Statistical Analysis Plan

Study alias & e-track number(s): HPV-067 EXT 015 (113621)

Detailed Title:	A phase IIIb, open-label, multi-centre immunization study to evaluate the safety of GlaxoSmithKline (GSK) Biologicals' HPV-16/18 L1 VLP AS04 vaccine administered intramuscularly according to a 0, 1, 6-month schedule in healthy female subjects who received the placebo control in the GSK HPV-015 study
SAP version	Version 1
SAP date	25-SEP-2015
Scope:	All data pertaining to the above study.
Co-ordinating author:	PPD
Other author(s):	
Adhoc reviewers:	PPD (safety)
Approved by:	PPD (CRDL), PPD (Lead statistician), PPD (Project statistician), PPD (scientific writer)

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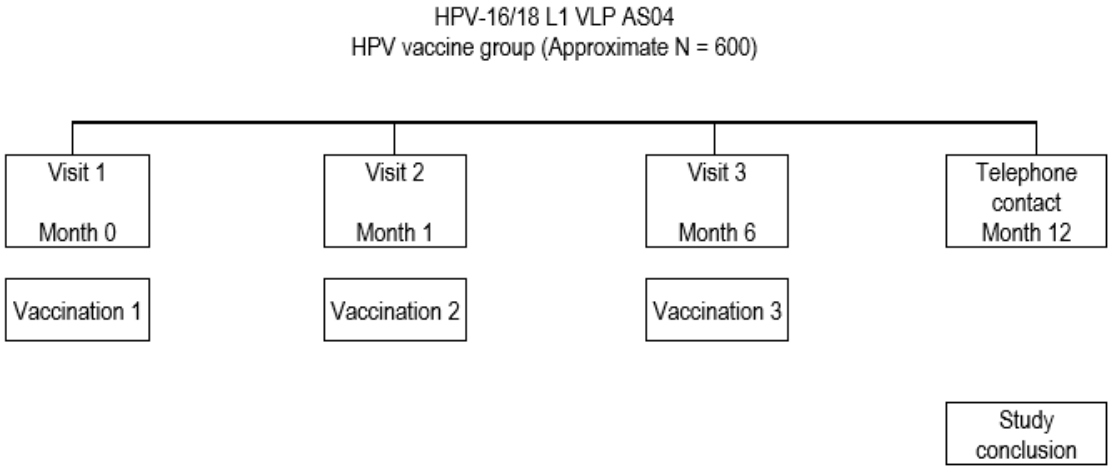
LIST OF ABBREVIATIONS

AE	Adverse event
AS04	GlaxoSmithKline's proprietary adjuvant system consisting of aluminium salt plus 3-O-desacyl-4'-monophosphoryl lipid A (MPL)
ATP	According-To-Protocol
CARS	Computer Aided for Regulatory Submission
CI	Confidence Interval
eCRF	electronic Case Report Form
Eli Type	Internal GSK database code for type of elimination code
GSK	GlaxoSmithKline
HPV	Human Papillomavirus
LL	Lower Limit of the confidence interval
µg	microgram
pIMD	potential Immune-Mediated Disease
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDD	SAS Drug development
TFL	Tables Figures and Listing template annexed to SAP
UL	Upper Limit of the confidence interval
VLP	Virus-like particles

1. DOCUMENT HISTORY

Date	Description	Protocol Version
25-SEP-2015	Version 1	Amendment 2 - 13-JAN-2011

2. STUDY DESIGN



- **Experimental design**: Phase IIIB multi-centric, single-group: HPV vaccine group (HPV-16/18 L1 VLP AS04).
- **Treatment allocation**: sequential allocation of subjects to receive the HPV-16/18 L1 VLP AS04 vaccine
- **Blinding**: open-label
- **Treatment group**: HPV vaccine group (HPV-16/18 L1 VLP AS04)
- **Vaccination schedule**: Three doses of HPV-16/18 L1 VLP AS04 vaccine (20 µg HPV-16, 20 µg HPV-18) administered intramuscularly according to a 0, 1, 6-month schedule.
- **Control**: uncontrolled .
- **Type of study**: e.g. self-contained, extension of study HPV-015
- **Data collection**: eCRF
- **Duration of the study**: Approximately 12 months per subject.
- **Study visits per subject**: Three scheduled visits are planned at Months 0, 1, 6. There will be a telephone contact with the subject at Month 12 (i.e. six months after the third dose of the HPV-16/18 L1 VLP AS04 vaccine).

- **Safety monitoring:**
  - All serious adverse events (SAEs) occurring throughout the study period (i.e. from Day 0 up to the telephone contact at Month 12) will be reported for all subjects.
  - Medically significant conditions (including pIMDs) will be reported for all subjects throughout the study period.
  - Pregnancies and pregnancy outcomes will be reported for all subjects throughout the study
- **Number of subjects:**

  Of all subjects participating in the HPV-015 conclusion visits who received the control placebo in the HPV-015 study, approximately 600 subjects are expected to enrol in this study. Subjects who participated in the HPV-015 study may decide to conclude their participation in the HPV-015 study at Visit 9, Visit 11 or at the last study visit in HPV-015 planned under protocol amendment 4.

  These subjects will be contacted and invited to participate in this cross-over vaccination study with GSK Biologicals' HPV-16/18 L1 VLP AS04 vaccine. Enrolment should take place within two years after the subject has completed the HPV-015 study.

3. OBJECTIVES

- To assess the safety of the HPV-16/18 L1 VLP AS04 vaccine throughout the study period.

4. ENDPOINTS

- Occurrence, intensity and causal relationship to vaccination of medically significant conditions (including pIMDs) throughout the study
- Occurrence, intensity and causal relationship to vaccination of SAEs throughout the study
- Occurrence of pregnancies and pregnancy outcomes throughout the study

5. STUDY POPULATION

The list of applicable elimination codes for each cohort can be found in the study specific form FORM-BIO-CLIN-9004-05 Criteria for eliminating subjects from the analyses.

Cohort	Elimination codes	Eli Type
Total Vaccinated Cohort	900,1030	MA

MA: main analysis

6. STATISTICAL METHODS

6.1. Study cohorts to be evaluated

The analysis will be performed on the Total vaccinated cohort.

The Total Vaccinated Cohort will include all vaccinated subjects (i.e. subjects who received at least one dose of HPV-16/18 L1 VLP AS04 vaccine in this study) for whom safety data are available.

Intervals between study visits

Interval	Optimal length of interval (months)	Recommended interval between scheduled visits/contact (months)
1 (visit 1→ visit 2)	1 – 2.5	1
2 (visit 1→ visit 3)	5 - 12	6
3 (visit 3→ phone contact)	6 - 7	6

Analysis of demographics/baseline characteristics

Demographic characteristics (age, region, race) will be tabulated.

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

The distribution of subjects enrolled among the study sites will be tabulated.

Analysis of safety

No inferential analysis will be performed. Analyses of safety endpoints will only be descriptive.

The proportion of subjects with at least one report of an SAE and/or at least one medically significant condition (including pIMDs) will be tabulated with exact 95% confidence interval (CI) throughout the study period.

SAEs and other medically significant conditions (including pIMDs) will be described in detail. SAEs and other medically significant conditions (including pIMDs) will be further evaluated for relationship to vaccination.

Pregnancies and pregnancy outcomes will be described in detail.

7. STATISTICAL CALCULATIONS

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

The exact 95% CIs for a proportion within a group will be based on the method by Clopper [Clopper]

7.1. Derived and transformed data

7.1.1. 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.

7.1.2. Demography Age: Age of a subject is computed by considering the date of birth and date of the first vaccination in this study for that subject.In case day is missing, 15 is used. In case day & month are missing, 30June is used.

Number of decimals: The following decimal description will be used for the demography and safety analyses.

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

8. CONDUCT OF ANALYSES

SAEs, other medically significant conditions, pregnancies and pregnancy outcomes will be described in detail. These safety data will be presented in a clinical study report.

8.1. Sequence of analyses

Description	Analysis ID (SDD & CARS sub-folder)	Disclosure Purpose	Reference for TFL
Final Analysis	E1_01	Study report	All tables from TFL dated 19-OCT-2015

8.2. Statistical considerations for interim analyses

No interim analysis is planned for this study.

9. CHANGES FROM PLANNED ANALYSES

None

10. REFERENCES

The exact 95% CIs for a proportion within a group will be calculated [Clopper, 1934*].