PASS INFORMATION

Title:	A prospective, multi-centre post marketing surveillance (PMS) cohort study to monitor the safety of GlaxoSmithKline (GSK) Biologicals' Human papillomavirus (HPV)-16/18 L1 VLP AS04 vaccine in female Chinese subjects aged between 9 and ***45*** years, when administered according to the Prescribing Information (PI) as per routine practice.
Protocol version identifier:	207350 (EPI-HPV-070 VS CN PMS)
Date of last version of the protocol:	Amendment 1 Final: 27 June 2018
EU PAS Register No:	Not applicable
Active substance:	HPV-16 L1 VLP protein HPV-18 L1 VLP protein
Medicinal product(s):	Bivalent human papillomavirus (HPV-16/18 L1 VLP AS04) recombinant vaccine
Product reference:	PFS or-1 dose vial
Procedure number:	To be allocated
Marketing Authorisation Holder(s) (MAH):	GlaxoSmithKline Biologicals Rue de l'Institut, 89 1330 Rixensart, Belgium
Joint PASS:	No
Research question and objectives:	To assess the risk of safety outcomes, including medically attended adverse event following immunisation (AEFIs), serious AEFIs, potential immune mediated diseases (pIMDs) and pregnancy related outcomes following vaccination with *Cervarix* according to the Prescribing Information (PI) in female Chinese subjects aged between 9 and ***45*** years.
Country of study:	China
Author(s):	**Contributing authors:** • PPD and PPD, Epidemiologists • PPD, Study Statistician • PPD, Lead Statistician • PPD ***and*** PPD, Study Delivery Lead***s*** • PPD, Safety Scientist • PPD ***and*** PPD, Safety Physician***s***

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MARKETING AUTHORISATION HOLDER

MAH(s):	GlaxoSmithKline Biologicals Rue de l'Institut, 89 1330 Rixensart, Belgium
MAH contact person:	PPD***, MD*** Director, Clinical and Epidemiology R&D Project Lead, HPV, Hepatitis and Pneumococcal vaccines GlaxoSmithKline Biologicals SA

GSK Biologicals' protocol for post-authorisation safety studies INS-BIO-PASS-1000 v16.0

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2. LIST OF ABBREVIATIONS

AE:	Adverse Event
AEFI:	Adverse Event Following Immunisation
AIT:	Autoimmune Thyroiditis
ANSM study:	French National Agency for Medicines and Health Products Safety
CEP:	Clinical and Epidemiology Plan
CIN1:	Cervical Intra epithelial Neoplasia Grade 1
CIN2:	Cervical Intra epithelial Neoplasia Grade 2
CIN3:	Cervical Intra epithelial Neoplasia Grade 3
***CNDA*:**	***National Drug Administration of China***
CPRD GOLD:	Clinical Practice Research Datalink General Practice Online Database
eCRF:	electronic Case Report Form
EPI:	Epidemiology
EoS:	End of Study
ES:	Exposed Set
GBS:	Guillain-Barré syndrome
GCP:	Good Clinical Practice
GSK:	GlaxoSmithKline
HPV:	Human Papillomavirus
HR:	Hazard Ratio
HR-HPV:	High Risk-Human Papillomavirus
IBD:	Inflammatory Bowel Disease
ICF:	Informed Consent Form
ICH:	International Conference on Harmonisation

IDM	Intensive Drug Monitoring
IEC:	Independent Ethics Committee
IRB:	Institutional Review Board
IRR:	Incidence Rate Ratio
LAR:	Legally Acceptable Representative
LMP:	Last Menstrual Period
MAH:	Marketing Authorisation Holder
MedDRA:	Medical Dictionary for Regulatory Activities
MPL:	3-O-desacyl-4'-monophosphoryl lipid A
PASS:	Post-Authorisation Safety Study
PCD:	Primary Completion Date
PI:	Prescribing Information
pIMD:	Potential Immune Mediated Disease
PMS:	Post Marketing Surveillance
PO:	Pregnancy Outcome
POV:	Points of Vaccination
PP:	Per Protocol
SA:	Spontaneous Abortion
SAE:	Serious Adverse Event
SmPC:	Summary of Product Characteristics
TSS:	Targeted Safety Study

3. RESPONSIBLE PARTIES

GSK Biologicals has the overall responsibility for the conduct of the study.

PPD (Clinical and Epidemiology R&D Project Lead) is the GSK Biologicals designated contact person for this study.

PPD (Local Medical Lead) is the local contact person for this study in China.

Refer to Annex 4 for the list of principal and coordinating investigators.

4. ABSTRACT

Title	A prospective, multi-centre post marketing surveillance (PMS) cohort study to monitor the safety of GlaxoSmithKline (GSK) Biologicals' Human papillomavirus (HPV)-16/18 L1 VLP AS04 vaccine in female Chinese subjects aged between 9 and ***45*** years, when administered according to the Prescribing Information (PI) as per routine practice.
Version and date of the protocol	Amendment 1 Final: 27 June 2018
Main author	PPD ***, MD, Director, Clinical and Epidemiology R&D Project Lead, HPV, Hepatitis and Pneumococcal vaccines, GlaxoSmithKline Biologicals SA***
Rationale and background	*Cervarix* is a prophylactic HPV (Human papillomavirus) vaccine developed by GlaxoSmithKline (GSK) Biologicals. It is based on the 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]), indicated for women aged 9 to ***45*** years of age. The post marketing data is similar to the pre-licensure data with respect to the most commonly reported adverse reactions such as injection site reactions, headache, myalgia, pyrexia and gastrointestinal symptoms. Also, additional adverse reactions of unknown frequency such as lymphadenopathy, allergic reactions and angioedema have been identified during the post marketing experience and listed in the summary of product characteristics (SmPC). Adverse events (AE) of interest identified during pre-licensure clinical development are monitored. For *Cervarix*, these AE of interest include the new onset and exacerbation of potential immune-mediated diseases (pIMDs) after vaccination, and pregnancy outcomes (PO) associated with unintended vaccine exposure during pregnancy. *Cervarix* ***was*** the first HPV vaccine licensed for use in China to help prevent cervical cancer caused by HPV types 16 and 18. The vaccine was approved by ***National Drug Administration of China*** (***CNDA***) in July 2016, for use in females between 9 and 25 years of age, for the prevention of cervical cancer, cervical intraepithelial neoplasia grade 1 (CIN1), cervical intraepithelial neoplasia grade 2, grade 3 (CIN 2/3) and adenocarcinoma in situ caused by high-risk human papillomavirus (HR-HPV) types 16 and 18. As per the ***CNDA*** regulations, GSK Biologicals should conduct an intensive drug monitoring (IDM) study following the launch

of *Cervarix* in China. In addition, the *Cervarix* approval letter specified the following points: "set up the follow-up register system following vaccination; collect related information on immune-mediated diseases, the effect on PO (including neonates' birth defect)". Hence, as per the ***CNDA*** commitment, the present study will collect data regarding the safety of the vaccine, related information on immune-mediated diseases and the effect on PO including neonatal birth defects.

In May 2018, Cervarix was also approved for use in women of age up to 45 years. Hence, this protocol is being amended to enable the inclusion of healthy female Chinese subjects 26-45 years of age into this PMS study.

Research question and objectives

The aim of this post marketing surveillance study is to assess the safety of *Cervarix* among healthy female Chinese subjects aged between 9 and ***45*** years, who were vaccinated on a voluntary basis as per standard practice.

Primary Objective:

- To assess the safety of *Cervarix* in terms of medically-attended AEFIs occurring within 30 days (Day 1-30) following each immunisation, in all enrolled subjects.

Secondary Objectives:

- To assess the safety of *Cervarix* in terms of serious AEFIs occurring during the period starting at the first immunisation and ending either 12 months following the third immunisation or 24 months following the first immunisation with *Cervarix* (whichever occurs first), in all enrolled subjects.
- To assess the safety of *Cervarix* in terms of pIMDs detected during the period starting at the first immunisation and ending either 12 months following the third immunisation or 24 months following the first immunisation with *Cervarix* (whichever occurs first), in all enrolled subjects.
- To assess the safety of *Cervarix* in terms of ***pregnancy outcomes (***PO***)*** when administered inadvertently within 60 days before pregnancy onset or any time during pregnancy.
- To assess the safety of *Cervarix* in terms of congenital anomalies when administered inadvertently within 60 days before pregnancy onset or any time during pregnancy.

Study design

- Type of design: A prospective, descriptive, self-contained, multi-centre cohort study.
- This is a Targeted Safety Study (TSS) and a Post-Authorisation Safety Study (PASS).
- Study population: The study will involve approximately 3000 female Chinese subjects aged between 9 and ***45*** years of age, vaccinated voluntarily as per standard practice.
- Data collection: electronic Case Report form (eCRF) will be used to collect data.
- Study duration: The follow-up will be performed from enrolment until 12 months following the third immunisation or 24 months following the first immunisation with *Cervarix* (whichever occurs first). This represents an individual subjects' total follow-up time, between 18 and 24 months, for subjects completing the immunisation course (3 doses) as per *Cervarix* PI schedule. Subjects who report exposure to *Cervarix* during pregnancy or pregnancy onset up to 60 days following the last immunisation will be followed-up till end of pregnancy, to observe the PO and for any possible congenital anomalies diagnosed during the first 12 months of the child's life. Thus, in such cases, an extended follow-up beyond 24 months may occur.

  – Epoch 001: Prospective data collection starting at Visit 1 (Day 1) and ending at Call 3 (either 12 months following the third immunisation or 24 months following the first immunisation, whichever occurs first).

Population

The study will involve female Chinese subjects aged between 9 and ***45*** years of age, vaccinated voluntarily as per standard practice.

Variables

Primary endpoint:

- Occurrence, intensity and causal relationship to vaccination, of medically attended AEFIs reported during the 30-day period (Day 1-30) following each immunisation with *Cervarix*.

Secondary endpoints:

- Occurrence, intensity and causal relationship to vaccination of serious AEFI reported during the period starting at the first immunisation and ending either 12 months following the third immunisation or 24 months following the first immunisation with *Cervarix*

(whichever occurs first), in all enrolled subjects.

- Occurrence, intensity and causal relationship of pIMDs detected during the period starting at the first immunisation and ending either 12 months following the third immunisation or 24 months following the first immunisation with *Cervarix* (whichever occurs first), in all enrolled subjects.
- Occurrence of PO when *Cervarix* is administered inadvertently within 60 days before pregnancy onset or any time during pregnancy.
- Occurrence of any congenital anomalies when *Cervarix* is administered inadvertently within 60 days before pregnancy onset or any time during pregnancy.

Data sources

This prospective study will collect data using active and enhanced passive surveillance methods:

- Subject interview and observation at immunisation visits (events that have occurred since the previous visits or that occur during or just after the visit)
- Structured telephone follow-up.
- Direct reporting by the subjects/subjects parent(s)/legally acceptable representative(s) [LAR(s)].
- Reporting by physician not part of this study: A physician can report a suspected AEFI by contacting the study investigator or his/her delegate.

*Note: The details of surveillance methods for data collection **are** provided in section 9.4*

Study size

The planned sample size of the study is approximately 3000 subjects.

Data analysis

The primary analysis will be based on the Exposed Set (ES).

The percentage of subjects with at least one medically attended AEFI occurring within the 30-day (Day 1-30) follow-up period will be tabulated with exact 95% CI after each vaccine dose and overall per dose.

The same tabulation will be performed for medically attended AEFI causally related to vaccination occurring within the 30-day (Day 1-30) follow-up period.

All secondary endpoints (serious AEFIs, pIMDs and POs) will be summarized by percentage of subjects reporting the endpoint with exact 95% CI.

Milestones

Data collection is planned to start ***in Quarter 2-2018*** and end in Quarter ***1-2021***. The final report of study results is planned in Quarter ***4***-2021.

Note: *The above-mentioned timelines are tentative and are subject to change*.

5. AMENDMENTS AND UPDATES

Amendment	Date	Section of study protocol	Amendment	Reason
1	27 June 2018	Title, Research question, Rationale and background, Abstract and study objectives	9-45 years of age	*Cervarix* was approved for use by the CNDA among women 9-45 years of age.

The summary of the amendment is provided in Annex 6.

6. MILESTONES

Note: The timelines mentioned below are tentative and are subject to change.

Milestone	Planned date
Start of data collection	Quarter ***2*** 2018
End of data collection	Quarter ***1 2021***
Study progress report 1	Quarter ***2*** 2019
Study progress report 2	Quarter 1 2020
Interim report 1 (for license renewal)	Quarter ***1 2019***
Final report of study results	Quarter ***4*** 2021

7. RATIONALE AND BACKGROUND

Cervarix is a prophylactic HPV (Human papillomavirus) vaccine developed by GlaxoSmithKline (GSK) Biologicals. It is based on the 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]), indicated for women aged 9 to ***45*** years of age in China.

The safety profile of *Cervarix* vaccine has been characterised during clinical development and during the post marketing phase. Characterisation of *Cervarix* safety profile during the post marketing phase was achieved through passive reporting systems for adverse events following immunisation (AEFI) and the conduct of several post marketing studies [Angelo, 2014; Stillo, 2015].

The post marketing data is similar to the pre-licensure data with respect to the most commonly reported adverse reactions such as injection site reactions, headache, myalgia, pyrexia and gastrointestinal symptoms. Also, additional adverse reactions of unknown frequency such as lymphadenopathy, allergic reactions, angioedema have been identified during the post marketing experience and listed in the summary of product characteristics (SmPC) **[***Cervarix* Summary of Product Characteristics**,** 2016].

Adverse events (AE) of interest identified during pre-licensure clinical development are monitored. For *Cervarix*, these AE of interest include the new onset and exacerbation of potential immune-mediated diseases (pIMDs) after vaccination, and pregnancy outcomes (PO) associated with unintended vaccine exposure during pregnancy ***[Lopez-Frauqued, 2017]***.

Adverse events of interest

pIMDs

pIMDs are adverse events of interest during the assessment of safety of any adjuvanted vaccine like *Cervarix*. Several post marketing studies, have assessed the risk of developing pIMDs following vaccination with *Cervarix*, as detailed below.

A retrospective, observational cohort study in the United Kingdom Clinical Practice Research Datalink General Practice Online Database (CPRD GOLD) compared 4 cohorts of 65,000 subjects each, consisting of one exposed female cohort and three unexposed cohorts-historical female, concurrent male, historical male [Willame, 2016]. An increased risk of autoimmune thyroiditis (AIT) with an incidence rate ratio (IRR) of 3.75 (95% CI 1.25-11.31) when the analysis was performed on confirmed cases was not considered significant when compared to the IRR of 1.45 with non-confirmed cases (95% CI; 0.79-2.64). In conclusion, the study did not show evidence of an increased risk of autoimmune diseases after vaccination with *Cervarix* ***[Andrews, 2017]***.

A retrospective cohort study in French health care databases performed by the French National Agency for Medicines and Health Products Safety (referred to as "ANSM study"), [ANSM, 2015] included a cohort of 2.25 million girls aged 13-16 years. Of this

enrolled cohort, 37% received HPV vaccination, of which 93% received the quadrivalent HPV vaccine *Gardasil* and 7% received *Cervarix*.

This study detected a statistically significant increased risk of Guillian Barré Syndrome (GBS) following exposure to any HPV vaccine (cases that occurred during the entire follow-up period) with adjusted Hazard Ratio (HR) of 4.00 (95% CI 1.84-8.69). The study did not identify a significant association between exposure to HPV vaccine (pooled bivalent and quadrivalent vaccine) and thyroiditis. A subgroup analysis identified a statistically significant association between vaccination with *Cervarix* and thyroiditis (possibly of autoimmune origin) with an adjusted hazard ratio (HR) of 2.43 (1.27-4.66). Also, a slight increased risk of Inflammatory Bowel Disease (IBD) was observed, following HPV vaccination (pooling *Gardasil* and *Cervarix*), with a HR of 1.19 (95% CI: 1.02-1.39). The interpretation of the analysis by brand should be performed cautiously, as a small proportion of the vaccinated cohort received *Cervarix* (7%). ***However, recent studies show that vaccination with Cervarix does not present a higher risk of thyroiditis [Colin, 2018].***

An observational case-control study performed in France, which enrolled 478 definite cases of various autoimmune diseases and matched to 1869 controls, [Grimaldi-Bensouda 2017] did not report an increased risk of autoimmune disorder following vaccination with *Cervarix*.

A prospective, community-based cluster randomized trial conducted in Finland (HPV-040 clinical trial) enrolled 32,175 subjects aged between 12 and 15 years from 33 communities (20,518 females and 11,657 males) [Lehtinen, 2016]. This study did not report any safety concerns.

Pregnancy outcomes (PO)

POs are of interest because the target population includes women of child-bearing age. The overall pregnancy data generated so far from large clinical trials, post marketing passive surveillance (including the pregnancy registry set up in the UK and in the United States from 2007 to 2015 [GlaxoSmithKline Biologicals Clinical Study Report 201337] and from the epidemiological study EPI-HPV-018 [Baril, 2015], are reassuring for the vast majority of women and their offspring, if vaccination occurred during pregnancy ***[Lopez-Frauqued, 2017]***. Data from the observational epidemiology study EPI-HPV-018 showed no increased risk of spontaneous abortion (SA), among women exposed to a single dose of *Cervarix* around 6 or 12 weeks before and up to four weeks after the first day of their Last Menstrual Period (LMP), when compared to the control group [Baril, 2015]. Also, data regarding the potential risk of SA, in the rare case that a woman received two doses of *Cervarix* in the same time period was found to be inconclusive. Considering all data available and the inconsistency in findings concerning the risk of SA when exposed to two doses, women who are pregnant or trying to become pregnant are advised to postpone vaccination until completion of pregnancy. Also, there is no evidence that suggests vaccination with *Cervarix* alters the risk of abnormal outcomes including birth defects in neonates.

Assessment of *Cervarix* reactogenicity and safety in Chinese subjects

The efficacy, immunogenicity and safety of *Cervarix* have been assessed in Chinese female subjects aged between 18 and 25 years in the clinical trial HPV-039 [Zhu, 2014]. The total vaccinated cohort included 6051 subjects, of which 3026 received *Cervarix* and 3025 received the comparator. Solicited local symptoms were reported more frequently in the *Cervarix* group than in the Control group. Fatigue, headache and fever were the most commonly reported solicited general symptoms in both the groups. Rates of grade 3 solicited symptoms and grade 3 related solicited general symptoms were low and similar between the two groups. The incidence rates of unsolicited symptoms, grade 3 unsolicited symptoms and unsolicited symptoms assessed by the investigator as related to vaccination was similar in both groups.

A total of 137 subjects reported at least one serious adverse event (SAE) [56 subjects (1.9%) in the HPV group and 81 subjects (2.7%) in the Control group]. Also, new onset chronic diseases, new onset autoimmune diseases and medically significant AEs were reported by a similar percentage of subjects in both groups. A total of 1683 pregnancies were reported in the end of study analysis. The majority of pregnancies resulted in the birth of live infants with no apparent congenital anomalies. Nine pregnancies reported during the study period resulted in an offspring with congenital anomaly of which three pregnancies (one in the HPV group and two in the Control group) were terminated by elective abortion because of congenital anomalies, one subject in the Control group reported stillbirth with congenital anomaly and five subjects in the HPV group gave birth to live infants with congenital anomalies. No pattern in the nature of the congenital anomalies was identified.

7.1. Rationale for the post marketing surveillance (PMS) study

Cervarix ***was*** the first HPV vaccine licensed for use in China to help prevent cervical cancer caused by HPV types 16 and 18. The vaccine was approved by ***National Drug Administration of China*** (***CNDA***) in July 2016, for use in females between 9 and 25 years of age, for the prevention of cervical cancer, cervical intraepithelial neoplasia grade 1 (CIN1), cervical intraepithelial neoplasia grade 2, grade 3 (CIN 2/3) and adenocarcinoma in situ caused by high-risk human papillomavirus (HR-HPV) types 16 and 18. As per the ***CNDA*** regulations, GSK Biologicals should conduct an IDM study following the launch of *Cervarix* in China. In addition, the *Cervarix* approval letter specified the following points: “set up the follow-up register system following vaccination; collect related information on immune-mediated diseases, the effect on PO (including neonates’ birth defect)”. Hence, as per the ***CNDA*** commitment, the present study will collect data regarding the safety of the vaccine, related information on immune-mediated diseases and the effect on PO including neonatal birth defects.

In May 2018, Cervarix was also approved for use in women of age up to 45 years. Hence, this protocol is being amended to enable the inclusion of healthy female Chinese subjects 26-45 years of age into this PMS study.

8. RESEARCH QUESTION AND OBJECTIVES

The aim of this post marketing surveillance study is to assess the safety of *Cervarix* among healthy female Chinese subjects aged between 9 and ***45*** years, who were vaccinated on a voluntary basis as per standard practice.

8.1. Primary objective

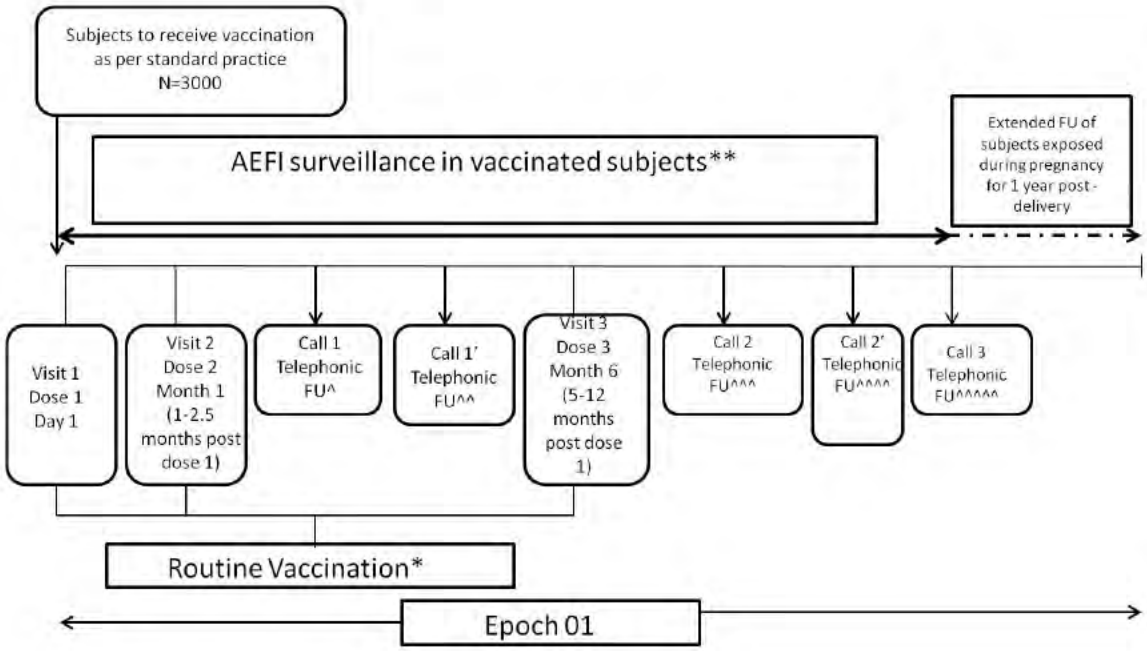
- To assess the safety of *Cervarix* in terms of medically-attended AEFIs occurring within 30 days (Day 1-30) following each immunisation, in all enrolled subjects.

8.2. Secondary objectives

- To assess the safety of *Cervarix* in terms of serious AEFIs occurring during the period starting at the first immunisation and ending either 12 months following the third immunisation or 24 months following the first immunisation with *Cervarix* (whichever occurs first), in all enrolled subjects.
- To assess the safety of *Cervarix* in terms of pIMDs detected during the period starting at the first immunisation and ending either 12 months following the third immunisation or 24 months following the first immunisation with *Cervarix* (whichever occurs first), in all enrolled subjects.
- To assess the safety of *Cervarix* in terms of PO when administered inadvertently within 60 days before pregnancy onset or any time during pregnancy.
- To assess the safety of *Cervarix* in terms of congenital anomalies when administered inadvertently within 60 days before pregnancy onset or any time during pregnancy.

9. RESEARCH METHODS

9.1. Study design



N= Number of subjects planned to be enrolled
AEFI: Adverse Event Following Immunisation
* Three doses of the vaccine administered intramuscularly according to the Prescribing Information (PI) for China
** Data pertaining to medically attended AEFIs, PO and pIMDs will be collected through
- patient interview and observation at immunisation visits (events that have occurred since the previous visits or that occur during or just after the visit),
- structured telephonic FU
- direct reporting by the subjects/subjects parent(s)/LAR(S)
- reporting by physician not part of this study: A physician can report a suspected AEFI by contacting the study investigator or his/her delegate).

FU: Follow-up
^ Call 1 will occur 31-45 days post second immunisation (if second immunisation was done according to PI schedule within 2.5 months post first immunisation) or 2.5 months post first immunisation if second immunisation was not done by Month 2.5.
^^ Call 1' will be scheduled 31-45 days post second immunisation in case the second immunisation occurs more than 2.5 months following the first immunisation
^^^ Call 2 will occur 31-45 days following the third immunisation
^^^^ Call 2' will be scheduled 31-45 days post third immunisation in case the third immunisation occurs more than 12 months following the first immunisation.
^^^^^ Call 3 will occur either 12 months following the third immunisation or 24 months following the first immunisation with *Cervarix* (whichever occurs first)

- Type of design: A prospective, descriptive, self-contained, multi-centre cohort study.
- This is a Targeted Safety Study (TSS) and a Post-Authorisation Safety Study (PASS).

- Study population: The study will involve approximately 3000 female Chinese subjects aged between 9 and ***45*** years of age, vaccinated voluntarily as per standard practice.
- *Cervarix* will be administered as per standard practice according to the PI for China (please refer to sections on dosage and administration, instructions for administration, contraindications, warning and precautions, pregnancy, nursing mothers, drug interactions in the PI) [*Cervarix* Product Information, 2016].
- Vaccination schedule: Chinese female subjects aged between 9 and ***45*** years, who consented to participate in the study, are expected to receive three doses of *Cervarix* at 0, 1 and 6 months. The second dose can be administered between 1 month and 2.5 months after the first dose and the third dose between 5 and 12 months after the first dose. The vaccine will be administered intra-muscularly, in the deltoid region of the upper arm.

  Note: Cervarix will be available for purchase at immunisation centres or Point of Vaccination (POV).
- Data collection: electronic Case Report form (eCRF) will be used to collect data.
- Study duration: The follow-up will be performed from enrolment until either 12 months following the third immunisation or 24 months following the first immunisation with *Cervarix* (whichever occurs first). This represents an individual subjects' total follow-up time between 18 and 24 months for subjects completing the immunisation course (3 doses) as per *Cervarix* PI schedule. Subjects who report exposure to *Cervarix* during pregnancy or pregnancy onset up to 60 days following the last immunisation will be followed-up till end of pregnancy, to observe the PO and for any possible congenital anomalies diagnosed during the first 12 months of the child's life. Thus, in such cases, an extended follow-up beyond 24 months may occur.
- Epoch 001: Prospective data collection (for each subject) starting at Visit 1 (Day 1) and ending either 12 months following the third immunisation or 24 months following the first immunisation with *Cervarix*, whichever occurs first.

The study cohorts and epoch foreseen in the study are presented in Table 1.

Table 1 Study groups and epochs foreseen in the study

Study Group	Number of subjects	Age (Min/Max)	Epochs
			Epoch 001
HPV group	3000	09 years - ***45*** years	x

9.1.1. Discussion of study design

This prospective, surveillance study will collect data regarding the safety of *Cervarix* vaccine. The study will be conducted in Chinese population receiving the vaccine voluntarily as per standard practice, complementing the safety and reactogenicity data collected in the clinical trial HPV-039 [Zhu, 2014].

The study will actively collect data on a large range of AEFIs, complementing passive routine pharmacovigilance from the China Adverse Drug Reaction Monitoring System (CADRMS) [Zhang, 2014].

The present study considers a follow-up of 12 months following the third immunisation with *Cervarix*, as it represents a reasonable maximum theoretical risk interval for new onset of pIMDs [Tavares, 2013].

The study is descriptive in nature, without any hypothesis testing. The conduct of a hypothesis testing study analysing the risk of a specific AEFI by comparing vaccine exposed subjects to non-exposed subjects would require electronic data collection system. This system should enable the linkage at the individual level of AEFI with the immunisation status. While such linked databases exist in some countries (for example in the UK with CPRD GOLD), they are not yet available in China. A prospective cohort design was seen as the only feasible design, given that healthcare databases which allow analysis of epidemiological association between specific AEFIs and vaccination are not available in China [Liu, 2015].

9.1.2. Feasibility assessment

Study enrolment will be initiated following the launch of *Cervarix* when vaccine uptake is confirmed. It is anticipated that enrolment will occur in approximately 10-15 vaccination centres to allow recruitment of approximately 3000 subjects. The operational feasibility will assess the capacity of the vaccination centre to perform enrolment, data collection and data entry.

9.2. Setting, monitoring populations and collaborative parties

9.2.1. Number of subjects/centres

As per the requirements of the Chinese regulation, safety information will be collected from approximately 3000 subjects. The follow-up time for each subject will be a maximum of 24 months, and in case of exposure to *Cervarix* during pregnancy, an extended follow-up until one year post-delivery will occur.

Overview of the recruitment plan:

- This prospective PMS will be conducted at multiple vaccination centres or POV in China.
- Study population will include Chinese female subjects aged between 9 and 45 years, who have satisfied the inclusion criteria at study start and who will receive voluntary vaccination at the vaccination centres or POV as per standard practice.
- *Cervarix* will be available for purchase by the subject/subjects parent(s)/LAR(s) at vaccination centres or POV.
- The recruitment will be monitored by the study monitors.

9.2.2. Inclusion criteria

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

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

- Any Chinese female subject aged between 9 and ***45*** years, at the time of first vaccination dose, who will receive voluntary vaccination.
- Subjects for whom the investigator believes that they or their parent(s)/LAR(s) can and will comply with the requirements mentioned in the protocol (e.g., return for the subsequent dose of vaccination and follow-up visits) will be included in the study.
- Written informed consent will be obtained from the subject. For subjects who are below the legal age of consent, written informed consent must be obtained from the parent(s)/LAR(s) of the subject and informed assent must be obtained from the subject according to EC requirement as well as local law.

9.2.3. Exclusion criteria

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

- Child in care.

Note: Refer to the Cervarix PI for China for complete eligibility criteria.

9.2.4. Outline of study procedures

The outline of study procedures is presented in Table 2.

Table 2 List of study procedures

Visit Timing	VISIT 1 Day 1	VISIT 2 Month 1 (range 1-2.5 months. post 1st imm. as per *Cervarix* PI)	CALL 1 31-45 days post 2nd imm. (if done within 2.5 months post 1st imm.) or 2.5 months. post 1st imm. if 2nd imm. not done by M2.5	CALL 1' 31-45 days post 2nd imm. if done > 2.5 months. post 1st imm. (ie outside *Cervarix* PI schedule)	VISIT 3 Month 6 (range 5-12 m. post 1st imm. as per *Cervarix* PI)	CALL 2 31-45 days post 3rd imm. (if done by M12) or M13 if 3rd imm. not done by M12	CALL 2' 31-45 days post 3rd imm if done > 12 months post 1st imm. (ie outside *Cervarix* PI schedule)	CALL 3 12 months post 3rd imm. (if done by M12) or M24 otherwise
	Imm 1	Imm 2	Telephone FU	Telephone FU	Imm 3	Telephone FU	Telephone FU	Telephone FU
Informed consent obtained from the subject/ subjects parent(s)/LAR(s)	●							
Informed assent from the subject	●							
Check inclusion criteria and exclusion criteria	●							
Medical history and vaccination history^	●							
History-directed physical examination	●							
Collect demography data	●							
Investigator to check for contraindication to subsequent vaccination #	●	●			●			
Vaccination with *Cervarix*^Δ	●	●			●			
Recording of medically attended AEFIs occurring within 30 days post-vaccination, by investigator		●	●	●		●	●	
Record any concomitant medication/vaccination	●	●	●	●	●	●	●	●
Reporting of serious AEFIs and any pIMDs	●	●	●	●	●	●	●	●
Reporting of pregnancies (outcomes and congenital anomalies) **	●	●	●	●	●	●	●	●
Study Conclusion^^								●

● is used to indicate a study procedure that requires documentation in the individual eCRF.
Investigator will check with the subjects, if they are pregnant or planning to get pregnant before administration of any dose of *Cervarix*

Δ is used to indicate that the procedure is performed as per routine and standard practice.
^ Vaccination history: Record any vaccinations administered in the 12 months preceding visit 1.
AEFI: Adverse Event Following Immunisation.
* The (FU) follow-up period will be extended until 1 year post-delivery to check for any neonatal birth defects/congenital anomalies.
Imm = immunisation
M: Month
** Only applies to pregnancies where it is documented that *Cervarix* was administered within 60 days before pregnancy onset or anytime during pregnancy (pregnancies starting more than 60 days after the last immunisation with *Cervarix* will not be reported).
^^ In case of pregnancy follow-up, the study conclusion for the subject and the new-born child will be the collection of information on potential congenital anomalies when the child is about 12 months old.

9.2.5. Detailed description of study procedures

9.2.5.1. Procedures prior to study participation

9.2.5.1.1. Informed consent/assent

Before performing any study procedure, the signed informed consent of the subject or subject's parent(s)/LAR needs to be obtained. Subjects who can only be enrolled in the study with the consent of the subject's LARs (e.g. minors), should be informed about the study to the extent compatible with the subject's understanding and, if capable, these subjects should sign and personally date a written informed assent. Refer to Section 10.1 for information on how to obtain informed consent/assent.

9.2.5.2. Procedures during study participation

9.2.5.2.1. Check inclusion and exclusion criteria

Check all applicable inclusion and exclusion criteria as described in Sections 9.2.2 and 9.2.3 before enrolment.

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

9.2.5.2.2. Collect medical history and perform history directed physical examination and recent vaccination history at enrolment

Record any pre-existing conditions as reported by the subject at the moment of the interview in the eCRF. Pre-existing conditions include, but are not limited to:

- spleen dysfunction
- chronic respiratory, heart, renal and liver diseases
- immunosuppression
- immune system, neurological, haematological, metabolic and cardiovascular disorders

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

Record any vaccine administered within 12 months preceding visit 1, as reported by the subject at the moment of the interview in the eCRF and check if the administration is recorded in the subject's vaccination record.

9.2.5.2.3. Collect demography data at enrolment

Record demographic data on age as reported by the subject at the moment of the interview in the eCRF.

9.2.5.2.4. Investigator to check for contraindication to vaccination

The investigator will check with the subjects if they are pregnant, or planning to get pregnant before administration of any dose of *Cervarix*. He/she will also check for any contraindication such as known hypersensitivity to the active substance or any of the excipients in the vaccine. Also, he/she will record any reason for not administering the vaccine. The collected data will be recorded in the eCRF.

9.2.5.2.5. Vaccination

Record *Cervarix* vaccine administration in the eCRF at each immunisation visit. In case the investigator or his/her delegate is informed that a subject has received the second and/or third immunisation with *Cervarix* in a centre other than the centre of first immunisation, the investigator or his/her delegate will try to collect information regarding these immunisations retrospectively. The investigator or his/her delegate will also try to schedule the surveillance calls, whenever possible.

Note: Cervarix will be administered as per standard practice according to the PI for China.

9.2.5.2.6. Record any concomitant medication/vaccination

For all subjects, the investigator will record any other vaccine administered, as reported by the subject, during the period starting at the first immunisation and ending either 12 months following the third immunisation or 24 months following the first immunisation with *Cervarix* (whichever occurs first), in the eCRF. The investigator or his/her delegate will check if the administration is recorded in the subject's vaccination record.

For all subjects, use of any medication that may help to explain the occurrence of an AEFI that may have caused or were used to treat this event will be recorded.

For pregnant subjects, medications and vaccines administered during pregnancy will also be recorded.

9.2.5.2.7. Investigator to record any medically attended AEFIs occurring within 30 days post-vaccination

The investigator will record any medically attended AEFIs that occur within 30 days post each immunisation with *Cervarix* as reported by the subject/subjects parent/LAR. The data will be recorded in the eCRF.

9.2.5.2.8. Reporting of serious AEFIs and any pIMDs

The investigator will record any serious AEFIs or pIMDs reported by the subject or by the physician during any of the immunisation visits or telephone calls. The reporting period will begin from the first immunisation and will end either 12 months following the third immunisation or 24 months following the first immunisation with *Cervarix* (whichever occurs first). A follow-up may be required to collect the relevant medical data. The data collected will be recorded in the eCRF.

9.2.5.2.9. Reporting of pregnancies (outcomes and congenital anomalies)

The investigator will record any PO or congenital anomalies only in cases where it is documented that *Cervarix* was administered within 60 days before pregnancy onset or anytime during pregnancy. Pregnancies that occur 60 days following the last immunisation with *Cervarix* will not be reported. Pregnant women will be followed-up until end of pregnancy to determine the PO, which will be documented. Any congenital anomaly diagnosed during the first 12 months of the child's life will be recorded in the eCRF.

9.2.5.2.10. Study Conclusion

The follow-up will be performed either till 12 months following the third immunisation or 24 months following the first immunisation with *Cervarix* (whichever occurs first). Subjects who report exposure to *Cervarix* during pregnancy or pregnancy onset up to 60 days following last immunisation will be followed-up till end of pregnancy, to observe the PO. An extended follow-up beyond 24 months may occur to look for any possible congenital anomalies diagnosed during the first 12 months of the child's life.

9.3. Variables

9.3.1. Safety definitions

9.3.1.1. Adverse event following immunisation (AEFI)

Any untoward medical occurrence in a subject which follows immunisation, whether or not considered related to the vaccine.

An adverse event following immunisation (AEFI) 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 vaccine. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

9.3.1.2. Medically attended AEFI

Medically attended AEFIs are defined as events leading to an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. If a medically-attended AEFI leads to hospitalisation (or meets any other serious AEFI criteria), it will be reported as serious AEFI.

9.3.1.3. Serious AEFI

A serious AEFI is any untoward medical occurrence that:

- Results in death.
- Is life-threatening
  - 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.
- Requires hospitalisation or prolongation of existing hospitalisation.
  - In general, hospitalisation signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are also considered AEFIs. 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 AEFI should be considered serious. Hospitalisation for elective treatment of a pre-existing condition (known/diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an AEFI.
- Results in disability/incapacity, or
  - NB: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect in the offspring of a subject.

9.3.1.4. Potential immune mediated disease (pIMD)

Potential immune mediated diseases (pIMDs) are a subset of AEFIs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. A list is provided in Table 3.

Table 3 List of pIMDs

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-Barrė 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), • Necrotising vasculitis (cutaneous or systemic), • anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), • Henoch-Schonlein purpura (IgA vasculitis), • Behcet's syndrome, • Leukocytoclastic vasculitis.	• Autoimmune haemolytic 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.

9.3.2. Endpoints

9.3.2.1. Primary endpoint

- Occurrence, intensity and causal relationship to vaccination, of medically attended AEFIs reported during the 30-day period (Day 1-30) following each immunisation with *Cervarix*.

9.3.2.2. Secondary endpoints

- Occurrence, intensity and causal relationship to vaccination of serious AEFI reported during the period starting at the first immunisation and ending either 12 months following the third immunisation or 24 months following the first immunisation with *Cervarix* (whichever occurs first), in all enrolled subjects.
- Occurrence, intensity and causal relationship of pIMDs detected during the period starting at the first immunisation and ending either 12 months following the third immunisation or 24 months following the first immunisation with *Cervarix* (whichever occurs first), in all enrolled subjects.
- Occurrence of PO when *Cervarix* is administered inadvertently within 60 days before pregnancy onset or any time during pregnancy.
- Occurrence of any congenital anomalies when *Cervarix* is administered inadvertently within 60 days before pregnancy onset or any time during pregnancy.

9.4. Data sources

This prospective study will collect data using active and enhanced passive surveillance methods. Following methods will be used to collect data:

- Patient interview and observation at immunisation visits (events that have occurred since the previous visits or that occur during or just after the visit).
  - During the immunisation visit, the investigator will enquire about the occurrence of AEFI or pregnancies (as defined in section 9.3.2) that may have occurred

since the last contact with the subject. The investigator will also report any relevant AEFI that may occur during the visit.

- Structured telephone follow-up: The investigator or other delegated study team member will contact the subject by phone at specific time points to enquire about AEFI and pregnancies (as defined in section 9.3.2). Three rounds of telephone follow-up calls will be scheduled. Additional calls will be organised if any immunisations occur outside the schedule defined in the *Cervarix* PI for China, as detailed below:
  - Call 1 will occur between 31-45 days following the second immunisation or about 2.5 months following the first immunisation with *Cervarix* (if the second immunisation was not performed within 2.5 months).

    Note: In case the second immunisation occurs more than 2.5 months following the first immunisation, Call 1' will be scheduled 31-45 days post second immunisation.
  - Call 2 will occur between 31-45 days following the third immunisation with Cervarix.

    Note: In case the third immunisation occurs more than 12 months following the first immunisation, Call 2' will be scheduled 31-45 days post third immunisation.
  - Call 3 will occur either 12 months following the third immunisation or 24 months following the first immunisation (whichever occurs first).
- For each planned contact, there should be at least three documented attempts to reach the subject. If any clinically relevant event is reported at the time of the contact, and the event has not been recorded so far, then a follow-up will be made to collect the relevant medical data.
- Direct reporting by the subject/subjects parent(s)/LAR(s).
  - A phone contact number/e-mail id will be provided to the subjects to report AEFI and pregnancy which were not recorded previously by the investigator.
- Reporting by physician not part of this study: A physician can report a suspected AEFI by contacting the study investigator or his/her delegate.

9.4.1. Baseline information

At the time of the enrolment, the following information will be collected:

- Enrolment date
- Vaccination centre
- Basic demographic information of subjects such as age
- Medical history and recent vaccination history
- Concomitant medication/vaccination
- Occurrence of serious AEFI or pIMD requiring medical attention during the visit.

9.4.2. Follow-up information

The follow-up information will be collected at immunisation visits, at telephone follow-up contacts defined in the protocol and through spontaneous reporting by the patient or his LAR or a physician. This will include information about:

- concomitant medication/vaccination
- occurrence of medically attended AEFI occurring during the 30 days following each immunisation with *Cervarix*
- occurrence of serious AEFI during the period starting at the first immunisation and ending either 12 months following the third immunisation or 24 months following the first immunisation with *Cervarix* (whichever occurs first).
- occurrence of pIMD during the period starting at the first immunisation and ending either12 months following the third immunisation or 24 months following the first immunisation with *Cervarix* (whichever occurs first).
- exposure to *Cervarix* during pregnancy or pregnancy onset within 60 days following any immunisation, as well as the related PO and presence of congenital anomalies.

9.4.3. Safety events

All events described under section 9.3, exposure to *Cervarix* during pregnancy or pregnancy onset within 60 days following any immunisation, as well as the related PO and presence of congenital anomalies are described as safety events.

9.5. Study size

9.5.1. Overall sample size estimation

As per the Chinese regulation requirement, safety information will be collected from approximately 3000 subjects for the PMS study [3000 subjects is the minimum target for the Exposed Set (ES)].

Table 4 presents the exact two-sided 95% CI of the proportion of subjects reporting medically attended AEFI for a sample size of 3000 subjects. The percentage of subjects reporting at least one medically significant AE was 6.1% [95% CI; 5.3%-7.1%] during a follow-up period of 72 months in the efficacy clinical trial conducted in China [Zhu, 2014]. The follow-up of the medically attended AEFI for this study will be 30 days after each dose of the vaccination, therefore 90 days in total after 3 doses of the vaccination. Under a conservative assumption of constant incidence of AE's during the 72 months of follow-up period, the percentage of subjects reporting at least one medically attended AEFI during the 90-day follow-up period of this study is assumed to be 0.25%. Since decreasing incidence rate with time from vaccination is plausible, a range of percentage from 0.20 to 1.0% is presented in Table 4.

Table 4 Exact two-sided 95 percent CI for a sample size of 3000 according to different proportion of subjects reporting medically attended AEFI 30 days after each dose of vaccination

Proportion (number of subjects reporting at least one medically attended AE or SAE)	Exact two-sided 95% CI	
	Lower limit (LL)	Upper limit (UL)
0.20% (6)	0.07%	0.43%
0.25% (7.5)	0.10%	0.50%
0.30% (9)	0.14%	0.57%
0.35% (10.5)	0.17%	0.63%
0.50% (15)	0.28%	0.82%
1.00% (30)	0.68%	1.42%

Table 5 presents the exact two-sided 95% CI of the proportion of subjects reporting serious AEFI for a sample size of 3000 subjects. The percentage of subjects reporting at least one SAE was 1.9% [95% CI; 1.4%-2.4%] during a follow-up period of 72 months in the efficacy clinical trial conducted in China [Zhu, 2014]. The follow up of serious AEFI for this study will be at least 18 months after the first dose of vaccination for a subject completing the full vaccination course (three doses). Therefore, the percentage of subjects reporting serious AEFI is assumed to be 0.5%.

Table 5 Exact two-sided 95 percent CI for a sample size of 3000 according to different proportion of subjects reporting serious AEFIs

Proportion (number of subjects reporting at least one medically attended AE or SAE)	Exact two-sided 95% CI	
	Lower limit (LL)	Upper limit (UL)
0.50% (15)	0.28%	0.82%
1.00% (30)	0.68%	1.42%
1.50% (45)	1.10%	2.00%
2.00% (60)	1.53%	2.57%

9.6. Data management

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

Adverse events and concomitant medications terms will be coded using medical dictionary for regulatory activities (MedDRA) and validated medication dictionary, such as GSK drug dictionary (GSKDRUG). In all cases, Personally Identifiable Information (PII) will not be collected nor transmitted to GSK (refer to Annex 2 for definition). Subject data necessary for analysis and reporting will be entered 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 or his/her delegate at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

Once the database is archived and the study report is complete and approved by all responsible parties, the participating investigator will be provided with a CD-ROM of the final version of the data generated from the investigational site.

9.7. Data analysis

All the statistical calculations will be done in SAS 9.2 or higher.

9.8. Analysis set

9.8.1. Exposed Set

The ES will include all subjects exposed to *Cervarix*.

9.9. Statistical analyses

9.9.1. Analysis of demographics/baseline characteristics

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

The vaccination history of the vaccinated subjects will be also presented.

The distribution of subjects enrolled in different centres will be tabulated.

9.9.2. Analysis for Primary endpoint

The analysis will be based on the ES.

The percentage of subjects with at least one medically attended AEFI occurring within the 30-day (Day 1-30) follow-up period will be tabulated with exact 95% CI after each vaccine dose and overall per dose.

The same tabulation will be performed for medically attended AEFI causally related to vaccination occurring within the 30-day (Day 1-30) follow-up period.

9.9.3. Analysis for Secondary endpoints

The occurrence of serious AEFIs will be assessed throughout the entire follow-up period in all enrolled subjects. Serious AEFIs will be further evaluated for their clinical relevance and relationship to vaccination.

The occurrence of pIMD(s) will be collected and summarized through the entire follow-up period in all enrolled subjects.

The PO and congenital anomalies will be summarized when *Cervarix* is administered within 60 days before pregnancy onset or any time during pregnancy. In addition, the PO

will be summarized by the time of the vaccination, such as vaccination before the pregnancy, vaccination during the first trimester of the pregnancy, vaccination during the second trimester of the pregnancy etc.

All secondary endpoints (serious AEFIs, pIMDs and POs) will be summarized by percentage of subjects reporting the endpoint with exact 95% CI.

9.10. Conduct of analysis

9.10.1. Sequence of analyses

A final analysis of all data collected up to either 12 months following the third immunisation or 24 months following the first immunisation with *Cervarix* (whichever occurs first), will be conducted. This will include final analysis of safety. In case of regulatory submission before license renewal, interim report(s)***/progress report(s)*** will be prepared. The statistical analyses for the interim report preparation will be performed on data collected until early 2019. The interim analyses will be described in the statistical analysis plan (SAP).

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

9.10.2. Statistical considerations for interim analyses

Following study start, yearly progress reports (update on recruitment, follow-up status, and any other data that can be included such as simple safety description data) will be submitted to the regulatory authorities.

A comprehensive report will be prepared and submitted as part of the license renewal application process planned in ***2019***. An interim analysis is anticipated for the preparation of this comprehensive report. The trigger for analysis will be the data lock point (DLP) required to meet the timelines for report preparation. Since there is no hypothesis testing, no adjustment of type I error is required. A final report will be prepared when the follow-up of all enrolled subjects has been completed.

9.11. Quality control

To comply with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) or other applicable guidelines administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality, ownership and publications must be met.

9.11.1. Monitoring by GSK Biologicals site monitors or delegates

- Monitoring visits by a GSK Site Monitor or delegate are for the purpose of confirming that GSK Biologicals' sponsored studies are being conducted in accordance with the ethical principles that have their origins in the Declaration of

Helsinki and that are consistent with GCP or other applicable guidelines and the applicable regulatory requirement(s) (verifying continuing compliance with the protocol, amendment(s), verifying that the site staff and facilities continue to be adequate to conduct the study).

- GSK will monitor the study to verify that, amongst others, the:
  - Data are authentic, accurate, and complete.
  - Safety and rights of study participants 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) agree 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 an eCRF review and a Source Document Verification (SDV). By SDV GSK understands 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 monitor's and 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.

For eCRF, the monitor will freeze the screen, after she/he estimates that data are authentic, accurate and complete.

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.

9.11.2. Archiving of data at study sites

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. However, the investigator/institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by ICH GCP or other applicable guidelines, any institutional requirements or applicable laws or regulations, or GSK standards/procedures.

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

9.11.3. Audits

To ensure compliance with GCP or other applicable guidelines 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. The Principal Investigator has to inform GSK (study sponsor) of any external audit/inspection. 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.

9.12. Limitations of the research methods

The study population may not be representative of the entire population eligible for vaccination. This is because the administration of vaccine will not be part of the universal vaccination programme but performed on a voluntary basis as per standard practice in vaccination centres. In particular, there may be an uneven age distribution of the study participants.

The study is descriptive and is not designed to assess an epidemiological association between a given adverse event and vaccination.

The sample size of approximately 3000 subjects meets the requirements of the Chinese regulation. Due to the low incidence of pIMDs (generally < 40 per 100,000) in adolescent girls and young women and the limited number of expected exposure to *Cervarix* during pregnancy, the study will be limited for the detection of these rare events.

The study will only enroll subjects vaccinated with *Cervarix* and thus will not have a control group. Therefore, the observed frequency of AEFI will be interpreted in terms of safety data generated in clinical trials, post-licensure epidemiological studies and background incidence rates reported in the literature.

9.13. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

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

The study will be conducted in accordance with the ICH Guideline for GCP, Guidelines for Good Pharmacoepidemiology Practices (GPP) [ISPE, 2015], other applicable guidelines, all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

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

GSK will obtain favourable opinion/approval to conduct the study prior to a site initiating the study in any country, according to local requirements, or will document that neither a favourable opinion nor an approval to conduct the study is needed.

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

- Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subjects/Subjects' parent(s)/LAR(s) informed consent.
- Investigator reporting requirements as stated in the protocol.

GSK Biologicals will provide full details of the above procedures to the investigator verbally as well as in writing.

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

GSK Biologicals will prepare a model ICF which will embody the applicable ICH GCP or other applicable guidelines, and GSK Biologicals required elements. While it is strongly recommended that this model ICF 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.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The definitions of the safety endpoints are provided in section 9.3.1.

11.1. Detecting and recording medically attended AEFIs, serious AEFIs, pIMDs and pregnancies

11.1.1. Prompt reporting of medically attended AEFIs, serious AEFIs, pIMDs and pregnancy to GSK Biologicals

Any causally related medically attended AEFIs occurring within 30 days following each immunisation with *Cervarix*, serious AEFIs, pIMDs and pregnancies will be reported promptly to GSK as described in Table 6 once the investigator determines that the event meets the protocol definition.

Table 6 Time frames for submitting medically attended AEFIs, serious AEFIs, pIMDs and pregnancy reports to GSK Biologicals

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
Causally related medically attended AEFIs	5 days*	Expedited AEFI screen	5 days*	Expedited AEFI screen
All serious AEFIs	24 hours*	Expedited AEFI screen	24 hours*	Expedited AEFI screen
pIMDs	24 hours*	Expedited AEFI screen	24 hours*	Expedited AEFI screen
Pregnancies	24 hours*	Pregnancy report form	24 hours*	Pregnancy report form

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

In case the electronic reporting system is temporarily unavailable, a back-up system is in place. Please refer to Section 11.1.4.1 for a detailed description.

Study Contact for Reporting serious AEFIs
Please see the Sponsor Information Sheet for contact details of who to contact in the event of a serious AEFI. In addition, the GSK Biologicals Clinical Safety Physician can be contacted in an emergency.
Back-up study contact for reporting serious AEFIs
GSK Biologicals Clinical Safety & Pharmacovigilance **Fax:** PPD / PPD **China Pharmacovigilance** **Fax:** PPD **Email:** PPD **Back-up e-mail ID** PPD **24/24 hour and 7/7 day availability**

11.1.2. Evaluation of AEFIs

11.1.2.1. Assessment of intensity

The investigator will assess the maximum intensity that occurred over the duration of the event for all medically attended AEFIs, serious AEFIs and pIMDs reported 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 AEFI/pIMD which is easily tolerated by the study participant, causing minimal discomfort and not interfering with everyday activities.
2 (moderate)	=	An AEFI/pIMD which is sufficiently discomforting to interfere with normal everyday activities.
3 (severe)	=	An AEFI/pIMD which prevents normal, everyday activities (in a young child, such an AEFI would, for example, prevent attendance at school/kindergarten/a day-care centre and would cause the parent(s)/LAR(s) to seek medical advice.

11.1.2.2. Assessment of causality

In case of any medically attended AEFI occurring within the 30 days following each immunisation with *Cervarix*, serious AEFI, pIMDs or PO (elective abortion for medical reasons or spontaneous abortion or congenital anomaly), the investigator should assess the causality. The investigator will use clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying diseases, other concomitant therapy and other risk factors will be considered and investigated. The investigator will

also consult the Product Information (Summary of Product Characteristics) to determine his/her assessment.

There may be situations when a serious AEFI 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 serious AEFI to GSK Biologicals. The investigator may change his/ her opinion of causality in light of follow-up information and update the serious AEFI information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

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

Is there a reasonable possibility that the AEFI/serious AEFI/pIMD may have been caused by the vaccine?

YES	:	There is a reasonable possibility that the vaccine contributed to the AEFI/pIMD.
NO	:	There is no reasonable possibility that the vaccine contributed to the AEFI/pIMD. There are other, more likely causes and administration of the vaccine is not suspected to have contributed to the AEFI/pIMD.

Possible contributing factors include:

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

11.1.3. Regulatory reporting requirements for AEFIs, pIMDs and POs

The investigator will promptly report all AEFIs (medically attended and serious), pIMDs and POs to GSK in accordance with the procedures detailed in Section 11.1.1. 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. Prompt notification of serious AEFIs by the investigator to the Study Contact for Reporting serious AEFIs is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

11.1.4. Completion and transmission of AEFIs, pIMDs and POs report to GSK Biologicals

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

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

11.1.4.1. Back-up system in case the electronic AEFI, pIMD and PO reporting system does not work

If the AEFI, pIMD and/or PO reporting system has been down for 24 hours, the investigator or delegate should fax an AEFI/pIMD report form or pregnancy report form directly to the GSK Central Safety department (please refer to Section 11.1.1) within 24 hours. The maximum timeline for reporting AEFIs/pIMDs/POs to central safety is therefore 48 hours.

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

As soon as the electronic reporting system is working again, the investigator or delegate must update the expedited AEFI screens and/or pregnancy report forms in the eCRF within 24 hours.

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

When additional information is received on an AEFI/pIMD/PO after freezing of the subject's eCRF, new or updated information is to be recorded on the paper AEFI/pIMD/pregnancy Report Form, with all changes signed and dated by the investigator. The updated AEFI/pIMD/pregnancy Report Form should be resent to GSK Biologicals by facsimile WITHIN 24 HOURS of receipt of the follow-up information.

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

In the event of a death, determined by the investigator to be related to vaccination, completion of expedited AEFI screens in the eCRF/sending of the fax (if electronic serious AEFI reporting system does not work or after freezing of the subject's eCRF) must be accompanied by telephone call to the study contact for reporting serious AEFIs.

11.1.5. Follow-up of AEFI and serious AEFI

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

All serious AEFIs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the end of the study.

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

Investigators will follow-up subjects:

- With serious AEFIs and other AEFIs until the event has resolved, subsided, stabilised, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up/has terminated follow-up.

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

GSK Biologicals may request that, the investigator perform or arrange for the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible the nature and/or causality of the AEFI or serious AEFI. The investigator is obliged to assist.

11.2. Treatment of AEFI

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

11.2.1. Time period for detecting and recording medically attended AEFIs, serious AEFIs, pIMDs and pregnancies

The reporting period of AEFIs will be as per AEFI guidelines and IDM regulations [AEFI, 2010, IDM, 2013].

An overview of the protocol-required reporting periods for medically attended AEFIs, serious AEFIs, pregnancy, PO, congenital anomalies and pIMDs are given in Table 7.

Table 7 Reporting periods for medically attended AEFIs, serious AEFIs, pIMDs and pregnancy outcomes

Study activity	V1	V2	30 days post V2	Call 1 FU (Telephone interview)	Call 1' FU (Telephone interview)	V3	30 days post V3	Call 2 FU (Telephone interview)	Call 2' FU (Telephone interview)	Call 3 FU (Telephone interview)	End of pregnancy	12 months post-delivery (live births)
	D1	M1	M2	31-45 days post 2nd immunisation (if done within 2.5 months post 1st imm.) or 2.5 months post 1st immunisation if 2nd immunisation was not done by M 2.5	31-45 days post V2. if done > 2.5 m. after V1. (ie outside *Cervarix* PI schedule)	M6	M7	31-45 days post 3rd immunisation	31-45 days post V3 if done > 12 m after V1 (ie outside *Cervarix* PI schedule)	12 months post V3 (if done by M12) or M 24		
Medically attended AEFIs reported during the 30-day period (day 1-30) following each immunisation with *Cervarix*												
Serious AEFIs reported during the study period												
pIMDs reported during the study period												
Reporting of pregnancy (from enrolment until 60 days post dose 3)												

Study activity	V1	V2	30 days post V2	Call 1 FU (Telephone interview)	Call 1' FU (Telephone interview)	V3	30 days post V3	Call 2 FU (Telephone interview)	Call 2' FU (Telephone interview)	Call 3 FU (Telephone interview)	End of pregnancy	12 months post-delivery (live births)
	D1	M1	M2	31-45 days post 2nd immunisation (if done within 2.5 months post 1st imm.) or 2.5 months post 1st immunisation if 2nd immunisation was not done by M 2.5	31-45 days post V2. if done > 2.5 m. after V1. (ie outside *Cervarix* PI schedule)	M6	M7	31-45 days post 3rd immunisation	31-45 days post V3 if done > 12 m after V1 (ie outside *Cervarix* PI schedule)	12 months post V3 (if done by M12) or M 24		
Reporting of pregnancy outcome												
Reporting of congenital anomalies (from enrolment until 12 months post-delivery)												

V: Vaccine dose; D: Day; M: Month; FU: Follow-up; AEFI: Adverse Event Following Immunisation;
* Pregnancy outcomes will be reported within 1 month post-delivery. 1 year follow-up post-delivery will occur to look for any congenital anomalies.

Type	Medically attended AEFIs/serious AEFIs/pIMDs/PO
Method for reporting medically attended AEFIs, serious AEFIs, pIMDs, pregnancies, PO and birth defects/congenital anomalies	• Patient interview and observation at immunisation visits (events that have occurred since the previous visits or that occur during or just after the visit). • Structured telephone follow-up (events that have occurred after administration of the complete *Cervarix* course). • Direct reporting by the subject/subjects parent(s)/LAR(s). • Reporting by physician not part of this study: A physician can report a suspected AEFI by contacting the study investigator or his/her delegate).

11.3. Reporting and follow-up of AEFIs, serious AEFIs, pIMD and pregnancies

GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies and will comply with the Chinese guidelines of National Monitoring Program for Suspected Adverse Event Following Immunisation (AEFI).

- To provide real-time safety information, medically-attended AEFIs, serious AEFIs, pIMDs and pregnancies will be reviewed on a continuous basis by GSK safety physicians.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1. Posting of information on publicly available registers and publication policy

Study information from this protocol will be posted on publicly available clinical trial registers following finalisation of the protocol and, whenever possible, before initiation of enrolment.

Summary results of observational studies that are designed to inform the safety, effectiveness, including cost-effectiveness, of GSK vaccines/products (and other informative studies) are publicly registered within 8 months of completion of the analysis. GSK also aims to publish the results of these studies in the searchable, peer-reviewed scientific literature; manuscripts are submitted within 18 months of the completion of the analysis. At the time of publication, this protocol will be fully disclosed.

12.2. Provision of study results to investigators

Where required by applicable regulatory requirements, the investigator signatory will be requested 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-agreed location.

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Annex 1 List of stand-alone documents

No.	Document Reference No	Date	Title
1	207350	27 June 2018	List of stand-alone documents
2	207350	27 June 2018	Glossary of terms
3	207350	27 June 2018	Trademarks
4	207350	27 June 2018	List of principal and coordinating investigators
5	207350	27 June 2018	Sponsor Information
6	***207350***	***27 June 2018***	***Amendments to the protocol***
7	207350	27 June 2018	Feasibility assessment
8	207350	27 June 2018	Protocol Amendment 1 Sponsor Signatory Approval
9	207350	27 June 2018	Protocol Amendment 1 Investigator Agreement
10	207350	27 June 2018	ENCePP checklist for study protocols

Annex 2 Glossary of terms

Adverse event following immunisation:	Any untoward medical occurrence in a subject which follows immunisation, whether or not considered related to the vaccine. An adverse event following immunisation (AEFI) 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/vaccine. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.
Child in care:	A child who has been placed under the control or protection of an agency, organisation, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legal guardian.
Coded:	Data from which personal identifier information has been removed and replaced by a key. These data are not anonymised since a decode listing exists and it is therefore possible to identify the patient under certain circumstances by an authorised or legally appointed third party data custodian, or by the original holder of the data.
Commitment:	Agreement made with Regulatory Authorities as specific condition of regulatory approval and authorisation, either made at the time of product approval or during the lifecycle of the approved product.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Epidemiology study:	An observational study or an interventional study without administration of medicinal products as described in a research protocol.
End of Study: **(Synonym of End of Trial)**	For studies without collection of human biological samples or imaging data EoS is the Last Subject Last Visit (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 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, immunogenicity follow-up, safety follow-up, ESFU, follow-up.
eTrack:	GSK's tracking tool for clinical/epidemiology trials.
Legally acceptable representative: **(The terms legal representative or legally authorized representative are used in some settings.)**	An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the trial.
Medically attended AEFI:	Defined as events leading to an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. If a medically-attended AEFI leads to hospitalisation (or meets any other Serious AEFI criteria), it will be reported as Serious AEFI.
Non-interventional (observational) Human Subject Research:	Studies where medicinal products, should they be administered, are prescribed in normal (routine) medical practice. No medical care or medical/scientific procedures as required in a research protocol are administered to participants except as part of routine medical care.
Post Marketing Surveillance (PMS study):	Routine country-specific post vaccine/drug approval surveillance study mandated by regulatory authorities that applies an observational approach for the collection of safety information from subjects in a normal healthcare setting.
Prospective study:	A study in which the subjects/cases are identified and then followed forward in time in order to address one or more study objectives.

Research protocol:	A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.
Self-contained study:	Study with objectives not linked to the data of another study.
Serious adverse event:	Any untoward medical occurrence in a subject that: results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, or is a congenital anomaly/birth defect in the offspring of a study subject.
Study population:	Sample of population of interest.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the clinical/ epidemiological study, or a person about whom some medical information has been recorded in a database.
Surveillance:	The ongoing systematic collection, collation, analysis, and interpretation of descriptive epidemiological health data on a specific disease. Surveillance can monitor incidence and/or prevalence, and/or inform about when and where health problems are occurring and who is affected.

Annex 3 Trademarks

The following trademarks are used in the present protocol.

Note: In the body of the protocol (including the abstract), the names of the vaccines will be written without the superscript symbol ™ or ® and in *italics*.

Trademarks of the GSK group of companies	Generic description
Cervarix™	Human papillomavirus (HPV) vaccine Types 16 and 18 (recombinant, AS04-adjuvanted)

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

Annex 4 List of principal and coordinating investigators

The table below presents the key sub-investigators. The contact details and list of all investigators are available upon request.

Investigator's name	*Sub-investigators*	*Center number**	*Investigational site (institution /hospital)*	*Location (complete address)*	*Phone number Fax number*
Hongjie Yu	*Shaojie Lin*	PPD	*Shenzhen Longgang Center for Disease Control and Prevention*	*No. 39, Hexie Road, Longgang District, Shenzhen, China*	*Phone:* PPD *Fax:* PPD
	Qizhang Wang	PPD	*Shanghai Pudong New Area Centre for Disease Control and Prevention*	*NO.3039 Zhangyang Road, Pudong New Area District, Shanghai, China*	*Phone:* PPD *Fax:* PPD
	Qinghai Wang	PPD	*Beijing Xicheng Center for Disease Control and Prevention*	*Public Health Building, No.38, Deshengmenwai Street, Xicheng District, Beijing, China*	*Phone:* PPD *Fax:* PPD
	Taoying Zhu	PPD	*Chengdu City Wuhou District Center for Disease Control and Prevention*	*No.6 Guangfuqiao Street, Wuhou District, Chengdu City, Sichuan Province, China*	*Phone:* PPD *Fax:* PPD

* GSK Biologicals' assigned center number

Annex 5 Sponsor Information

Sponsor:

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

Refer to the local study contact information document.

Study Contact for Reporting of a Serious Adverse Event Following Immunisation (Serious AEFI):

GSK Biologicals Central Back-up Study Contact for Reporting serious AEFIs: refer to protocol Section 10 Management and reporting of adverse events /adverse reactions.

Annex 6 Amendments and administrative changes to the protocol

GlaxoSmithKline Biologicals SA Vaccines R & D Protocol Amendment 1	
eTrack study number and Abbreviated Title:	207350 (EPI-HPV-070 VS CN PMS)
Amendment number:	Amendment 1 Final
Amendment date:	27 June 2018
Co-ordinating author:	PPD, Scientific Writer
Rationale/background for changes: In May 2018, *Cervarix* was approved for use in women of age up to 45 years. Hence, this protocol is being amended to enable the inclusion of healthy female Chinese subjects 26-45 years of age into this PMS study.	

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

- Title: A prospective, multi-centre post marketing surveillance (PMS) cohort study to monitor the safety of GlaxoSmithKline (GSK) Biologicals' Human papillomavirus (HPV)-16/18 L1 VLP AS04 vaccine in female Chinese subjects aged between 9 and ~~25~~ ***45*** years, when administered according to the Prescribing Information (PI) as per routine practice.
- Research question and objectives: To assess the risk of safety outcomes, including medically attended adverse event following immunisation (AEFIs), serious AEFIs, potential immune mediated diseases (pIMDs) and pregnancy related outcomes following vaccination with *Cervarix* according to the Prescribing Information (PI) in female Chinese subjects aged between 9 and ~~25~~ ***45*** years.
- Contributing authors: PPD
  - PPD
  - PPD, ***Global*** Regulatory Affairs ***Lead***
  - PPD
- MAH contact person: PPD***, MD***
- List of abbreviations:
  - *CNDA*~~CFDA~~: *National Drug Administration of China* ~~Chinese Food and Drug Administration~~
  - ~~CRDB: Clinical Research and Development Board~~

- Responsible Parties: PPD PPD (Clinical and Epidemiology R&D Project Lead) is the GSK Biologicals designated contact person for this study.
- Section 4: Abstract – Main Author: PPD ~~, Clinical and Epidemiology R&D Project Lead, GSK Biologicals.~~ PPD ***, MD, Director, Clinical and Epidemiology R&D Project Lead, HPV, Hepatitis and Pneumococcal vaccines, GlaxoSmithKline Biologicals SA***
- Section 4: Abstract – Rationale and Background:
  - *Cervarix* is a prophylactic HPV (Human papillomavirus) vaccine developed by GlaxoSmithKline (GSK) Biologicals. It is based on the 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]), indicated for women aged 9 to ~~25~~ 45 years of age.
  - *Cervarix* is was the first HPV vaccine licensed for use in China to help prevent cervical cancer caused by HPV types 16 and 18. The vaccine was approved by National Drug Administration of China ~~China Food and Drug Administration~~ (~~CFDA~~CNDA) in July 2016, for use in females between 9 and 25 years of age, for the prevention of cervical cancer, cervical intraepithelial neoplasia grade 1 (CIN1), cervical intraepithelial neoplasia grade 2, grade 3 (CIN 2/3) and adenocarcinoma in situ caused by high-risk human papillomavirus (HR-HPV) types 16 and 18.
  - ***In May 2018, Cervarix was also approved for use in women of age up to 45 years. Hence, this protocol is being amended to enable the inclusion of healthy female Chinese subjects 26-45 years of age into this PMS study.***
- Section 4: Abstract and Section 7.1 – Research question and objectives:
  - The aim of this post marketing surveillance study is to assess the safety of *Cervarix* among healthy female Chinese subjects aged between 9 and ~~25~~ 45 years, who were vaccinated on a voluntary basis as per standard practice.
  - Secondary Objectives: To assess the safety of *Cervarix* in terms of ***pregnancy outcomes (PO)*** when administered inadvertently within 60 days before pregnancy onset or any time during pregnancy.
  - Note: The details of surveillance methods for data collection have been are provided in section 9.4
  - Milestones: Data collection is planned to start within 6 months following the *Cervarix* launch date in Quarter 2-2018 and end in Quarter ~~3~~1-~~2020~~2021. The final report of study results is planned in Quarter ~~2~~4-2021
- Section 5: Amendments and updates
- Section 6: Milestones – Table was updated

Milestone	Planned date
Start of data collection	Quarter ***2*** 2018
End of data collection	Quarter ***1 2021***
Study progress report 1	Quarter 1 2019
Study progress report 2	Quarter 1 2020
Interim report 1 (for license renewal)	Quarter ***1 2019***
Final report of study results	Quarter ***4*** 2021

- Section 7: Rationale and background – New literature references were included to support the age extension of *Cervarix*.
  - *Cervarix* is a prophylactic HPV (Human papillomavirus) vaccine developed by GlaxoSmithKline (GSK) Biologicals. It is based on the 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]), indicated for women aged 9 to ~~25~~45 years of age in China.
  - Adverse events (AE) of interest identified during pre-licensure clinical development are monitored. For Cervarix, these AE of interest include the new onset and exacerbation of potential immune-mediated diseases (pIMDs) after vaccination, and pregnancy outcomes (PO) associated with unintended vaccine exposure during pregnancy ***[Lopez-Frauqued, 2017].***
  - A retrospective, observational cohort study in the United Kingdom Clinical Practice Research Datalink General Practice Online Database (CPRD GOLD) compared 4 cohorts of 65,000 subjects each, consisting of one exposed female cohort and three unexposed cohorts-historical female, concurrent male, historical male [Willame, 2016]. An increased risk of autoimmune thyroiditis (AIT) with an incidence rate ratio (IRR) of 3.75 (95% CI 1.25-11.31) when the analysis was performed on confirmed cases was not considered significant when compared to the IRR of 1.45 with non-confirmed cases (95% CI; 0.79-2.64). In conclusion, the study did not show evidence of an increased risk of autoimmune diseases after vaccination with *Cervarix* ***[Andrews, 2017].***
  - This study detected a statistically significant increased risk of Guillian Barré Syndrome (GBS) following exposure to any HPV vaccine (cases that occurred during the entire follow-up period) with adjusted Hazard Ratio (HR) of 4.00 (95% CI 1.84-8.69). The study did not identify a significant association between exposure to HPV vaccine (pooled bivalent and quadrivalent vaccine) and thyroiditis. A subgroup analysis identified a statistically significant association between vaccination with *Cervarix* and thyroiditis (possibly of autoimmune origin) with an adjusted hazard ratio (HR) of 2.43 (1.27-4.66). Also, a slight increased risk of Inflammatory Bowel Disease (IBD) was observed, following HPV vaccination (pooling Gardasil and Cervarix), with a HR of 1.19 (95% CI: 1.02-1.39). The interpretation of the analysis by brand should be performed

cautiously, as a small proportion of the vaccinated cohort received *Cervarix* (7%). ***However, recent studies show that vaccination with Cervarix does not present a higher risk of thyroiditis [Colin, 2018].***

- An observational case-control study performed in France, which enrolled 478 definite cases of various autoimmune diseases and matched to 1869 controls, [Grimaldi-Bensouda 2017]. This study did not report an increased risk of autoimmune disorder following vaccination with *Cervarix*.
- POs are of interest because the target population includes women of child-bearing age. The overall pregnancy data generated so far from large clinical trials, post marketing passive surveillance (including the pregnancy registry set up in the UK and in the United States from 2007 to 2015 [GlaxoSmithKline Biologicals Clinical Study Report 201337]) and from the epidemiological study EPI-HPV-018 [Baril, 2015], are reassuring for the vast majority of women and their offspring, if vaccination occurred during pregnancy ***[Lopez-Frauqued, 2017]***.
- The vaccine was approved by National Drug Administration of China (CNDA) China Food and Drug Administration (CFDA) in July 2016, for use in females between 9 and 25 years of age, for the prevention of cervical cancer, cervical intraepithelial neoplasia grade 1 (CIN1), cervical intraepithelial neoplasia grade 2, grade 3 (CIN 2/3) and adenocarcinoma in situ caused by high-risk human papillomavirus (HR-HPV) types 16 and 18.
- ***In May 2018, Cervarix was approved for use in women of age up to 45 years. Hence, this protocol is being amended to enable the inclusion of healthy female Chinese subjects 26-45 years of age into this PMS study.***

- Section 8: Research question and objectives - The aim of this post marketing surveillance study is to assess the safety of *Cervarix* among healthy female Chinese subjects aged between 9 and ~~25~~45 years, who were vaccinated on a voluntary basis as per standard practice.
- Section 9: Research Methods –
  - Study Population: The study will involve approximately 3000 female Chinese subjects aged between 9 and ~~25~~45 years of age, vaccinated voluntarily as per standard practice.
  - Vaccination schedule: Chinese female subjects aged between 9 and ~~25~~45 years, who consented to participate in the study, are expected to receive three doses of *Cervarix* at 0, 1 and 6 months. The second dose can be administered between 1 month and 2.5 months after the first dose and the third dose between 5 and 12 months after the first dose. The vaccine will be administered intra-muscularly, in the deltoid region of the upper arm.

Table 1 Study groups and epochs foreseen in the study

Study Group	Number of subjects	Age (Min/Max)	Epochs
			Epoch 001
HPV group	3000	09 years - ~~25~~45 years	x

- Section 9.1.1 Discussion of study design
  - This prospective, surveillance study will collect data regarding the safety of *Cervarix* vaccine.
- Section 9.2.1 Number of subjects/centres
  - Study population will include Chinese female subjects aged between 9 and ~~25~~45 years, who have satisfied the inclusion criteria at study start and who will receive voluntary vaccination at the vaccination centres or POV as per standard practice.
- Section 9.2.2 Inclusion criteria
  - Any Chinese female subject aged between 9 and ~~25~~45 years, at the time of first vaccination dose, who will receive voluntary vaccination.
- Table 3: List of pIMDs

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,	• 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.	• Psoriasis. • Vitiligo. • Erythema nodosum. • Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis). • Lichen planus. • Sweet's syndrome. • Localised Scleroderma (Morphoea).

• Multifocal motor neuropathy • Polyneuropathies associated with monoclonal gammopathy. • Narcolepsy.	• Relapsing Polychondritis. • Mixed Connective Tissue disorder. • Gout.	
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), • Necrotising vasculitis (cutaneous or systemic), • anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), • Henoch-Schonlein purpura (IgA vasculitis), • Behcet's syndrome, • Leukocytoclastic vasculitis.	• Autoimmune haemolytic 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.

- Section 9.10.1 Sequence of analyses
  - A final analysis of all data collected up to either 12 months following the third immunisation or 24 months following the first immunisation with *Cervarix* (whichever occurs first), will be conducted. This will include final analysis of safety. In case of regulatory submission before license renewal, interim report(s)/progress report(s) will be prepared.
- Section 9.10.2 Statistical considerations for interim analyses
  - A comprehensive report will be prepared and submitted as part of the license renewal application process planned in ~~2021~~2019.
- Section 13 – References:
  - ***Andrews N, Stowe J, Miller E. No increased risk of Guillain-Barré syndrome after human papilloma virus vaccine: A self-controlled case-series study in England. Vaccine 2017;35(13):1729-1732***
  - ***Colin C, Miranda S, Chaignot C, Poidvin A et al:, Vaccins anti-HPV et risque de thyroïdite chez les jeunes filles âgées de 13 à 17 ans. Revue d'Épidémiologie et de Santé Publique. 2018; 66(1):S21***
  - ***Lopez-Frauqued, Zima J, Angelo M G. Results on exposure during pregnancy from a pregnancy registry for AS04-HPV-16/18 vaccine. Vaccine 2017; 35(40):5325-5330***
- Annex 4 – List of principal and coordinating investigators

- ***The table below presents the key sub-investigators***. The contact details and list of all investigators are available upon request.

Investigator's name	*Sub-investigators*	*Center number**	*Investigational site (institution /hospital)*	*Location (complete address)*	*Phone number Fax number*
Hongjie Yu	*Shaojie Lin*	PPD	*Shenzhen Longgang Center for Disease Control and Prevention*	*No. 39, Hexie Road, Longgang District, Shenzhen, China*	*Phone:* PPD *Fax:* PPD
	Qizhang Wang	PPD	*Shanghai Pudong New Area Centre for Disease Control and Prevention*	*NO.3039 Zhangyang Road, Pudong New Area District, Shanghai, China*	*Phone:* PPD *Fax:* PPD
	Qinghai Wang	PPD	*Beijing Xicheng Center for Disease Control and Prevention*	*Public Health Building, No.38, Deshengmenwai Street, Xicheng District, Beijing, China*	*Phone:* PPD *Fax:* PPD
	Taoying Zhu	PPD	*Chengdu City Wuhou District Center for Disease Control and Prevention*	*No.6 Guangfuqiao Street, Wuhou District, Chengdu City, Sichuan Province, China*	*Phone:* PPD *Fax:* PPD

* GSK Biologicals' assigned center number

- Annex 6 - Amendments and administrative changes to the protocol, was added.
- Some minor formatting changes were also made to the document.

Annex 7 Feasibility assessment

The details on feasibility assessment are available upon request.

Annex 8 Protocol Amendment 1 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	207350 (EPI-HPV-070 VS CN PMS)
Date of protocol amendment	Amendment 1 Final: 27 June 2018
Detailed Title	A prospective, multi-centre post marketing surveillance (PMS) cohort study to monitor the safety of GlaxoSmithKline (GSK) Biologicals' Human papillomavirus (HPV)-16/18 L1 VLP AS04 vaccine in female Chinese subjects aged between 9 and ***45*** years, when administered according to the Prescribing Information (PI) as per routine practice.
Sponsor signatory	Dorota Borys, MD Director, Clinical and Epidemiology R&D Project Lead, HPV, Hepatitis and Pneumococcal vaccines GlaxoSmithKline Biologicals SA
Signature	_____
Date	_____

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Annex 9 Protocol Amendment 1 Investigator Agreement

I agree:

- **To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments or protocol administrative changes, with the terms of the study 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) or other applicable guidelines and all applicable regulatory requirements.**
- **To ensure that all persons assisting me with the study are adequately informed about study-related duties and functions as described in the protocol.**
- **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, 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.**

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Investigator name	_____
Signature	_____
Date	_____

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Annex 10 ENCePP Checklist for study protocols

Section 1: Milestones	Yes	No	N/A	Page Number(s)
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	14
1.1.2 End of data collection[2]	☒	☐	☐	14
1.1.3 Study progress report(s)	☒	☐	☐	14
1.1.4 Interim progress report(s)	☒	☐	☐	14
1.1.5 Registration in the EU PAS register	☐	☐	☒	
1.1.6 Final report of study results.	☒	☐	☐	14

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 2: Research question	Yes	No	N/A	Page Number(s)
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	17
2.1.2 The objective(s) of the study?	☒	☐	☐	17
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	17
2.1.4 Which formal hypothesis (-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no a priori hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	Yes	No	N/A	Page Number(s)
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	18-20
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	32-33
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	

Comments:

Section 4: Source and study populations	Yes	No	N/A	Page Number(s)
4.1 Is the source population described?	☒	☐	☐	18
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	19
4.2.2 Age and sex?	☒	☐	☐	19
4.2.3 Country of origin?	☒	☐	☐	19
4.2.4 Disease/indication?	☒	☐	☐	16-17
4.2.5 Co-morbidity?	☒	☐	☐	22
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	20-21

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	19
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	19
5.3 Is exposure classified according to time windows? (adapted as per this study design)	☒	☐	☐	22

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Section 6: Endpoint definition and measurement	Yes	No	N/A	Page Number(s)
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	26, 33-34
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	19-20

Comments:

Section 7: Confounders and effect modifiers	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (E.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	25
8.1.2 Endpoints? (E.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	32-33
8.1.3 Covariates?	☒	☐	☐	24-25
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	25
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	25, 42-43
8.2.3 Covariates? (E.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	24-25
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☒	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	36
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 9: Study size and power	Yes	No	N/A	Page Number(s)
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	35

Comments:

Section 10: Analysis plan	Yes	No	N/A	Page Number(s)
10.1 Does the plan include measurement of excess risks?	☐	☒	☐	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	36-37
10.3 Are descriptive analyses included?	☒	☐	☐	36-37
10.4 Are stratified analyses included?	☐	☐	☒	
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Page Number(s)
11.1 Is information provided on the management of missing data?	☒	☐	☐	36
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	36
11.3 Are methods of quality assurance described?	☒	☐	☐	36
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	39-40
11.5 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	Yes	No	N/A	Page Number(s)
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	39-40
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	39-40
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	20
12.3 Does the protocol address other limitations?	☒	☐	☐	39-40

Comments:

Section 13: Ethical issues	Yes	No	N/A	Page Number(s)
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	40-41
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	40-41
13.3 Have data protection requirements been described?	☒	☐	☐	39

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Page Number(s)
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	14

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Page Number(s)
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	37, 48-49
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	48-49

Comments:

Name of the main author of the protocol: PPD Clinical and Epidemiology R&D Project Lead, GSK Biologicals

Date:

Signature: _____