Certain information within this clinical study report has been redacted (ie, specific content is masked irreversibly from view with a black bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

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

PROTOCOL

An exploratory study to evaluate the effects of Trelagliptin and Alogliptin by CGM on glucose variability for one week with type 2 diabetes mellitus (TRACK)

Sponsor	Takeda Pharmaceutical Company Limited 2-12-10 Nihonbashi, Chuo-ku, Tokyo
Protocol number	Trelagliptin-4001
Version number	3rd Version
Study drug:	Trelagliptin Alogliptin
Creation date	February 16, 2017

1.0 CLINICAL STUDY PRINCIPLES AND CLINICAL STUDY MANAGEMENT INFORMATION

1.1 Clinical Study Principals

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- Ethical Guideline for Clinical Research (the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare, December 22, 2014).
- Good Clinical Practice: Consolidated Guideline (ICH. E6)
- All applicable laws and regulations, including, without limitation, data privacy laws and conflict of interest guidelines.

1.2 CLINICAL STUDY ADMINISTRATIVE STRUCTURE

This study will be conducted under the administrative structure described in the attached sheet 1 in accordance with the protocol prepared and planned by the sponsor.

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LIST OF APPENDICES

2.0 STUDY SUMMARY

<table>
<tr><td>Sponsor:
Takeda Pharmaceutical Company Limited</td><td>Study drug:
Trelagliptin
Alogliptin</td></tr>
<tr><td colspan="2">Study title:
An exploratory study of the effects of trelagliptin and alogliptin on glycemic variation in patients with type 2 diabetes mellitus</td></tr>
<tr><td colspan="2">Protocol number: Trelagliptin-4001 (122/NRP-001)</td></tr>
<tr><td colspan="2">Clinical study design:
This is a multi-center, randomized, open-label, parallel-group comparative, exploratory study to evaluate the effect of trelagliptin administered at a dose of 100 mg once weekly or alogliptin administered at a dose of 25 mg once daily for 4 weeks on glycemic variation in patients with type 2 diabetes mellitus using continuous glucose monitoring (CGM).
After informed consent, patients determined to be eligible for this study based on the eligibility assessment will be randomized to either the trelagliptin 100 mg group or the alogliptin 25 mg group (at a ratio of 1:1), using "HbA1c at the start of the observation period (< 7.5% or ≥ 7.5%)" and age (< 65 or ≥ 65) as a stratification factor for randomization.
The total duration of evaluation will be 31 days, consisting of the observation period for 2 days and a treatment period for 29 days (4 weeks). CGM will be performed on research subjects on an outpatient basis (in 2 assessments) for 2 days from the start of the observation period (Day -2) and for 9 days from Day 21 of the treatment period.</td></tr>
<tr><td colspan="2">Objective:
To evaluate the effect of trelagliptin administered orally at a dose of 100 mg once weekly or alogliptin administered orally at a dose of 25 mg once daily for 4 weeks on glycemic variation in an exploratory manner and as preliminary to examine the influence of the once-weekly administration and blood glucose fluctuations due to the difference in the daily administration in patients with type 2 diabetes mellitus</td></tr>
<tr><td colspan="2">Study population:
Patients with type 2 diabetes mellitus</td></tr>
<tr><td>Planned number of research subjects:
The planned minimum number of research subjects evaluable for the primary endpoint in each group is as follows:
Trelagliptin 100 mg group: 15
Alogliptin 25 mg group: 15</td><td>Number of study research implementing entities:
3 medical institutions</td></tr>
</table>

Total: 30	
Dose and method of administration: Trelagliptin 100 mg once weekly or alogliptin 25 mg once daily, taken orally before breakfast	**Route of administration:** Oral
Duration of treatment: 4 weeks	**Duration of evaluation:** 31 days (observation period for 2 days and treatment period for 4 weeks [29 days])

Inclusion criteria

1. Research subjects who, in the opinion of the principal investigator or the investigator, are capable of understanding the content of the clinical research and complying with the research protocol requirements.
2. Patients who are able to sign and date the informed consent form and information sheet prior to the start of study procedures
3. Patients diagnosed with type 2 diabetes mellitus
4. Patients with an HbA1c (NGSP value) value ≥ 6.5% and < 8.5% at the start of the observation period (Day -2)
5. Patients who experience a ≤ ±1.0% change in HbA1c (NGSP value) at the start of the observation period (Day -2) as compared with an HbA1c value obtained during the preceding 6 weeks
6. Patients receiving stable dietetic therapy and exercise therapy (if performed) for ≥ 4 weeks before the start of the observation period
7. Patients, who in the opinion of the principal investigator or the investigator, does not have to change (including discontinuation or interruption) HMG-CoA reductase inhibitors or add new HMG-CoA reductase inhibitors during treatment period.
8. Men or women aged 20 years or older at the time of informed consent

Exclusion criteria:

1. Patients who received anti-diabetic medications within 4 weeks prior to the start of the observation period
2. Patients who have changed (including discontinuation or interruption) HMG-CoA reductase inhibitors or received new HMG-CoA reductase inhibitors ≤ 4 weeks before the start of the observation period.
3. Patients with clinically evident hepatic dysfunction (e.g., AST or ALT ≥ 2.5-fold the upper limit of normal at the start of the observation period [Day -2])

4. Patients with moderate renal dysfunction, severe renal dysfunction or renal failure (e.g., creatinine clearance < 50 mL/min or serum creatinine > 1.4 mg/dL in men or > 1.2 mg/dL in women [equivalent to the creatinine clearance for persons aged 60 years with a body weight of 65 kg] at the start of the observation period [Day -2])
5. Patients with severe heart disease, cerebrovascular disorder, or severe pancreatic, hematologic or other diseases
6. Patients with a history of gastric or small intestinal resection
7. Patients with proliferative diabetic retinopathy
8. Patients warranting insulin therapy for glycemic control (e.g., patients with severe ketosis, diabetic coma or precoma, type 1 diabetes mellitus, severe infection, perioperative patients, or serious trauma)
9. Patients with a history of hypersensitivity or allergy to DPP-4 inhibitors
10. Patients who experience an allergic reaction to metal during CGM at the start of the observation period (Day -2)
11. Patients with any malignant tumors
12. Habitual drinkers whose average daily alcohol consumption is > 100 mL
13. Patients who have any contraindications for the study drug or are taking any contraindicated concomitant drugs listed in the package insert
14. Patients anticipated to require any prohibited concomitant medications during the study period
15. Patients who are day and night lifestyle reversal
16. Patients participating in any other clinical studies at the time of informed consent for this study
17. Pregnant women, nursing mothers, women who are possible pregnant, or women who plan to become pregnant
18. Other patients who are considered inappropriate for participation in this study in the opinion of the principal investigator or investigator

Endpoints:

<Primary endpoints>

- Changes in the standard deviation (SD) of 24-hour blood glucose values (mg/dL) for each 7-day period between Week 3 and Week 4 (between Day 22 and Day 28) of the treatment period, calculated from the value at the start of the observation period

<Secondary endpoints>

Efficacy endpoints:

- Changes in AUC over time when specific blood glucose levels (110, 140, 160, or 180 mg/dL) are observed during the 3 hour time period after breakfast, lunch and evening meal[*1, 2]
- Change in AUC over time during periods when blood glucose 140, 160, or 180 mg/dL

(hyperglycemia) is observed[*1, 2]

- Changes in blood glucose 140, 160, or 180 mg/dL (hyperglycemia) over time[*1, 2]
- Changes in AUC over time during periods when blood glucose < 70 mg/dL (hypoglycemia) is observed[*1,2]
- Change in peak postprandial glucose levels over time 3 hours after breakfast, lunch, and evening meal[*1,2]
- Change in maximum variation of blood glucose levels over time between before and after breakfast, lunch, and evening meal[*1,2]
- Changes in MAGE[*1, 2]
- Changes in mean 24-hour blood glucose levels[*1, 2]
- Changes in mean daytime blood glucose levels[*1, 2]
- Changes in mean nocturnal blood glucose levels[*1, 2]
- Changes in AUC[*1, 2]
- Changes in AUC over time during periods when blood glucose 110 mg/dL (hypoglycemia) is observed[*1,2]
- Changes in the SD of 24-hour blood glucose values[*1,2]
- Changes in the SD of daytime blood glucose values[*1,2]
- Changes in the SD of nocturnal blood glucose values[*1,2]

[*1]: Measured value and percent changes for each 7-day period between Week 3 and Week 4 (between Day 22 and Day 28) of the treatment period calculated from the value at the start of the observation period (however changes in the SD of 24-hour blood glucose values shall be measured value only)

[*2]: Measured value and percent change from the value at the start of the observation period to the mean value during the 7-day period between Week 3 and Week 4 (between Day 22 and Day 28) of the treatment period

[Safety endpoint]

- Adverse events

<Other endpoints>

- 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

Statistical method

(1) Analysis set

Two analysis sets, “full analysis set” and “safety data analysis set” are used in this study. "The Full Analysis Set" used as a primary analysis set in the efficacy analysis shall be defined as "the research subjects who were randomized and given at least one dose of the study drug." The safety data analysis set shall be defined as “the research subjects who were given at least one dose of the study drug”.

(2) Efficacy analysis

<Primary endpoints>

- For the “full analysis set”, summary statistics (number of subjects, mean, SDs, maximum values, minimum values, quartiles [same apply hereafter]) and 95% confidence interval (two sides) of mean shall be calculated for each treatment group at each evaluation point (each day), and illustrating changes in mean and SD in order to evaluate changes in the SD of 24-hour blood glucose values (mg/dL) for each 7-day period between Week 3 and Week 4 (between Day 22 and Day 28) of the treatment period, calculated from the value at the start of the observation period for trelagliptin or alogliptin separately. Preliminary, for the “full analysis set”, calculate point estimation and 95% confidence interval (two sides) in difference of mean in treatment groups (trelagliptin 100 mg group – alogliptin 25 mg group) in order to examine the influence of the once-weekly administration and blood glucose fluctuations due to the difference in the daily administration exploratory.
- As well, for the “full analysis set ,” conduct analysis of covariance at each evaluation point with changes in the SD of 24-hour blood glucose values between Week 3 and Week 4 from the value at the start of the observation period as dependent variable, treatment groups as independent variable, HbA1c (NGSP value) at the start of the observation period, changes in the SD of 24-hour blood glucose values at the start of the observation period, and age as covariates, and calculate point estimation and 95% confidence interval (two sides) in difference of adjusted mean for each group.
- Preliminary, “full analysis set ,” calculate point estimation and 95% confidence interval (two sides) in difference of adjusted mean in treatment groups (trelagliptin 100 mg group – alogliptin 25 mg group)

<Secondary endpoints>

- Conduct the same analysis as the primary endpoints for *1 and *2 of the each endpoint section.

However, for changes in mean/SD, only measured values of *1 and *2 shall be illustrated.

<Additional endpoints>

- For the "full analysis set", while calculating summary statistics and 95% confidence interval (two sides) of mean at each evaluation point (the start of the observation period by each treatment group, first day, 1 point during third to fifth day, and ninth day of CGM which is to be performed for 9 days from Day 21) in measured values and changes from the start of the observation period, and illustrate changes in mean and SD.

(3) Safety analysis

- Adverse events shall be reported using MedDRA terminology and summarized using the Preferred Term (PT) and System Organ Class (SOC) of the MedDRA. For the "safety data analysis set", frequency tabulation shall be conducted for adverse events after start of treatment with study drug by each treatment group:
  - Frequency tabulation of all adverse events
  - Frequency tabulation of adverse events that causal relationship is "related" to study drug.
  - Frequency tabulation of the degree of all adverse events
  - Frequency tabulation of degree of adverse events that causal relationship is "related" to study drug.
  - Frequency tabulation of adverse events that were "discontinued" as a measurement concerning study drug.
  - Frequency tabulation of serious adverse events

Rationale for the number of planned research subjects:

The planned minimum number of research subjects evaluable for the primary endpoint in each group is as follows:

Trelagliptin 100 mg group: 15

Alogliptin 25 mg group: 15

Set in consideration with the feasibility of the number of research subjects for exploring the effects of trelagliptin 100 mg and alogliptin 25 mg on glycemic variation. It is not based on statistical power calculation.

3.0 ABBREVIATION

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	Area under the curve
1,5-AG	1,5-anhydroglucitol
BMI	body mass index
CGM	continuous glucose monitoring
COI	conflict of interest
CRO	contract research organization
DPP-4	dipeptidyl-peptidase-4
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon like peptide-1
HbA1c	hemoglobin A1c
ICH	International Conference on Harmonisation
MAGE	Mean Amplitude Glycemic Excursions
MedDRA	Medical Dictionary for Regulatory Activities
PT	preferred term
SAE	serious adverse event
SD	standard deviation
SMBG	Self Monitoring of Blood Glucose
SOC	system organ class
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

Conventionally, although HbA1c has been used as an indicator for glycemic control for patients with diabetes mellitus, it has been indicated that it is insufficient for inhibiting cardiovascular events by only controlling HbA1c which reflects the long term glycemic variation [1-3] On the other hand, it has been reported that persistent hyperglycemia and the range of glycemic variation is related to oxidative stress and cardiovascular events, and it has been indicated that treatment is necessary in consideration of daily glycemic variation [4-6]. Also, it is anticipated that the glycemic variation of patients with diabetes mellitus and the characteristics of each anti-diabetic medications may be revealed and to be able to make a choice for a more appropriate treatment.

Self-measurement of blood glucose (SMBG) is used frequently for measuring glycemic variation and although one may understand the blood glucose level at the time of measurement, it is difficult to know if the blood glucose level has an upward trend or not changing or a downward trend at that time point, and it is reported that 80% hypoglycemia or hyperglycemia may be missed [7,8]. That is why the continuous glucose monitor (CGM) was developed and it became possible to accurately evaluate variance of blood glucose which was difficult and planning of treatment course according to each patient's condition is anticipated. Actually, in many researches that was conducted to collect various glycemic variation patterns to verify the optimization of treatment of diabetes mellitus, the benefits of various indicators of glycemic variation obtained from CGM has been reported [9].

Dipeptidyl-peptidase-4 (DPP-4) inhibitors are used widely as oral treatment drug for type 2 diabetes mellitus and it has an effect to promote insulin secretion blood glucose dependently by raising blood concentration of glucagon like peptide-1 (GLP-1). Conventionally, although DPP-4 inhibitors are taken once to twice daily commonly, once weekly trelagliptin was developed for a new treatment option as good glycemic control from improvement of drug compliance rate and flexibility of timing of taking drug according to lifestyle and further improvement of Quality Of Life(QOL) from less number of doses was in need. The phase III clinical study conducted at the development stage has shown that trelagliptin, when administered for 24 weeks, was not inferior to alogliptin, a DPP-4 inhibitor used as control, in terms of the change in HbA1c at the end of the treatment period [10]. However, effect on glycemic variation of trelagliptin and alogliptin has not been clarified efficiently, and it is anticipated that understanding the characteristics of once weekly DPP-4 inhibitors and once daily DPP-4 inhibitors may be an efficient rational for therapeutic use.

4.2 Rationale for the proposed research

Because there is no enough evidence assayed for glycemic variation of not only once weekly DPP-4 inhibitors but also once daily DPP-4 inhibitor, Trelagliptin, once weekly DPP-4 inhibitor, and Alogliptin, once daily DPP -4 inhibitor, were set as study drugs to collect the consecutive data of glycemic variation obtained from CGM and to evaluate difference of DPP-4 inhibitors.

Although trelagliptin was non-inferior to alogliptin, once daily DPP-4 inhibitor, in terms of the change from baseline in HbA1c at the phase III clinical study conducted during the development period, the effect on glycemic variation of alogliptin have to be clarified when the effect of different dose and method of administration of DPP-4 inhibitors on glycemic variation would like to be evaluated.

In this present study, therefore, the effect of once weekly trelagliptin or once daily alogliptin on glycemic variation will be evaluated in patients with type 2 diabetes mellitus in an exploratory manner as a primary objective, and the effect by difference of dose and method of administration on glycemic variation will be evaluated as secondary as far as possible.

5.0 RESEARCH OBJECTIVES AND ENDPOINTS

5.1 Objectives

To evaluate the effect of trelagliptin administered orally at a dose of 100 mg once weekly or alogliptin orally administered at a dose of 25 mg once daily for 4 weeks on glycemic variation in an exploratory manner as a primary objective and to evaluate, as far as possible, the effect of difference method of administration of DPP-4 on glycemic variation as secondary objective.

5.2 Definition of endpoints

5.2.1 Primary endpoints

Changes in the standard deviation (SD) of 24-hour blood glucose values (mg/dL) for each 7-day period between Week 3 and Week 4 (between Day 22 and Day 28) of the treatment period, calculated from the value at the start of the observation period

5.2.2 Secondary endpoints

(1) Efficacy:

- Changes in AUC over time when specific blood glucose levels (110, 140, 160, or 180 mg/dL) are observed during the 3 hour time period after breakfast, lunch and evening meal
- Change in AUC over time during periods when blood glucose 140, 160, or 180 mg/dL (hyperglycemia) is observed
- Changes in blood glucose 140, 160, or 180 mg/dL (hyperglycemia) over time
- Changes in AUC over time during periods when blood glucose < 70 mg/dL (hypoglycemia) is observed
- Change in peak postprandial glucose levels over time 3 hours after breakfast, lunch, and evening meal
- Change in maximum variation of blood glucose levels over time between before and after breakfast, lunch, and evening meal
- Changes in MAGE
- Changes in mean 24-hour blood glucose levels
- Changes in mean daytime blood glucose levels
- Changes in mean nocturnal blood glucose levels

- Changes in AUC
- Changes in AUC over time during periods when blood glucose 110 mg/dL is observed
- Changes in the SD of 24-hour blood glucose values
- Changes in the SD of daytime blood glucose values
- Changes in the SD of nocturnal blood glucose values

(2) Safety: Adverse events

5.2.3 Other endpoints

(1) Efficacy:

- 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

6.0 CLINICAL RESEARCH DESIGN

6.1 Clinical research design

<Clinical study design>

This is a multi-center, randomized, open-label, parallel-group comparative, exploratory study to evaluate the effect of trelagliptin administered at a dose of 100 mg once weekly or alogliptin at a dose of 25 mg once daily for 4 weeks on glycemic variation in patients with type 2 diabetes mellitus using continuous glucose monitoring (CGM).

<Research TREATMENT>

After informed consent, patients determined to be eligible for this study based on the eligibility assessment will be randomized to either the trelagliptin 100 mg group or the alogliptin 25 mg group (at a ratio of 1:1), using "HbA1c at the start of the observation period (< 7.5% or ≥ 7.5%)" and age (< 65 or ≥ 65) as a stratification factor for randomization.

The principal investigator or investigator shall prescribe trelagliptin 100 mg/week or alogliptin 25 mg/day according to the allocation results notified from the enrollment center.

Trelagliptin 100 mg once weekly or alogliptin 25 mg once daily, taken orally before breakfast

Planned number of research subjects:

The planned minimum number of research subjects evaluable for the primary endpoint in each group is as follows:

Trelagliptin 100 mg group: 15
Alogliptin 25 mg group: 15

Number of study research implementing entities:

3 medical institutions

<Duration of evaluation and number of visits of research subjects>

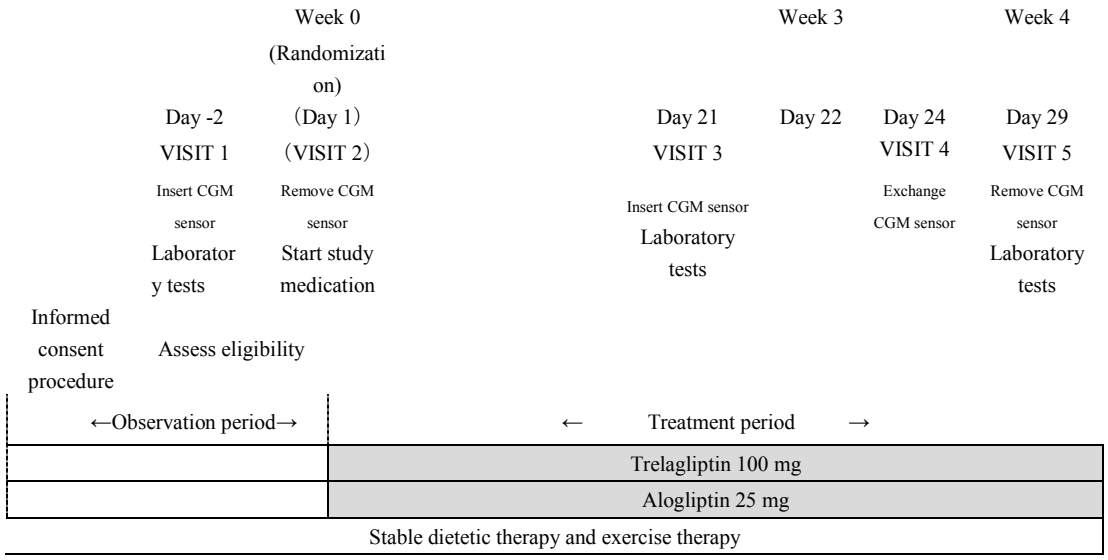
Duration of evaluation: 31 days, consisting of the observation period for 2 days and a treatment period for 29 days (4 weeks).

Number of visits: a total of 5 visits. Research subjects shall visit the study site at the start of the observation period (VISIT 1: Day-2), at the start of the treatment period (VISIT 2: Day 1), during the treatment period for CGM insertion (VISIT 3: Day 21) and for CGM sensor exchange (VISIT 4: Day 24), and at the end of the treatment period (VISIT 5: Day 29).

Figure 6 (a) shows a schematic of the clinical research design. Refer to Appendix A for schedule of examinations, observations, and assessments.

Figure 6.a Outline of clinical research design

< Outline of clinical research >



6.2 Rationale for the clinical research design

(1) Rationale for the clinical research design

Because there is no enough evidence assayed for glycemic variation of not only once weekly DPP-4 inhibitors but also once daily DPP-4 inhibitor, Trelagliptin, once weekly DPP-4 inhibitor, and Alogliptin, once daily DPP -4 inhibitor, were set as study drugs to collect the consecutive data of glycemic variation obtained from CGM and to evaluate difference of DPP-4 inhibitors.

Although trelagliptin was non-inferior to alogliptin, once daily DPP-4 inhibitor, in terms of the change from baseline in HbA1c at the phase III clinical study conducted during the development period, the effect on glycemic variation of alogliptin have to be clarified when the effect of different dose and method of administration of DPP-4 inhibitors on glycemic variation would like to be evaluated.

In this present study, therefore, the effect of once weekly trelagliptin or once daily alogliptin on glycemic variation will be evaluated in patients with type 2 diabetes mellitus in an exploratory manner as a primary objective, and the effect by difference of dose and method of administration on glycemic variation will be evaluated as secondary as far as possible.

Therefore this unblind study was designed to objectively evaluate the effect on glycemic variation of trelagliptin 100 mg and alogliptin 25 mg administered in patients with type 2 diabetes mellitus. And also to evaluate the effect of different method of administration on glycemic variation, stratified randomization comparison method between 2 groups was adopted with "HbA1c at the start of the observation period (< 7.5% or ≥ 7.5%) and age (< 65 or ≥ 65)" as a stratification factor for randomization.

Also, to exclude effect on glycemic variation from other anti-diabetic medications, research subjects who were taking anti-diabetic medications ≤ 4 weeks before start of observation period were excluded.

(2) Rationale for dosage

The dosages of trelagliptin and alogliptin were set at 100 mg/week and 25 mg/day, respectively, to evaluate glycemic variation at the usual dosage in clinical settings.

(3) Rationale for dosage

Study drugs show the glucose lowering effect by increasing incretin which are secreted by food intake. Thus, in order to eliminate the influence on the blood glucose by food intake. To further unify the administration timing of the research subjects prior to breakfast in terms of evaluating their glycemic variation.

(4) Rationale for duration of treatment

From the results of trelagliptin and alogliptin in phase II and III trials, duration was set at 4 weeks taking into account that the effect on blood glucose levels stabilize after 2 to 4 weeks with either drugs.

(5) Rationale for the number of planned research subjects:

Refer section 13.3

6.3 Premature termination of entire clinical research or premature termination of clinical research at a research implementing entity

6.3.1 Premature termination criteria of entire clinical research

The sponsor should immediately discontinue the study when at least one of the following criteria is applicable:

- When new information or other evaluation on the safety or efficacy of the study drug becomes available that shows a change in the known risk/benefit profile of the concerned compound, and risks/benefits are no longer tolerable for research subject participation in the study.

- When there is serious deviation from ethical guidelines or ICH-GCP that may threaten safety of the research subjects.

6.3.2 Criteria for premature termination of research implementing entities

A study site may be notified by the sponsor to discontinue clinical study if the site (including the principal investigator) is found in significant violation of Ethical Guideline for Clinical Research, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures of clinical study suspension and premature termination of entire clinical study or study at a research implementing entity

In the event that the sponsor or a research implementing entity committee such as an ethics review committee decides to prematurely suspend or terminate the entire clinical study or clinical study at a research implementing entity, a study-specific procedure shall be provided by the sponsor. The procedure shall be followed by applicable research implementing entities during the course of clinical study suspension or premature termination.

6.4 Procedures for protocol revision

If the protocol needs to be revised, the sponsor shall consider and decide whether to revise the protocol.

The principal investigator of each research implementing entity shall be informed of the details of each protocol revision. Also, principal investigators shall confirm the content of the revision of the protocol and submit a letter of agreement to the sponsor as evidence of agreement with the protocol revision.

Upon notification, the principal investigator at each research implementing entity shall submit the revised contents to committees such as the IEC, as necessary according to institutional regulations for review, and obtain approval from the director of the entity.

7.0 SELECTION AND WITHDRAWAL CRITERIA OF RESEARCH SUBJECTS

7.1 Inclusion criteria

Research subjects shall fulfill all of the following criteria to be included in this clinical study:

1. Research subjects who, in the opinion of the principal investigator or the investigator, are capable of understanding the content of the clinical research and complying with the research protocol requirements.
2. Patients who are able to sign and date the informed consent form and information sheet prior to the start of study procedures
3. Patients diagnosed with type 2 diabetes mellitus
4. Patients with an HbA1c (NGSP value) value ≥ 6.5% and < 8.5% at the start of the observation period (Day -2)
5. Patients who experience a ≤ ±1.0% change in HbA1c (NGSP value) at the start of the observation period (Day -2) as compared with an HbA1c value obtained during the preceding 6 weeks
6. Patients receiving stable dietetic therapy and exercise therapy (if performed) for ≥ 4 weeks before the start of the observation period
7. Patients who in the opinion of the principal investigator or the investigator, does not have to change (including discontinuation or interruption) HMG-CoA reductase inhibitors or addition of new HMG-CoA reductase inhibitors during treatment period.
8. Men or women aged 20 years or older at the time of informed consent

[Rational for the inclusion criteria]

1.2. These were set as essential conditions for the clinical research.

3. Set as target disease for this study.
4. To evaluate the glycemic variation caused by the study drug accurately, the upper limit value was set at 8.5% (NGSP value) to exclude research subject with insufficient glycemic control.
5. To evaluate the glycemic variation accurately, the change variation of HbA1c was set to exclude research subject with unstable glycemic control
6. Set in consideration of the possibility of change in dietetic/exercise therapy may affect evaluation of glycemic variation.

7. This was set in consideration of the possibility that HMG-CoA reductase inhibitors may affect glycemic variation.
8. This was set to allow for separate assessment of men/women. The lower age limit was set to 20 years to allow patients to make a voluntary decision regarding their participation in this clinical research.

7.2 Exclusion criteria

Research subjects meeting any of the criteria below shall not be included in this research.

1. Patients who received anti-diabetic medications within 4 weeks prior to the start of the observation period.
2. Patients who have changed (including discontinuation or interruption) HMG-CoA reductase inhibitors or received new HMG-CoA reductase inhibitors ≤ 4 weeks before the start of the observation period.
3. Patients with clinically evident hepatic dysfunction (e.g., AST or ALT ≥ 2.5-fold the upper limit of normal at the start of the observation period [Day -2])
4. Patients with moderate renal dysfunction, severe renal dysfunction or renal failure (e.g., creatinine clearance < 50 mL/min or serum creatinine > 1.4 mg/dL in men or > 1.2 mg/dL in women [equivalent to the creatinine clearance for persons aged 60 years with a body weight of 65 kg] at the start of the observation period [Day -2])
5. Patients with severe heart disease, cerebrovascular disorder, or severe pancreatic, hematologic or other diseases
6. Patients with a history of gastric or small intestinal resection
7. Patients with proliferative diabetic retinopathy
8. Patients warranting insulin therapy for glycemic control (e.g., patients with severe ketosis, diabetic coma or precoma, type 1 diabetes mellitus, severe infection, perioperative patients, or serious trauma)
9. Patients with a history of hypersensitivity or allergy to DPP-4 inhibitors
10. Patients who experience an allergic reaction to metal during CGM at the start of the observation period (Day -2)
11. Patients with any malignant tumors
12. Habitual drinkers whose average daily alcohol consumption is > 100 mL[Note 1)]

13. Patients who have any contraindications for the study drug or are taking any contraindicated concomitant drugs listed in the package insert
14. Patients anticipated to require any prohibited concomitant medications during the study period
15. Patients who are day and night lifestyle reversal
16. Patients participating in any other clinical studies at the time of informed consent for this study
17. Pregnant women, nursing mothers, women who are possible pregnant, or women who plan to become pregnant
18. Other patients who are considered inappropriate for participation in this study in the opinion of the principal investigator or investigator

Note 1: Alcohol conversion table (for reference)

Alcohol type	Variation	Alcohol strength (%)	Amount equivalent to alcohol 100 mL
Brewed alcohol	Sake	15%	670 mL (about 3 gos, 1 go=180 mL)
	Beer	5%	2,000 mL (about 3 large bottles)
	Happoshu (low-malt beer - like beverage)	5%	2,000 mL
	Wine	12%	830 mL
	Shaoxing rice wine	18%	560 mL
Spirits	Shochu (group ko)	35%	290 mL
	Shochu (group otsu)	25%	400 mL
	Whisky	40%	250 mL (about 3 double glasses)
	Brandy	40%	250 mL (about 3 double glasses)
	Vodka	40%	250 mL (about 3 double glasses)
Combined alcohol	Plum wine	13%	770 mL
	Combined sake	16%	630 mL

[Rationale for the exclusion criteria]

1, 2. Set in order to evaluate drug efficacy accurately.

3, 5, 7, 10, 11, 13. These were set in consideration of safety of research subjects.

4. Severe renal dysfunction and renal failure shall be excluded because trelagliptin is contraindicated for these conditions. Moderate renal dysfunction shall be excluded in consideration of safety of research subjects.

6, 12, 14. Set in order to take in consideration of safety of research subjects and to evaluate drug efficacy accurately.

8, 9. Set as contraindication for trelagliptin and alogliptin treatment.

15..,16 Set in order to establish rational for evaluation of this study.

17. Set as safety of trelagliptin and alogliptin in pregnant women has not been established. Also, set as excretion of trelagliptin and alogliptin in breast milk was confirmed in non-clinical trials.

18. These were set as fundamental items for the research.

7.3 Prohibited concomitant drugs and restricted concomitant drugs

7.3.1 Prohibited concomitant drugs

The following drugs are prohibited from the start of observation period to end of treatment period.

1. Anti-diabetic medications other than the allocated oral hypoglycemic drug
2. Glucocorticoids (medications for local effect such as external preparations are excluded)
3. Estrogen preparations
4. HMG-CoA reductase inhibitors* other than those used at the time of informed consent

   *Dosage of HMG-CoA reductase inhibitors those used at the time of informed consent may not be changed.
5. Acetaminophen

[Rational for prohibited concomitant drugs]

1 to 5. Set as it may affect evaluation of drug efficacy.

7.3.2 Restricted concomitant drugs

The following drugs those used at the time of informed consent are permitted from the start of observation period to end of treatment period. However, change of dosage, addition of or change to a new drug for those drugs is prohibited unless the principal investigator and investigator consider necessary due to adverse events.

1. Lipid lowering agents other than HMG-CoA reductase inhibitors
2. Anti-hypertensive drug

7.4 Research Subject Management

The principal investigator and investigator shall instruct the research subject the items below.

(1) Give instructions to take allocated oral hypoglycemic drug as directed. If poor compliance with study treatment (e.g., < 75% of the prescribed dose) after the previous visit has been found and does not improve, the research subject may be withdrawn from the research if appropriate for the circumstances.

(2) If hypoglycemia symptom (hunger abnormal, feeling of weakness, trembling of hands and fingers, cold sweat, palpitations, etc.) is observed, take glucose or sucrose (sugar), and if it does not improve give instructions to visit promptly.

(3) For dietetic therapy and exercise therapy (if performed), the principal investigator and investigator shall make sure prescriptions (instructions for calories, etc.) are consistent throughout the research period, and instruct the research subject to adhere to the dietetic therapy and exercise therapy (if performed).

(4) When CGM is being conducted, the principal investigator and investigator shall instruct exercise therapy (if performed) that may be performed under the same conditions every day, and instruct the research subject to adhere to it.

(5) When CGM is being conducted, give instruction to photograph every meal contents.

(6) Instruct the research subject not to eat high-sugar, high-calorie food or beverage between meals during CGM.

(7) When CGM is being conducted, give instructions to note necessary items into the research subject diary.

(8) On visit days for planned laboratory tests, give instructions not to take oral hypoglycemic drug scheduled to be taken on that day. Further, at each visit, have the research subject report if drug has been taken or not the day before, and on the day of visit.

(9) On visit days for planned laboratory tests, give instructions for fasting $\geq$ 10 hours before visit.

(10) For research subjects of childbearing potential, give instructions to use adequate contraception. If pregnancy is discovered, have the research subject report promptly, and discontinue the research immediately.

(11) The principal investigator and investigator shall instruct the research subject to adhere to instructed prohibited concomitant drugs. When drugs are taken other than the drugs prescribed by the principal investigator and investigator, have the research subject report its content.

(12) Regarding subjective symptoms/objective findings, have the research subject report at visit the necessary items from its contents, onset date, degree, outcome and date of outcome.

7.5 Criteria for discontinuation or withdrawal of a research subject

The principal investigator or investigator shall record the main reason for discontinuation of protocol treatment on the case report form according to the classification described below. Refer section 9.1.12 for discontinuation case before randomization.

1. **Adverse event**

   When the research subject had an adverse event that requires withdrawal of the research subject from the study because continued participation in the study would impose an unacceptable risk to the research subject's health, or when the research subject is unwilling to continue study participation because of the pretreatment event or adverse event.

2. **Major protocol deviation**

   When it is discovered after randomization that a research subject does not meet the eligibility criteria or is not adhering to the protocol, and continued participation in the research would impose an unacceptable risk to the research subject's health.

3. **Lost to follow-up**

   When the research subject failed to make visits and could not be contacted. The attempts that were made to contact the research subject shall be recorded in the source documents.

4. **Voluntary termination**

When the research subject wishes to withdraw from the research. The reason for discontinuation shall be recorded on the CRF when it is clarified.

5. **Research termination**

When the sponsor or a committee such as the IEC or regulatory authority has decided to terminate the study. Refer to Section 6.3.1 for details.

6. **Pregnancy**

When a female research subject is found to be pregnant.

Note: Research participation shall be immediately discontinued when pregnancy is known. Refer to Section 9.1.11 for procedure.

7. **Others**

Note: The specific reasons should be recorded on the CRF.

7.6 Procedures for discontinuation of individual research subjects

The principal investigator or investigator shall terminate a research subject's research participation when the research subject meets the criteria described in Section 7.5. Individual research subjects may discontinue their research participation without giving a reason at any time during the research. Should a research subject's participation be discontinued, the primary reason for termination shall be recorded on the CRF by the principal investigator or investigator. In addition, efforts shall be made to perform all tests/observations/evaluations scheduled at the time of discontinuation.

8.0 RESEARCH TREATMENT

This section indicates the treatment regimen of this clinical research. See the latest package insert for details and handling of each drug.

8.1 Treatment with the study drug

8.1.1 Study drug

(1) Study drug:

Generic name: Trelagliptin Succinate

Chemical name: 2- ({6- [（3R）-3-Aminopiperidin-1-yl] -3-methyl-2, 4-dioxo-3, 4-dihydropyrimidin -1 (2H)-yl})methyl-4-fluorobenzonitrile monosuccinate

Generic name: Alogliptin benzonate

Chemical name:2- ({6- [(3R) -3-Aminopiperidin-1-yl] -3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1 (2H) -yl} methyl) benzonitrile monobenzoate

8.1.2 Dose and administration method

Trelagliptin 100 mg (once weekly) or alogliptin 25 mg (once daily) shall be administered orally before breakfast. However, the drug shall be administered as described below at the start of the treatment period (VISIT 2: Day 1) or during the treatment period (VISIT 3: Day 21).

At the start of the treatment period (VISIT 2: Day 1): The drug shall be administered after required tests/observations, etc.

During the treatment period (from VISIT 3 to VISIT 5):

Trelagliptin 100 mg/week group shall insert the sensor on a day between 3day and a day before Trelagliptin administration day. Trelagliptin 100 mg/week shall be administered before breakfast on the day of the drug administration. The next administration of Trelagliptin 100 mg is after the sensor removal.

Alogliptin 25 mg/day shall be administered after required tests/observations, etc at every VISIT without taking study drug. Research subjects shall take study drug prior to the every breakfast at home.

Duration of treatment shall be start of treatment period (Day 1) to end of treatment period (Day 29).

Dose and administration method for each administration group are shown in table 8.a.

Table8.a Administration group and administration method

Administration group	Dose	Route of administration:	Administration method
Trelagliptin group	Trelagliptin 100 mg	Oral administration	Once weekly, before breakfast
Alogliptin group	Alogliptin 25 mg	Oral administration	Once daily, before breakfast

8.1.3 Overdose

Overdose is defined as intentional or accidental administration of the study drug at a higher dose than that specified in the protocol, either by a health professional or by the research subject.

To consistently collect important safety information about overdose, the principal investigator or investigator(s) shall record all cases of overdose on the "Overdose" page of the CRF, irrespective of the presence or absence of accompanying adverse event. Adverse events associated with overdose shall be recorded on the "Adverse events" page of the CRF, in accordance with the procedures described in Section 10.0, "ADVERSE EVENTS."

In addition, serious adverse events associated with overdose shall be recorded in accordance with the procedures described in Section 10.2.2, "Collection and reporting of SAEs."

In the event of overdose, the principal investigator or investigator shall treat the subject as required based on symptoms.

8.2 Medication other than the study drug

Prohibited concomitant drugs (refer to Section 7.3.1) may not be used. Also, restricted drugs (refer to Section 7.3.2) may be used if used at the time of informed consent. However, dose change for those restricted drugs or addition of or change to a new drug shall be prohibited unless the principal investigator and investigator consider necessary due to adverse events. Other treatments shall be conducted under normal medical practice

8.3 Allocation and prescription of the study drug and administration procedure

The principal investigator or its designee shall access the web case enrollment system to allocate research subjects. In addition the principal investigator or its designee shall notify information necessary for allocation such as the research subject ID number. Thereafter, the drug to be administered to the research subjects shall be notified by the web case enrollment system. The principal investigator and investigator shall prescribe the study drug according to the notification and record the drug information into the CRF of each research subject.

8.4 Preparation and storage of allocation list

The person responsible for allocation (designated by the sponsor) shall create an allocation list.

Allocation shall be conducted at the enrollment center using web case enrollment system at start of treatment period (Day 1) with "HbA1c at the start of the observation period (< 7.5% or ≥ 7.5%)" and age (< 65 or ≥ 65) as a stratification factor for randomization. The enrollment center shall use the allocation list for stratified randomization created by the allocation responsible person.

Information on the allocation shall be kept in a safe place and shall not be available to anyone other than authorized persons, to secure independency from the clinical research.

9.0 CLINICAL STUDY PROTOCOL

9.1 Research procedures

The principal investigator or investigator shall collect data in accordance with the procedure below. The same principal investigator or investigator shall perform tests/observations/evaluation of research subjects, in principle. The study schedule is provided in Appendix A.

9.1.1 Informed consent procedure

The procedures for obtaining informed consent are described in Section 15.3.

Consent shall be obtained from the research subject before initiation of research procedures.

Research subject ID code is given to each research subject from whom informed consent was acquired and who was randomized. The research subject ID code shall be used throughout the research period and shall not be changed.

9.1.2 Demographic data, medical history, and previous therapeutic drugs

(1) Demographic information

Demographic data shall be collected regarding birth, gender, smoking history, drinking history, time (year/month) of onset (or diagnosis of diabetes).

(2) Medical history

Medical history data shall be collected regarding clinically problematic diseases or symptoms that disappeared within 1 year or were terminated from the start of observation period. When the symptoms or disease continues, it shall be considered as a concurrent disease (Refer to Section 9.1.6).

(3) Pre-treatment

Regarding pre-treatment, name of drug, route of administration and date of final administration shall be collected for all anti-diabetic medication (including injections) that ended use $\leq$ 12 weeks before start of observation period.

9.1.3 Physical examination

All subsequent physical examinations after the start of the treatment period shall be assessed for clinically significant changes from the baseline examination.

9.1.4 Weight, height and BMI

Body weight shall be measured to one decimal place in kilograms.

Height shall be measured or asked to the nearest whole number in centimeters.

BMI shall be calculated by the sponsor using the following formula and shown to one decimal place:

Body Mass Index: BMI = weight (kg) / (height (m))^2

Example:

Height = 176 cm, weight = 79.2 kg, BMI = 79.2/1.76^2 = 25.6 kg/m^2

9.1.5 Concomitant drugs

Concomitant drugs are all drugs to be given in addition to the study drug. Drugs prescribed by doctors or the over-the-counter medicines purchased by the research subjects shall be included. At every hospital visit of the research subject, the status of use of drugs (name of drug, route of administration) other than the allocated oral hypoglycemic drug, from start of observation period to the completion of the clinical research shall be monitored.

9.1.6 Concurrent disease

A concurrent disease is defined as a disease or symptom that is present at the start of the observation period or that develops between the start of the observation period and the start of study treatment. Clinically significant abnormalities, including laboratory test data and physical examination findings, observed in tests and physical examinations at the start of study treatment shall be considered as a concurrent disease at the discretion of the principal investigator or investigator. The content of concurrent disease (diagnosis) shall be investigated.

9.1.7 Laboratory tests

Laboratory tests in table 9.a shall be measured at clinical laboratory institutions according to the observation schedule (Appendix A). Regarding tests at fasting, blood sampling shall be conducted after ≥ 10 hours of fasting. The principal investigator and investigator shall evaluate and keep the reported laboratory test results.

Inhibitory rate of DPP-4 activity will be calculated by the sponsor using formula below:

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

Table 9.a Laboratory tests

Serum chemistry	
Fasting blood glucose	Glycoalbumin
Fasting insulin	1,5-AG
Fasting glucagon	
Fasting proinsulin	
FastingGLP-1	
Fasting GIP	
DPP-4 activity	

The principal investigator shall keep laboratory test reference values, including the historical data.

9.1.8 HbA1c (NGSP value)

Measured at research implementing entities to confirm eligibility of research subject at start of observation period. The principal investigator and investigator shall evaluate and keep the reported laboratory test results.

9.1.9 Continuous glucose monitoring (CGM)

Conducted according to Schedule of Research Procedures (Appendix A) Details shall be specified separately in the operation procedures manual.

(1) Device used in this study

[redacted], leased from the sponsor.

(2) Self-measurement of blood glucose (SMBG)

Use device leased from sponsor

Research subjects shall measure blood glucose levels every day during CGM in the observation and treatment periods. At least, blood glucose levels shall be measured at three time points on the first day of CGM ([1] at least 2 hours after the recorder is connected and [2] 2 hours after the first is measured. [3] at bedtime) and at four time points from the second day onward ([1] before breakfast, (2) before lunch, (3) before evening meal, and (4) at bedtime).

The glucose levels from SMBG shall be used for correction of glucose levels obtained from CGM.

(3) Observation period

A sensor shall be inserted at the start of the observation period (Day -2) and removed at the start of treatment (Day 1)

(4) Treatment period

A sensor shall be inserted (VISIT 3: Day 21), exchanged (VISIT 4: Days 24 to 26), and removed (VISIT 5: Day 29) during the treatment period.

(5) Dietetic therapy and exercise therapy

Research subjects shall present photographs of all meals to the principal investigator or investigator during CGM. Also, the meal provided by the sponsor shall be taken according to the calories prescribed by the sponsor for each research subject at the meal times shown below.

Time point of provision of meals: evening meal at start of observation period (Day-2), evening meal on first and seventh of CGM to be performed from Day 21 for 9 days.

Research subjects shall only conduct exercise therapy feasible (if performed) under the same conditions every day during CGM.

The principal investigator or investigator shall prescribe consistent dietetic therapy and exercise therapy (if performed) throughout the research period. Compliance with dietetic therapy and exercise therapy(if performed) shall be investigated and rated on a four-point scale as follows:

1. Compliant (compliance rate ≥ 90%)
2. Almost compliant (compliance rate ≥ 70%)
3. Generally compliant (compliance rate ≥ 50%)
4. Minimally compliant (compliance rate < 50%)

(6) Research subject diary

Research subjects shall complete the subject diary every day during CGM and submit the diary to the principal investigator or investigator.

The following information shall be recorded in the subject diary: date and time of dosing, time of SMBG and blood glucose levels, meal time and contents, exercise time, wake-up time, bedtime, etc.

9.1.10 Contraception

Women of childbearing potential (e.g., women who have not undergone surgical sterilization, women who have not reached menopause) shall use appropriate contraception during participation in this clinical research from the time of informed consent. During the informed consent process, appropriate contraceptive methods and the necessity of avoiding pregnancy during participation in

the clinical research shall be fully explained to women of childbearing potential with the use of the informed consent form and information sheet, and the research subjects shall fully understand these explanations before providing consent.

9.1.11 Pregnancy

When a study subject or a partner of study subject was found to be pregnant during the study period, the principal investigator or investigator notify the monitoring staff of the sponsor. The principal investigator or investigator provide detailed information using the Follow-up Form for Pregnancy separately wherever possible.

9.1.12 Record of cases withdrawn before randomization

The consent form shall be signed, and a CRF shall be created for all research subjects who are withdrawn before randomization.

The following items are to be described on the CRF.

- Informed consent procedure
- <MMM/DD/YYYY>
- Sex
- Eligibility
- Reason for discontinuation

The primary reason for withdrawal before randomization shall be recorded on the CRF according to the following classification:

- Not meeting inclusion criteria or meeting exclusion criteria
- Serious deviation from protocol
- Lost to follow-up
- Voluntary discontinuation (specify the reason)
- Premature termination criteria of entire clinical research
- Others (specify the reason)

Research subject ID numbers assigned to research subjects withdrawn from the research before randomization shall not be reused.

9.1.13 Record of randomization

Research subjects to be randomized shall meet all of the inclusion criteria and shall not meet any of the exclusion criteria according to Section 8.2. The principal investigator or investigator shall specify the reason why the subject cannot be randomized to the treatment period.

9.2 Drug-taking status of the research subjects

The principal investigator or investigator shall confirm the treatment compliance and the date and time of dosing during CGM with the research subject at every visit. At the end of study drug administration, Treatment compliance shall be rated on a two-point scale as follows:

1. Compliant (compliance rate ≥ 75%)

2. Not compliant (compliance rate < 75%)

Medication instruction shall be given to research subjects throughout the clinical research period. If poor compliance with study treatment (e.g., < 75% of the prescribed dose) after the previous visit has been found and does not improve, the research subject may be withdrawn from the research if appropriate for the circumstances.

9.3 Implementation time point of the test and observation items

The schedule for all tests, observations, and evaluations is shown in Appendix A. The principal investigator or investigator shall perform the tests, observations, and evaluations at the time points shown below.

9.3.1 Start of observation period (Visit 1: Day -2)

After consent is obtained, physical examination/tests are to be conducted for research enrollment. Eligibility of research subjects shall be determined in accordance with the inclusion and exclusion criteria as described in section 7.0. Refer to section 9.1.12 for the recording of research subjects who are withdrawn before randomization.

Tests and observations to be performed and endpoints to be assessed during the observation period (VISIT 1: Day -2) are shown below.

- Informed consent procedure
- Demographic information
- Medical history, pre-treatment
- Physical examination
- Height
- Concomitant drugs
- Concurrent disease
- Prescription of and compliance with dietetic therapy and exercise therapy

Tests and observations to be performed and endpoints to be assessed during the observation period VISIT 1(Day -2) are shown below.

- Physical examination
- Body weight
- Laboratory tests
- HbA1c
- CGM (remove sensor)
- Self-measurement of blood glucose (self-measured by research subject)

9.3.2 At start of treatment period (Visit 2: Day 1)

Research subjects whose eligibility has been confirmed shall be randomized according to section 8.3 following the results of test, observation and endpoints implemented before start of treatment period.

Randomization is performed at the visit when the principal investigator or investigator is considered as necessity.

The test, observation, and endpoints to be implemented at the start of treatment period (Visit 2: Day 1) are shown below.

- Physical examination
- Concomitant drugs
- Compliance with dietetic therapy and exercise therapy
- CGM (remove sensor)
- SMBG (research subject perform by own)
- Adverse Event

9.3.3 Treatment period (Visit 3: Day 21)

The test, observation, and endpoints to be implemented during the treatment period (Visit 3: Day 21) are shown below.

- Physical examination
- Body weight
- Concomitant drugs
- Laboratory tests

- Treatment status
- Compliance with dietetic therapy and exercise therapy
- CGM (remove)
- Self-measurement of blood glucose (self-measured by research subject)
- Adverse event

9.3.4 Treatment period (Visit 4: Day 24)

The test, observation, and endpoints to be implemented during the treatment period (Visit 4: Day 24) are shown below.

- Physical examination
- Concomitant drugs
- Laboratory tests Drug-taking status
- Compliance with dietetic therapy and exercise therapy
- CGM (exchange sensor)
- Self-measurement of blood glucose (self-measured by research subject)
- Adverse event

9.3.5 At end of treatment period (Visit 5: Day 29) or discontinuation during treatment period

The test, observation, and evaluation items to be implemented during at the end of treatment period (Visit 5: Day 29) are shown below.

- Physical examination
- Body weight
- Concomitant drugs
- Laboratory tests
- Drug-taking status
- Compliance with dietetic therapy and exercise therapy
- CGM (remove sensor)
- Self-measurement of blood glucose (self-measured by research subject until removal of CGM sensor)

- Adverse event

The test, observation, and endpoints to be implemented at discontinuation of treatment period are shown below.

- Physical examination
- Body weight
- Concomitant drugs
- Laboratory tests
- Drug-taking status
- Compliance with dietetic therapy and exercise therapy
- Adverse event
- Reason of discontinuation

The status of all randomized research subjects at the end of the clinical research shall be recorded on the CRF.

10.0 ADVERSE EVENT

10.1 Definitions

10.1.1 Adverse event

An adverse event is defined as any untoward medical occurrence in a patient or a research 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).

An adverse event can therefore be any unfavorable or unintended sign (e.g., clinically significant laboratory abnormality), symptom, or disease temporally associated with the use of a pharmaceutical product (including the study drug), regardless of whether it is considered related to the pharmaceutical product (including the study drug) or not.

10.1.2 Considerations for adverse events

Generally unfavorable findings are described below:

- Newly diagnosed disease or unexpected aggravation of existing symptom (intermittent event of an existing symptom is not considered an adverse event)
- Requiring action or medical practice
- Requiring invasive diagnostic treatment
- Requiring discontinuation or a change in the dose of the study drug or a concomitant medication
- Considered unfavorable by the principal investigator or the investigator

Diagnosis name and signs/symptoms:

Adverse events shall be recorded by diagnosis name. Accompanying signs (including abnormal laboratory values, abnormal ECG findings) and symptoms shall not be recorded as adverse events. If an adverse event could not be expressed by a diagnosis name, the signs or symptoms shall be recorded as the adverse event.

Laboratory test values and ECG findings:

Abnormal laboratory values and ECG findings shall be recorded as adverse events when the principal investigator or investigator judges the results are clinically problematic (in other words, when certain action or medical practice is required, or when the principal investigator or the investigator judges the change has exceeded the normal physiological variation range of the research subject). Retest and/or continued monitoring of an abnormality are not considered medical practice.

Also, repeated or additional conduction of non-invasive tests for verification, evaluation, and monitoring of an abnormality are not considered medical practice.

However, when abnormal laboratory values and ECG findings are the accompanying symptoms of a disease diagnosed as an adverse event (e.g., increased creatinine due to renal dysfunction, etc.), the adverse event shall be handled by its diagnosis name.

Pre-existing conditions (disease or symptom that has been present since before the start of study treatment): Pre-existing disease or symptom that has been present since before the start of study treatment shall be regarded as a concurrent disease and not an adverse event. When a concurrent medical condition is aggravated, the aggravation shall be determined as an adverse event and the principal investigator or the investigator shall record on the CRF that the adverse event is an aggravation of the concurrent disease (e.g., "aggravation of hypertension," etc.).

If a research subject has a pre-existing episodic condition (e.g., asthma, epilepsy), each episode shall be recorded as an adverse event if the episodes become more frequent, serious, or severe in nature. If a research subject has a chronic concurrent condition (e.g., cataracts, rheumatoid arthritis), worsening of the condition shall be recorded as adverse event if the degree of the worsening exceeds that which would be expected. The principal investigator or investigator shall ensure that the adverse event term to be recorded represents the change in the condition from baseline (e.g. "worsening of…").

Worsening of adverse events:
If a research subject experiences a worsening of the adverse event after a change to the study drug, or secondary signs and symptoms are caused by the adverse event, the worsening or the secondary signs and symptoms shall be recorded as a new adverse event on the CRF. The principal investigator or investigator shall use an adverse event term that explicitly means a change of the condition (e.g., "worsening of…").

Change of severity of adverse events:
If the research subject experiences changes in the severity of an adverse event, the event shall be recorded once, at its peak severity.

Previously planned surgery or treatment:
Preplanned surgeries or interventions that were scheduled before study treatment shall not be considered adverse events. However, when the existing symptom is aggravated to a degree requiring emergency surgery or treatment, the condition or the event shall be considered an adverse event. A concurrent disease that resulted from previously planned surgery shall be reported as an adverse event.

Non-urgent surgery or treatment:
Non-urgent surgery or treatment that does not induce a change in the condition of a research subject (cosmetic surgery, etc.) shall not be considered an adverse event; However, it shall be recorded in the source documents. Concurrent diseases due to a non-urgent surgery shall be reported as an adverse event.

The insufficient clinical response (lack of efficacy): insufficient clinical response, efficacy, or pharmacological action shall not be recorded as an adverse event. The principal investigator or investigator shall make the distinction between worsening of a pre-existing condition and lack of therapeutic efficacy.

Overdose of the study drug:
Overdose of any medication without onset of event shall not be recorded as an adverse event, but the overdose shall be recorded on the "Overdose" page of the CRF. Any onset of event shall be recorded as adverse events on the "Adverse events" of the CRF.

10.1.3 Serious adverse event

Of all unfavorable medical events that develop after administration of a pharmaceutical product (including the study drug) (irrespective of dose), a serious adverse event is an event that:

1. results in death,
2. is life threatening*,
3. requires inpatient hospitalization or prolongation of existing hospitalization,
4. results in persistent or significant disability/incapacity,
5. leads to a congenital anomaly/birth defect, or
6. Medically important event that causes a risk to the research subject even if it is not immediately life-threatening and does not result in death or hospitalization, or requires an action or treatment to prevent the results described in 1 to 5 above. Points described in the Takeda Medically Significant Adverse Event List (Table 10.a) are included in this section.

* The term "life threatening" refers to an event in which the research subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

Table 10.a Takeda Medically Significant AE List

Acute respiratory failure/acute respiratory distress syndrome (ARDS)	Hepatic necrosis
Torsades de pointes/ ventricular fibrillation/ventricular tachycardia	Acute hepatic failure
Malignant hypertension	Anaphylactic shock
Convulsive seizure (including convulsion and epilepsy)	Acute renal failure
Agranulocytosis	Pulmonary hypertension
Aplastic anemia	Pulmonary fibrosis (including interstitial pneumonia)
Toxic epidermal necrolysis/ Oculomucocutaneous syndrome (Stevens-Johnson syndrome)	Neuroleptic malignant syndrome/ malignant hyperpyrexia
	Spontaneous abortion/ stillbirth and fetal death
	Confirmed or suspected transmission of infection by a medicinal product
	Confirmed or suspected endotoxin shock

10.1.4 Adverse events of special interest (specific adverse events)

An AE of Special Interest (AESI) (serious or non-serious) is one of scientific and medical concern specific to the study drug, for which ongoing monitoring and rapid communication by the principal investigator or investigator to Takeda may be appropriate. Such events may require further investigation in order to establish assessment, and instructions provided to investigators on how and when they should be reported to the sponsor are described in Section 10.2.1.3.

AESIs: Hypoglycemia-related AEs, intestinal obstruction-related AEs and acute pancreatitis-related AEs (for both Trelagliptin and Alogliptin), QT/QTc interval prolongation-related AEs (for Trelagliptin), and Liver dysfunction or jaundice-related AEs (for Alogliptin).

<For both Trelagliptin and Alogliptin>

[Hypoglycemia-related AEs]

Hypoglycemia-related AEs are designated as AESIs because, in general, attention should be paid to the events in the treatment of diabetes mellitus.

[Intestinal obstruction-related AEs]

Intestinal obstruction-related AEs are designated as AESIs because there are accumulated reports of intestinal obstruction as an adverse reaction to similar incretin-related drugs (GLP-1 receptor agonists and other DPP-4 inhibitors).

[Acute pancreatitis-related AEs]

Acute pancreatitis-related AEs are designated as AESIs because there are accumulated reports of acute pancreatitis as an adverse reaction to similar incretin-related drugs.

<For Trelagliptin>

[QT/QTc interval prolongation-related AEs]

QT/QTc interval prolongation-related AEs are designated as AESIs because, in the QT/QTc assessment study conducted during the development, QT/QTc interval prolongation was reported in the trelagliptin 800 mg group although it did not occur in the trelagliptin 200 mg group.

<For Alogliptin>

【Liver dysfunction or jaundice-related AEs】

Liver dysfunction or jaundice-related AEs are designated as AESIs because there are accumulated reports as serious adverse reaction.

10.1.5 Severity of adverse events

The severity of adverse events shall be classified and defined as shown below.

Mild	The event is transient and easily tolerated by the subject.
Moderate	The event interrupts the subject's usual activities.
Severe	The event causes considerable interference with the subject's usual activities.

10.1.6 Causality of adverse events

The causal relationship of each adverse event to the study drug shall be classified and defined as shown below.

Related	An adverse event that follows an apparent temporal sequence (including clinical course after discontinuation). An adverse event the causal relationship could not be denied and there is reasonable possibility due to the study drug, although other factors such as underlying disease, concurrent diseases, or concomitant drugs/treatment are also suspected.
Not related	An adverse event that does not follow an apparent temporal sequence from administration of the study drug. Very likely due to other factors such as underlying

	disease, concurrent diseases, or concomitant drugs/treatment.

10.1.7 Relationship to study procedures

The relationship shall be recorded as “Yes” if the principal investigator or investigator considers that there is reasonable possibility that an adverse event is due to a study procedure. Otherwise, the relationship shall be recorded as “No.”

10.1.8 Date of onset

The date of onset of adverse events shall be determined according to the following rules:

Adverse event	Date of onset
Signs, symptoms, diseases (diagnoses)	The date on which the first signs/symptoms were noted by the research subject and/or the principal investigator or investigator.
Asymptomatic diseases	The date on which a diagnosis was confirmed through a test(s). The date on which a diagnosis was confirmed, even when the test results indicate an old sign(s) of the disease or an approximate time of its onset.
Exacerbation of concurrent diseases	The date on which the first worsening of diseases/symptoms was noted by the research subject and/or the principal investigator or investigator.
Onset of a test abnormality after the start of the study drug administration	The date on which a clinically significant laboratory abnormality was detected.
Worsening of a baseline test abnormality after initiation of study treatment	The date on which a clear increase/decrease in a laboratory parameter was clinically confirmed based on the time profile of the parameter.

10.1.9 Date of resolution

The date of resolution of an adverse event is the date on which the research subject recovered (including resolution with sequelae). If a research subject died due to the adverse event concerned, it shall be the date of death. The adverse event shall be recorded as “ongoing” if the research subject has not yet recovered by the end of the study.

10.1.10 Actions taken for the study drug

Actions taken for the study drug shall be classified or defined as shown below.

Drug withdrawn	The study drug is discontinued because of an adverse event (including withdrawal by the research subject at his/her own discretion). When the treatment with the study drug is continued after withdrawal from the study, it shall be defined as “Dose not changed.”

Dose not changed	If the dose was unchanged after the onset of the adverse event it shall be defined as “Dose not changed.” If the study drug was discontinued, reduced, or increased because of another adverse event it shall be defined as “Dose not changed.” If the study drug was discontinued or reduced for a reason other than for the adverse event, e.g., inadvertence of the research subject, it shall be defined as “Dose not changed”.
Unknown	It has not been possible to determine what action has been taken because the research subject is lost to follow-up.
Not Applicable	The study treatment had already been completed or discontinued before the onset of the adverse event.
Dose reduced	The dose of the study drug was reduced because of the adverse event (including dose reduction by the research subject at his/her own discretion).
Dose increased	The dose of the study drug was increased because of the adverse event (including dose increase by the research subject at his/her discretion).
Washout	If the study treatment is suspended (i.e., interrupted) (including suspension/interruption by the research subject at his/her discretion) because of the adverse event but resumed thereafter, shall be defined as “washout”.

10.1.11 Outcome

Outcome of adverse events is classified as follows:

Category	Criteria
Recovered	Disappearance or recovery of symptoms and findings Laboratory values returned to normal or baseline
Improved	The intensity is lowered by one or more stages Symptoms or findings mostly disappeared Laboratory values improved, but have not returned to normal or baseline The research subject died from a cause other than the concerned adverse event while the condition was resolving (recording of the date of death unnecessary)
Not recovered	No change in symptoms, findings, or laboratory data The symptoms, findings, or laboratory data on the final day of observable period were aggravated compared with the date of onset Irreversible congenital anomaly The research subject died from another cause before resolution of the concerned adverse event (recording of the date of death unnecessary)
Recovered with sequelae	Disability that disturbs daily life

Death	Direct relationship between death and the concerned adverse event "Direct relationship" means that the concerned adverse event was the cause of death, or the concerned adverse event was clearly responsible for death. Outcome of an adverse event which was not determined (judged, presumed) a direct cause of death observed in the same research subject is not considered as death. If outcome is death, the date of death shall be recorded.
Unknown	Follow-up specified in the protocol after the date of onset was not possible due to change of hospitals or relocation, etc.

10.2 Procedures

10.2.1 Collection and reporting of adverse events

10.2.1.1 Adverse event collection period

Collection of the adverse events shall commence at the start of administration of the study drug (Day 1) and shall continue until end of treatment (Day 29).

10.2.1.2 Reporting of adverse events

At each study visit, the principal investigator or investigator shall check for the presence of any onset of subjective symptoms. A neutral question, such as "How have you been feeling since your last visit?" may be asked to collect any adverse events that occurred between the previous and present visits.

The principal investigator or investigator shall follow up all research subjects experiencing an adverse event irrespective of the causal relationship with the study drug, until the symptom resolves, or any clinically significant abnormal laboratory values have returned to baseline or there is a satisfactory explanation for the change (permanent or irreversible adverse events). All adverse events shall be entered on the CRF. Adverse event term, onset date, resolution date, severity, causal relationship with the study drug (i.e. "Unrelated" or "Related"), action taken for the study drug, outcome, causal relationship with any study procedure (with specific procedure if assessed to be causally related), and seriousness shall be entered.

Follow-up period of adverse events shall be until recovery of the adverse events, or the time when the principal investigator or investigator judges that further follow-up would be unnecessary.

10.2.1.3 Reporting of adverse events of special interest (specific adverse events)

If AESI occurring during the AE collection period is considered to be clinically significant based on the criteria below, it should be reported to the sponsor (refer to the attachment for contact information) within 1 business day of first onset, or subject's notification of the event by the

principal investigator or investigator. AESI Form should be completed and signed (or signed and sealed) by the principal investigator and reported to the sponsor within 10 business days.

The criteria for AESIs (hypoglycemia-related AEs, intestinal obstruction-related AEs, acute pancreatitis-related AEs, and QT/QTc interval prolongation-related AEs) are as shown below. If any other AEs potentially related to the study drug occur, it will be considered whether to include them in the AESIs.

[Hypoglycemia-related AEs]

AEs related to hypoglycemia

[Intestinal obstruction-related AEs]

Intestinal obstruction, ileus, subileus, obstruction of the digestive tract, gastrointestinal motility disorder, impaired gastric emptying, and AEs related to these conditions

[Acute pancreatitis-related AEs]

AEs related to pancreatitis or acute pancreatitis

[QT/QTc interval prolongation-related AEs]

Torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation, ventricular flutter, consciousness disturbed, convulsion, ECG QT prolonged, and AEs related to these conditions

【Liver dysfunction or jaundice-related AEs】

Adverse events corresponding to ' Liver dysfunction related to drug - comprehensive search' in MedDRA standard search formula.

The AESIs have to be recorded as AEs in the CRF. A report along with all other required documentation must be submitted to the sponsor.

10.2.2 Collection and reporting of serious adverse events

When a serious adverse event develops during the period of collecting adverse events, it shall be reported according to the following procedures. At the time of onset of a serious adverse event or notification of the onset by the research subject, the principal investigator shall report the serious adverse event to the chief executive of the research implementing entity immediately, and the sponsor or CRO to whom the sponsor has entrusted responsibility shall notify the principal investigator of the research implementing entity.

The principal investigator shall then report the serious adverse event to the sponsor (for the contact information, refer to the attachment) within 1 day of notification of the event onset. Further, the principal investigator shall submit a formal report within 10 calendar days to the sponsor.

Furthermore, it shall be mandatory to include the contents below in the report to be submitted to the sponsor within 1 working day, and other items shall be reported as far as possible.

- Brief description of adverse event and the reason for why it was determined as serious
- Research subject ID number
- Name of principal investigator or the investigator
- Name of the study drug
- Determined causal relationship

The principal investigator or investigator shall report spontaneously reported serious adverse events that are collected even after the adverse event collection period to the sponsor.

10.2.3 Reporting of additional information concerning adverse events

If the sponsor requests provision of additional information concerning adverse events for reporting to regulatory authorities, the principal investigator or the investigator shall confirm the necessary additional information and enter in the EDC system or submit a report within the period specified by the sponsor.

10.3 Follow-up of serious adverse events

When information that was not included in the detailed report was obtained later, the principal investigator or investigator shall state it in the copy of the report on serious adverse events, or create another document and submit it to the contact address shown on the attached sheet within 1 working day. Relevant data collected at the research implementing entity (e.g., ECG charts, laboratory test values, discharge summary, postmortem results) shall be sent to the sponsor or the committee such as the IEC upon request.

The principal investigator or the investigator shall follow-up all serious adverse events, etc., until recovery is confirmed, or the final outcome is determined.

10.3.1 Reporting of serious adverse events to Ethics Review Committee, etc., and regulatory authorities

When the chief executive of the research implementing entity receives a report of a serious adverse event from the principal investigator, the chief shall consult the Ethics Review Committee, etc., and notify the research implementing entities that are conducting the clinical research through the sponsor or the CRO consigned by the sponsor.

If the serious adverse event reported by the principal investigator in which direct causal relationship cannot be denied with this study (the study drug) and is unexpected, the chief executive of the

research implementing entity shall prepare a written report of the unexpected serious adverse event containing the information reported by the principal investigator plus the information below, and submit the report to the Minister of Health, Labour and Welfare, and notify other clinical research implementing entities. (Reporting to the Minister of Health, Labour and Welfare via the sponsor, or notification to other clinical research implementing entities via the sponsor may also be possible)

- Actions taken for serious adverse events (discontinuation of new enrollment, revision of informed consent form, re-consents to other research subjects, etc.)
- Date of review, summery of review, result, necessary action, etc., related to Ethics Review Committee, etc.
- Notification to other research implementing entities

The sponsor shall report, in accordance with regulations, unexpected serious adverse drug reactions and other serious adverse events that are subject to emergency reporting to regulatory authorities, the principal investigators, and chief executives of the research implementing entities.

From the time point of first acknowledging the event or receiving additional information, the sponsor or the CRO consigned by the sponsor shall comply with regulatory required time frames for reporting, and make emergency reports concerning unexpected serious adverse drug reactions and expected serious adverse drug reactions to regulatory authorities. Also, the sponsor shall, in the same way, make an emergency report of other critical safety information that may have a major effect on the study drug risk-benefit, continuation of study drug administration, or continuation of clinical research. The research implementing entity shall submit copies of emergency report documents to the Ethics Review Committee, etc.

11.0 COMMITTEES ESTABLISHED FOR THIS STUDY

In this clinical research, none of Clinical Research Steering Committee, Data and Safety Monitoring Committee, or Central Assessment Committee shall be established.

12.0 DATA MANAGEMENT AND STORAGE OF RECORDS

Data management operations shall be performed according to the standard operating procedure by the data management department of the sponsor independent from the medical affairs department. Adverse events, medical history, and concurrent conditions shall be coded using MedDRA. Drugs shall be translated using the WHO Drug Dictionary.

12.1 Case report form

The principal investigator or investigator shall complete a CRF for each research subject who has signed the informed consent form.

The sponsor or its designee shall provide research implementing entities with access authorization to the electronic CRF. Before use of the electric CRF system, the sponsor shall provide training to the principal investigator, investigators, and study collaborators. The CRF shall be used to report the information collected during the study period to the sponsor. The CRF shall be made in Japanese. Data shall be directly entered in preparing the CRF.

A change or correction of the CRF shall be recorded as an audit trail that records the information before and after the change or correction, the person who made the change or correction, date of change or correction, and its reason.

The principal investigator shall ensure the accuracy and completeness of the CRF, and provide an electronic signature on the relevant page of the case report form. The principal investigator shall bear full responsibility for the accuracy and reliability of all data entered on the CRF.

The following data shall be recorded on the CRF directly. (Except if there is a description in the source material)

- Eligibility, end state, reason of termination, severity, degree, the causal relationship with the study drug or the study procedures, outcome of the adverse event.

The following data shall not be recorded on the CRF directly.

- Measurement results of CGM
- Laboratory result tested at central.

When the principal investigator or the investigator makes a change or correction in the data entered on the CRF after fixation of clinical data base, a record (Data Clarification Form) of change or correction on the CRF provided by the sponsor shall be used. The principal investigator shall confirm that the record of change or correction on the CRF is accurate and complete, and sign or write name/ affix a seal, and date it.

The sponsor or its designee shall confirm that CRFs have been made appropriately according to the procedures defined for each study. The sponsor or its designee shall have access to the medical records of the research subjects and in-house records to ensure the accuracy of the CRF as necessary. The completed CRF is the property of the sponsor, and the principal investigator or investigator shall not disclose the information to a third party without a written permission from the sponsor.

12.2 Timing of data entry into the electronic CRF system

The sponsor or its designee shall request the principal investigator and investigator to promptly enter data into the EDC at enrollment of the research subject, each visit during study treatment, completion/discontinuation of study treatment, and follow-up period. Details of deadlines for data entry shall be specified separately in a procedure manual.

12.3 Storage of records

The principal investigator or the chief executive of research implementing entity shall store the following materials, including those specified in section 12.1, and study-specific documents to be used by the regulatory authority and the sponsor or its designee for investigation and audit. The documents include research subject ID code, medical records, clinical study worksheets (if used), original signed and dated informed consent forms, the change and fix record of CRF (copy) and electric copies of electronic CRF including audit trail. The principal investigator and the chief executive of the research implementing entity shall appropriately retain the material/information related to this study for at least 5 years from the date of reporting the end of the research by the principal investigator, or for 3 years from the date of reporting final publication of the study result, whichever date is later. However, when the sponsor requires a longer storage period, the chief executive of the research implementing entity shall discuss the period and methods of storage with the sponsor.

13.0 STATISTICAL ANALYSIS METHODS

The person responsible for statistical analysis and the designee (a person employed by a CRO independent of the sponsor; the person in charge of analysis) shall conduct analyses. The sponsor will not be involved in statistical analyses.

13.1 Statistical and analytical plans

The person in charge of analysis shall prepare a statistical analysis plan (hereinafter referred to as SAP) before the acquisition of the informed consent of the earliest research subject, and issue the first edition. Detailed definition of endpoints and analysis methods should be specified in the SAP to deal with all the purposes of the research.

13.1.1 Analysis set

Two analysis sets, “full analysis set” and “Safety data analysis set” are used in this study. The “full analysis set" used as a primary analysis set in the efficacy analysis shall be defined as "the research subjects who were randomized and given at least one dose of the study drug." The “Safety data analysis set” shall be defined as "the research subjects who are given at least one dose of the study drug."

13.1.2 Analysis of demographic and other baseline characteristics

From the “full analysis set” primary research subject background items will be tabulated by each treatment group and by merging the treatment groups.

13.1.3 Efficacy analysis

[Primary endpoints]

- Changes in the SD of 24-hour blood glucose values (mg/dL) for each 7-day period between Week 3 and Week 4 (between Day 22 and Day 28) of the treatment period, calculated from the value at the start of the observation period

(Analysis method)

・For the “full analysis set”, summary statistics (number of subjects, mean, SDs, maximum values, minimum values, quartiles [same apply hereafter]) and 95% confidence interval (two sides) of mean shall be calculated for each treatment group at each evaluation point (each day), and illustrating changes in mean and SD in order to evaluate changes in the SD of 24-hour blood glucose values (mg/dL) for each 7-day period between Week 3 and Week 4 (between Day 22 and Day 28) of the treatment period, calculated from the value at the start of the observation period for trelagliptin or alogliptin separately.

・Preliminary, for the “full analysis set”, calculate point estimation and 95% confidence interval (two

sides) in difference of mean in treatment groups (trelagliptin 100 mg group – alogliptin 25 mg group) in order to examine the influence of the once-weekly administration and blood glucose fluctuations due to the difference in the daily administration exploratory.

・As well, for the "full analysis set ," conduct analysis of covariance at each evaluation point with changes in the SD of 24-hour blood glucose values between Week 3 and Week 4 from the value at the start of the observation period as dependent variable, treatment groups as independent variable, HbA1c (NGSP value) at the start of the observation period, changes in the SD of 24-hour blood glucose values at the start of the observation period, and age as covariates, and calculate point estimation and 95% confidence interval (two sides) in difference of adjusted mean for each group.

・Preliminary, "full analysis set ," calculate point estimation and 95% confidence interval (two sides) in difference of adjusted mean in treatment groups (trelagliptin 100 mg group – alogliptin 25 mg group)

[Secondary endpoints]

- Changes in AUC over time when specific blood glucose levels (110, 140, 160, or 180 mg/dL) are observed during the 3 hour time period after breakfast, lunch and evening meal[*1, 2]
- Change in AUC over time during periods when blood glucose 140, 160, or 180 mg/dL (hyperglycemia) is observed[*1, 2]
- Changes in blood glucose 140, 160, or 180 mg/dL (hyperglycemia) over time[*1, 2]
- Changes in AUC over time during periods when blood glucose < 70 mg/dL (hypoglycemia) is observed[*1,2]
- Change in peak postprandial glucose levels over time 3 hours after breakfast, lunch, and evening meal[*1, 2]
- Change in maximum variation of blood glucose levels over time between before and after breakfast, lunch, and evening meal [*1, 2]
- Changes in MAGE[*1, 2]
- Changes in mean 24-hour blood glucose levels [*1, 2]
- Changes in mean daytime blood glucose levels[*1, 2]
- Changes in mean nocturnal blood glucose levels[*1, 2]
- Changes in AUC[*1, 2]
- Changes in AUC over time during periods when blood glucose 110 mg/dL is observed[*1,2]
- Changes in the SD of 24-hour blood glucose values[*1,2]
- Changes in the SD of mean daytime blood glucose values[*1,2]
- Changes in the SD of mean nocturnal blood glucose values[*1,2]

[*1]: Measured value and percent changes for the each 7-day period between Week 3 and Week 4 (between Day 22 and Day 28) of the treatment period calculated from the value at the start of

the observation period (however changes in the SD of 24-hour blood glucose values shall be measured value only)

*2: Percent change from the value at the start of the observation period to the mean value during the 7-day period between Week 3 and Week 4 (between Day 22 and Day 28) of the treatment period

(Analysis method)

- Conduct the same analysis as the primary endpoints for *1 and *2 of the above endpoint section. However, for changes in mean/SD, only measured values of *1 and *2 shall be illustrated.

[Other endpoints]

- Glycoalbumin
- 1,5-AG
- Fasting blood glucose
- Fasting insulin
- Fasting glucagon
- Fasting proinsulin
- FastingGLP-1
- Fasting GIP
- DPP-4 activity
- Inhibitory rate of DPP-4 activity

(Analysis method)

- Calculate summary statistics and 95% confidence interval (two sides) of mean at each evaluation point (the start of the observation period by each treatment group, first day, 1 point during third to fifth day, and ninth day of CGM which is to be performed for 9 days from Day 21) in measured values and changes from the start of the observation period, and illustrate changes in mean and SD

13.1.4 Conversion method of data and handling of missing data

Details shall be specified separately in the statistical analysis plan.

13.1.5 Significance level and confidence coefficient

Confidence coefficient: 95% (two-sided estimation)

13.1.6 Safety analysis

[Secondary endpoints]

- Adverse event

(Analysis method)

- Adverse events shall be reported using MedDRA terminology and summarized using the Preferred Term (PT) and System Organ Class (SOC) of the MedDRA. For the "safety data analysis set", frequency tabulation shall be conducted for adverse events after start of treatment with study drug by each treatment group.
    - Frequency tabulation of all adverse events
    - Frequency tabulation of adverse events that causal relationship is "related" to study drug.
    - Frequency tabulation of the degree of all adverse events
    - Frequency tabulation of degree of adverse events that causal relationship is "related" to study drug.
    - Frequency tabulation of adverse events that were "discontinued" as a measurement concerning study drug.
    - Frequency tabulation of serious adverse events

13.2 Criteria for interim analysis and premature discontinuation

No interim analysis is planned.

13.3 Determination of the number of planned research subject

Planned number of research subjects that are evaluable for primary endpoints in each group is as follows.

Trelagliptin 100 mg group: 15

Alogliptin 25 mg group: 15

Set in consideration with the feasibility of the number of research subjects for exploring the effects of trelagliptin 100 mg and alogliptin 25 mg on glycemic variation. It is not based on statistical power calculation.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Monitoring of the research implementing entity

The sponsor or its designee shall perform periodic monitoring of research implementing entities during the research to confirm that the research is conducted in accordance with all specifications in the research protocol. The data recorded on the CRF will be checked by comparing them with those in the source documents. Source documents are the original documents, data and records. The principal investigator and the chief executive of the research implementing entity shall ensure that the sponsor or its designee and the Ethics Review Committee, etc., have access to the source documents.

The sponsor or its designee shall access the records, including the list of research subject ID numbers, medical records of the research subjects, and signed and dated original consent forms to confirm that the research is appropriately conducted in compliance with the research protocol. Also, confirm the consistency between CRF and the related source documents. The principal investigator, investigator, and other personnel involved in the research shall spare sufficient time to facilitate monitoring procedures during visits to the research implementing entity.

Detailed procedures for monitoring shall be specified separately in a procedure manual.

14.2 Deviation from the Ethical Guidelines for Medical and Health Research Involving Human Subjects and the research protocol.

The principal investigator or investigator shall record all deviations from Ethical Guidelines for Medical and Health Research Involving Human Subjects, and research protocol.

If any deviation is found, the principal investigator shall promptly notify the chief executive of the research implementing entity for the clinical research and the sponsor. As necessary, the principal investigator will discuss protocol revisions with the sponsor to reach agreement. For protocol revisions, draft revisions should be submitted as early as possible to the chief executive of the research implementing entity for approval of the committee such as the IEC.

14.3 Quality assurance audits and regulatory agency inspections

The research implementing entity may be subject to audits by the sponsor or its designee. In such a case, the auditor designated by the sponsor shall contact the research implementing entity in advance to determine the date of audit. The auditor may ask to visit the facilities where laboratory specimens are collected and any other facilities used during the clinical research. In addition, this research may be inspected by regulatory agencies, including those of foreign governments (e.g., the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency [MHRA]). If the research implementing entity is contacted for an inspection by a regulatory

body, the sponsor should be notified promptly. The principal investigator and the chief executive of the research implementing entity shall ensure that the auditor has access to all the research-related source documents.

15.0 ETHICAL CONDUCT OF CLINICAL RESEARCH

This research shall be conducted with the highest respect for the individual participants (i.e., research subjects) according to the research protocol, and the ethical principles that have their origin in the Declaration of Helsinki, Ethical Guidelines for Medical and Health Research Involving Human Subjects. Each principal investigator shall conduct the study according to regulatory requirements and in accordance with “Responsibilities of the Investigator” in Appendix B.

15.1 Approval of the Ethical Review Board, etc.

The Ethical Review Board, etc., shall be constituted in accordance with the regulations.

The sponsor or its designee should obtain the document listing the name and title of each committee member. When a committee member directly participates in this clinical research, the document describing that he/she is not participating in deliberation or voting for the study shall be obtained.

The sponsor or its designee shall provide related documents for review and approval of the research protocol to the Ethical Review Board, etc. In addition to the research protocol, a copy of the informed consent form and information sheet, written materials related to research subject recruitment, advertisement, and other documents required by regulations, when necessary, shall be submitted to the central committee or a research implementing entity committee such as the Ethics Review Committee to obtain approval. The sponsor or its designee shall obtain records of approval by the Ethical Review Board, etc., for the research protocol and the informed consent form and information sheet before the start of the protocol therapy. The records of approval by the Ethical Review Board, etc., shall include the clinical research title, protocol number, preparation / revision date of the research protocol, and version number and approval date of other reviewed documents (example: informed consent and information sheet). The sponsor shall notify the research implementing entity, the principal investigator, and investigator after confirming the validity of the regulatory documents of the research implementing entity. Protocol procedures such as obtainment of consent shall not be started until the research implementing entity, the principal investigator, and investigator receive notification.

The research implementing entity shall observe all requirements that the Ethical Review Board, etc. prescribe. The requirements may include notifications to committees such as the IEC, for example, revision of the protocol, revision of the informed consent form and information sheet, revision of materials related to research subject recruitment, reports on safety in accordance with the regulatory requirements, reports on status of implementation of the research at intervals determined by a research implementing entity committee such as the Ethics Review Committee, and submission of the study completion report. The sponsor or its designee shall obtain written approval from a

research implementing entity committee such as the Ethics Review Committee related to the above mentioned items and all related materials.

15.2 Conflict of interest

This clinical research shall be conducted with the support of the sponsor.

Prior to the conduction of this clinical research, the investigators involved in this clinical research shall ensure appropriate management of any conflicts (COI) in the conduct of the research in accordance with the rules of the research implementing entity [11-15].

The research implementing entity shall comply with all requirements specified by a committee such as the Ethics Review Committee This includes the COI self-statement form, the research protocol, and the informed consent form and information sheet.

15.3 Informed consent and information sheet, and the agreement of the research subjects

The informed consent and information sheet form shall contain specific requirements of the Declaration of Helsinki, Ethical Guidelines for Medical and Health Research Involving Human Subjects and all applicable laws and regulations. The informed consent form and information sheet shall specify the use of personal information and medical information of research subjects in this clinical research (both in and outside Japan: supply to a third party), and disclosure. The informed consent form and the information sheet will explain in detail the nature of the research, its objectives, and potential risks and benefits. Also, the informed consent form will detail the requirements for participation and the fact that research subject is free to withdraw at any time without giving a reason and without any negative effect on the further medical care.

The principal investigator is responsible for the preparation, contents, and approval of the informed consent form and information sheet by the committee such as the IEC. The informed consent form and information sheet must be approved by the committee prior to use.

The informed consent form and information sheet shall be written in language that can be easily understood by the potential research subjects. The principal investigator or investigator shall be responsible for providing detailed explanation of the informed consent form and information sheet to the potential subjects. Information should be given in both oral and written form whenever possible and in manner deemed appropriate by the committee such as the IEC.

The principal investigator or investigator shall ensure that the potential research subjects have (1) an opportunity to inquire about the research and (2) sufficient time to decide on their participation. If a potential research subject decides he or she is willing to participate in the research, then the informed consent form must be signed and dated by the potential research subject prior to entering into the

research as a subject. The principal investigator or investigator shall instruct the potential research subject to sign using their legal names, not nicknames, using a blue or black ball point ink pen. Also the principal investigator or investigator shall sign and date the informed consent form prior to potential research subject entering into the research.

Once signed, the original informed consent form shall be retained by the principal investigator or investigator. The principal investigator or investigator shall record the date that the potential research subject signed the informed consent form in the subject’ s medical record. A copy of the signed informed consent form shall be given to the research subject.

If the informed consent form and information sheet is revised, the principal investigator or investigator shall newly obtain re-consent from the concerned research subject by following the same procedure as for obtaining the initial consent. The date of obtaining new consent shall be recorded in the research subject’ s medical record, and a copy of the revised consent form shall be provided to the research subject.

15.4 Personal information of the research subjects

The sponsor or the designee shall affirm the principle of the protection of research subjects' private/personal information, etc. Throughout this study, research subject ID numbers shall be used to link the subject's source data to the sponsor's research database and research-related documents. Limited information on research subjects such as gender, age, and date of birth may be used within the scope of all applicable laws and regulations for identification of research subjects and confirmation of accuracy of research subject ID number.

For verification of the conduct of the research in compliance with this protocol and the Ethical Guidelines for Medical and Health Research Involving Human Subjects, the sponsor shall require the principal investigator to provide the research sponsor’s designee, representatives of regulatory authorities, designated auditors, and committees such as the Ethical Review Board direct access to research subjects’ original medical records (source data or documents), including laboratory test results, ECG results, admission and discharge records during a subject’s research participation, and autopsy reports. The principal investigator or investigator shall obtain specific authorization from the research subject as part of the informed consent process for access to research subject's original medical records by research sponsor’s designee and representatives of regulatory authorities (see section 15.3).

When providing a copy of source documents to the sponsor, the principal investigator or investigator shall delete information that may lead to identification of an individual (name and address of research subject, other personal information not recorded on the CRF of the research subject).

15.5 Consultation windows for the research subjects or persons related to the research concerned

The principal investigator shall establish a contact service to respond to inquiries concerning this clinical research from research subjects or concerned people. Details of the contacts for inquiries will be described in the informed consent form.

15.6 Financial burden or reward to the research subjects

Of the expenses for this clinical research, the sponsor shall offer compensation for medical treatment not covered by health insurance as research expenses. The research subjects shall pay expenses for medical treatment covered by ordinary health insurance.

In addition, the principal investigator shall pay expenses such as transportation expenses for participation in this clinical research to the research subjects at each visit from the research funds. Details of the financial burden on the research subjects and rewards shall be described in the informed consent form.

15.7 Benefits and inconveniences to the research subjects

15.7.1 Benefits to research subjects

By participating in this clinical research, the research subjects may understand one’s own condition of type 2 diabetes mellitus in detail.

15.7.2 Inconveniences to research subjects

By participating in this clinical research the burden of the research subject may increase as number of visits will increase compared to daily medical care.

15.8 Attribution of research results and access rights

15.8.1 Attribution of research results

The research results and data obtained from this research shall belong to the sponsor. In addition, secondary use (meta-analysis, etc.) of the data obtained in this clinical research may be possible if used in such a way that the data shall not be linked to personal identification information.

15.8.2 Data access rights

Access rights for all data and information generated from this study will be given to personnel approved by the sponsor.

15.9 Reporting of results, publication, disclosure, and clinical research registration policy

15.9.1 Reporting of results, publication and disclosure

The principal investigator shall report a written summary of results of the research to the chief executive of the research implementing entity and provide the sponsor with all the results and data obtained from the research. Only the sponsor may disclose the research information to other principal investigators, investigators or regulatory authorities during the research period, except when required by laws and regulations. The sponsor shall be responsible for publication of the research protocol and research-related results (including the public web site) except for other cases permitted in the research contract.

During research period and after the end of research, the sponsor or its designee should promptly summarize the results and present it to medical journals and academic conferences, etc. The sponsor may publish any data or information obtained from the research (including data and information provided by the principal investigator) without obtaining consent of the principal investigator.

The principal investigator or the investigator should obtain the prior written approval from the sponsor when publishing the information obtained in this research at an academic conference, etc.

15.9.2 Clinical research registration

To ensure that information on clinical research is made accessible to the public in a timely manner and to comply with applicable laws, regulations, and guidelines, Takeda Pharmaceutical Company Limited shall register all clinical research being conducted in patients around the world at public trial registration sites, including at least the website(s) of ClinicalTrials.gov (and) Japan Pharmaceutical Information Center Clinical Trials Information (JAPIC). On such websites, the research location (city, country), subject recruitment status, and contact information for Takeda Pharmaceutical Company Limited are open to the public.

15.9.3 Clinical trial results disclosure

Takeda Pharmaceutical Company Limited shall post the research results, irrespective of the nature of the results, at the public trial registration site(s) of Clinical Trials.gov (and) JAPIC in accordance with applicable laws and regulations.

15.10 Insurance and compensation for injury

The research subjects participating in this research shall be compensated for any injury resulting from participation in the research according to local regulations applicable to the research

implementing entity. The sponsor or its designee shall buy an insurance policy to compensate for health injury in research subjects.

Healthy injury in a research subject will be compensated as specified in the study contract. Compensation-related questions by the principal investigator or investigators should be made to the sponsor or its designee.

16.0 REFERENCES

1. Rimei Nishimura, Glucose variability and vascular disease risk. The Journal of the Japanese Society of Internal Medicine. 2013; 102: 922-930

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11. Report of the Working Group on Conflict of Interest (Ministry of Education, Culture, Sports, Science and Technology dated November 1, 2002)

12. Guidelines for determining the conflict of interest polity for clinical research (Review group for ethical aspects of clinical research and conflict of interest, March 2006)

13. Guidelines on the Management of Conflict of Interest (COI) in Health and Labour Sciences Research (March 31, 2008)

14. Guidelines for management of COI in medical research (COI Committee of Japan Association of Medical Sciences, February 2011)

15. Common guidelines for conflict of interest (COI) in clinical research (Japanese Society of Internal Medicine, Japan Society of Hematology, Japanese Circulation Society, Japan Endocrine Society, Japan Diabetes Society, Japanese Respiratory Society, Japanese Society of Hematology, Japanese Society of Allergology, Japanese Association for Infectious Diseases, Aug 2011)

Appendix A Schedule of Research Procedures

		Observation period		Treatment period				
Time of Visit	Week			0			4	Discontinuation[g]
	Day	-14	-2	1[b]	21[c]	24[c]	29[c]	-
Allowable range (Day)		-28 to -2	-4 to -2	1	19 to 35	24~39[f]	29 to 43	-
VISIT Number			1	2	3	4	5	-
Informed consent procedure		×						
Inclusion/Exclusion criteria		×	×					
Demographic information		×						
Medical history, pre-treatment		×	×					
Physical examination		×	×	(×)	×	×	×	×
Body weight, BMI			×		×		×	×
Height		×						
Concomitant drugs		×	×	(×)	×	×	×	×
Concurrent disease		×	×					
Laboratory tests [a]			×		×	×	×	×
HbA1c			×					
Drug -taking status					×	×	×	×
Prescription of dietetic therapy and exercise therapy and assessment of compliance		×	×	(×)	×	×	×	×
CGM			× [d] (Sensor insertion)	× [d] (Sensor remove)	× [d] (Sensor insertion)	× [d] (Exchange sensor)	× [d] (Sensor remove)	
Self-measurement of blood glucose			× [e]	× [e]	× [e]	× [e]	× [e]	
Adverse event monitoring				×				

(a) Measured on VISIT1 (Day-2), and the first and ninth days of the 9-day CGM starting on Day 21

Blood tests: glycoalbumin, 1,5-AG, fasting insulin, fasting glucagon, fasting proinsulin, fasting GLP-1, fasting GIP*, DPP-4 activity

Measured on 1 point during fourth and sixth day of the 9-day CGM starting on Day 21

Blood tests: fasting GLP-1, fasting GIP, DPP-4 activity

(b) The starting day of study treatment in the treatment period is designated as Day 1. The study drug shall be administered after required tests/observations, etc. The day before the start of study treatment in the treatment period is designated as Day -1. It is performed at the visit when principal investigator or investigator consider as needed.

(c) Trelagliptin 100 mg/week group shall insert the sensor on a day between 3 day and a day before Trelagliptin administration day. Trelagliptin 100 mg/week shall be administered before breakfast on the day of the drug administration.

Alogliptin 25 mg/day shall be administered after required tests/observations, etc at every VISIT without taking study drug. Research subjects shall take study drug prior to the every breakfast at home.

(d) To be performed by study site personnel

(e) At least, blood glucose levels shall be measured at three time points on the first day of CGM ([1] at least 2 hours after the recorder is connected and [2] 2 hours after the first is measured. [3] at bedtime) and at four time points from the second day onward ([1] before breakfast, (2) before lunch, (3) before evening meal, and (4) at bedtime).

(f) Research subjects should visit the study site on a day between fourth and sixth day of the 9-day CGM starting on Day 21.

(g) To be performed to the extent possible

Appendix B Responsibilities of the sponsor

1. To appropriately conduct the clinical research in compliance with this research protocol and the Ethical Guidelines for Medical and Health Research Involving Human Subjects and with the highest respect for human rights, safety, and welfare of research subjects.
2. To prepare a list of any other investigators and/or research collaborators when certain important research-related activities are divided by investigators and/or research collaborators, and submit the list to the sponsor as required.
3. To prepare the informed consent form and revise it as necessary.
4. To check the contents of the study contract.
5. To provide sufficient information on the protocol, drug and duties of each personnel to subinvestigators and study collaborators, and give guidance and supervision.
6. To select research subjects who satisfy the inclusion criteria, give explanation using written information, and obtain consent in writing.
7. To be responsible for all medical judgments related to the research.
8. Corresponding to request from the chief executive of the research implementing entity, to report the latest progress status at least once a year to the chief executive of the research implementing entity.
9. To ensure that the most update status is confirmed and comprehended regarding the COI of the investigators participating in the clinical research according to the research implementing entity.
10. To ensure, together with the chief executive of the research implementing entity, that sufficient medical care is provided to research subjects for all research-related clinically problematic adverse events throughout the period of subjects' research participation and thereafter.
11. When a research subject is treated at another medical institution or department, to inform the acting physician at the medical institution or department in writing of the research subject's study participation and research completion/discontinuation after obtaining the research subject's consent, and prepare a record.
12. When emergency reporting of serious adverse events, is required, to immediately report it in writing to the chief executive of the research implementing entity and the sponsor.
13. To ensure that the CRFs are accurate and complete, electronically sign and submit them to the sponsor.
14. To verify any entries on the CRFs made by the investigator or transcribed by the collaborator from source documents, electronically sign and submit them to the sponsor.
15. To discuss a revision of the protocol, etc., when proposed by the sponsor.

16. To report the research completion in writing to the chief executive of the research implementing entity.
17. To receive continuing education and training for conducting the study properly including Ethical Guideline and GCP during the study period (at least once a year is recommended).

PROTOCOL

An exploratory study to evaluate the effects of Trelagliptin and Alogliptin by CGM on glucose variability for one week with type 2 diabetes mellitus (TRACK)

Sponsor	Takeda Pharmaceutical Company Limited 2-12-10 Nihonbashi, Chuo-ku, Tokyo
Protocol number	Trelagliptin-4001
Version number	2nd Version
Study drug:	Trelagliptin Alogliptin
Creation date	November 11, 2016

1.0 CLINICAL STUDY PRINCIPLES AND CLINICAL STUDY MANAGEMENT INFORMATION

1.1 Clinical Study Principals

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- Ethical Guideline for Clinical Research (the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labor and Welfare, December 22, 2014).
- Good Clinical Practice: Consolidated Guideline (ICH. E6)
- All applicable laws and regulations, including, without limitation, data privacy laws and conflict of interest guidelines.

1.2 CLINICAL STUDY ADMINISTRATIVE STRUCTURE

This study will be conducted under the administrative structure described in the attached sheet 1 in accordance with the protocol prepared and planned by the sponsor.

Table of Contents

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

2.0 STUDY SUMMARY

<table>
<tr><td>Sponsor:
Takeda Pharmaceutical Company Limited</td><td>Study drug:
Trelagliptin
Alogliptin</td></tr>
<tr><td colspan="2">Study title:
An exploratory study of the effects of trelagliptin and alogliptin on glycemic variation in patients with type 2 diabetes mellitus</td></tr>
<tr><td colspan="2">Protocol number: Trelagliptin-4001 (122/NRP-001)</td></tr>
<tr><td colspan="2">Clinical study design:
This is a multi-center, randomized, open-label, parallel-group comparative, exploratory study to evaluate the effect of trelagliptin administered at a dose of 100 mg once weekly or alogliptin administered at a dose of 25 mg once daily for 4 weeks on glycemic variation in patients with type 2 diabetes mellitus using continuous glucose monitoring (CGM).
After informed consent, patients determined to be eligible for this study based on the eligibility assessment will be randomized to either the trelagliptin 100 mg group or the alogliptin 25 mg group (at a ratio of 1:1), using "HbA1c at the start of the observation period (< 7.5% or ≥ 7.5%)" and age (< 65 or ≥ 65) as a stratification factor for randomization.
The total duration of evaluation will be 31 days, consisting of the observation period for 2 days and a treatment period for 29 days (4 weeks). CGM will be performed on research subjects on an outpatient basis (in 2 assessments) for 2 days from the start of the observation period (Day -2) and for 9 days from Day 21 of the treatment period.</td></tr>
<tr><td colspan="2">Objective:
To evaluate the effect of trelagliptin administered orally at a dose of 100 mg once weekly or alogliptin administered orally at a dose of 25 mg once daily for 4 weeks on glycemic variation in an exploratory manner and as preliminary to examine the influence of the once-weekly administration and blood glucose fluctuations due to the difference in the daily administration in patients with type 2 diabetes mellitus</td></tr>
<tr><td colspan="2">Study population:
Patients with type 2 diabetes mellitus</td></tr>
<tr><td>Planned number of research subjects:
The planned minimum number of research subjects evaluable for the primary endpoint in each group is as follows:
Trelagliptin 100 mg group: 15
Alogliptin 25 mg group: 15</td><td>Number of study research implementing entities:
3 medical institutions</td></tr>
</table>

Total: 30	
Dose and method of administration: Trelagliptin 100 mg once weekly or alogliptin 25 mg once daily, taken orally before breakfast	**Route of administration:** Oral
Duration of treatment: 4 weeks	**Duration of evaluation:** 31 days (observation period for 2 days and treatment period for 4 weeks [29 days])

Inclusion criteria

1. Research subjects who, in the opinion of the principal investigator or the investigator, are capable of understanding the content of the clinical research and complying with the research protocol requirements.
2. Patients who are able to sign and date the informed consent form and information sheet prior to the start of study procedures
3. Patients diagnosed with type 2 diabetes mellitus
4. Patients with an HbA1c (NGSP value) value ≥ 6.5% and < 8.5% at the start of the observation period (Day -2)
5. Patients who experience a ≤ ±1.0% change in HbA1c (NGSP value) at the start of the observation period (Day -2) as compared with an HbA1c value obtained during the preceding 4 weeks
6. Patients receiving stable dietetic therapy and exercise therapy (if performed) for ≥ 4 weeks before the start of the observation period
7. Patients, who in the opinion of the principal investigator or the investigator, does not have to change (including discontinuation or interruption) HMG-CoA reductase inhibitors or add new HMG-CoA reductase inhibitors during treatment period.
8. Men or women aged 20 years or older at the time of informed consent

Exclusion criteria:

1. Patients who received anti-diabetic medications within 4 weeks prior to the start of the observation period
2. Patients who have changed (including discontinuation or interruption) HMG-CoA reductase inhibitors or received new HMG-CoA reductase inhibitors ≤ 4 weeks before the start of the observation period.
3. Patients with clinically evident hepatic dysfunction (e.g., AST or ALT ≥ 2.5-fold the upper limit of normal at the start of the observation period [Day -2])

4. Patients with moderate renal dysfunction, severe renal dysfunction or renal failure (e.g., creatinine clearance < 50 mL/min or serum creatinine > 1.4 mg/dL in men or > 1.2 mg/dL in women [equivalent to the creatinine clearance for persons aged 60 years with a body weight of 65 kg] at the start of the observation period [Day -2])
5. Patients with severe heart disease, cerebrovascular disorder, or severe pancreatic, hematologic or other diseases
6. Patients with a history of gastric or small intestinal resection
7. Patients with proliferative diabetic retinopathy
8. Patients warranting insulin therapy for glycemic control (e.g., patients with severe ketosis, diabetic coma or precoma, type 1 diabetes mellitus, severe infection, perioperative patients, or serious trauma)
9. Patients with a history of hypersensitivity or allergy to DPP-4 inhibitors
10. Patients who experience an allergic reaction to metal during CGM at the start of the observation period (Day -2)
11. Patients with any malignant tumors
12. Habitual drinkers whose average daily alcohol consumption is > 100 mL
13. Patients who have any contraindications for the study drug or are taking any contraindicated concomitant drugs listed in the package insert
14. Patients anticipated to require any prohibited concomitant medications during the study period
15. Patients who are day and night lifestyle reversal
16. Patients participating in any other clinical studies at the time of informed consent for this study
17. Pregnant women, nursing mothers, women who are possible pregnant, or women who plan to become pregnant
18. Other patients who are considered inappropriate for participation in this study in the opinion of the principal investigator or investigator

Endpoints:

<Primary endpoints>

- Changes in the standard deviation (SD) of 24-hour blood glucose values (mg/dL) for each 7-day period between Week 3 and Week 4 (between Day 22 and Day 28) of the treatment period, calculated from the value at the start of the observation period

<Secondary endpoints>

Efficacy endpoints:

- Changes in AUC over time when specific blood glucose levels (110, 140, 160, or 180 mg/dL) are observed during the 3 hour time period after breakfast, lunch and evening meal[*1, 2]
- Change in AUC over time during periods when blood glucose 140, 160, or 180 mg/dL

(hyperglycemia) is observed[*1, 2]

- Changes in blood glucose 140, 160, or 180 mg/dL (hyperglycemia) over time[*1, 2]
- Changes in AUC over time during periods when blood glucose < 70 mg/dL (hypoglycemia) is observed[*1,2]
- Change in peak postprandial glucose levels over time 3 hours after breakfast, lunch, and evening meal[*1,2]
- Change in maximum variation of blood glucose levels over time between before and after breakfast, lunch, and evening meal[*1,2]
- Changes in MAGE[*1, 2]
- Changes in mean 24-hour blood glucose levels[*1, 2]
- Changes in mean daytime blood glucose levels[*1, 2]
- Changes in mean nocturnal blood glucose levels[*1, 2]
- Changes in AUC[*1, 2]
- Changes in AUC over time during periods when blood glucose 110 mg/dL (hypoglycemia) is observed[*1,2]
- Changes in the SD of 24-hour blood glucose values[*1,2]
- Changes in the SD of daytime blood glucose values[*1,2]
- Changes in the SD of nocturnal blood glucose values[*1,2]

[*1]: Measured value and percent changes for each 7-day period between Week 3 and Week 4 (between Day 22 and Day 28) of the treatment period calculated from the value at the start of the observation period (however changes in the SD of 24-hour blood glucose values shall be measured value only)

[*2]: Measured value and percent change from the value at the start of the observation period to the mean value during the 7-day period between Week 3 and Week 4 (between Day 22 and Day 28) of the treatment period

[Safety endpoint]

- Adverse events

<Other endpoints>

- 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

Statistical method

(1) Analysis set

Two analysis sets, “full analysis set” and “safety data analysis set” are used in this study. "The Full Analysis Set" used as a primary analysis set in the efficacy analysis shall be defined as "the research subjects who were randomized and given at least one dose of the study drug." The safety data analysis set shall be defined as “the research subjects who were given at least one dose of the study drug”.

(2) Efficacy analysis

<Primary endpoints>

- For the “full analysis set”, summary statistics (number of subjects, mean, SDs, maximum values, minimum values, quartiles [same apply hereafter]) and 95% confidence interval (two sides) of mean shall be calculated for each treatment group at each evaluation point (each day), and illustrating changes in mean and SD in order to evaluate changes in the SD of 24-hour blood glucose values (mg/dL) for each 7-day period between Week 3 and Week 4 (between Day 22 and Day 28) of the treatment period, calculated from the value at the start of the observation period for trelagliptin or alogliptin separately. Preliminary, for the “full analysis set”, calculate point estimation and 95% confidence interval (two sides) in difference of mean in treatment groups (trelagliptin 100 mg group – alogliptin 25 mg group) in order to examine the influence of the once-weekly administration and blood glucose fluctuations due to the difference in the daily administration exploratory.
- As well, for the “full analysis set ,” conduct analysis of covariance at each evaluation point with changes in the SD of 24-hour blood glucose values between Week 3 and Week 4 from the value at the start of the observation period as dependent variable, treatment groups as independent variable, HbA1c (NGSP value) at the start of the observation period, changes in the SD of 24-hour blood glucose values at the start of the observation period, and age as covariates, and calculate point estimation and 95% confidence interval (two sides) in difference of adjusted mean for each group.
- Preliminary, “full analysis set ,” calculate point estimation and 95% confidence interval (two sides) in difference of adjusted mean in treatment groups (trelagliptin 100 mg group – alogliptin 25 mg group)

<Secondary endpoints>

- Conduct the same analysis as the primary endpoints for *1 and *2 of the each endpoint section.

However, for changes in mean/SD, only measured values of *1 and *2 shall be illustrated.

<Additional endpoints>

- For the "full analysis set", while calculating summary statistics and 95% confidence interval (two sides) of mean at each evaluation point (the start of the observation period by each treatment group, first day, 1 point during fourth to sixth day, and ninth day of CGM which is to be performed for 9 days from Day 21) in measured values and changes from the start of the observation period, and illustrate changes in mean and SD.

(3) Safety analysis

- Adverse events shall be reported using MedDRA terminology and summarized using the Preferred Term (PT) and System Organ Class (SOC) of the MedDRA. For the "safety data analysis set", frequency tabulation shall be conducted for adverse events after start of treatment with study drug by each treatment group:
  - Frequency tabulation of all adverse events
  - Frequency tabulation of adverse events that causal relationship is "related" to study drug.
  - Frequency tabulation of the degree of all adverse events
  - Frequency tabulation of degree of adverse events that causal relationship is "related" to study drug.
  - Frequency tabulation of adverse events that were "discontinued" as a measurement concerning study drug.
  - Frequency tabulation of serious adverse events

Rationale for the number of planned research subjects:

The planned minimum number of research subjects evaluable for the primary endpoint in each group is as follows:

Trelagliptin 100 mg group: 15

Alogliptin 25 mg group: 15

Set in consideration with the feasibility of the number of research subjects for exploring the effects of trelagliptin 100 mg and alogliptin 25 mg on glycemic variation. It is not based on statistical power calculation.

3.0 ABBREVIATION

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	Area under the curve
1,5-AG	1,5-anhydroglucitol
BMI	body mass index
CGM	continuous glucose monitoring
COI	conflict of interest
CRO	contract research organization
DPP-4	dipeptidyl-peptidase-4
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon like peptide-1
HbA1c	hemoglobin A1c
ICH	International Conference on Harmonisation
MAGE	Mean Amplitude Glycemic Excursions
MedDRA	Medical Dictionary for Regulatory Activities
PT	preferred term
SAE	serious adverse event
SD	standard deviation
SMBG	Self Monitoring of Blood Glucose
SOC	system organ class
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

Conventionally, although HbA1c has been used as an indicator for glycemic control for patients with diabetes mellitus, it has been indicated that it is insufficient for inhibiting cardiovascular events by only controlling HbA1c which reflects the long term glycemic variation [1-3] On the other hand, it has been reported that persistent hyperglycemia and the range of glycemic variation is related to oxidative stress and cardiovascular events, and it has been indicated that treatment is necessary in consideration of daily glycemic variation [4-6]. Also, it is anticipated that the glycemic variation of patients with diabetes mellitus and the characteristics of each anti-diabetic medications may be revealed and to be able to make a choice for a more appropriate treatment.

Self-measurement of blood glucose (SMBG) is used frequently for measuring glycemic variation and although one may understand the blood glucose level at the time of measurement, it is difficult to know if the blood glucose level has an upward trend or not changing or a downward trend at that time point, and it is reported that 80% hypoglycemia or hyperglycemia may be missed [7,8]. That is why the continuous glucose monitor (CGM) was developed and it became possible to accurately evaluate variance of blood glucose which was difficult and planning of treatment course according to each patient's condition is anticipated. Actually, in many researches that was conducted to collect various glycemic variation patterns to verify the optimization of treatment of diabetes mellitus, the benefits of various indicators of glycemic variation obtained from CGM has been reported [9].

Dipeptidyl-peptidase-4 (DPP-4) inhibitors are used widely as oral treatment drug for type 2 diabetes mellitus and it has an effect to promote insulin secretion blood glucose dependently by raising blood concentration of glucagon like peptide-1 (GLP-1). Conventionally, although DPP-4 inhibitors are taken once to twice daily commonly, once weekly trelagliptin was developed for a new treatment option as good glycemic control from improvement of drug compliance rate and flexibility of timing of taking drug according to lifestyle and further improvement of Quality Of Life(QOL) from less number of doses was in need. The phase III clinical study conducted at the development stage has shown that trelagliptin, when administered for 24 weeks, was not inferior to alogliptin, a DPP-4 inhibitor used as control, in terms of the change in HbA1c at the end of the treatment period [10]. However, effect on glycemic variation of trelagliptin and alogliptin has not been clarified efficiently, and it is anticipated that understanding the characteristics of once weekly DPP-4 inhibitors and once daily DPP-4 inhibitors may be an efficient rational for therapeutic use.

4.2 Rationale for the proposed research

Because there is no enough evidence assayed for glycemic variation of not only once weekly DPP-4 inhibitors but also once daily DPP-4 inhibitor, Trelagliptin, once weekly DPP-4 inhibitor, and Alogliptin, once daily DPP -4 inhibitor, were set as study drugs to collect the consecutive data of glycemic variation obtained from CGM and to evaluate difference of DPP-4 inhibitors.

Although trelagliptin was non-inferior to alogliptin, once daily DPP-4 inhibitor, in terms of the change from baseline in HbA1c at the phase III clinical study conducted during the development period, the effect on glycemic variation of alogliptin have to be clarified when the effect of different dose and method of administration of DPP-4 inhibitors on glycemic variation would like to be evaluated.

In this present study, therefore, the effect of once weekly trelagliptin or once daily alogliptin on glycemic variation will be evaluated in patients with type 2 diabetes mellitus in an exploratory manner as a primary objective, and the effect by difference of dose and method of administration on glycemic variation will be evaluated as secondary as far as possible.

5.0 RESEARCH OBJECTIVES AND ENDPOINTS

5.1 Objectives

To evaluate the effect of trelagliptin administered orally at a dose of 100 mg once weekly or alogliptin orally administered at a dose of 25 mg once daily for 4 weeks on glycemic variation in an exploratory manner as a primary objective and to evaluate, as far as possible, the effect of difference method of administration of DPP-4 on glycemic variation as secondary objective.

5.2 Definition of endpoints

5.2.1 Primary endpoints

Changes in the standard deviation (SD) of 24-hour blood glucose values (mg/dL) for each 7-day period between Week 3 and Week 4 (between Day 22 and Day 28) of the treatment period, calculated from the value at the start of the observation period

5.2.2 Secondary endpoints

(1) Efficacy:

- Changes in AUC over time when specific blood glucose levels (110, 140, 160, or 180 mg/dL) are observed during the 3 hour time period after breakfast, lunch and evening meal
- Change in AUC over time during periods when blood glucose 140, 160, or 180 mg/dL (hyperglycemia) is observed
- Changes in blood glucose 140, 160, or 180 mg/dL (hyperglycemia) over time
- Changes in AUC over time during periods when blood glucose < 70 mg/dL (hypoglycemia) is observed
- Change in peak postprandial glucose levels over time 3 hours after breakfast, lunch, and evening meal
- Change in maximum variation of blood glucose levels over time between before and after breakfast, lunch, and evening meal
- Changes in MAGE
- Changes in mean 24-hour blood glucose levels
- Changes in mean daytime blood glucose levels
- Changes in mean nocturnal blood glucose levels

- Changes in AUC
- Changes in AUC over time during periods when blood glucose 110 mg/dL is observed
- Changes in the SD of 24-hour blood glucose values
- Changes in the SD of daytime blood glucose values
- Changes in the SD of nocturnal blood glucose values

(2) Safety: Adverse events

5.2.3 Other endpoints

(1) Efficacy:

- 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

6.0 CLINICAL RESEARCH DESIGN

6.1 Clinical research design

<Clinical study design>

This is a multi-center, randomized, open-label, parallel-group comparative, exploratory study to evaluate the effect of trelagliptin administered at a dose of 100 mg once weekly or alogliptin at a dose of 25 mg once daily for 4 weeks on glycemic variation in patients with type 2 diabetes mellitus using continuous glucose monitoring (CGM).

<Research TREATMENT>

After informed consent, patients determined to be eligible for this study based on the eligibility assessment will be randomized to either the trelagliptin 100 mg group or the alogliptin 25 mg group (at a ratio of 1:1), using "HbA1c at the start of the observation period (< 7.5% or ≥ 7.5%)" and age (< 65 or ≥ 65) as a stratification factor for randomization.

The principal investigator or investigator shall prescribe trelagliptin 100 mg/week or alogliptin 25 mg/day according to the allocation results notified from the enrollment center.

Trelagliptin 100 mg once weekly or alogliptin 25 mg once daily, taken orally before breakfast

Planned number of research subjects:

The planned minimum number of research subjects evaluable for the primary endpoint in each group is as follows:

Trelagliptin 100 mg group: 15
Alogliptin 25 mg group: 15

Number of study research implementing entities:

3 medical institutions

<Duration of evaluation and number of visits of research subjects>

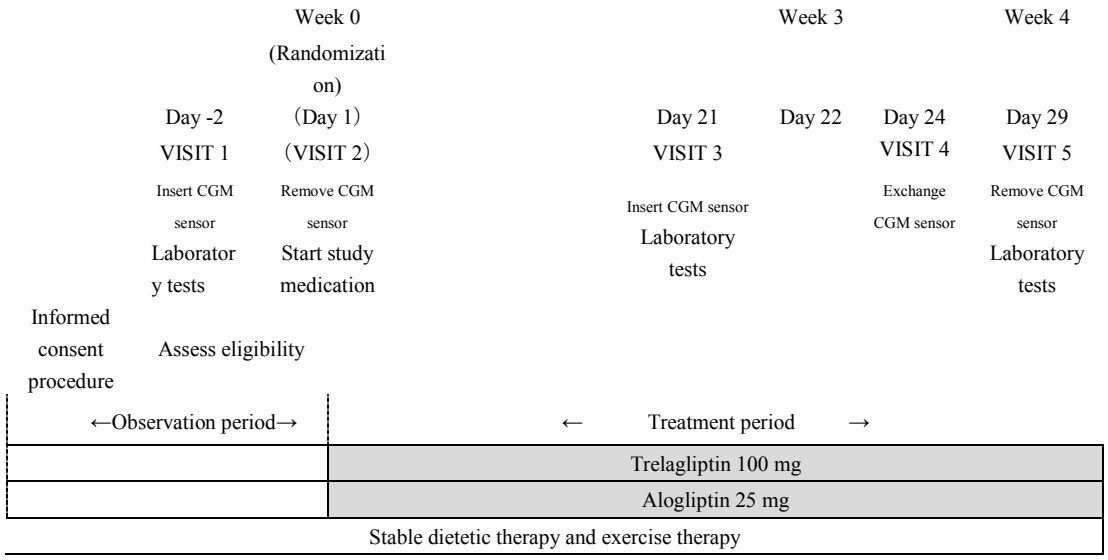
Duration of evaluation: 31 days, consisting of the observation period for 2 days and a treatment period for 29 days (4 weeks).

Number of visits: a total of 5 visits. Research subjects shall visit the study site at the start of the observation period (VISIT 1: Day-2), at the start of the treatment period (VISIT 2: Day 1), during the treatment period for CGM insertion (VISIT 3: Day 21) and for CGM sensor exchange (VISIT 4: Day 24), and at the end of the treatment period (VISIT 5: Day 29).

Figure 6 (a) shows a schematic of the clinical research design. Refer to Appendix A for schedule of examinations, observations, and assessments.

Figure 6.a Outline of clinical research design

< Outline of clinical research >



*: In the trelagliptin 100 mg group, a sensor shall be inserted on the day before dosing.

6.2 Rationale for the clinical research design

(1) Rationale for the clinical research design

Because there is no enough evidence assayed for glycemic variation of not only once weekly DPP-4 inhibitors but also once daily DPP-4 inhibitor, Trelagliptin, once weekly DPP-4 inhibitor, and Alogliptin, once daily DPP -4 inhibitor, were set as study drugs to collect the consecutive data of glycemic variation obtained from CGM and to evaluate difference of DPP-4 inhibitors.

Although trelagliptin was non-inferior to alogliptin, once daily DPP-4 inhibitor, in terms of the change from baseline in HbA1c at the phase III clinical study conducted during the development period, the effect on glycemic variation of alogliptin have to be clarified when the effect of different dose and method of administration of DPP-4 inhibitors on glycemic variation would like to be evaluated.

In this present study, therefore, the effect of once weekly trelagliptin or once daily alogliptin on glycemic variation will be evaluated in patients with type 2 diabetes mellitus in an exploratory manner as a primary objective, and the effect by difference of dose and method of administration on glycemic variation will be evaluated as secondary as far as possible.

Therefore this unblind study was designed to objectively evaluate the effect on glycemic variation of trelagliptin 100 mg and alogliptin 25 mg administered in patients with type 2 diabetes mellitus. And also to evaluate the effect of different method of administration on glycemic variation, stratified randomization comparison method between 2 groups was adopted with "HbA1c at the start of the observation period (< 7.5% or ≥ 7.5%) and age (< 65 or ≥ 65)" as a stratification factor for randomization.

Also, to exclude effect on glycemic variation from other anti-diabetic medications, research subjects who were taking anti-diabetic medications ≤ 4 weeks before start of observation period were excluded.

(2) Rationale for dosage

The dosages of trelagliptin and alogliptin were set at 100 mg/week and 25 mg/day, respectively, to evaluate glycemic variation at the usual dosage in clinical settings.

(3) Rationale for dosage

Study drugs show the glucose lowering effect by increasing incretin which are secreted by food intake. Thus, in order to eliminate the influence on the blood glucose by food intake. To further unify the administration timing of the research subjects prior to breakfast in terms of evaluating their glycemic variation.

(4) Rationale for duration of treatment

From the results of trelagliptin and alogliptin in phase II and III trials, duration was set at 4 weeks taking into account that the effect on blood glucose levels stabilize after 2 to 4 weeks with either drugs.

(5) Rationale for the number of planned research subjects:

Refer section 13.3

6.3 Premature termination of entire clinical research or premature termination of clinical research at a research implementing entity

6.3.1 Premature termination criteria of entire clinical research

The sponsor should immediately discontinue the study when at least one of the following criteria is applicable:

- When new information or other evaluation on the safety or efficacy of the study drug becomes available that shows a change in the known risk/benefit profile of the concerned compound, and risks/benefits are no longer tolerable for research subject participation in the study.

- When there is serious deviation from ethical guidelines or ICH-GCP that may threaten safety of the research subjects.

6.3.2 Criteria for premature termination of research implementing entities

A study site may be notified by the sponsor to discontinue clinical study if the site (including the principal investigator) is found in significant violation of Ethical Guideline for Clinical Research, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures of clinical study suspension and premature termination of entire clinical study or study at a research implementing entity

In the event that the sponsor or a research implementing entity committee such as an ethics review committee decides to prematurely suspend or terminate the entire clinical study or clinical study at a research implementing entity, a study-specific procedure shall be provided by the sponsor. The procedure shall be followed by applicable research implementing entities during the course of clinical study suspension or premature termination.

6.4 Procedures for protocol revision

If the protocol needs to be revised, the sponsor shall consider and decide whether to revise the protocol.

The principal investigator of each research implementing entity shall be informed of the details of each protocol revision. Also, principal investigators shall confirm the content of the revision of the protocol and submit a letter of agreement to the sponsor as evidence of agreement with the protocol revision.

Upon notification, the principal investigator at each research implementing entity shall submit the revised contents to committees such as the IEC, as necessary according to institutional regulations for review, and obtain approval from the director of the entity.

7.0 SELECTION AND WITHDRAWAL CRITERIA OF RESEARCH SUBJECTS

7.1 Inclusion criteria

Research subjects shall fulfill all of the following criteria to be included in this clinical study:

1. Research subjects who, in the opinion of the principal investigator or the investigator, are capable of understanding the content of the clinical research and complying with the research protocol requirements.
2. Patients who are able to sign and date the informed consent form and information sheet prior to the start of study procedures
3. Patients diagnosed with type 2 diabetes mellitus
4. Patients with an HbA1c (NGSP value) value ≥ 6.5% and < 8.5% at the start of the observation period (Day -2)
5. Patients who experience a ≤ ±1.0% change in HbA1c (NGSP value) at the start of the observation period (Day -2) as compared with an HbA1c value obtained during the preceding 4 weeks
6. Patients receiving stable dietetic therapy and exercise therapy (if performed) for ≥ 4 weeks before the start of the observation period
7. Patients who in the opinion of the principal investigator or the investigator, does not have to change (including discontinuation or interruption) HMG-CoA reductase inhibitors or addition of new HMG-CoA reductase inhibitors during treatment period.
8. Men or women aged 20 years or older at the time of informed consent

[Rational for the inclusion criteria]

1.2. These were set as essential conditions for the clinical research.

3. Set as target disease for this study.
4. To evaluate the glycemic variation caused by the study drug accurately, the upper limit value was set at 8.5% (NGSP value) to exclude research subject with insufficient glycemic control.
5. To evaluate the glycemic variation accurately, the change variation of HbA1c was set to exclude research subject with unstable glycemic control
6. Set in consideration of the possibility of change in dietetic/exercise therapy may affect evaluation of glycemic variation.

7. This was set in consideration of the possibility that HMG-CoA reductase inhibitors may affect glycemic variation.
8. This was set to allow for separate assessment of men/women. The lower age limit was set to 20 years to allow patients to make a voluntary decision regarding their participation in this clinical research.

7.2 Exclusion criteria

Research subjects meeting any of the criteria below shall not be included in this research.

1. Patients who received anti-diabetic medications within 4 weeks prior to the start of the observation period.
2. Patients who have changed (including discontinuation or interruption) HMG-CoA reductase inhibitors or received new HMG-CoA reductase inhibitors ≤ 4 weeks before the start of the observation period.
3. Patients with clinically evident hepatic dysfunction (e.g., AST or ALT ≥ 2.5-fold the upper limit of normal at the start of the observation period [Day -2])
4. Patients with moderate renal dysfunction, severe renal dysfunction or renal failure (e.g., creatinine clearance < 50 mL/min or serum creatinine > 1.4 mg/dL in men or > 1.2 mg/dL in women [equivalent to the creatinine clearance for persons aged 60 years with a body weight of 65 kg] at the start of the observation period [Day -2])
5. Patients with severe heart disease, cerebrovascular disorder, or severe pancreatic, hematologic or other diseases
6. Patients with a history of gastric or small intestinal resection
7. Patients with proliferative diabetic retinopathy
8. Patients warranting insulin therapy for glycemic control (e.g., patients with severe ketosis, diabetic coma or precoma, type 1 diabetes mellitus, severe infection, perioperative patients, or serious trauma)
9. Patients with a history of hypersensitivity or allergy to DPP-4 inhibitors
10. Patients who experience an allergic reaction to metal during CGM at the start of the observation period (Day -2)
11. Patients with any malignant tumors
12. Habitual drinkers whose average daily alcohol consumption is > 100 mL[Note 1)]

13. Patients who have any contraindications for the study drug or are taking any contraindicated concomitant drugs listed in the package insert
14. Patients anticipated to require any prohibited concomitant medications during the study period
15. Patients who are day and night lifestyle reversal
16. Patients participating in any other clinical studies at the time of informed consent for this study
17. Pregnant women, nursing mothers, women who are possible pregnant, or women who plan to become pregnant
18. Other patients who are considered inappropriate for participation in this study in the opinion of the principal investigator or investigator

Note 1: Alcohol conversion table (for reference)

Alcohol type	Variation	Alcohol strength (%)	Amount equivalent to alcohol 100 mL
Brewed alcohol	Sake	15%	670 mL (about 3 gos, 1 go=180 mL)
	Beer	5%	2,000 mL (about 3 large bottles)
	Happoshu (low-malt beer - like beverage)	5%	2,000 mL
	Wine	12%	830 mL
	Shaoxing rice wine	18%	560 mL
Spirits	Shochu (group ko)	35%	290 mL
	Shochu (group otsu)	25%	400 mL
	Whisky	40%	250 mL (about 3 double glasses)
	Brandy	40%	250 mL (about 3 double glasses)
	Vodka	40%	250 mL (about 3 double glasses)
Combined alcohol	Plum wine	13%	770 mL
	Combined sake	16%	630 mL

[Rationale for the exclusion criteria]

1, 2. Set in order to evaluate drug efficacy accurately.

3, 5, 7, 10, 11, 13. These were set in consideration of safety of research subjects.

4. Severe renal dysfunction and renal failure shall be excluded because trelagliptin is contraindicated for these conditions. Moderate renal dysfunction shall be excluded in consideration of safety of research subjects.

6, 12, 14. Set in order to take in consideration of safety of research subjects and to evaluate drug efficacy accurately.

8, 9. Set as contraindication for trelagliptin and alogliptin treatment.

15..,16 Set in order to establish rational for evaluation of this study.

17. Set as safety of trelagliptin and alogliptin in pregnant women has not been established. Also, set as excretion of trelagliptin and alogliptin in breast milk was confirmed in non-clinical trials.

18. These were set as fundamental items for the research.

7.3 Prohibited concomitant drugs and restricted concomitant drugs

7.3.1 Prohibited concomitant drugs

The following drugs are prohibited from the start of observation period to end of treatment period.

1. Anti-diabetic medications other than the allocated oral hypoglycemic drug
2. Glucocorticoids (medications for local effect such as external preparations are excluded)
3. Estrogen preparations
4. HMG-CoA reductase inhibitors* other than those used at the time of informed consent

   *Dosage of HMG-CoA reductase inhibitors those used at the time of informed consent may not be changed.
5. Acetaminophen

[Rational for prohibited concomitant drugs]

1 to 5. Set as it may affect evaluation of drug efficacy.

7.3.2 Restricted concomitant drugs

The following drugs those used at the time of informed consent are permitted from the start of observation period to end of treatment period. However, change of dosage, addition of or change to a new drug for those drugs is prohibited unless the principal investigator and investigator consider necessary due to adverse events.

1. Lipid lowering agents other than HMG-CoA reductase inhibitors
2. Anti-hypertensive drug

7.4 Research Subject Management

The principal investigator and investigator shall instruct the research subject the items below.

(1) Give instructions to take allocated oral hypoglycemic drug as directed. If poor compliance with study treatment (e.g., < 75% of the prescribed dose) after the previous visit has been found and does not improve, the research subject may be withdrawn from the research if appropriate for the circumstances.

(2) If hypoglycemia symptom (hunger abnormal, feeling of weakness, trembling of hands and fingers, cold sweat, palpitations, etc.) is observed, take glucose or sucrose (sugar), and if it does not improve give instructions to visit promptly.

(3) For dietetic therapy and exercise therapy (if performed), the principal investigator and investigator shall make sure prescriptions (instructions for calories, etc.) are consistent throughout the research period, and instruct the research subject to adhere to the dietetic therapy and exercise therapy (if performed).

(4) When CGM is being conducted, the principal investigator and investigator shall instruct exercise therapy (if performed) that may be performed under the same conditions every day, and instruct the research subject to adhere to it.

(5) When CGM is being conducted, give instruction to photograph every meal contents.

(6) Instruct the research subject not to eat high-sugar, high-calorie food or beverage between meals during CGM.

(7) When CGM is being conducted, give instructions to note necessary items into the research subject diary.

(8) On visit days for planned laboratory tests, give instructions not to take oral hypoglycemic drug scheduled to be taken on that day. Further, at each visit, have the research subject report if drug has been taken or not the day before, and on the day of visit.

(9) On visit days for planned laboratory tests, give instructions for fasting $\geq$ 10 hours before visit.

(10) For research subjects of childbearing potential, give instructions to use adequate contraception. If pregnancy is discovered, have the research subject report promptly, and discontinue the research immediately.

(11) The principal investigator and investigator shall instruct the research subject to adhere to instructed prohibited concomitant drugs. When drugs are taken other than the drugs prescribed by the principal investigator and investigator, have the research subject report its content.

(12) Regarding subjective symptoms/objective findings, have the research subject report at visit the necessary items from its contents, onset date, degree, outcome and date of outcome.

7.5 Criteria for discontinuation or withdrawal of a research subject

The principal investigator or investigator shall record the main reason for discontinuation of protocol treatment on the case report form according to the classification described below. Refer section 9.1.12 for discontinuation case before randomization.

1. **Adverse event**

   When the research subject had an adverse event that requires withdrawal of the research subject from the study because continued participation in the study would impose an unacceptable risk to the research subject's health, or when the research subject is unwilling to continue study participation because of the pretreatment event or adverse event.

2. **Major protocol deviation**

   When it is discovered after randomization that a research subject does not meet the eligibility criteria or is not adhering to the protocol, and continued participation in the research would impose an unacceptable risk to the research subject's health.

3. **Lost to follow-up**

   When the research subject failed to make visits and could not be contacted. The attempts that were made to contact the research subject shall be recorded in the source documents.

4. **Voluntary termination**

When the research subject wishes to withdraw from the research. The reason for discontinuation shall be recorded on the CRF when it is clarified.

5. **Research termination**

When the sponsor or a committee such as the IEC or regulatory authority has decided to terminate the study. Refer to Section 6.3.1 for details.

6. **Pregnancy**

When a female research subject is found to be pregnant.

Note: Research participation shall be immediately discontinued when pregnancy is known. Refer to Section 9.1.11 for procedure.

7. **Others**

Note: The specific reasons should be recorded on the CRF.

7.6 Procedures for discontinuation of individual research subjects

The principal investigator or investigator shall terminate a research subject's research participation when the research subject meets the criteria described in Section 7.5. Individual research subjects may discontinue their research participation without giving a reason at any time during the research. Should a research subject's participation be discontinued, the primary reason for termination shall be recorded on the CRF by the principal investigator or investigator. In addition, efforts shall be made to perform all tests/observations/evaluations scheduled at the time of discontinuation.

8.0 RESEARCH TREATMENT

This section indicates the treatment regimen of this clinical research. See the latest package insert for details and handling of each drug.

8.1 Treatment with the study drug

8.1.1 Study drug

(1) Study drug:

Generic name: Trelagliptin Succinate

Chemical name: 2- ({6- [（3R）-3-Aminopiperidin-1-yl] -3-methyl-2, 4-dioxo-3, 4-dihydropyrimidin -1 (2H)-yl})methyl-4-fluorobenzonitrile monosuccinate

Generic name: Alogliptin benzonate

Chemical name:2- ({6- [(3R) -3-Aminopiperidin-1-yl] -3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1 (2H) -yl} methyl) benzonitrile monobenzoate

8.1.2 Dose and administration method

Trelagliptin 100 mg (once weekly) or alogliptin 25 mg (once daily) shall be administered orally before breakfast. However, the drug shall be administered as described below at the start of the treatment period (VISIT 2: Day 1) or during the treatment period (VISIT 3: Day 21).

At the start of the treatment period (VISIT 2: Day 1): The drug shall be administered after required tests/observations, etc.

During the treatment period (from VISIT 3 to VISIT 5):

Trelagliptin 100 mg/week group shall insert the sensor on the day before Trelagliptin administration day. Trelagliptin 100 mg/week shall be administered before breakfast on the next day of the sensor insertion day. The next administration of Trelagliptin 100 mg is after the sensor removal.

Alogliptin 25 mg/day shall be administered after required tests/observations, etc at every VISIT without taking study drug. Research subjects shall take study drug prior to the every breakfast at home.

Duration of treatment shall be start of treatment period (Day 1) to end of treatment period (Day 29).

Dose and administration method for each administration group are shown in table 8.a.

Table8.a Administration group and administration method

Administration group	Dose	Route of administration:	Administration method
Trelagliptin group	Trelagliptin 100 mg	Oral administration	Once weekly, before breakfast
Alogliptin group	Alogliptin 25 mg	Oral administration	Once daily, before breakfast

8.1.3 Overdose

Overdose is defined as intentional or accidental administration of the study drug at a higher dose than that specified in the protocol, either by a health professional or by the research subject.

To consistently collect important safety information about overdose, the principal investigator or investigator(s) shall record all cases of overdose on the "Overdose" page of the CRF, irrespective of the presence or absence of accompanying adverse event. Adverse events associated with overdose shall be recorded on the "Adverse events" page of the CRF, in accordance with the procedures described in Section 10.0, "ADVERSE EVENTS."

In addition, serious adverse events associated with overdose shall be recorded in accordance with the procedures described in Section 10.2.2, "Collection and reporting of SAEs."

In the event of overdose, the principal investigator or investigator shall treat the subject as required based on symptoms.

8.2 Medication other than the study drug

Prohibited concomitant drugs (refer to Section 7.3.1) may not be used. Also, restricted drugs (refer to Section 7.3.2) may be used if used at the time of informed consent. However, dose change for those restricted drugs or addition of or change to a new drug shall be prohibited unless the principal investigator and investigator consider necessary due to adverse events. Other treatments shall be conducted under normal medical practice

8.3 Allocation and prescription of the study drug and administration procedure

The principal investigator or its designee shall access the web case enrollment system to allocate research subjects. In addition the principal investigator or its designee shall notify information necessary for allocation such as the research subject ID number. Thereafter, the drug to be administered to the research subjects shall be notified by the web case enrollment system. The principal investigator and investigator shall prescribe the study drug according to the notification and record the drug information into the CRF of each research subject.

8.4 Preparation and storage of allocation list

The person responsible for allocation (designated by the sponsor) shall create an allocation list.

Allocation shall be conducted at the enrollment center using web case enrollment system at start of treatment period (Day 1) with "HbA1c at the start of the observation period (< 7.5% or ≥ 7.5%)" and age (< 65 or ≥ 65) as a stratification factor for randomization. The enrollment center shall use the allocation list for stratified randomization created by the allocation responsible person.

Information on the allocation shall be kept in a safe place and shall not be available to anyone other than authorized persons, to secure independency from the clinical research.

9.0 CLINICAL STUDY PROTOCOL

9.1 Research procedures

The principal investigator or investigator shall collect data in accordance with the procedure below. The same principal investigator or investigator shall perform tests/observations/evaluation of research subjects, in principle. The study schedule is provided in Appendix A.

9.1.1 Informed consent procedure

The procedures for obtaining informed consent are described in Section 15.3.

Consent shall be obtained from the research subject before initiation of research procedures.

Research subject ID code is given to each research subject from whom informed consent was acquired and who was randomized. The research subject ID code shall be used throughout the research period and shall not be changed.

9.1.2 Demographic data, medical history, and previous therapeutic drugs

(1) Demographic information

Demographic data shall be collected regarding birth, gender, smoking history, drinking history, time (year/month) of onset (or diagnosis of diabetes).

(2) Medical history

Medical history data shall be collected regarding clinically problematic diseases or symptoms that disappeared within 1 year or were terminated from the start of observation period. When the symptoms or disease continues, it shall be considered as a concurrent disease (Refer to Section 9.1.6).

(3) Pre-treatment

Regarding pre-treatment, name of drug, route of administration and date of final administration shall be collected for all anti-diabetic medication (including injections) that ended use $\leq$ 12 weeks before start of observation period.

9.1.3 Physical examination

All subsequent physical examinations after the start of the treatment period shall be assessed for clinically significant changes from the baseline examination.

9.1.4 Weight, height and BMI

Body weight shall be measured to one decimal place in kilograms.

Height shall be measured or asked to the nearest whole number in centimeters.

BMI shall be calculated by the sponsor using the following formula and shown to one decimal place:

Body Mass Index: BMI = weight (kg) / (height (m))^2

Example:

Height = 176 cm, weight = 79.2 kg, BMI = 79.2/1.76^2 = 25.6 kg/m^2

9.1.5 Concomitant drugs

Concomitant drugs are all drugs to be given in addition to the study drug. Drugs prescribed by doctors or the over-the-counter medicines purchased by the research subjects shall be included. At every hospital visit of the research subject, the status of use of drugs (name of drug, route of administration) other than the allocated oral hypoglycemic drug, from start of observation period to the completion of the clinical research shall be monitored.

9.1.6 Concurrent disease

A concurrent disease is defined as a disease or symptom that is present at the start of the observation period or that develops between the start of the observation period and the start of study treatment. Clinically significant abnormalities, including laboratory test data and physical examination findings, observed in tests and physical examinations at the start of study treatment shall be considered as a concurrent disease at the discretion of the principal investigator or investigator. The content of concurrent disease (diagnosis) shall be investigated.

9.1.7 Laboratory tests

Laboratory tests in table 9.a shall be measured at clinical laboratory institutions according to the observation schedule (Appendix A). Regarding tests at fasting, blood sampling shall be conducted after ≥ 10 hours of fasting. The principal investigator and investigator shall evaluate and keep the reported laboratory test results.

Inhibitory rate of DPP-4 activity will be calculated by the sponsor using formula below:

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

Table 9.a Laboratory tests

Serum chemistry	
Fasting blood glucose	Glycoalbumin
Fasting insulin	1,5-AG
Fasting glucagon	
Fasting proinsulin	
FastingGLP-1	
Fasting GIP	
DPP-4 activity	

The principal investigator shall keep laboratory test reference values, including the historical data.

9.1.8 HbA1c (NGSP value)

Measured at research implementing entities to confirm eligibility of research subject at start of observation period. The principal investigator and investigator shall evaluate and keep the reported laboratory test results.

9.1.9 Continuous glucose monitoring (CGM)

Conducted according to Schedule of Research Procedures (Appendix A) Details shall be specified separately in the operation procedures manual.

(1) Device used in this study

[redacted], leased from the sponsor.

(2) Self-measurement of blood glucose (SMBG)

Use device leased from sponsor

Research subjects shall measure blood glucose levels every day during CGM in the observation and treatment periods. At least, blood glucose levels shall be measured at three time points on the first day of CGM ([1] at least 2 hours after the recorder is connected and [2] 2 hours after the first is measured. [3] at bedtime) and at four time points from the second day onward ([1] before breakfast, (2) before lunch, (3) before evening meal, and (4) at bedtime).

The glucose levels from SMBG shall be used for correction of glucose levels obtained from CGM.

(3) Observation period

A sensor shall be inserted at the start of the observation period (Day -2) and removed at the start of treatment (Day 1)

(4) Treatment period

A sensor shall be inserted (VISIT 3: Day 21), exchanged (VISIT 4: Days 24 to 26), and removed (VISIT 5: Day 29) during the treatment period.

(5) Dietetic therapy and exercise therapy

Research subjects shall present photographs of all meals to the principal investigator or investigator during CGM. Also, the meal provided by the sponsor shall be taken according to the calories prescribed by the sponsor for each research subject at the meal times shown below.

Time point of provision of meals: evening meal at start of observation period (Day-2), evening meal on first and seventh of CGM to be performed from Day 21 for 9 days.

Research subjects shall only conduct exercise therapy feasible (if performed) under the same conditions every day during CGM.

The principal investigator or investigator shall prescribe consistent dietetic therapy and exercise therapy (if performed) throughout the research period. Compliance with dietetic therapy and exercise therapy(if performed) shall be investigated and rated on a four-point scale as follows:

1. Compliant (compliance rate ≥ 90%)
2. Almost compliant (compliance rate ≥ 70%)
3. Generally compliant (compliance rate ≥ 50%)
4. Minimally compliant (compliance rate < 50%)

(6) Research subject diary

Research subjects shall complete the subject diary every day during CGM and submit the diary to the principal investigator or investigator.

The following information shall be recorded in the subject diary: date and time of dosing, time of SMBG and blood glucose levels, meal time and contents, exercise time, wake-up time, bedtime, etc.

9.1.10 Contraception

Women of childbearing potential (e.g., women who have not undergone surgical sterilization, women who have not reached menopause) shall use appropriate contraception during participation in this clinical research from the time of informed consent. During the informed consent process, appropriate contraceptive methods and the necessity of avoiding pregnancy during participation in

the clinical research shall be fully explained to women of childbearing potential with the use of the informed consent form and information sheet, and the research subjects shall fully understand these explanations before providing consent.

9.1.11 Pregnancy

When a study subject or a partner of study subject was found to be pregnant during the study period, the principal investigator or investigator notify the monitoring staff of the sponsor. The principal investigator or investigator provide detailed information using the Follow-up Form for Pregnancy separately wherever possible.

9.1.12 Record of cases withdrawn before randomization

The consent form shall be signed, and a CRF shall be created for all research subjects who are withdrawn before randomization.

The following items are to be described on the CRF.

- Informed consent procedure
- <MMM/DD/YYYY>
- Sex
- Eligibility
- Reason for discontinuation

The primary reason for withdrawal before randomization shall be recorded on the CRF according to the following classification:

- Not meeting inclusion criteria or meeting exclusion criteria
- Serious deviation from protocol
- Lost to follow-up
- Voluntary discontinuation (specify the reason)
- Premature termination criteria of entire clinical research
- Others (specify the reason)

Research subject ID numbers assigned to research subjects withdrawn from the research before randomization shall not be reused.

9.1.13 Record of randomization

Research subjects to be randomized shall meet all of the inclusion criteria and shall not meet any of the exclusion criteria according to Section 8.2. The principal investigator or investigator shall specify the reason why the subject cannot be randomized to the treatment period.

9.2 Drug-taking status of the research subjects

The principal investigator or investigator shall confirm the treatment compliance and the date and time of dosing during CGM with the research subject at every visit. At the end of study drug administration, Treatment compliance shall be rated on a two-point scale as follows:

1. Compliant (compliance rate ≥ 75%)

2. Not compliant (compliance rate < 75%)

Medication instruction shall be given to research subjects throughout the clinical research period. If poor compliance with study treatment (e.g., < 75% of the prescribed dose) after the previous visit has been found and does not improve, the research subject may be withdrawn from the research if appropriate for the circumstances.

9.3 Implementation time point of the test and observation items

The schedule for all tests, observations, and evaluations is shown in Appendix A. The principal investigator or investigator shall perform the tests, observations, and evaluations at the time points shown below.

9.3.1 Start of observation period (Visit 1: Day -2)

After consent is obtained, physical examination/tests are to be conducted for research enrollment. Eligibility of research subjects shall be determined in accordance with the inclusion and exclusion criteria as described in section 7.0. Refer to section 9.1.12 for the recording of research subjects who are withdrawn before randomization.

Tests and observations to be performed and endpoints to be assessed during the observation period (VISIT 1: Day -2) are shown below.

- Informed consent procedure
- Demographic information
- Medical history, pre-treatment
- Physical examination
- Height
- Concomitant drugs
- Concurrent disease
- Prescription of and compliance with dietetic therapy and exercise therapy

Tests and observations to be performed and endpoints to be assessed during the observation period VISIT 1(Day -2) are shown below.

- Physical examination
- Body weight
- Laboratory tests
- HbA1c
- CGM (remove sensor)
- Self-measurement of blood glucose (self-measured by research subject)

9.3.2 At start of treatment period (Visit 2: Day 1)

Research subjects whose eligibility has been confirmed shall be randomized according to section 8.3 following the results of test, observation and endpoints implemented before start of treatment period.

Randomization is performed at the visit when the principal investigator or investigator is considered as necessity.

The test, observation, and endpoints to be implemented at the start of treatment period (Visit 2: Day 1) are shown below.

- Physical examination
- Concomitant drugs
- Compliance with dietetic therapy and exercise therapy
- CGM (remove sensor)
- SMBG (research subject perform by own)
- Adverse Event

9.3.3 Treatment period (Visit 3: Day 21)

The test, observation, and endpoints to be implemented during the treatment period (Visit 3: Day 21) are shown below.

- Physical examination
- Body weight
- Concomitant drugs
- Laboratory tests

- Treatment status
- Compliance with dietetic therapy and exercise therapy
- CGM (remove)
- Self-measurement of blood glucose (self-measured by research subject)
- Adverse event

9.3.4 Treatment period (Visit 4: Day 24)

The test, observation, and endpoints to be implemented during the treatment period (Visit 4: Day 24) are shown below.

- Physical examination
- Concomitant drugs
- Laboratory tests
- Drug-taking status
- Compliance with dietetic therapy and exercise therapy
- CGM (exchange sensor)
- Self-measurement of blood glucose (self-measured by research subject)
- Adverse event

9.3.5 At end of treatment period (Visit 5: Day 29) or discontinuation during treatment period

The test, observation, and evaluation items to be implemented during at the end of treatment period (Visit 5: Day 29) are shown below.

- Physical examination
- Body weight
- Concomitant drugs
- Laboratory tests
- Drug-taking status
- Compliance with dietetic therapy and exercise therapy
- CGM (remove sensor)

- Self-measurement of blood glucose (self-measured by research subject until removal of CGM sensor)
- Adverse event

The test, observation, and endpoints to be implemented at discontinuation of treatment period are shown below.

- Physical examination
- Body weight
- Concomitant drugs
- Laboratory tests
- Drug-taking status
- Compliance with dietetic therapy and exercise therapy
- Adverse event
- Reason of discontinuation

The status of all randomized research subjects at the end of the clinical research shall be recorded on the CRF.

10.0 ADVERSE EVENT

10.1 Definitions

10.1.1 Adverse event

An adverse event is defined as any untoward medical occurrence in a patient or a research 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).

An adverse event can therefore be any unfavorable or unintended sign (e.g., clinically significant laboratory abnormality), symptom, or disease temporally associated with the use of a pharmaceutical product (including the study drug), regardless of whether it is considered related to the pharmaceutical product (including the study drug) or not.

10.1.2 Considerations for adverse events

Generally unfavorable findings are described below:

- Newly diagnosed disease or unexpected aggravation of existing symptom (intermittent event of an existing symptom is not considered an adverse event)
- Requiring action or medical practice
- Requiring invasive diagnostic treatment
- Requiring discontinuation or a change in the dose of the study drug or a concomitant medication
- Considered unfavorable by the principal investigator or the investigator

Diagnosis name and signs/symptoms:

Adverse events shall be recorded by diagnosis name. Accompanying signs (including abnormal laboratory values, abnormal ECG findings) and symptoms shall not be recorded as adverse events. If an adverse event could not be expressed by a diagnosis name, the signs or symptoms shall be recorded as the adverse event.

Laboratory test values and ECG findings:

Abnormal laboratory values and ECG findings shall be recorded as adverse events when the principal investigator or investigator judges the results are clinically problematic (in other words, when certain action or medical practice is required, or when the principal investigator or the investigator judges the change has exceeded the normal physiological variation range of the research subject). Retest and/or continued monitoring of an abnormality are not considered medical practice.

Also, repeated or additional conduction of non-invasive tests for verification, evaluation, and monitoring of an abnormality are not considered medical practice.

However, when abnormal laboratory values and ECG findings are the accompanying symptoms of a disease diagnosed as an adverse event (e.g., increased creatinine due to renal dysfunction, etc.), the adverse event shall be handled by its diagnosis name.

Pre-existing conditions (disease or symptom that has been present since before the start of study treatment): Pre-existing disease or symptom that has been present since before the start of study treatment shall be regarded as a concurrent disease and not an adverse event. When a concurrent medical condition is aggravated, the aggravation shall be determined as an adverse event and the principal investigator or the investigator shall record on the CRF that the adverse event is an aggravation of the concurrent disease (e.g., "aggravation of hypertension," etc.).

If a research subject has a pre-existing episodic condition (e.g., asthma, epilepsy), each episode shall be recorded as an adverse event if the episodes become more frequent, serious, or severe in nature. If a research subject has a chronic concurrent condition (e.g., cataracts, rheumatoid arthritis), worsening of the condition shall be recorded as adverse event if the degree of the worsening exceeds that which would be expected. The principal investigator or investigator shall ensure that the adverse event term to be recorded represents the change in the condition from baseline (e.g. "worsening of…").

Worsening of adverse events :
If a research subject experiences a worsening of the adverse event after a change to the study drug, or secondary signs and symptoms are caused by the adverse event, the worsening or the secondary signs and symptoms shall be recorded as a new adverse event on the CRF. The principal investigator or investigator shall use an adverse event term that explicitly means a change of the condition (e.g., "worsening of…").

Change of severity of adverse events:
If the research subject experiences changes in the severity of an adverse event, the event shall be recorded once, at its peak severity.

Previously planned surgery or treatment:
Preplanned surgeries or interventions that were scheduled before study treatment shall not be considered adverse events. However, when the existing symptom is aggravated to a degree requiring emergency surgery or treatment, the condition or the event shall be considered an adverse event. A concurrent disease that resulted from previously planned surgery shall be reported as an adverse event.

Non-urgent surgery or treatment:
Non-urgent surgery or treatment that does not induce a change in the condition of a research subject (cosmetic surgery, etc.) shall not be considered an adverse event; However, it shall be recorded in the source documents. Concurrent diseases due to a non-urgent surgery shall be reported as an adverse event.

The insufficient clinical response (lack of efficacy): insufficient clinical response, efficacy, or pharmacological action shall not be recorded as an adverse event. The principal investigator or investigator shall make the distinction between worsening of a pre-existing condition and lack of therapeutic efficacy.

Overdose of the study drug:
Overdose of any medication without onset of event shall not be recorded as an adverse event, but the overdose shall be recorded on the "Overdose" page of the CRF. Any onset of event shall be recorded as adverse events on the "Adverse events" of the CRF.

10.1.3 Serious adverse event

Of all unfavorable medical events that develop after administration of a pharmaceutical product (including the study drug) (irrespective of dose), a serious adverse event is an event that:

1. results in death,
2. is life threatening*,
3. requires inpatient hospitalization or prolongation of existing hospitalization,
4. results in persistent or significant disability/incapacity,
5. leads to a congenital anomaly/birth defect, or
6. Medically important event that causes a risk to the research subject even if it is not immediately life-threatening and does not result in death or hospitalization, or requires an action or treatment to prevent the results described in 1 to 5 above. Points described in the Takeda Medically Significant Adverse Event List (Table 10.a) are included in this section.

* The term "life threatening" refers to an event in which the research subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

Table 10.a Takeda Medically Significant AE List

Acute respiratory failure/acute respiratory distress syndrome (ARDS)	Hepatic necrosis
Torsades de pointes/ ventricular fibrillation/ventricular tachycardia	Acute hepatic failure
Malignant hypertension	Anaphylactic shock
Convulsive seizure (including convulsion and epilepsy)	Acute renal failure
Agranulocytosis	Pulmonary hypertension
Aplastic anemia	Pulmonary fibrosis (including interstitial pneumonia)
Toxic epidermal necrolysis/ Oculomucocutaneous syndrome (Stevens-Johnson syndrome)	Neuroleptic malignant syndrome/ malignant hyperpyrexia
	Spontaneous abortion/ stillbirth and fetal death
	Confirmed or suspected transmission of infection by a medicinal product
	Confirmed or suspected endotoxin shock

10.1.4 Adverse events of special interest (specific adverse events)

An AE of Special Interest (AESI) (serious or non-serious) is one of scientific and medical concern specific to the study drug, for which ongoing monitoring and rapid communication by the principal investigator or investigator to Takeda may be appropriate. Such events may require further investigation in order to establish assessment, and instructions provided to investigators on how and when they should be reported to the sponsor are described in Section 10.2.1.3.

AESIs: Hypoglycemia-related AEs, intestinal obstruction-related AEs and acute pancreatitis-related AEs (for both Trelagliptin and Alogliptin), QT/QTc interval prolongation-related AEs (for Trelagliptin), and Liver dysfunction or jaundice-related AEs (for Alogliptin).

<For both Trelagliptin and Alogliptin>

[Hypoglycemia-related AEs]

Hypoglycemia-related AEs are designated as AESIs because, in general, attention should be paid to the events in the treatment of diabetes mellitus.

[Intestinal obstruction-related AEs]

Intestinal obstruction-related AEs are designated as AESIs because there are accumulated reports of intestinal obstruction as an adverse reaction to similar incretin-related drugs (GLP-1 receptor agonists and other DPP-4 inhibitors).

[Acute pancreatitis-related AEs]

Acute pancreatitis-related AEs are designated as AESIs because there are accumulated reports of acute pancreatitis as an adverse reaction to similar incretin-related drugs.

<For Trelagliptin>

[QT/QTc interval prolongation-related AEs]

QT/QTc interval prolongation-related AEs are designated as AESIs because, in the QT/QTc assessment study conducted during the development, QT/QTc interval prolongation was reported in the trelagliptin 800 mg group although it did not occur in the trelagliptin 200 mg group.

<For Alogliptin>

【Liver dysfunction or jaundice-related AEs】

Liver dysfunction or jaundice-related AEs are designated as AESIs because there are accumulated reports as serious adverse reaction.

10.1.5 Severity of adverse events

The severity of adverse events shall be classified and defined as shown below.

Mild	The event is transient and easily tolerated by the subject.
Moderate	The event interrupts the subject's usual activities.
Severe	The event causes considerable interference with the subject's usual activities.

10.1.6 Causality of adverse events

The causal relationship of each adverse event to the study drug shall be classified and defined as shown below.

Related	An adverse event that follows an apparent temporal sequence (including clinical course after discontinuation). An adverse event the causal relationship could not be denied and there is reasonable possibility due to the study drug, although other factors such as underlying disease, concurrent diseases, or concomitant drugs/treatment are also suspected.
Not related	An adverse event that does not follow an apparent temporal sequence from administration of the study drug. Very likely due to other factors such as underlying

	disease, concurrent diseases, or concomitant drugs/treatment.

10.1.7 Relationship to study procedures

The relationship shall be recorded as "Yes" if the principal investigator or investigator considers that there is reasonable possibility that an adverse event is due to a study procedure. Otherwise, the relationship shall be recorded as "No."

10.1.8 Date of onset

The date of onset of adverse events shall be determined according to the following rules:

Adverse event	Date of onset
Signs, symptoms, diseases (diagnoses)	The date on which the first signs/symptoms were noted by the research subject and/or the principal investigator or investigator.
Asymptomatic diseases	The date on which a diagnosis was confirmed through a test(s). The date on which a diagnosis was confirmed, even when the test results indicate an old sign(s) of the disease or an approximate time of its onset.
Exacerbation of concurrent diseases	The date on which the first worsening of diseases/symptoms was noted by the research subject and/or the principal investigator or investigator.
Onset of a test abnormality after the start of the study drug administration	The date on which a clinically significant laboratory abnormality was detected.
Worsening of a baseline test abnormality after initiation of study treatment	The date on which a clear increase/decrease in a laboratory parameter was clinically confirmed based on the time profile of the parameter.

10.1.9 Date of resolution

The date of resolution of an adverse event is the date on which the research subject recovered (including resolution with sequelae). If a research subject died due to the adverse event concerned, it shall be the date of death. The adverse event shall be recorded as "ongoing" if the research subject has not yet recovered by the end of the study.

10.1.10 Actions taken for the study drug

Actions taken for the study drug shall be classified or defined as shown below.

Drug withdrawn	The study drug is discontinued because of an adverse event (including withdrawal by the research subject at his/her own discretion). When the treatment with the study drug is continued after withdrawal from the study, it shall be defined as "Dose not changed."

Dose not changed	If the dose was unchanged after the onset of the adverse event it shall be defined as "Dose not changed." If the study drug was discontinued, reduced, or increased because of another adverse event it shall be defined as "Dose not changed." If the study drug was discontinued or reduced for a reason other than for the adverse event, e.g., inadvertence of the research subject, it shall be defined as "Dose not changed".
Unknown	It has not been possible to determine what action has been taken because the research subject is lost to follow-up.
Not Applicable	The study treatment had already been completed or discontinued before the onset of the adverse event.
Dose reduced	The dose of the study drug was reduced because of the adverse event (including dose reduction by the research subject at his/her own discretion).
Dose increased	The dose of the study drug was increased because of the adverse event (including dose increase by the research subject at his/her discretion).
Washout	If the study treatment is suspended (i.e., interrupted) (including suspension/interruption by the research subject at his/her discretion) because of the adverse event but resumed thereafter, shall be defined as "washout".

10.1.11 Outcome

Outcome of adverse events is classified as follows:

Category	Criteria
Recovered	Disappearance or recovery of symptoms and findings Laboratory values returned to normal or baseline
Improved	The intensity is lowered by one or more stages Symptoms or findings mostly disappeared Laboratory values improved, but have not returned to normal or baseline The research subject died from a cause other than the concerned adverse event while the condition was resolving (recording of the date of death unnecessary)
Not recovered	No change in symptoms, findings, or laboratory data The symptoms, findings, or laboratory data on the final day of observable period were aggravated compared with the date of onset Irreversible congenital anomaly The research subject died from another cause before resolution of the concerned adverse event (recording of the date of death unnecessary)
Recovered with sequelae	Disability that disturbs daily life

Death	Direct relationship between death and the concerned adverse event "Direct relationship" means that the concerned adverse event was the cause of death, or the concerned adverse event was clearly responsible for death. Outcome of an adverse event which was not determined (judged, presumed) a direct cause of death observed in the same research subject is not considered as death. If outcome is death, the date of death shall be recorded.
Unknown	Follow-up specified in the protocol after the date of onset was not possible due to change of hospitals or relocation, etc.

10.2 Procedures

10.2.1 Collection and reporting of adverse events

10.2.1.1 Adverse event collection period

Collection of the adverse events shall commence at the start of administration of the study drug (Day 1) and shall continue until end of treatment (Day 29).

10.2.1.2 Reporting of adverse events

At each study visit, the principal investigator or investigator shall check for the presence of any onset of subjective symptoms. A neutral question, such as "How have you been feeling since your last visit?" may be asked to collect any adverse events that occurred between the previous and present visits.

The principal investigator or investigator shall follow up all research subjects experiencing an adverse event irrespective of the causal relationship with the study drug, until the symptom resolves, or any clinically significant abnormal laboratory values have returned to baseline or there is a satisfactory explanation for the change (permanent or irreversible adverse events). All adverse events shall be entered on the CRF. Adverse event term, onset date, resolution date, severity, causal relationship with the study drug (i.e. "Unrelated" or "Related"), action taken for the study drug, outcome, causal relationship with any study procedure (with specific procedure if assessed to be causally related), and seriousness shall be entered.

Follow-up period of adverse events shall be until recovery of the adverse events, or the time when the principal investigator or investigator judges that further follow-up would be unnecessary.

10.2.1.3 Reporting of adverse events of special interest (specific adverse events)

If AESI occurring during the AE collection period is considered to be clinically significant based on the criteria below, it should be reported to the sponsor (refer to the attachment for contact information) within 1 business day of first onset, or subject's notification of the event by the

principal investigator or investigator. AESI Form should be completed and signed (or signed and sealed) by the principal investigator and reported to the sponsor within 10 business days.

The criteria for AESIs (hypoglycemia-related AEs, intestinal obstruction-related AEs, acute pancreatitis-related AEs, and QT/QTc interval prolongation-related AEs) are as shown below. If any other AEs potentially related to the study drug occur, it will be considered whether to include them in the AESIs.

[Hypoglycemia-related AEs]

AEs related to hypoglycemia

[Intestinal obstruction-related AEs]

Intestinal obstruction, ileus, subileus, obstruction of the digestive tract, gastrointestinal motility disorder, impaired gastric emptying, and AEs related to these conditions

[Acute pancreatitis-related AEs]

AEs related to pancreatitis or acute pancreatitis

[QT/QTc interval prolongation-related AEs]

Torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation, ventricular flutter, consciousness disturbed, convulsion, ECG QT prolonged, and AEs related to these conditions

【Liver dysfunction or jaundice-related AEs】

Adverse events corresponding to ' Liver dysfunction related to drug - comprehensive search' in MedDRA standard search formula.

The AESIs have to be recorded as AEs in the CRF. A report along with all other required documentation must be submitted to the sponsor.

10.2.2 Collection and reporting of serious adverse events

When a serious adverse event develops during the period of collecting adverse events, it shall be reported according to the following procedures. At the time of onset of a serious adverse event or notification of the onset by the research subject, the principal investigator shall report the serious adverse event to the chief executive of the research implementing entity immediately, and the sponsor or CRO to whom the sponsor has entrusted responsibility shall notify the principal investigator of the research implementing entity.

The principal investigator shall then report the serious adverse event to the sponsor (for the contact information, refer to the attachment) within 1 day of notification of the event onset. Further, the principal investigator shall submit a formal report within 10 calendar days to the sponsor.

Furthermore, it shall be mandatory to include the contents below in the report to be submitted to the sponsor within 1 working day, and other items shall be reported as far as possible.

- Brief description of adverse event and the reason for why it was determined as serious
- Research subject ID number
- Name of principal investigator or the investigator
- Name of the study drug
- Determined causal relationship

The principal investigator or investigator shall report spontaneously reported serious adverse events that are collected even after the adverse event collection period to the sponsor.

10.2.3 Reporting of additional information concerning adverse events

If the sponsor requests provision of additional information concerning adverse events for reporting to regulatory authorities, the principal investigator or the investigator shall confirm the necessary additional information and enter in the EDC system or submit a report within the period specified by the sponsor.

10.3 Follow-up of serious adverse events

When information that was not included in the detailed report was obtained later, the principal investigator or investigator shall state it in the copy of the report on serious adverse events, or create another document and submit it to the contact address shown on the attached sheet within 1 working day. Relevant data collected at the research implementing entity (e.g., ECG charts, laboratory test values, discharge summary, postmortem results) shall be sent to the sponsor or the committee such as the IEC upon request.

The principal investigator or the investigator shall follow-up all serious adverse events, etc., until recovery is confirmed, or the final outcome is determined.

10.3.1 Reporting of serious adverse events to Ethics Review Committee, etc., and regulatory authorities

When the chief executive of the research implementing entity receives a report of a serious adverse event from the principal investigator, the chief shall consult the Ethics Review Committee, etc., and notify the research implementing entities that are conducting the clinical research through the sponsor or the CRO consigned by the sponsor.

If the serious adverse event reported by the principal investigator in which direct causal relationship cannot be denied with this study (the study drug) and is unexpected, the chief executive of the

research implementing entity shall prepare a written report of the unexpected serious adverse event containing the information reported by the principal investigator plus the information below, and submit the report to the Minister of Health, Labour and Welfare, and notify other clinical research implementing entities. (Reporting to the Minister of Health, Labour and Welfare via the sponsor, or notification to other clinical research implementing entities via the sponsor may also be possible)

- Actions taken for serious adverse events (discontinuation of new enrollment, revision of informed consent form, re-consents to other research subjects, etc.)
- Date of review, summery of review, result, necessary action, etc., related to Ethics Review Committee, etc.
- Notification to other research implementing entities

The sponsor shall report, in accordance with regulations, unexpected serious adverse drug reactions and other serious adverse events that are subject to emergency reporting to regulatory authorities, the principal investigators, and chief executives of the research implementing entities.

From the time point of first acknowledging the event or receiving additional information, the sponsor or the CRO consigned by the sponsor shall comply with regulatory required time frames for reporting, and make emergency reports concerning unexpected serious adverse drug reactions and expected serious adverse drug reactions to regulatory authorities. Also, the sponsor shall, in the same way, make an emergency report of other critical safety information that may have a major effect on the study drug risk-benefit, continuation of study drug administration, or continuation of clinical research. The research implementing entity shall submit copies of emergency report documents to the Ethics Review Committee, etc.

11.0 COMMITTEES ESTABLISHED FOR THIS STUDY

In this clinical research, none of Clinical Research Steering Committee, Data and Safety Monitoring Committee, or Central Assessment Committee shall be established.

12.0 DATA MANAGEMENT AND STORAGE OF RECORDS

Data management operations shall be performed according to the standard operating procedure by the data management department of the sponsor independent from the medical affairs department. Adverse events, medical history, and concurrent conditions shall be coded using MedDRA. Drugs shall be translated using the WHO Drug Dictionary.

12.1 Case report form

The principal investigator or investigator shall complete a CRF for each research subject who has signed the informed consent form.

The sponsor or its designee shall provide research implementing entities with access authorization to the electronic CRF. Before use of the electric CRF system, the sponsor shall provide training to the principal investigator, investigators, and study collaborators. The CRF shall be used to report the information collected during the study period to the sponsor. The CRF shall be made in Japanese. Data shall be directly entered in preparing the CRF.

A change or correction of the CRF shall be recorded as an audit trail that records the information before and after the change or correction, the person who made the change or correction, date of change or correction, and its reason.

The principal investigator shall ensure the accuracy and completeness of the CRF, and provide an electronic signature on the relevant page of the case report form. The principal investigator shall bear full responsibility for the accuracy and reliability of all data entered on the CRF.

The following data shall be recorded on the CRF directly. (Except if there is a description in the source material)

- Eligibility, end state, reason of termination, severity, degree, the causal relationship with the study drug or the study procedures, outcome of the adverse event.

The following data shall not be recorded on the CRF directly.

- Measurement results of CGM
- Laboratory result tested at central.

When the principal investigator or the investigator makes a change or correction in the data entered on the CRF after fixation of clinical data base, a record (Data Clarification Form) of change or correction on the CRF provided by the sponsor shall be used. The principal investigator shall confirm that the record of change or correction on the CRF is accurate and complete, and sign or write name/ affix a seal, and date it.

The sponsor or its designee shall confirm that CRFs have been made appropriately according to the procedures defined for each study. The sponsor or its designee shall have access to the medical records of the research subjects and in-house records to ensure the accuracy of the CRF as necessary. The completed CRF is the property of the sponsor, and the principal investigator or investigator shall not disclose the information to a third party without a written permission from the sponsor.

12.2 Timing of data entry into the electronic CRF system

The sponsor or its designee shall request the principal investigator and investigator to promptly enter data into the EDC at enrollment of the research subject, each visit during study treatment, completion/discontinuation of study treatment, and follow-up period. Details of deadlines for data entry shall be specified separately in a procedure manual.

12.3 Storage of records

The principal investigator or the chief executive of research implementing entity shall store the following materials, including those specified in section 12.1, and study-specific documents to be used by the regulatory authority and the sponsor or its designee for investigation and audit. The documents include research subject ID code, medical records, clinical study worksheets (if used), original signed and dated informed consent forms, the change and fix record of CRF (copy) and electric copies of electronic CRF including audit trail. The principal investigator and the chief executive of the research implementing entity shall appropriately retain the material/information related to this study for at least 5 years from the date of reporting the end of the research by the principal investigator, or for 3 years from the date of reporting final publication of the study result, whichever date is later. However, when the sponsor requires a longer storage period, the chief executive of the research implementing entity shall discuss the period and methods of storage with the sponsor.

13.0 STATISTICAL ANALYSIS METHODS

The person responsible for statistical analysis and the designee (a person employed by a CRO independent of the sponsor; the person in charge of analysis) shall conduct analyses. The sponsor will not be involved in statistical analyses.

13.1 Statistical and analytical plans

The person in charge of analysis shall prepare a statistical analysis plan (hereinafter referred to as SAP) before the acquisition of the informed consent of the earliest research subject, and issue the first edition. Detailed definition of endpoints and analysis methods should be specified in the SAP to deal with all the purposes of the research.

13.1.1 Analysis set

Two analysis sets, “full analysis set” and “Safety data analysis set” are used in this study. The “full analysis set" used as a primary analysis set in the efficacy analysis shall be defined as "the research subjects who were randomized and given at least one dose of the study drug." The “Safety data analysis set” shall be defined as "the research subjects who are given at least one dose of the study drug."

13.1.2 Analysis of demographic and other baseline characteristics

From the “full analysis set” primary research subject background items will be tabulated by each treatment group and by merging the treatment groups.

13.1.3 Efficacy analysis

[Primary endpoints]

- Changes in the SD of 24-hour blood glucose values (mg/dL) for each 7-day period between Week 3 and Week 4 (between Day 22 and Day 28) of the treatment period, calculated from the value at the start of the observation period

(Analysis method)

・For the “full analysis set”, summary statistics (number of subjects, mean, SDs, maximum values, minimum values, quartiles [same apply hereafter]) and 95% confidence interval (two sides) of mean shall be calculated for each treatment group at each evaluation point (each day), and illustrating changes in mean and SD in order to evaluate changes in the SD of 24-hour blood glucose values (mg/dL) for each 7-day period between Week 3 and Week 4 (between Day 22 and Day 28) of the treatment period, calculated from the value at the start of the observation period for treagliptin or alogliptin separately.

・Preliminary, for the “full analysis set”, calculate point estimation and 95% confidence interval (two

sides) in difference of mean in treatment groups (trelagliptin 100 mg group – alogliptin 25 mg group) in order to examine the influence of the once-weekly administration and blood glucose fluctuations due to the difference in the daily administration exploratory.

・As well, for the "full analysis set ," conduct analysis of covariance at each evaluation point with changes in the SD of 24-hour blood glucose values between Week 3 and Week 4 from the value at the start of the observation period as dependent variable, treatment groups as independent variable, HbA1c (NGSP value) at the start of the observation period, changes in the SD of 24-hour blood glucose values at the start of the observation period, and age as covariates, and calculate point estimation and 95% confidence interval (two sides) in difference of adjusted mean for each group.

・Preliminary, "full analysis set ," calculate point estimation and 95% confidence interval (two sides) in difference of adjusted mean in treatment groups (trelagliptin 100 mg group – alogliptin 25 mg group)

[Secondary endpoints]

- Changes in AUC over time when specific blood glucose levels (110, 140, 160, or 180 mg/dL) are observed during the 3 hour time period after breakfast, lunch and evening meal[*1, 2]
- Change in AUC over time during periods when blood glucose 140, 160, or 180 mg/dL (hyperglycemia) is observed[*1, 2]
- Changes in blood glucose 140, 160, or 180 mg/dL (hyperglycemia) over time[*1, 2]
- Changes in AUC over time during periods when blood glucose < 70 mg/dL (hypoglycemia) is observed[*1,2]
- Change in peak postprandial glucose levels over time 3 hours after breakfast, lunch, and evening meal[*1, 2]
- Change in maximum variation of blood glucose levels over time between before and after breakfast, lunch, and evening meal [*1, 2]
- Changes in MAGE[*1, 2]
- Changes in mean 24-hour blood glucose levels [*1, 2]
- Changes in mean daytime blood glucose levels[*1, 2]
- Changes in mean nocturnal blood glucose levels[*1, 2]
- Changes in AUC[*1, 2]
- Changes in AUC over time during periods when blood glucose 110 mg/dL is observed[*1,2]
- Changes in the SD of 24-hour blood glucose values[*1,2]
- Changes in the SD of mean daytime blood glucose values[*1,2]
- Changes in the SD of mean nocturnal blood glucose values[*1,2]

[*1]: Measured value and percent changes for the each 7-day period between Week 3 and Week 4 (between Day 22 and Day 28) of the treatment period calculated from the value at the start of

the observation period (however changes in the SD of 24-hour blood glucose values shall be measured value only)

*2: Percent change from the value at the start of the observation period to the mean value during the 7-day period between Week 3 and Week 4 (between Day 22 and Day 28) of the treatment period

(Analysis method)

- Conduct the same analysis as the primary endpoints for *1 and *2 of the above endpoint section. However, for changes in mean/SD, only measured values of *1 and *2 shall be illustrated.

[Other endpoints]

- Glycoalbumin
- 1,5-AG
- Fasting blood glucose
- Fasting insulin
- Fasting glucagon
- Fasting proinsulin
- FastingGLP-1
- Fasting GIP
- DPP-4 activity
- Inhibitory rate of DPP-4 activity

(Analysis method)

- Calculate summary statistics and 95% confidence interval (two sides) of mean at each evaluation point (the start of the observation period by each treatment group, first day, 1 point during fourth to sixth day, and ninth day of CGM which is to be performed for 9 days from Day 21) in measured values and changes from the start of the observation period, and illustrate changes in mean and SD

13.1.4 Conversion method of data and handling of missing data

Details shall be specified separately in the statistical analysis plan.

13.1.5 Significance level and confidence coefficient

Confidence coefficient: 95% (two-sided estimation)

13.1.6 Safety analysis

[Secondary endpoints]

- Adverse event

(Analysis method)

- Adverse events shall be reported using MedDRA terminology and summarized using the Preferred Term (PT) and System Organ Class (SOC) of the MedDRA. For the "safety data analysis set", frequency tabulation shall be conducted for adverse events after start of treatment with study drug by each treatment group.
    - Frequency tabulation of all adverse events
    - Frequency tabulation of adverse events that causal relationship is "related" to study drug.
    - Frequency tabulation of the degree of all adverse events
    - Frequency tabulation of degree of adverse events that causal relationship is "related" to study drug.
    - Frequency tabulation of adverse events that were "discontinued" as a measurement concerning study drug.
    - Frequency tabulation of serious adverse events

13.2 Criteria for interim analysis and premature discontinuation

No interim analysis is planned.

13.3 Determination of the number of planned research subject

Planned number of research subjects that are evaluable for primary endpoints in each group is as follows.

Trelagliptin 100 mg group: 15

Alogliptin 25 mg group: 15

Set in consideration with the feasibility of the number of research subjects for exploring the effects of trelagliptin 100 mg and alogliptin 25 mg on glycemic variation. It is not based on statistical power calculation.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Monitoring of the research implementing entity

The sponsor or its designee shall perform periodic monitoring of research implementing entities during the research to confirm that the research is conducted in accordance with all specifications in the research protocol. The data recorded on the CRF will be checked by comparing them with those in the source documents. Source documents are the original documents, data and records. The principal investigator and the chief executive of the research implementing entity shall ensure that the sponsor or its designee and the Ethics Review Committee, etc., have access to the source documents.

The sponsor or its designee shall access the records, including the list of research subject ID numbers, medical records of the research subjects, and signed and dated original consent forms to confirm that the research is appropriately conducted in compliance with the research protocol. Also, confirm the consistency between CRF and the related source documents. The principal investigator, investigator, and other personnel involved in the research shall spare sufficient time to facilitate monitoring procedures during visits to the research implementing entity.

Detailed procedures for monitoring shall be specified separately in a procedure manual.

14.2 Deviation from the Ethical Guidelines for Medical and Health Research Involving Human Subjects and the research protocol.

The principal investigator or investigator shall record all deviations from Ethical Guidelines for Medical and Health Research Involving Human Subjects, and research protocol.

If any deviation is found, the principal investigator shall promptly notify the chief executive of the research implementing entity for the clinical research and the sponsor. As necessary, the principal investigator will discuss protocol revisions with the sponsor to reach agreement. For protocol revisions, draft revisions should be submitted as early as possible to the chief executive of the research implementing entity for approval of the committee such as the IEC.

14.3 Quality assurance audits and regulatory agency inspections

The research implementing entity may be subject to audits by the sponsor or its designee. In such a case, the auditor designated by the sponsor shall contact the research implementing entity in advance to determine the date of audit. The auditor may ask to visit the facilities where laboratory specimens are collected and any other facilities used during the clinical research. In addition, this research may be inspected by regulatory agencies, including those of foreign governments (e.g., the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency [MHRA]). If the research implementing entity is contacted for an inspection by a regulatory

body, the sponsor should be notified promptly. The principal investigator and the chief executive of the research implementing entity shall ensure that the auditor has access to all the research-related source documents.

15.0 ETHICAL CONDUCT OF CLINICAL RESEARCH

This research shall be conducted with the highest respect for the individual participants (i.e., research subjects) according to the research protocol, and the ethical principles that have their origin in the Declaration of Helsinki, Ethical Guidelines for Medical and Health Research Involving Human Subjects. Each principal investigator shall conduct the study according to regulatory requirements and in accordance with "Responsibilities of the Investigator" in Appendix B.

15.1 Approval of the Ethical Review Board, etc.

The Ethical Review Board, etc., shall be constituted in accordance with the regulations.

The sponsor or its designee should obtain the document listing the name and title of each committee member. When a committee member directly participates in this clinical research, the document describing that he/she is not participating in deliberation or voting for the study shall be obtained.

The sponsor or its designee shall provide related documents for review and approval of the research protocol to the Ethical Review Board, etc. In addition to the research protocol, a copy of the informed consent form and information sheet, written materials related to research subject recruitment, advertisement, and other documents required by regulations, when necessary, shall be submitted to the central committee or a research implementing entity committee such as the Ethics Review Committee to obtain approval. The sponsor or its designee shall obtain records of approval by the Ethical Review Board, etc., for the research protocol and the informed consent form and information sheet before the start of the protocol therapy. The records of approval by the Ethical Review Board, etc., shall include the clinical research title, protocol number, preparation / revision date of the research protocol, and version number and approval date of other reviewed documents (example: informed consent and information sheet). The sponsor shall notify the research implementing entity, the principal investigator, and investigator after confirming the validity of the regulatory documents of the research implementing entity. Protocol procedures such as obtainment of consent shall not be started until the research implementing entity, the principal investigator, and investigator receive notification.

The research implementing entity shall observe all requirements that the Ethical Review Board, etc. prescribe. The requirements may include notifications to committees such as the IEC, for example, revision of the protocol, revision of the informed consent form and information sheet, revision of materials related to research subject recruitment, reports on safety in accordance with the regulatory requirements, reports on status of implementation of the research at intervals determined by a research implementing entity committee such as the Ethics Review Committee, and submission of the study completion report. The sponsor or its designee shall obtain written approval from a

research implementing entity committee such as the Ethics Review Committee related to the above mentioned items and all related materials.

15.2 Conflict of interest

This clinical research shall be conducted with the support of the sponsor.

Prior to the conduction of this clinical research, the investigators involved in this clinical research shall ensure appropriate management of any conflicts (COI) in the conduct of the research in accordance with the rules of the research implementing entity [11-15].

The research implementing entity shall comply with all requirements specified by a committee such as the Ethics Review Committee This includes the COI self-statement form, the research protocol, and the informed consent form and information sheet.

15.3 Informed consent and information sheet, and the agreement of the research subjects

The informed consent and information sheet form shall contain specific requirements of the Declaration of Helsinki, Ethical Guidelines for Medical and Health Research Involving Human Subjects and all applicable laws and regulations. The informed consent form and information sheet shall specify the use of personal information and medical information of research subjects in this clinical research (both in and outside Japan: supply to a third party), and disclosure. The informed consent form and the information sheet will explain in detail the nature of the research, its objectives, and potential risks and benefits. Also, the informed consent form will detail the requirements for participation and the fact that research subject is free to withdraw at any time without giving a reason and without any negative effect on the further medical care.

The principal investigator is responsible for the preparation, contents, and approval of the informed consent form and information sheet by the committee such as the IEC. The informed consent form and information sheet must be approved by the committee prior to use.

The informed consent form and information sheet shall be written in language that can be easily understood by the potential research subjects. The principal investigator or investigator shall be responsible for providing detailed explanation of the informed consent form and information sheet to the potential subjects. Information should be given in both oral and written form whenever possible and in manner deemed appropriate by the committee such as the IEC.

The principal investigator or investigator shall ensure that the potential research subjects have (1) an opportunity to inquire about the research and (2) sufficient time to decide on their participation. If a potential research subject decides he or she is willing to participate in the research, then the informed consent form must be signed and dated by the potential research subject prior to entering into the

research as a subject. The principal investigator or investigator shall instruct the potential research subject to sign using their legal names, not nicknames, using a blue or black ball point ink pen. Also the principal investigator or investigator shall sign and date the informed consent form prior to potential research subject entering into the research.

Once signed, the original informed consent form shall be retained by the principal investigator or investigator. The principal investigator or investigator shall record the date that the potential research subject signed the informed consent form in the subject’ s medical record. A copy of the signed informed consent form shall be given to the research subject.

If the informed consent form and information sheet is revised, the principal investigator or investigator shall newly obtain re-consent from the concerned research subject by following the same procedure as for obtaining the initial consent. The date of obtaining new consent shall be recorded in the research subject’ s medical record, and a copy of the revised consent form shall be provided to the research subject.

15.4 Personal information of the research subjects

The sponsor or the designee shall affirm the principle of the protection of research subjects' private/personal information, etc. Throughout this study, research subject ID numbers shall be used to link the subject's source data to the sponsor's research database and research-related documents. Limited information on research subjects such as gender, age, and date of birth may be used within the scope of all applicable laws and regulations for identification of research subjects and confirmation of accuracy of research subject ID number.

For verification of the conduct of the research in compliance with this protocol and the Ethical Guidelines for Medical and Health Research Involving Human Subjects, the sponsor shall require the principal investigator to provide the research sponsor’s designee, representatives of regulatory authorities, designated auditors, and committees such as the Ethical Review Board direct access to research subjects’ original medical records (source data or documents), including laboratory test results, ECG results, admission and discharge records during a subject’s research participation, and autopsy reports. The principal investigator or investigator shall obtain specific authorization from the research subject as part of the informed consent process for access to research subject's original medical records by research sponsor’s designee and representatives of regulatory authorities (see section 15.3).

When providing a copy of source documents to the sponsor, the principal investigator or investigator shall delete information that may lead to identification of an individual (name and address of research subject, other personal information not recorded on the CRF of the research subject).

15.5 Consultation windows for the research subjects or persons related to the research concerned

The principal investigator shall establish a contact service to respond to inquiries concerning this clinical research from research subjects or concerned people. Details of the contacts for inquiries will be described in the informed consent form.

15.6 Financial burden or reward to the research subjects

Of the expenses for this clinical research, the sponsor shall offer compensation for medical treatment not covered by health insurance as research expenses. The research subjects shall pay expenses for medical treatment covered by ordinary health insurance.

In addition, the principal investigator shall pay expenses such as transportation expenses for participation in this clinical research to the research subjects at each visit from the research funds. Details of the financial burden on the research subjects and rewards shall be described in the informed consent form.

15.7 Benefits and inconveniences to the research subjects

15.7.1 Benefits to research subjects

By participating in this clinical research, the research subjects may understand one’s own condition of type 2 diabetes mellitus in detail.

15.7.2 Inconveniences to research subjects

By participating in this clinical research the burden of the research subject may increase as number of visits will increase compared to daily medical care.

15.8 Attribution of research results and access rights

15.8.1 Attribution of research results

The research results and data obtained from this research shall belong to the sponsor. In addition, secondary use (meta-analysis, etc.) of the data obtained in this clinical research may be possible if used in such a way that the data shall not be linked to personal identification information.

15.8.2 Data access rights

Access rights for all data and information generated from this study will be given to personnel approved by the sponsor.

15.9 Reporting of results, publication, disclosure, and clinical research registration policy

15.9.1 Reporting of results, publication and disclosure

The principal investigator shall report a written summary of results of the research to the chief executive of the research implementing entity and provide the sponsor with all the results and data obtained from the research. Only the sponsor may disclose the research information to other principal investigators, investigators or regulatory authorities during the research period, except when required by laws and regulations. The sponsor shall be responsible for publication of the research protocol and research-related results (including the public web site) except for other cases permitted in the research contract.

During research period and after the end of research, the sponsor or its designee should promptly summarize the results and present it to medical journals and academic conferences, etc. The sponsor may publish any data or information obtained from the research (including data and information provided by the principal investigator) without obtaining consent of the principal investigator.

The principal investigator or the investigator should obtain the prior written approval from the sponsor when publishing the information obtained in this research at an academic conference, etc.

15.9.2 Clinical research registration

To ensure that information on clinical research is made accessible to the public in a timely manner and to comply with applicable laws, regulations, and guidelines, Takeda Pharmaceutical Company Limited shall register all clinical research being conducted in patients around the world at public trial registration sites, including at least the website(s) of ClinicalTrials.gov (and) Japan Pharmaceutical Information Center Clinical Trials Information (JAPIC). On such websites, the research location (city, country), subject recruitment status, and contact information for Takeda Pharmaceutical Company Limited are open to the public.

15.9.3 Clinical trial results disclosure

Takeda Pharmaceutical Company Limited shall post the research results, irrespective of the nature of the results, at the public trial registration site(s) of Clinical Trials.gov (and) JAPIC in accordance with applicable laws and regulations.

15.10 Insurance and compensation for injury

The research subjects participating in this research shall be compensated for any injury resulting from participation in the research according to local regulations applicable to the research

implementing entity. The sponsor or its designee shall buy an insurance policy to compensate for health injury in research subjects.

Healthy injury in a research subject will be compensated as specified in the study contract. Compensation-related questions by the principal investigator or investigators should be made to the sponsor or its designee.

16.0 REFERENCES

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2. Gerstein HC. et al; The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. The New England Journal of Medicine. 2008; 358: 2545-2559.

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4. Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterology. 2007; 132(6): 2131-2157.

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11. Report of the Working Group on Conflict of Interest (Ministry of Education, Culture, Sports, Science and Technology dated November 1, 2002)

12. Guidelines for determining the conflict of interest polity for clinical research (Review group for ethical aspects of clinical research and conflict of interest, March 2006)

13. Guidelines on the Management of Conflict of Interest (COI) in Health and Labour Sciences Research (March 31, 2008)

14. Guidelines for management of COI in medical research (COI Committee of Japan Association of Medical Sciences, February 2011)

15. Common guidelines for conflict of interest (COI) in clinical research (Japanese Society of Internal Medicine, Japan Society of Hematology, Japanese Circulation Society, Japan Endocrine Society, Japan Diabetes Society, Japanese Respiratory Society, Japanese Society of Hematology, Japanese Society of Allergology, Japanese Association for Infectious Diseases, Aug 2011)

Appendix A Schedule of Research Procedures

		Observation period		Treatment period				
Time of Visit	Week			0			4	Discontinuation[g]
	Day	-14	-2	1[b]	21[c]	24[c]	29[c]	-
Allowable range (Day)		-28 to -2	-2	1	21 to 35	24~39[f]	29 to 43	-
VISIT Number			1	2	3	4	5	-
Informed consent procedure		×						
Inclusion/Exclusion criteria		×	×					
Demographic information		×						
Medical history, pre-treatment		×	×					
Physical examination		×	×	(×)	×	×	×	×
Body weight, BMI			×		×		×	×
Height		×						
Concomitant drugs		×	×	(×)	×	×	×	×
Concurrent disease		×	×					
Laboratory tests [a]			×		×	×	×	×
HbA1c			×					
Drug -taking status					×	×	×	×
Prescription of dietetic therapy and exercise therapy and assessment of compliance		×	×	(×)	×	×	×	×
CGM			×[d] (Sensor insertion)	×[d] (Sensor remove)	×[d] (Sensor insertion)	×[d] (Exchange sensor)	×[d] (Sensor remove)	
Self-measurement of blood glucose			×[e]	×[e]	×[e]	×[e]	×[e]	
Adverse event monitoring				×				

(a) Measured on VISIT1 (Day-2), and the first and ninth days of the 9-day CGM starting on Day 21

Blood tests: glycoalbumin, 1,5-AG, fasting insulin, fasting glucagon, fasting proinsulin, fasting GLP-1, fasting GIP*, DPP-4 activity

Measured on 1 point during fourth and sixth day of the 9-day CGM starting on Day 21

Blood tests: fasting GLP-1, fasting GIP, DPP-4 activity

(b) The starting day of study treatment in the treatment period is designated as Day 1. The study drug shall be administered after required tests/observations, etc. The day before the start of study treatment in the treatment period is designated as Day -1. It is performed at the visit when principal investigator or investigator consider as needed.

(c) Trelagliptin 100 mg/week group shall insert the sensor on the day before Trelagliptin administration day. Trelagliptin 100 mg/week shall be administered before breakfast on the day after the sensor insertion day.

Alogliptin 25 mg/day shall be administered after required tests/observations, etc at every VISIT without taking study drug. Research subjects shall take study drug prior to the every breakfast at home.

(d) To be performed by study site personnel

(e) At least, blood glucose levels shall be measured at three time points on the first day of CGM ([1] at least 2 hours after the recorder is connected and [2] 2 hours after the first is measured. [3] at bedtime) and at four time points from the second day onward ([1] before breakfast, (2) before lunch, (3) before evening meal, and (4) at bedtime).

(f) After taking trelagliptin 100 mg/week or alogliptin 25 mg/day on the nest day from sensor insertion on Visit3 (Day 21), research subjects should visit the study site between the third day and the fifth day.

(g) To be performed to the extent possible

Appendix B Responsibilities of the sponsor

1. To appropriately conduct the clinical research in compliance with this research protocol and the Ethical Guidelines for Medical and Health Research Involving Human Subjects and with the highest respect for human rights, safety, and welfare of research subjects.
2. To prepare a list of any other investigators and/or research collaborators when certain important research-related activities are divided by investigators and/or research collaborators, and submit the list to the sponsor as required.
3. To prepare the informed consent form and revise it as necessary.
4. To check the contents of the study contract.
5. To provide sufficient information on the protocol, drug and duties of each personnel to subinvestigators and study collaborators, and give guidance and supervision.
6. To select research subjects who satisfy the inclusion criteria, give explanation using written information, and obtain consent in writing.
7. To be responsible for all medical judgments related to the research.
8. Corresponding to request from the chief executive of the research implementing entity, to report the latest progress status at least once a year to the chief executive of the research implementing entity.
9. To ensure that the most update status is confirmed and comprehended regarding the COI of the investigators participating in the clinical research according to the research implementing entity.
10. To ensure, together with the chief executive of the research implementing entity, that sufficient medical care is provided to research subjects for all research-related clinically problematic adverse events throughout the period of subjects' research participation and thereafter.
11. When a research subject is treated at another medical institution or department, to inform the acting physician at the medical institution or department in writing of the research subject's study participation and research completion/discontinuation after obtaining the research subject's consent, and prepare a record.
12. When emergency reporting of serious adverse events, is required, to immediately report it in writing to the chief executive of the research implementing entity and the sponsor.
13. To ensure that the CRFs are accurate and complete, electronically sign and submit them to the sponsor.
14. To verify any entries on the CRFs made by the investigator or transcribed by the collaborator from source documents, electronically sign and submit them to the sponsor.
15. To discuss a revision of the protocol, etc., when proposed by the sponsor.

16. To report the research completion in writing to the chief executive of the research implementing entity.
17. To receive continuing education and training for conducting the study properly including Ethical Guideline and GCP during the study period (at least once a year is recommended).

PROTOCOL

An exploratory study to evaluate the effects of Trelagliptin and Alogliptin by CGM on glucose variability for one week with type 2 diabetes mellitus (TRACK)

Sponsor	Takeda Pharmaceutical Company Limited 2-12-10 Nihonbashi, Chuo-ku, Tokyo
Protocol number	Trelagliptin-4001
Version number	Initial Version
Study drug:	Trelagliptin Alogliptin
Creation date	Mar 29, 2016

1.0 CLINICAL STUDY PRINCIPLES AND CLINICAL STUDY MANAGEMENT INFORMATION

1.1 Clinical Study Principals

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- Ethical Guideline for Clinical Research (the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labor and Welfare, December 22, 2014).
- Good Clinical Practice: Consolidated Guideline (ICH. E6)
- All applicable laws and regulations, including, without limitation, data privacy laws and conflict of interest guidelines.

1.2 CLINICAL STUDY ADMINISTRATIVE STRUCTURE

This study will be conducted under the administrative structure described in the attached sheet 1 in accordance with the protocol prepared and planned by the sponsor.

Table of Contents

2.0 STUDY SUMMARY

<table>
<tr><td>Sponsor:
Takeda Pharmaceutical Company Limited</td><td>Study drug:
Trelagliptin
Alogliptin</td></tr>
<tr><td colspan="2">Study title:
An exploratory study of the effects of trelagliptin and alogliptin on glycemic variation in patients with type 2 diabetes mellitus</td></tr>
<tr><td colspan="2">Protocol number: Trelagliptin-4001 (122/NRP-001)</td></tr>
<tr><td colspan="2">Clinical study design:
This is a multi-center, randomized, open-label, parallel-group comparative, exploratory study to evaluate the effect of trelagliptin administered at a dose of 100 mg once weekly or alogliptin administered at a dose of 25 mg once daily for 4 weeks on glycemic variation in patients with type 2 diabetes mellitus using continuous glucose monitoring (CGM).
After informed consent, patients determined to be eligible for this study based on the eligibility assessment will be randomized to either the trelagliptin 100 mg group or the alogliptin 25 mg group (at a ratio of 1:1), using "HbA1c at the start of the observation period (< 7.5% or ≥ 7.5%)" and age (< 65 or ≥ 65) as a stratification factor for randomization.
The total duration of evaluation will be 31 days, consisting of the observation period for 2 days and a treatment period for 29 days (4 weeks). CGM will be performed on research subjects on an outpatient basis (in 2 assessments) for 2 days from the start of the observation period (Day -2) and for 9 days from Day 21 of the treatment period.</td></tr>
<tr><td colspan="2">Objective:
To evaluate the effect of trelagliptin administered orally at a dose of 100 mg once weekly or alogliptin administered orally at a dose of 25 mg once daily for 4 weeks on glycemic variation in an exploratory manner and as preliminary to examine the influence of the once-weekly administration and blood glucose fluctuations due to the difference in the daily administration in patients with type 2 diabetes mellitus</td></tr>
<tr><td colspan="2">Study population:
Patients with type 2 diabetes mellitus</td></tr>
<tr><td>Planned number of research subjects:
The planned minimum number of research subjects evaluable for the primary endpoint in each group is as follows:
Trelagliptin 100 mg group: 15
Alogliptin 25 mg group: 15</td><td>Number of study research implementing entities:
3 medical institutions</td></tr>
</table>

Total: 30	
Dose and method of administration: Trelagliptin 100 mg once weekly or alogliptin 25 mg once daily, taken orally before breakfast	**Route of administration:** Oral
Duration of treatment: 4 weeks	**Duration of evaluation:** 31 days (observation period for 2 days and treatment period for 4 weeks [29 days])

Inclusion criteria

1. Research subjects who, in the opinion of the principal investigator or the investigator, are capable of understanding the content of the clinical research and complying with the research protocol requirements.
2. Patients who are able to sign and date the informed consent form and information sheet prior to the start of study procedures
3. Patients diagnosed with type 2 diabetes mellitus
4. Patients with an HbA1c (NGSP value) value ≥ 6.5% and < 8.5% at the start of the observation period (Day -2)
5. Patients who experience a ≤ ±1.0% change in HbA1c (NGSP value) at the start of the observation period (Day -2) as compared with an HbA1c value obtained during the preceding 4 weeks
6. Patients receiving stable dietetic therapy and exercise therapy (if performed) for ≥ 4 weeks before the start of the observation period
7. Patients, who in the opinion of the principal investigator or the investigator, does not have to change (including discontinuation or interruption) HMG-CoA reductase inhibitors or add new HMG-CoA reductase inhibitors during treatment period.
8. Men or women aged 20 years or older at the time of informed consent

Exclusion criteria:

1. Patients who received anti-diabetic medications within 4 weeks prior to the start of the observation period
2. Patients who have changed (including discontinuation or interruption) HMG-CoA reductase inhibitors or received new HMG-CoA reductase inhibitors ≤ 4 weeks before the start of the observation period.
3. Patients with clinically evident hepatic dysfunction (e.g., AST or ALT ≥ 2.5-fold the upper limit of normal at the start of the observation period [Day -2])

4. Patients with moderate renal dysfunction, severe renal dysfunction or renal failure (e.g., creatinine clearance < 50 mL/min or serum creatinine > 1.4 mg/dL in men or > 1.2 mg/dL in women [equivalent to the creatinine clearance for persons aged 60 years with a body weight of 65 kg] at the start of the observation period [Day -2])
5. Patients with severe heart disease, cerebrovascular disorder, or severe pancreatic, hematologic or other diseases
6. Patients with a history of gastric or small intestinal resection
7. Patients with proliferative diabetic retinopathy
8. Patients warranting insulin therapy for glycemic control (e.g., patients with severe ketosis, diabetic coma or precoma, type 1 diabetes mellitus, severe infection, perioperative patients, or serious trauma)
9. Patients with a history of hypersensitivity or allergy to DPP-4 inhibitors
10. Patients who experience an allergic reaction to metal during CGM at the start of the observation period (Day -2)
11. Patients with any malignant tumors
12. Habitual drinkers whose average daily alcohol consumption is > 100 mL
13. Patients who have any contraindications for the study drug or are taking any contraindicated concomitant drugs listed in the package insert
14. Patients anticipated to require any prohibited concomitant medications during the study period
15. Patients who are day and night lifestyle reversal
16. Patients participating in any other clinical studies at the time of informed consent for this study
17. Pregnant women, nursing mothers, women who are possible pregnant, or women who plan to become pregnant
18. Other patients who are considered inappropriate for participation in this study in the opinion of the principal investigator or investigator

Endpoints:

<Primary endpoints>

- Changes in the standard deviation (SD) of 24-hour blood glucose values (mg/dL) for each 7-day period between Week 3 and Week 4 (between Day 22 and Day 28) of the treatment period, calculated from the value at the start of the observation period

Secondary endpoints

Efficacy endpoints:

- Changes in AUC over time when specific blood glucose levels (110, 140, 160, or 180 mg/dL) are observed during the 3 hour time period after breakfast, lunch and evening meal[*1, 2]
- Change in AUC over time during periods when blood glucose 140, 160, or 180 mg/dL

(hyperglycemia) is observed[*1, 2]

- Changes in blood glucose 140, 160, or 180 mg/dL (hyperglycemia) over time[*1, 2]
- Changes in AUC over time during periods when blood glucose < 70 mg/dL (hypoglycemia) is observed[*1,2]
- Change in peak postprandial glucose levels over time 3 hours after breakfast, lunch, and evening meal[*1,2]
- Change in maximum variation of blood glucose levels over time between before and after breakfast, lunch, and evening meal[*1,2]
- Changes in MAGE[*1, 2]
- Changes in mean 24-hour blood glucose levels[*1, 2]
- Changes in mean daytimeblood glucose levels[*1, 2]
- Changes in mean nocturnal blood glucose levels[*1, 2]
- Changes in AUC[*1, 2]
- Changes in AUC over time during periods when blood glucose 110 mg/dL (hypoglycemia) is observed[*1,2]
- Changes in the SD of 24-hour blood glucose values[*1,2]
- Changes in the SD of daytime blood glucose values[*1,2]
- Changes in the SD of nocturnal blood glucose values[*1,2]

[*1]: Measured value and percent changes for each 7-day period between Week 3 and Week 4 (between Day 22 and Day 28) of the treatment period calculated from the value at the start of the observation period (however changes in the SD of 24-hour blood glucose values shall be measured value only)

[*2]: Measured value and percent change from the value at the start of the observation period to the mean value during the 7-day period between Week 3 and Week 4 (between Day 22 and Day 28) of the treatment period

[Safety endpoint]

- Adverse events

<Other endpoints>

- Glycoalbumin
- 1,5-AG
- Fasting blood glucose
- Fasting insulin
- Fasting glucagon
- Fasting proinsulin

- Fasting GLP-1
- Fasting GIP

Statistical method

(1) Analysis set

Two analysis sets, “full analysis set” and “safety data analysis set” are used in this study. "The Full Analysis Set" used as a primary analysis set in the efficacy analysis shall be defined as "the research subjects who were randomized and given at least one dose of the study drug." The safety data analysis set shall be defined as “the research subjects who were given at least one dose of the study drug”.

(2) Efficacy analysis

<Primary endpoints>

- For the “full analysis set”, summary statistics (number of subjects, mean, SDs, maximum values, minimum values, quartiles [same apply hereafter]) and 95% confidence interval (two sides) of mean shall be calculated for each treatment group at each evaluation point (each day), and illustrating changes in mean and SD in order to evaluate changes in the SD of 24-hour blood glucose values (mg/dL) for each 7-day period between Week 3 and Week 4 (between Day 22 and Day 28) of the treatment period, calculated from the value at the start of the observation period for treagliptin or alogliptin separately.Preliminary, for the “full analysis set”, calculate point estimation and 95% confidence interval (two sides) in difference of mean in treatment groups (trelagliptin 100 mg group – alogliptin 25 mg group) in order to examine the influence of the once-weekly administration and blood glucose fluctuations due to the difference in the daily administration exploratory.
- As well, for the “full analysis set ,” conduct analysis of covariance at each evaluation point with changes in the SD of 24-hour blood glucose values between Week 3 and Week 4 from the value at the start of the observation period as dependent variable, treatment groups as independent variable, HbA1c (NGSP value) at the start of the observation period, changes in the SD of 24-hour blood glucose values at the start of the observation period, and age as covariates, and calculate point estimation and 95% confidence interval (two sides) in difference of adjusted mean for each group.
- Preliminary, “full analysis set ,” calculate point estimation and 95% confidence interval (two sides) in difference of adjusted mean in treatment groups (trelagliptin 100 mg group – alogliptin 25 mg group)

Secondary endpoints

- Conduct the same analysis as the primary endpoints for *1 and *2 of the each endpoint section. However, for changes in mean/SD, only measured values of *1 and *2 shall be illustrated.

Additional endpoints:

- For the “full analysis set”, while calculating summary statistics and 95% confidence interval (two sides) of mean at each evaluation point (the start of the observation period by each treatment group, first and ninth of CGM which is to be performed for 9 days from Day 21) in measured values and changes from the start of the observation period, and illustrate changes in mean and SD.

(3) Safety analysis

- Adverse events shall be reported using MedDRA terminology and summarized using the Preferred Term (PT) and System Organ Class (SOC) of the MedDRA. For the “safety data analysis set”, frequency tabulation shall be conducted for adverse events after start of treatment with study drug by each treatment group:
  - Frequency tabulation of all adverse events
  - Frequency tabulation of adverse events that causal relationship is “related” to study drug.
  - Frequency tabulation of the degree of all adverse events
  - Frequency tabulation of degree of adverse events that causal relationship is “related” to study drug.
  - Frequency tabulation of adverse events that were “discontinued” as a measurement concerning study drug.
  - Frequency tabulation of serious adverse events

Rationale for the number of planned research subjects:

The planned minimum number of research subjects evaluable for the primary endpoint in each group is as follows:

Trelagliptin 100 mg group: 15

Alogliptin 25 mg group: 15

Set in consideration with the feasibility of the number of research subjects for exploring the effects of trelagliptin 100 mg and alogliptin 25 mg on glycemic variation. It is not based on statistical power calculation.

3.0 ABBREVIATION

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	Area under the curve
1,5-AG	1,5-anhydroglucitol
BMI	body mass index
CGM	continuous glucose monitoring
COI	conflict of interest
CRO	contract research organization
DPP-4	dipeptidyl-peptidase-4
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon like peptide-1
HbA1c	hemoglobin A1c
ICH	International Conference on Harmonisation
MAGE	Mean Amplitude Glycemic Excursions
MedDRA	Medical Dictionary for Regulatory Activities
PT	prefferd term
SAE	serious adverse event
SD	standard deviation
SMBG	Self Monitoring of Blood Glucose
SOC	system organ class
WHO	World Health Organaization

4.0 INTRODUCTION

4.1 Background

Conventionally, although HbA1c has been used as an indicator for glycemic control for patients with diabetes mellitus, it has been indicated that it is insufficient for inhibiting cardiovascular events by only controlling HbA1c which reflects the long term glycemic variation[1-3] On the other hand, it has been reported that persistent hyperglycemia and the range of glycemic variation is related to oxidative stress and cardiovascular events, and it has been indicated that treatment is necessary in consideration of daily glycemic variation[4-6]. Also, it is anticipated that the glycemic variation of patients with diabetes mellitus and the characteristics of each anti-diabetic medications may be revealed and to be able to make a choice for a more appropriate treatment.

Self-measurement of blood glucose (SMBG) is used frequently for measuring glycemic variation and although one may understand the blood glucose level at the time of measurement, it is difficult to know if the blood glucose level has an upward trend or not changing or a downward trend at that time point, and it is reported that 80% hypoglycemia or hyperglycemia may be missed[7,8]. That is why the continuous glucose monitor (CGM) was developed and it became possible to accurately evaluate variance of blood glucose which was difficult and planning of treatment course according to each patient's condition is anticipated. Actually, in many researches that was conducted to collect various glycemic variation patterns to verify the optimization of treatment of diabetes mellitus, the benefits of various indicators of glycemic variation obtained from CGM has been reported[9].

Dipeptidyl-peptidase-4 (DPP-4) inhibitors are used widely as oral treatment drug for type 2 diabetes mellitus and it has an effect to promote insulin secretion blood glucose dependently by raising blood concentration of glucagon like peptide-1 (GLP-1). Conventionally, although DPP-4 inhibitors are taken once to twice daily commonly, once weekly trelagliptin was developed for a new treatment option as good glycemic control from improvement of drug compliance rate and flexibility of timing of taking drug according to lifestyle and further improvement of Quality Of Life(QOL) from less number of doses was in need. The phase III clinical study conducted at the development stage has shown that trelagliptin, when administered for 24 weeks, was not inferior to alogliptin, a DPP-4 inhibitor used as control, in terms of the change in HbA1c at the end of the treatment period [10]. However, effect on glycemic variation of trelagliptin and alogliptin has not been clarified efficiently, and it is anticipated that understanding the characteristics of once weekly DPP-4 inhibitors and once daily DPP-4 inhibitors may be an efficient rational for therapeutical use.

4.2 Rationale for the proposed research

Because there is no enough evidence assayed for glycemic variation of not only once weekly DPP-4 inhibitors but also once daily DPP-4 inhibitor, Trelagliptin, once weekly DPP-4 inhibitor, and Alogliptin, once daily DPP -4 inhibitor, were set as study drugs to collect the consecutive data of glycemic variation obtained from CGM and to evaluate difference of DPP-4 inhibitors.

Although trelagliptin was non-inferior to alogliptin, once daily DPP-4 inhinitor, in terms of the change from baseline in HbA1c at the phase III clinical study conducted during the development period, the effect on glycemic variation of alogliptin have to be clarified when the effect of different dose and method of administraion of DPP-4 inhibitors on glycemic variation would like to be evaluated.

In this present study, therefore, the effect of once weekly trelagliptin or once daily alogliptin on glycemic variation will be evaluated in patients with type 2 diabetes mellitus in an exploratory manner as a primary objective, and the effect by difference of dose and method of administraion on glycemic variation will be evaluated as secondary as far as possible.

5.0 RESEARCH OBJECTIVES AND ENDPOINTS

5.1 Objectives

To evaluate the effect of trelagliptin administered orally at a dose of 100 mg once weekly or alogliptin orally administered at a dose of 25 mg once daily for 4 weeks on glycemic variation in an exploratory manner as a primary objective and to evaluate, as far as possible, the effect of difference method of administration of DPP-4 on glycemic variation as secondary objective.

5.2 Definition of endpoints

5.2.1 Primary endpoints

Changes in the standard deviation (SD) of 24-hour blood glucose values (mg/dL) for each 7-day period between Week 3 and Week 4 (between Day 22 and Day 28) of the treatment period, calculated from the value at the start of the observation period

5.2.2 Secondary endpoints

(1) Efficacy:

- Changes in AUC over time when specific blood glucose levels (110, 140, 160, or 180 mg/dL) are observed during the 3 hour time period after breakfast, lunch and evening meal
- Change in AUC over time during periods when blood glucose 140, 160, or 180 mg/dL (hyperglycemia) is observed
- Changes in blood glucose 140, 160, or 180 mg/dL (hyperglycemia) over time
- Changes in AUC over time during periods when blood glucose < 70 mg/dL (hypoglycemia) is observed
- Change in peak postprandial glucose levels over time 3 hours after breakfast, lunch, and evening meal
- Change in maximum variation of blood glucose levels over time between before and after breakfast, lunch, and evening meal
- Changes in MAGE
- Changes in mean 24-hour blood glucose levels
- Changes in mean daytimeblood glucose levels
- Changes in mean nocturnalblood glucose levels

- Changes in AUC
- Changes in AUC over time during periods when blood glucose 110 mg/dL is observed
- Changes in the SD of 24-hour blood glucose values
- Changes in the SD of daytime blood glucose values
- Changes in the SD of nocturnal blood glucose values

(2) Safety: Adverse events

5.2.3 Other endpoints

(1) Efficacy:

- Glycoalbumin
- 1,5-AG
- Fasting blood glucose
- Fasting insulin
- Fasting glucagon
- Fasting proinsulin
- FastingGLP-1
- Fasting GIP

6.0 CLINICAL RESEARCH DESIGN

6.1 Clinical research design

<Clinical study design>

This is a multi-center, randomized, open-label, parallel-group comparative, exploratory study to evaluate the effect of trelagliptin administered at a dose of 100 mg once weekly or alogliptin at a dose of 25 mg once daily for 4 weeks on glycemic variation in patients with type 2 diabetes mellitus using continuous glucose monitoring (CGM).

<Research TREATMENT>

After informed consent, patients determined to be eligible for this study based on the eligibility assessment will be randomized to either the trelagliptin 100 mg group or the alogliptin 25 mg group (at a ratio of 1:1), using "HbA1c at the start of the observation period (< 7.5% or ≥ 7.5%)" and age (< 65 or ≥ 65) as a stratification factor for randomization.

The principal investigator or investigator shall prescribe trelagliptin 100 mg/week or alogliptin 25 mg/day according to the allocation results notified from the enrollment center.

Trelagliptin 100 mg once weekly or alogliptin 25 mg once daily, taken orally before breakfast

Planned number of research subjects:

The planned minimum number of research subjects evaluable for the primary endpoint in each group is as follows:

Trelagliptin 100 mg group: 15
Alogliptin 25 mg group: 15

Number of study research implementing entities:

3 medical institutions

<Duration of evaluation and number of visits of research subjects>

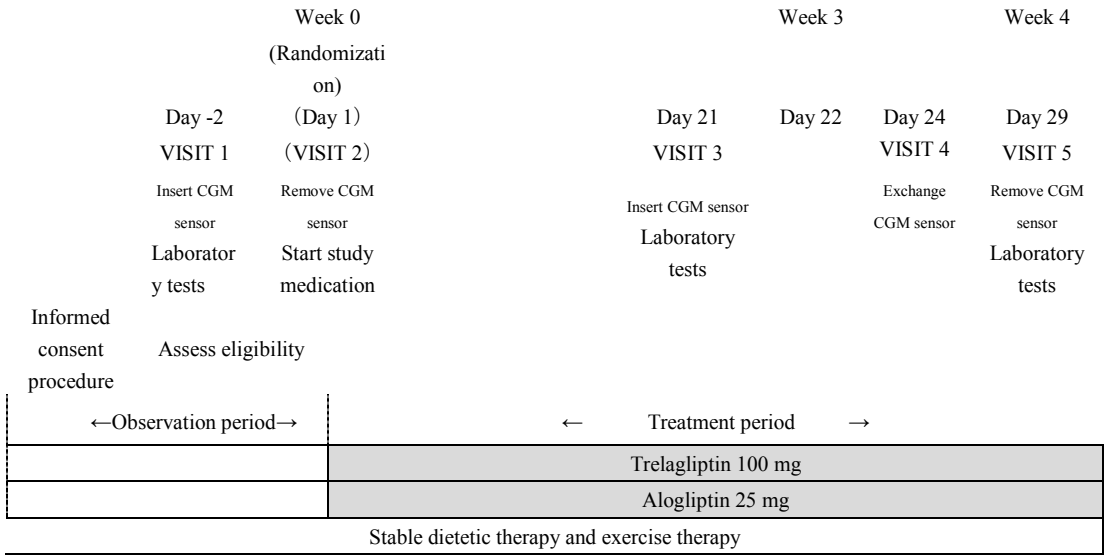
Duration of evaluation: 31 days, consisting of the observation period for 2 days and a treatment period for 29 days (4 weeks).

Number of visits: a total of 5 visits. Research subjects shall visit the study site at the start of the observation period (VISIT 1: Day-2), at the start of the treatment period (VISIT 2: Day 1), during the treatment period for CGM insertion (VISIT 3: Day 21) and for CGM sensor exchange (VISIT 4: Day 24), and at the end of the treatment period (VISIT 5: Day 29).

Figure 6 (a) shows a schematic of the clinical research design. Refer to Appendix A for schedule of examinations, observations, and assessments.

Figure6.a Outline of clinical research design

< Outline of clinical research >



*: In the trelagliptin 100 mg group, a sensor shall be inserted on the day before dosing.

6.2 Rationale for the clinical research design

(1) Rationale for the clinical research design

Because there is no enough evidence assayed for glycemic variation of not only once weekly DPP-4 inhibitors but also once daily DPP-4 inhibitor, Trelagliptin, once weekly DPP-4 inhibitor, and Alogliptin, once daily DPP -4 inhibitor, were set as study drugs to collect the consecutive data of glycemic variation obtained from CGM and to evaluate difference of DPP-4 inhibitors.

Although trelagliptin was non-inferior to alogliptin, once daily DPP-4 inhinitor, in terms of the change from baseline in HbA1c at the phase III clinical study conducted during the development period, the effect on glycemic variation of alogliptin have to be clarified when the effect of different dose and method of administraion of DPP-4 inhibitors on glycemic variation would like to be evaluated.

In this present study, therefore, the effect of once weekly trelagliptin or once daily alogliptin on glycemic variation will be evaluated in patients with type 2 diabetes mellitus in an exploratory manner as a primary objective, and the effect by difference of dose and method of administraion on glycemic variation will be evaluated as secondary as far as possible.

Therefore this unblind study was designed to objectively evaluate the effect on glycemic variation of trelagliptin 100 mg and alogliptin 25 mg administered in patients with type 2 diabetes mellitus. And also to evaluate the effect of different method of administraion on glycemic variation, stratified randomization comparison method between 2 groups was adopted with "HbA1c at the start of the observation period (< 7.5% or ≥ 7.5%) and age (< 65 or ≥ 65)" as a stratification factor for randomization.

Also, to exclude effect on glycemic variation from other anti-diabetic medications, research subjects who were taking anti-diabetic medications ≤ 4 weeks before start of observation period were excluded.

(2) Rationale for dosage

The dosages of trelagliptin and alogliptin were set at 100 mg/week and 25 mg/day, respectively, to evaluate glycemic variation at the usual dosage in clinical settings.

(3) Rationale for dosage

Study drugs show the glucose lowering effect by increasing incretin which are secreted by food intake. Thus, in order to eliminate the influence on the blood glucose by food intake. To further unify the administration timing of the research subjects prior to breakfast in terms of evaluating their glycemic variation.

(4) Rationale for duration of treatment

From the results of trelagliptin and alogliptin in phase II and III trials, duration was set at 4 weeks taking into account that the effect on blood glucose levels stabilize after 2 to 4 weeks with either drugs.

(5) Rationale for the number of planned research subjects:

Refer section 13.3

6.3 Premature termination of entire clinical research or premature termination of clinical research at a research implementing entity

6.3.1 Premature termination criteria of entire clinical research

The sponsor should immediately discontinue the study when at least one of the following criteria is applicable:

- When new information or other evaluation on the safety or efficacy of the study drug becomes available that shows a change in the known risk/benefit profile of the concerned compound, and risks/benefits are no longer tolerable for research subject participation in the study.

- When there is serious deviation from ethical guidelines or ICH-GCP that may threaten safety of the research subjects.

6.3.2 Criteria for premature termination of research implementing entities

A study site may be notified by the sponsor to discontinue clinical study if the site (including the principal investigator) is found in significant violation of Ethical Guideline for Clinical Research, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures of clinical study suspension and premature termination of entire clinical study or study at a research implementing entity

In the event that the sponsor or a research implementing entity committee such as an ethics review committee decides to prematurely suspend or terminate the entire clinical study or clinical study at a research implementing entity, a study-specific procedure shall be provided by the sponsor. The procedure shall be followed by applicable research implementing entities during the course of clinical study suspension or premature termination.

6.4 Procedures for protocol revision

If the protocol needs to be revised, the sponsor shall consider and decide whether to revise the protocol.

The principal investigator of each research implementing entity shall be informed of the details of each protocol revision. Also, principal investigators shall confirm the content of the revision of the protocol and submit a letter of agreement to the sponsor as evidence of agreement with the protocol revision.

Upon notification, the principal investigator at each research implementing entity shall submit the revised contents to committees such as the IEC, as necessary according to institutional regulations for review, and obtain approval from the director of the entity.

7.0 SELECTION AND WITHDRAWAL CRITERIA OF RESEARCH SUBJECTS

7.1 Inclusion criteria

Research subjects shall fulfill all of the following criteria to be included in this clinical study:

1. Research subjects who, in the opinion of the principal investigator or the investigator, are capable of understanding the content of the clinical research and complying with the research protocol requirements.
2. Patients who are able to sign and date the informed consent form and information sheet prior to the start of study procedures
3. Patients diagnosed with type 2 diabetes mellitus
4. Patients with an HbA1c (NGSP value) value ≥ 6.5% and < 8.5% at the start of the observation period (Day -2)
5. Patients who experience a ≤ ±1.0% change in HbA1c (NGSP value) at the start of the observation period (Day -2) as compared with an HbA1c value obtained during the preceding 4 weeks
6. Patients receiving stable dietetic therapy and exercise therapy (if performed) for ≥ 4 weeks before the start of the observation period
7. Patients who in the opinion of the principal investigator or the investigator, does not have to change (including discontinuation or interruption) HMG-CoA reductase inhibitors or addition of new HMG-CoA reductase inhibitors during treatment period.
8. Men or women aged 20 years or older at the time of informed consent

[Rational for the inclusion criteria]

1.2. These were set as essential conditions for the clinical research.

3. Set as target disease for this study.
4. To evaluate the glycemic variation caused by the study drug accurately, the upper limit value was set at 8.5% (NGSP value) to exclude research subject with insufficient glycemic control.
5. To evaluate the glycemic variation accurately, the change variation of HbA1c was set to exclude research subject with unstable glycemic control
6. Set in consideration of the possibility of change in dietetic/exercise therapy may affect evaluation of glycemic variation.

7. This was set in consideration of the possibility that HMG-CoA reductase inhibitors may affect glycemic variation.
8. This was set to allow for separate assessment of men/women. The lower age limit was set to 20 years to allow patients to make a voluntary decision regarding their participation in this clinical research.

7.2 Exclusion criteria

Research subjects meeting any of the criteria below shall not be included in this research.

1. Patients who received anti-diabetic medications within 4 weeks prior to the start of the observation period.
2. Patients who have changed (including discontinuation or interruption) HMG-CoA reductase inhibitors or received new HMG-CoA reductase inhibitors ≤ 4 weeks before the start of the observation period.
3. Patients with clinically evident hepatic dysfunction (e.g., AST or ALT ≥ 2.5-fold the upper limit of normal at the start of the observation period [Day -2])
4. Patients with moderate renal dysfunction, severe renal dysfunction or renal failure (e.g., creatinine clearance < 50 mL/min or serum creatinine > 1.4 mg/dL in men or > 1.2 mg/dL in women [equivalent to the creatinine clearance for persons aged 60 years with a body weight of 65 kg] at the start of the observation period [Day -2])
5. Patients with severe heart disease, cerebrovascular disorder, or severe pancreatic, hematologic or other diseases
6. Patients with a history of gastric or small intestinal resection
7. Patients with proliferative diabetic retinopathy
8. Patients warranting insulin therapy for glycemic control (e.g., patients with severe ketosis, diabetic coma or precoma, type 1 diabetes mellitus, severe infection, perioperative patients, or serious trauma)
9. Patients with a history of hypersensitivity or allergy to DPP-4 inhibitors
10. Patients who experience an allergic reaction to metal during CGM at the start of the observation period (Day -2)
11. Patients with any malignant tumors
12. Habitual drinkers whose average daily alcohol consumption is > 100 mL[Note 1)]

13. Patients who have any contraindications for the study drug or are taking any contraindicated concomitant drugs listed in the package insert
14. Patients anticipated to require any prohibited concomitant medications during the study period
15. Patients who are day and night lifestyle reversal
16. Patients participating in any other clinical studies at the time of informed consent for this study
17. Pregnant women, nursing mothers, women who are possible pregnant, or women who plan to become pregnant
18. Other patients who are considered inappropriate for participation in this study in the opinion of the principal investigator or investigator

Note 1: Alcohol conversion table (for reference)

Alcohol type	Variation	Alcohol strength (%)	Amount equivalent to alcohol 100 mL
Brewed alcohol	Sake	15%	670 mL (about 3 gos, 1 go=180 mL)
	Beer	5%	2,000 mL (about 3 large bottles)
	Happoshu (low-malt beer - like beverage)	5%	2,000 mL
	Wine	12%	830 mL
	Shaoxing rice wine	18%	560 mL
Spirits	Shochu (group ko)	35%	290 mL
	Shochu (group otsu)	25%	400 mL
	Whisky	40%	250 mL (about 3 double glasses)
	Brandy	40%	250 mL (about 3 double glasses)
	Vodka	40%	250 mL (about 3 double glasses)
Combined alcohol	Plum wine	13%	770 mL
	Combined sake	16%	630 mL

[Rationale for the exclusion criteria]

1, 2. Set in order to evaluate drug efficacy accurately.

3, 5, 7, 10, 11, 13. These were set in consideration of safety of research subjects.

4. Severe renal dysfunction and renal failure shall be excluded because trelagliptin is contraindicated for these conditions. Moderate renal dysfunction shall be excluded in consideration of safety of research subjects.

6, 12, 14. Set in order to take in consideration of safety of research subjects and to evaluate drug efficacy accurately.

8, 9. Set as contraindication for trelagliptin and alogliptin treatment.

15..,16 Set in order to establish rational for evaluation of this study.

17. Set as safety of trelagliptin and alogliptin in pregnant women has not been established. Also, set as excretion of trelagliptin and alogliptin in breast milk was confirmed in non-clinical trials.

18. These were set as fundamental items for the research.

7.3 Prohibited concomitant drugs and restricted concomitant drugs

7.3.1 Prohibited concomitant drugs

The following drugs are prohibited from the start of observation period to end of treatment period.

1. Anti-diabetic medications other than the allocated oral hypoglycemic drug
2. Glucocorticoids (medications for local effect such as external preparations are excluded)
3. Estrogen preparations
4. HMG-CoA reductase inhibitors* other than those used at the time of informed consent

   *Dosage of HMG-CoA reductase inhibitors those used at the time of informed consent may not be changed.
5. Acetaminophen

[Rational for prohibited concomitant drugs]

1 to 5. Set as it may affect evaluation of drug efficacy.

7.3.2 Restricted concomitant drugs

The following drugs those used at the time of informed consent are permitted from the start of observation period to end of treatment period. However, change of dosage, addition of or change to a new drug for those drugs is prohibited unless the principal investigator and investigator consider necessary due to adverse events.

1. Lipid lowering agents other than HMG-CoA reductase inhibitors
2. Anti-hypertensive drug

7.4 Research Subject Management

The principal investigator and investigator shall instruct the research subject the items below.

(1) Give instructions to take allocated oral hypoglycemic drug as directed. If poor compliance with study treatment (e.g., < 75% of the prescribed dose) after the previous visit has been found and does not improve, the research subject may be withdrawn from the research if appropriate for the circumstances.

(2) If hypoglycemia symptom (hunger abnormal, feeling of weakness, trembling of hands and fingers, cold sweat, palpitations, etc.) is observed, take glucose or sucrose (sugar), and if it does not improve give instructions to visit promptly.

(3) For dietetic therapy and exercise therapy (if performed), the principal investigator and investigator shall make sure prescriptions (instructions for calories, etc.) are consistent throughout the research period, and instruct the research subject to adhere to the dietetic therapy and exercise therapy (if performed).

(4) When CGM is being conducted, the principal investigator and investigator shall instruct exercise therapy (if performed) that may be performed under the same conditions every day, and instruct the research subject to adhere to it.

(5) When CGM is being conducted, give instruction to photograph every meal contents.

(6) Instruct the research subject not to eat high-sugar, high-calorie food or beverage between meals during CGM.

(7) When CGM is being conducted, give instructions to note necessary items into the research subject diary.

(8) On visit days for planned laboratory tests, give instructions not to take oral hypoglycemic drug scheduled to be taken on that day. Further, at each visit, have the research subject report if drug has been taken or not the day before, and on the day of visit.

(9) On visit days for planned laboratory tests, give instructions for fasting $\geq$ 10 hours before visit.

(10) For research subjects of childbearing potential, give instructions to use adequate contraception. If pregnancy is discovered, have the research subject report promptly, and discontinue the research immediately.

(11) The principal investigator and investigator shall instruct the research subject to adhere to instructed prohibited concomitant drugs. When drugs are taken other than the drugs prescribed by the principal investigator and investigator, have the research subject report its content.

(12) Regarding subjective symptoms/objective findings, have the research subject report at visit the necessary items from its contents, onset date, degree, outcome and date of outcome.

7.5 Criteria for discontinuation or withdrawal of a research subject

The principal investigator or investigator shall record the main reason for discontinuation of protocol treatment on the case report form according to the classification described below. Refer section 9.1.12 for discontinuation case before randomization.

1. **Adverse event**

   When the research subject had an adverse event that requires withdrawal of the research subject from the study because continued participation in the study would impose an unacceptable risk to the research subject's health, or when the research subject is unwilling to continue study participation because of the pretreatment event or adverse event.

2. **Major protocol deviation**

   When it is discovered after randomization that a research subject does not meet the eligibility criteria or is not adhering to the protocol, and continued participation in the research would impose an unacceptable risk to the research subject's health.

3. **Lost to follow-up**

   When the research subject failed to make visits and could not be contacted. The attempts that were made to contact the research subject shall be recorded in the source documents.

4. **Voluntary termination**

When the research subject wishes to withdraw from the research. The reason for discontinuation shall be recorded on the CRF when it is clarified.

5. **Research termination**

When the sponsor or a committee such as the IEC or regulatory authority has decided to terminate the study. Refer to Section 6.3.1 for details.

6. **Pregnancy**

When a female research subject is found to be pregnant.

Note: Research participation shall be immediately discontinued when pregnancy is known. Refer to Section 9.1.11 for procedure.

7. **Others**

Note: The specific reasons should be recorded on the CRF.

7.6 Procedures for discontinuation of individual research subjects

The principal investigator or investigator shall terminate a research subject's research participation when the research subject meets the criteria described in Section 7.5. Individual research subjects may discontinue their research participation without giving a reason at any time during the research. Should a research subject's participation be discontinued, the primary reason for termination shall be recorded on the CRF by the principal investigator or investigator. In addition, efforts shall be made to perform all tests/observations/evaluations scheduled at the time of discontinuation.

8.0 RESEARCH TREATMENT

This section indicates the treatment regimen of this clinical research. See the latest package insert for details and handling of each drug.

8.1 Treatment with the study drug

8.1.1 Study drug

(1) Study drug:

Generic name: Trelagliptin Succinate

Chemical name: 2- ({6- [（3R）-3-Aminopiperidin-1-yl] -3-methyl-2, 4-dioxo-3, 4-dihydropyrimidin -1 (2H)-yl})methyl-4-fluorobenzonitrile monosuccinate

Generic name: Alogliptin benzonate

Chemical name:2- ({6- [(3R) -3-Aminopiperidin-1-yl] -3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1 (2H) -yl} methyl) benzonitrile monobenzoate

8.1.2 Dose and administration method

Trelagliptin 100 mg (once weekly) or alogliptin 25 mg (once daily) shall be administered orally before breakfast. However, the drug shall be administered as described below at the start of the treatment period (VISIT 2: Day 1) or during the treatment period (VISIT 3: Day 21).

At the start of the treatment period (VISIT 2: Day 1): The drug shall be administered after required tests/observations, etc.

During the treatment period (from VISIT 3 to VISIT 5):

Trelagliptin 100 mg/week group shall insert the sensor on the day before Trelagliptin administration day. Trelagliptin 100 mg/week shall be administered before breakfast on the next day of the sensor insertion day. The next administration of Trelagliptin 100 mg is after the sensor removal.

Alogliptin 25 mg/day shall be administered after required tests/observations, etc at every VISIT without taking study drug. Research subjects shall take study drug prior to the every breakfast at home.

Duration of treatment shall be start of treatment period (Day 1) to end of treatment period (Day 29).

Dose and administration method for each administration group are shown in table 8.a.

Table8.a Administration group and administration method

Administration group	Dose	Route of	Administration method

		administration:	
Trelagliptin group	Trelagliptin 100 mg	Oral administration	Once weekly, before breakfast
Alogliptin group	Alogliptin 25 mg	Oral administration	Once daily, before breakfast

8.1.3 Overdose

Overdose is defined as intentional or accidental administration of the study drug at a higher dose than that specified in the protocol, either by a health professional or by the research subject.

To consistently collect important safety information about overdose, the principal investigator or investigator(s) shall record all cases of overdose on the "Overdose" page of the CRF, irrespective of the presence or absence of accompanying adverse event. Adverse events associated with overdose shall be recorded on the "Adverse events" page of the CRF, in accordance with the procedures described in Section 10.0, "ADVERSE EVENTS."

In addition, serious adverse events associated with overdose shall be recorded in accordance with the procedures described in Section 10.2.2, "Collection and reporting of SAEs."

In the event of overdose, the principal investigator or investigator shall treat the subject as required based on symptoms.

8.2 Medication other than the study drug

Prohibited concomitant drugs (refer to Section 7.3.1) may not be used. Also, restricted drugs (refer to Section 7.3.2) may be used if used at the time of informed consent. However, dose change for those restricted drugs or addition of or change to a new drug shall be prohibited unless the principal investigator and investigator consider necessary due to adverse events. Other treatments shall be conducted under normal medical practice

8.3 Allocation and prescription of the study drug and administration procedure

The principal investigator or its designee shall access the web case enrollment system to allocate research subjects. In addition the principal investigator or its designee shall notify information necessary for allocation such as the research subject ID number. Thereafter, the drug to be administered to the research subjects shall be notified by the web case enrollment system. The principal investigator and investigator shall prescribe the study drug according to the notification and record the drug information into the CRF of each research subject.

8.4 Preparation and storage of allocation list

The person responsible for allocation (designated by the sponsor) shall create an allocation list.

Allocation shall be conducted at the enrollment center using web case enrollment system at start of treatment period (Day 1) with "HbA1c at the start of the observation period (< 7.5% or ≥ 7.5%)" and age (< 65 or ≥ 65) as a stratification factor for randomization. The enrollment center shall use the allocation list for stratified randomization created by the allocation responsible person.

Information on the allocation shall be kept in a safe place and shall not be available to anyone other than authorized persons, to secure independency from the clinical research.

9.0 CLINICAL STUDY PROTOCOL

9.1 Research procedures

The principal investigator or investigator shall collect data in accordance with the procedure below. The same principal investigator or investigator shall perform tests/observations/evaluation of research subjects, in principle. The study schedule is provided in Appendix A.

9.1.1 Informed consent procedure

The procedures for obtaining informed consent are described in Section 15.3.

Consent shall be obtained from the research subject before initiation of research procedures.

Research subject ID code is given to each research subject from whom informed consent was acquired and who was randomized. The research subject ID code shall be used throughout the research period and shall not be changed.

9.1.2 Demographic data, medical history, and previous therapeutic drugs

(1) Demographic information

Demographic data shall be collected regarding birth, gender, smoking history, drinking history, time (year/month) of onset (or diagnosis of diabetes).

(2) Medical history

Medical history data shall be collected regarding clinically problematic diseases or symptoms that disappeared within 1 year or were terminated from the start of observation period. When the symptoms or disease continues, it shall be considered as a concurrent disease (Refer to Section 9.1.6).

(3) Pre-treatment

Regarding pre-treatment, name of drug, route of administration and date of final administration shall be collected for all anti-diabetic medication (including injections) that ended use $\leq$ 12 weeks before start of observation period.

9.1.3 Physical examination

All subsequent physical examinations after the start of the treatment period shall be assessed for clinically significant changes from the baseline examination.

9.1.4 Weight, height and BMI

Body weight shall be measured to one decimal place in kilograms.

Height shall be measured or asked to the nearest whole number in centimeters.

BMI shall be calculated by the sponsor using the following formula and shown to one decimal place:

Body Mass Index: BMI = weight (kg) / (height (m))^2

Example:

Height = 176 cm, weight = 79.2 kg, BMI = 79.2/1.76^2 = 25.6 kg/m^2

9.1.5 Concomitant drugs

Concomitant drugs are all drugs to be given in addition to the study drug. Drugs prescribed by doctors or the over-the-counter medicines purchased by the research subjects shall be included. At every hospital visit of the research subject, the status of use of drugs (name of drug, route of administration) other than the allocated oral hypoglycemic drug, from start of observation period to the completion of the clinical research shall be monitored.

9.1.6 Concurrent disease

A concurrent disease is defined as a disease or symptom that is present at the start of the observation period or that develops between the start of the observation period and the start of study treatment. Clinically significant abnormalities, including laboratory test data and physical examination findings, observed in tests and physical examinations at the start of study treatment shall be considered as a concurrent disease at the discretion of the principal investigator or investigator. The content of concurrent disease (diagnosis) shall be investigated.

9.1.7 Laboratory tests

Laboratory tests in table 9.a shall be measured at clinical laboratory instituions according to the observation schedule (Appendix A). Regarding tests at fasting, blood sampling shall be conducted after ≥ 10 hours of fasting. The principal investigator and investigator shall evaluate and keep the reported laboratory test results.

Table 9.a Laboratory tests

Serum chemistry	
Fasting blood glucose	Glycoalbumin
Fasting insulin	1,5-AG
Fasting glucagon	
Fasting proinsulin	
FastingGLP-1	
Fasting GIP	

The principal investigator shall keep laboratory test reference values, including the historical data.

9.1.8 HbA1c (NGSP value)

Measured at research implementing entities to confirm eligibility of research subject at start of observation period. The principal investigator and investigator shall evaluate and keep the reported laboratory test results.

9.1.9 Continuous glucose monitoring (CGM)

Conducted according to Schedule of Research Procedures (Appendix A) Details shall be specified separately in the operation procedures manual.

(1) Device used in this study

[redacted], leased from the sponsor.

(2) Self-measurement of blood glucose (SMBG)

Use device leased from sponsor

Research subjects shall measure blood glucose levels every day during CGM in the observation and treatment periods. At least, blood glucose levels shall be measured at three time points on the first day of CGM ([1] at least 2 hours after the recorder is connected and [2] 2 hours after the first is measured. [3] at bedtime) and at four time points from the second day onward ([1] before breakfast, (2) before lunch, (3) before evening meal, and (4) at bedtime).

The glucose levels from SMBG shall be used for correction of glucose levels obtained from CGM.

(3) Observation period

A sensor shall be inserted at the start of the observation period (Day -2) and removed at the start of treatment (Day 1)

(4) Treatment period

A sensor shall be inserted (VISIT 3: Day 21), exchanged (VISIT 4: Days 24 to 26), and removed (VISIT 5: Day 29) during the treatment period.

(5) Dietetic therapy and exercise therapy

Research subjects shall present photographs of all meals to the principal investigator or investigator during CGM. Also, the meal provided by the sponsor shall be taken according to the calories prescribed by the sponsor for each research subject at the meal times shown below.

Time point of provision of meals: evening meal at start of observation period (Day-2), evening meal on first and seventh of CGM to be performed from Day21 for 9 days.

Research subjects shall only conduct exercise therapy feasible (if performed) under the same conditions every day during CGM.

The principal investigator or investigator shall prescribe consistent dietetic therapy and exercise therapy (if performed) throughout the research period. Compliance with dietetic therapy and exercise therapy(if performed) shall be investigated and rated on a four-point scale as follows:

1. Compliant (compliance rate ≥ 90%)
2. Almost compliant (compliance rate ≥ 70%)
3. Generally compliant (compliance rate ≥ 50%)
4. Minimally compliant (compliance rate < 50%)

(6) Research subject diary

Research subjects shall complete the subject diary every day during CGM and submit the diary to the principal investigator or investigator.

The following information shall be recorded in the subject diary: date and time of dosing, time of SMBG and blood glucose levels, meal time and contents, exercise time, wake-up time, bedtime, etc.

9.1.10 Contraception

Women of childbearing potential (e.g., women who have not undergone surgical sterilization, women who have not reached menopause) shall use appropriate contraception during participation in this clinical research from the time of informed consent. During the informed consent process, appropriate contraceptive methods and the necessity of avoiding pregnancy during participation in the clinical research shall be fully explained to women of childbearing potential with the use of the

informed consent form and information sheet, and the research subjects shall fully understand these explanations before providing consent.

9.1.11 Pregnancy

If pregnancy of a female research subject or a partner of male research subject is found during the participation in this clinical research, the principal investigator or investigator shall inform the sponsorwith pregnancy sheetincluded the detail information as possible.

9.1.12 Record of cases withdrawn before randomization

The consent form shall be signed, and a CRF shall be created for all research subjects who are withdrawn before randomization.

The following items are to be described on the CRF.

- Informed consent procedure
- <MMM/DD/YYYY>
- Sex
- Eligibility
- Reason for discontinuation

The primary reason for withdrawal before randomization shall be recorded on the CRF according to the following classification:

- Not meeting inclusion criteria or meeting exclusion criteria
- Serious deviation from protocol
- Lost to follow-up
- Voluntary discontinuation (specify the reason)
- Premature termination criteria of entire clinical research
- Others (specify the reason)

Research subject ID numbers assigned to research subjects withdrawn from the research before randomization shall not be reused.

9.1.13 Record of randomization

Research subjects to be randomized shall meet all of the inclusion criteria and shall not meet any of the exclusion criteria according to Section 8.3. The principal investigator or investigator shall specify the reason why the subject cannot be randomized to the treatment period.

9.2 Drug-taking status of the research subjects

The principal investigator or investigator shall confirm the treatment compliance and the date and time of dosing during CGM with the research subject at every visit. At the end of study drug administration, Treatment compliance shall be rated on a two-point scale as follows:

1. Compliant (compliance rate ≥ 75%)

2. Not compliant (compliance rate < 75%)

Medication instruction shall be given to research subjects throughout the clinical research period. If poor compliance with study treatment (e.g., < 75% of the prescribed dose) after the previous visit has been found and does not improve, the research subject may be withdrawn from the research if appropriate for the circumstances.

9.3 Implementation time point of the test and observation items

The schedule for all tests, observations, and evaluations is shown in Appendix A. The principal investigator or investigator shall perform the tests, observations, and evaluations at the time points shown below.

9.3.1 Start of observation period (Visit 1: Day -2)

After consent is obtained, physical examination/tests are to be conducted for research enrollment. Eligibility of research subjects shall be determined in accordance with the inclusion and exclusion criteria as described in section 7.0. Refer to section 9.1.12 for the recording of research subjects who are withdrawn before randomization.

Tests and observations to be performed and endpoints to be assessed during the observation period (VISIT 1: Day -2) are shown below.

- Informed consent procedure
- Demographic information
- Medical history, pre-treatment
- Physical examination
- Height
- Concomitant drugs
- Concurrent disease
- Prescription of and compliance with dietetic therapy and exercise therapy

Tests and observations to be performed and endpoints to be assessed during the observation period VISIT 1(Day -2) are shown below.

- Physical examination
- Body weight
- Laboratory tests
- HbA1c
- CGM (remove sensor)
- Self-measurement of blood glucose (self-measured by research subject)

9.3.2 At start of treatment period (Visit 2: Day 1)

Research subjects whose eligibility has been confirmed shall be randomized according to section 8.3 following the results of test, observation and endpoints implemented before start of treatment period.

Randomization is performed at the visit when the principal investigator or investigator is considered as necessity.

The test, observation, and endpoints to be implemented at the start of treatment period (Visit 2: Day 1) are shown below.

- Physical examination
- Concomitant drugs
- Compliance with dietetic therapy and exercise therapy
- CGM (remove sensor)
- SMBG (research subject perform by own)
- Adverse Event

9.3.3 Treatment period (Visit 3: Day 21)

The test, observation, and endpoints to be implemented during the treatment period (Visit 3: Day 21) are shown below.

- Physical examination
- Body weight
- Concomitant drugs
- Laboratory tests

- Treatment status
- Compliance with dietetic therapy and exercise therapy
- CGM (remove)
- Self-measurement of blood glucose (self-measured by research subject)
- Adverse event

9.3.4 Treatment period (Visit 4: Day 24)

The test, observation, and endpoints to be implemented during the treatment period (Visit 4: Day 24) are shown below.

- Physical examination
- Concomitant drugs
- Drug-taking status
- Compliance with dietetic therapy and exercise therapy
- CGM (exchange sensor)
- Self-measurement of blood glucose (self-measured by research subject)
- Adverse event

9.3.5 At end of treatment period (Visit 5: Day 29) or discontinuation during treatment period

The test, observation, and evaluation items to be implemented during at the end of treatment period (Visit 5: Day 29) are shown below.

- Physical examination
- Body weight
- Concomitant drugs
- Laboratory tests
- Drug-taking status
- Compliance with dietetic therapy and exercise therapy
- CGM (remove sensor)
- Self-measurement of blood glucose (self-measured by research subject until removal of CGM sensor)

- Adverse event

The test, observation, and endpoints to be implemented at discontinuation of treatment period are shown below.

- Physical examination
- Body weight
- Concomitant drugs
- Laboratory tests
- Drug-taking status
- Compliance with dietetic therapy and exercise therapy
- Adverse event
- Reason of discontinuation

The status of all randomized research subjects at the end of the clinical research shall be recorded on the CRF.

10.0 ADVERSE EVENT

10.1 Definitions

10.1.1 Adverse event

An adverse event is defined as any untoward medical occurrence in a patient or a research 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).

An adverse event can therefore be any unfavorable or unintended sign (e.g., clinically significant laboratory abnormality), symptom, or disease temporally associated with the use of a pharmaceutical product (including the study drug), regardless of whether it is considered related to the pharmaceutical product (including the study drug) or not.

10.1.2 Considerations for adverse events

Generally unfavorable findings are described below:

- Newly diagnosed disease or unexpected aggravation of existing symptom (intermittent event of an existing symptom is not considered an adverse event)
- Requiring action or medical practice
- Requiring invasive diagnostic treatment
- Requiring discontinuation or a change in the dose of the study drug or a concomitant medication
- Considered unfavorable by the principal investigator or the investigator

Diagnosis name and signs/symptoms:

Adverse events shall be recorded by diagnosis name. Accompanying signs (including abnormal laboratory values, abnormal ECG findings) and symptoms shall not be recorded as adverse events. If an adverse event could not be expressed by a diagnosis name, the signs or symptoms shall be recorded as the adverse event.

Laboratory test values and ECG findings:

Abnormal laboratory values and ECG findings shall be recorded as adverse events when the principal investigator or investigator judges the results are clinically problematic (in other words, when certain action or medical practice is required, or when the principal investigator or the investigator judges the change has exceeded the normal physiological variation range of the research subject). Retest and/or continued monitoring of an abnormality are not considered medical practice.

Also, repeated or additional conduction of non-invasive tests for verification, evaluation, and monitoring of an abnormality are not considered medical practice.

However, when abnormal laboratory values and ECG findings are the accompanying symptoms of a disease diagnosed as an adverse event (e.g., increased creatinine due to renal dysfunction, etc.), the adverse event shall be handled by its diagnosis name.

Pre-existing conditions (disease or symptom that has been present since before the start of study treatment): Pre-existing disease or symptom that has been present since before the start of study treatment shall be regarded as a concurrent disease and not an adverse event. When a concurrent medical condition is aggravated, the aggravation shall be determined as an adverse event and the principal investigator or the investigator shall record on the CRF that the adverse event is an aggravation of the concurrent disease (e.g., "aggravation of hypertension," etc.).

If a research subject has a pre-existing episodic condition (e.g., asthma, epilepsy), each episode shall be recorded as an adverse event if the episodes become more frequent, serious, or severe in nature. If a research subject has a chronic concurrent condition (e.g., cataracts, rheumatoid arthritis), worsening of the condition shall be recorded as adverse event if the degree of the worsening exceeds that which would be expected. The principal investigator or investigator shall ensure that the adverse event term to be recorded represents the change in the condition from baseline (e.g. "worsening of…").

Worsening of adverse events:
If a research subject experiences a worsening of the adverse event after a change to the study drug, or secondary signs and symptoms are caused by the adverse event, the worsening or the secondary signs and symptoms shall be recorded as a new adverse event on the CRF. The principal investigator or investigator shall use an adverse event term that explicitly means a change of the condition (e.g., "worsening of…").

Change of severity of adverse events:
If the research subject experiences changes in the severity of an adverse event, the event shall be recorded once, at its peak severity.

Previously planned surgery or treatment:
Preplanned surgeries or interventions that were scheduled before study treatment shall not be considered adverse events. However, when the existing symptom is aggravated to a degree requiring emergency surgery or treatment, the condition or the event shall be considered an adverse event. A concurrent disease that resulted from previously planned surgery shall be reported as an adverse event.

Non-urgent surgery or treatment:
Non-urgent surgery or treatment that does not induce a change in the condition of a research subject (cosmetic surgery, etc.) shall not be considered an adverse event; However, it shall be recorded in the source documents. Concurrent diseases due to a non-urgent surgery shall be reported as an adverse event.

The insufficient clinical response (lack of efficacy): insufficient clinical response, efficacy, or pharmacological action shall not be recorded as an adverse event. The principal investigator or investigator shall make the distinction between worsening of a pre-existing condition and lack of therapeutic efficacy.

Overdose of the study drug:
Overdose of any medication without onset of event shall not be recorded as an adverse event, but the overdose shall be recorded on the "Overdose" page of the CRF. Any onset of event shall be recorded as adverse events on the "Adverse events" of the CRF.

10.1.3 Serious adverse event

Of all unfavorable medical events that develop after administration of a pharmaceutical product (including the study drug) (irrespective of dose), a serious adverse event is an event that:

1. results in death,
2. is life threatening*,
3. requires inpatient hospitalization or prolongation of existing hospitalization,
4. results in persistent or significant disability/incapacity,
5. leads to a congenital anomaly/birth defect, or
6. Medically important event that causes a risk to the research subject even if it is not immediately life-threatening and does not result in death or hospitalization, or requires an action or treatment to prevent the results described in 1 to 5 above. Points described in the Takeda Medically Significant Adverse Event List (Table 10.a) are included in this section.

* The term "life threatening" refers to an event in which the research subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

Table 10.a Takeda Medically Significant AE List

Acute respiratory failure/acute respiratory distress syndrome (ARDS)	Hepatic necrosis
Torsades de pointes/ ventricular fibrillation/ventricular tachycardia	Acute hepatic failure
Malignant hypertension	Anaphylactic shock
Convulsive seizure (including convulsion and epilepsy)	Acute renal failure
Agranulocytosis	Pulmonary hypertension
Aplastic anemia	Pulmonary fibrosis (including interstitial pneumonia)
Toxic epidermal necrolysis/ Oculomucocutaneous syndrome (Stevens-Johnson syndrome)	Neuroleptic malignant syndrome/ malignant hyperpyrexia
	Spontaneous abortion/ stillbirth and fetal death
	Confirmed or suspected transmission of infection by a medicinal product
	Confirmed or suspected endotoxin shock

10.1.4 Adverse events of special interest (specific adverse events)

An AE of Special Interest (AESI) (serious or non-serious) is one of scientific and medical concern specific to the study drug, for which ongoing monitoring and rapid communication by the principal investigator or investigator to Takeda may be appropriate. Such events may require further investigation in order to establish assessment, and instructions provided to investigators on how and when they should be reported to the sponsor are described in Section 10.2.1.3.

AESIs: Hypoglycemia-related AEs, intestinal obstruction-related AEs and acute pancreatitis-related AEs (for both Trelagliptin and Alogliptin), QT/QTc interval prolongation-related AEs (for Trelagliptin), and Liver dysfunction or jaundice-related AEs (for Alogliptin).

<For both Trelagliptin and Alogliptin>

[Hypoglycemia-related AEs]

Hypoglycemia-related AEs are designated as AESIs because, in general, attention should be paid to the events in the treatment of diabetes mellitus.

[Intestinal obstruction-related AEs]

Intestinal obstruction-related AEs are designated as AESIs because there are accumulated reports of intestinal obstruction as an adverse reaction to similar incretin-related drugs (GLP-1 receptor agonists and other DPP-4 inhibitors).

[Acute pancreatitis-related AEs]

Acute pancreatitis-related AEs are designated as AESIs because there are accumulated reports of acute pancreatitis as an adverse reaction to similar incretin-related drugs.

<For Trelagliptin>

[QT/QTc interval prolongation-related AEs]

QT/QTc interval prolongation-related AEs are designated as AESIs because, in the QT/QTc assessment study conducted during the development, QT/QTc interval prolongation was reported in the trelagliptin 800 mg group although it did not occur in the trelagliptin 200 mg group.

<For Alogliptin>

【Liver dysfunction or jaundice-related AEs】

Liver dysfunction or jaundice-related AEs are designated as AESIs because there are accumulated reports as serious adverse reaction.

10.1.5 Severity of adverse events

The severity of adverse events shall be classified and defined as shown below.

Mild	The event is transient and easily tolerated by the subject.
Moderate	The event interrupts the subject's usual activities.
Severe	The event causes considerable interference with the subject's usual activities.

10.1.6 Causality of adverse events

The causal relationship of each adverse event to the study drug shall be classified and defined as shown below.

Related	An adverse event that follows an apparent temporal sequence (including clinical course after discontinuation). An adverse event the causal relationship could not be denied and there is reasonable possibility due to the study drug, although other factors such as underlying disease, concurrent diseases, or concomitant drugs/treatment are also suspected.
Not related	An adverse event that does not follow an apparent temporal sequence from administration of the study drug. Very likely due to other factors such as underlying

	disease, concurrent diseases, or concomitant drugs/treatment.

10.1.7 Relationship to study procedures

The relationship shall be recorded as "Yes" if the principal investigator or investigator considers that there is reasonable possibility that an adverse event is due to a study procedure. Otherwise, the relationship shall be recorded as "No."

10.1.8 Date of onset

The date of onset of adverse events shall be determined according to the following rules:

Adverse event	Date of onset
Signs, symptoms, diseases (diagnoses)	The date on which the first signs/symptoms were noted by the research subject and/or the principal investigator or investigator.
Asymptomatic diseases	The date on which a diagnosis was confirmed through a test(s). The date on which a diagnosis was confirmed, even when the test results indicate an old sign(s) of the disease or an approximate time of its onset.
Exacerbation of concurrent diseases	The date on which the first worsening of diseases/symptoms was noted by the research subject and/or the principal investigator or investigator.
Onset of a test abnormality after the start of the study drug administration	The date on which a clinically significant laboratory abnormality was detected.
Worsening of a baseline test abnormality after initiation of study treatment	The date on which a clear increase/decrease in a laboratory parameter was clinically confirmed based on the time profile of the parameter.

10.1.9 Date of resolution

The date of resolution of an adverse event is the date on which the research subject recovered (including resolution with sequelae). If a research subject died due to the adverse event concerned, it shall be the date of death. The adverse event shall be recorded as "ongoing" if the research subject has not yet recovered by the end of the study.

10.1.10 Actions taken for the study drug

Actions taken for the study drug shall be classified or defined as shown below.

Drug withdrawn	The study drug is discontinued because of an adverse event (including withdrawal by the research subject at his/her own discretion). When the treatment with the study drug is continued after withdrawal from the study, it shall be defined as "Dose not changed."

Dose not changed	If the dose was unchanged after the onset of the adverse event it shall be defined as “Dose not changed.” If the study drug was discontinued, reduced, or increased because of another adverse event it shall be defined as “Dose not changed.” If the study drug was discontinued or reduced for a reason other than for the adverse event, e.g., inadvertence of the research subject, it shall be defined as “Dose not changed”.
Unknown	It has not been possible to determine what action has been taken because the research subject is lost to follow-up.
Not Applicable	The study treatment had already been completed or discontinued before the onset of the adverse event.
Dose reduced	The dose of the study drug was reduced because of the adverse event (including dose reduction by the research subject at his/her own discretion).
Dose increased	The dose of the study drug was increased because of the adverse event (including dose increase by the research subject at his/her discretion).
Washout	If the study treatment is suspended (i.e., interrupted) (including suspension/interruption by the research subject at his/her discretion) because of the adverse event but resumed thereafter, shall be defined as “washout”.

10.1.11 Outcome

Outcome of adverse events is classified as follows:

Category	Criteria
Recovered	Disappearance or recovery of symptoms and findings Laboratory values returned to normal or baseline
Improved	The intensity is lowered by one or more stages Symptoms or findings mostly disappeared Laboratory values improved, but have not returned to normal or baseline The research subject died from a cause other than the concerned adverse event while the condition was resolving (recording of the date of death unnecessary)
Not recovered	No change in symptoms, findings, or laboratory data The symptoms, findings, or laboratory data on the final day of observable period were aggravated compared with the date of onset Irreversible congenital anomaly The research subject died from another cause before resolution of the concerned adverse event (recording of the date of death unnecessary)
Recovered with sequelae	Disability that disturbs daily life

Death	Direct relationship between death and the concerned adverse event "Direct relationship" means that the concerned adverse event was the cause of death, or the concerned adverse event was clearly responsible for death. Outcome of an adverse event which was not determined (judged, presumed) a direct cause of death observed in the same research subject is not considered as death. If outcome is death, the date of death shall be recorded.
Unknown	Follow-up specified in the protocol after the date of onset was not possible due to change of hospitals or relocation, etc.

10.2 Procedures

10.2.1 Collection and reporting of adverse events

10.2.1.1 Adverse event collection period

Collection of the adverse events shall commence at the start of administration of the study drug (Day 1) and shall conitue until end of treatment (Day 29).

10.2.1.2 Reporting of adverse events

At each study visit, the principal investigator or investigator shall check for the presence of any onset of subjective symptoms. A neutral question, such as "How have you been feeling since your last visit?" may be asked to collect any adverse events that occurred between the previous and present visits.

The principal investigator or investigator shall follow up all research subjects experiencing an adverse event irrespective of the causal relationship with the study drug, until the symptom resolves, or any clinically significant abnormal laboratory values have returned to baseline or there is a satisfactory explanation for the change (permanent or irreversible adverse events). All adverse events shall be entered on the CRF. Adverse event term, onset date, resolution date, severity, causal relationship with the study drug (i.e. "Unrelated" or "Related"), action taken for the study drug, outcome, causal relationship with any study procedure (with specific procedure if assessed to be causally related), and seriousness shall be entered.

Follow-up period of adverse events shall be until recovery of the adverse events, or the time when the principal investigator or investigator judges that further follow-up would be unnecessary.

10.2.1.3 Reporting of adverse events of special interest (specific adverse events)

If AESI occurring during the AE collection period is considered to be clinically significant based on the criteria below, it should be reported to the sponsor (refer to the attachment for contact information) within 1 business day of first onset, or subject's notification of the event by the

principal investigator or investigator. AESI Form should be completed and signed (or signed and sealed) by the principal investigator and reported to the sponsor within 10 business days.

The criteria for AESIs (hypoglycemia-related AEs, intestinal obstruction-related AEs, acute pancreatitis-related AEs, and QT/QTc interval prolongation-related AEs) are as shown below. If any other AEs potentially related to the study drug occur, it will be considered whether to include them in the AESIs.

[Hypoglycemia-related AEs]

AEs related to hypoglycemia

[Intestinal obstruction-related AEs]

Intestinal obstruction, ileus, subileus, obstruction of the digestive tract, gastrointestinal motility disorder, impaired gastric emptying, and AEs related to these conditions

[Acute pancreatitis-related AEs]

AEs related to pancreatitis or acute pancreatitis

[QT/QTc interval prolongation-related AEs]

Torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation, ventricular flutter, consciousness disturbed, convulsion, ECG QT prolonged, and AEs related to these conditions

【Liver dysfunction or jaundice-related AEs】

Adverse events corresponding to ' Liver dysfunction related to drug - comprehensive search' in MedDRA standard search formula.

The AESIs have to be recorded as AEs in the CRF. A report along with all other required documentation must be submitted to the sponsor.

10.2.2 Collection and reporting of serious adverse events

When a serious adverse event develops during the period of collecting adverse events, it shall be reported according to the following procedures. At the time of onset of a serious adverse event or notification of the onset by the research subject, the principal investigator shall report the serious adverse event to the chief executive of the research implementing entity immediately, and the sponsor or CRO to whom the sponsor has entrusted responsibility shall notify the principal investigator of the research implementing entity.

The principal investigator shall then report the serious adverse event to the sponsor (for the contact information, refer to the attachment) within 1 day of notification of the event onset. Further, the principal investigator shall submit a formal report within 10 calendar days to the sponsor.

Furthermore, it shall be mandatory to include the contents below in the report to be submitted to the sponsor within 1 working day, and other items shall be reported as far as possible.

- Brief description of adverse event and the reason for why it was determined as serious
- Research subject ID number
- Name of principal investigator or the investigator
- Name of the study drug
- Determined causal relationship

The principal investigator or investigator shall report spontaneously reported serious adverse events that are collected even after the adverse event collection period to the sponsor.

10.2.3 Reporting of additional information concerning adverse events

If the sponsor requests provision of additional information concerning adverse events for reporting to regulatory authorities, the principal investigator or the investigator shall confirm the necessary additional information and enter in the EDC system or submit a report within the period specified by the sponsor.

10.3 Follow-up of serious adverse events

When information that was not included in the detailed report was obtained later, the principal investigator or investigator shall state it in the copy of the report on serious adverse events, or create another document and submit it to the contact address shown on the attached sheet. Relevant data collected at the research implementing entity (e.g., ECG charts, laboratory test values, discharge summary, postmortem results) shall be sent to the sponsor or the committee such as the IEC upon request.

The investigator or the subinvestigator shall follow-up all serious adverse events, etc., until recovery is confirmed, or the final outcome is determined.

10.3.1 Reporting of serious adverse events to Ethics Review Committee, etc., and regulatory authorities

When the chief executive of the research implementing entity receives a report of a serious adverse event from the principal investigator, the chief shall consult the Ethics Review Committee, etc., and notify the research implementing entities that are conducting the clinical research through the sponsor or the CRO consigned by the sponsor.

If the serious adverse event reported by the principal investigator in which direct causal relationship cannot be denied with this study (the study drug) and is unexpected, the chief executive of the

research implementing entity shall prepare a written report of the unexpected serious adverse event containing the information reported by the principal investigator plus the information below, and submit the report to the Minister of Health, Labor and Welfare, and notify other clinical research implementing entities. (Reporting to the Minister of Health, Labor and Welfare via the sponsor, or notification to other clinical research implementing entities via the sponsor may also be possible)

- Actions taken for serious adverse events (discontinuation of new enrollment, revision of informed consent form, re-consents to other research subjects, etc.)
- Date of review, summery of review, result, necessary action, etc., related to Ethics Review Committee, etc.
- Notification to other research implementing entities

The sponsor shall report, in accordance with regulations, unexpected serious adverse drug reactions and other serious adverse events that are subject to emergency reporting to regulatory authorities, the principal investigators, and chief executives of the research implementing entities.

From the time point of first acknowledging the event or receiving additional information, the sponsor or the CRO consigned by the sponsor shall comply with regulatory required time frames for reporting, and make emergency reports concerning unexpected serious adverse drug reactions and expected serious adverse drug reactions to regulatory authorities. Also, the sponsor shall, in the same way, make an emergency report of other critical safety information that may have a major effect on the study drug risk-benefit, continuation of study drug administration, or continuation of clinical research. The research implementing entity shall submit copies of emergency report documents to the Ethics Review Committee, etc.

11.0 COMMITTEES ESTABLISHED FOR THIS STUDY

In this clinical research, none of Clinical Research Steering Committee, Data and Safety Monitoring Committee, or Central Assessment Committee shall be established.

12.0 DATA MANAGEMENT AND STORAGE OF RECORDS

Data management operations shall be performed according to the standard operating procedure by the data management department of the sponsor independent from the medical affairs department. Adverse events, medical history, and concurrent conditions shall be coded using MedDRA. Drugs shall be translated using the WHO Drug Dictionary.

12.1 Case report form

The principal investigator or investigator shall complete a CRF for each research subject who has signed the informed consent form.

The sponsor or its designee shall provide research implementing entities with access authorization to the electronic CRF. Before use of the electric CRF system, the sponsor shall provide training to the principal investigator, investigators, and study collaborators. The CRF shall be used to report the information collected during the study period to the sponsor. The CRF shall be made in Japanese. Data shall be directly entered in preparing the CRF.

A change or correction of the CRF shall be recorded as an audit trail that records the information before and after the change or correction, the person who made the change or correction, date of change or correction, and its reason.

The principal investigator shall ensure the accuracy and completeness of the CRF, and provide an electronic signature on the relevant page of the case report form. The principal investigator shall bear full responsibility for the accuracy and reliability of all data entered on the CRF.

The following data shall be recorded on the CRF directly. (Except if there is a description in the source material)

- Eligibility, end state, reason of termination, severity, degree, the causal relationship with the study drug or the study procedures, outcome of the adverse event.

The following data shall not be recorded on the CRF directly.

- Measurement results of CGM
- Laboratory result tested at central.

When the principal investigator or the investigator makes a change or correction in the data entered on the CRF after fixation of clinical data base, a record (Data Clarification Form) of change or correction on the CRF provided by the sponsor shall be used. The principal investigator shall confirm that the record of change or correction on the CRF is accurate and complete, and sign or write name/ affix a seal, and date it.

The sponsor or its designee shall confirm that CRFs have been made appropriately according to the procedures defined for each study. The sponsor or its designee shall have access to the medical records of the research subjects and in-house records to ensure the accuracy of the CRF as necessary. The completed CRF is the property of the sponsor, and the principal investigator or investigator shall not disclose the information to a third party without a written permission from the sponsor.

12.2 Timing of data entry into the electronic CRF system

The sponsor or its designee shall request the principal investigator and investigator to promptly enter data into the EDC at enrollment of the research subject, each visit during study treatment, completion/discontinuation of study treatment, and follow-up period. Details of deadlines for data entry shall be specified separately in a procedure manual.

12.3 Storage of records

The principal investigator or the chief executive of research implementing entity shall store the following materials, including those specified in section 12.1, and study-specific documents to be used by the regulatory authority and the sponsor or its designee for investigation and audit. The documents include research subject ID code, medical records, clinical study worksheets (if used), original signed and dated informed consent forms, the change and fix record of CRF (copy) and electric copies of electronic CRF including audit trail. The principal investigator and the chief executive of the research implementing entity shall appropriately retain the material/information related to this study for at least 5 years from the date of reporting the end of the research by the principal investigator, or for 3 years from the date of reporting final publication of the study result, whichever date is later. However, when the sponsor requires a longer storage period, the chief executive of the research implementing entity shall discuss the period and methods of storage with the sponsor.

13.0 STATISTICAL ANALYSIS METHODS

The person responsible for statistical analysis and the designee (a person employed by a CRO independent of the sponsor; the person in charge of analysis) shall conduct analyses. The sponsor will not be involved in statistical analyses.

13.1 Statistical and analytical plans

The person in charge of analysis shall prepare a statistical analysis plan (hereinafter referred to as SAP) before the acquisition of the informed consent of the earliest research subject, and issue the first edition. Detailed definition of endpoints and analysis methods should be specified in the SAP to deal with all the purposes of the research.

13.1.1 Analysis set

Two analysis sets, “full analysis set” and “Safety data analysis set” are used in this study. The “full analysis set" used as a primary analysis set in the efficacy analysis shall be defined as "the research subjects who were randomized and given at least one dose of the study drug." The “Safety data analysis set” shall be defined as "the research subjects who are given at least one dose of the study drug."

13.1.2 Analysis of demographic and other baseline characteristics

From the “full analysis set” primary research subject background items will be tabulated by each treatment group and by merging the treatment groups.

13.1.3 Efficacy analysis

[Primary endpoints]

- Changes in the SD of 24-hour blood glucose values (mg/dL) for each 7-day period between Week 3 and Week 4 (between Day 22 and Day 28) of the treatment period, calculated from the value at the start of the observation period

(Analysis method)

·For the “full analysis set”, summary statistics (number of subjects, mean, SDs, maximum values, minimum values, quartiles [same apply hereafter]) and 95% confidence interval (two sides) of mean shall be calculated for each treatment group at each evaluation point (each day), and illustrating changes in mean and SD in order to evaluate changes in the SD of 24-hour blood glucose values (mg/dL) for each 7-day period between Week 3 and Week 4 (between Day 22 and Day 28) of the treatment period, calculated from the value at the start of the observation period for treagliptin or alogliptin separately.

·Preliminary, for the “full analysis set”, calculate point estimation and 95% confidence interval (two

sides) in difference of mean in treatment groups (trelagliptin 100 mg group – alogliptin 25 mg group) in order to examine the influence of the once-weekly administration and blood glucose fluctuations due to the difference in the daily administration exploratory.

・As well, for the "full analysis set ," conduct analysis of covariance at each evaluation point with changes in the SD of 24-hour blood glucose values between Week 3 and Week 4 from the value at the start of the observation period as dependent variable, treatment groups as independent variable, HbA1c (NGSP value) at the start of the observation period, changes in the SD of 24-hour blood glucose values at the start of the observation period, and age as covariates, and calculate point estimation and 95% confidence interval (two sides) in difference of adjusted mean for each group.

・Preliminary, "full analysis set ," calculate point estimation and 95% confidence interval (two sides) in difference of adjusted mean in treatment groups (trelagliptin 100 mg group – alogliptin 25 mg group)

[Secondary endpoints]

- Changes in AUC over time when specific blood glucose levels (110, 140, 160, or 180 mg/dL) are observed during the 3 hour time period after breakfast, lunch and evening meal[*1, 2]
- Change in AUC over time during periods when blood glucose 140, 160, or 180 mg/dL (hyperglycemia) is observed[*1, 2]
- Changes in blood glucose 140, 160, or 180 mg/dL (hyperglycemia) over time[*1, 2]
- Changes in AUC over time during periods when blood glucose < 70 mg/dL (hypoglycemia) is observed[*1,2]
- Change in peak postprandial glucose levels over time 3 hours after breakfast, lunch, and evening meal[*1, 2]
- Change in maximum variation of blood glucose levels over time between before and after breakfast, lunch, and evening meal [*1, 2]
- Changes in MAGE[*1, 2]
- Changes in mean 24-hour blood glucose levels [*1, 2]
- Changes in mean daytime blood glucose levels[*1, 2]
- Changes in mean nocturnal blood glucose levels[*1, 2]
- Changes in AUC[*1, 2]
- Changes in AUC over time during periods when blood glucose 110 mg/dL is observed[*1,2]
- Changes in the SD of 24-hour blood glucose values[*1,2]
- Changes in the SD of mean daytime blood glucose values[*1,2]
- Changes in the SD of mean nocturnal blood glucose values[*1,2]

[*1]: Measured value and percent changes for the each 7-day period between Week 3 and Week 4 (between Day 22 and Day 28) of the treatment period calculated from the value at the start of

the observation period (however changes in the SD of 24-hour blood glucose values shall be measured value only)

*2: Percent change from the value at the start of the observation period to the mean value during the 7-day period between Week 3 and Week 4 (between Day 22 and Day 28) of the treatment period

(Analysis method)

- Conduct the same analysis as the primary endpoints for *1 and *2 of the above endpoint section. However, for changes in mean/SD, only measured values of *1 and *2 shall be illustrated.

[Other endpoints]

- Glycoalbumin
- 1,5-AG
- Fasting blood glucose
- Fasting insulin
- Fasting glucagon
- Fasting proinsulin
- FastingGLP-1
- Fasting GIP

(Analysis method)

- Calculate summary statistics and 95% confidence interval (two sides) of mean at each evaluation point (the start of the observation period by each treatment group, first and ninth of CGM which is to be performed for 9 days from Day 21) in measured values and changes from the start of the observation period, and illustrate changes in mean and SD

13.1.4 Conversion method of data and handling of missing data

Details shall be specified separately in the statistical analysis plan.

13.1.5 Significance level and confidence coefficient

Confidence coefficient: 95% (two-sided estimation)

13.1.6 Safety analysis

[Secondary endpoints]

- Adverse event

(Analysis method)

- Adverse events shall be reported using MedDRA terminology and summarized using the Preferred Term (PT) and System Organ Class (SOC) of the MedDRA. For the "safety data analysis set", frequency tabulation shall be conducted for adverse events after start of treatment with study drug by each treatment group.
  - Frequency tabulation of all adverse events
  - Frequency tabulation of adverse events that causal relationship is "related" to study drug.
  - Frequency tabulation of the degree of all adverse events
  - Frequency tabulation of degree of adverse events that causal relationship is "related" to study drug.
  - Frequency tabulation of adverse events that were "discontinued" as a measurement concerning study drug.
  - Frequency tabulation of serious adverse events

13.2 Criteria for interim analysis and premature discontinuation

No interim analysis is planned.

13.3 Determination of the number of planned research subject

Planned number of research subjects that are evaluable for primary endpoints in each group is as follows.

Trelagliptin 100 mg group: 15

Alogliptin 25 mg group: 15

Set in consideration with the feasibility of the number of research subjects for exploring the effects of trelagliptin 100 mg and alogliptin 25 mg on glycemic variation. It is not based on statistical power calculation.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Monitoring of the research implementing entity

The sponsor or its designee shall perform periodic monitoring of research implementing entities during the research to confirm that the research is conducted in accordance with all specifications in the research protocol. The data recorded on the CRF will be checked by comparing them with those in the source documents. Source documents are the original documents, data and records. The principal investigator and the chief executive of the research implementing entity shall ensure that the sponsor or its designee and the Ethics Review Committee, etc., have access to the source documents.

The sponsor or its designee shall access the records, including the list of research subject ID numbers, medical records of the research subjects, and signed and dated original consent forms to confirm that the research is appropriately conducted in compliance with the research protocol. Also, confirm the consistency between CRF and the related source documents. The principal investigator, investigator, and other personnel involved in the research shall spare sufficient time to facilitate monitoring procedures during visits to the research implementing entity.

Detailed procedures for monitoring shall be be specified separately in a procedure manual.

14.2 Deviation from the Ethical Guidelines for Medical and Health Research Involving Human Subjects and the research protocol.

The principal investigator or investigator shall record all deviations from Ethical Guidelines for Medical and Health Research Involving Human Subjects, and research protocol.

If any deviation is found, the principal investigator shall promptly notify the chief executive of the research implementing entity for the clinical research and the sponsor. As necessary, the principal investigator will discuss protocol revisions with the sponsor to reach agreement. For protocol revisions, draft revisions should be submitted as early as possible to the chief executive of the research implementing entity for approval of the committee such as the IEC.

14.3 Quality assurance audits and regulatory agency inspections

The research implementing entity may be subject to audits by the sponsor or its designee. In such a case, the auditor designated by the sponsor shall contact the research implementing entity in advance to determine the date of audit. The auditor may ask to visit the facilities where laboratory specimens are collected and any other facilities used during the clinical research. In addition, this research may be inspected by regulatory agencies, including those of foreign governments (e.g., the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency [MHRA]). If the research implementing entity is contacted for an inspection by a regulatory

body, the sponsor should be notified promptly. The principal investigator and the chief executive of the research implementing entity shall ensure that the auditor has access to all the research-related source documents.

15.0 ETHICAL CONDUCT OF CLINICAL RESEARCH

This research shall be conducted with the highest respect for the individual participants (i.e., research subjects) according to the research protocol, and the ethical principles that have their origin in the Declaration of Helsinki, Ethical Guidelines for Medical and Health Research Involving Human Subjects. Each principal investigator shall conduct the study according to regulatory requirements and in accordance with “Responsibilities of the Investigator” in Appendix B.

15.1 Approval of the Ethical Review Board, etc.

The Ethical Review Board, etc., shall be constituted in accordance with the regulations.

The sponsor or its designee should obtain the document listing the name and title of each committee member. When a committee member directly participates in this clinical research, the document describing that he/she is not participating in deliberation or voting for the study shall be obtained.

The sponsor or its designee shall provide related documents for review and approval of the research protocol to the Ethical Review Board, etc. In addition to the research protocol, a copy of the informed consent form and information sheet, written materials related to research subject recruitment, advertisement, and other documents required by regulations, when necessary, shall be submitted to the central committee or a research implementing entity committee such as the Ethics Review Committee to obtain approval. The sponsor or its designee shall obtain records of approval by the Ethical Review Board, etc., for the research protocol and the informed consent form and information sheet before the start of the protocol therapy. The records of approval by the Ethical Review Board, etc., shall include the clinical research title, protocol number, preparation / revision date of the research protocol, and version number and approval date of other reviewed documents (example: informed consent and information sheet). The sponsor shall notify the research implementing entity, the principal investigator, and investigator after confirming the validity of the regulatory documents of the research implementing entity. Protocol procedures such as obtainment of consent shall not be started until the research implementing entity, the principal investigator, and investigator receive notification.

The research implementing entity shall observe all requirements that the Ethical Review Board, etc. prescribe. The requirements may include notifications to committees such as the IEC, for example, revision of the protocol, revision of the informed consent form and information sheet, revision of materials related to research subject recruitment, reports on safety in accordance with the regulatory requirements, reports on status of implementation of the research at intervals determined by a research implementing entity committee such as the Ethics Review Committee, and submission of the study completion report. The sponsor or its designee shall obtain written approval from a

research implementing entity committee such as the Ethics Review Committee related to the above mentioned items and all related materials.

15.2 Conflict of interest

This clinical research shall be conducted with the support of the sponsor.

Prior to the conduction of this clinical research, the investigators involved in this clinical research shall ensure appropriate management of any conflicts (COI) in the conduct of the research in accordance with the rules of the research implementing entity[11-15].

The research implementing entity shall comply with all requirements specified by a committee such as the Ethics Review Committee This includes the COI self-statement form, the research protocol, and the informed consent form and information sheet.

15.3 Informed consent and information sheet, and the agreement of the research subjects

The informed consent and information sheet form shall contain specific requirements of the Declaration of Helsinki, Ethical Guidelines for Medical and Health Research Involving Human Subjects and all applicable laws and regulations. The informed consent form and information sheet shall specify the use of personal information and medical information of research subjects in this clinical research (both in and outside Japan: supply to a third party), and disclosure. The informed consent form and the information sheet will explain in detail the nature of the research, its objectives, and potential risks and benefits. Also, the informed consent form will detail the requirements for participation and the fact that research subject is free to withdraw at any time without giving a reason and without any negative effect on the further medical care.

The principal investigator is responsible for the preparation, contents, and approval of the informed consent form and information sheet by the committee such as the IEC. The informed consent form and information sheet must be approved by the committee prior to use.

The informed consent form and information sheet shall be written in language that can be easily understood by the potential research subjects. The principal investigator or investigator shall be responsible for providing detailed explanation of the informed consent form and information sheet to the potential subjects. Information should be given in both oral and written form whenever possible and in manner deemed appropriate by the committee such as the IEC.

The principal investigator or investigator shall ensure that the potential research subjects have (1) an opportunity to inquire about the research and (2) sufficient time to decide on their participation. If a potential research subject decides he or she is willing to participate in the research, then the informed consent form must be signed and dated by the potential research subject prior to entering into the

research as a subject. The principal investigator or investigator shall instruct the potential research subject to sign using their legal names, not nicknames, using a blue or black ball point ink pen. Also the principal investigator or investigator shall sign and date the informed consent form prior to potential research subject entering into the research.

Once signed, the original informed consent form shall be retained by the principal investigator or investigator. The principal investigator or investigator shall record the date that the potential research subject signed the informed consent form in the subject’ s medical record. A copy of the signed informed consent form shall be given to the research subject.

If the informed consent form and information sheet is revised, the principal investigator or investigator shall newly obtain re-consent from the concerned research subject by following the same procedure as for obtaining the initial consent. The date of obtaining new consent shall be recorded in the research subject’ s medical record, and a copy of the revised consent form shall be provided to the research subject.

15.4 Personal information of the research subjects

The sponsor or the designee shall affirm the principle of the protection of research subjects' private/personal information, etc. Throughout this study, research subject ID numbers shall be used to link the subject's source data to the sponsor's research database and research-related documents. Limited information on research subjects such as gender, age, and date of birth may be used within the scope of all applicable laws and regulations for identification of research subjects and confirmation of accuracy of research subject ID number.

For verification of the conduct of the research in compliance with this protocol and the Ethical Guidelines for Medical and Health Research Involving Human Subjects, the sponsor shall require the principal investigator to provide the research sponsor’s designee, representatives of regulatory authorities, designated auditors, and committees such as the Ethical Review Board direct access to research subjects’ original medical records (source data or documents), including laboratory test results, ECG results, admission and discharge records during a subject’s research participation, and autopsy reports. The principal investigator or investigator shall obtain specific authorization from the research subject as part of the informed consent process for access to research subject's original medical records by research sponsor’s designee and representatives of regulatory authorities (see section 15.3).

When providing a copy of source documents to the sponsor, the principal investigator or investigator shall delete information that may lead to identification of an individual (name and address of research subject, other personal information not recorded on the CRF of the research subject).

15.5 Consultation windows for the research subjects or persons related to the research concerned

The principal investigator shall establish a contact service to respond to inquiries concerning this clinical research from research subjects or concerned people. Details of the contacts for inquiries will be described in the informed consent form.

15.6 Financial burden or reward to the research subjects

Of the expenses for this clinical research, the sponsor shall offer compensation for medical treatment not covered by health insurance as research expenses. The research subjects shall pay expenses for medical treatment covered by ordinary health insurance.

In addition, the principal investigator shall pay expenses such as transportation expenses for participation in this clinical research to the research subjects at each visit from the research funds. Details of the financial burden on the research subjects and rewards shall be described in the informed consent form.

15.7 Benefits and inconveniences to the research subjects

15.7.1 Benefits to research subjects

By participating in this clinical research, the research subjects may understand one’s own condition of type 2 diabetes mellitus in detail.

15.7.2 Inconveniences to research subjects

By participating in this clinical research the burden of the research subject may increase as number of visits will increase compared to daily medical care.

15.8 Attribution of research results and access rights

15.8.1 Attribution of research results

The research results and data obtained from this research shall belong to the sponsor. In addition, secondary use (metaanalysis, etc.) of the data obtained in this clinical research may be possible if used in such a way that the data shall not be linked to personal identification information.

15.8.2 Data access rights

Access rights for all data and information generated from this study will be given to personnel approved by the sponsor.

15.9 Reporting of results, publication, disclosure, and clinical research registration policy

15.9.1 Reporting of results, publication and disclosure

The principal investigator shall report a written summary of results of the research to the chief executive of the research implementing entity and provide the sponsor with all the results and data obtained from the research. Only the sponsor may disclose the research information to other principal investigators, investigators or regulatory authorities during the research period, except when required by laws and regulations. The sponsor shall be responsible for publication of the research protocol and research-related results (including the public web site) except for other cases permitted in the research contract.

During research period and after the end of research, the sponsor or its designee should promptly summarize the results and present it to medical journals and academic conferences, etc. The sponsor may publish any data or information obtained from the research (including data and information provided by the principal investigator) without obtaining consent of the principal investigator.

The principal investigator or the investigator should obtain the prior written approval from the sponsor when publishing the information obtained in this research at an academic conference, etc.

15.9.2 Clinical research registration

To ensure that information on clinical research is made accessible to the public in a timely manner and to comply with applicable laws, regulations, and guidelines, Takeda Pharmaceutical Company Limited shall register all clinical research being conducted in patients around the world at public trial registration sites, including at least the website(s) of ClinicalTrials.gov (and) Japan Pharmaceutical Information Center Clinical Trials Information (JAPIC). On such websites, the research location (city, country), subject recruitment status, and contact information for Takeda Pharmaceutical Company Limited are open to the public.

15.9.3 Clinical trial results disclosure

Takeda Pharmaceutical Company Limited shall post the research results, irrespective of the nature of the results, at the public trial registration site(s) of Clinical Trials.gov (and) JAPIC in accordance with applicable laws and regulations.

15.10 Insurance and compensation for injury

The research subjects participating in this research shall be compensated for any injury resulting from participation in the research according to local regulations applicable to the research

implementing entity. The sponsor or its designee shall buy an insurance policy to compensate for health injury in research subjects.

Healthy injury in a research subject will be compensated as specified in the study contract. Compensation-related questions by the principal investigator or investigators should be made to the sponsor or its designee.

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12. Guidelines for determining the conflict of interest polity for clinical research (Review group for ethical aspects of clinical research and conflict of interest, March 2006)

13. Guidelines on the Management of Conflict of Interest (COI) in Health and Labour Sciences Research (March 31, 2008)

14. Guidelines for management of COI in medical research (COI Committee of Japan Association of Medical Sciences, February 2011)

15. Common guidelines for conflict of interest (COI) in clinical research (Japanese Society of Internal Medicine, Japan Society of Hematology, Japanese Circulation Society, Japan Endocrine Society, Japan Diabetes Society, Japanese Respiratory Society, Japanese Society of Hematology, Japanese Society of Allergology, Japanese Association for Infectious Diseases, Aug 2011)

Appendix A Schedule of Research Procedures

		Observation period		Treatment period				
Time of Visit	Week			0			4	Discontinuation[g]
	Day	-14	-2	1[b]	21[c]	24[c]	29[c]	-
Allowable range (Day)		-28 to -2	-2	1	21 to 35	24~39[f]	29 to 43	-
VISIT Number			1	2	3	4	5	-
Informed consent procedure		×						
Inclusion/Exclusion criteria		×	×					
Demographic information		×						
Medical history, pre-treatment		×	×					
Physical examination		×	×	(×)	×	×	×	×
Body weight, BMI			×		×		×	×
Height		×						
Concomitant drugs		×	×	(×)	×	×	×	×
Concurrent disease		×	×					
Laboratory tests [a]			×		×		×	×
HbA1c			×					
Drug -taking status					×	×	×	×
Prescription of dietetic therapy and exercise therapy and assessment of compliance		×	×	(×)	×	×	×	×
CGM			×[d] (Sensor insertion)	×[d] (Sensor remove)	×[d] (Sensor insertion)	×[d] (Exchange sensor)	×[d] (Sensor remove)	
Self-measurement of blood glucose			×[e]	×[e]	×[e]	×[e]	×[e]	
Adverse event monitoring				×				

(a) Measured on VISIT1 (Day-2), and the first and ninth days of the 9-day CGM starting on Day 21

Blood tests: glycoalbumin, 1,5-AG, fasting insulin*, fasting glucagon*, fasting proinsulin*, fasting GLP-1*, fasting GIP*

(b) The starting day of study treatment in the treatment period is designated as Day 1. The study drug shall be administered after required tests/observations, etc. The day before the start of study treatment in the treatment period is designated as Day -1.It is performed at the visit when principal investigator or investigator consider as needed.

(c) Trelagliptin 100 mg/week group shall insert the sensor on the day before Trelagliptin administration day. Trelagliptin 100 mg/week shall be administered before breakfast on the day after the sensor insertion day.

Alogliptin 25 mg/day shall be administered after required tests/observations, etc at every VISIT without taking study drug. Research subjects shall take study drug prior to the every breakfast at home.

(d) To be performed by study site personnel

(e) At leaset, blood glucose levels shall be measured at three time points on the first day of CGM ([1] at least 2 hours after the recorder is

connected and [2] 2 hours after the first is measured. [3] at bedtime) and at four time points from the second day onward ([1] before breakfast, (2) before lunch, (3) before evening meal, and (4) at bedtime).

(f) After taking trelagliptin 100 mg/week or alogliptin 25 mg/day on the nest day from sensor insertion on Visit3 (Day 21), research subjects should visit the study site between the third day and the fifth day.

(g) To be performed to the extent possible

Appendix B Responsibilities of the sponsor

1. To appropriately conduct the clinical research in compliance with this research protocol and the Ethical Guidelines for Medical and Health Research Involving Human Subjects and with the highest respect for human rights, safety, and welfare of research subjects.
2. To prepare a list of any other investigators and/or research collaborators when certain important research-related activities are divided by investigators and/or research collaborators, and submit the list to the sponsor as required.
3. To prepare the informed consent form and revise it as necessary.
4. To check the contents of the study contract.
5. To provide sufficient information on the protocol, drug and duties of each personnel to subinvestigators and study collaborators, and give guidance and supervision.
6. To select research subjects who satisfy the inclusion criteria, give explanation using written information, and obtain consent in writing.
7. To be responsible for all medical judgments related to the research.
8. Corresponding to request from the chief executive of the research implementing entity, to report the latest progress status at least once a year to the chief executive of the research implementing entity.
9. To ensure that the most update status is confirmed and comprehended regarding the COI of the investigators participating in the clinical research according to the research implementing entity.
10. To ensure, together with the chief executive of the research implementing entity, that sufficient medical care is provided to research subjects for all research-related clinically problematic adverse events throughout the period of subjects' research participation and thereafter.
11. When a research subject is treated at another medical institution or department, to inform the acting physician at the medical institution or department in writing of the research subject's study participation and research completion/discontinuation after obtaining the research subject's consent, and prepare a record.
12. When emergency reporting of serious adverse events, is required, to immediately report it in writing to the chief executive of the research implementing entity and the sponsor.
13. To ensure that the CRFs are accurate and complete, electronically sign and submit them to the sponsor.
14. To verify any entries on the CRFs made by the investigator or transcribed by the collaborator from source documents, electronically sign and submit them to the sponsor.
15. To discuss a revision of the protocol, etc., when proposed by the sponsor.

16. To report the research completion in writing to the chief executive of the research implementing entity.