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Note; This document was translated into English and the language in original document was Japanese.

An exploratory study of the effects of trelagliptin and alogliptin on glucose variability in patients with type 2 diabetes mellitus

(Protocol number: Trelagliptin-4001)

Statistical Analysis Plan

(Ver.4.0: 25 Oct 2017)

Sponsor: Takeda Pharmaceutical Company Limited

Authorizer:

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Takeda Pharmaceutical Company Limited

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Biostatistics Manager:

[redacted]

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Contents

1. DEFINITIONS of TERMS

- Summary Statistics: Number of subjects, mean, SDs, maximum values, minimum values, and quartiles
- Treatment Group: Trelagliptin 100 mg group and Alogliptin 25 mg group

2. TIME WINDOW

For each inspection, observation and evaluation item, evaluable data is handled according to the following table. When there are multiple data that can be evaluated at the same time point, the one with the closest inspection date, observation, and evaluation date to the reference date is adopted, and if the difference from the reference date is the same, the later data is adopted.

[CGM]

Time Point	Reference Date
Start of the observation period	4 hours before breakfast to 20 hours after breakfast at “Day -1” after the date of administration.
The 2nd day of the treatment period for CGM insertion	4 hours before breakfast to 20 hours after breakfast at “Day 1” after the date of administration after CGM insertion
The 3rd day of the treatment period for CGM insertion	In 24 hours from the end time of “Day 2” after the date of administration after CGM insertion
The 4th day of the treatment period for CGM insertion	In 24 hours from the end time of “Day 3” after the date of administration after CGM insertion
The 5th day of the treatment period for CGM insertion	In 24 hours from the end time of “Day 4” after the date of administration after CGM insertion
The 6th day of the treatment period for CGM insertion	In 24 hours from the end time of “Day 5” after the date of administration after CGM insertion
The 7th day of the treatment period for CGM insertion	In 24 hours from the end time of “Day 6” after the date of administration after CGM insertion
The 8th day of the treatment period for CGM insertion	In 24 hours from the end time of “Day 7” after the date of administration after CGM insertion

[Laboratory Tests] Glycoalbumin, 1,5-AG, Fasting Insulin, Fasting Glucagon, Fasting Proinsulin

Time Point	Reference Date	Time Allowance
		Number of days after the first administration
Start of the observation	Days after administration: -2	Applicable for Visit 1

Time Point	Reference Date	Time Allowance Number of days after the first administration
period		(Day -4 to Day -2)
"Day 1" of week 3-4 of the treatment period	Days after administration: 21	Applicable for Visit 3 (Day 19 to Day 35)
"Day 9" of week 3-4 of the treatment period	The number of days after administration is determined as follows according to the timing of Day 1[*1]. 1. "Day 1[*1]" is days 19 - 25 after administration; 29 2. "Day 1[*1]" is days 26 - 32 after administration; 36 3. "Day 1[*1]" is days 33 - 35 after administration; 43	Applicable for Visit 5 (Day 1[*1] + 1 to Day 43)

*1 Day1: Days after administration regarded as "Day 1" of treatment period 3-4 week.

[Laboratory Tests] Fasting GLP-1, Fasting GIP, DPP-4 Activity, Inhibitory Rate of DPP-4 Activity

Time Point	Reference Date	Time Allowance Number of days after the first administration
Start of the observation period	Days after administration: -2	Applicable for Visit 1 (Day -4 to Day -2)
"Day1" of week 3-4 of the treatment period	Days after administration: 21	Applicable for Visit 3 (Day 19 to Day 35)
"Day 4" to "Day 6" of week 3-4 of the treatment period	The number of days after administration is determined as follows according to the timing of Day 1[*1]. 1. "Day 1[*1]" is days 19 - 23 after administration; 24 2. "Day 1[*1]" is days 24 - 30 after administration; 31 3. "Day 1*1" is days 31 - 35 after administration; 38	Applicable for Visit 4 (Day 1[*1] + 1 to Day 2[*2])

Time Point	Reference Date	Time Allowance
		Number of days after the first administration
"Day 9" of week 3-4 of the treatment period	The number of days after administration is determined as follows according to the timing of Day 1[*1]. 1. "Day 1[*1]" is days 19 - 25 after administration; 29 2. "Day 1[*1]" is days 26 - 32 after administration; 36 3. "Day 1*1" is days 33 - 35 after administration; 43	Applicable for Visit 5 (Day 1[*1] + 1 to Day 43)

*1 Day1: Days after administration regarded as "Day 1" of treatment period 3-4 week.
""Day 9" of week 3-4 of the treatment period" will be evaluated prior to ""Day 4" to "Day 6" of week 3-4 of the treatment period"

*2 Day2: Days after administration regarded as "Day 9" of treatment period 3-4 week.

[Treatment Compliance, Dietetic Therapy, Exercise Therapy]

Time Point	Reference Date	Time Allowance
		Number of days after administration
Visit 3	Visit of the time of actual visit	-
Visit 4	Visit of the time of actual visit	-
Visit 5 or time of discontinuation	Visit of the time of actual visit	-

- The reference implementation date and the number of days after administration in the treatment period are indicated as "Day -1" for the day before study drug administration and "Day 1" for the administration day.
- The time points of treatment compliance are only Visit5 and time of discontinuation.

3. ANALYSIS SET

- Full Analysis Set
  The subjects who were randomized and given at least one dose of the study drug.
- Safety Analysis Set
  The subjects who are given at least one dose of the study drug.

4. CONSIDERATIONS for ANALYSIS

- Confidence coefficient

  95% (two-sided estimation)

- Display digit

  [Mean, Confidence coefficient, Quartiles]

  Round statistics down to the 1 digits lower than significant digits of the data.

  [Standard Deviation]

  Round statistics down to the 2 digits lower than significant digits of the data.

  [Minimum and Maximum Values]

  Display the data at the significant digits.

  [Proportion, Percentage]

  Round statistics off to 1 decimal places.

5. OTHER DATA HANDLING

[Definition of Daytime]

- Time zone from wake-up time to bedtime

[Definition of Nocturnal Period]

- Time zone from bedtime to wake-up time

[Data Handling for Study Drug]

- Duration of Treatment

  Duration of Treatment = Date of the Last Dose – Date of the First Dose + 1

[Data Handling for Adverse Event]

- An adverse event is defined as any untoward medical occurrence in a patient or a subject receiving a pharmaceutical product (including the study drug). It does not necessarily have an apparent causal relationship with this pharmaceutical product (including study drug).
- Adverse events, excluding serious adverse events (protocol 10.1.3), shall be non-serious adverse events in the case of an incidence of over 5% in at least one treatment group.

[Data Handling for Laboratory Test Results]

- Inhibitory Rate of DPP-4 Activity (%)

  Inhibitory rate of DPP-4 activity (%) = (DPP-4 activity at start of observation period – DPP-4 activity at each visit of treatment period) / DPP-4 activity at start of observation period x 100

[Data Handling for Duration of Diabetes (year)]

- Duration of Diabetes (year)

Duration of diabetes (year) = (Date of Informed Consent (year/month) – Onset Date of Diabetes (year/month)) / 12 (rounded off two decimal places)

If only the month of the onset of diabetes is unknown, the month of the onset of diabetes is regarded as “January”.

6. SUBJECTS, DEMOGRAPHIC and OTHER BASELINE CHARACTERISTICS

6.1. Subject Disposition

6.1.1. Study Information

Analysis Set: All subjects who were obtained informed consent

Analysis Variables: The earliest date of informed consent

The latest date of the last date of administration

Version of MedDRA

Version of SAS

Analysis Methods: For the above analysis items, the following analysis is performed.

(1) Show above items.

6.1.2. Eligibility of Subjects

Analysis Set: All subjects who were obtained informed consent

Analysis Variables: Randomization into the treatment period of the study

[Yes, No (and the reason)]

Analysis Methods: For the above analysis items, the following analysis is performed.

(1) Frequency distribution

6.1.3. Exit Status of Subjects

Analysis Set: Randomized subjects

Analysis Variables: Exit status from the study

[Complete, Incomplete (and the reason)]

Analysis Methods: For the above analysis items, the following analysis is performed for each treatment group and all subjects in the analysis set.

(1) Frequency distribution

6.1.4. Protocol Deviations and Analysis Datasets

6.1.4.1. Protocol Deviations

Analysis Set: Randomized subjects

Analysis Variables: Protocol Deviations

[Major GCP Violations, Deviations of Protocol Entry Criteria, Deviations of Discontinuation Criteria, Deviations Related to Treatment Procedure or Dose, Deviations Concerning Excluded Medication or Therapy, Deviations to Avoid Emergency Risk, Other Deviations]

Analysis Methods: For the above analysis items, the following analysis is performed for each treatment group and all subjects in the analysis set.

(1) Frequency distribution

Summarize the number of subjects who have deviated from the protocol, classify the deviations into above category, and show the breakdown of deviations. Subjects applicable for multiple categories will be counted once in each category.

6.1.4.2. Datasets Analyzed

Analysis Set: Randomized subjects

Analysis Variables: Subjects excluded from analysis datasets [Reason of exclusion]

Full Analysis Set [Adopted]

Safety Analysis Set [Adopted]

Analysis Methods: For the above analysis items, the following analysis is performed for each treatment group (both (1) and (2)) and all subjects (for (2)) in the analysis set. For analysis (1), Subjects applicable for multiple categories will be counted once in each category.

(1) Frequency distribution in each analysis set about handling for subjects

(2) Frequency distribution in each analysis set of adopted subjects.

6.2. Demographics and Other Baseline Characteristics

6.2.1. Distribution of Demographics Items

Analysis Set: Full Analysis Set

Analysis Variables:

Age (years old) [Min<= - <65, 65<= - <75, 75<= - <=Max]

Sex [Male, Female]

Height (Start of the observation period) (cm)
[Min<= - <150, 150<= - <160,
160<= - <170, 170<= - <=Max]

Weight (Start of the observation period) (kg)
[Min<= - <50.0, 50.0<= - <60.0,
60.0<= - <70.0, 70.0<= - <80.0,
80.0<= - <=Max]

BMI (Start of the observation period) (kg/m^2)
[Min<= - <18.5, 18.5<= - <25.0,
25.0<= - <=Max]

Smoking Classification [Never Smoked, Current Smoker, Ex-Smoker]

Drink Alcohol Almost Every Day? [Yes, No]

Duration of Diabetes Mellitus (Years) [Min<= - <5, 5<= - <10,
10<= - <=Max]

HbA1c (NGSP) (Start of the observation period) (%)
[Min<= - <7, 7<= - <8, 8<= - <=Max]

AUC over time when blood glucose 110 mg/dL is observed during the 3 hour time period after breakfast (Start of the observation period)

AUC over time when blood glucose 140 mg/dL is observed during the 3 hour time period after breakfast (Start of the observation period)

AUC over time when blood glucose 160 mg/dL is observed during the 3 hour time period after breakfast (Start of the observation period)

AUC over time when blood glucose 180 mg/dL is observed during the 3 hour time period after breakfast (Start of the observation period)

AUC over time when blood glucose 110 mg/dL is observed during the 3 hour time period after lunch (Start of the observation period)

AUC over time when blood glucose 140 mg/dL is observed during the 3 hour time period after lunch (Start of the observation period)

AUC over time when blood glucose 160 mg/dL is observed during the 3 hour time period after lunch (Start of the observation period)

AUC over time when blood glucose 180 mg/dL is observed during the 3 hour time period after lunch (Start of the observation period)

AUC over time when blood glucose 110 mg/dL is observed during the 3 hour time period after evening meal (Start of the observation period)
AUC over time when blood glucose 140 mg/dL is observed during the 3 hour time period after evening meal (Start of the observation period)
AUC over time when blood glucose 160 mg/dL is observed during the 3 hour time period after evening meal (Start of the observation period)
AUC over time when blood glucose 180 mg/dL is observed during the 3 hour time period after evening meal (Start of the observation period)
AUC over time during periods when blood glucose 140 mg/dL is observed (start of the observation period)
AUC over time during periods when blood glucose 160 mg/dL is observed (Start of the observation period)
AUC over time during periods when blood glucose 180 mg/dL is observed (Start of the observation period)
Cumulative time during periods when blood glucose 140 mg/dL is observed (Start of the observation period)
Cumulative time during periods when blood glucose 160 mg/dL is observed (Start of the observation period)
Cumulative time during periods when blood glucose 180 mg/dL is observed (Start of the observation period)
AUC over time during periods when blood glucose <70 mg/dL is observed (Start of the observation period)
Peak postprandial glucose over time 3 hours after breakfast (Start of the observation period)
Peak postprandial glucose over time 3 hours after lunch (Start of the observation period)
Peak postprandial glucose over time 3 hours after evening meal (Start of the observation period)
Maximum variation of blood glucose over time between before and after breakfast (Start of the observation period)
Maximum variation of blood glucose over time between before and after lunch (Start of the observation period)
Maximum variation of blood glucose over time between before and after evening meal (Start of the observation period)
MAGE (Start of the observation period)
Mean 24-hour blood glucose (Start of the observation period)

Mean daytime blood glucose (Start of the observation period)

Mean nocturnal blood glucose (Start of the observation period)

AUC (Start of the observation period)

AUC over time during periods when blood glucose 110 mg/dL is observed (Start of the observation period)

SD of 24-hour blood glucose (Start of the observation period)

SD of daytime blood glucose (Start of the observation period)

SD of nocturnal blood glucose (Start of the observation period)

Glycoalbumin (Start of the observation period)

1,5-AG (Start of the observation period) [Min<= - <10, 10<= - <14, 14<= - <=Max]

Fasting blood glucose (Start of the observation period)

Fasting insulin (Start of the observation period)

Fasting glucagon (Start of the observation period)

Fasting proinsulin (Start of the observation period)

Fasting GLP-1 (Start of the observation period)

Fasting GIP (Start of the observation period)

DPP-4 Activity (Start of the observation period)

Analysis Methods: For the above analysis items, the following analysis is performed for each treatment group and all subjects in the analysis set.

(1) Frequency distribution for discrete variables and summary statistics for continuous variables

6.2.2. Medical History and Concurrent Disease

Analysis Set: Safety Analysis Set

Analysis Variables: Medical history, Concurrent disease

Analysis Methods: For the above analysis items, the following analysis is performed for each treatment group. Analysis variables will be coded using the MedDRA dictionary and be summarized into SOC and PT. SOCs will be sorted in alphabetical order, then PTs will be sorted in frequency order.

(1) Frequency of medical history by SOC/PT

(2) Frequency of concurrent disease by SOC/PT

The method of accounting for the frequency is as follows.

[Number of subjects with AE]

Within each summary, subjects with one or more events within a level of SOC term is counted only once in that level. Similarly, subjects with one or more events within a level of PT term is counted only once in that level.

6.2.3. Prior and Concomitant Medication

Analysis Set: Safety Analysis Set

Analysis Variables: Prior medication

Concomitant medication

Analysis Methods: For the above analysis items, the following analysis is performed for each treatment group. Analysis variables will be coded using the WHO (World Health Organization) Drug. Coded medications will be sorted in frequency order. Medications used more than once within a subject will be counted only once for the subject.

(1) Frequency of prior medication

(2) Frequency of concomitant medication

6.3. Treatment Compliance

6.3.1. Study Medication Compliance

Analysis Set: Safety Analysis Set

Analysis Variables: Study medication compliance

[Fully Complied (75% or More),

Not Compliant (Less than 75%)]

Time Point: Visit 5 or time of discontinuation

Analysis Methods: For the above analysis items, the following analysis is performed for each treatment group and all subjects in the analysis set by time point.

(1) Frequency

6.3.2. Diet Therapy Compliance

Analysis Set: Safety Analysis Set

Analysis Variables: Diet therapy [Yes, No]

Diet therapy compliance [Fully complied (90% or More),

Almost complied (70% or more),

Occasionally complied (50% or more),
Rarely complied (Less than 50%)]

Time Point: Visit3, Visit4, Visit 5 or time of discontinuation

Analysis Methods: For the above analysis items, the following analysis is performed for each treatment group and all subjects in the analysis set by time point.

(1) Frequency

6.3.3. Exercise Therapy Compliance

Analysis Set: Safety Analysis Set

Analysis Variables: Exercise therapy [Yes, No]

Exercise therapy compliance

[Fully complied (90% or more),
Almost complied (70% or more),
Occasionally complied (50% or more),
Rarely complied (Less than 50%)]

Time Point: Visit3, Visit4, Visit 5 or time of discontinuation

Analysis Methods: For the above analysis items, the following analysis is performed for each treatment group and all subjects in the analysis set by time point.

(1) Frequency

6.3.4. Study Medication Exposure

Analysis Set: Safety Analysis Set

Analysis Variables: Duration of exposure (days)

Analysis Methods: For the above analysis items, the following analysis is performed for each treatment group and all subjects in the analysis set.

(1) Summary statistics of continuous variables

7. EFFICACY EVALUATIONS

7.1. Primary Endpoint and the Analytical Methods

Analysis Set: Full Analysis Set

Analysis Variables: Changes in the standard deviation (SD) of 24-hour blood glucose values

Time Point: Start of the observation period, CGM in treatment period (Day 2, Day 3,

Day 4, Day 5, Day 6, Day 7, Day 8)

Covariate: HbA1c (NGSP) at start of the observation period (%)
[Continuous variable]

SD of 24-hour blood glucose at start of the observation period
[Continuous variable]

Age (years old) [< 65, 65 <=Max]

Analysis Methods: For the above analysis items, the following analysis is performed.

(1) Summary statistics and two-sided 95% confidence interval (CI) by time point (each Day) will be calculated by treatment group. The time course will be presented graphically using the mean change and SD. Then, point estimates of the difference of mean between treatment groups (Trelagliptin 100 mg group - Alogliptin 25 mg group) and its two-sided 95% CI will be calculated.

(2) To estimate adjusted mean and two-sided 95% CI of each treatment group, adjusted difference of mean between treatment groups (Trelagliptin 100 mg group - Alogliptin 25 mg group) and its two-sided 95% CI, analysis of covariance (ANCOVA) will be performed by time point using change from start of the observation period of SD of 24-hour blood glucose as a dependent variable, treatment group as an independent variable, HbA1c (NGSP) and SD of 24-hour blood glucose at start of the observation period and age as covariates.

7.2. Secondary Endpoints and the Analytical Methods

Analysis Set: Full Analysis Set

Analysis Variables:

AUC over time when blood glucose 110 mg/dL is observed during the 3 hour time period after breakfast

AUC over time when blood glucose 140 mg/dL is observed during the 3 hour time period after breakfast

AUC over time when blood glucose 160 mg/dL is observed during the 3 hour time period after breakfast

AUC over time when blood glucose 180 mg/dL is observed during the 3 hour time period after breakfast

AUC over time when blood glucose 110 mg/dL is observed during the 3

hour time period after lunch
AUC over time when blood glucose 140 mg/dL is observed during the 3 hour time period after lunch
AUC over time when blood glucose 160 mg/dL is observed during the 3 hour time period after lunch
AUC over time when blood glucose 180 mg/dL is observed during the 3 hour time period after lunch
AUC over time when blood glucose 110 mg/dL is observed during the 3 hour time period after evening meal
AUC over time when blood glucose 140 mg/dL is observed during the 3 hour time period after evening meal
AUC over time when blood glucose 160 mg/dL is observed during the 3 hour time period after evening meal
AUC over time when blood glucose 180 mg/dL is observed during the 3 hour time period after evening meal
AUC over time during periods when blood glucose 140 mg/dL is observed
AUC over time during periods when blood glucose 160 mg/dL is observed
AUC over time during periods when blood glucose 180 mg/dL is observed
Cumulative time during periods when blood glucose 140 mg/dL is observed
Cumulative time during periods when blood glucose 160 mg/dL is observed
Cumulative time during periods when blood glucose 180 mg/dL is observed
AUC over time during periods when blood glucose <70 mg/dL is observed
Peak postprandial glucose over time 3 hours after breakfast
Peak postprandial glucose over time 3 hours after lunch
Peak postprandial glucose over time 3 hours after evening meal
Maximum variation of blood glucose over time between before and after breakfast
Maximum variation of blood glucose over time between before and after lunch

Maximum variation of blood glucose over time between before and after evening meal

MAGE

Mean 24-hour blood glucose

Mean daytime blood glucose

Mean nocturnal blood glucose

AUC

AUC over time during periods when blood glucose 110 mg/dL is observed

SD of 24-hour blood glucose

SD of daytime blood glucose

SD of nocturnal blood glucose

Time Point: Start of the observation period, CGM in treatment period (Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, Day 8)

Covariate: HbA1c (NGSP) at start of the observation period (%)
[Continuous variable]

SD of 24-hour blood glucose at start of the observation period
[Continuous variable]

Age (years old) [< 65, 65 <=Max]

Analysis Methods: For the above analysis items, the following analysis is performed

(1) The same analyses described in 7.1(1) and (2) will be performed on measurement values and changes from start of the observation period at each time point. For the SD of 24-hour blood glucose, only the measured value will be shown.

(2) The same analyses described in 7.1(1) and (2) will be performed on means of 7days and changes from start of the observation period during Week 3-4 at treatment period. The time course will be presented graphically using only means and SDs of each treatment group.

7.3. Other Analyses

7.3.1. Clinical Laboratory Test

Analysis Set: Full Analysis Set

Analysis Variables: Glycoalbumin

1,5-AG

Fasting blood glucose

Fasting insulin

Fasting glucagon

Fasting proinsulin

Fasting GLP-1

Fasting GIP

DPP-4 Activity

Inhibitory Rate of DPP-4 Activity

Time Point: Start of the observation period, Week 3-4 of the treatment period (Day 1, Day 4-6, Day 9)

Analysis Methods: For the above analysis items, the following analysis is performed

(1) For measurement values and changes from start of the observation period, summary statistics and two-sided 95% CI by time point (each Day) will be calculated by treatment group. The time course will be presented graphically using the mean change and SD.

7.3.2. Relationship Between Secondary Endpoints and Covariate

Analysis Set: Full Analysis Set

Analysis Variables: AUC over time when blood glucose 110 mg/dL is observed during the 3 hour time period after breakfast

AUC over time when blood glucose 140 mg/dL is observed during the 3 hour time period after breakfast

AUC over time when blood glucose 160 mg/dL is observed during the 3 hour time period after breakfast

AUC over time when blood glucose 180 mg/dL is observed during the 3 hour time period after breakfast

AUC over time when blood glucose 110 mg/dL is observed during the 3 hour time period after lunch

AUC over time when blood glucose 140 mg/dL is observed during the 3 hour time period after lunch

AUC over time when blood glucose 160 mg/dL is observed during the 3 hour time period after lunch

AUC over time when blood glucose 180 mg/dL is observed during the 3 hour time period after lunch

AUC over time when blood glucose 110 mg/dL is observed during the 3 hour time period after evening meal

AUC over time when blood glucose 140 mg/dL is observed during the 3 hour time period after evening meal

AUC over time when blood glucose 160 mg/dL is observed during the 3 hour time period after evening meal

AUC over time when blood glucose 180 mg/dL is observed during the 3 hour time period after evening meal

AUC over time during periods when blood glucose 140 mg/dL is observed

AUC over time during periods when blood glucose 160 mg/dL is observed

AUC over time during periods when blood glucose 180 mg/dL is observed

Cumulative time during periods when blood glucose 140 mg/dL is observed

Cumulative time during periods when blood glucose 160 mg/dL is observed

Cumulative time during periods when blood glucose 180 mg/dL is observed

AUC over time during periods when blood glucose <70 mg/dL is observed

Peak postprandial glucose over time 3 hours after breakfast

Peak postprandial glucose over time 3 hours after lunch

Peak postprandial glucose over time 3 hours after evening meal

Maximum variation of blood glucose over time between before and after breakfast

Maximum variation of blood glucose over time between before and after lunch

Maximum variation of blood glucose over time between before and after evening meal

MAGE

Mean 24-hour blood glucose

Mean daytime blood glucose

Mean nocturnal blood glucose

AUC

AUC over time during periods when blood glucose 110 mg/dL is observed

SD of 24-hour blood glucose

SD of daytime blood glucose

SD of nocturnal blood glucose

Time Point: Start of the observation period, CGM in treatment period (Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, Day 8)

Covariate: HbA1c at start of the observation period (NGSP) (%) [Continuous variable]

SD of 24-hour blood glucose at start of the observation period [Continuous variable]

Age (years old) [Continuous variable]

Analysis Methods: For the above analysis items, the following analysis is performed

(1) Correlation coefficients between secondary endpoints and covariates will be calculated by time Point.

7.3.3. Individual Profiles of Blood Glucose Obtained from CGM

Analysis Set: Full Analysis Set

Analysis Variables: Blood Glucose Obtained from CGM

Time Point: CGM in treatment period (Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, Day 8)

Analysis Methods: For the above analysis items, the following analysis is performed

(1) The time course will be presented graphically by subject by treatment group.

7.3.4. Effect on mean 24-hour blood glucose

Analysis Set: Full Analysis Set

Analysis Variables: Change from start of the observation period of mean 24-hour blood glucose

Covariate: HbA1c (NGSP) at start of the observation period (%) [Continuous variable]

SD of 24-hour blood glucose at start of the observation period [Continuous variable]

Age (years old) [< 65, 65 <=Max]

Background Factor:

Gender [Male, Female]

Height (Start of the observation period) (cm) [Continuous variable]

Weight (Start of the observation period) (cm) [Continuous variable]

BMI (Start of the observation period) (kg/m^2) [Continuous variable]

Smoking Classification [Never Smoke, Current Smoker, Ex-Smoker]

Drink Alcohol Almost Every Day? [Yes, No]

Duration of Diabetes Mellitus (Years) [Continuous variable]

HbA1c (NGSP) (Start of the observation period) (%) [Continuous variable]

Time Point : CGM in treatment period (Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, Day 8)

Analysis Methods: For the above analysis items, the following analysis is performed

(1) To estimate parameter estimates of background factors and its confidence intervals, ANCOVA will be performed by background factor using change from start of the observation period of mean 24-hour blood glucose as a dependent variable, treatment group as an independent variable, HbA1c (NGSP) and SD of 24-hour blood glucose at start of the observation period, age and each background factor as covariates.

(2) Perform the same analysis as (1) with the covariate including the treatment group × each background factor (one factor).

7.3.5. Proportion of Frequency for Blood Glucose Obtained from CGM

Analysis Set: Full Analysis Set

Analysis Variables: Blood glucose level obtained by CGM

Time Point: Start of the observation period, CGM in treatment period (Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, Day 8)

Analysis Methods: For the above analysis items, the following analysis is performed

(1) Calculate proportion of frequency and graphically show distribution of the data using proportion of frequency as vertical axis and blood glucose level as horizontal axis.

8. SAFETY EVALUATION

8.1. Frequency of Adverse Event Occurrence

8.1.1. Brief Summary of Adverse Events

Analysis Set: Safety Analysis Set

Analysis Variables: Adverse Event

Category Classification:

Causal relationship with the investigational products [related, unrelated]

Severity [Mild, Moderate, Severe]

For the above analysis items, the following analyses of frequency distribution is performed.

(1) All of the TEAEs
(2) TEAEs Related to Investigational Drug
(3) TEAEs by Severity
(4) TEAEs Related to Investigational Drug by Severity
(5) TEAEs leading to Discontinuation of Administration of Investigational Drug
(6) Serious TEAEs
(7) Non-serious TEAEs
(8) Serious TEAEs Related to Investigational Drug
(9) Serious TEAEs leading to Discontinuation of Administration of Investigational Drug
(10) TEAEs Leading to Death

Incidence rates will be calculated as following on each analysis.

[Frequency of Subjects]

・Frequency by Severity

Subjects with one or more adverse events within a level of MedDRA term is counted only once in that level using the most severe incident. The denominator when calculating the incidence of adverse events is the number of subjects of safety analysis set.

・Analyses Other Than the Above

Subjects with one or more adverse events within a level of MedDRA term is counted only once for that MedDRA term. The denominator when calculating the incidence of adverse events is the number of subjects of safety analysis set.

8.1.2. Display of TEAE

Analysis Set: Safety Analysis Set

Analysis Variables: TEAE

Category Classification:

Causal relationship with the investigational products [related, unrelated]

Severity [Mild, Moderate, Severe]

Analysis Methods: For the above analysis items, the following analysis is performed for each treatment group. Analysis variables will be coded using the MedDRA dictionary and be summarized into SOC and PT. SOCs will be sorted in alphabetical order, then PTs will be sorted in frequency order.

1) All of the TEAEs (by SOC/PT)
2) TEAEs Related to Investigational Drug (by SOC/PT)
3) TEAEs by Severity (by SOC/PT)
4) TEAEs Related to Investigational Drug by Severity (by SOC/PT)
5) TEAEs leading to Discontinuation of Administration of Investigational Drug (by SOC/PT)
6) Serious TEAEs (by SOC/PT)
7) Non-serious TEAEs (by SOC/PT)
8) Serious TEAEs Related to Investigational Drug (by SOC/PT)
9) Serious TEAEs leading to Discontinuation of Administration of Investigational Drug (by SOC/PT)
10) TEAEs Leading to Death (by SOC/PT)

Incidence rates will be calculated as following on each analysis.

[Frequency of Subjects]

・Frequency (by SOC/PT)

Within each summary, subjects with one or more adverse events within a level of SOC term is counted only once in that level. Similarly, subjects with one or more adverse events within a level of PT term is counted only once in that level. The denominator when calculating the incidence of adverse events is the number of subjects of safety analysis set.

・Frequency by Severity (by SOC/PT)

Subjects with one or more adverse events within a level of SOC/PT term is counted only once in that level using the most severe incident. The denominator when calculating the incidence of adverse events is the number of subjects of safety analysis set.

9. LISTING

Following lists will be create for randomized subjects

・Demographics

10. CONSIDERATIONS on STATISTICAL ANALYSIS

10.1. Adjustments for Covariates

ANCOVA will be performed on primary and secondary endpoints using treatment group as independent variables, HbA1c (NGSP) at the start of the observation period and SD of 24-hour blood glucose at the start of observation period as covariate. Details are described in 7.1, 7.2 and 7.3.4.

10.2. Handling of Dropouts or Missing Data

For laboratory test, a value below determination limit are treated as zero.

10.3. Criteria for Interim Analysis and Early Discontinuation

Interim analysis will not be performed.

10.4. Multicenter Studies

Analyses for consideration of medical institution will not be performed.

10.5. Multiple Comparisons/Multiplicity

It does not adjust multiplicity.

10.6. Examination of Subgroups

Subgroup analysis will not be performed.

11. REVISION HISTORY

Ver.	Date	Author	Revised Content	Reason for Revision
1.0	12 JUL 2016	[redacted]	-	
2.0	24 JUL 2017	[redacted]	[2.TIME WINDOW] ・Modification on some reference implementation date of CGM ・Modification on description of time window of Laboratory Tests	・To avoid doble count of evening meal ・To make a distinction between items measured three times and items measured twice and to reflect updated protocol
			[5.OTHER DATA HANDLING] ・Modification on Definition of "Daytime" and "Nocturnal Period" ・Modification on Definition of Non-seriousAE ・Add definition of inhibitory rate of DPP-4 activity ・Add definition of duration of diabetes	・To follow specification document of CGM database ・Requirement of Clinical Trial.gov ・To reflect updated Protocol ・Clarification
			[6.2.1.Distribution of Demographics items] ・Add items that were not described as Demographics items in secondary evaluation items	・Additional items

Ver.	Date	Author	Revised Content	Reason for Revision
			[6.3.2. Diet Therapy Compliance and 6.3.3.Exercise Therapy Compliance]	・Clarification
			[7.3.1. Clinical Laboratory Test] ・Add DPP-4activity a nd inhibitory rate of DPP-4 activity ・Add Day 4-6 as time point	・To reflect updated protocol
			[7.3.5. Proportion of Frequency for Blood Glucose Obtained from CGM] ・Delete the description in the second edition, "Add analysis as necessary".	・Clerical corrections
			[8.1.1.Brief Summary of Adverse Events and 8.1.2.Display of TEAE] ・Add analysis of frequency distribution of non-serious adverse events, deleted analysis of frequency distribution count by onset time point.	・Requirement of Clinical Trial.gov ・Remove unnecessary items
			[9.2. Handling of Dropout or Missing Value] ・Add treatment of values below quantitation limit	・Clarification

Ver.	Date	Author	Revised Content	Reason for Revision
3.0	28 JUL 2017	[redacted]	[6.1.3. Exit Status of Subjects] ・Remove “Exit status from the treatment of study drug” and add “Exit status from the study”	・Clerical corrections
4.0	25 JUL 2017	[redacted]	[Title page] ・Modification on organization name	・Clerical corrections ・Organizational change
			[9. Listing] ・Add listing of background factor	・Addition of listing