[redacted]

STATISTICAL ANALYSIS PLAN

A regulatory requirement non interventional study to monitor the safety and effectiveness of Trajenta (Linagliptin, 5 mg, q.d) in Korean patients with type 2 diabetes mellitus (SELINA study)

Product Name : Trajenta

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Approvals

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Revisions

DATE OF REVISION	INDICATION REVISION	REASON FOR CHANGE	AUTHOR NAME
2014-07-24	6.1 Demographics and Baseline Characteristics	Change pediatric group criteria	[redacted]
	6.2 Effectiveness Analyses		
	7.2 Baseline Characteristics		
2015-07-28	3.1 Safety Analysis Set	Change dosage/capacity details	[redacted]
		Add 'Subjects who are not Korean'	
13-APR-2017	ALL	Reflecting guideline of MFDS, edit terms	[redacted]
	4.1 Effectiveness Endpoint 5.1 Effectiveness Assessment Criteria 6.2 Effectiveness Analyses 7.3 Effectiveness Analyses	Add final effectiveness assessment	
	6.1 Demographics and Baseline Characteristics 7.2 Baseline Characteristics	Change the average daily dose to the total dose	
	6.2 Effectiveness Analyses 7.3 Effectiveness Analyses	Add multiple regression analysis on the change of HbA1c	
	6.2 Effectiveness Analyses 6.3.2 Adverse Events by Preferred Terms 7.3 Effectiveness Analyses 7.4 Safety Analyses	Add long/short-term analysis set	
	6.3.1 Adverse events by Demographics and Baseline Characteristics 7.4 Safety Analyses	Add logistic regression analysis on the incidence proportion of AEs	
21-AUG-2017	3.1 Safety Analysis Set	Change dosage/capacity details	[redacted]
	6.3.2 Adverse Events by Preferred Terms 7.4 Safety Analyses	Add representing the preferred terms according to the proportion of AE in the local product document	

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1. Study Objectives

1.1 Primary Objective

The primary objective of this study is to monitor the safety profile of Trajenta in Korean patients with type 2 diabetes mellitus (T2DM) in a routine clinical setting.

1.2 Secondary Objective

The secondary objective of the study is to monitor the effectiveness of Trajenta by evaluating the change from baseline to endpoint in the glycosylated hemoglobin (HbA1c), fasting plasma glucose (FPG) of Korean T2DM patients.

2. Study Period and Study Method

2.1 Study Period

This rNIS is a prospective, non-interventional, open-label, multi-centre study. As per regulation, the re-examination period extends from 14 Sep 2011 until 13 Sep 2017 (6 years). However, active enrollment is to be initiated in 2012 after finalizing the re-imbursement agreement with the authority. Before initiation of the study, any newly reported adverse events collected from other sources such as spontaneous cases, literature cases etc will be closely monitored. The last patient follow up is expected in 2016.

2.2 Number of Sybjects

A total of 3,000 patients will be enrolled at approximately 80 sites by as many as 100 or more NIS physicians. To minimize the selection bias at the site level, the goal is to have participating centers reflect a balance between general hospitals and clinics for surveillance. The treating physicians will mainly be internists. To minimize the selection bias, consecutive patients from each site who meet inclusion criteria will be enrolled in this study.

2.3 Study Population

2.3.1 Inclusion Criteria

- Patients who have been started on Trajenta in accordance with the approved label in Korea
- Patients who have signed on the data release consent form

2.3.2 Exclusion criteria

- Patients with previous exposure to Trajenta
- Current participation in clinical trials

2.4 Study Method

This is a prospective, non-interventional, open-label, multi-centre study. It will provide additional safety information of Trajenta in Korean patients with type 2 diabetes mellitus in routine clinical settings.

3. Anlysis Sets

3.1 Safety Analysis Set

Subjects who administrated Trajenta at least once will be included in the safety analysis set.

Reflecting MFDS guideline, the subjects below shall be excluded from safety analysis set in the following order:

(1) Subjects administered Trajenta prior to the contract date

(2) Subjects who have not taken Trajenta

(3) Follow-up failure: The subjects whose safety follow up have not been completed

(4) Subjects who were prescribed for other indications except target indication:

[Target indication]

- Patients with type 2 diabetes mellitus

(5) Subjects who violated inclusion/exclusion criteria

(6) Subjects who did not follow dosage/capacity

[Dosage/Capacity]

- The recommended dose 5 mg once daily
- Administration by monotherapy
- Combination with metformin
- Combination with sulfonylurea
- Combination with both sulfonylurea and metformin
- Combination with insulin
- Combination with both insulin and metformin
- Combination with both empagliflozin (25mg) and metformin

(7) Subjects of contraindications

- Who are hypersensitive to the principle components and additives of this product
- Patients with type 1 diabetes or diabetic ketoacidosis

(8) Subjects who are not Korean

3.2 Effectiveness Analysis Set

The subjects below shall be excluded from effectiveness analysis set in the following order:

(1) Subjects who excluded from safety analysis set

(2) Missing HbA1c value at both baseline and after administration of Trajent

4. Endpoints

4.1 Effectiveness Endpoints

- Glycosylated hemoglobin (HbA1c)
- Fasting plasma glucose (FPG)
- Final effectiveness assessment

4.2 Safety Endpoint

- The incidence proportion of all AEs

5. Assessment Criteria

5.1 Effectiveness Assessment Criteria

- The change from baseline to last visit[‡] of HbA1c
- Achievement rate of target effectiveness (HbA1c of < 6.5% at last visit)
- Achievement rate for target of reduction (At least 0.5% HbA1c lowering at last visit)
- The change from baseline to last visit of FPG
- Final effectiveness assessment

  Defines the final effectiveness assessment (Improved, No changed, Worsened, Uevaluable) based on both HbA1c and FPG that measured at baseline and last visit. The final effectiveness assessment is as the following criteria:

- Improved: In case the symptoms, such as symptoms of improvement or maintenance[†], are judged
  I. In the last visit compared to the baseline, in case the both HbA1c and FPG are maintained or decreased
  II. In the last visit compared to the baseline, in case the HbA1c is maintained or decreased and the FPG is increased
  III. In the last visit compared to the baseline, in case the HbA1c is increased and the FPG is maintained or decreased

- No changed: In case there is no significant change between baseline and last visit, that is, in case it is not judged to be maintenance effect
  I. In the last visit compared to the baseline, in case the HbA1c is increased, but the FPG is unknown

- Worsened: In case the symptoms are worse in the last visit compared to the baseline
  I. In the last visit compared to the baseline, in case the both HbA1c and FPG are increased

- Not evaluable: In case the collected information is insufficient and the final effectiveness

assessment can not be classified as 'Improved', 'No changed' or 'Worsened'

† Maintenance: In case the symptoms are likely to worsen when the administration of Trajenta is interrupt, or, in case the same effect is continue when replacing to existing drugs, etc.

‡ Last visit: The last visit point that measured HbA1c after administration of Trajenta

5.2 Safety Assessment Criteria

- All AEs which is occurred at least once after administration of Trajenta.

6. Statistical Analyses

6.1 Demographics and Baseline Characteristics

Data for the demographics and baseline characteristics in safety analysis set is demonstrated by descriptive statistics. In the descriptive statistics, number of subjects, mean, standard deviation, median, minimum and maximum will be calculated for continuous variables, and frequency and percentage will be presented for categorical variables.

The following demographics and baseline characteristics will be reported.

< Demographic information >

- Age, Gender, Pregnancy, Allergy, Height, Weight, Waist circumference, Smoking status, Diabetes mellitus complications and their classification, Other medical history and its classification, duration of T2DM, Family history, Pediatric group (Under 19 years), Geriatric group (65 years or older), Kidney disorder, Liver disorder, Subjects whose drug administration period of long-term (24 weeks or more)

< Medication information >

- Concomitant medication and its classification, Trajenta administration status (Total administration period of Trajenta, Total administration dose of Trajenta), Reason of prematurely study withdrawal, Other anti-diabetic agent and its classification

6.2 Effectiveness Analyses

Effectiveness analysis shall be conducted for subjects of the effectiveness analysis set.

The change from baseline to last visit of HbA1c will be calculated for each subject. The difference of HbA1c between baseline and last visit shall be described by mean, and shall be analyzed with paired t-test.

According to the following baseline characteristics, the change from baseline to last visit of HbA1c will be analyzed with t-test or ANOVA (Analysis of Variance).

- Age, Gender, Pregnancy, Allergy, Diabetes mellitus complications and their classification, Other medical history and its classification, duration of T2DM, Family history, Pediatric group (Under 19 years), Geriatric group (65 years or older), Kidney disorder, Liver disorder, Subjects whose drug administration period of long-term (24 weeks or more), Concomitant medication and its classification, Total administration period of Trajenta, Reason of prematurely study withdrawal, Other anti-diabetic agent and its classification

If necessary, analysis for the impact of the change from baseline to last visit of HbA1c may be carried out using multiple regression analysis. In general, the variables corresponding to the baseline characteristics listed in section 6.1 are used as an independent variable. However, as considering the structure and characteristics of the collected data, the variables used for the actual analysis can be added or subtracted.

The frequency and percentage of the final effectiveness assessment will be summarized.

The final effectiveness assessment of “Improved” will be classified as “Effective”. The final effectiveness assessment of “No changed” and “Worsened” will be classified as “Ineffective”. The effectiveness rate and its 95% confidence intervals will be estimated with exact method.

The effectiveness rate will be analyzed according to the baseline characteristics listed in section 6.1. Chi-square test or Fisher’s exact test will be used for comparing between subcategories of each baseline characteristic and will be estimated with its 95% confidence interval.

According to the following subgroup, the frequency and percentage of subjects whose HbA1c of <

6.5% at last visit and whose HbA1c lowering is at least 0.5% at last visit will be calculated. Additionally, the difference of FPG between baseline and last visit shall be analyzed with paired t-test.

① All of effectiveness analysis set
② Short-term effectiveness analysis set (Administration of Tragenta less than 24 weeks)
③ Long-term effectiveness analysis set (Administration of Tragenta for 24 weeks or more)
④ Subjects in effectiveness analysis set who administered DPP-4 inhibitor before administration of Trajenta
⑤ Subjects in effectiveness analysis set who did not administer DPP-4 inhibitor before administration of Trajenta

6.3 Safety Analyses

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

6.3.1 Adverse Events by Demographics and Baseline Characteristics

For the AE(s) by demographics and baseline characteristics in the safety analysis set:

- 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. Chi-square test or Fisher's exact test will be used for comparing between subcategories of each demographics and baseline characteristics.
- If necessary, analysis for the impact of the safety may be carried out using logistic multiple regression analysis. In general, the variables corresponding to the baseline characteristics listed in section 6.1 are used as an independent variable. However, as considering the structure and characteristics of the collected data, the variables used for the actual analysis can be added or subtracted.

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 terms, and all AEs excluding the AEs where causal relationship with Trajenta is "Unlikely" will be treated as AEs which causality cannot be excluded (hereafter "Adverse Drug Reaction(ADR)").

For subjects to whom AE occurred, the incidence proportion of AEs and the number of AEs will be summarized.

Details are as follows.

① The frequency and percentage of the number of AEs according to serious adverse event, intensity, outcome of the event, action taken, causality, therapy of the event will be calculated.

② All AEs will be classified into the preferred terms according to serious adverse event, intensity, outcome of the event, action taken, causality, therapy of the event. The frequency and percentage of the number of each AE will also be calculated.

③ The number of subjects and the number of AE/ADR, Serious AE/Serious ADR, unexpected AE/ADR, unexpected Serious AE/unexpected Serious ADR will be calculated according to the preferred terms. In this case, the following subgroups are presented separately. Also, the incidence proportion and its 95% confidence interval will be estimated.

- All of safety analysis set
- Short-term effectiveness analysis set (Administration of Tragenta less than 24 weeks)
- Long-term effectiveness analysis set (Administration of Tragenta for 24 weeks or more)
- Subjects in effectiveness analysis set who administered DPP-4 inhibitor before administration of Trajenta
- Subjects in effectiveness analysis set who did not administer DPP-4 inhibitor before administration of Trajenta

④ 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.

⑤ For subjects excluded from the safety analysis set†, the number of subjects and the number of AE/ADR, Serious AE/Serious ADR, unexpected AE/ADR, unexpected Serious AE/unexpected Serious ADR will be calculated according to the preferred terms. Also, the incidence proportion and its 95% confidence interval will be estimated.

†Subject excluded from safety analysis set: 'Subjects who have not taken Trajenta' and 'Follow-up failure' of patients excluded from safety analysis sets will be excluded (Reflecting the Ministry of Food and Drug Safety (MFDS) guideline).

6.4. Handling of Missing Values

All available data will be used for data analysis. No imputation of missing data will be performed.

6.5 Interim Analyses

As required by the MFDS regulations, the periodic report should be submitted to the MFDS every 6 months for the first two years and then annual report should be submitted to the MFDS.

7. List of Table and Data Listing

7.1 Distribution of Patients

- Number of subject contracted to the study: The number of patients are to be collected as contracted by the investigator
- Number of retrieving completed CRFs: Total number of patients who completed CRFs
- Number of safety analysis set
- Number of effectiveness analysis set

7.2 Baseline Characteristics

- Mean and standard deviation (SD) or frequency and percentage by Age, Gender, Pregnancy, Allergy, Height, Weight, Waist circumference, Smoking status, Diabetes mellitus complications and their classification, Other medical history and its classification, duration of T2DM, Family history, Pediatric group (Under 19 years), Geriatric group (65 years or older), Kidney disorder, Liver disorder, Subjects whose drug administration period of long-term (24 weeks or more)
- Mean and SD or frequency and percentage by Concomitant medication and its classification, Trajenta administration status (Total administration period of Trajenta, Total administration dose of Trajenta), Reason of prematurely study withdrawal, Other anti-diabetic agent and its classification

7.3 Effectiveness Analyses

- Mean, SD and p-value on the change from baseline to last visit of HbA1c
- Mean, SD and p-value on the change from baseline to last visit of HbA1c by baseline characteristics

- Frequency and percentage on final effectiveness assessment
- Effectiveness rate and 95% confidence interval on final effectiveness assessment
- Frequency, effectiveness rate, 95% confidence interval and p-value on final effectiveness assessment by baseline characteristics
- Frequency and percentage on subjects whose HbA1c of < 6.5% at last visit
- Frequency and percentage on subjects whose HbA1c lowering is at least 0.5% at last visit
- Mean, SD and p-value on the change from baseline to last visit of FPG
- According to whether or not administered Tragenta for more than 24 weeks and whether or not administered DPP-4 inhibitor before administration of Trajenta, Mean, SD and p-value on the change from baseline to last visit of HbA1c.
- According to whether or not administered Tragenta for more than 24 weeks and whether or not administered DPP-4 inhibitor before administration of Trajenta, frequency and percentage on subjects whose HbA1c of < 6.5% at last visit.
- According to whether or not administered Tragenta for more than 24 weeks and whether or not administered DPP-4 inhibitor before administration of Trajenta, frequency and percentage on subjects whose HbA1c lowering is at least 0.5% at last visit.
- According to whether or not administered Tragenta for more than 24 weeks and whether or not administered DPP-4 inhibitor before administration of Trajenta, Mean, SD and p-value on the change from baseline to last visit of FPG.
- Multiple regression analysis on the change of HbA1c

7.4 Safety Analyses

- According to the baseline characteristics, incidence proportion and the number of AEs (frequency and percentage)
- The number of AEs for serious adverse event, intensity, outcome of the event, action taken, causality, therapy of the event (frequency and percentage)
- The number of AEs for serious adverse event, intensity, outcome of the event, action taken, causality, therapy of the event by preferred terms (frequency and percentage)
- For safety analysis set, according to whether or not administered Tragenta for more than 24 weeks and whether or not administered DPP-4 inhibitor before administration of Trajenta, the number of AE/ADR, Serious AE/Serious ADR, unexpected AE/ADR, unexpected Serious AE/unexpected Serious ADR by preferred terms (frequency, percentage, incidence proportion and its 95% confidence interval)
- Preferred terms of Serious AE/Serious ADR, unexpected AE/ADR according to the proportion of AE

- For subjects excluded from the safety analysis set†, the number of AE/ADR, Serious AE/Serious ADR, unexpected AE/ADR, unexpected Serious AE/unexpected Serious ADR according to the preferred terms (frequency, percentage, incidence proportion and its 95% confidence interval)
- Multiple logistic regression analysis on the incidence proportion of AEs

†Subject excluded from safety analysis set: 'Subjects who didn't receive Trajenta' and 'Follow-up failure' of patients excluded from safety analysis sets will be excluded (Reflecting the Ministry of Food and Drug Safety (MFDS) guideline).

8. Note

- Each statistical analysis will be carried out with SAS Software version 9.4 or more recent version.
- In the descriptive statistics, mean, SD, median, minimum and maximum will be calculated for continuous variables, and frequency and percentage for categorical variables.
- 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 of 0.05.
- The followings shall be included only in re-examination report:
  - Estimation of 95% confidence interval for incidence proportion of AEs by baseline characteristics