Statistical Analysis Plan

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Signature Page

Post-marketing surveillance of GlaxoSmithKline (GSK) Biologicals' human papillomavirus (HPV)-16/18 vaccine, Cervarix when administered according to the approved Prescribing Information in Korea.

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1. Purpose of the Statistical Analysis Plan

The purpose of this document is to describe in more detail the analysis of the data collected in the 208710 Study.

This document is based on the statistical analysis method described in the protocol. The results of the analysis described in document will be included in the clinical study report.

If any additional analysis not described in this document is required, it will be written in separate document (e.g. Additional Analysis Plan).

2. Study Features

2.1 Study Objective

To assess the safety of GSK Biologicals' HPV vaccine containing HPV-16/18 L1 virus-like particles (VLPs) and AS04 adjuvant, in terms of frequency and intensity of adverse events (AEs) and serious adverse events (SAEs) when administered according to the local Prescribing Information (PI).

2.2 Number of Subjects

According to Ministry of Food and Drug Safety (MFDS) (Korea) regulation requirement, at least 600 evaluable subjects will be recruited for the post-marketing surveillance (PMS). Therefore, 660 subjects are expected to be enrolled through the PMS period considering a dropout rate of 10% (out of 600 subjects). Depending on the status of enrollment, the plan can be adjusted.

2.3 Study Period

The intended duration of this study is approximately 4 years.

2.4 Study Method

This prospective, observational PMS will be conducted at multiple centres in private clinics and hospitals (department of pediatrics and obstetrics & gynecology, etc.) in Korea for a period of 4 years.

3. Sequence of Planned Analyses

According to the standard for re-examination of new drugs, etc.(2012), the points to be reported are defined as follows (Chapter 3, item 1).

> B. The regulation requires that periodical interim reports should be submitted to MFDS bi-annually for the first 2 years and annually for the remaining follow-up years. A comprehensive analysis will be performed at the end of the PMS. Regulatory post-marketing surveillance or special investigation results, which can be submitted to the MFDS (Korea) head within 2 months after the expiration of the investigation period.

According to the above, the analysis will be performed at the time of the second half of 2nd year period, end of 3rd year period and re-examination report.
However, statistical analysis may not proceed in the following cases.

- If report for non-execution is written due to no subject
- If case-report is written when the number of enrolled subject is less than 10 [a]

[a] This criterion can be changed in accordance with GSK's request.

4. Analysis Sets (Study Cohorts)

This study set up the analysis sets for the safety analysis set (section 4.1) and non-safety analysis set (section 4.2). All analysis sets are based on all vaccination subjects who receive at least one dose of Cervarix (Total vaccinated cohort).

4.1 Safety Analysis Set (Total Safety cohort)

In standard for re-examination of new drugs, etc.(2012), the point to reported is defined as follow. (Chapter Ⅱ, no 3).

> 2) Patient Population for Surveillance
> A) Patients planned to receive a drug under surveillance by investigator's medical judgment shall be defined as a subject.

B) Subject who do not use within approved range shall not be included in the safety analysis set in principal.
※ However, if data of subject whose use is beyond approved range is collected, perform analysis as a separate item.
C) How to actually select subjects shall be described in detail.

The definition of the safety analysis set to this study is as follows.
Subjects who have been completed 30-days follow-up after at least once vaccinated Cervarix, will be included in the safety analysis set.

The below cases shall be excluded from the safety analysis set in the following order.

(1) Subject who consented prior to the site initiation date

(2) Subject who completed administration of Cervarix prior to the site initiation date

(3) Subject who completed administration of Cervarix prior to the consent date

(4) Subject who did not receive Cervarix

(5) Follow-up failure: Subject for whom adverse event status (Adverse events status is unknown or missing) could not be established

(6) Subject who has been violated the inclusion/exclusion criteria

[Inclusion criteria]

- Subject or/and subjects whose parent(s)/Legally Acceptable Representative(s) [LAR(s)], in the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., complete the diary cards, return for follow-up visits).
- Korean male or female subjects aged 9-25 years who are eligible for the series of Cervarix according to the locally approved PI.
- Written informed consent obtained from the subject/from the parent(s)/LAR of the subject.

[Exclusion criteria]

- At the time of PMS entry, the contraindications and precautions of use indicated in the locally approved PI. PI should be checked and the subject must not be included in the PMS if there is any contraindication.
- Subjects who had previous administration of a HPV vaccine other than Cervarix will not be enrolled into the study.
- Subjects who are not eligible for vaccination with Cervarix according to the medical judgement of physician

- Child in care.

(7) Subject who has been violated the dosage

[Dosage]

- Receive 0.5mL dose by intramuscular injection
- The 9-14 years old subjects can be vaccinated with 2 doses, 0 and 6-12 months schedule or with 3 doses, 0, 1 and 6 months schedule.
- The 15-25 years old subjects should be vaccinated with 3 doses (0.5 mL each), 0, 1 and 6 months schedule.
- In the 2-dose schedule, if the second dose is administered before 5 months after the first dose, the third dose vaccination is required. In the 3 doses schedule, if the vaccination schedule requires flexibility, the second dose can be administered between 1 and 2.5 months and the third dose can be administered between 5 and 12 months after the first dose.

4.2 Non-Safety Analysis Set

The definition of the non-safety analysis set to this study is as follows.
Subjects who excluded from the safety analysis set except for 'Subject who did not receive Cervarix', 'Follow-up failure (unknown or missing adverse event status)'.

4.3 Effectiveness Analysis Set

Not Applicable

5. General Specifications for Statistical Analyses

5.1 Analysis Software

All statistical analysis will be carried out with SAS Software version 9.4 or more recent version.

5.2 Planned Covariate

In this study, analysis of covariance (ANCOVA) is not planned. All the categorical baseline background factors will be considered in the multiple logistic regression model. Except when noted otherwise, the factors which showed significant difference (p-value <0.05) in the analysis of AE incidence proportion by baseline background factors will be included.

5.3 Summary Statistics

For the continuous data, descriptive statistics such as number of subjects, mean, standard deviation, median, minimum and maximum value shall be presented. For the categorical data, descriptive statistics such as frequency and percentage shall be provided.

5.4 Methods for Missing Data and Incomplete Data

If there is missing or incomplete data, proceed as follows.

- If there is missing data that is not about this drug, it will be analyzed using intactly the data collected without replacement.
- Data including sign of inequality such as "≥20", ">20" of continuous data used in analysis will be excluded from analysis.

5.5 Other Statistical Considerations

The analysis will be performed considering the following, and if a separate consideration is required for each analysis item, the content will be described in section in 7.1 Derivation.

- All test statistics will be the results of two-sided test with the statistical significant level of 0.05.
- When calculating percentage in categorical variables in accordance with baseline background factor, the denominator will be defined by total number of subjects in each category. However, the denominator of detail items such as past / current medical history, Cervarix vaccination history, prior / concomitant medication, prior / concomitant vaccination will be defined by the number of subjects who recorded as 'Yes'.
- When calculating incidence proportion of adverse event in accordance with baseline background

factor, the denominator will be defined by the number of subjects in each category. However, the denominator of detail items such as past / current medical history, Cervarix vaccination history, prior / concomitant medication, prior / concomitant vaccination will be defined by the number of subjects in each category who recorded as 'Yes'.

- When calculating incidence proportion of adverse event such as adverse event, adverse drug reaction, serious adverse event, serious adverse drug reaction, unexpected adverse event, unexpected adverse drug reaction, unexpected serious adverse event, unexpected serious adverse drug reaction, unexpected non-serious adverse event and unexpected non-serious adverse drug reaction the denominator will be defined by the number of subjects in safety analysis set. Only in case of analysis by non-safety analysis set, the denominator is the number who does not include 'Subject who did not receive Cervarix' and 'Follow-up failure' of the total number of subjects excluded from safety analysis set.
- When calculating percentage in analysis of the variable collected only for some subjects such as pregnancy, the denominator will be defined by the number of subjects related with each variable.
- If the number of subjects with adverse event is less than 10, the analysis of incidence proportion of adverse event accordance with baseline background factor may be replaced with adverse event list.
- When more than 20% of expected frequency of the cell count is less than 5, Fisher's exact test should be used instead of Chi-square test.
- The 95% confidence interval will be estimated by using exact methods.
- If there are two or fewer variables that have significantly differed in the analysis of incidence proportion of adverse event in accordance with baseline background factor, multiple logistic regression analysis will be not performed.

5.6 Reporting Conventions

- P-value is rounded to four decimal places.
- If the calculated p-value is less than 0.0001, offer it as < 0.0001.
- Descriptive statistic (mean, standard deviation, median, minimum, maximum, percentage) is rounded to two decimal places.

6. Evaluation of Study Data

The analysis dataset applied to each analysis item is as follows.

Analyses	Safety Analysis Set	Non-Safety Analysis Set
Special Group	✓	
Demographics	✓	
Medical History	✓	
Medication	✓	
Vaccination	✓	
Cervarix vaccination Information	✓	
Safety Evaluation	✓	✓†

† Only 6.8.4 analysis

6.1 Disposition of Subjects

For the subjects who participated in a PMS, the following analysis group information will be presented as frequency and percentage (%)

- Number of enrollment subjects
- Number of Cervarix vaccination subjects
- Number of subjects in safety analysis set
- Number of subjects and reasons in non-safety analysis set

6.2 Special Group

In standard for re-examination of new drugs, etc.(2012), the point to reported is defined as follow. (Chapter 2, no 3).

> (2) Investigation of specific subjects
> Investigation for specific subjects includes investigation for children, elderly, pregnant women, subjects with renal failure, subjects with hepatic failure, and other specific subjects.
> For investigation of such items, if there are specific subjects in general Clinical Experience Program, they may be extracted for investigation. For example, if 'Attention shall be paid to administration to children' is mentioned in approvals (precautions) and there are children in the

results of general Clinical Experience Program, investigation shall be conducted for the subjects.

According to the above, a special group is defined as follows and descriptive statistics is presented.

- Pediatric group [a]
- Geriatric group [b]
- Pregnancy group
- Renal disease group
- Liver disease group

[a] Pediatric subject: subjects who under 18 years old

[b] Geriatric subject: subjects who 65 years old or more (Not applicable)

6.3 Demographics

The following continuous data will be summarized with descriptive statistics.

- Age
- Height
- Weight
- BMI

The following categorical data will be summarized with descriptive statistics.

- Age group
- Gender
- Ethnicity

6.4 Medical History

The following categorical data will be summarized with descriptive statistics.

- Past medical history [a]
- Current medical history [b]

[a] Past medical history: In case of conditions, signs or symptoms prior to the start of the study

[b] Current medical history: In case of conditions, signs or symptoms lasting after the start of the study

In re-examination report, the past / current medical history could be classified by main title by disease of Korean Standard Classification of Disease (KCD).

If one subjects has two or more medical history in one category, it will be analyzed as one subject within the category. Also, the one subject may appear as a duplicate in different categories.

6.5 Medication

The following categorical data will be summarized with descriptive statistics. The concomitant medication during the 30-day (Day 1 to Day 30) after each vaccine dose will be also tabulated using descriptive statistics.

- Prior medication [a]
- Concomitant medication [b]

[a] Prior medication: In case of that has/have been administered medication(s)/treatment(s) within 30 days (day -29 to day 1) prior Cervarix vaccination

[b] Concomitant medication: In case of that has/have been administered medication(s)/treatment(s) within 30 days (day 1 to day 30) after Cervarix vaccination

In re-examination report, the prior / concomitant medication could be classified by main category and sub category of Korea Index of Medical Specialties (KIMS).

If one subjects has two or more medication in one category, it will be analyzed as one subject within the category. Also, the one subject may appear as a duplicate in different categories.

6.6 Vaccination

The following categorical data will be summarized with descriptive statistics. The concomitant vaccination during the 30-day (Day 1 to Day 30) after each vaccine dose will be also tabulated using descriptive statistics.

- Prior vaccination [a]
- Concomitant vaccination [b]

[a] Prior vaccination: In case of that has/have been administered any vaccine(s) other than Cervarix within 30 days (day -29 to day 1) prior Cervarix vaccination

[b] Concomitant vaccination: In case of that has/have been administered any vaccine(s) other than Cervarix within 30 days (day 1 to day 30) after Cervarix vaccination

In re-examination report, the prior / concomitant vaccination could be classified by main category and sub category of Korea Index of Medical Specialties (KIMS).
If one subjects has two or more vaccination in one category, it will be analyzed as one subject within the category. Also, the one subject may appear as a duplicate in different categories.

6.7 Cervarix Vaccination Information

The following continuous data will be summarized with descriptive statistics.

- Pre-vaccination body temperature

The following categorical data will be summarized with descriptive statistics.

- Vaccination history of prior Cervarix [a]
- Dose number of Vaccination history of prior Cervarix
- Total number of Cervarix vaccination in the PMS
- Order of Cervarix vaccination

Pre-vaccination body temperature will be presented per each visit.

[a] vaccination history of prior Cervarix: In case of that has/have received one or two dose(s) of Cervarix before the enrollment

6.8 Safety Evaluation

Section 6.8.1 shall be conducted for both safety analysis set and non-safety analysis set. Section 6.8.2, 6.8.3 and 6.8.5 will be performed on the safety analysis dataset and section 6.8.4 will be performed on the non-safety analysis set.

6.8.1 Summary of Adverse Events

The summary table of adverse events will be presented about the following items. The number of

subjects, incidence proportion, its 95% confidence interval and the number of adverse events will be presented in the summary table. The analysis of adverse event/serious adverse event during the 30-day (Day 1 to Day 30) after each vaccine dose will be also performed separately.

- Adverse event (AE) · Adverse drug reaction (ADR) [a]
- Serious adverse event · Serious adverse drug reaction
- Unexpected adverse event [b] · Unexpected adverse drug reaction
- Unexpected serious adverse event · Unexpected serious adverse drug reaction
- Unexpected non-serious adverse event [c] · Unexpected non-serious adverse drug reaction

[a] Adverse drug reaction (ADR): Adverse event that the 'relate to Cervarix' is 'Certain', 'Probable / Likely', 'Possible', 'Conditional / Unclassified' and 'Unassessable / Unclassfiable'

[b] Unexpected adverse event: Adverse event that is not included in the local product insert

[c] Unexpected non-serious adverse event: Adverse event that is non-serious and not included in the local product insert

6.8.2 Adverse Events by Preferred Term

All adverse events that occurred after the vaccination of Cervarix will be classified by terminology of System Organ Classes (SOC) and Preferred Term (PT) or Included Term (IT) of World Health Organization–Adverse Reaction Terminology (WHO-ART).

About the following items, adverse events of the subjects which occurred during or after the vaccination of Cervarix in accordance with SOC, PT or IT will be presented for the number of subjects, incidence proportion and its 95% confidence interval using exact method and the number of adverse events. At the time, even if one subject has 2 or more adverse events in one category, it will be analyzed as one within the category. Also, one subject may be presented as a duplicate in different categories.

- Adverse event · Adverse drug reaction
- Serious adverse event · Serious adverse drug reaction
- Unexpected adverse events · Unexpected adverse drug reaction
- Unexpected serious adverse events · Unexpected serious adverse drug reaction
- Unexpected non-serious adverse events · Unexpected non-serious adverse drug reaction

For all adverse events, the number of adverse events will be presented by following items. Additionally, all adverse events will be classified by System Organ Classes (SOC) and Preferred Term

(PT) or Included Term (IT) and presented as the number of each adverse events.

- Site
- Outcome
- Maximum intensity
- Relate to Cervarix
- Medically attended visit

Detailed adverse events will be listed by subjects for the following items.

- Serious adverse event
- Unexpected adverse event
- Unexpected serious adverse event
- Adverse event of subject with liver disease
- Adverse event of subject with renal disease
- Adverse event leading to withdrawal [a]

[a] Adverse event leading to withdrawal: In case that 'Did the subject return for the visit?' is 'No' and major reason is 'Serious Adverse Event and/or Non-Serious related AE' in at least one visit

6.8.3 Incidence Proportion by Baseline Background Factor

For all adverse events, the number of subjects to whom adverse event occurred and the number of adverse events will be presented per each categorical baseline background factor and special study group described in section 6.2 ~ 6.7. Also, the incidence proportion of adverse event and its 95% confidence interval will be presented.

The incidence proportion of adverse event and its 95% confidence interval will be presented and analyzed using Chi-square test or Fisher's exact test per each baseline background factor. However, some continuous variables not categorized such as height, weight will be excluded from analysis.

In the re-examination, multiple logistic regression will be performed to identify the factors that affect the incidence proportion by baseline background factor and special study group. All of factors that are statistically significant (p-value < 0.05) will be included in the model. However, as considering the structure and characteristics of the collected data, the factors used for the actual analysis can be added or subtracted.

6.8.4 Adverse Events for Subjects in Non-Safety Analysis Set

According to chapter 2, Item 3 of the Ministry of Food & Drug Safety (MFDS) guideline, the incidence proportion of adverse event of subjects whose use is beyond approved range will be presented. However, 'subjects who have not taken this study drug' and 'follow-up failure' will be excluded from this analysis because their safety assessment is not available.

Below items of adverse event in accordance with SOC and PT or IT will be presented for the number of subjects, incidence proportion, its 95% confidence interval using exact method and the number of adverse events.

- Adverse event · Adverse drug reaction
- Serious adverse event · Serious adverse drug reaction
- Unexpected adverse event · Unexpected adverse drug reaction
- Unexpected serious adverse event · Unexpected serious adverse drug reaction
- Unexpected non-serious adverse event · Unexpected non-serious adverse drug reaction

Detailed adverse events will be listed by subjects for the following items

- Serious adverse event
- Unexpected adverse event
- Unexpected serious adverse event
- Adverse event of subject with liver disease
- Adverse event of subject with renal disease
- Adverse event leading to withdrawal

6.8.5 Other Safety Analyses

Preferred terms of serious adverse event · serious adverse drug reaction, unexpected adverse event · unexpected adverse drug reaction will be presented respectively according to the proportion category of AEs in the local PI.

6.9 Effectiveness Evaluation

Not Applicable

7. Derivation and Categorization for Variable

7.1 Derivation

The calculation formulas are as follow. However, the following may be considered.

- If statistical analysis requires additional calculation formula, SAP may not be revised unless it relates to key variable, but the calculation formula will be specified in TLFs.

Age (years)

- In case of month of Informed Consent ≥ Month of Birth:
  Age = (Year of Informed Consent) – (Year of Birth)
- In case of month of Informed Consent < Month of Birth:
  Age = (Year of Informed Consent) – (Year of Birth) – 1
- In case of missing month:
  Age = (Year of Informed Consent) – (Year of Birth)

BMI (kg/m^2)

- Weight(kg) / $Height^2(m^2)$

7.2 Categorization

Categories for each item are as follows.
However, the following defined category for continuous variable can be changed according to the distribution of actual collected data.

Item	Category
• Pediatric subject	< 18 years, ≥ 18 years
• Geriatric subject	< 65 years, ≥ 65 years
• Pregnant subject	Yes, No, NA
• Liver disease	Yes, No
• Renal disease	Yes, No

Item	Category
• Age	9 ~ 14 years, 15 ~ 25 years
• Gender	Male, Female
• Ethnicity	Korean, Non-Korean
• Past medical history	Yes, No
• Current medical history	Yes, No
• Prior medication	Yes, No
• Concomitant medication	Yes, No
• Prior vaccination	Yes, No
• Concomitant vaccination	Yes, No
• Vaccination history of prior Cervarix	Yes, No
• Dose number of Vaccination history of prior Cervarix	Dose 1, Dose 1 and Dose 2
• Total number of Cervarix vaccination in the PMS	One dose, Two doses, Three doses
• Order of Cervarix vaccination	1st dose, 2nd dose, 3rd dose
• Site	Non-Administration site, Administration site
• Outcome	Recovered, Not recovered, Recovering, Resolved with sequelae, Fatal (SAEs only), Unknown
• Maximum intensity	Mild, Moderate, Severe
• Relate to Cervarix	Certain, Probable / Likely, Possible, Unlikely,

Item	Category
	Conditional / Unclassified, Unassessible / Unclassifiable
• Medical attended visit	None, Hospitalization, Emergency Room, Medical Personnel

References

The minister of Food and Drug Safety. Practical guideline for re-examination of new drugs. 2012

GlaxoSmithKline (GSK). A prospective, observational, multi-centre, post-marketing surveillance (PMS) to monitor the safety of GlaxoSmithKline (GSK) Biologicals' human papillomavirus (HPV)-16/18 vaccine, Cervarix when administered to 9-25 years old subjects according to the approved Prescribing Information in Korea.

Appendix

Mock up TLFs