Statistical Analysis Plan

Study alias & e-track number(s): HPV-062 EXT:015 (113617)

Detailed Title:	A phase IIIb, open, multi-centre gynaecological extension study for the follow-up of a subset of HPV-015 study subjects
SAP version	Version 1 (final)
SAP date	22-OCT-2014
Scope:	All data pertaining to the above study.
Co-ordinating author:	PPD
Other author(s):	PPD
Approved by:	PPD (Clinical Research and Development Lead), PPD (Project Statistician), PPD (Lead Statistician), PPD (Scientific writer)

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LIST OF ABBREVIATIONS

AE	Adverse event
AGC	Atypical glandular cells
ASCCP	American Society for Colposcopy and Cervical Pathology
ASC-US	Atypical squamous cells of undetermined significance
ASC-H	Atypical squamous cells cannot exclude HSIL
CARS	Computer Aided for Regulatory Submission
CI	Confidence Interval
Eli Type	Internal GSK database code for type of elimination code
GSK	GlaxoSmithKline
HCII	Hybrid Capture II
HPV	Human papillomavirus
HSIL	High grade squamous intraepithelial lesion
LL	Lower Limit of the confidence interval
LSIL	Low grade squamous intraepithelial lesion
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDD	SAS Drug development
UL	Upper Limit of the confidence interval

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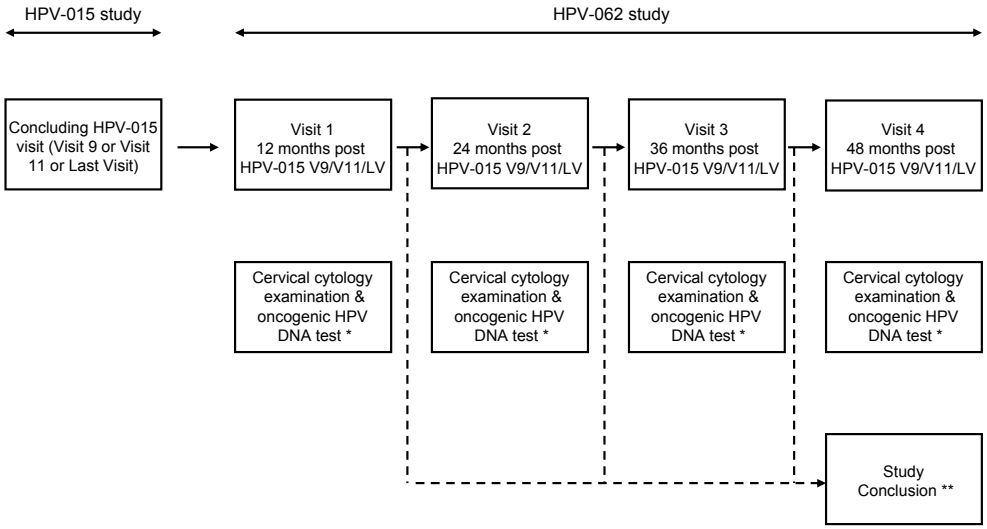
1. DOCUMENT HISTORY

Date	Description	Protocol Version
22-OCT-2014	Version 1	Administrative Change 1 Final: 18 August 2010

2. STUDY DESIGN

Figure 1 Study visits and study procedures



*Subjects with two positive oncogenic HPV DNA tests or one cervical cytology reading ≥ASC-US (atypical squamous cells of undetermined significance) positive for oncogenic HPV DNA or one cervical cytology reading ≥LSIL (low grade squamous intraepithelial lesion) will be referred for colposcopy evaluation according to the clinical management algorithm. Oncogenic HPV tests (HCII) will only be performed on normal and ASCUS cytological samples.
** Study conclusion, see dotted line (--), will occur after any given visit that required treatment of cytological abnormality, any given visit with a negative oncogenic HPV DNA test and normal cervical cytology or the closing of study activities related to Visit 4.

- **Experimental design:** A phase IIIb, open, multi-centre study with one group.
- **Treatment allocation:** None.
- **Blinding:** Open.
- **HPV-015 concluding visit**: 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.

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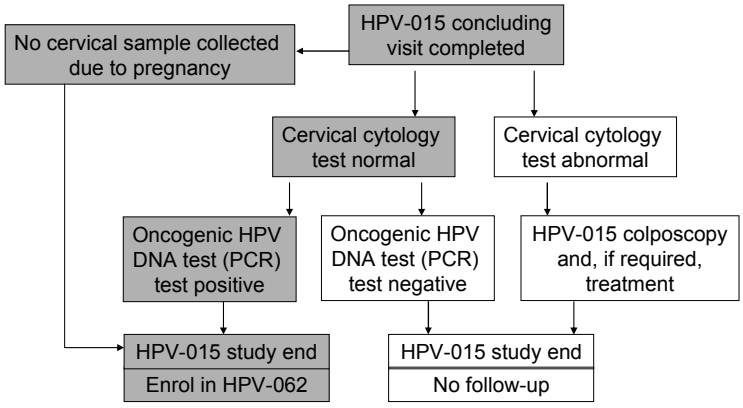
- **Treatment groups:** One study group consisting of a subset of HPV-015 subjects who at their concluding HPV-015 study visit:
  - displayed normal cervical cytology but tested positive for oncogenic HPV infection
  - were pregnant so that no cervical sample could be collected at that visit

The study eligibility algorithm is presented in Figure 2.

Figure 2 HPV-062 EXT:015 study eligibility algorithm



- **Vaccination schedule(s):** None.
- **Control:** None.
- **Type of study:** Gynaecological follow-up extension study of a subset of HPV-015 study subjects.
- **Data collection:** Remote Data Entry (RDE).
- **Duration of the study:** Maximum of four years for each subject.
- **Study visits per subject:** Up to four scheduled visits at approximately Months 12, 24, 36 and 48 after each subject's concluding HPV-015 study visit.

  Subjects are eligible to join the study at any visit.
- **Study procedures:**

  Subjects will enter the study approximately one year after their HPV-015 concluding visit. Annual visits will be scheduled for a maximum study duration of approximately four years.

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At each visit, a gynaecological examination will be performed and cervical liquid-based cytology samples will be collected for cervical cytology examination and oncogenic HPV DNA testing, if the cytology reading is normal or ASCUS.

The presence of oncogenic HPV infection will be determined by the Hybrid Capture® II (HCII) test, which detects HPV DNA types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 [Vernick, 2003, Digene Corporation 2002]. Cervical cytology examination will be performed using the ThinPrep®Pap test.

Continued study participation as well as further referral/treatment will be based on the test results from each visit, and will be aligned with the clinical management algorithm which is aligned with the 2009 American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines for use of HPV DNA testing as an adjunct to cytology for cervical cancer screening in women 30 years or older.

The following clinical management algorithm will be applied, refer to Figure 3.

- Subjects with normal cervical cytology and who are oncogenic HPV DNA negative, will end their participation in the study.
- Subjects with normal cervical cytology, but who are oncogenic HPV DNA positive in one single test, will be asked to return at the next study visit.

  This outcome will only be applicable to subjects who were pregnant at their concluding HPV-015 study visit so that no cervical sample could be collected at that visit.
- Subjects with normal cervical cytology, but who are oncogenic HPV DNA positive in two subsequent tests, will be referred to colposcopy. The result of the subjects' last HPV-015 study visit will be taken into account at Visit 1.
- Subjects with a single cervical cytology reading of ≥ASC-US (atypical squamous cells of undetermined significance) and positive for oncogenic HPV DNA will be referred to colposcopy.
- Subjects with a single cervical cytology reading of ≥LSIL (low grade squamous intraepithelial lesion) will be referred to colposcopy.

Please note that a missing result for HCII will be managed as oncogenic HPV positive.

In case of referral for colposcopy, the post-colposcopy follow-up strategies are:

- If no lesion is detected or the detected lesion does not require any treatment, subjects will be asked to return at the next study visit.
- If a lesion that requires treatment is detected, the subject should be referred to treatment according to local medical practice. Any further management following local cervical therapy for cervical lesions will be handled according to

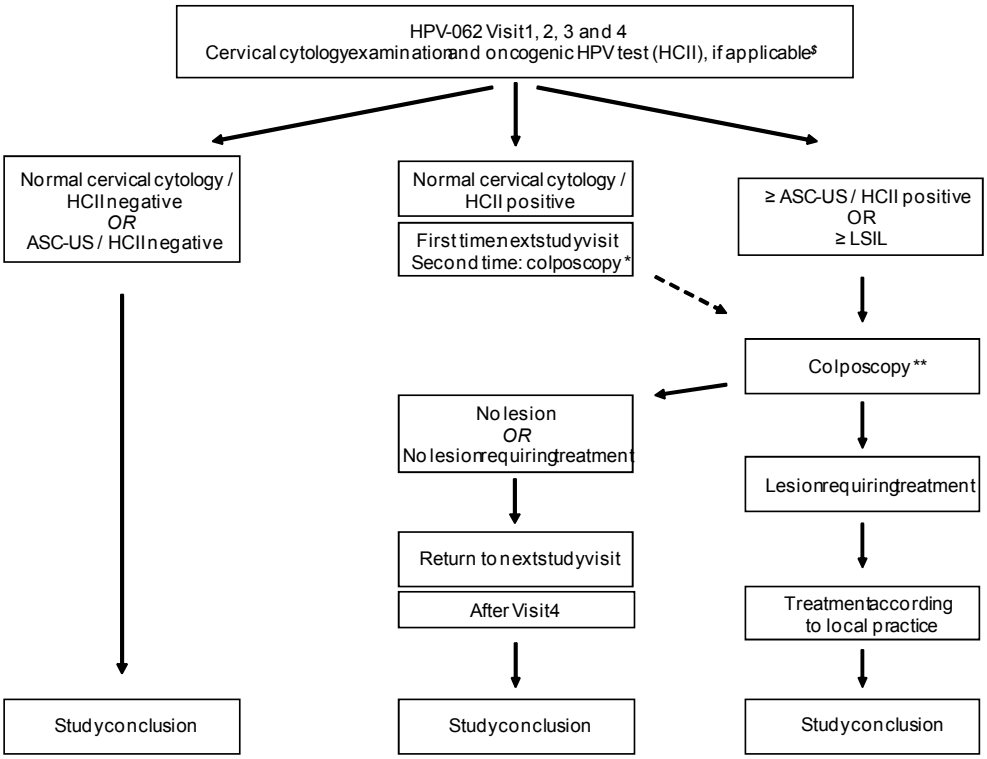
local medical practice within the local health care system. After treatment, the subject's participation in the study will end.

As management algorithms cannot define every clinical situation, it is the investigator's (or his/her designee's) responsibility to exercise appropriate clinical judgement in the medical management of each individual case.

Once their study participation ends, all subjects should be referred to their local health care system.

Subjects who have not developed cervical lesions by the end of the study, but who are still positive for oncogenic HPV infection, should be informed of the potential risks of being positive for oncogenic HPV DNA, and the importance of continued follow-up.

Figure 3 Clinical management algorithm



HPV DNA test (HCII) = Hybrid Capture® II test detecting HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68.
Specimens will be reported as "Quantity Not Sufficient" (QNS) in the case where there is an inadequate amount of cells for HCII and preferentially, a repeat sample will be collected. Missing HCII test results should be managed as oncogenic HPV positive
* = The result of the subject's concluding HPV-015 study visit will be taken into account. Subjects who were pregnant at that visit so that no cervical sample could be collected, and who display normal cytology but are positive for oncogenic HPV DNA at Visit 1, will return for the next study visit.

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** = Colposcopy and/or colposcopy-directed biopsies will be performed according to local medical practice.
$ = Oncogenic HPV tests (HCII) will only be performed on normal and ASCUS cytological samples.

- **Study visit activities and gynaecological follow-up reporting**
  - Gynaecological examination at Visit 1, Visit 2, Visit 3 and Visit 4.
  - Collection of cervical liquid-based cytology samples at Visit 1, Visit 2, Visit 3 and Visit 4 for cervical cytology examination and oncogenic HPV DNA testing, if the cytology reading is normal or ASCUS.
  - Referral to colposcopy according to protocol clinical management algorithm, if required.
  - Conduct of colposcopy, colposcopy directed biopsies and local cervical therapy according to local medical practice, if required.
  - Recording of colposcopic referral according to management algorithm, if required.
  - Recording of treatment referrals according to local medical practice, if required.
- **Safety reporting:**
  - All fatal SAEs will be reported.
  - All SAEs assessed as being possibly related to study participation will be reported.
  - All SAEs assessed as being possibly related to a concurrent GSK medication will be reported.
  - Withdrawal from the study due to adverse events (AEs) or SAEs will be reported.

No other AEs or SAEs for HPV-015 study subjects will be reported in this study. AEs and SAEs related to the vaccine administrated in the HPV-015 trial should be reported as part of the HPV-015 study, as described in the HPV-015 study protocol.

The following group names will be used for the statistical analyses:

Group order in tables	Group label in tables	Group definition for footnote
1	HPV-062 study subjects	HPV-015 study subjects enrolled in HPV-062 who displayed normal cervical cytology but tested positive for oncogenic HPV infection at their concluding HPV-015 study visit. or who were pregnant at their concluding study visit were not able to provide a cervical sample

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3. OBJECTIVES

- To provide clinical management and, if required, treatment to subjects who at their concluding HPV-015 study visit displayed normal cervical cytology but tested positive for oncogenic HPV infection or who were pregnant at their concluding visit of the HPV-015 study so that no cervical sample could be collected.

Refer to Section 4**Error! Reference source not found.** for the definition of the study endpoints.

4. ENDPOINTS

- Occurrence of positive oncogenic HPV DNA results in cervical samples by HPV DNA testing (Hybrid Capture® II test [HCII]).
- Occurrence of cervical cytological abnormalities in cervical samples by ThinPrep® PapTest.
- Occurrence of referral to colposcopy.
- Occurrence of referral to treatment.

5. STUDY POPULATION

The study population will contain a subset of HPV-015 study enrolled in HPV-062 study

- Subjects who displayed normal cervical cytology but tested positive for oncogenic HPV infection at their concluding HPV-015 study visit.

or

- Subjects who were pregnant at their concluding HPV-015 study visit were not able to provide a cervical sample.

HPV-062 -Total cohort

The HPV-062 cohort includes the HPV-015 subjects

- who conclude their participation in the HPV-015 study at Visit 9, Visit 11 or at the last study visit in HPV-015 study displayed normal cervical cytology but tested positive for oncogenic HPV infection

or

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- who were pregnant during HPV-015 study so that no cervical sample could be collected at that visit.
- who attend any visit in this study.

The list of applicable elimination codes for this cohort

Cohort	Elimination codes	Eli Type
HPV-062 -Total cohort	900,1500	MA

MA: Main analysis

6. STATISTICAL METHODS

The analysis will be performed on the HPV-062 Total cohort

6.1.1. Analysis of demographics

Demographic characteristics (age, race and gender), withdrawal status will be summarised using descriptive statistics:

Age: Age of a subject is computed by considering the date of birth and date of the first visit in this study for that subject. Age of a subject was computed as the time interval between two dates in specified time unit.

- Frequency tables will be generated for categorical variable such as race and gender.
- Mean, median, standard deviation will be provided for continuous data such as age.

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

6.1.2. Descriptive analysis of clinical management

For each visit and overall:

- Results of oncogenic HPV DNA tests.
- Results of cervical cytology tests.
- Referrals to colposcopy, if required.
- Referrals to treatment according to local medical practice, if required.

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7. STATISTICAL CALCULATIONS

7.1. Derived and transformed data

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

The following categories for cervical cytology reading will be specified:

- Negative for intraepithelial lesion or malignancy (negative).
  - Negative/HCII negative (Normal/oncogenic HPV negative)
  - Negative/HCII positive (Normal/oncogenic HPV positive).
  - Negative/HCII quantity not sufficient (Normal/QNS).
- Unsatisfactory.
- Atypical squamous cells of undetermined significance (ASC-US).
  - ASC-US/HCII negative (ASC-US/oncogenic HPV negative)
  - ASC-US/HCII positive (ASC-US/oncogenic HPV positive).
  - ASC-US/HCII quantity not sufficient (ASC-US/QNS).
- Atypical squamous cells cannot exclude HSIL (ASC-H).
- Low-grade squamous intraepithelial lesion (LSIL).
- High-grade squamous intraepithelial lesion (HSIL).
- Atypical glandular cells (AGC).
- Invasive malignancy.

Handling of missing data:

Demography

For a given subject and a given demographic variable, missing measurement will not be replaced. Therefore, analysis of demography will exclude subjects with missing measurements.

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7.2. Data presentation description

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

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

8.1. Sequence of analyses

The final analyses will be conducted when all data are available. This analysis will include the final analysis of Demography and safety. These analyses will be the basis of a Clinical Study Report and will be made available to the investigator(s).

Description	Analysis ID (SDD & CARS sub-folder)
Final Analysis	E1_01

8.2. Statistical considerations for interim analyses

No interim analysis is planned for this study.

9. CHANGES FROM PLANNED ANALYSES

Since SAE is not the endpoints of study protocol, following analysis related to SAE will not be generated

- All fatal SAEs occurring throughout the study period.
- All SAEs assessed as being possibly related to study participation occurring throughout the study period.
- All SAEs assessed as being possibly related to GSK products occurring throughout the study period.
- Withdrawal from the study due to AEs or SAEs

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10. REFERENCES

- Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. *Biometrika*. 1934;26:404-413