GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A phase III/IV open-label, multi-centre study to evaluate the safety of GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed, administered intramuscularly according to a 0,1,6-month schedule, in healthy Chinese female subjects above 26 years of age who received the control vaccine in study HPV-039 and to evaluate the protective effect of GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, Adsorbed, up to approximately 10 years after vaccination, in reducing HPV-associated cervical infection in subjects who participated in the HPV-039 study.
eTrack study number and Abbreviated Title	205779 (HPV-092 EXT:039)
Scope:	All data pertaining to the above study.
Date of Statistical Analysis Plan	Final: 20 May 2020

APP 9000058193 Statistical Analysis Plan Template V4 (Effective date: 3June2019)

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

LIST OF ABBREVIATIONS

AE	Adverse event
AIS	Adenocarcinoma In-Situ
ASC-US	Atypical Squamous Cells of Undetermined Significance
CI	Confidence Interval
CIN	Cervical Intraepithelial Neoplasia
CRF	Case Report Form
CSR	Clinical Study Report
CTRS	Clinical Trial Registry Summary
Eli Type	Internal GSK database code for type of elimination code
ELISA	Enzyme-Linked Immunosorbent Assay
ES	Exposed Set
HCGIN	High-grade Cervical Glandular Intraepithelial Neoplasia
HPV	Human Papillomavirus
HSIL	High-grade Squamous Intraepithelial Lesion
LCGIN	Low-grade Cervical Glandular Intraepithelial Neoplasia
LL	Lower Limit of the confidence interval
MedDRA	Medical Dictionary for Regulatory Activities
N.A.	Not Applicable
PCR	Polymerase chain reaction
PD	Protocol Deviation
PPS	Per Protocol Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation

SR	Study Report
TFL	Tables Figures and Listings
TOC	Table of Content
TVC	Total Vaccinated Cohort
UL	Upper Limit of the confidence interval
VAIN	Vaginal Intraepithelial Neoplasia
VE	Vaccine Efficacy
VIN	Vulvar Intraepithelial Neoplasia

1. DOCUMENT HISTORY

Date	Description	Protocol Version
20 MAY 2020	Final version	Amendment 1: Final 21 JUN 2018

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary objective:

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

Secondary objectives:

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

Tertiary objectives:

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

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

2.2. Endpoints

Primary Endpoint:

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

Secondary endpoints:

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

Tertiary endpoints:

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

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

– Histopathologically-confirmed VaIN1+ irrespective of HPV type.

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

3. STUDY DESIGN

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

Table 1 Study groups and epoch foreseen in the study

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

– Vacc-HPV-039 group i.e. subjects who received HPV vaccine in HPV-039 study and who will undergo cervical sample collection only in the current study. This group will be referred as "Vacc-039" group in the analysis of protective effect and efficacy (Refer table below for the group labels to be used for the analysis of efficacy).

– HPV group (Ctrl-HPV-039 group) i.e. subjects who received control vaccine in HPV-039 study will receive HPV vaccine in the current study and undergo cervical sample collection before HPV vaccination. This group will be referred as "Vacc-092" group in the analysis of protective effect, vaccine efficacy and in the analysis of safety following 3 doses of HPV vaccine (Refer table below for the group labels to be used for the analysis of safety and efficacy).

Group labels used for analysis of efficacy:

Group order in tables	Group label in tables	Group definition for footnote	Pooled Groups label in tables	Pooled definition for footnote
1	Vacc-039	Subjects who received HPV-16/18 L1AS04 vaccine in study HPV-039	-	-
2	Vacc-092	Subjects who received control vaccine in HPV-039 study and HPV-16/18 L1AS04 vaccine in HPV-092 study	-	-

Group labels used for analysis of safety:

Group order in tables	Group label in tables	Group definition for footnote	Pooled Groups label in tables	Pooled definition for footnote
1	Vacc-092	Subjects who received control vaccine in HPV-039 study and HPV-16/18 L1AS04 vaccine in HPV-092 study	-	-

Table 2 Study groups and treatment foreseen in the study

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

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

Table 3 Blinding of study epoch

Study Epoch	Blinding
Epoch 001	open-label

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

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

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

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

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

  – Approximately 12 months per subject (approximately 6 months for 3-dose vaccination followed by 6-month extended safety follow-up after last dose).
    - Epoch 001: starting at Visit 1 (Day 1) and ending at Call 2 (Month 12)

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

- **Primary completion Date (PCD):** Call 2 (Month 12)
- **End of Study (EoS):** Last subject's last visit/contact (Call 2 [Month 12]) or last testing results released for samples collected at Visit 1 and related call-back visit, whatever comes later
- **Data collection:** Electronic Case Report Form (eCRF).
- **Safety monitoring:**
  - All subjects: SAEs related to study participation.
  - HPV group (Ctrl-HPV-039 group):
    - All SAEs, and any AE/SAE leading to premature discontinuation of the study will be reported throughout the study.
    - pIMDs will be reported throughout the study.

  Pregnancies and pregnancy outcomes will be reported throughout the study

4. ANALYSIS SETS

4.1. Definition

4.1.1. Total enrolled set

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

4.1.2. Exposed set HPV-092 (ES-HPV-092)

The Exposed Set (ES-HPV-092) includes all vaccinated subjects in the study HPV-092 EXT:039 for whom data were available. This set will be used for the analysis of safety.

4.1.3. Exposed set for analysis of protective effect and efficacy HPV-092 (ES-E-HPV-092)

ES-E-HPV-092 includes all subjects who participated in the study HPV-092 EXT:039 study and were included in the Total Vaccinated Cohort for efficacy (TVC-E) in the study HPV-039 (ES-E-HPV-039-092). This analysis set will be used for the analysis of protective effect and vaccine efficacy.

4.1.4. Per-protocol set (PPS-E-HPV-092) for analysis of efficacy

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

- Who meet all eligibility criteria in the study HPV-092 EXT:039.
- Who do not meet any of the criteria for elimination from the PPS analysis during the study HPV-092 EXT:039.
- For whom data concerning endpoint measures are available.

- Who belong to the ATP cohort for efficacy of the study HPV-039.

This cohort will be used for the analysis of protective effect and vaccine efficacy.

4.1.5. Exposed set HPV-039 (ES-HPV-039)

The Exposed Set (ES-HPV-039) includes all vaccinated subjects in HPV-039 study. This is the Total Vaccinated Cohort (TVC) of the study HPV-039.

4.1.6. Exposed set for analysis of protective effect and efficacy HPV-039 (ES-E-HPV-039-092)

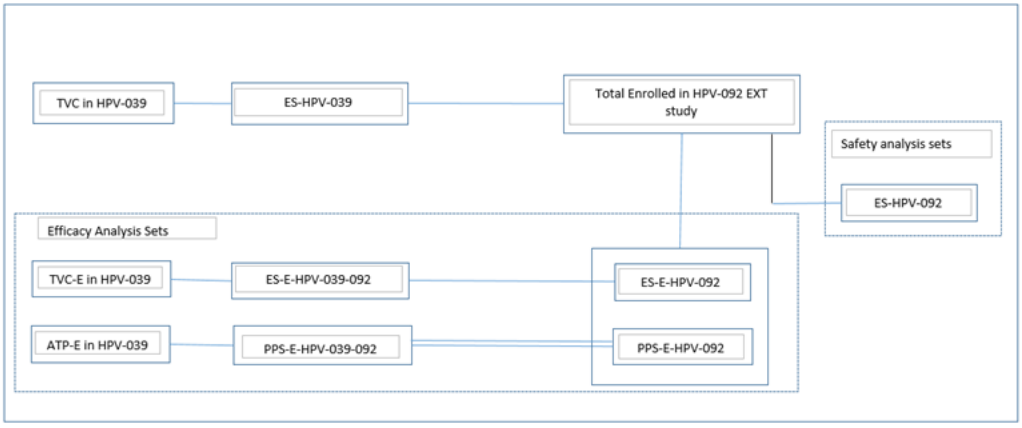
Total Vaccinated Cohort for efficacy (TVC-E) in study HPV-039 will be used for the analysis of protective effect and vaccine efficacy. In this study analysis, the analysis set will be referred as ES-E-HPV-039-092.

4.1.7. Per-protocol set of study HPV-039 (PPS-E-HPV-039-092) for analysis of efficacy

ATP cohort for efficacy (ATP-E) in study HPV-039 will be used for the analysis of protective effect and efficacy. In addition, the data from the subjects eliminated from the PPS-E-HPV-092 will be censored from this analysis set for the time period after last contact in HPV-039. In this study, the analysis set will be referred as PPS-E-HPV-039-092.

4.2. Criteria for eliminating data from Analysis Sets

Elimination codes are used to identify subjects to be eliminated from analysis. Details are provided in the below sections.



4.2.1. Elimination from Exposed Set HPV-092 (ES-HPV-092)

Only group Vacc-092 in the study HPV-092 EXT:039 will be considered for this cohort.

The following codes are assigned to subjects in the control group from the study HPV-039 who participate in the HPV-092 EXT:039 study.

Table 4 Exposed Set (ES-HPV-092)

Code	Description	Study Objective/ Period	All Exposed Set
900	Invalid informed consent or fraud data in the HPV-092 EXT:039 study	From visit 1 of HPV-092 EXT:039 study	ELI
1030	Study vaccine not administered at all in the HPV-092 EXT:039 study	From visit 1 of HPV-092 EXT:039 study	ELI

ELI = eliminated from this analysis set.

4.2.2. Elimination from Exposed Set for the analysis of efficacy (ES-E-HPV-092)

This analysis set will be derived from the subjects who participate in HPV-092 EXT:039 study and belonging to the TVC for efficacy in (TVC-E) HPV-039.

Table 5 Exposed Set for efficacy (ES-E-HPV-092)

Codes are assigned to subjects in ES-E-HPV-039-092 who participate in the HPV-092 EXT:039 study.

Code	Description	Study Objective/ Period	ES
900	Invalid informed consent or fraud data in the HPV-039 and/or HPV-092 EXT:039 study	From visit 1 of HPV-039 study	ELI
1030	Study vaccine not administered at all in the HPV-039	From visit 1 of HPV-039 study	ELI
3000	Subjects with high-grade (ASC-H, HSIL, AGC, MALIGNANCY) or missing cytology at baseline in the study HPV-039	From visit 1 of HPV-039 study	ELI

ELI = eliminated from this analysis set.

4.2.3. Elimination from Per-Protocol analysis Set for the analysis of efficacy (PPS-E-HPV-092)

The analysis set will be derived from the subjects who participate in HPV-092 EXT:039 study and belonging to the ATP cohort for efficacy in HPV-039. In addition, the subjects receiving the following elimination codes in HPV-092 EXT:039 will be eliminated from the analysis set PPS-E-HPV-092 for the analysis at year 10 and the data at year 10 from these subjects will be censored for the analysis of protective effect and efficacy from dose 1 in HPV-039 up to year 10.

Table 6 Per protocol Set for efficacy (PPS-E-HPV-092)

Codes are assigned to subjects in PPS-E-HPV-039-092 who participate in the HPV-092 EXT:039 study.

Code	Description	Study Objective/ Period	PPS
900	Invalid informed consent or fraud data in the HPV-039 and/or HPV-092 EXT:039 study	From visit 1 of HPV-039 study	ELI
2010	Protocol violation (inclusion/exclusion criteria) in the HPV-092 EXT:039 study	From visit 1 of HPV-092 EXT:039 study	ELI
2040	Administration of any medication forbidden by the protocol in the HPV-092 EXT:039 study	From visit 1 of HPV-092 EXT:039 study	ELI
2050	Underlying medical condition forbidden by the protocol in the HPV-092 EXT:039 study	From visit 1 of HPV-092 EXT:039 study	ELI
1030	Study vaccine not administered at all in the study HPV-039.	From visit 1 of HPV-039 study	ELI
1040	Administration of vaccine(s) forbidden in the protocol in the study HPV-039.	From visit 1 of HPV-039 study	ELI
1060	Randomisation code broken at the investigator site in the study HPV-039.	From visit 1 of HPV-039 study	ELI
1070	Study vaccine dose not administered according to protocol in the study HPV-039.	From visit 1 of HPV-039 study	ELI
1500	Subject with a positive pregnancy test at visit 1, 2 or 3 in the study HPV-039.	From visit 1 of HPV-039 study	ELI
2010	Protocol violation (inclusion/exclusion criteria) in the study HPV-039.	From visit 1 of HPV-039 study	ELI
2040	Administration of any medication forbidden by the protocol in the study HPV-039.	From visit 1 of HPV-039 study	ELI
3000	Subjects with high-grade (ASC-H, HSIL, AGC, MALIGNANCY) or missing cytology at baseline in the study HPV-039.	From visit 1 of HPV-039 study	ELI
3100	Subject with two cervices in the study HPV-039.	From visit 1 of HPV-039 study	ELI

ELI = eliminated from this analysis set.

4.2.4. Elimination from Exposed Set HPV-039 (ES-HPV-039)

Subjects with the elimination codes assigned for elimination from the TVC in HPV-039 will be eliminated from this analysis set.

Table 7 Exposed Set (ES-HPV-039)

These codes are carried forward from the HPV-039 study.

Code	Description	Study Objective/ Period	All Exposed Set
900	Invalid informed consent or fraud data in the HPV-039	From visit 1 of HPV-039 study	ELI
1030	Study vaccine not administered at all in the HPV-039	From visit 1 of HPV-039 study	ELI

ELI = eliminated from this analysis set.

4.2.5. Elimination from Exposed Set for the analysis of efficacy (ES-E-HPV-039-092)

Subjects with the elimination codes assigned for elimination from the TVC for efficacy in HPV-039 will be eliminated from this analysis set.

Table 8 Exposed Set for efficacy (ES-E-HPV-039-092)

These codes are carried forward from the HPV-039 study.

Code	Description	Study Objective/ Period	ES
900	Invalid informed consent or fraud data in the study HPV-039 and/or HPV-092 EXT:039.	From visit 1 of HPV-039 study	ELI
1030	Study vaccine not administered at all in the study HPV-039.	From visit 1 of HPV-039 study	ELI
3000	Subjects with high-grade (ASC-H, HSIL, AGC, MALIGNANCY) or missing cytology at baseline in the study HPV-039	From visit 1 of HPV-039 study	ELI

ELI = eliminated from this analysis set.

4.2.6. Elimination from Per-Protocol analysis Set for the analysis of efficacy (PPS-E-HPV-039- 092)

Subjects with the elimination codes assigned for elimination from the ATP cohort for efficacy in HPV-039 will be eliminated from this analysis set. In addition, the data from the subjects receiving the elimination codes in HPV-092 EXT:039 will be censored from the analysis set PPS-E-HPV-039-092.

Table 9 Per protocol Set for efficacy (PPS-E-HPV-039-092)

These codes are carried forward from the HPV-039 study.

Code	Description	Study Objective/ Period	PPS
900	Invalid informed consent or fraud data in the study HPV-039 and/or HPV-092 EXT:039.	From visit 1 of HPV-039 study	ELI
1030	Study vaccine not administered at all in the study HPV-039.	From visit 1 of HPV-039 study	ELI
1040	Administration of vaccine(s) forbidden in the protocol in the study HPV-039.	From visit 1 of HPV-039 study	ELI
1060	Randomisation code broken at the investigator site in the study HPV-039.	From visit 1 of HPV-039 study	ELI
1070	Study vaccine dose not administered according to protocol in the study HPV-039.	From visit 1 of HPV-039 study	ELI
1500	Subject with a positive pregnancy test at visit 1, 2 or 3 in the study HPV-039.	From visit 1 of HPV-039 study	ELI
2010	Protocol violation (inclusion/exclusion criteria)	From visit 1 of HPV-039 study	ELI
2040	Administration of any medication forbidden by the protocol in the study HPV-039.	From visit 1 of HPV-039 study	ELI
3000	Subjects with high-grade (ASC-H, HSIL, AGC, MALIGNANCY) or missing cytology at baseline in the study HPV-039.	From visit 1 of HPV-039 study	ELI

Code	Description	Study Objective/ Period	PPS
3100	Subject with two cervices in the study HPV-039.	From visit 1 of HPV-039 study	ELI
2010	Protocol violation (inclusion/exclusion criteria) in the HPV-092 EXT:039 study	From visit 1 of HPV-092 EXT:039 study	ELI
2040	Administration of any medication forbidden by the protocol in the HPV-092 EXT:039 study	From visit 1 of HPV-092 EXT:039 study	ELI
2050	Underlying medical condition forbidden by the protocol in the HPV-092 EXT:039 study	From visit 1 of HPV-092 EXT:039 study	ELI

ELI = eliminated from this analysis set.

4.3. Important protocol deviation not leading to elimination from analysis

The following important protocol deviations will be reported by groups:

- In case unexpected vaccinations at study start were administered due to national recommendation, the subjects who had such vaccination will be mentioned.
- Shorter follow-up than planned per protocol: subjects who completed the last study contact before the minimum length of follow-up requirement.
- Subjects for whom cervical sample is collected after vaccination in HPV-092 EXT:039 study.

5. STATISTICAL ANALYSES

That standard data derivation rules and stat methods are described in section 10.1 while the study specific data derivation rules and stat methods are described in section 9.

5.1. Summary of analysis sets used for each analysis

The table below provides summary the analysis sets used for all the analysis.

Analysis Sets	**Analysis of demography and baseline characteristics**	**Analysis of exposure, safety and concomitant vaccination**	**Analysis of protective effect/efficacy (Follow-up from Dose 1 up to year 10)**	**Analysis of protective effect (snapshot analysis at year 10 visit)**
ES-HPV-092*	Yes	Yes		
ES-HPV-039	Yes			
ES-E-HPV-039-092	Yes		Yes	
PPS-E-HPV-039-092	Yes		Yes	
ES-E-HPV-092***	Yes		Yes	Yes
PPS-E-HPV-092***	Yes		Yes**	Yes**

* Only group Vacc-092 in the study HPV-092 EXT:039 will be considered for this cohort.
**Analysis on PPS-E-HPV-092 would be performed, if more than 5% subjects are eliminated from ES-E-HPV-092.
*** Only subjects participating in HPV-092 EXT:039 study.

5.2. Demography

5.2.1. Analysis of demographics/baseline characteristics planned in the protocol

Demographic characteristics at first visit in study HPV-092 EXT:039 and HPV vaccination history in study HPV-039 will be summarised overall and by group using descriptive statistics.

The mean age (plus range and standard deviation) of the subjects at time of Dose 1 administration in study HPV-092 EXT:039 will be calculated.

The mean age (plus range and standard deviation) of the subjects at the time of cervical sampling activity in study HPV-092 EXT:039, overall and per group, will be calculated.

Mean interval (plus range and standard deviation) from the dose 1 in the study HPV-039 to time of the cervical sampling activity in the study HPV-092 EXT:039 will be calculated.

Mean interval (plus range and standard deviation) from the last visit in the study HPV-039 to time of the cervical sampling activity in the study HPV-092 EXT:039 will be calculated.

Baseline characteristics (HPV DNA and serostatus) in study HPV-039 will be summarised overall and by group.

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

The distribution of subjects enrolled among the study sites will be tabulated overall and per group.

The above analyses will be performed on exposed sets and per protocol sets.

5.3. Exposure

5.3.1. Analysis of exposure planned in the protocol

The number and percentage of subjects who received study vaccine doses in the study HPV-092 will be summarized. This analysis will be performed on the ES-HPV-092.

5.4. Efficacy/Protective effect

5.4.1. Analysis of protective effect

The analysis of the protective effect will be performed on the ES for analysis of efficacy (ES-E-HPV-039-092) and PPS for analysis of efficacy (PPS-E-HPV-039-092), considering the data from the entire follow-up period of studies HPV-039 and HPV-092 EXT:039 combined, i.e., pooled dataset (from Month 0 in study HPV-039 up to Month 120 in study HPV-092 EXT:039). The same pooled analysis will be performed on ES-E-HPV-092.

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

  The above-mentioned analysis will also be performed for ES-E-HPV-092 and PPS-E-HPV-092 at visit 1 of HPV-092 EXT:039 study.

5.4.2. Analysis of efficacy

Analysis of long-term efficacy is exploratory.

The analysis of long-term efficacy will be performed on the ES for analysis of efficacy (ES-E-HPV-039-092) and PPS for analysis of efficacy (PPS-E-HPV-039-092), considering the data from the entire follow-up period of studies HPV-039 and HPV-092 EXT:039 combined, i.e., pooled dataset (from Month 0 in study HPV-039 up to Month 120 in study HPV-092). The same pooled analysis will be performed on ES-E-HPV-092.

Vaccine efficacy with a 95% CI will be calculated using the conditional exact method.

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

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

The vaccine efficacy for all endpoints will be calculated using a conditional exact method as described in the section 10.1.5.2.

Kaplan-Meier curves for both groups will be generated.

Number and percentage of subjects at year 10-time point with colposcopy, biopsy, and referrals to treatment according to local medical practice will be summarized by group.

This analysis will be performed on ES-E-HPV-092 and PPS-E-HPV-092.

5.4.3. Case definition

For all subjects suspected to meet criteria for either secondary and tertiary efficacy endpoints (histopathological endpoints), all available clinical and laboratory data will be reviewed as described in the section 10.2 to make final case assignments.

The primary analysis of vaccine efficacy against histopathological endpoints will be performed by applying the type assignment algorithm described in the section 10.2.2.4.

The analysis of incidence rate for histopathological endpoints at year 10 timepoint (Visit 1 in HPV-092 EXT:039) will be performed based on the HPV DNA detected in the lesion in the HPV-092 EXT:039 study.

As a sensitivity analysis, vaccine efficacy against histopathological endpoints will also be analysed by considering the above defined type assignment algorithm for the cases reported till end of the study HPV-039 and based on the HPV DNA detected in the lesion at year 10 in the HPV-092 EXT:039 study.

5.5. Analysis of safety

5.5.1. Analysis of safety

Analysis of safety events reported following vaccination in the HPV-092 study will be performed on the ES-HPV-092.

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

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

5.6. Concomitant vaccination.

The proportion of subjects who receive any concomitant vaccination during the study will be summarized.

6. INTERPRETATION OF RESULTS

All analyses are descriptive with the aim to characterise the observed outcomes.

Limitations of this study:

In the HPV-039 study, the efficacy of GSK Biologicals' Human Papillomavirus (Types 16, 18) Vaccine, adsorbed against virological, cytological and histopathological endpoints associated with HPV types 16 and 18, was demonstrated up to 6 years after vaccination and subjects were screened every 6 months. The study was unblinded at the end of 6 year follow up period. Since the end of HPV-039 study, 3-4 years have elapsed prior start of HPV-092 study with no follow-up of the subjects. Therefore, there might be high subject attrition, leading to a potential imbalance in the numbers of subjects from the vaccinated versus control group returning for the current study. This as well as a lack of regular gynaecological follow-up between Year 6 and Year 10 may compromise assessment of vaccine efficacy in this study. Therefore, all the analyses related to efficacy endpoints will be exploratory in nature.

7. CONDUCT OF ANALYSES

7.1. Sequence of analyses

Description	Analysis ID	Disclosure Purpose (CTRS=public posting, SR=study report, internal)	Dry run review needed (Y/N)	Study Headline Summary (SHS) requiring expedited communication to upper management (Yes/No)	Reference for TFL
Final Analysis	E1_01	SR	Y	Y	TFL TOC

7.2. Statistical considerations for interim analyses

No interim analysis planned for the study.

8. CHANGES FROM PLANNED ANALYSES

The analysis of protective effect and vaccine efficacy on PPS-E-HPV-092 will be performed to complement the analysis on ES-E-HPV-092, if, in any vaccine group, the percentage of subjects excluded from the PPS-E-HPV-092 as compared to ES-E-HPV-092 is 5% or more.

9. NON-STANDARD DATA DERIVATION RULES AND STATISTICAL METHODS

Not applicable.

10. ANNEXES

10.1. Business rules for standard data derivations and statistical methods

10.1.1. Date derivation

SAS date derived from a character date: In case day is missing, 15 is used. In case day & month are missing, 30June is used.

10.1.2. Dose number

- The study dose number is defined about the number of study visits at which vaccination occurred.
- The number of doses for a product is the number of times the product was administered to a subject.

10.1.3. Demography

- Age: Age at the reference activity is computed as the number of units (years) between the date of birth and the date of the reference activity.

10.1.4. Number of decimals displayed:

The following decimal description will be used for the demography, immunogenicity and efficacy/rate ratio.

Display Table	Parameters	Number of decimal digits
Demographic characteristics	Mean, median age	1
Demographic characteristics	SD (age)	1
All summaries	% of count, including LL & UL of CI	1

10.1.5. Statistical methodology

10.1.5.1. Exact confidence intervals around proportions

The exact confidence intervals around within-group proportions are derived using the method of Clopper and Pearson [Clopper, 1934].

10.1.5.2. Vaccine efficacy and protective effect

- Vaccine efficacy using conditional exact method
  - This method computes an exact CI around the rate ratio (ratio of the event rates in the vaccine versus control groups) and takes into account the follow-up time of subjects within each group. For the calculation of vaccine efficacy using the conditional exact method, the following rules are applied:
- VE is defined as 1 minus the rate ratio.

- The follow-up time for each subject started:
  - at the day of first vaccination (Month 0) if analyses are done on the ES-E
  - at the day of third vaccination (Month 6) if analyses are done on the PPS for efficacy.
- The follow-up time for each subject ended,
  - at the time of the event (e.g.,the time of the histopathological endpoint).
  - at Visit 1 in HPV-092 study (Month 120 EXT-039) for subjects who returned for HPV-092 but did not have an event, or
  - last available timepoint for subjects who do not have an event and do not return for study HPV-092 EXT:039.
- The follow-up time was calculated in days as date of end of follow-up time minus the Date of vaccination + 1 and expressed in person-years at risk (number of days/365.25).
- The CI for vaccine efficacy can then be derived from the exact CI from p [Dragalin, 2002].

10.2. Laboratory testing and case assignment

10.2.1. Virological endpoints

10.2.1.1. HPV DNA PCR testing algorithm

The process to derive laboratory PCR testing collected in cervical sample is explained below:

To test for HPV DNA, SPF10 primers which amplify a 65-nucleotide region of the HPV L1 gene for most of the known HPV isolates are used; the generic amplification products are detected by hybridization on a microtitre plate (DEIA). HPV-positive specimens will be typed by reverse hybridization line probe assay (LiPA), using 28 HPV-specific hybridization probes enabling detection of 14 oncogenic HPV types [HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68] and 11 non-oncogenic HPV types [HPV-6, -11, -34, -40, -42, -43, -44, -53, -54, -70 and -74].

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

For example, a subject with HPV-16 infection had positive result for SPF10 primers general test and for LIPA test and/or type-specific test.

10.2.2. Histopathological endpoints

10.2.2.1. Overview of the histopathological endpoint determination process

This blind review process is conducted by a Panel of three expert gynaecological pathologists from CICAMS under the supervision of a fourth pathologist. The endpoints of CIN1 and CIN2+ are determined following a simple majority-rule protocol.

Three expert gynecological pathologists (named Pathologist #1, #2, #3) from the Study Panel are involved in the review of the histopathological specimen of the study. A fourth pathologist (referred to as "coordinating pathologist" in this document) co-ordinates the independent and blind review process and ensures that agreement on the location and grade level of the lesion in the tissue is obtained between at least two members of the panel. The sequence of slides produced per block at CICAMS is summarized in Figure 1.

During the cutting of the slides and the refacing of the block, all efforts are made to ensure that the sections shown in Figure 1 are available and that the loss of tissue is minimized.

Histopathological specimens that will be reviewed by the Panel include all the blocks prepared from cervical biopsies and excision specimens.

For each relevant specimen, material to be reviewed by the Study Panel consists of all Haematoxylin and Eosin (H&E) stained sections plus any additional slides with biomarker and the appropriate negative control slides, that are produced for each block during the routine histopathology review process at CICAMS (**see Figure 1**). Additionally, each member of the Study Panel has a colour-paper copy of the digital image of the deepest H&E slide of the block made at low magnification level, to allow location of all observed lesions. This digitized image is made by a technician under the supervision of the coordinating pathologist. One copy of this image is distributed to each of the pathologists of the panel and to the coordinator, respectively.

For each individual block, reviewers individually enter the diagnosis onto a specific form, using the CIN classification system. The reviewer also highlights on the digital image all the lesions observed on the H&E slide. The most severe area constitutes the study endpoint when multiple areas of abnormality of different grades are present. Any indeterminate or unsure combination or negative is considered as non-endpoint. Pathologists are asked when possible to make a firm decision but are not required to decide on cases that they consider absolutely uncertain.

The coordinating pathologist reviews the diagnoses made by Pathologists #1 and #2, to evaluate whether there is an agreement both on the location of the lesion and on the severity of the intra-epithelial neoplasia (CIN, VIN, VAIN). If Pathologists #1 and #2 agree on the diagnosis and its location on the digitized image, then the review stops, and the diagnosis is assigned accordingly. In case of disagreement, the coordinating pathologist requests Pathologist #3 to review the case. It should be noted that if Pathologist #1 and #2 agree on the CIN1+ category and on its location, but do not agree on the CIN1+ subcategories (CIN1, CIN2, CIN3, …. diagnosis) and/or on their location

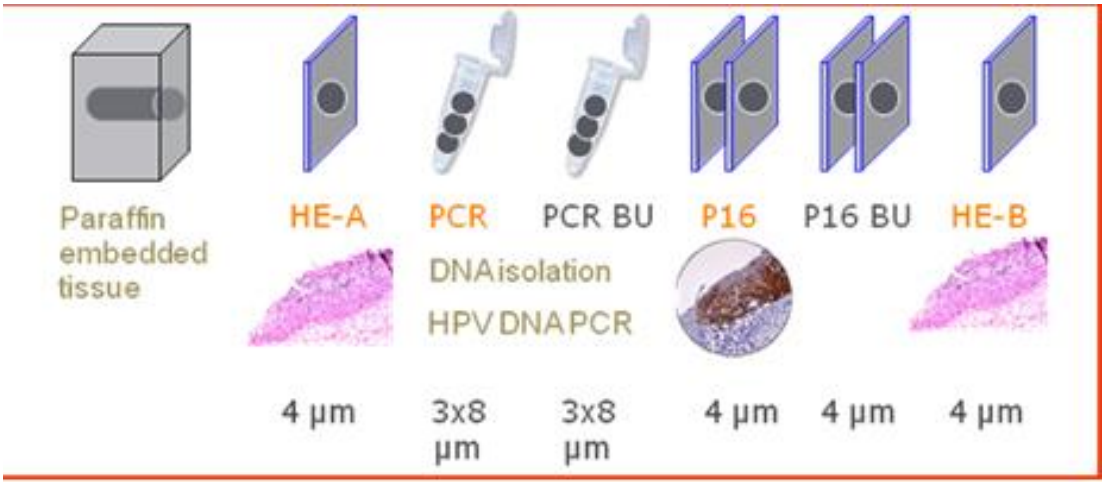
in the section, then the coordinating pathologist must request Pathologist #3 to review the cases to enable the majority-rule protocol.

Upon identification of a CIN1+ case by the panel, the coordinating pathologist identifies cases for which the majority-rule is met for the study endpoints. He eventually prepares additional digital images at higher magnification level as appropriate to highlight the location of the above lesions.

The lesional PCR result matched to the highest grade of histopathological abnormality reported by the Study Panel constitutes the study endpoint 'associated with' a high-risk HPV type.

The sponsor may, after reviewing all available data from a subject, decide to request additional testing on selected cases. This will generally be the case when a biopsy shows evidence for the presence of a grade 1 or higher lesion, but no association between the lesion and a high-risk HPV type can be made according to the case definition. In these cases, additional material may be used in order to confirm or exclude such an association.

Figure 1 Sequence of slides produced per block at CICAMS (BU=back-up slide; HE-A=HE slide-Before; HE-B=HE slide-After)



10.2.2.2. Case definition of histopathological endpoint

Table 10 identifies the slides which will be used for the definition of the study endpoint.

CIN1+ is defined as CIN1, CIN2, CIN3, LCGIN, HCGIN**,** adenocarcinoma in-situ (AIS) or invasive cervical cancer.

For the endpoints irrespective of HPV DNA result (any cytological abnormality, CIN1+ and CIN2+), an endpoint (e.g. CIN1+) should be detected on the H&E slide before PCR or on the slide after PCR. For all histopathological endpoints associated with specific virus types (e.g. HPV-16 and/or HPV-18), CIN1+ has to appear in the H&E slide before PCR, i.e., PCR has to appear on the H&E slide adjacent to the PCR slide:

Table 10 Case definition of histopathological endpoint

Result of H&E slide *before* PCR	Result of H&E slide *after* PCR	Case CIN1+	Case CIN1+ associated with specific virus type
< CIN1+	< CIN1+	No	No
CIN1+	CIN1+	Yes	Yes
CIN1+	< CIN1+	Yes	Yes
< CIN1+	CIN1+	Yes	No

10.2.2.3. HPV DNA PCR testing in tissue

The process to derive laboratory PCR testing collected in biopsy is explained below:

The formalin fixed and paraffin embedded tissue blocks used for histopathological analysis will be sectioned for PCR examination at CICAMS/CFC using an appropriate clean technique. Sections will be tested for HPV DNA using PCR methodology. Samples of lesions will be selected for further analysis using micro-dissection as appropriate. To test for HPV DNA, SPF10 primers which amplify a 65-nucleotide region of the HPV L1 gene for most of the known HPV isolates are used; the generic amplification products are detected by hybridization on a microtitre plate (DEIA). HPV-positive specimens will be typed by reverse hybridization line probe assay (LiPA), using 28 type-specific hybridization probes. This typing process enables detection of 14 oncogenic HPV types [HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68] and 11 non-oncogenic HPV types [HPV-6, -11, -34, -40, -42, -43, -44, -53, -54, -70 and -74]. All HPV positive samples will also be tested by HPV-16 specific PCR and HPV-18 specific PCR. Redundant testing using generic SPF10 PCR with LiPA, followed by HPV-16/18 type-specific PCR (TS-PCR) affords maximum test sensitivity. The results of this testing algorithm will be considered definitive for all HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66 and -68 and HPV-6, -11, -34, -40, -42, -43, -44, -53, -54, -70 and -74 related study endpoints using HPV DNA testing from histopathology.

10.2.2.4. Association between a CIN lesion and HPV type(s)

If more than one HPV type is found in a lesion, the presence of HPV types in the two immediately preceding cytology samples will be evaluated:

- The HPV type present in both the lesion and in at least one of the two immediately preceding cytology samples will be considered to be associated with that lesion.
- In case none of the HPV types present in the lesion will be found in any of the two immediately preceding cytology samples, then the HPV types present in the lesion will be considered to be associated with that lesion.

If only a single HPV type is found in a lesion, then this type will be considered to be associated with the lesion.

These rules are referring to the HPV type assignment algorithm [Paavonen, 2007]. This will be the primary analysis of vaccine efficacy for all cases reported in HPV-039 as well as in HPV-092 EXT:039.

However, the analysis of incidence of histopathological endpoints at year 10 timepoint (Visit 1 in HPV-092 EXT:039) will be performed based on the HPV DNA detected in the lesion in the HPV-092 EXT:039 study.

As a sensitivity analysis, vaccine efficacy against histopathological endpoints will also be analysed by considering the above defined type assignment algorithm for the cases reported till end of the study HPV-039 and based on the HPV DNA detected in the lesion at year 10 in the HPV-092 EXT:039 study.

10.3. TFL TOC

The Table Figure Listing (TFL) Table Of Content (TOC) which itemizes the planned list of TFL and their associated lay-out is developed as a separate document.

11. REFERENCES

Clopper CJ, Pearson E. The Use of Confidence or Fiducial Limits Illustrated in the case of the Binomial. Biometrika. 1934; 26:404-13.

Dragalin V, Fedorov V and Cheuvart B. Statistical approaches to establishing vaccine safety. *Stat Med.* 2002; 21:877-893

Paavonen J, Jenkins D, Bosch FX, Naud P, Salmeron J, Wheele CM, Chow S-N, Apter DL, Kitchener HC, Castellsague X, de Carvalho NS, Skinner SR, Harper DM, Hedrick JA, Jaisamrarn U, Limson GAM, Dionne M, Quint W, Spiessens B, Peeters P, Struyf F, Wieting SL, Lehtinen MO, Dubin G, for the HPV PATRICIA study group. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomized controlled trial. *The Lancet*. 2007; 369:2161-70.