GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	A phase III, open-label, mono-centre, follow-up extension study to evaluate the persistence of immune response to GSK Biologicals' HPV vaccine in healthy Chinese female subjects who received three doses of the vaccine in the HPV-058 study
eTrack study number and Abbreviated Title	207347 (HPV-093 EXT 058)
Scope:	All data pertaining to the HPV-093 study.
Date of Statistical Analysis Plan	Final: 21-MAR-2018
Co-ordinating author:	PPD
Reviewed by:	PPD - Lead Statistician PPD -Lead stat analyst PPD and PPD -CRDL, PPD - SC Writer, PPD -Lead SC-writer, PPD - Clinical Safety representatives PPD, Regulatory Affairs representative
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APP 9000058193 Statistical Analysis Plan Template (Effective date: 14 April 2017)	

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LIST OF ABBREVIATIONS

AE	Adverse event
CI	Confidence Interval
CRF	Case Report Form
CTRS	Clinical Trial Registry Summary
EL.U/ml	ELISA unit per millilitre
Eli Type	Internal GSK database code for type of elimination code
ELISA	Enzyme-linked immunosorbent assay
ES	Exposed Set
FAS	Full Analysis Set
GMC	Geometric mean antibody Concentration
GSK	GlaxoSmithKline
IU/ml	International units per millilitre
LL	Lower Limit of the confidence interval
MedDRA	Medical Dictionary for Regulatory Activities
N.A.	Not Applicable
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
UL	Upper Limit of the confidence interval

1. DOCUMENT HISTORY

Date	Description	Protocol Version
21-MAR-2018	Final Version	Final Version 1: 19 May 2017

2. STUDY DESIGN

- **Experimental design**: Phase III, open-label, mono-centric, single country study with a single group.
- **Duration of the study**: One day
  - Epoch 001: starting at Visit 1 (Day 1) and ending at Visit 1 (Day 1)
- **Primary completion Date (PCD)**: Visit 1 (Day 1).
- **End of Study (EoS)**: Last testing results released for samples collected at Visit 1.
- **Study group:** The study group is as follows:
  - HPV group: Subjects from HPV-058 study who received all three doses of the HPV-16/18 vaccine will be eligible to take part in this extension study

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

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

3. OBJECTIVES

3.1. Primary objective

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

3.2. Secondary objective

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

4. ENDPOINTS

4.1. Primary endpoint

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

4.2. Secondary endpoint

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

5. ANALYSIS SETS

5.1. Definition

Two cohorts are defined for the purpose of analysis

5.1.1. Exposed Set

- The Exposed Set (ES) will include all subjects who participate in this study.

5.1.2. Per-protocol cohort for analysis of immunogenicity(PPS)

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

5.2. Criteria for eliminating data from Analysis Sets

Elimination codes are used to identify subjects to be eliminated from analysis. Details are provided for each set below.

A consolidated table is also available in Annex 2.

5.2.1. Elimination from Exposed Set (ES)

Code 900 (invalid informed consent or fraud data) will be used for identifying subjects eliminated from ES.

5.2.2. Elimination from Per-protocol analysis Set (PPS)

5.2.2.1. Excluded subjects

A subject will be excluded from the PPS analysis under the following conditions

Code	Condition under which the code is used
900	Invalid informed consent or fraud data
1500	Subjects who were not included in the according to protocol (ATP) immunogenicity analysis in the primary vaccination study (HPV-058),
2010	Protocol violation linked to the inclusion\exclusion criteria
2040	Administration of any concomitant medication forbidden by the protocol
2050	Underlying medical condition based on medical history
2100	Serological results not available

5.2.2.2. Right censored Data

NA

5.2.2.3. Visit-specific censored Data

NA

5.3. Important protocol deviation not leading to elimination from per-protocol analysis set

- In case unexpected vaccinations at study start were granted due to regulatory recommendation, the subjects who had such vaccination could be mentioned.
- Protocol deviations related to informed consent and not leading to eliminations.

6. STATISTICAL ANALYSES

Note that standard data derivation rules and statistical methods are described in annex 1.

6.1. Demography

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

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

6.1.2. Additional considerations

None

6.2. Exposure

6.2.1. Analysis of exposure planned in the protocol

None

6.2.2. Additional considerations

None

6.3. Immunogenicity

6.3.1. Analysis of immunogenicity planned in the protocol

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

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

6.4. Analysis of safety

6.4.1. Analysis of safety planned in the protocol

None

6.4.2. Additional considerations

- Listing of SAEs related to the study participation or concurrent GSK medications/vaccination or any fatal SAE reported during the study period will be described in detail.

7. ANALYSIS INTERPRETATION

All analyses are descriptive.

8. CONDUCT OF ANALYSES

8.1. Sequence of analyses

The analysis will be performed when all data will be available.

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**
Analysis of epoch 1	E1_01	SR	YES	YES	TFL TOC Statistical peer review version- All TFLs

8.2. Statistical considerations for interim analyses

No interim analyses planned for this study

9. CHANGES FROM PLANNED ANALYSES

Not applicable

10. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

The TFL TOC provides the list of tables/listings and figures needed for the study report. It also identifies the tables eligible for each analyses and their role (synopsis, in-text, post-text, SHS, CTRS,…). Note that all TFL aimed to be included as post-text are noted as post-text even if these are tabulation of individual data such as listing of SAE. The post-text material contain all source material for the study report and accordingly a post-text table may be redundant with an in-text table.

The following group names will be used in the TFLs, to be in line with the T-domains:

Group order in tables	Group label in tables	Group definition for footnote	Pooled Groups label in tables	Pooled definition for footnote
1	HPV	Subjects who completed three dose vaccination schedule in HPV-058 study	HPV group	HPV group

11. ANNEX 1 STANDARD DATA DERIVATION RULE AND STATISTICAL METHODS

11.1. Statistical Method References

The exact two-sided 95% CIs for a proportion within a group will be the Clopper-Pearson exact CI [Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. Biometrika. 1934;26:404-413].

11.2. Standard data derivation

- 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

- Demography

Age: Age at the reference activity, computed as the number of units between the date of birth and the reference activity. Note that due to incomplete date, the derived age may be incorrect by 1 month when month is missing from the birthdate. This may lead to apparent inconsistency between the derived age and the eligibility criteria/the age category used for randomization.

- Immunogenicity

For a given subject and given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.

The Geometric Mean Concentration (GMCs) calculations are performed by taking the anti-log of the mean of the log concentration transformations. Antibody concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off of the assay for the purpose of GMC calculation. The cut-off values for HPV-16 and HPV-18 are defined as 19 ELU/mL and 18 ELU/mL respectively

A seronegative subject is a subject whose antibody concentration is below the cut-off value of the assay. A seropositive subject is a subject whose antibody concentration is greater than or equal to the cut-off value of the assay.

ELISA results (number and percentage of subjects with serum antibody concentration equal to or above assay cut-off and GMC) are also expressed in IU/ml.

The conversion factors between El.U/ml and IU/ml for HPV-16 and HPV-18 are 6.1 and 5.7 respectively.

The assay cut off of19 El.U/ml for HPV-16 converts to 3.1 IU/ml.

The assay cut off of 18 El.U/ml for HPV-18 converts to 3.2 IU/ml.

All CI computed will be two-sided 95% CI.

- Number of decimals displayed:

The following decimal description from the decision rules will be used for the demography, immunogenicity.

Display Table	Parameters	Number of decimal digits
Demographic characteristics	Mean, median age, SD (age)	1
Demographic characteristics	Minimum and Maximum (age)	0
Immunogenicity	Anti-HPV GMC including LL & UL of CI	1
All summaries	% of count, including LL & UL of CI	1

12. ANNEX 2: SUMMARY ON ELIMINATION CODES

Refer to section 5.2

13. ANNEX 3: STUDY SPECIFIC MOCK TFL

The following drafted study specific mocks will be used.

The data display, title and footnote is for illustration purpose and will be adapted to the study specificity as indicated in the TFL TOC. Note that there may be few changes between the study specific SAP mock TFL and the final TFLs as editorial/minor changes do not require a SAP amendment

Table 1 Number of subjects enrolled into the study as well as the number excluded from PPS analyses with reasons for exclusion

	HPV		
Title	**n**	**s**	**%**
Exposed set			
Reasons for elimination			
Per-Protocol Set			

HPV = Subjects who completed three dose vaccination schedule in HPV-058 study
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered cohort relative to the Exposed set

Table 2 Summary of demographic characteristics (Exposed set)

		HPV N =	
Characteristics	**Parameters or Categories**	**Value or n**	**%**
Age (years)	Mean		-
	SD		-
	Median		-
	Minimum		-
	Maximum		-
Race	Black		
	White/caucasian		
	Arabic/north african		
	Hispanic		
	Chinese		

HPV = Subjects who completed three dose vaccination schedule in HPV-058 study
N = number of subjects
n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
SD = Standard deviation

Table 3 Summary of demographic characteristics (Per-Protocol Set)

		HPV N =	
Characteristics	**Parameters or Categories**	**Value or n**	**%**
Age (years)	Mean		-
	SD		-
	Median		-
	Minimum		-
	Maximum		-
Race	Black		
	White/caucasian		
	Arabic/north african		
	Hispanic		
	Chinese		

HPV = Subjects who completed three dose vaccination schedule in HPV-058 study
N = number of subjects
n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
SD = Standard deviation

Table 4 Number and percentage of subjects with an anti-HPV-16 serum antibody concentration equal to or above the cut-off (19 EL.U/mL) and GMC (Per-Protocol Set)

				≥ 19				GMC				
						95% CI			95% CI			
Antibody	Group	Timing	N	N	%	LL	UL	value	LL	UL	Min	Max
HPV 16.	HPV											

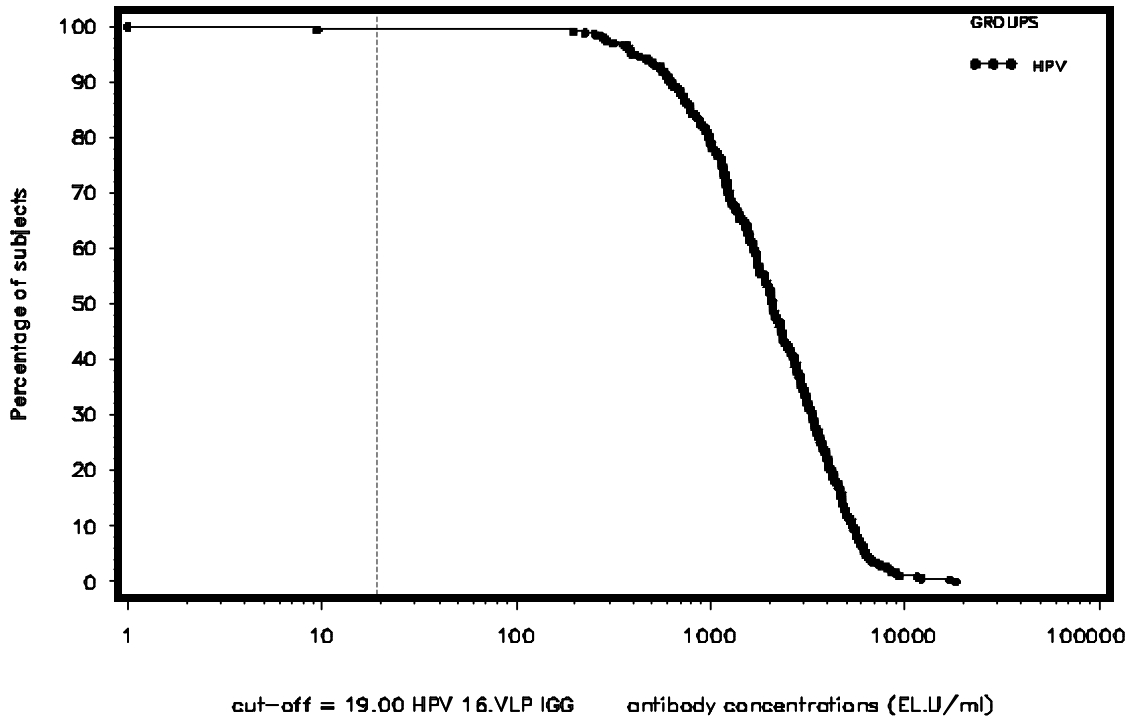
HPV = Subjects who completed three dose vaccination schedule in HPV-058 study
GMC = geometric mean antibody concentration
N = number of subjects with results available
n/% = number/percentage of subjects with concentration equal to or above 19 ELU/mL
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum

Table 5 Number and percentage of subjects with an anti-HPV 18. serum antibody concentration equal to or above the cut-off (18 EL.U/mL) and GMC (Per-Protocol Set)

				≥ 18				GMC				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
HPV 18.	HPV											

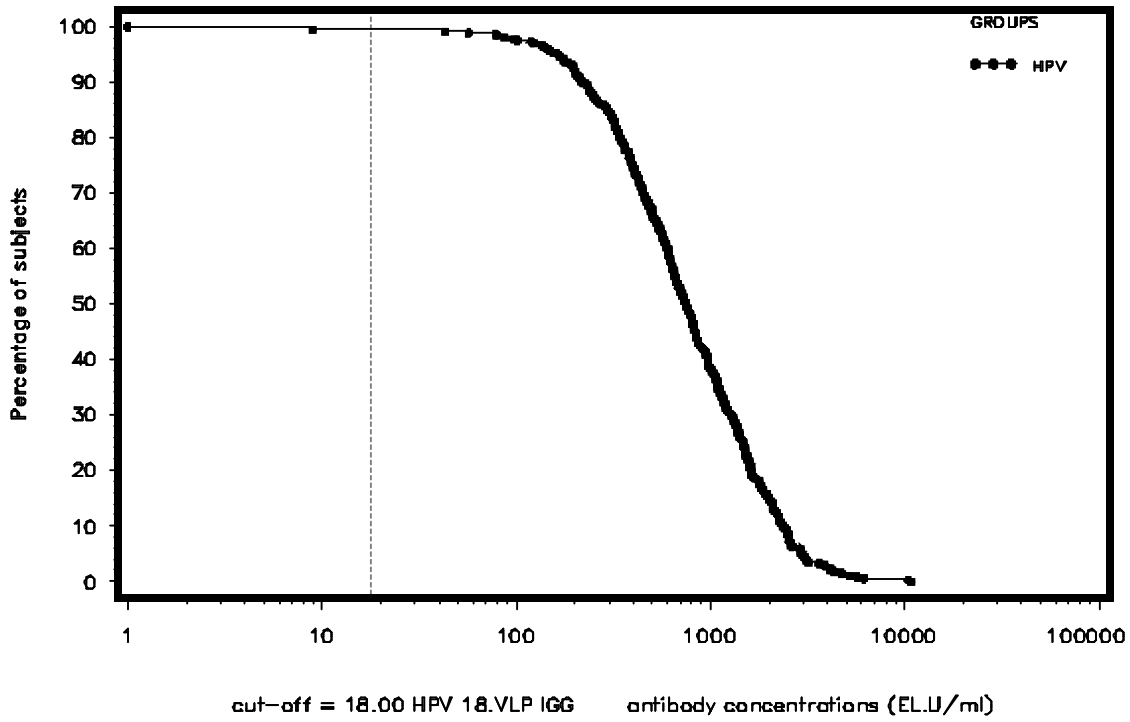
HPV = Subjects who completed three dose vaccination schedule in HPV-058 study
GMC = geometric mean antibody concentration
N = number of subjects with results available
n/% = number/percentage of subjects with concentration equal to or above 18 ELU/mL
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum

Figure 1 Reverse cumulative distribution curve for anti-HPV-16 serum antibody concentrations (Per-Protocol Set)



HPV = Subjects from HPV-058 study who received all three doses of the HPV-16/18 vaccine

Figure 2 Reverse cumulative distribution curve for anti-HPV-18 serum antibody concentrations (Per-Protocol Set)



HPV = Subjects from HPV-058 study who received all three doses of the HPV-16/18 vaccine

Table 6 Listing of SAEs (Exposed set)

Group	Pid	Case Id	Age (Month)	Sex	Verbatim	Preferred term	System Organ Class	MA type	Dose	Day of onset	Duration	Causality	Outcome
HPV													

HPV = Subjects who completed three dose vaccination schedule in HPV-058 study

Table 7 HPV-16/18 antibody concentrations in subjects in this study versus antibody concentrations at Year 6 in subjects from the HPV-039 study (Per-Protocol Set)

Antibody	N at Y6 (HPV-039)	HPV-039 GMC at Y6	95% CI		N (HPV-093)	HPV-093 GMC(7 to 8 years after vaccination in HPV-058)	95% CI	
			LL	LL			LL	UL
HPV-16								
HPV-18								

N: Number of subjects with available results
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 8 Study population (Exposed Set)

Number of subjects	HPV
Planned, N	
Enrolled, N (ES)	
Completed, n (%)	
Demographics	
N (ES)	
Females:Males	
Mean Age, years (SD)	
Median Age, years (minimum, maximum)	

HPV = Subjects who completed three dose vaccination schedule in HPV-058 study
SD = Standard Deviation
N = Total number of subjects enrolled in the study
n/% = number / percentage of subjects in a given category

Table 9 Number (%) of subjects with serious adverse events including number of events reported during the study (Exposed Set)

			HPV p N =		
Type of Event	**Primary System Organ Class**	**Preferred Term (CODE)**	**n***	**n**	**%**
SAE	At least one symptom				
Related SAE*	At least one symptom				
Fatal SAE	At least one symptom				
Related fatal SAE	At least one symptom				

HPV = Subjects who completed three dose vaccination schedule in HPV-058 study
N = number of subjects enrolled
n* = number of events reported
n/% = number/percentage of subjects reporting the symptom at least once

* Related = Related to the study participation or concurrent GSK medications/vaccination

Table 10 Number of enrolled subjects by age category

		HPV N =
Characteristics	**Categories**	**n**
Age category	Adolescents (12-17 years	
Age category	Adults (18-64 years)	

HPV = Subjects who completed three dose vaccination schedule in HPV-058 study
N = Number of enrolled subjects
n= number of enrolled subjects included for a given age category

Table 11 Number of enrolled subjects by country

	HPV N =
Country	**n**
China	

HPV = Subjects who completed three dose vaccination schedule in HPV-058 study
N = Number of enrolled subjects
n= number of enrolled subjects included in a given age category

Table 12 Number and percentage of subjects with an anti-HPV-16 serum antibody concentration equal to or above the cut-off and GMC expressed in IU/ml (Per-Protocol Set)

				≥ 3.1 IU/mL				GMC				
					95% CI			95% CI				
Antibody	Group	Timing	N	N	%	LL	UL	value	LL	UL	Min	Max
HPV 16	HPV											

HPV = Subjects who completed three dose vaccination schedule in HPV-058 study
GMC = geometric mean antibody concentration
N = number of subjects with results available
n/% = number/percentage of subjects with concentration equal to or above 3.1 IU/mL
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum

Table 13 Number and percentage of subjects with an anti-HPV 18. serum antibody concentration equal to or above the cut-off and GMC expressed in IU/ml (Per-Protocol Set)

				≥ 3.2 IU/ml				GMC				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
HPV 18	HPV											

HPV = Subjects who completed three dose vaccination schedule in HPV-058 study
GMC = geometric mean antibody concentration
N = number of subjects with results available
n/% = number/percentage of subjects with concentration equal to or above 3.2 IU/mL
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum