Statistical Analysis Plan

Assessment of safety GlaxoSmithKline (GSK) Vaccines' quadrivalent seasonal influenza vaccine, Fluarix Tetra when administered according to the approved Prescribing Information in Korea

204687

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STATISTICAL ANALYSIS PLAN

Assessment of safety of GlaxoSmithKline (GSK) Vaccines' quadrivalent seasonal influenza vaccine, Fluarix Tetra when administered according to the approved Prescribing Information in Korea.

Product Name	**:**	**Fluarix Tetra**
Protocol No.	**:**	**204687[EPI-FLU-050 VS KR PMS]**
Version	**:**	**V5.0**
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Approvals

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Revisions

DATE OF REVISION	INDICATION REVISION	REASON FOR CHANGE	AUTHOR NAME
20-OCT-2017	3.1 Safety Analysis Sets 3.2 Non-Safety Analysis Sets	Change the inclusion/exclusion criteria for the Analysis Sets	PPD
	6. Statistical Analysis 6.3.2 Adverse Events by Preferred Terms	Add representing the preferred terms according to the proportion of AE in the local product document	
	6.2 Subject characteristics 6.3.1 Adverse Events by Subject Characteristics	Add the item for analysis	
04-NOV-2019	1.1 Study Background 1.2 Study Objective 2.1 Study Period 2.2 Number of Subjects 2.3 Study Population 2.3.1 Inclusion criteria 2.4 Study Method 3.1 Safety Analysis Sets 3.2 Non-Safety Analysis Sets 6.2 Subject characteristics	Update the extension of an age indication to include 6 to 35 months of age	PPD
	2.4 Study Method 5.1 Safety Assessment Criteria 6.2 Subject characteristics	Wording revision according to protocol amendment	
	6. Statistical Analysis	Clarification of condition for analysis of pregnancy report and each study group / Addition of other analyses	
	6.2 Subject characteristics	Clarification of not applicable items for study group aged 6-35 months	
	6.3.1 Adverse Events by Subject Characteristics	Clarification of variables excluded from the analysis	
	6.3.3 Other Analyses	Addition of analyses as per GSK central team request	

13-JUL-2020	6.2 Subject characteristics	Change of pediatric age range	PPD
	6.3.2 Adverse Events by Preferred Terms	Change of AE coding dictionary / Clarification of analysis method 4) and 5)	
23-SEP-2021	6. Statistical Analysis 6.3.1 Adverse Events by Subject Characteristics	Addition of logistic regression analysis of occurrence of AE	PPD
	6.2 Subject characteristics	Wording revision for clarity	

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1. Study Background and Study Objective

1.1 Study Background

Vaccination is currently the most effective means of controlling the impact of influenza in populations at risk (elderly and children). Influenza viruses circulate in humans virtually every winter in temperate regions of both hemispheres and throughout the year in tropical regions.

Currently, the strategy is to use a trivalent influenza vaccine which contains two A strains (H1N1 and H3N2) and one B strain. Since 1983, two evolutionarily distinct strains of influenza B virus coexist in the human population and since 1988 both strains are circulating in various countries worldwide [Barr, 2006]. In five of the last eight years, more influenza cases were due to the mismatched B virus than to H1N1 virus [CDC, 2010].

Data in literature suggest that children, without appropriate immunologic priming, vaccinated with a vaccine containing the recommended B-strain might not be protected against an infection with the co-circulating strain from the other B-lineage. Indeed, in a study on non-immunized (unprimed) infants, no cross-reactive antibodies were found in the sera [Levandowski, 1991].

As the two evolutionarily distinct strains of influenza B virus co-circulate and as cross-reactivity between those two lineages is low and even almost non-existing in an unprimed population, an additional B-strain antigen in the seasonal vaccine may offer a better protection [Englund, 2006; Levandowski, 1991].

GSK Vaccines has developed a QIV which contains two A-strains and two B-strains. The drug use investigation was designed to evaluate the safety of the QIV in adults and children from six months of age in Korea.

1.2 Study Objective

To assess the safety of GSK Vaccines' quadrivalent seasonal influenza vaccine D-QIV, Fluarix Tetra, in terms of frequency and intensity of AEs and SAEs when administered according to the local PI in adults and children from six months of age in Korea.

2. Study Design

2.1 Study Period

GSK Vaccines' quadrivalent seasonal influenza vaccine D-QIV, Fluarix Tetra was registered in Korea in December 2014. As per MFDS requirements, this drug use investigation (as part of PMS) is being conducted to collect safety information on the use of Fluarix Tetra over a 6 years period.
In addition to the extension of an age indication to include 6 to 35 months of age for Fluarix Tetra, additional drug use investigation for new age group is being conducted to collect safety information on the use of Fluarix Tetra for 4 years according to the MFDS requirement.

2.2 Number of Subjects

According to MFDS requirement, at least 600 evaluable subjects should be recruited for each drug use investigation. Therefore, max 1440 subjects (720 vaccinees ≥ 3 years old and above and 720 vaccinees between 6-35 months old) will be enrolled through the drug use investigation period. We assume that 20% of enrolled participants might drop out (depending on the status of actual enrolment), then the plan can be adjusted accordingly.

2.3 Study Population

Subjects aged ≥6 months who receive Fluarix Tetra as a part of routine practice at a private clinic or hospital. Only subjects to whom Fluarix Tetra is administered in routine clinical practice will be invited to participate in the drug use investigation.

2.3.1 Inclusion criteria

All subjects must satisfy the following criteria at drug use investigation entry:

(1) Male or female subjects who were vaccinated with Fluarix Tetra or eligible to receive Fluarix Tetra according to the locally approved PI.

*Note: According to current approved PI, the subjects below are included.

Subjects	1st dose	Follow-up contact after 21 days	2nd dose	Follow-up contact after 21 days
Primed	●	●		
Unprimed [1]	●	●	●	●
Unprimed [2]	●	●		
Unprimed with history of *Fluarix Tetra* [3]			●	●

- Primed: adults and previously vaccinated children aged ≥6 months
- Unprimed: previously unvaccinated children aged 6 months to <9 years

[1] Unprimed children who participate in the drug use investigation following the administration of both doses of Fluarix Tetra

[2] Unprimed children who participate in the drug use investigation following the administration of the first dose of Fluarix Tetra

[3] Unprimed children who participate in the drug use investigation following the administration of the second dose of Fluarix Tetra

- 2nd dose would be given at least 4 weeks after the 1st dose.

(2) Signed informed consent as ICF/IAF obtained from the subject/subject's parent(s)/LAR(s).

2.3.2 Exclusion criteria

The following criteria should be checked at the time of drug use investigation entry. If the exclusion criterion applies, the subject must not be included in the study:

(1) Those who are not eligible for vaccination with Fluarix Tetra according to the local PI.
- Hypersensitivity reaction to Fluarix Tetra
- History of hypersensitivity reaction to Influenza vaccine
- History of Guillain-Barre syndrome or other nervous abnormalities to Influenza vaccine within 6 weeks post-vaccination

(2) Those who are not eligible for vaccination with Fluarix Tetra according to the medical judgement of physician.

2.4 Study Method

This prospective, observational drug use investigation will be conducted at multiple centers (mainly in hospitals and private clinics) in Korea.
Only subjects to whom Fluarix Tetra is administered in routine clinical practice will be invited to participate in the drug use investigation.

3. Analysis Sets

3.1 Safety Analysis Sets

The safety analysis set will include all subjects who receive Fluarix Tetra, participated in the drug use investigation and provide post vaccination safety data.

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

(1) Subjects who have consented prior to the contract
(2) Subjects who have been administered prior to the contract*
(3) Subjects who didn't receive Fluarix Tetra within this study
(4) Follow-up failure: Subjects for whom adverse event status (Adverse Events status is unknown or missing in CRF) could not be established
(5) Subjects who violated inclusion/exclusion criteria (see section 2.3)
(6) Subjects who were prescribed for other indications except indications in the local product document.
[Target Indication]
- Fluarix Tetra is indicated for active immunisation of adults and children from 6 months of age for the prevention of influenza disease caused by the influenza A virus subtypes and the influenza B virus types contained in the vaccine.

(7) Subjects who violate the dosage
[Dosage]
- Children from 6 months and older receive 0.5 ml dose by intramuscular injection and is revaccination each year.
- For children aged < 9 years, who have not previously been vaccinated against influenza, a second dose should be given after an interval of at least 4 weeks.

(8) Subjects of contraindications

[Contraindication]

- History of hypersensitivity to the active substances or to any of the excipients or to any component that may be present as traces such as eggs (ovalbumin, chicken proteins), formaldehyde, gentamicin sulphate and sodium deoxycholate
- Immunisation should be postponed in patients with febrile illness or acute infection.
- History of hypersensitivity reaction to Influenza vaccine
- History of Guillain-Barre syndrome or other nervous abnormalities to Influenza vaccine within 6 weeks post-vaccination

* But subjects not administered the Fluarix Tetra this season shall be included from safety analysis set. In addition, subjects under age 9 years who participating in the drug use investigation with a second dose of Fluarix Tetra shall be included from safety analysis set.

3.2 Non-Safety Analysis Sets

The cases below shall be included in Non-safety analysis set in the following order:

(1) Subjects who have consented prior to the contract
(2) Subjects who have been administered prior to the contract*
(3) Subjects who violated inclusion/exclusion criteria (see section 2.3)
(4) Subjects who were prescribed for other indications except indications in the local product document.

[Target Indication]

- Fluarix Tetra is indicated for active immunisation of adults and children from 6 months of age for the prevention of influenza disease caused by the influenza A virus subtypes and the influenza B virus types contained in the vaccine.

(5) Subjects who violate the dosage

[Dosage]

- Children from 6 months and older receive 0.5 ml dose by intramuscular injection and is revaccination each year.
- For children aged < 9 years, who have not previously been vaccinated against influenza, a second dose should be given after an interval of at least 4 weeks.

(6) Subjects of contraindications

[Contraindication]

- History of hypersensitivity to the active substances or to any of the excipients or to any component that may be present as traces such as eggs (ovalbumin, chicken proteins), formaldehyde, gentamicin sulphate and sodium deoxycholate
- Immunisation should be postponed in patients with febrile illness or acute infection.
- History of hypersensitivity reaction to Influenza vaccine
- History of Guillain-Barre syndrome or other nervous abnormalities to Influenza vaccine within 6 weeks post-vaccination

* But subjects not administered the Fluarix Tetra this season shall be included from safety analysis set. In addition, subjects under age 9 years who participating in the drug use investigation with a second dose of Fluarix Tetra shall be included from safety analysis set.

3.3 Efficacy Analysis Sets

Not Applicable

4. Endpoint

4.1 Safety Endpoint

- Occurrence of expected and unexpected AEs during the 21 days (Day 0 to Day 20) follow-up period after vaccination
- Occurrence of SAEs starting from the date of vaccination in the drug use investigation up to 21 days (Day 0 to Day 20) after vaccination of the subject in the drug use investigation

5. Assessment Criteria

5.1 Safety Assessment Criteria

All AEs including ADRs and SAEs reported during the 21 days (Day 0 to Day 20) follow-up period after administration.

6. Statistical Analysis

- Each statistical analysis will be carried out with SAS Software version 9.4 or more recent version.
- Data including sign of inequality such as "≥20", ">20" will be excluded from analysis.
- All test statistics will be the results of two-sided tests with the statistical significant level 0.05.
- The followings will be included in the final report only.
  - Analysis by type of general medical history/physical examination (Past/Current)
  - Analysis by type of vaccination history
  - Analysis by type of concomitant medications
  - Analysis by type of concomitant vaccination
  - Logistic regression analysis of occurrence of AE
  - Pregnancy report analysis, if the data is collected
  - Preferred terms of Serious AE/Serious ADR, unexpected AE/ADR according to the proportion of AE
  - Other analyses (see section 6.3.3)
- Each study group (3 years old and above, and 6-35 months old) will be analyzed separately.

6.1 Composition of Subjects

- Number of enrollment subjects
- Number of subjects for safety analysis set
- Number of subjects excluded from the safety analysis set

6.2 Subject characteristics

Data for the subject characteristics is demonstrated by descriptive statistics for safety analysis set.

In the descriptive statistics, number of subjects (N), mean, standard deviation, median, minimum and maximum will be calculated for continuous variables, and frequency and percentage for categorical variables.

The following subject characteristics will be reported:

< Subject baseline Information >

- Gender, Age, Height, Weight, BMI, Ethnicity, General medical history/physical examination

(Past/Current)

< Study Medication Information >

- Vaccination history (influenza vaccination, any non-influenza vaccination), Pre-vaccination body temperature, Dose of Fluarix Tetra administration(All subjects, Subjects under age 9 years*), Concomitant medication, Concomitant vaccination, Route of concomitant vaccination

< Special Subject Information >

- Pediatric group (≥3 years and <19 years)*, Elderly group (≥65 years)*, Pregnancy*, Liver disorder, Kidney disorder

* Not applicable for study group aged 6-35 months

6.3 Safety Analyses

Safety analysis on safety parameter will be done on safety analysis set.

In the safety analysis set, the number of subjects to whom AE occurred and the number of AEs will be calculated. Also, the incidence proportion of AEs and its 95% confidence interval will be estimated.

6.3.1 Adverse Events by Subject Characteristics

For the AE(s) according to the subject characteristics* such as gender and age in the safety assessment population:

- The number of subjects to whom AE occurred and the number of AEs will be calculated.
- The incidence proportion of AEs and its 95% confidence interval will be estimated and exploratory comparison between the group distributions will be performed using Chi-square test or Fisher's exact test. If there are two or more baseline characteristics that are statistically significant (p-value < 0.05), they will be included in the logistic regression model to examine the effect of baseline characteristics on incidence of AEs. However, as considering the structure and characteristics of the collected data, the factors used for the actual analysis can be added or subtracted.

* Incidence proportion for Route of concomitant vaccination and continuous variables not categorized

such as Height will be excluded from analysis.

6.3.2 Adverse Events by Preferred Terms

All AEs recorded in the CRF will be classified by body organs and terms under the classification standard of MedDRA (The most update version of MedDRA at the time of conducting data analysis will be used; the first level is System Organ Class (SOC) and the second level is Preferred Term (PT)) terms, and all AEs excluding the AEs whose causal relation with Fluarix Tetra is 'Not-Related' will be treated as AEs whose causal relation cannot be excluded (hereafter "Adverse Drug Reaction (ADR)")

① The number of subjects and the number of AE/ADR, Serious AE/Serious ADR, Unexpected AE/ADR, Unexpected Serious AE/Serious ADR and Unexpected non-serious AE/ADR will be calculated according to the preferred terms. Also, the incidence proportion and its 95% confidence interval using the exact method will be estimated.

② Preferred terms of Serious AE/Serious ADR, unexpected AE/ADR will be presented respectively according to the proportion of AE in the local product document.

③ For Non-safety analysis set, the number of subjects and the number of AE/ADR, Serious AE/Serious ADR, Unexpected AE/ADR, Unexpected Serious AE/Serious ADR and Unexpected non-serious AE/ADR will be calculated according to the preferred terms. Also, the incidence proportion and its 95% confidence interval using the exact method will be estimated.

④ The number and percentage of AE according to the maximum intensity, outcome, relationship to marketed vaccine/product, medically attended visit will be calculated.

⑤ All AEs will be classified into the preferred terms according to the maximum intensity, outcome, relationship to marketed vaccine/product, medically attended visit. Also, the number and percentage of each AE will be calculated.

6.3.3 Other Analyses

① The distribution of the following will be tabulated with descriptive statistics. Also, 95% confidence interval for the percentage will be estimated using the exact method.

- Subjects by concomitant medication and pre-existing medical conditions
- Subjects with concomitant medication by treatment purpose and treatment start date
- Concomitant medication by treatment purpose and treatment start date

② The number of subjects with AE/ADR and the number of AE/ADR by the following will be calculated. Also, the incidence proportion and its 95% confidence interval using the exact method will be estimated.

- Concomitant medication and pre-existing medical conditions
- Treatment purpose
- Treatment start date

Note: Pre-existing medical conditions (yes/no) is defined as any significant pre-existing conditions or signs and/or symptoms present prior to the start of the study recorded in the general medical history/physical examination section of the CRF. Treatment purpose of concomitant medication is recorded on the CRF 'Is drug used for treating AE?' of concomitant medication section. Concomitant medication by treatment start date will be classified into yes/no depending on whether concomitant medication started before vaccination.

Appendix

Mock up TLFs