss, including:
  - spontaneous abortion, (spontaneous pregnancy loss before/at 22 weeks of gestation)
  - ectopic and molar pregnancy
  - stillbirth (intrauterine death of foetus after 22 weeks of gestation).

  Note: the 22 weeks cut-off in gestational age is based on WHO-ICD 10 noted in the EMA Guideline on pregnancy exposure [EMA, 2006]. It is recognised that national regulations might be different.
- Any early neonatal death (i.e. death of a live born infant occurring within the first 7 days of life).
- Any congenital anomaly or birth defect (as per [CDC MACDP] guidelines) identified in the offspring of a study subject (either during pregnancy, at birth or later) regardless of whether the foetus is delivered dead or alive. This includes anomalies identified by prenatal ultrasound, amniocentesis or examination of the products of conception after elective or spontaneous abortion.

Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered by the investigator to be reasonably related to the study vaccine will be reported to GSK Biologicals as described in Section 8.4.3. 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.

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

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

The time period for collecting and recording SAEs will begin at the first receipt of study vaccine (Day 1) and will end six months following administration of the last dose of study vaccine (Call 2 [Month 12]) for each ***vaccinated*** subject. See Section 8.4 for instructions on reporting of SAEs.

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of the first receipt of study vaccine.

SAEs that are related to the study vaccine will be collected and recorded from the time of the first receipt of study vaccine until the subject is discharged from the study.

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 ***for all subjects*** and recorded from the time the subject consents to participate in the study until she is discharged from the study.

The time period for collecting and recording pregnancies will begin at the first receipt of study vaccine (Day 1) and will end six months following administration of the last dose of study vaccine (Call 2 [Month 12]). See Section 8.4 for instructions on reporting of pregnancies.

The time period for collecting and recording of pIMDs will begin at the first receipt of study vaccine and will end six months following administration of the last dose of study vaccine (Call 2 [Month 12]). See Section 8.4 for instructions on reporting of pIMDs.

An overview of the protocol-required reporting periods for SAEs, pIMDs, and pregnancies is given in Table 11.

Table 11 Reporting periods for collecting safety information

Event	V1 D1	V2 M1	V3 M6	Call 1 M7	Call 2 M12
Vacc-HPV-039					
Reporting of SAEs related to study participation or concurrent GSK medication/vaccine*					
HPV Group (Ctrl-HPV-039 group)					
Reporting of SAEs					
Reporting of AEs/SAEs leading to withdrawal from the study					
Reporting of SAEs related to the study vaccine					
Reporting of SAEs related to study participation or concurrent GSK medication/vaccine					
Reporting of pregnancies and pregnancy outcomes					
Reporting of pIMDs					

V: vaccination; D: Day, M: Month

**** Serious adverse events will be collected up to end of call back visit (if applicable).***

Note: Pregnancy outcomes of subjects who are pregnant at the time of study conclusion will be recorded and reported to GSK Biologicals' Safety department.

8.3.2. Post-study adverse events and serious adverse events

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 11. Investigators are not obligated to actively seek AEs or 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 he/she considers the event reasonably related to the study vaccine, the investigator will promptly notify the Study Contact for Reporting SAEs.

8.3.3. Evaluation of adverse events and serious adverse events

8.3.3.1. Active questioning to detect *adverse events and* serious adverse events

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

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

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 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 AE/SAE and not the individual signs/symptoms.

8.3.3.2. Assessment of adverse events

8.3.3.2.1. Assessment of intensity

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

The intensity 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, such an AE would, for example, prevent attendance at work 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 used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 8.1.2.

8.3.3.2.2. Assessment of causality

The investigator is obligated to assess the relationship between study vaccine and the occurrence of each AE/SAE using clinical judgement. In case of concomitant administration of multiple vaccines/products, if possible, the investigator should specify if the AE could be causally related to a specific vaccine/product administered (i.e investigational, control/placebo or co-administered vaccine). When causal relationship to a specific vaccine(s)/product(s) cannot be determined the investigator should indicate the AE to be related to all products.

Alternative plausible causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study vaccine will be considered and investigated. The investigator will also consult the IB and/or Prescribing Information for marketed products to determine his/her assessment.

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

Causality of AEs should be assessed by the investigator using the following question:

Is there a reasonable possibility that the AE may have been caused by the study vaccine?

YES : There is a reasonable possibility that the study vaccine contributed to the AE.

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

If an event meets the criteria to be determined as 'serious' (see Section 8.1.2), additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

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

8.3.3.3. Assessment of outcomes

The investigator will assess the outcome of all unsolicited AEs (including SAEs) recorded during the study as:

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

8.4. Reporting of serious adverse events, pregnancies, and other events

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

SAEs that occur in the time period defined in Section 8.3 will be reported promptly to GSK within the timeframes described in Table 12, once the investigator determines that the event meets the protocol definition of a SAE.

Pregnancies that occur in the time period defined in Section 8.3 will be reported promptly to GSK within the timeframes described in Table 12, once the investigator becomes aware of the pregnancy.

pIMDs that occur in the time period defined in Section 8.3 will be reported promptly to GSK within the timeframes described in Table 12, once the investigator determines that the event meets the protocol definition of a pIMD.

Table 12 Timeframes for submitting serious adverse event, pregnancy and other events reports to GSK Biologicals

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
Pregnancies	2 weeks*	electronic pregnancy report	2 weeks*	electronic pregnancy report
pIMDs	24 hours** ‡	electronic Expedited Adverse Events Report	24 hours*	electronic Expedited Adverse Events Report

* Timeframe allowed after receipt or awareness of the information.
**Timeframe allowed once the investigator determines that the event meets the protocol definition of a pIMD.
‡ The investigator will be required to confirm review of the SAE/pIMD causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the SAE/pIMD.

8.4.2. Contact information for reporting serious adverse events, pregnancies and pIMDs

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

8.4.3. 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.

8.4.3.1. 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.

8.4.4. Completion and transmission of pregnancy reports to GSK Biologicals

Once the investigator becomes aware that a subject is pregnant, the investigator (or designate) must complete the required information onto the electronic pregnancy report WITHIN 2 WEEKS.

Note: Conventionally, the estimated gestational age (EGA) of a pregnancy is dated from the first day of the last menstrual period (LMP) of the cycle in which a woman conceives. If the LMP is uncertain or unknown, dating of EGA and the estimated date of delivery (EDD) should be estimated by ultrasound examination and recorded in the pregnancy report.

8.4.5. Reporting of pIMDs to GSK Biologicals

Once a pIMD is diagnosed (serious or non-serious) in a study subject, the investigator (or designate) must complete the information in the electronic Expedited Adverse Events Report WITHIN 24 HOURS after he/she becomes aware of the diagnosis. The report allows to specify that the event is a pIMD and whether it is serious or non serious. The report will always be completed as thoroughly as possible with all available details of the event, in accordance with the pIMD standard questionnaire provided. Even if the investigator does not have all information regarding a pIMD, the 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 pIMD causality by ticking the 'reviewed' box in the electronic Expedited Adverse Events Report within 72 hours of submission of the pIMD.

Refer to Section 8.4.3.1 for back-up system in case the electronic reporting system does not work.

8.4.6. Updating of SAE, pregnancy, and pIMD information after removal of write access to the subject's eCRF

When additional SAE, pregnancy, or pIMD 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 12.

8.4.7. 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 study vaccine and unexpected. The purpose of the report is to fulfil specific regulatory and GCP requirements, regarding the product under investigation.

8.5. Follow-up of serious adverse events, and pregnancies

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

8.5.1.1. Follow-up during the study

After the initial ***AE/***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 12).

All SAEs and pIMDs (serious or non-serious) 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 last visit of the subject.

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

The investigator will follow subjects:

- with SAEs, pIMDs (serious or non-serious), 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.

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

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.

8.5.2. Follow-up of pregnancies

Pregnant subjects will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK Biologicals using the electronic pregnancy report and the Expedited Adverse Events Report if applicable. Generally, the follow-up period doesn't need to be longer than six to eight weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs for this study, if the pregnancy outcome is a SAE, it should always be reported as SAE.

8.6. Treatment of adverse events

Treatment of any AE is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of a SAE / pIMDs should be recorded in Expedited Adverse Event Report of the subject's eCRF (refer to Section 6.7).

8.7. Subject card

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

The investigator (or designate) must therefore provide a "subject card" to each subject. In an emergency situation this card serves to inform the responsible attending physician that the subject is in a clinical study and that relevant information may be obtained by contacting the investigator.

Subjects must be instructed to keep subject cards in their possession at all times during the study duration.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject completion

A subject who is available for the concluding ***visit/***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 was not available for the concluding ***visit/***contact foreseen in the protocol.

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

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

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

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

- Serious adverse event.
- Unsolicited non-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 has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject, in the eCRF.

Subjects who are withdrawn from the study because of SAEs/AEs 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/AE until resolution of the event (see Section 8.5.1.2).

9.2.2. Subject withdrawal from study vaccine

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

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

- Serious adverse event.
- Unsolicited non-serious adverse event.
- Not willing to be vaccinated
- Other (specify).

10. STATISTICAL METHODS (AMENDED: 21 JUN 2018)

10.1. Primary endpoint

- ***Safety endpoint***
  - ***HPV group (Ctrl-HPV-039 group)***
    - ***Occurrence of SAEs related to study vaccine.***

10.2. Secondary endpoints

- ***Safety endpoints***
  - ***HPV group (Ctrl-HPV-039 group)***
    - Occurrence of pIMDs throughout the study.
    - Occurrence of pregnancies and pregnancy outcomes throughout the study.
    - Occurrence of SAEs.
    - Any AE/SAE leading to premature discontinuation ***from*** the study.
  - ***All subjects***
    - ***Occurrence of SAEs related to study participation.***
- ***Virological endpoints***
  - ***Incident cervical infection associated with HPV-16 and/or HPV-18 (by PCR).***
  - ***Incident cervical infection associated with any oncogenic HPV type (e.g. HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68 or combination of oncogenic HPV types; by PCR).***

10.3. Tertiary endpoints

- ***Virological endpoint***
  - ***Incident infection associated with HPV-16/18, any other oncogenic type, irrespective of HPV type.***
- ***Cytological endpoints***
  - ***Any cytological abnormality (i.e., [ASC-US] associated with HPV-16 and/or HPV-18 cervical infection (by PCR).***
  - ***Any cytological abnormality associated with any oncogenic HPV type (e.g. HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68 or combination of oncogenic HPV types; by PCR).***
  - ***Any cytological abnormality irrespective of the HPV type.***

- ***Histopathological endpoints.***
  - ***Histopathologically-confirmed CIN1+ associated with HPV-16 and/or HPV-18 (by PCR).***
  - ***Histopathologically-confirmed CIN2+ associated with HPV-16 and/or HPV-18 (by PCR).***

    CIN2+ is defined as CIN2, CIN3, LCGIN, HCGIN, adenocarcinoma in-situ (AIS) or invasive cervical cancer.
  - ***Histopathologically-confirmed CIN1+ associated with cervical infection with any oncogenic HPV type (e.g. HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68 or combination of oncogenic HPV types; by PCR).***
  - ***Histopathologically-confirmed CIN2+ associated with cervical infection with any oncogenic HPV type (e.g. HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68 or combination of oncogenic HPV types; by PCR).***
  - ***Histopathologically-confirmed CIN1+ lesions irrespective of HPV type.***
  - ***Histopathologically-confirmed CIN2+ lesions irrespective of HPV type.***
  - ***Histopathologically-confirmed VIN1+ associated with HPV-16 and/or HPV-18 infection (by PCR).***
  - ***Histopathologically-confirmed VaIN1+ associated with HPV-16 and/or HPV-18 infection (by PCR).***
  - ***Histopathologically-confirmed VIN1+ associated with any oncogenic HPV type (e.g. HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68 or combination of oncogenic HPV types; by PCR).***
  - ***Histopathologically-confirmed VaIN1+ associated with any oncogenic HPV type (e.g. HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68 or combination of oncogenic HPV types; by PCR).***
  - ***Histopathologically-confirmed VIN1+ irrespective of HPV type.***
  - ***Histopathologically-confirmed VaIN1+ irrespective of HPV type.***

For the above mentioned tertiary endpoints, VIN (Vulvar Intraepithelial Neoplasia) is defined as VIN1+ or VIN2+, and VaIN (Vaginal Intraepithelial Neoplasia) is defined as VaIN1+ or VaIN2+.

10.4. Determination of sample size (Amended: 21 Jun 2018)

Since the objectives of the study are descriptive, the sample size for this study is not estimated using any power based computations.

Sample size for this study depends on the recruitment of the subjects who previously participated in study HPV-039. Up to 6051 subjects who participated in the HPV-039 study will be invited to participate in this study, of which 3025 subjects did not receive the HPV vaccine and are therefore eligible to receive the HPV vaccine in this study.

It is estimated that approximately 1500 to 3000 subjects from the control group in HPV-039 will effectively participate in this study and will receive at least one dose of HPV vaccine and will be available for the evaluation of the primary objective of the study.

The exact 95% confidence interval (CI) for different sample sizes and the value observed for the percentage of subjects reporting at least one related SAE is presented in the table below.

Table 13 Exact two-sided 95% CI for different sample sizes and the value observed for the percentage of subjects reporting at least one related SAE

No. of evaluable subjects to be expected (N)	*Subjects who reported related SAEs post vaccination*			
	n	*%*	*Exact 95% CI*	
			LL	*UL*
3000	*1*	*0.0*	*0.0*	*0.2*
	3	*0.1*	*0.0*	*0.3*
	5	*0.2*	*0.1*	*0.4*
	15	*0.5*	*0.3*	*0.8*
	30	*1.0*	*0.7*	*1.4*
1500	*1*	*0.1*	*0.0*	*0.4*
	3	*0.2*	*0.0*	*0.6*
	5	*0.3*	*0.1*	*0.8*
	8	*0.5*	*0.2*	*1.0*
	10	*1.0*	*0.6*	*1.6*

n = Number of subjects who reported related SAEs.
*% = (n/N) *100; LL = Lower limit; UL = Upper limit*
Reference: HPV-039 (107638): At least one SAE throughout the study period (72 Months) in HPV Group = 1.9% [95% CI: 1.4; 2.4]. At least one related SAE was reported by one subject in control group.

10.5. Cohort for Analyses (Amended: 21 Jun 2018)

10.5.1. Total enrolled set

The total enrolled set includes all subjects enrolled in study HPV-092 EXT 039.

10.5.2. Exposed set HPV-092

The Exposed Set (ES) includes all vaccinated subjects in HPV-092 EXT 039 for whom data were available.

10.5.3. Per-protocol set *(PPS-HPV-092)*

The Per-Protocol Set (PPS) will include all evaluable subjects, i.e.,

- ***Who meet all eligibility criteria.***
- ***Who do not meet any of the criteria for elimination from an PPS analysis during the study (see Section 6.7.2).***
- ***For whom data concerning endpoint measures are available.***
- ***Who belong to the ATP cohort for efficacy of the study HPV-039.***

Total Vaccinated Cohort (TVC) and the ATP cohort for the analysis of efficacy in study HPV-039 will be used for the analysis of protective effect.

10.6. Derived and transformed data

The follow-up time for each subject starts:

- ***at the day after first vaccination (Month 0 study HPV-039) if analyses were done on the TVC of HPV-039, or***
- ***at the day after third vaccination (Month 6 study HPV-039) if analyses were done on the ATP cohort of efficacy of HPV-039.***

The follow-up time for each subject ends:

- ***at the time of the event (e.g. the start of incident infection or the time of the histopathological endpoint),***
- ***at Visit 1 in HPV-092 study (Month 120 EXT-039) for subjects who returned for HPV-092 but did not have an event, or***
- ***last available timepoint for subjects who do not have an event and do not return for study HPV-092 EXT 039.***

10.7. Analysis of demographics

Demographic characteristics (age) at first visit in study HPV-092 EXT 039 and HPV vaccination history in study HPV-039 will be summarised overall and by group using descriptive statistics. In addition, baseline characteristics (HPV DNA and serostatus) in study HPV-039 will be summarised overall and by group for subjects enrolled in study HPV-092 EXT 039.

The mean age (plus range and standard deviation) of the enrolled subjects at Dose 1 in study HPV-039 as a whole, and per group, will be calculated.

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

10.8. Analysis of safety (Amended: 21 Jun 2018)

Analysis of safety events reported after vaccination in HPV-092 will be performed on the Exposed set HPV-092.

Related SAEs, any AEs/SAEs leading to premature discontinuation of the study, pregnancies and pIMDs up to the end of the study (Month 12) will be described in detail.

Analysis of SAEs related to study participation will be performed on the total enrolled set.

10.9. Analysis of protective effect (Amended: 21 Jun 2018)

The analysis of protective effect will be performed on the ATP cohort for efficacy and TVC of study HPV-039, considering the data from the entire follow-up period of studies HPV-039 and HPV-092 combined, i.e., pooled analyses (from Month 0 in study HPV-039 up to Month 120 in study HPV-092).

- ***Number and percentage of subjects with incident cervical infection associated with HPV-16 and HPV-18 will be summarized by group.***
- ***Number and percentage of subjects with incident cervical infection associated with any oncogenic HPV type (e.g. HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68 or combination of oncogenic HPV types; by PCR) will be summarized by group.***

10.10. Exploratory analysis of long term efficacy

Analysis of long term efficacy will be exploratory. Vaccine efficacy with a 95% CI will be calculated using the conditional exact method.

Efficacy analysis of histopathological, virological and cytological endpoints associated with HPV-16/18 will be performed and stratified by HPV-16/18 serostatus (by ELISA) at baseline in the study HPV-039 with the primary analysis performed on subjects who were seronegative (by ELISA) prior to vaccination in study HPV-039 for the corresponding HPV type considered in the analysis.

Additional efficacy analyses will be performed irrespective of baseline HPV DNA, cytology and serostatus.

The vaccine efficacy for all endpoints will be calculated using a conditional exact method. This method computes an exact CI around the rate ratio (ratio of the incidence rates in the HPV group versus the Control group) and takes into account the follow-up time of the subjects within each group. Vaccine efficacy is then defined as 1 minus the rate ratio. In addition, p-values will be calculated using the Fisher's exact test.

Kaplan-Meier curves for both groups will be generated.

The analysis of long term vaccine efficacy will be performed on the ATP cohort for efficacy and TVC of study HPV-039, considering the data from the entire follow-up period of studies HPV-039 and HPV-092 combined, i.e., pooled analyses (from Month 0 in study HPV-039 up to Month 120 in study HPV-092).

Number and percentage of subjects with referrals to treatment according to local medical practice will be summarized by group.

Analyses will be further described in detail in the Statistical Analysis Plan (SAP).

10.11. Interpretation of analyses

All analyses will be descriptive with the aim to characterise the observed outcomes. These descriptive analyses should be interpreted with caution. ***Refer to limitations of the study in the rationale for study design section.***

10.12. 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.

10.12.1. Sequence of analyses

- ***Interim analyses of available safety and protective effect data, may be performed if deemed necessary for regulatory or reporting obligations.***
- A final analysis of all data collected up to Call 2 (Month 12) will be conducted ***for all subjects.***

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

10.12.2. Statistical considerations for interim analyses

All analyses in the study will be descriptive. Hence, no statistical considerations for interim analysis will be done.

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 (AMENDED: 21 JUN 2018)

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APPENDIX A LABORATORY ASSAYS (Amended: 21 Jun 2018)

Polymerase chain reaction (PCR) for HPV DNA detection

To test for HPV DNA, SPF_{10} primers which amplify a 65 nucleotide region of the HPV L1 gene for most of the known HPV isolates are used; the generic amplification products are detected by hybridization on a microtiter plate (DEIA). HPV-positive specimens will be typed by reverse hybridization line probe assays (LiPA), using 25 type-specific hybridization probes. This typing process enables detection of 14 oncogenic HPV types [HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68] and 11 non-oncogenic HPV types [HPV-6, -11, -34, -40, -42, -43, -44, -53, -54, -70 and -74.

All HPV positive samples will also be tested by HPV-16 specific PCR and HPV-18 specific PCR. Redundant testing using generic SPF10 PCR with LiPA, followed by HPV-16/18 type-specific PCR (TS-PCR) affords maximum test sensitivity. The results of this testing algorithm will be considered definitive for all HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68 and HPV-6, -11, -34, -40, -42, -43, -44, -53, -54, -70 and -74 related study endpoints using HPV DNA testing from PreservCyt® specimens.

The aliquots and tissue samples may be used to further characterize HPV cervical infections (if appropriate, determination of viral load using quantitative HPV PCR, sequencing and/or subtyping of HPV types, other type-specific PCR and other PCR typing methods).

Cytology

All original cervical samples collected will be prepared by trained laboratory personnel using the ThinPrep® 2000 Processor to transfer and fix the cells onto glass slides. All cytology specimens will be processed and then evaluated according to the Bethesda 2001 classification system for reporting cervical cytology diagnoses.

Cervical cytology will be performed using the ThinPrep® PapTest. (Cytyc Corporation, Boxborough, MA, USA). Cervical cells for ThinPrep® cytology will be collected using the sampling device provided rinsed into a collection vial containing PreservCyt® medium. Specimens will be stored according to the CICAMS/CFC manual until shipment to CICAMS/CFC. Cytological specimens must be shipped at ambient temperature within one month of collection.

From the PreservCyt® specimen (original sample), one 1 mL aliquot will be prepared and withdrawn prior to ThinPrep® slide preparation (to avoid possible specimen-to-specimen contamination) for HPV DNA testing. The remaining sample will be used for cytological analysis at CICAMS/CFC.

APPENDIX B CLINICAL LABORATORIES (Amended: 21 Jun 2018)

Table 14 Outsourced laboratories

Laboratory	*Address*
Cancer Institute/Hospital, Chinese Academy of Medical Sciences and Cancer Foundation of China (CICAMS/CFC)	*17# Pan Jia Yuan Nan Li, Chaoyang District, Beijing, China*

APPENDIX C AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals SA Vaccines R &D **Protocol Amendment 1**	
eTrack study number and Abbreviated Title	205779 (HPV-092 EXT 039)
Amendment number:	Amendment 1
Amendment date:	21 June 2018
Co-ordinating author:	PPD

Rationale/background for changes: The protocol has been amended to support the post-licensure commitment to the Center for Drug Evaluation (CDE) of National Drug Administration of China (CNDA) with regard to the assessment of long term protective effect of GSK Biologicals' HPV vaccine, Adsorbed in subjects who participated in the HPV-039 study. To address this, the following changes have been made:

- The study design has been modified to include the HPV-vaccinated subjects from the HPV-039 study. The number of subjects for the study has been updated from up to 3025 to up to 6051.
- Assessment of rates of HPV-16/18 incident infection up to approximately 10 year after vaccination in the study HPV-039 has been added as a secondary objective. Long term efficacy against virological, cytological, histopathological endpoints will be assessed as a tertiary objective.
- Procedures namely; gynaecological examination, cervical sampling, follow-up colposcopy and biopsy in subjects with abnormal cytology have been added at Visit 1.
- The assay section has been updated to include testing related to cervical samples and biopsy.
- The statistical section has been updated to describe "Analysis of long term protective effect " on HPV infection.
- Additionally, regulatory approval of Gardasil and Gardasil 9 and approval of *Cervarix* age indication extension up to 45 years in China has been mentioned.
- Owing to the extension of age indication of *Cervarix* up to 45 years, it is specified in the protocol that subjects also have the opportunity to receive *Cervarix* free of charge outside of the current study, when commercially available.

The changes with regard to CDE feedback in the main sections of the protocol are described here.

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

Throughout this protocol amendment, the name of the vaccine has been updated from "human papillomavirus (HPV) vaccine containing HPV-16/18 L1 virus-like particles (VLPs) and AS04 adjuvant" to "Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed" as this is the name which appears in the Chinese license.

Title

Safety ***and protective effect*** study of GSK Biologicals' ~~human papillomavirus vaccine~~ ***Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed*** (GSK580299) in healthy female subjects from the HPV-039 study.

Detailed Title

A phase III~~b~~/***IV*** open-label, multi-centre ~~immunisation~~ study to evaluate the safety of ***GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed,*** administered intramuscularly according to a 0,1,6-month schedule***,*** in healthy Chinese female subjects above 26 years of age ***who received the*** ~~placebo~~ ***control vaccine*** in ***study*** HPV-039 ~~study~~ ***and*** to evaluate the ~~safety~~ ***protective effect*** of GSK Biologicals' ~~HPV-~~ ***Human Papillomavirus (Types 16/, 18*** ~~L1 VLP AS04 vaccine~~ ***) Vaccine, Adsorbed, up to approximately 10 years after vaccination, in reducing HPV-associated cervical infection in subjects who participated in the HPV-039 study.***

Indication

The GDS indication was deleted from the synopsis and only indication specific to China was retained.

~~From the age of nine years for the prevention of premalignant ano-genital lesions (cervical, vulvar, vaginal and anal) and cervical and anal cancers causally related to certain oncogenic Human Papillomavirus (HPV) types. In China,~~ *Cervarix* is approved for use in females 9 through ***45***~~25~~ years of age for the prevention of cervical cancer, cervical intraepithelial neoplasia grade 2, grade 3 (CIN 2/3) and adenocarcinoma in situ ***(AIS)*** and cervical intraepithelial neoplasia grade 1 (CIN1) caused by high risk human papillomavirus (HPV) types 16 and 18.

Introduction

The following changes were made in this section.

Cervarix was first licensed in ***May 2007*** in Australia, for use in 10 to 45 year old females. In September 2007, the vaccine was licensed in Europe ***for use from the age of 9 years*** for the ***prevention of persistent infection, premalignant ano-genital lesions (cervical, vulvar, vaginal and anal) and cervical, vulvar, vaginal and anal cancers (squamous-cell carcinoma and adenocarcinoma) caused by oncogenic Human Papillomaviruses (HPVs).*** The vaccine has been licensed in over 133 countries and regions worldwide. In July 2016, *Cervarix* (hereafter referred to as the ***Human Papillomavirus [Types 16, 18]***

Vaccine, Adsorbed) was approved for use as a 3-dose schedule at 0, 1, 6 months in females from 9 to 25 years in China. ***The extension of the vaccine indication up to 45 years of age was approved by the Chinese authorities on 10-May-2018.***

In May 2017, Merck's recombinant quadrivalent HPV vaccine, Gardasil, also received approval in China. In April 2018, Gardasil 9 was granted conditional approval by National Drug Administration of China (CNDA) with additional requirements in China.

To date, ***safety and immunogenicity data were evaluated in*** more than 60,000 adolescents and adults aged 9 years and above ~~have received at least one dose of the HPV vaccine~~ in clinical studies. The vaccine is known to be immunogenic and generally well tolerated. Pooled safety analyses of girls and women aged 9 years and above have shown that the vaccine was generally well tolerated in women of all ages [Descamps, 2009; Angelo, 2014].

Section 1.1: Background

The number of countries where *Cervarix* has been licensed since then was changed from 136 to 133 countries.

Rationale for the study

~~In China, the HPV-16/18 L1 VLP AS04 vaccine is not indicated for women over 26 years, and therefore approximately 3025 subjects from the control group in the HPV-039 study are currently unable to receive the HPV-16/18 L1 VLP AS04 vaccine.~~ This study ~~is being conducted~~ ***has been designed*** following ethical considerations, to enable all subjects who received placebo in the HPV-039 study, to also receive ~~the~~ GSK Biologicals' ***Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed***. ~~Subjects in the control group of HPV-058 study may also be invited to participate in this study if they are 26 years of age or above at the time when cross-over vaccination is offered to HPV-058 participants.~~ Safety data in terms of serious adverse events (SAEs), any adverse events (AEs)/SAEs leading to premature discontinuation of the study, potential immune mediated diseases (pIMDs) and pregnancies (and their outcomes) will be collected during the study period. ***In addition, this study also aims to assess the long term protective effect of the vaccine, in an exploratory manner, in terms of rates of HPV-related (vaccine type) incident cervical infection (secondary objective), cytological abnormalities and CIN2+ lesions (tertiary objective) up to approximately 10 years after vaccination in subjects who participated in HPV-039 study, to support the post-licensure commitment from the Center for Drug Evaluation (CDE) of CNDA. At the availability of the commercial vaccine for use in individuals above 25 years, subjects will be offered the opportunity to receive Cervarix free of charge either by participating to this study or without participating to this study.***

Rationale for the study design

~~Since all subjects will receive three doses of the HPV-16/18 L1 VLP AS04 vaccine, this~~ ***This*** study will be conducted in an open-label and non-randomised manner, ***since the subjects who had participated in study HPV-039 already know the treatment they received and only those of the control group in study HPV-039 will receive Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in the current study***. Safety data will be collected from Dose 1 until the end of the study ***in subjects vaccinated in this study***. ~~No blood or other biological samples~~ ***Cervical samples will be collected*** ~~in this study~~ ***at Visit 1 from all subjects to test for HPV incident infection and cytological abnormalities. Subjects with abnormal cytology will be called back for colposcopy follow-up and biopsy to examine for the presence of CIN lesions***.

Limitations:

In the HPV-039 study, the efficacy of GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed against virological, cytological and histopathological endpoints associated with HPV types 16 and 18, was demonstrated up to 6 years after vaccination and subjects were screened every 6 months. The study was unblinded after completion and since the Year 6, 3-4 years have elapsed with no regular follow-up of the subjects. As a consequence, at Year 10, there might be high subject attrition, leading to a potential imbalance in the numbers of subjects from the vaccinated versus control group returning for the current study. This as well as a lack of regular gynaecological follow-up between Year 6 and Year 10 may compromise assessment of vaccine efficacy in this study. Therefore, vaccine efficacy analyses will be exploratory.

Section 1.3.1: Risk assessment

Angioedema was added as a risk associated with study procedure of vaccination. Additionally, risks and benefits associated with colposcopy were added and overall benefit risk assessment was updated as follows.

Risk assessment table was updated as follows:

Important Potential Risk	**Data/Rationale for Risk**	**Mitigation Strategy**
Investigational vaccine		
Theoretical potential risk of inducing or exacerbating an autoimmune disease following vaccination.*	Potential concern that ***Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed***, and adjuvanted vaccines in general, might be associated with an increased risk of new onset of autoimmune diseases. Analysis of cumulative data so far remains inconclusive with respect to any potential pathogenic link between ***Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed*** and autoimmune diseases.	Naturally occurring autoimmune diseases are multi-aetiological conditions with multiple risk factors, including genetic predisposition. Relative risks for autoimmune diseases following ***Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed*** administration are derived from the most recent pooled analysis of clinical trial data, which showed no difference between groups. The incidence of autoimmune diseases is being monitored closely in the ongoing clinical trials, post-marketing spontaneous reports, literature and observational epidemiological studies specifically designed to evaluate the risk of autoimmune diseases following vaccination with ***Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed***.
Study Procedures		
Allergic reactions (including anaphylactic and anaphylactoid reactions), ***angioedema***, or other immediate reactions such as syncope or vasovagal response following vaccination.	Spontaneous data	Subjects will be observed for at least 30 minutes after vaccine administration, with medical attention available in case of anaphylactic reactions.
Colposcopy with targeted biopsies may involve rare events such as lower abdominal pain, vaginal bleeding, fever, chills and yellow colored vaginal discharge.	***Spontaneous data*** ***In general, the colposcopy and biopsy procedures are relatively simple and safe***	***Colposcopy and biopsy will be conducted by experts from the Cancer Institute/Hospital, Chinese Academy of Medical Sciences and Cancer Foundation of China***

Only for subjects being vaccinated in this study.

Section 1.3.2: Benefit Assessment was updated as follows:

Cervical cancer is one of the most common cancers in women, and is often fatal. Vaccination with ***Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed*** is likely to prevent the occurrence of HPV infection, premalignant genital lesions and cervical cancers associated with HPV types 16 and 18. All study participants ***who belonged to the control group in the HPV-039 study*** will ***be invited to*** receive ***Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed***. ***In addition, subjects from HPV-039 study will also be invited to take part in gynaecological examination and cervical sampling during the study. In case of abnormal cytology results of cervical samples, the subjects will be called back for a follow-up colposcopy examination. Colposcopy is an important routine procedure in the initial evaluation of cervical abnormalities for cancer screening in many countries. Colposcopy with targeted biopsies provides accurate identification of cervical diseases when present, as well as reassurance of the absence***

of disease in the subjects. Since cervical screening in this age group is not the standard of care in China at present, the study provides an opportunity for the enrolled subjects to have a cervical cancer screening.

Section 1.3.3: Overall Benefit : Risk Conclusion was updated as follows:

Taking into account the measures taken to minimise risk to subjects participating in this study, the potential or identified risks identified in association with ***Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed or in association with the study procedures*** are justified by the potential benefits (prevention of HPV infection, ***screening of HPV-related diseases***) that may be afforded to subjects. ~~receiving ***Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed.***~~

Section 2: Objectives

Objectives were updated to add vaccine efficacy-related objectives in addition to the safety objective of the study.

Primary objective:

To assess the safety of the ~~HPV~~ ***-GSK Biologicals' Human Papillomavirus (Types 16~~/~~, 18~~L1 VLP AS04 vaccine~~) Vaccine, Adsorbed*** ~~throughout the study period~~ ***in subjects above 26 years of age who previously received placebo in the HPV-039 study in terms of related SAEs***.

Secondary objectives:

- ***To assess the safety of GSK Biologicals Human Papillomavirus (Types 16, 18) Vaccine in terms of occurrence of unsolicited AEs in subjects above 26 years of age, who previously received placebo in the HPV-039 study***.
- ***To assess the protective effect of GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in all subjects who participated in the HPV-039 study in terms of the rates of HPV 16/18 incident infection up to approximately 10 years after vaccination.***
- ***To assess the protective effect of GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in all subjects who participated in the HPV-039 study in terms of the rates of incident infection associated with any or combination of oncogenic HPV types, up to approximately 10 years after vaccination.***

Tertiary objectives

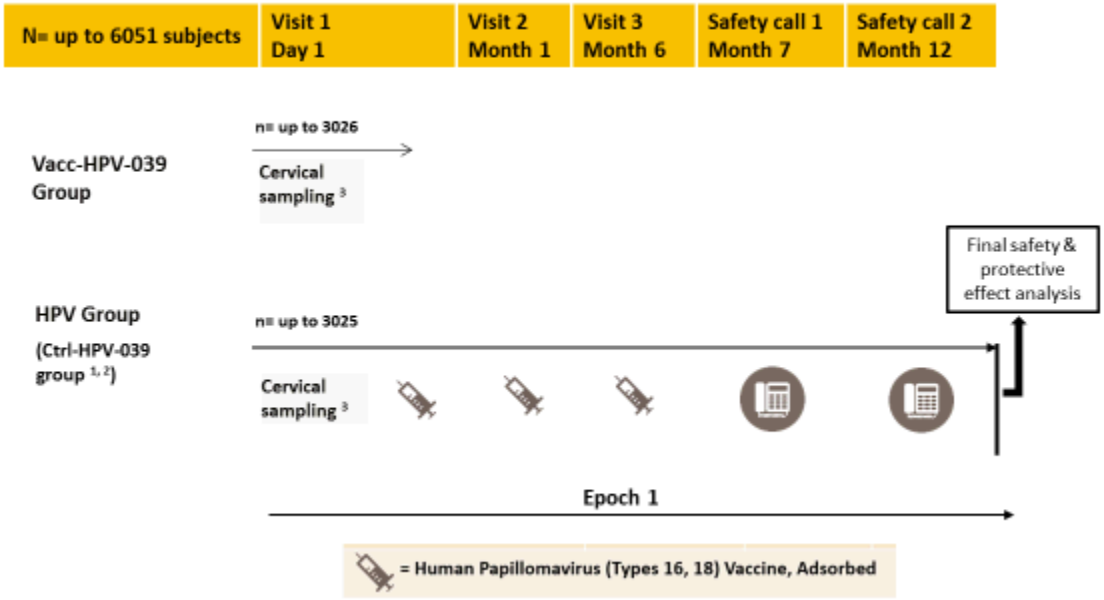
- ***To assess the long term efficacy of GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in the prevention of incident infection associated with HPV-16 and or HPV-18 or with any or combination of oncogenic HPV types.***
- ***To assess the long term efficacy of GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in the prevention of cytological abnormalities associated with HPV-16 and/or HPV-18.***

- ***To assess the long term efficacy of GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in the prevention of cytological abnormalities associated with any or combination of oncogenic HPV types.***
- ***To assess the long term efficacy of the GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in the prevention of histopathologically-confirmed CIN1+ associated with HPV-16 and/or HPV-18.***
- ***To assess the long term efficacy of the GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in the prevention of histopathologically-confirmed CIN1+ associated with any or combination of oncogenic HPV types.***
- ***To assess the long term efficacy of GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in the prevention of histopathologically-confirmed CIN2+ associated with HPV-16 and/or HPV-18.***
- ***To assess long term efficacy of the GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in the prevention of histopathologically-confirmed CIN2+ associated with any or combination of oncogenic HPV types.***
- ***To assess the long term efficacy of the GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in the prevention of other histopathologically-confirmed endpoints associated with HPV-16 and/or HPV-18 or any or combination of oncogenic HPV types.***

Section 3: Study design

- The study design was updated to add a group with HPV vaccinated subjects from HPV-039. Consequently, the study design was updated to have two study groups, as follows:
  - ***Vacc-HPV-039 group i.e. subjects who received HPV vaccine in HPV-039 study who will undergo cervical sample collection only.***
  - ***HPV group (Ctrl-HPV-039 group) i.e. subjects who received control vaccine in HPV-039 study will receive HPV vaccine in the current study and undergo cervical sample collection before HPV vaccination.***
- The study design figure was also updated:

	HPV – 16/18 L1 VLP AS04 Vaccine			N=Approximately 6000 Subjects*	
Visit:	**Visit 1**	**Visit 2**	**Visit 3**	**Call 1**	**Call 2**
~~**Time point:**~~	~~Day 1~~	~~Month 1~~	~~Month 6~~	~~Month 7~~	~~Month 12~~
Sampling:	CS**				
Vacc***:	Vacc 1	Vacc 2	Vacc 3		



N: Number of subjects

[1] Sampling from the subjects of Ctrl-HPV-039 group will be done before vaccination.

[2] Subjects can choose to consent to both cervical sampling and vaccination procedures or one of the two procedures during the informed consent process.

[3] Call back visit for colposcopy and follow-up of subjects with abnormal cytology. Medical care of subjects with abnormal cervical lesions will be outside of the study, according to the local medical practice.

- Throughout the protocol amendment, the tables and text was updated to reflect two study groups (where applicable). Consequently, duration of study for different groups were updated as one day (Visit 1) for HPV vaccinated subjects from HPV-039 study (Vacc-HPV-039 Group) and Month 12 for control group subjects from HPV-039 study (HPV Group). Individual changes have not been tracked in bold and italics.
- **End of Study (EoS):** Last subject's last visit/contact (Call 2 [Month 12]) or ***last testing results released for samples collected at Visit 1 and related call back visits, whatever comes later.***

- **Treatment allocation:** ~~sequential allocation of treatment to subjects by randomisation system on internet (SBIR).~~ ***Treatment allocation depends on the randomization in the previous study i.e. only the subjects from the control group of HPV-039 study will receive HPV vaccination in the current study. Subjects who previously received the Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed in HPV-039 will not receive vaccination in this study.***

As the study now involves collection of cervical samples, sampling schedule was added as follows:

- ***Sampling schedule: A cervical sample will be taken at Visit 1 before vaccine administration.***

  For subjects who have abnormal cytology findings in the cervical sample collected at Visit 1, there will be a call-back follow-up visit for colposcopy examination. A cervical biopsy will be taken depending on the results of the colposcopy examination.

- **Data collection:** ~~Standardised~~ Electronic Case Report Form (eCRF).

- **Safety monitoring:**
  - ***All subjects:***
    - ***SAEs related to study participation.***
  - ***HPV Group (Ctrl-HPV-039 group):***
    - All SAEs, and any AE/SAE leading to premature discontinuation of the study will be reported throughout the study.
    - pIMDs will be reported ~~for all subjects~~ throughout the study.
    - Pregnancies and pregnancy outcomes will be reported ~~for all subjects~~ throughout the study.

Section 4.1: Number of subjects/centres

Overview of recruitment plan

~~Approximately~~ ~~3025~~***Up to 6051*** subjects who ***participated*** ~~received placebo~~ in the HPV-039 study ~~and above 26 years of age at the time of entry in this study~~ will be invited to participate in this study. ~~cross-over vaccination study with GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine. Subjects~~ ***Subjects*** ~~in the control group of HPV-058 study may also be invited to participate in this study if they are above 26 years of age at the time when cross-over vaccination~~ ***will be*** ~~offered to HPV-058 participants.~~

The study recruitment period is expected to last approximately 6 months and the recruitment period will be communicated to all study investigators. Investigators will make all efforts to invite and enrol subjects during this period.

Women who are pregnant during the recruitment period will be offered participation in the study or free of charge vaccination outside the study using commercial vaccine three months after the pregnancy ends.

Hence, the study end may change depending on study progress.

Section 4.2: Inclusion criteria for enrolment

The inclusion criteria were updated to organize the criterion as per the study procedure.

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

- Subjects who, in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g. return for study visits, available for follow-up telephone contacts).
- Written informed consent obtained from the subject prior to performing any study specific procedure.
- ~~A~~ Subjects previously enrolled in the HPV-039 study.~~, who received the control vaccine, and who is above 26 years of age at the time of entry in this study. Subjects in the control group of HPV-058 study may also be invited to participate in this study if they are above 26 years of age at the time when cross-over vaccination is offered to HPV-058 participants.~~
- ***Subjects with negative pregnancy test at Visit 1.***

Additional inclusion criteria for subjects of HPV group undergoing vaccination ONLY:

- Healthy subjects as established by medical history and clinical examination before entering into the study.
- Female subjects of non-childbearing potential may be enrolled in the study.
  - Non-childbearing potential is defined as pre-menarche, current bilateral tubal ligation or occlusion, hysterectomy, bilateral ovariectomy or post-menopause.

Please refer to the glossary of terms for the definition of menarche and menopause.

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

Please refer to the glossary of terms for the definition of adequate contraception.

Section 4.3: Exclusion criteria for enrolment

The exclusion criteria were updated to organize the criterion as per study procedure.

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:

- Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product (pharmaceutical product or device).

- Previous vaccination against HPV ***outside of study HPV-039.*** ~~or planned administration of another HPV vaccine during the study other than that foreseen in the protocol.~~

Additional exclusion criteria for subjects of HPV group undergoing vaccination ONLY:

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine during the period starting 30 days before the first dose of study vaccine (Day -29 to Day 1), or planned use during the study period.
- Any medical condition that in the judgment of the investigator would make intramuscular injection unsafe.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting six months prior to the first vaccine dose. For corticosteroids, this will mean prednisone (≥20 mg/day, or equivalent. Inhaled and topical steroids are allowed.
- Planned administration/administration of a vaccine/product not foreseen by the study protocol in the period starting 30 days before and after each dose of vaccine administration, with the exception of administration of routine meningococcal, hepatitis B, hepatitis A, inactivated influenza and/or rabies vaccine up to eight days before and after each dose of study vaccine. Enrolment will be deferred until the subject is outside of the specified window.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine.
- Previous administration of MPL or AS04 adjuvant.
- Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening tests.
- Cancer or autoimmune disease under treatment.
- Hypersensitivity to latex.
- Acute disease and/or fever at the time of enrolment.
  - Fever is defined as temperature ≥ 37.0°C. The preferred location for measuring temperature in this study will be the axilla.
  - Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may, be enrolled at the discretion of the investigator.
- Pregnant or ~~lactating female~~ ***breastfeeding. Subjects must be at least three months post-pregnancy and not breastfeeding to enter the study. For pregnant or lactating women, also please refer to Section 4.1***

- Female planning to become pregnant or planning to discontinue contraceptive precautions during the vaccination phase of the study, i.e. up to two months after the last vaccine dose.

Section 5.2: Subject identification and randomisation

Section 5.2.1: Subject identification

~~Subject identification numbers will be assigned sequentially to the subjects who have consented to participate in the study, according to the range of subject identification numbers allocated to each study centre.~~

Subjects will be allocated the same identification numbers as in study HPV-039.

Section 5.2.1.2: Treatment allocation to the subject was re-organized for clear flow of information and to minimize the redundant information as follows:

The treatment numbers will be allocated by dose.

A sequential list of treatment numbers will be generated by MATerial EXcellence (MATEX). The Randomisation and Treatment Allocation System on Internet (SBIR) will be used to allocate treatment numbers to the subjects.

After obtaining the signed and dated ICF from the subject and having checked the eligibility of the subject, the site staff in charge of the vaccine administration will access SBIR. Upon providing the subject identification number, the ~~randomisation~~ system will provide the treatment number to be used for the first dose.

When SBIR is not available, please refer to the SBIR user guide for specific instructions.

For each dose subsequent to the first dose, the study staff in charge of the vaccine administration will access SBIR, provide the subject identification number, and the system will provide a treatment number.

The number of each administered treatment must be recorded in the eCRF on the Vaccine Administration screen.

Section 5.3: Method of blinding

~~This is an open-label study since all subjects who received placebo in the HPV-039 study will receive GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine.~~ ***Not applicable since this is an open-label study. However the laboratory in charge of the laboratory testing: personnel will 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.***

The laboratory testing mentioned above refers to cytology and PCR testing.

Section 5.4: General study aspects was updated to include procedures of HPV DNA testing and cytology testing as follows:

Section 5.4.1: HPV DNA testing

All the assessment of cervical samples for this study will be done by the Cancer Institute/Hospital, Chinese Academy of Medical Sciences and Cancer Foundation of China (CICAMS/CFC).

"Reflex" testing by the US FDA and China FDA-approved hybridization assay (Hybrid Capture® 2 test [HCII]) will be used to guide a subject's management in case of atypical squamous cells of undetermined significance (ASC-US, see Section 5.6.8.2). CICAMS/CFC will automatically perform HPV DNA Hybrid Capture II (HCII) testing on the liquid-based cytology specimen. Study personnel do not need to request the HCII testing.

Currently available data do not support the use of HPV DNA PCR testing in the routine management of subjects diagnosed with abnormal cervical cytology. The HPV DNA PCR testing, which will be used in this study, has been developed for investigational use only. For this reason, clinical management will not be driven by the results of this testing. A number of procedures will be followed to ensure that HPV DNA PCR test results do not bias either the conduct of the trial, or the clinical management of the study subjects.

These procedures include:

1. ***Study sites and study personnel will be blinded to HPV DNA PCR test results throughout the study to ensure that these results do not bias either the conduct of the trial, or the clinical management of study subjects. This includes bias that might result from deviations from regular study interval visits for cervical cytological follow-up and/or colposcopic procedures.***
2. ***HPV DNA PCR test results will NOT be provided to the investigators or study subjects until the end of the study. A summary report on results will be distributed to the investigators after study completion. It will be the responsibility of the investigators to inform study subjects of their results. The clinical management of subjects should follow the recommended guidelines outlined below and should be based solely on cervical cytology or biopsy results and HCII testing (not HPV DNA PCR test results).***

Section 5.4.2: Management of subjects with abnormal cytology

Cervical cytology specimens will be collected using the sampling device provided. Cytological examination will be performed using the ThinPrep® PapTest (Cytyc Corporation, Boxborough, MA, USA). HPV DNA PCR testing will be performed on the cervical cytology specimens collected on Day 1 (Visit 1). In case of abnormal cytology results, the subjects will be called back for a follow-up visit for colposcopy examination. The following algorithms (see Figure 2, Figure 3, Figure 4 and Figure 5) describe clinical management guidelines to be followed by the investigator (and/or designee). Treatment of subjects with abnormal findings is not within the scope of this

study; however, the subjects will be referred to local healthcare centres to follow local medical practices. The algorithms are based on the guidelines of the American Society for Colposcopy and Cervical Pathology and European guidelines, and are designed to provide a consistent method of detection, clinical management and reporting for cervical lesions. The clinical management algorithms cannot define every clinical situation and, therefore, it is the investigator's (or designee's) responsibility to exercise appropriate clinical judgment in the medical management of exceptional cases. Compliance with the algorithm will be monitored.

Section 5.4.2.1: Cytology and histology report terminology

Each cytopathology specimen will be reported according to the Bethesda 2001 Classification of cytological findings. The terminology will include a statement as to whether a specimen is satisfactory or unsatisfactory. In addition, specimens that are satisfactory but show no endocervical component will be identified for quality control of cytological sampling.

For the purposes of the trial, management is specified for the categories:

- ***Unsatisfactory***
- ***Negative for intraepithelial lesion or malignancy (negative)***
- ***Atypical squamous cells of undetermined significance (ASC-US):***
  - ***ASC-US / Hybrid Capture II negative (ASC-US/oncogenic HPV negative)***
  - ***ASC-US / Hybrid Capture II positive (ASC-US/oncogenic HPV positive)***
  - ***ASC-US / Hybrid Capture 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***

Specimens will be reported as "Quantity Not Sufficient" when there is an inadequate amount of cells for HCII testing. In case of ASC-US/QNS or missing HCII test results, subjects will be informed and encouraged to follow regular gynaecological examination according to local practice.

Histopathological reports on biopsy and excision specimens will classify the findings as:

- ***Negative***
- ***Condyloma***

- ***Cervical intraepithelial neoplasia grade 1 [CIN1]***
  Vaginal intraepithelial neoplasia grade 1 [VaIN1]
  Vulvar intraepithelial neoplasia grade 1 [VIN1])
- ***Cervical intraepithelial neoplasia grade 2 [CIN2]***
  Vaginal intraepithelial neoplasia grade 2 [VaIN2]
  Vulvar intraepithelial neoplasia grade 2 [VIN2])
- ***Cervical intraepithelial neoplasia grade 3 [CIN3]***
  Vaginal intraepithelial neoplasia grade 3 [VaIN3]
  Vulvar intraepithelial neoplasia grade 3 [VIN3])
- ***Low grade cervical glandular intraepithelial neoplasia (LCGIN)***
- ***High grade cervical glandular intraepithelial neoplasia (HCGIN)***
- ***Adenocarcinoma in-situ (AIS)***
- ***Invasive malignancy***

Section 5.4.2.2: Cytology and colposcopy management algorithms

The algorithm in Figure 2 describes the clinical management of all cytology results obtained at Day 1 (Visit 1). Subjects with cytology reported as negative or as ASC-US/ oncogenic HPV negative will not be called back for a follow-up biopsy sample. Subjects with abnormal cytological findings (except ASC-US/oncogenic HPV negative) should be managed according to the recommendations for follow-up in Figure 2 and the colposcopy algorithms in Figure 3, Figure 4 and Figure 5. The results of the cytology will be communicated to the investigator (or designee) by CICAMS/CFC. The investigator (or designee) will notify the subject of the test result and, when appropriate, the subject should receive colposcopy within approximately 30 days after cytology results have been communicated by CICAMS/CFC.

Section 5.4.2.3: Unsatisfactory cytological findings and missing cytology results

When the laboratory results deem a cervical liquid-based cytology (cervical-LBC) specimen unsatisfactory, study personnel are required to repeat the cervical-LBC specimen as soon as possible after cytology results have been communicated. Only satisfactory results of a repeat cytology result will count as the final cytology result. Likewise, HPV DNA PCR testing will not be performed on unsatisfactory cytology specimens.

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 will be used for quality control monitoring. Abnormal cytology should be managed according to the appropriate protocol-specified algorithm. Missing cytology results will be recorded as missing results (in the case of lost damaged sample).

Section 5.5: Outline to study procedures

Three different tables on list of study procedures, one for each group and sub-group, were added, as follows:

Table 4 List of study procedures – Vacc-HPV-039 group

Epoch	*Epoch 001*
Type of contact	*Visit 1*
Time points	*Day 1*
Informed consent	●
Check inclusion/exclusion criteria	●
Collect demographic data	●
Medical history†	●
Physical examination	●
Pregnancy test	●
Gynaecological examination	●
Cervical sampling	●
*Referral for colposcopy (if applicable)***	○
*Report colposcopy results (if applicable)***	●
Safety assessments	
*Record any concomitant medication/vaccination**	●
Recording of SAEs related to study participation	●
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.
† Medical history since the last visit in study HPV- 039 will be recorded. The subjects should also provide their history of any HPV related infection/disease with all available information.
****Including only HPV vaccination and others which may lead to elimination from per-protocol analysis.***
***** Subjects with abnormal cervical cytology will be evaluated according to the cytology and colposcopy clinical management algorithms (see Section 5.4.2 and Section 5.6.9) at unscheduled visits following Visit 1.***

Table 5 List of study procedures – HPV Group (Ctrl-HPV-039 group)

Epoch	Epoch 001				
Type of contact	**Visit 1**	**Visit 2**	**Visit 3**	**Call 1**	**Call 2**
Time points	**Day 1**	**Month 1**	**Month 6**	**Month 7**	**Month 12**
Informed consent	●				
Check inclusion/exclusion criteria	●				
Collect demographic data	●				
Medical and vaccination history†	●				
Physical examination	●				
Pregnancy test	●	●	●		
Check contraindications and warnings and precautions to vaccination	●	●	●		
Gynaecological examination	●				
Cervical sampling	●				
Referral for colposcopy (if applicable)*	○				
Report colposcopy results (if applicable)*	●				
Pre-vaccination body temperature	●	●	●		
Vaccine					
Treatment number allocation	O				
Treatment number allocation for subsequent doses		O	O		
Recording of administered treatment number	●	●	●		
Vaccine administration	●	●	●		
Safety assessments					
Record any concomitant medications/vaccinations	●	●	●	●	●
Recording of pregnancies and outcomes	●	●	●	●	●
Recording of SAEs	●	●	●	●	●
Recording of AEs/SAEs leading to premature withdrawal from the study	●	●	●	●	●
Recording of pIMDs	●	●	●	●	●
Safety follow-up contact				●	●
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.
† Medical history since the last visit in study HPV- 039 must be recorded. The subjects should also provide their history of any HPV related infection/disease with all available information.
***** Subjects with abnormal cervical cytology will be evaluated according to the cytology and colposcopy clinical management algorithms (see Section 5.4.2 and Section 5.6.9) at unscheduled visits following Visit 1.***

The title of the table for intervals between study visits was updated as follows:

"Intervals between study visits (*for the HPV Group*)"

Section 5.6: Detailed description of study procedures

Note: Each study procedure is detailed in subsequent subsections only once, even if some of them need to be performed during more than one visit.

Section 5.6.1: Informed consent

The following text was added:

Subjects in the HPV group (Ctrl-HPV-039 group) will be given the choice to consent to either sampling or vaccination or both procedures during the informed consent process.

Section 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 prior to ***cervical sample collection or*** the first study vaccination in the eCRF.

The subjects should also provide their history of any HPV related infection/disease with all available information since their last visit in study HPV-039.

Section 5.6.5: Physical examination:

The following text was added:

For subjects in the Vacc-HPV-039 group, the investigator must use her medical judgement to decide if a subject can undergo cervical sampling procedure; Subjects may be rescheduled or excluded from the study on the basis of medical history.

Section 5.6.6: Pregnancy test

Female subjects of childbearing potential are to have a ***negative*** urine pregnancy test prior to any study ***gynaecological examination, cervical sample collection or*** vaccine administration~~. The study vaccine may only be administered if the pregnancy test is negative~~.

In case of a positive urine pregnancy test result, the subjects would not be allowed to receive vaccination or undergo cervical sampling until 3 months after the end of pregnancy.

Sections on gynaecological examination and cervical sampling were added.

Section 5.6.8: Gynaecological examination and cervical sampling

Section 5.6.8.1: Gynaecological examination

Gynaecological examination will be performed on Day 1 (Visit 1). At gynaecological examination, according to local medical practice, the vagina and vulva will be inspected using the unaided eye or the colposcope or a magnifying glass. If needed, acetic acid may be applied.

Any vaginal or vulvar lesions possibly associated with HPV (other than condylomas) will be biopsied and excised according to local medical practice. This may include referral to the study colposcopists. All tissues will be shipped to CICAMS/CFC. After completion of the gynaecological examination, women should be encouraged to continue follow-up in the context of local medical practice.

Section 5.6.8.1.1: Requirements for cervical specimen collection

Sexual intercourse must 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 are menstruating during planned

visits will be invited to reschedule cervical specimen collection 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 delivery.

Section 5.6.8.1.2: Cervical Sampling

All subjects should undergo pelvic examination during which a cervical liquid-based cytology (LBC) sample will be collected for HPV DNA testing by PCR and cytological examination (refer to Sections 5.4.2 and 5.6.9 for details on gynaecological examination and follow-up algorithms (colposcopy and biopsy procedures).

Section 5.6.8.2: ASC-US or LSIL

An observation of ASC-US will result in reflex testing by CICAMS/CFC for high-risk HPV types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) using HCII. Results will be communicated to the investigator (or designee) as "ASC-US/oncogenic HPV negative" or "ASC-US/oncogenic HPV positive".

Subjects with ASC-US/oncogenic HPV negative results will not be called back for a follow-up biopsy procedure; however, will be encouraged to continue follow-up in the context of local medical practice.

Subjects with ASC-US/oncogenic HPV positive results or LSIL will be referred for colposcopic evaluation (see Figure 3 for the low-grade colposcopy management algorithm).

Specimens will be reported as "Quantity Not Sufficient" (QNS) when there is an inadequate amount of cells for HCII testing. In case of ASC-US/QNS or missing HCII test results, subjects will be informed and encouraged to follow regular gynaecological examination according to local practice.

To ensure active follow-up with subjects missing a follow-up visit or a colposcopy visit, study personnel will contact the subject by using established local communication methods. The site will make at least three attempts to contact the subject. If contact cannot be achieved after three attempts, a certified/registered letter will be sent by the site.

Section 5.6.8.3: AGC

Observation of AGC will result in an immediate referral for colposcopic evaluation (see Figure 4 for the AGC colposcopy management algorithm).

Section 5.6.8.4: ASC-H / greater than or equal to HSIL

Observation of ASC-H or ≥HSIL will result in an immediate referral for colposcopic evaluation (see Figure 5 for the high-grade colposcopy management algorithm).

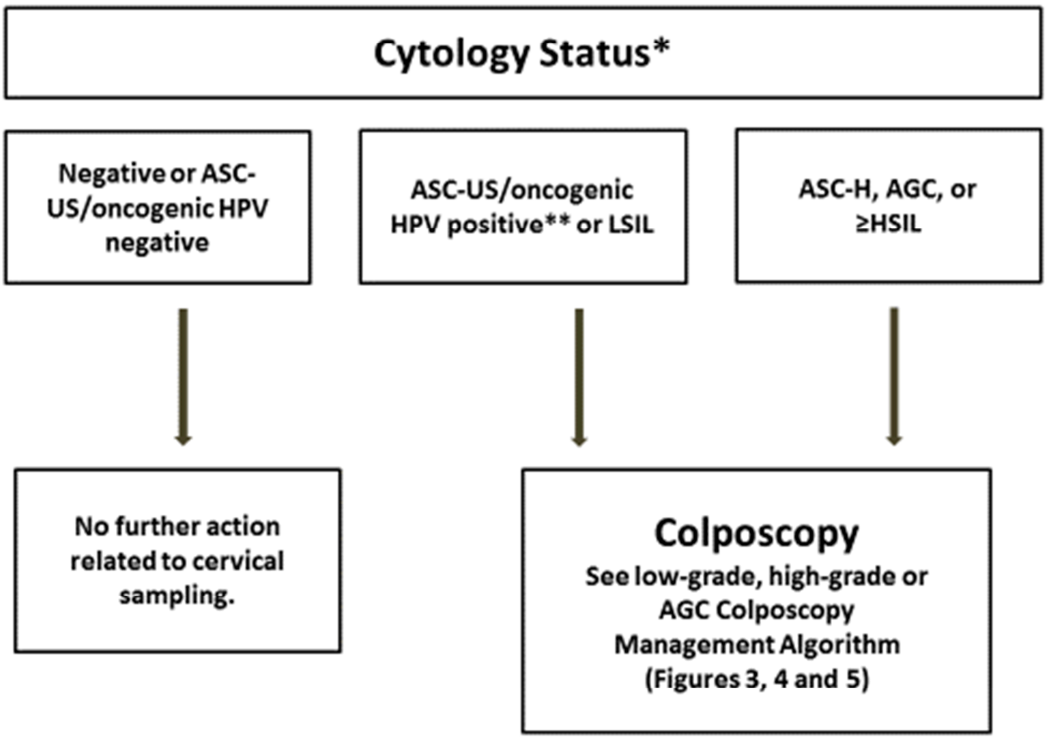
Section 5.6.9: Colposcopic evaluations of abnormal cytologies

Colposcopy provides the link between cytology and biopsy. Colposcopy will be performed by a trained and experienced colposcopist. Colposcopy will be performed on subjects with abnormal cytological findings (except ASC-US/oncogenic HPV negative, see Figure 2).

Given that the expertise of the clinical site teams varies in the field of cervical disease management and colposcopy, the qualifications and experience of the participating colposcopists will be reviewed.

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.

Figure 2 Cytology Management Algorithm



**** If a cervical liquid-based cytology (LBC) specimen is deemed "unsatisfactory" by the laboratory, the subject must be informed to arrange for another cervical sampling visit.***
***** Oncogenic HPV positive means that the cytology specimen is positive for an oncogenic HPV type by Hybrid Capture II (HCII) testing. This test will automatically be performed on specimens with an ASC-US result (reflex testing). Specimens will be reported as "Quantity Not Sufficient" (QNS) when there is an inadequate amount of cells for HCII testing. In case of ASC-US/QNS or missing HCII test results, subjects will be informed and encouraged to follow regular gynaecological examination according to local practice.***

Section 5.6.9.1: Colposcopic procedures

If the transformation zone is not fully visualized, the colposcopy is to be considered as not satisfactory. In these cases, an endocervical specimen by endocervical curettage will have to be collected during the colposcopy and the vagina carefully inspected.

- ***A normal colposcopy impression may result in taking an endocervical specimen by endocervical curettage according to the appropriate algorithm and local medical practices.***
- ***A colposcopy impression of LSIL or equivocal will result in biopsy. A colposcopy impression of ≥HSIL will also result in a biopsy.***

If the biopsy result/endocervical specimen is negative or ≤CIN1, no further action is required; however, the subjects can continue with protocol-specified procedures if applicable and will be encouraged to have a follow-up according to local medical practice. If the biopsy result or the endocervical specimen is ≥CIN2 or AIS, the subject will be referred for treatment according to local medical practice.

A biopsy specimen that cannot be adequately evaluated by the histopathologist will be reported as non-diagnostic. If the biopsy is reported as non-diagnostic, the subjects will be offered a repeat colposcopy as soon as possible and a further biopsy would be taken from any abnormal or equivocal area.

Any cervical lesions will be biopsied according to colposcopy management algorithms. In addition, the vagina and vulva will be inspected with each colposcopy and any vaginal or vulvar lesions possibly associated with HPV (other than condylomas) will be biopsied or excised according to local medical practice.

All tissues will be shipped to CICAMS/CFC. All tissues will be examined in CICAMS/CFC and the report from CICAMS/CFC will be used for clinical management.

Every effort should be made to encourage subjects to have the colposcopic examination within this study. Should a subject have a colposcopy performed outside of the study, she will be asked to consent to allow study staff to access her medical records and to obtain slides and tissue for evaluation if possible.

Section 5.6.9.2: Colposcopy management for low-grade cytology

The management algorithm shown in Figure 3 should be used for any subject who has cytological abnormalities graded as ASC-US/oncogenic HPV positive or LSIL.

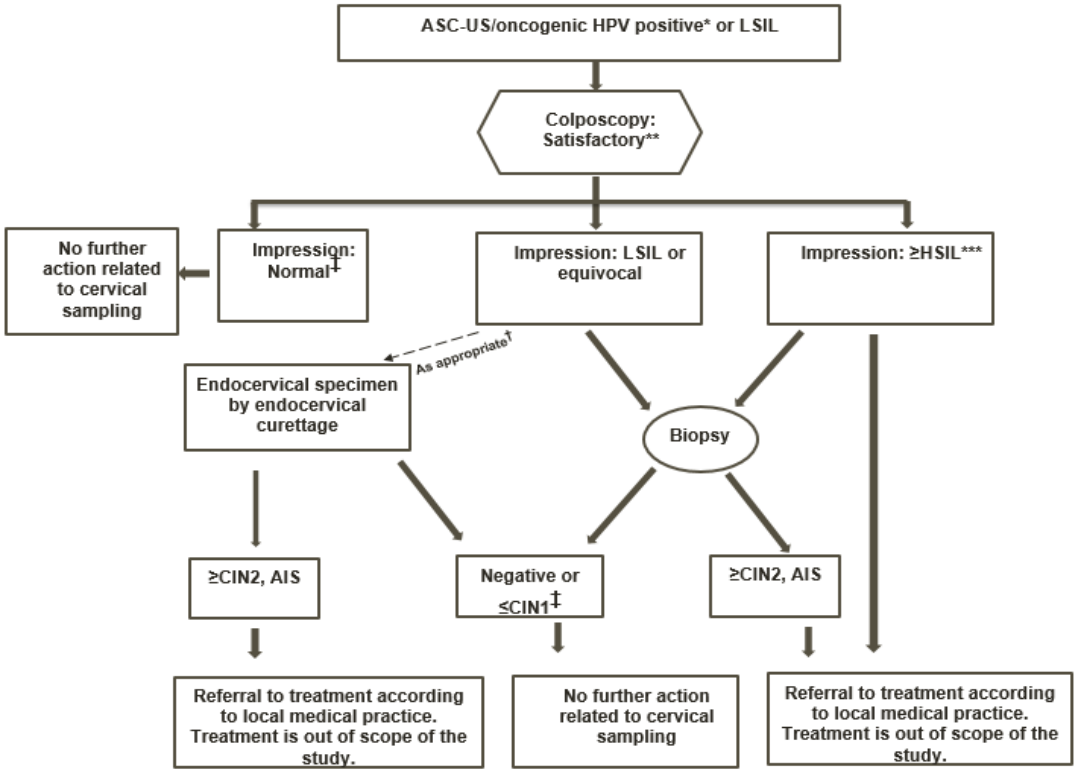
An unsatisfactory colposcopy indicates that the transformation zone is unable to be fully visualized. In these cases, an endocervical specimen must be taken by endocervical curettage and the vagina carefully inspected. If any abnormality is seen, this should be managed according to the algorithm.

If it is a normal colposcopy impression no further action is required and the subjects can continue with protocol-specified procedures, if applicable and will be encouraged to continue follow-up in the context of local medical practice.

A colposcopy impression of LSIL will result in biopsy - collection of an endocervical specimen by endocervical curettage is optional. If the biopsy result is negative or ≤CIN1, no further action is required and the subjects can continue with protocol-specified procedures, if applicable and is encouraged to be followed up according to the local medical practice. If biopsy or endocervical curettage show ≥CIN2 or AIS, subjects will be referred for treatment according to local medical practice.

For colposcopic impression of ≥HSIL, a biopsy will be performed. If the biopsy result is ≥CIN2 or AIS, the subject will be referred for treatment according to local medical practice. Subjects with ≥HSIL may also be referred to treatment without biopsy.

Figure 3 Colposcopy Management Algorithm for subjects with ASC-US/oncogenic HPV positive results or LSIL



Note: Specimens will be reported as "Quantity Not Sufficient" (QNS) when there is an inadequate amount of cells for HCII testing. In case of ASC-US/QNS or missing HCII test results, subjects will be informed and encouraged to follow regular gynaecological examination according to local practice
***** An unsatisfactory colposcopy indicates that the transformation zone is unable to be fully visualized. In these cases an endocervical specimen must be taken and the vagina inspected.***
******If invasive cancer is suspected, management should be according to accepted standard medical practice. Subjects who do not have a biopsy in the study will be asked to consent to allow study staff to obtain their tissue for evaluation if possible.***
† Collection of endocervical specimen will depend on local practice and clinical judgement.
‡ subjects will be encouraged to have gynaecological follow-up as per local practice.

Section 5.6.9.3: Colposcopy management algorithm for AGC

This management algorithm (Figure 4) should be used for any subject who has a single cytological abnormality graded as AGC.

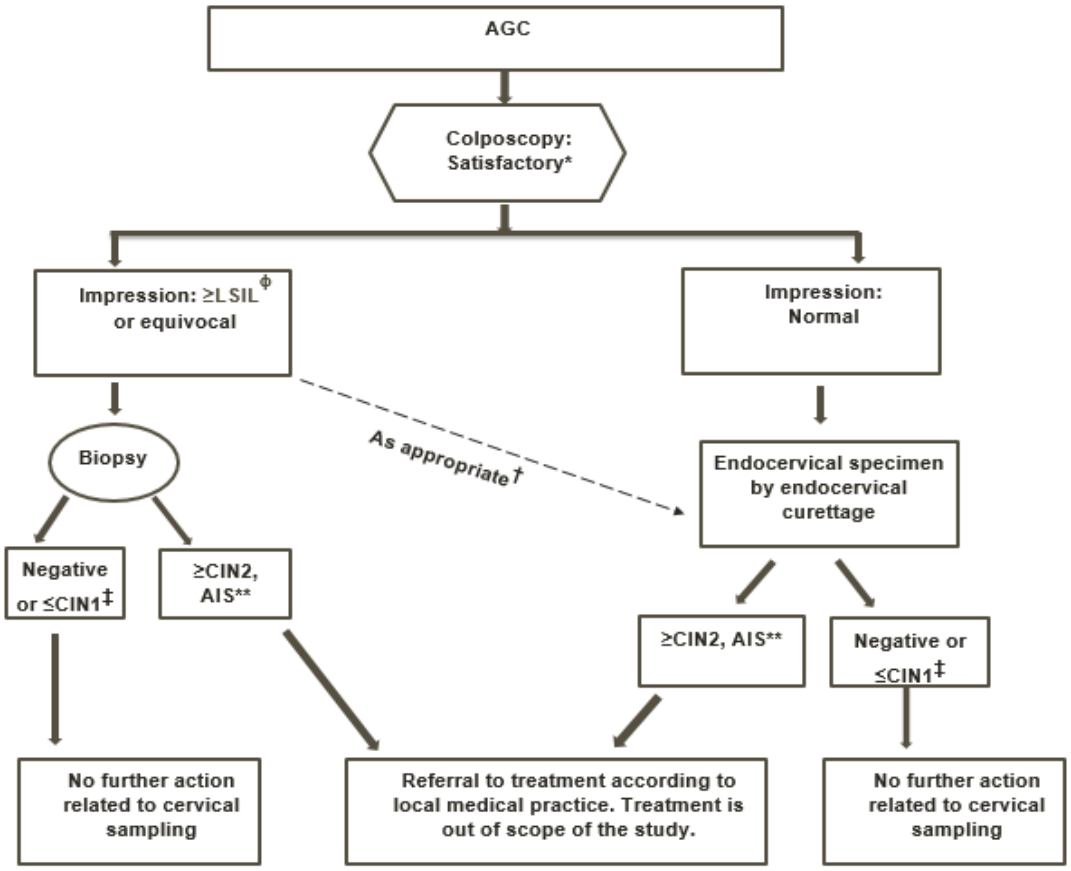
An unsatisfactory colposcopy indicates that the transformation zone is unable to be fully visualized. In these cases, an endocervical specimen must be taken and the vagina carefully inspected. If any abnormality is seen, this should be managed according to the algorithm.

If the colposcopic impression is normal, an endocervical specimen by endocervical curettage will be collected, cytology will be reviewed and the vagina should also be carefully inspected. If endocervical and cytological review results are negative or ≤LSIL or≤CIN1 or negative, no further action is required and the subjects can continue with protocol-specified procedures, if applicable and will be encouraged to continue follow-up in the context of local medical practice. If cytology result (except ASC-US/oncogenic HPV negative) or colposcopy is abnormal, please refer to appropriate colposcopy management algorithm.

If endocervical and cytological review results are ≥HSIL, AGC or AIS, the subjects will be referred for treatment as per local medical practice.

If the colposcopic impression is ≥LSIL or equivocal, a biopsy should be performed depending on the colposcopic impression and local medical practice. An endocervical specimen by endocervical curettage may be collected. If a biopsy confirms ≥CIN2 or AIS, the subjects will be referred for treatment as per local medical practice. If the biopsy result is negative or ≤CIN1, no further action is required and the subjects can continue with protocol-specified procedures, if applicable and will be encouraged to continue follow-up in the context of local medical practice. If cytology result (except ASC-US/oncogenic HPV negative) or colposcopy is abnormal, please refer to appropriate colposcopy management algorithm.

Figure 4 Colposcopy Management Algorithm for subjects with AGC



** An unsatisfactory colposcopy indicates that the transformation zone is unable to be fully visualized. In these cases, an endocervical specimen must be taken and the vagina inspected.*
† Collection of endocervical specimen and cytological review will depend on local practice and clinical judgement of discrepancy between findings. A high grade AGC should lead to excision biopsy.
ϕ If invasive cancer is suspected, management should be according to accepted standard medical practice.
‡ subjects will be encouraged to have gynaecological follow-up as per local practice

Section 5.6.9.4: Colposcopy management algorithm for high-grade cytology

This management algorithm (Figure 5) should be used for any subject who has a single cytological abnormality graded as ASC-H or ≥HSIL.

An unsatisfactory colposcopy indicates that the transformation zone is unable to be fully visualized. In these cases, an endocervical specimen must be taken and the vagina carefully inspected. If any abnormality is seen, this should be managed according to the algorithm.

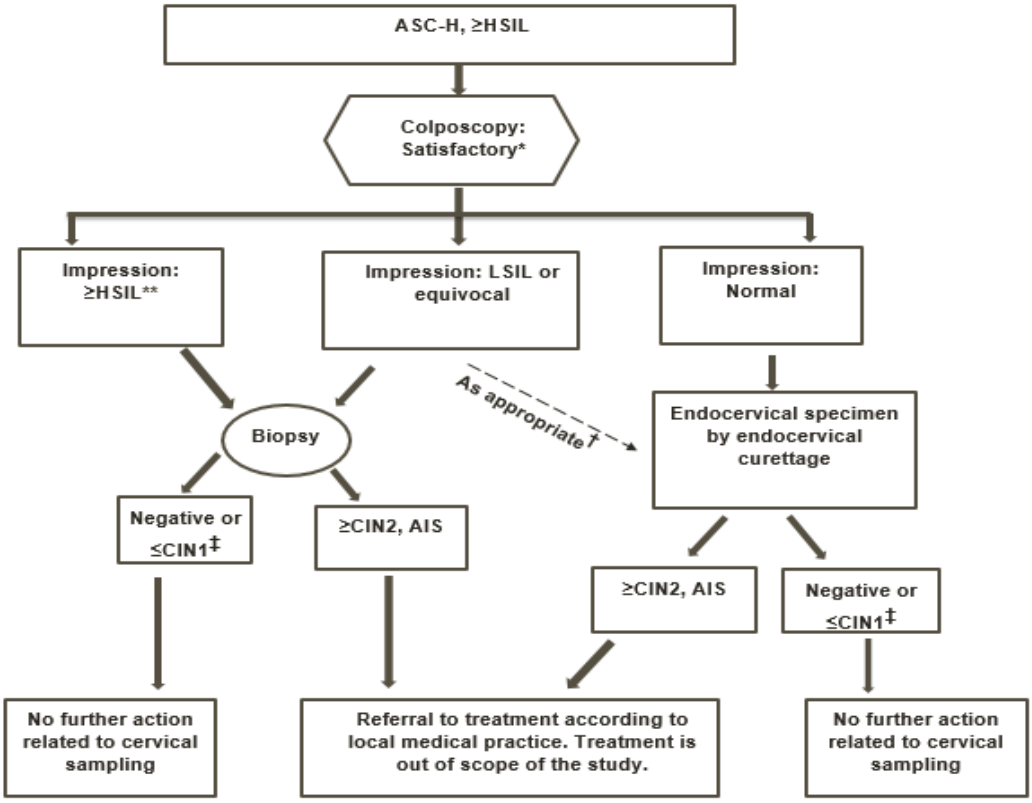
If the colposcopic impression is normal, an endocervical specimen by endocervical curettage will be collected, cytology will be reviewed and the vagina should also be carefully inspected. If the endocervical sampling and cytological review results are negative or ≤LSIL, ≤CIN1 no further action is required and the subjects can continue with protocol-specified procedures, if applicable. If cytological review or endocervical sampling confirms HSIL, ASC-H, AGC or AIS, the subjects will be referred for treatment as per local medical practice.

If the colposcopic impression is LSIL or equivocal, a biopsy should be performed. An endocervical specimen by endocervical curettage may be collected and cytology reviewed depending on local medical practice. If the biopsy result is negative or ≤CIN1, no further action is required and the subjects can continue with protocol-specified procedures, if applicable. If the biopsy result is ≥CIN2 or AIS, the subjects will be referred for treatment as per local medical practice.

For colposcopic impression of ≥HSIL, a biopsy will be performed. If the biopsy result is negative or ≤CIN1, no further action is required and the subjects can continue with protocol-specified procedures, if applicable. If the biopsy result is ≥CIN2 or AIS, the subjects will be referred for treatment as per local medical practice.

For any colposcopy/biopsy/endocervical specimen results ≤LSIL or ≤CIN1, subjects will be encouraged to continue follow-up in the context of local medical practice.

Figure 5 Coloposcopy Management Algorithm for subjects with ASC-H or HSIL



** An unsatisfactory colposcopy indicates that the transformation zone is unable to be fully visualized. In these cases,an endocervical specimen must be taken and the vagina inspected.*
*** If invasive cancer is suspected, management should be according to accepted standard medical practice.*
† Collection of endocervical specimen will depend on local practice and clinical judgement.
‡ subjects will be encouraged to have gynaecological follow-up as per local practice.

Section 5.6.10: Sampling

Refer to the Module on Biospecimen Management in the SPM for detailed instructions for the collection, handling and processing of the samples. Refer to section 5.6.8 for cervical sample collection.

The procedures listed in sections 5.6.11 to 5.6.13 are only applicable for subjects undergoing vaccination in this study.

Section 5.6.11: Assess pre-vaccination body temperature

The location of body temperature measurement was changed from "oral" to "axilla".

Section 5.6.16: Safety follow-up contact

- The investigator or his/her designee will contact the subjects ***who have been vaccinated,*** by telephone approximately one and six months after the third vaccine dose to obtain information on the occurrence of any of the safety endpoints.
- The procedures to be performed during the follow-up telephone contact such as recording of any concomitant medication/vaccination or medical treatment and recording of SAEs, pregnancies ***and its outcome (as applicable)*** and pIMDs are also performed during this phone contact and are described in Section 5.6.14 and Section 5.6.15, respectively.

Section 5.7: Biological sample handling and analysis

As the study now involves collection of a cervical sample from the subjects from HPV-039 study, a section on biological sample handling and analysis was added.

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.

- ***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.

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.

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.

Section 5.7.1: Use of specified study materials

~~Not applicable, as no clinical samples will be collected in this study.~~

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 10.5 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.

Section 5.7.2: Biological samples

Cervical samples will be collected at Visit 1 from all the subjects to check for HPV infection. Subjects who have abnormal cytology findings in the cervical sample collected at Visit 1 will be called back for a follow-up colposcopy visit. A cervical biopsy may be taken depending on the colposcopy findings. No blood samples will be taken during the study.

Section 5.7.3: Laboratory assays

The assays to be performed are summarized in Table 7.

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.

Section 5.7.3.1: Cervical Cytology

All original cervical samples collected will be prepared by trained laboratory personnel using the ThinPrep® 2000 Processor to transfer and fix the cells onto glass slides. All cytology specimens will be processed and then evaluated according to the Bethesda 2001 classification system for reporting cervical cytology diagnoses.

Cervical cytology will be performed using the ThinPrep® PapTest. (Cytyc Corporation, Boxborough, MA, USA). Cervical cells for ThinPrep® cytology will be collected using the sampling device provided rinsed into a collection vial containing PreservCyt® medium. Specimens will be stored according to the CICAMS/CFC procedure until shipment to CICAMS/CFC. Cytological specimens must be shipped at ambient temperature within one month of collection.

From the PreservCyt® specimen (original sample), one 1 mL aliquot will be prepared and withdrawn prior to ThinPrep® slide preparation (to avoid possible specimen-to-specimen contamination) for HPV DNA testing. The remaining sample will be used for cytological analysis at CICAMS/CFC.

In case a commercialized test/equipment is not available, an equivalent test/equipment may be used after approval by GSK.

Section 5.7.3.2: Polymerase chain reaction (PCR) typing of HPV DNA from PreservCyt specimens

To test for HPV DNA, SPF10 primers which amplify a 65 nucleotide region of the HPV L1 gene for most of the known HPV isolates are used; the generic amplification products are detected by hybridization on a microtitre plate (DEIA). HPV-positive specimens will be typed by reverse hybridization line probe assay (LiPA), using 25 HPV-specific hybridization probes enabling detection of 14 oncogenic HPV types [HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68] and 11 non-oncogenic HPV types [HPV-6, -11, -34, -40, -42, -43, -44, -53, -54, -70 and -74]. All HPV positive samples will also be tested by HPV-16 specific PCR and HPV-18 specific PCR. Redundant testing using generic SPF10 PCR with LiPA, followed by HPV-16/18 type-specific PCR (TS-PCR) affords maximum test sensitivity. The results of this testing algorithm will be considered definitive for all HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68 and HPV-6, -11, -34, -40, -42, -43, -44, -53, -54, -70 and -74 related study endpoints using HPV DNA testing from PreservCyt® specimens.

Section 5.7.3.3: Hybrid Capture II testing

Clinical management will be guided by Hybrid Capture II testing (see Section 5.4.2). After ThinPrep® cytology slides have been prepared, residual PreservCyt® specimens on slides read as ASC-US will be tested for HPV DNA. Testing will be done by CICAMS/CFC using the HCII test (Digene Corp., Gaithersburg, MD, USA). Probe B will be used and is designed to detect infections with 13 oncogenic HPV types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) [Vernick, 2003]. This test is fast, reliable and accurate, but does not provide type-specific data. Therefore,

additional HPV DNA testing by PCR will be required to define trial endpoints, as discussed above.

Vaginal and vulvar biopsies will be handled according to the same procedures as cervical biopsies.

Section 5.7.3.4: Histopathology

Biopsy specimens obtained during the trial will be fixed in buffered formalin (provided by the sponsor) and shipped to CICAMS/CFC for histopathological evaluation and PCR examination.

Vaginal and vulvar biopsies will be handled according to the same procedures as cervical biopsies.

Section 5.7.3.4.1: Histopathological analysis

Histopathological analysis will be performed by CICAMS/CFC. All biopsies will be reported independently by two designated, expert pathologists. In case of disagreement in diagnosis between the two pathologists, a third expert panel member will examine the specimen and a consensus diagnosis will be reached. These diagnoses will be placed in the results reporting system and made available electronically at each site within a designated timeframe (e.g. 7 days) of receipt at CICAMS/CFC. These results will be used for patient management. CICAMS/CFC will expedite reports on specimens marked urgent, engage in telephone consultation with clinicians and send slides to sites for review by local pathologists on request. Tissue blocks will be retained by CICAMS/CFC and, at the discretion of the sponsor, may be evaluated by additional techniques to assess the presence of HPV, expression of HPV genes, host responses elicited by HPV or other mechanisms involved in cervical carcinogenesis.

Specimens from subjects having biopsies performed outside the study (e.g. very urgent clinical need such as suspected invasive cancer) can be examined and entered into the study.

Section 5.7.3.5: HPV DNA PCR testing in tissue

The formalin fixed and paraffin embedded tissue blocks used for histopathological analysis will be sectioned for PCR examination at CICAMS/CFC using an appropriate clean technique. Sections will be tested for HPV DNA using PCR methodology. Samples of lesions will be selected for further analysis using micro-dissection as appropriate. To test for HPV DNA, SPF10 primers which amplify a 65 nucleotide region of the HPV L1 gene for most of the known HPV isolates are used; the generic amplification products are detected by hybridization on a microtitre plate (DEIA). HPV-positive specimens will be typed by reverse hybridization line probe assay (LiPA), using 25 type-specific hybridization probes. This typing process enables detection of 14 oncogenic HPV types [HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68] and 11 non-oncogenic HPV types [HPV-6, -11, -34, -40, -42, -43, -44, -53, -54, -70 and -74]. All HPV positive samples will also be tested by HPV-16 specific PCR and HPV-18 specific PCR. Redundant testing using generic SPF10 PCR with LiPA,

followed by HPV-16/18 type-specific PCR (TS-PCR) affords maximum test sensitivity. The results of this testing algorithm will be considered definitive for all HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68 and HPV-6, -11, -34, -40, -42, -43, -44, -53, -54, -70 and -74 related study endpoints using HPV DNA testing from histopathology.

Any remaining histopathological sample may be used to further characterize HPV infections and associated molecular changes. Histopathological samples may also be used for the purpose of validating HPV assays.

Because the proper role of HPV DNA PCR testing in clinical management is undefined, the results of this testing will be released to investigators and subjects only at the end of the study.

In cases where multiple HPV types are detected in the samples, additional exploratory assays, such as laser microdissection may be performed to investigate the causal role of individual HPV types.

Please refer to APPENDIX A for more details on the laboratory assays. Any remaining cytological sample may be used to further characterize HPV infections and associated molecular changes. This may include sequencing, determination of viral load using quantitative HPV PCR or subtyping of HPV detected.

Table 7 Laboratory Assays

Assay type	Marker	Assay method	Test kit/ Manufacturer	Assay unit	Assay cut-off	Laboratory
Qualitative cervical cytology	Bethesda 2001 System for reporting cervical cytology diagnoses	MICRLI (Microscopy of cervical cytology)	ThinPrep® PapTest™	No unit	N/A	CICAMS/CFC
Qualitative Histopathology	CIN classification	MICRLI (Microscopy of tissue sections)	Not applicable	Qualitative	Qualitative	CICAMS/CFC
Qualitative ("generic") PCR for HPV DNA (using SPF10 primers) + LiPA on cervical swab	HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 6, 11, 34, 40, 42, 43, 44, 53, 54, 70 and 74	PCR	HPV SPF10 PCR DEIA	No unit	N/A	CICAMS/CFC
		nucleic acid hybridization	HPV SPF10 PCR LIPA	No unit	N/A	CICAMS/CFC
Qualitative ("generic") PCR for HPV DNA (using SPF10 primers) + LiPA on cervical tissue	HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 6, 11, 34, 40, 42, 43, 44, 53, 54, 70 and 74	PCR	HPV SPF10 PCR DEIA	No unit Qualitative	N/A Qualitative	CICAMS/CFC
		nucleic acid hybridization	HPV SPF10 PCR LIPA	No unit	N/A	CICAMS/CFC
Qualitative ("type-specific") PCR for HPV DNA on cervical swab	HPV-16	PCR	HPV TS16 PCR/DEIA	No unit	N/A	CICAMS/CFC
	HPV-18	PCR	HPV TS18 PCR/DEIA	No unit	N/A	CICAMS/CFC
Qualitative ("type-specific") PCR for HPV DNA on cervical tissue	HPV-16	PCR	HPV TS16 PCR/DEIA	No unit	N/A	CICAMS/CFC
	HPV-18	PCR	HPV TS18 PCR/DEIA	No unit	N/A	CICAMS/CFC
Qualitative	HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 (Oncogenic probe [cocktail B])	NAH Nucleic acid hybridization	Hybrid Capture® 2 HPV DNA Test/Digene Corporation	No unit Qualitative	N/A Qualitative	CICAMS/CFC

CICAMS/CFC: Cancer Institute/Hospital Chinese Academy Medical Sciences and Cancer Foundation of China
PCR: Polymerase Chain Reaction

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.

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.

Section 6.2: Storage and handling of study vaccine

Temperature excursion form was changed to temperature excursion application.

Section 6.7.1: Recording of concomitant medications/products and concomitant vaccinations

- Any concomitant vaccination administered in the period starting 30 days before the first dose of study vaccine and ~~ending at Call 2 (Day -29 to Month 12).~~***last contact for each subject***.
- ***Any concomitant medications/products/vaccines listed in Section 6.7.2.***

Section 6.7.2: Concomitant medications/products/vaccines that may lead to the elimination of a subject from per-protocol analyses

As a per protocol analysis of protective effect will be performed, this section was added.

~~Not applicable.~~

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. See Section 10.5 for cohorts to be analysed.

- ***Previous vaccination against HPV outside of study HPV-039.***
- ***History of long-acting immune-modifying drugs administered at any time (e.g. infliximab).***
- ***Drug and/or alcohol abuse.***

Section 8.1.1: Definition of an adverse event

The following text was added:

Collection of solicited AEs is not planned in this study. All other AEs will be recorded as UNSOLICITED AEs.

Section 8.1.4.1: Potential immune mediated diseases

A new table on pIMDs which became effective in November 2017 was added to replace the older version, as follows.

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
• Cranial nerve disorders, including paralyses/paresis (e.g. Bell's palsy) • Optic neuritis • Multiple sclerosis • Transverse myelitis • Guillain-Barré syndrome, including Miller Fisher syndrome and other variants • Acute disseminated encephalomyelitis, including site specific variants: e.g. non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis • Myasthenia gravis, including Lambert-Eaton myasthenic syndrome • Immune-mediated peripheral neuropathies and plexopathies, (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy). • Narcolepsy	• Systemic lupus erythematosus and associated conditions • Systemic scleroderma (Systemic sclerosis), including diffuse systemic form and CREST syndrome Idiopathic inflammatory myopathies, including dermatomyositis • Polymyositis • Antisynthetase syndrome • Rheumatoid arthritis, and associated conditions including juvenile chronic arthritis and Still's disease • Polymyalgia rheumatica • Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis • Psoriatic arthropathy • Relapsing polychondritis • Mixed connective tissue disorder	• Psoriasis • Vitiligo • Erythema nodosum • Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis) • Alopecia areata • Lichen planus • Sweet's syndrome • Localised Scleroderma (Morphoea)
Vasculitides	**Blood disorders**	**Others**
• Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis. • Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome (allergic granulomatous angiitis), Buerger's disease (thromboangiitis obliterans), necrotizing vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified),	• Autoimmune hemolytic anemia • Autoimmune thrombocytopenia • Antiphospholipid syndrome • Pernicious anemia • Autoimmune aplastic anaemia • Autoimmune neutropenia • Autoimmune pancytopenia	• Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis) • Ocular autoimmune diseases (including autoimmune uveitis and autoimmune retinopathy) • Autoimmune myocarditis/cardiomyopathySarcoidosis • Stevens-Johnson syndrome • Sjögren's syndrome • Idiopathic pulmonary fibrosis • Goodpasture syndrome • Raynaud's phenomenon

~~Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis.~~		

~~**Liver disorders**~~	~~**Gastrointestinal disorders**~~	~~**Endocrine disorders**~~
• ~~Autoimmune hepatitis~~ • ~~Primary biliary cirrhosis~~ • ~~Primary sclerosing cholangitis~~ • ~~Autoimmune cholangitis~~	• ~~Inflammatory Bowel disease, including Crohn's disease, ulcerative colitis, microscopic colitis, ulcerative proctitis~~ • ~~Celiac disease~~ • ~~Autoimmune pancreatitis~~	• ~~Autoimmune thyroiditis (including Hashimoto thyroiditis)~~ • ~~Grave's or Basedow's disease~~ • ~~Diabetes mellitus type I~~ • ~~Addison's disease~~ • ~~Polyglandular autoimmune syndrome~~ • ~~Autoimmune hypophysitis~~

Neuroinflammatory disorders	*Musculoskeletal disorders*	*Skin disorders*
• *Cranial nerve neuropathy, including paralysis and paresis (e.g. Bell's palsy).* • *Optic neuritis.* • *Multiple sclerosis.* • *Transverse myelitis.* • *Guillain-Barré syndrome, including Miller Fisher syndrome and other variants.* • *Acute disseminated encephalomyelitis, including site specific variants e.g.: non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis.* • *Myasthenia gravis, including Lambert-Eaton myasthenic syndrome.* • *Demyelinating peripheral neuropathies including:* - *Chronic inflammatory demyelinating polyneuropathy,* - *Multifocal motor neuropathy* - *Polyneuropathies associated with monoclonal gammopathy.* • *Narcolepsy.*	• *Systemic lupus erythematosus and associated conditions* • *Systemic scleroderma (Systemic sclerosis), including:* - *Diffuse Scleroderma* - *CREST syndrome* • *Idiopathic inflammatory myopathies, including:* - *Dermatomyositis* - *Polymyositis* • *Anti-synthetase syndrome.* • *Rheumatoid Arthritis and associated conditions including:* - *Juvenile Idiopathic Arthritis* - *Still's disease.* • *Polymyalgia rheumatica.* • *Spondyloarthropathies, including:* - *Ankylosing Spondylitis,* - *Reactive Arthritis (Reiter's Syndrome),* - *Undifferentiated Spondyloarthritis,* - *Psoriatic Arthritis,* - *Enteropathic arthritis.* • *Relapsing Polychondritis.* • *Mixed Connective Tissue disorder.* • *Gout*	• *Psoriasis.* • *Vitiligo.* • *Erythema nodosum.* • *Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis).* • *Lichen planus.* • *Sweet's syndrome.* • *Localised Scleroderma (Morphoea).*
Vasculitis	*Blood disorders*	*Others*
• *Large vessels vasculitis including:* - *Giant Cell Arteritis (Temporal Arteritis),* - *Takayasu's Arteritis.* • *Medium sized and/or small vessels vasculitis including:* - *Polyarteritis nodosa,* - *Kawasaki's disease,* - *Microscopic Polyangiitis,* - *Wegener's Granulomatosis (granulomatosis with polyangiitis),* - *Churg–Strauss syndrome (allergic granulomatous angiitis or eosinophilic granulomatosis with polyangiitis),* - *Buerger's disease*	• *Autoimmune hemolytic anemia.* • *Autoimmune thrombocytopenia.* • *Antiphospholipid syndrome.* • *Pernicious anemia.* • *Autoimmune aplastic anemia.* • *Autoimmune neutropenia.* • *Autoimmune pancytopenia.*	• *Autoimmune glomerulonephritis including:* - *IgA nephropathy,* - *Glomerulonephritis rapidly progressive,* - *Membranous glomerulonephritis,* - *Membranoproliferative glomerulonephritis,* - *Mesangioproliferative glomerulonephritis.* - *Tubulointerstitial nephritis and uveitis syndrome.* • *Ocular autoimmune diseases including:* - *Autoimmune uveitis* - *Autoimmune retinitis.* • *Autoimmune myocarditis.* • *Sarcoidosis.*

(thromboangiitis obliterans), - *Necrotizing vasculitis (cutaneous or systemic),* - *anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified),* - *Henoch-Schonlein purpura (IgA vasculitis),* - *Behcet's syndrome,* - *Leukocytoclastic vasculitis.*		• *Stevens-Johnson syndrome.* • *Sjögren's syndrome.* • *Alopecia areata.* • *Idiopathic pulmonary fibrosis.* • *Goodpasture syndrome.* • *Raynaud's phenomenon.*
Liver disorders	***Gastrointestinal disorders***	***Endocrine disorders***
• *Autoimmune hepatitis.* • *Primary biliary cirrhosis.* • *Primary sclerosing cholangitis.* • *Autoimmune cholangitis.*	• *Inflammatory Bowel disease, including:* - *Crohn's disease,* - *Ulcerative colitis,* - *Microscopic colitis,* - *Ulcerative proctitis.* • *Celiac disease.* • *Autoimmune pancreatitis.*	• *Autoimmune thyroiditis (Hashimoto thyroiditis).* • *Grave's or Basedow's disease.* • *Diabetes mellitus type I.* • *Addison's disease.* • *Polyglandular autoimmune syndrome.* • *Autoimmune hypophysitis.*

Section 8.2.1: Pregnancy

It was clarified that female subjects from control group of HPV-039 study who are pregnant or lactating at the time of vaccination must not receive additional doses of study vaccine but may continue other study procedures at the discretion of the investigator.

Subjects from HPV group(Ctrl-HPV-039-group) who are pregnant or lactating at the time of vaccination must not receive additional doses of study vaccine but may continue other study procedures at the discretion of the investigator.

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

The time period for collecting and recording SAEs will begin at the first receipt of study vaccine (Day 1) and will end six months following administration of the last dose of study vaccine (Call 2 [Month 12]) for each ***vaccinated*** subject. See Section 8.4 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 ***for all subjects*** and recorded from the time the subject consents to participate in the study until she~~/he~~ is discharged from the study.

The table on "Reporting periods for collecting safety information" was updated to add reporting periods for each of the groups.

Section 8.3.3: Evaluation of serious adverse events

The title of this section was updated to "Evaluation of ***adverse events and*** serious adverse events." Correspondingly, the text in this section was updated to refer to AEs/SAEs rather than only SAEs.

Section 8.4.3.1: Back-up system in case the electronic reporting system does not work

The following statement was deleted: "~~The final valid information for regulatory reporting will be the information reported through the electronic SAE reporting system~~."

Section 10: Statistical methods

The statistical section was updated to update the objectives, endpoints, and to add interim analysis.

Section 10.1: Primary endpoint

- ***Safety endpoint (Ctrl-HPV-039 group)***
  - ***HPV group***
    - ***Occurrence of SAEs related to study vaccine.***

Section 10.2: Secondary endpoints

- ***Safety endpoints***
  - ***HPV group (Ctrl-HPV-039 group)***
    - Occurrence of pIMDs throughout the study.
    - Occurrence of pregnancies and pregnancy outcomes throughout the study.
    - Occurrence of SAEs.
    - Any AE/SAE leading to premature discontinuation ***from*** the study.
  - ***All subjects***
    - ***Occurrence of SAEs related to study participation.***
- ***Virological endpoints***
  - ***Incident cervical infection associated with HPV-16 and/or HPV-18 (by PCR).***
  - ***Incident cervical infection associated with any oncogenic HPV type (e.g. HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68 or combination of oncogenic HPV types; by PCR).***

Section 10.3: Tertiary endpoints

- ***Virological endpoint***
  - ***Incident infection associated with HPV-16/18, any other oncogenic type, irrespective of HPV type.***
- ***Cytological endpoints***
  - ***Any cytological abnormality (i.e., ≥ ASC-US) associated with HPV-16 and/or HPV-18 cervical infection (by PCR).***
  - ***Any cytological abnormality associated with any oncogenic HPV type (e.g. HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68 or combination of oncogenic HPV types; by PCR).***
  - ***Any cytological abnormality irrespective of the HPV type.***
- ***Histopathological endpoints***
  - ***Histopathologically-confirmed CIN1+ associated with HPV-16 and/or HPV-18 (by PCR).***
  - ***Histopathologically-confirmed CIN2+ associated with HPV-16 and/or HPV-18 (by PCR).***

    CIN2+ is defined as CIN2, CIN3, LCGIN, HCGIN, adenocarcinoma in-situ (AIS) or invasive cervical cancer.
  - ***Histopathologically-confirmed CIN1+ associated with cervical infection with any oncogenic HPV type (e.g. HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68 or combination of oncogenic HPV types; by PCR).***
  - ***Histopathologically-confirmed CIN2+ associated with cervical infection with any oncogenic HPV type (e.g. HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68 or combination of oncogenic HPV types; by PCR).***
  - ***Histopathologically-confirmed CIN1+ lesions irrespective of HPV type.***
  - ***Histopathologically-confirmed CIN2+ lesions irrespective of HPV type.***
  - ***Histopathologically-confirmed VIN1+ associated with HPV-16 and/or HPV-18 infection (by PCR).***
  - ***Histopathologically-confirmed VaIN1+ associated with HPV-16 and/or HPV-18 infection (by PCR).***
  - ***Histopathologically-confirmed VIN1+ associated with any oncogenic HPV type (e.g. HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68 or combination of oncogenic HPV types; by PCR).***
  - ***Histopathologically-confirmed VaIN1+ associated with any oncogenic HPV type (e.g. HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68 or combination of oncogenic HPV types; by PCR).***
  - ***Histopathologically-confirmed VIN1+ irrespective of HPV type.***
  - ***Histopathologically-confirmed VaIN1+ irrespective of HPV type.***

For the above mentioned tertiary endpoints, VIN (Vulvar Intraepithelial Neoplasia) is defined as VIN1+ or VIN2+, and VaIN (Vaginal Intraepithelial Neoplasia) is defined as VaIN1+ or VaIN2+.

Section 10.4: Determination of sample size

Since the objectives of the study are descriptive, the sample size for this study is not estimated using any power based computations.

Sample size for this study depends on the recruitment of the subjects who previously participated in study HPV-039. Up to 6051 subjects who participated in the HPV-039 study will be invited to participate in this study, of which 3025 subjects did not receive the HPV vaccine and are therefore eligible to receive the HPV vaccine in this study.

It is estimated that approximately 1500 to 3000 subjects from the control group in HPV-039 will effectively participate in this study and will receive at least one dose of HPV vaccine and will be available for the evaluation of the primary objective of the study.

The exact 95% confidence interval (CI) for different sample sizes and the value observed for the percentage of subjects reporting at least one related SAE is presented in the table below.

Table 13 Exact two-sided 95% CI for different sample sizes and the value observed for the percentage of subjects reporting at least one related SAE

No. of evaluable subjects to be expected (N)	Subjects who reported related SAEs post vaccination			
	n	%	Exact 95% CI	
			LL	UL
3000	1	0.0	0.0	0.2
	3	0.1	0.0	0.3
	5	0.2	0.1	0.4
	15	0.5	0.3	0.8
	30	1.0	0.7	1.4
1500	1	0.1	0.0	0.4
	3	0.2	0.0	0.6
	5	0.3	0.1	0.8
	8	0.5	0.2	1.0
	10	1.0	0.6	1.6

n = Number of subjects who reported related SAEs.
*% = (n/N) *100; LL = Lower limit; UL = Upper limit*
Reference: HPV-039 (107638): At least one SAE throughout the study period (72 Months) in HPV Group = 1.9% [95% CI: 1.4; 2.4]. At least one related SAE was reported by one subject in control group.

Section 10.5: Cohort for Analyses

Section 10.5.1: Total enrolled set

The total enrolled set includes all subjects enrolled in study HPV-092 EXT 039.

Section 10.5.2: Exposed set HPV-092

The Exposed Set (ES) includes all vaccinated subjects in HPV-092 EXT 039 for whom data were available.

Section 10.5.3: Per-protocol set (PPS-HPV-092)

The Per-Protocol Set (PPS) will include all evaluable subjects, i.e.,

- ***Who meet all eligibility criteria.***
- ***Who do not meet any of the criteria for elimination from an PPS analysis during the study (see Section 6.7.2).***
- ***For whom data concerning endpoint measures are available.***
- ***Who belong to the ATP cohort for efficacy of the study HPV-039.***

Total Vaccinated Cohort (TVC) and the ATP cohort for the analysis of efficacy in study HPV-039 will be used for the analysis of protective effect.

Section 10.6: Derived and transformed data

The follow-up time for each subject starts:

- ***at the day after first vaccination (Month 0 study HPV-039) if analyses were done on the TVC of HPV-039, or***
- ***at the day after third vaccination (Month 6 study HPV-039) if analyses were done on the ATP cohort of efficacy of HPV-039.***

The follow-up time for each subject ends:

- ***at the time of the event (e.g. the start of incident infection or the time of the histopathological endpoint),***
- ***at Visit 1 in HPV-092 study (Month 120 EXT-039) for subjects who returned for HPV-092 but did not have an event, or***
- ***last available timepoint for subjects who do not have an event and do not return for study HPV-092 EXT 039.***

Section 10.7: Analysis of demographics

Demographic characteristics (age) at first visit in study HPV-092 EXT 039 and HPV vaccination history in study HPV-039 will be summarised overall and by group using descriptive statistics. In addition, baseline characteristics (HPV DNA and serostatus) in study HPV-039 will be summarised overall and by group for subjects enrolled in study HPV-092 EXT 039.

The mean age (plus range and standard deviation) of the enrolled subjects at Dose 1 in study HPV-039 and as a whole, and per group, will be calculated.

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

Section 10.8: Analysis of safety

Analysis of safety events reported after vaccination in HPV-092 will be performed on the Exposed set HPV-092.

Related SAEs, any AEs/SAEs leading to premature discontinuation of the study, pregnancies and pIMDs up to the end of the study (Month 12) will be described in detail.

Analysis of SAEs related to study participation will be performed on the total enrolled set.

Section 10.9: Analysis of protective effect

The analysis of protective effect will be performed on the ATP cohort for efficacy and TVC of study HPV-039, considering the data from the entire follow-up period of studies HPV-039 and HPV-092 combined, i.e., pooled analyses (from Month 0 in study HPV-039 up to Month 120 in study HPV-092).

- ***Number and percentage of subjects with incident cervical infection associated with HPV-16 and HPV-18 will be summarized by group.***
- ***Number and percentage of subjects with incident cervical infection associated with any oncogenic HPV type (e.g. HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68 or combination of oncogenic HPV types; by PCR) will be summarized by group.***

Section 10.10: Exploratory analysis of long term efficacy

Analysis of long term efficacy will be exploratory. Vaccine efficacy with a 95% CI will be calculated using the conditional exact method.

Efficacy analysis of histopathological, virological and cytological endpoints associated with HPV-16/18 will be performed and stratified by HPV-16/18 serostatus (by ELISA) at baseline in the study HPV-039 with the primary analysis performed on subjects who were seronegative (by ELISA) prior to vaccination in study HPV-039 for the corresponding HPV type considered in the analysis.

Additional efficacy analyses will be performed irrespective of baseline HPV DNA, cytology and serostatus.

The vaccine efficacy for all endpoints will be calculated using a conditional exact method. This method computes an exact CI around the rate ratio (ratio of the incidence rates in the HPV group versus the Control group) and takes into account the follow-up time of the subjects within each group. Vaccine efficacy is then defined as 1 minus the rate ratio. In addition, p-values will be calculated using the Fisher's exact test.

Kaplan-Meier curves for both groups will be generated.

The analysis of long term vaccine efficacy will be performed on the ATP cohort for efficacy and TVC of study HPV-039, considering the data from the entire follow-up period of studies HPV-039 and HPV-092 combined, i.e., pooled analyses (from Month 0 in study HPV-039 up to Month 120 in study HPV-092).

Number and percentage of subjects with referrals to treatment according to local medical practice will be summarized by group.

Analyses will be further described in detail in the Statistical Analysis Plan (SAP).

Section 10.11: Interpretation of analyses

All analyses will be descriptive with the aim to characterise the observed outcomes. These descriptive analyses should be interpreted with caution. ***Refer to limitations of the study in the rationale for study design section.***

Section 10.12: 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.

Section 10.12.1: Sequence of analyses

- ***Interim analyses of available safety and protective effect data, may be performed if deemed necessary for regulatory or reporting obligations.***
- A final analysis of all data collected up to Call 2 (Month 12) will be conducted ***for all subjects.***

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

Section 10.12.2: Statistical considerations for interim analyses

All analyses in the study will be descriptive. Hence, no statistical considerations for interim analysis will be done.

Appendices

Appendix A on laboratory to be conducted in this study and Appendix B on laboratory which will perform this assays were added.