Title: Study of the QOL evaluation of Trelagliptin in patient with type 2 Diabetes mellitus (TRENDS)

NCT Number: NCT03014479

Protocol Approve Date: 05-Jul-2017

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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 as the language on original version was Japanese.

PROTOCOL

Study of the QOL evaluation of TRElagliptiN in patient with type 2 DiabeteS mellitus (TRENDS)

Sponsor	Takeda Pharmaceutical Company Limited 12-10 Nihonbashi 2-chome, Chuo-ku, Tokyo
Protocol number	Trelagliptin-4002
Version number/Revision number	Version 2.0
Study drug	Trelagliptin
Creation date	July 5, 2017

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1.0 STUDY ADMINISTRATIVE INFORMATION AND CLINICAL STUDY PRINCIPLES

1.1 Clinical study principles

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: International Conference on Harmonization of Technical Requirement for Registration on Pharmaceuticals for Human Use. E6)
- All applicable laws and regulations, including, without limitation, data privacy laws and conflict of interest guidelines.

1.2 Clinical study implementation system

This study will be conducted in accordance with the requirements of this clinical study protocol designed and prepared by the sponsor and also in accordance with the following. Other study administrative structures are shown in the separate documents.

Sponsor

Japan Medical Affairs, Japan Pharma Business Unit, Takeda Pharmaceutical Company Limited

The sponsor shall be responsible for matters related to planning/preparation, implementation/operation, and results/reporting in this clinical study. Methods of supervision of the contractor entrusted with the services related to this clinical study will be described in the procedure to be prepared separately.

Expenses* required for the operation of this clinical study will be paid by the sponsor.

* : Based on the "Consignment Service Contract," expenses incurred for the services of Office of Clinical Study, monitoring, registration/allocation center, and statistical processing shall be paid to the contractor entrusted with services related to this clinical study. Expenses agreed by the study site shall be paid to the site based on the "Research Expense Standard."

Chair of the Clinical Study Steering Committee:

PPD

Terms in this protocol are defined as follows:

Study site:

A corporation, governmental agency and sole proprietor conducting the study, excluding cases where only a part of the services related to storage of samples/information, statistical processing and other studies are entrusted.

Investigators:

Principal investigators and other parties involved in conduction of the study (including operations at institutions involved in collection/distribution of samples/information). Those involved only in providing existing samples/information outside the study sites and those engaged in part of the entrusted operations related to the study are excluded.

Principal Investigator:

An investigator who is engaged in implementation of the study and integrates the operations involved in this study at an affiliated study site.

Chief executive of the study site:

A representative of a corporation, head of a governmental agency, or a sole proprietor

Study subject:

A subject (including a dead subject) who meets any of the following:

1. Subjects being studied (including those who have been asked to be studied)
2. Subjects from whom existing samples/information to be used in the study have been obtained.

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2.0 STUDY SUMMARY

Sponsor: Takeda Pharmaceutical Company Limited	**Study drug:** Trelagliptin
Study title: Study of the QOL evaluation of Trelagliptin in patients with type 2 diabetes mellitus	
Protocol number: Trelagliptin-4002	
Clinical study design: This is a multi-center, randomized, open-label, parallel-group comparison study to assess the reduction in treatment burden during the administration of a DPP-4 inhibitor (trelagliptin or a daily DPP-4 inhibitor) for 12 weeks in patients with type 2 diabetes on diet and exercise therapy only. Subjects who are determined to be eligible based on the results of eligibility assessment after informed consent has been obtained will be randomized to either the study drug (trelagliptin) group or the comparative drug (daily DPP-4 inhibitor) group. Randomization was stratified by the total score (<80% (score 139.4), ≥80% (score 139.4)*)) for total score of the "Diabetes Therapy-Related QOL (DTR-QOL) Questionnaire" and "HbA1c (<8.0%, ≥8.0%)" at the start of the screening period. * A scale of 1 to 7 with 7 as the best was used for each QOL question item, and total score calculated by adding up scores of each question was expressed as a percentage of the maximum total score (i.e., the best score [203] = 100%; the worst score [29] = 0%.)	
Objectives: The objective is to assess the reduction in treatment burden during 12 weeks of trelagliptin administration in patients with type 2 diabetes on diet and exercise therapy only	
Subjects: Patients with type 2 diabetes on diet and exercise therapy alone	
Planned number of study subjects: As the number of randomized subjects: The study drug (Trelagliptin) group 120 subjects The comparative drug (daily DPP-4 inhibitor) group 120 subjects	**Number of study sites:** Approximately 15
Dose and method of administration: The study drug (Trelagliptin) group: Trelagliptin 100 mg is orally administered once weekly. Trelagliptin	**Route of administration:** Oral

50 mg is orally administered once weekly in patients with moderate renal impairment. The comparative drug (Daily DPP-4 inhibitor) group: An inhibitor is orally administered at the dosage and administration in the package inserts for each drug.	
Duration of treatment: 12 weeks	**Duration of evaluation:** 16 weeks (Screening period: 4 weeks; treatment period: 12 weeks)
Inclusion criteria: Eligibility of study subjects shall be determined in accordance with the following criteria. 1. Patients diagnosed as type 2 diabetes. 2. Patients with a stable diet and exercise therapy only for at least 12 weeks prior to the start of the screening period. 3. Patients who require a DPP-4 inhibitor treatment. 4. Patients with HbA1c ≥6.5 % and <10.0 % at the start of the screening period. 5. Patients who completed DTR-QOL questionnaire at the start of the screening period. 6. Patients who have receive less than 2 types of medication for treatment of comorbidities (such as hypertension or dyslipidemia) at the start of the screening period (any number of daily doses). 7. Patients who, in the opinion of the principal investigator or the investigator, are capable of understanding the content of the clinical study and complying with the study protocol requirements. 8. Patients who can provide the written informed consent prior to the initiation of any study procedures. 9. Patients aged ≥20 years at the time of informed consent. 10. Outpatient.	
Exclusion criteria: Study subjects meeting any of the criteria below shall not be included in this study. 1. Patients who are receiving any oral anti-diabetic medication for the treatment of type 2 diabetes at the start of the screening period. 2. Patients diagnosed as type 1 diabetes.	

3. Patients with severe renal impairment or renal failure (e.g., eGFR <30 mL/min/1.73 m^2 or on dialysis).
4. Patients with serious heart disease or cerebrovascular disorder, or serious pancreatic, blood, or other disease.
5. Patients with a history of gastrointestinal resection.
6. Patient with a proliferative diabetic retinopathy.
7. Patient with malignancy.
8. Patients with a history of hypersensitivity or allergy to DPP-4 inhibitors.
9. Pregnant, lactating or postmenopausal women.
10. Patients who may need to add or discontinue concomitant medication or change the dose during the study period.
11. Patients who will require treatment with a prohibited concomitant medication during the study period.
12. Patients participating in other clinical studies.
13. Patients assessed ineligible in the study by the principal investigator or the investigator.

ENDPOINTS:

<Primary endpoint>

Change from baseline (Week 0) in total score for all question items in the DTR-QOL Questionnaire at the end of the treatment period (Week 12).

<Secondary endpoints>

Efficacy assessment:

- Changes in the total score for each factor provided through the DTR-QOL Questionnaire [Factor 1: Burden on social activities and daily activities (13 questions in all), Factor 2: Anxiety and dissatisfaction with treatment (8 questions in all), Factor 3: Hypoglycemia (4 questions in all) and Factor 4: Treatment satisfaction (4 questions in all)] at each assessment time point.
- Change in the total score for all questions in the DTR-QOL Questionnaire at each assessment time point.
- Change in the total score for treatment satisfaction in the Diabetes Treatment Satisfaction Questionnaire (DTSQ) at each assessment time point.
- Changes in the total scores for all questions in the DTR-QOL Questionnaire and the total score

for treatment satisfaction in the DTSQ, stratified by the following factors at the start of the treatment period (Week 0) within each treatment group.

- Use of medication for treatment of comorbidities
- Number of daily doses of medication for treatment of comorbidities (<2 times or ≥2 times)
- Total number of daily tablets of medication for treatment of comorbidities (<2 tablets or ≥2 tablets)
- Number of doses of the study drug or comparative drug (once weekly, once daily or twice daily)

- Changes in the scores per question in the DTR-QOL Questionnaire at each assessment time point.
- Changes in the scores per question in the DTSQ at each assessment time point.

Safety assessment:

- Adverse events
- Incidence of hypoglycemia
- Hospitalization for type 2 diabetes (duration and number, excluding educational hospitalization without worsening of diabetes)

<Other Endpoints>

- Laboratory tests [HbA1c, fasting blood glucose, fasting insulin, fasting glucagon, glycoalbumin, 1,5-AG, serum creatinine, urinary 8-OHdG (using a correction value of uric creatinine (8-OHdG/creatinine)) and urinary creatinine]
- Treatment compliance
- The Basic Information on Study Subject (Your Basic Profile)

STATISTICAL ANALYSIS METHODS:

<Analysis Sets>

Two analysis sets comprising the "Full Analysis Set (FAS)" and the "Safety Population" will be established. The FAS used as the main efficacy analysis set is defined as "randomized subjects who receive at least one dose of trelagliptin or daily DPP-4 inhibitor." The safety population is defined as "subjects who receive at least 1 dose of trelagliptin or daily DPP-4 inhibitor."

<Primary endpoint>

- Change from baseline (Week 0) in total score for all question items in the DTR-QOL Questionnaire at the end of the treatment period (Week 12).

  (1) A comparison between the treatment groups will be carried out based on the ANCOVA model using a change in the total score by the end of treatment [the end of the treatment period (Week 12) - baseline (Week 0)] as a dependent variable; the total score at the baseline (Week 0), the total score of the DTR-QOL Questionnaire (<80% or ≥80%) at the start of the screening period and HbA1c (<8.0% or ≥8.0%) at the start of the screening period as covariates; and a treatment group as an independent variable. The level of significance will be 5% (two-sided).

<Secondary endpoints>

Efficacy endpoints:

- Change in the total score for each factor provided through the DTR-QOL Questionnaire ["Factor 1: Burden on social activities and daily activities (13 questions in all)", "Factor 2: Anxiety and dissatisfaction with treatment (8 questions in all)", "Factor 3: Hypoglycemia (4 questions in all)", and "Factor 4: Treatment satisfaction (4 questions in all)"] at each assessment time point.
- Change in the total score for all questions in the DTR-QOL Questionnaire at each assessment time point.
- Change in the total score for treatment satisfaction in the DTSQ at each assessment time point.

  (1) Summary statistics [sample size, mean, standard deviation (SD), maximum, minimum and quantile] and the two-sided 95% confidence interval (CI) for means per treatment group at each assessment time point will be calculated to plot the changes in means and SDs. Point estimates and the two-sided 95% CI for differences between the treatment groups will also be calculated.

  (2) Changes from the baseline (Week 0) to each assessment time point will be calculated to be similarly analyzed to 1) above.

  (3) The analyses below carried out on the total score for each factor provided through the DTR-QOL Questionnaire, and on the total score for treatment satisfaction in the DTSQ:

  A comparison between the treatment groups will be carried out based on the ANCOVA model using a change in the total score by the end of treatment [the end of the treatment period (Week 12) - baseline (Week 0)] as a dependent variable; the total score at the baseline (Week 0), the total score of "the DTR-QOL Questionnaire (<80% or ≥80%)" at the baseline (Week 0) and "HbA1c (<8.0% or ≥8.0%)" at the baseline (Week 0) as covariates; and a treatment group as an independent variable. The level of significance will

be 5% (two-sided). Note that the total score for all questions in the DTR-QOL is out of the scope of the analysis.

(4) To indicate the changes in the total scores for all questions in the DTR-QOL Questionnaire and the total score for treatment satisfaction in the DTSQ, the summary statistics and two-sided 95% CI for means per treatment group will be calculated, with stratification by the following factors at the start of the treatment period (Week 0):

- Use of medication for treatment of comorbidities
- Number of daily doses of medication for treatment of comorbidities (<2 times or ≥2 times)
- Total number of daily tablets of medication for treatment of comorbidities (<2 tablets or ≥2 tablets)
- Number of doses of the study drug or comparative drug (once weekly, once daily or twice daily)

- Changes in the scores per question in the DTR-QOL Questionnaire at each assessment time point.
- Changes in the scores for per question in the DTSQ at each assessment time point.

(1) Summary statistics for measurements and the changes from the baseline (Week 0) will be calculated per treatment group.

Safety endpoints:

Frequency tables will be prepared for the incidences of adverse events, hypoglycemia, and hospitalization (duration and number) for type 2 diabetes after the first administration of the study drug or comparative drug in the “safety population” in each treatment group.

<Other Endpoints>

Summarizations below will be performed in the "full analysis set" (FAS).

- Laboratory tests

  Summary statistics for measurements and the changes from the baseline (Week 0) will be calculated per treatment group to plot the changes in means and SDs.

- Treatment compliance

  Treatment compliance of each study subject will be calculated and summary statistics of compliance per treatment group will be presented.

- The Basic Information on Study Subject (Your Basic Profile)

  Frequency of answers to each question at each visit will be analyzed per treatment group.

Rationale for the number of planned study subjects:

In this clinical study, to discuss the changes in the total score for all questions in the DTR-QOL Questionnaire from the baseline (Week 0) to the end of the treatment period, as the primary endpoint, mean changes in the daily DPP-4 inhibitor and trelagliptin groups were assumed as 14.4% and 19.0%, respectively. The mean change in the daily DPP-4 inhibitor group was assumed by reference to the data on a sodium glucose transporter 2 (SGLT2) inhibitor, from the previous research; and that in trelagliptin group was assumed by reference to the data from the validation trial of the DTR-QOL Questionnaire. The common SD was assumed as 12.1 % considering the former assumption. When 5% of significance level (two-sided) is based for the analysis of the primary endpoint, 110 subjects per group would be needed to ensure 80% power in comparisons between the trelagliptin group and daily DPP-4 inhibitor group. As this is a study on treatment for type 2 diabetes with DPP-4 inhibitors currently used in the medical setting, the number of randomized subjects was established as 120 subjects per group, for a total of 240 subjects, assuming a type 2 diabetes treatment discontinuation rate of 8%*.

*Based on the results for Topic 2 of the “Strategic Studies on the Prevention of Diabetes” (JDOIT-2), the annual discontinuation rate for the “usual care group” without intervention is approximately 8%.

3.0 ABBREVIATION

AE	adverse event
COI	conflict of interest
CRO	contract research organization
DTSQ	Diabetes Treatment Satisfaction Questionnaire
DTR-QOL	Diabetes Therapy-Related QOL
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization of Technical Requirement for Registration on Pharmaceuticals for Human Use
MHRA	Medicines and Healthcare Products Regulatory Agency
MedDRA	Medical Dictionary for Regulatory Activities
QOL	Quality Of Life
SAE	serious adverse event
SAP	statistical analysis plan

4.0 INTRODUCTION

4.1 Background

The aim of diabetes treatment is to maintain Quality of Life (QOL) similar to that of healthy people and continue the same QOL for life as that of healthy people [1)]. Well controlled blood glucose, lipid and blood pressure levels to prevent complications in the early stages and greatly influence the patients' QOL and prognoses. One of the characteristics of diabetes is a tendency of frequent treatment discontinuation because a patient tends to be unaware of his/her disease even after a diagnosis of diabetes due to limited subjective symptoms during the early stages without notable complications. However, in diabetes treatment, prevention of complications or slow disease progression cannot be expected unless the patient is committed to the treatment; therefore, the key point in diabetes treatment is to improve the patients' QOL to enable continued management of diabetes. On the other hand, discontinuation of diabetes treatment leads to progression of disease complications and poor QOL. Patients' understanding of the treatment and the relationship between patients and medical personnel are important [2)]. The research using an auto-recording system captured medication use reported that the level of compliance is decreased as dosing frequency increased [3)]. In this context, to minimize the dosing frequency (number of tablets) is expected to contribute to the improvement in the QOL and treatment satisfaction.

Dipeptidyl peptidase 4 (DPP-4) inhibitors inhibit degradation of gastrointestinal hormones GIP and GLP-1, and thereby, enhance incretin effects glucose-level-dependently, and consequently decrease blood glucose. In Japan, the first DPP-4 inhibitor was approved in December 2009. Since then, many "daily-dosing" DPP-4 inhibitors have been approved one after another which required to be taken every day. In March 2015, trelagliptin was approved as the world's first "weekly-dosing" DPP-4 inhibitor. In the use of trelagliptin, benefits of improving medication adherence are expected due to less frequent dosing compared with existing oral glucose-lowering medications, especially in patients who are starting oral glucose-lowering monotherapy.

4.2 Rationale for the proposed study

QOL study in patients with type 2 diabetes starting treatment with oral glucose-lowering medications can be expected to provide useful rationales in choosing a therapeutic medication corresponding to various lifestyles of patients. DPP-4 inhibitors, including "daily-dosing" products, have presented limited evidence regarding effects on the QOL of diabetes patients.

Accordingly, this study has been proposed to assess trends in the reduction of treatment burden using the Diabetes Treatment Satisfaction Questionnaire (DTSQ). Also, to assess changes and trends in the QOL at pre- and post-treatment of trelagliptin or a daily DPP-4 inhibitor in diabetes patients solely

controlled by diet/exercise therapy, comparing the "weekly-dosing" product with "daily-dosing" products, using the Diabetes Therapy-Related QOL (DTR-QOL) Questionnaire.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

The objective is to assess the reduction in treatment burden during 12 weeks of trelagliptin administration in patients with type 2 diabetes on diet and exercise therapy only.

5.2 Definition of endpoints

5.2.1 Primary endpoints

Change from baseline (Week 0) in total score for all question items in the DTR-QOL Questionnaire at the end of the treatment period (Week 12) .

5.2.2 Secondary endpoints

5.2.2.1 Efficacy assessment:

- Changes in the total score for each factor provided through the DTR-QOL Questionnaire [Factor 1: Burden on social activities and daily activities (13 questions in all), Factor 2: Anxiety and dissatisfaction with treatment (8 questions in all), Factor 3: Hypoglycemia (4 questions in all) and Factor 4: Treatment satisfaction (4 questions in all)] at each assessment time point.
- Change in the total score for all questions in the DTR-QOL Questionnaire at each assessment time point.
- Change in the total score for treatment satisfaction in the Diabetes Treatment Satisfaction Questionnaire (DTSQ) at each assessment time point.
- Changes in the total scores for all questions in the DTR-QOL Questionnaire and the total scores for treatment satisfaction in the DTSQ, stratified by the following factors at the start of the treatment period (Week 0) within each treatment group.
  - Use of medication for treatment of comorbidities
  - Number of daily doses of medication for treatment of comorbidities (<2 times or ≥2 times)
  - Total number of daily tablets of medications for treatment of comorbidities (<2tablets or ≥2 tablets)
  - Number of doses of the study drug or comparative drug (once weekly, once daily or twice daily)
- Changes in the score per question in the DTR-QOL Questionnaire at each assessment time point.

- Changes in the score per question in the DTSQ at each assessment time point.

5.2.2.2 Safety endpoints

- Adverse events
- Incidence of hypoglycemia
- Hospitalization for type 2 diabetes (duration and number, excluding educational hospitalization without worsening of diabetes)

5.2.3 Other Endpoints

- Laboratory tests [HbA1c, fasting blood glucose, fasting insulin, fasting glucagon, glycoalbumin, 1,5-AG, serum creatinine, urinary 8-OHdG (using a correction value of uric creatinine (8-OHdG/creatinine)) and urinary creatinine]
- Treatment compliance
- The Basic Information on Study Subject (Your Basic Profile)

6.0 CLINICAL STUDY DESIGN

6.1 Clinical study design

<Clinical study design>

This is a multi-center, randomized, open-label, parallel-group comparison study to assess the reduction in treatment burden during the administration of a DPP-4 inhibitor (trelagliptin or a daily DPP-4 inhibitor) for 12 weeks in patients with type 2 diabetes on diet and exercise therapy only.

Eligible study subjects as a result of eligibility assessment after giving informed consent will be randomized to either of the study drug (trelagliptin) group or the comparative drug (daily DPP-4 inhibitor) group as specified in Section 8.4.

< Dosage and Administration>

The study drug group: Trelagliptin 100 mg is orally administered once weekly. Trelagliptin 50 mg is orally administered once weekly in patients with moderate renal impairment.

The comparative drug group: An inhibitor is orally administered at the dosage and administration in the package inserts for each drug.

<Evaluation period and visit frequency for study subjects>

Evaluation period: 16 weeks (Screening period: 4 weeks; treatment period: 12 weeks)

Number of visits: total 4 visits

A study subject will visit to his/her study site at the start of the screening period (Visit 1; Week -4), at the start of the treatment period (Visit 2; Week 0 of the treatment period), during the treatment period (Visit 3; Week 4 of the treatment period) and at the end of the treatment period (Visit 4; Week 12 of the treatment period).

<Planned number of study subjects>

As the number of randomized subjects:

The study drug (Trelagliptin) group 120 subjects

The comparative drug (daily DPP-4 inhibitor) group 120 subjects

<Number of study sites>

Approximately 15

Figure 6 (a) shows an outline of the clinical study design. Refer to Appendix A for schedule of examinations, observations, and evaluations.

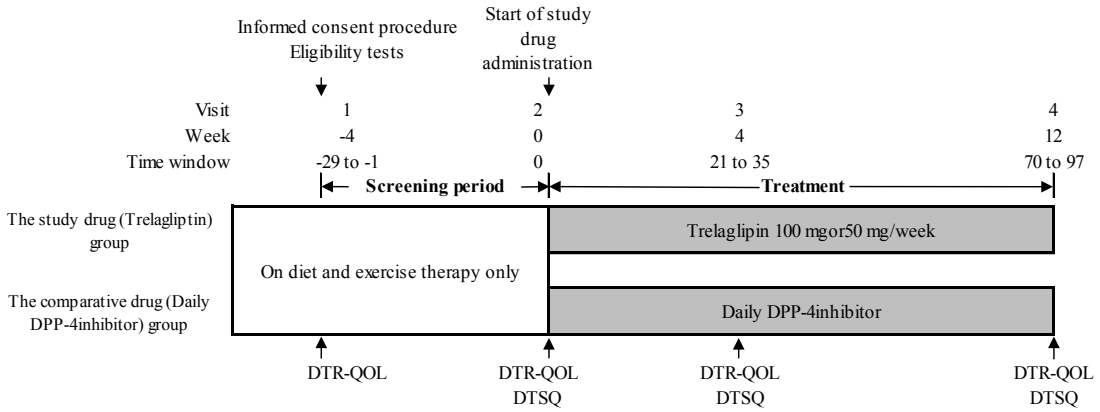
Informed consent procedure
Eligibility tests
Start of study drug administration
Visit 1 2 3 4
Week -4 0 4 12
Time window -29 to -1 0 21 to 35 70 to 97
Screening period
Treatment
The study drug (Trelagliptin) group
Trelaglipin 100 mgor50 mg/week
On diet and exercise therapy only
The comparative drug (Daily DPP-4inhibitor) group
Daily DPP-4inhibitor
DTR-QOL
DTR-QOL DTSQ
DTR-QOL DTSQ
DTR-QOL DTSQ

Figure 6.a Outline of the clinical study design

<Outline of the clinical study>

Duration of treatment: 12 weeks

Number of visits: 4 visits

6.2 Rationale for the clinical study design

(1) Rationale for the clinical study design

The study was designed as an open-label, parallel-group comparative study, to assess impact of trelagliptin on QOL of type 2 diabetes compared with Daily DPP-4 inhibitors. In conducting this parallel-group comparative study, randomization with stratification will be performed, using "the total score for all factors (1-4) in the DTR-QOL Questionnaire (<80% or ≥80%)" and "HbA1c (<8.0% or ≥8.0%)" as stratification factors, for the purpose of adjusting effects on the reduction level of diabetes treatment burdens in patients controlled by diet/exercise therapy during Visit 1.

(2) Rationale for the study period

The treatment period was designed as 12 weeks, because switch to other treatment including combination therapy with other medications is recommended for a case fails to achieve the therapeutic target following three-month continuous administration, as the evaluation on responses to treatment with oral diabetic medications [1)], and in a study which investigate changes in DTR-QOL score during treatment with sodium glucose transporter 2 (SGLT2) inhibitor, statistically significant increase in the score was observed at 12 weeks of treatment and scores at 12 weeks and 24 weeks was comparable.

(3) Rationale for the number of planned study subjects

See Section 13.3.

6.3 Premature termination of entire clinical study or premature termination of clinical study at a study site

6.3.1 Premature termination criteria of entire clinical study

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 study subject participation in the study.

- When there is serious deviation from Ethical Guidelines or ICH-GCP for medical and health study involving human subjects.

6.3.2 Criteria for premature termination of study sites

Termination of involvement of a study site in the study may be requested prematurely at the discretion of the sponsor if the entity (e.g., principal investigator) is found to have significant violation of the ethical guidelines, protocol, or contractual agreement for medical and health study involving human subjects or becomes unable to ensure proper conduct of the study, or otherwise as specified in the contractual agreement.

6.3.3 Procedures of clinical study suspension and premature termination of entire clinical study or clinical study at a study site

In the event that the sponsor or a study site committee such as an Ethical Review Board decides to prematurely suspend or terminate the entire clinical study or clinical study at a study site, a study-specific procedure shall be provided by the sponsor. The procedure shall be followed by applicable study sites 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 study site shall be informed of the details of each protocol revision. 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 study site shall submit the revised contents to committees such as the Ethical Review Board, as necessary according to institutional regulations for review, and obtain approval from the director of the entity.

7.0 SELECTION AND WITHDRAWAL CRITERIA OF STUDY SUBJECTS

The principal investigator or investigator shall check for all the inclusion/exclusion criteria including the test results prior to randomization.

7.1 Inclusion criteria

Eligibility of study subjects shall be determined in accordance with the following criteria.

1. Patients diagnosed as type 2 diabetes.
2. Patients with a stable diet and exercise therapy only for at least 12 weeks prior to the start of the screening period.
3. Patients who require a DPP-4 inhibitor treatment.
4. Patients with HbA1c ≥6.5 % and <10.0 % at the start of the screening period.
5. Patients who completed DTR-QOL questionnaire at the start of the screening period.
6. Patients who have receive less than 2 types of medication for treatment of comorbidities (such as hypertension or dyslipidemia) at the start of the screening period (any number of daily doses).
7. Patients who, in the opinion of the principal investigator or the investigator, are capable of understanding the content of the clinical study and complying with the study protocol requirements.
8. Patients who can provide the written informed consent prior to the initiation of any study procedures.
9. Patients aged ≥20 years at the time of informed consent.
10. Outpatient.

[Rationale for the inclusion criteria]

1-3: These were set to specify a study subject applicable to achieve objective of this study.

4: The lower and upper limits were set to include a study subject whom treatment with oral glucose-lowering medications is considered to require and who is suitable for glucose-lowering monotherapy.

5: This was set because total score of DTR-QOL questionnaire at the start of the screening period is stratifying factor of randomization.

6: This was set to minimize influences on drug taking behavior by medications for comorbidities in the QOL study.

7-10: These were set as fundamentals for this study.

7.2 Exclusion criteria

Study subjects meeting any of the criteria below shall not be included in this study.

1. Patients who are receiving any oral anti-diabetic medication for the treatment of type 2 diabetes at the start of the screening period.
2. Patients diagnosed as type 1 diabetes.
3. Patients with severe renal impairment or renal failure (e.g., eGFR <30 mL/min/1.73 m^2 or on dialysis).
4. Patients with serious heart disease or cerebrovascular disorder, or serious pancreatic, blood, or other disease.
5. Patients with a history of gastrointestinal resection.
6. Patient with a proliferative diabetic retinopathy.
7. Patient with malignancy.
8. Patients with a history of hypersensitivity or allergy to DPP-4 inhibitors.
9. Pregnant, lactating or postmenopausal women.
10. Patients who may need to add or discontinue concomitant medication or change the dose during the study period.
11. Patients who will require treatment with a prohibited concomitant medication during the study period.
12. Patients participating in other clinical studies.
13. Patients assessed ineligible in the study by the principal investigator or the investigator.

[Rationale for the exclusion criteria]

1, 10: These were set to exclude influences on senses of burden against treatment using concomitant medications including diabetic medications other than the allocated oral glucose-lowering medication.

2: This was set to exclude patients with type 1 diabetes, because the indications of trelagliptin and daily DPP-4 inhibitors are for "type 2 diabetes."

3: This was set to exclude patients with severe renal dysfunction or renal failure, because trelagliptin is contraindicated in such patients.

4-8, 11: These were set in consideration of patient safety.

9: This was set because trelagliptin should not be administered in pregnant or possibly pregnant females unless potential therapeutic benefits outweigh risks, and because excretion of trelagliptin and alogliptin into milk was observed in the non-clinical studies.

12, 13: These were set as fundamentals for this study.

7.3 Prohibited concomitant drugs and permitted concomitant drugs

The use of diabetic medications other than allocated oral glucose-lowering medication will be prohibited during from the start of the screening period (Week -4) until the end of the treatment period (Week 12).

<Rationale of prohibited concomitant drugs>

It was designed due to potential influences on the assessment of this clinical study.

7.4 Study 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.

(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) 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.

(4) On visit days for planned laboratory tests, give instructions for fasting ≥ 10 hours before visit (excluding start of observation period).

(5) 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.

(6) 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.

(7) 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 study subject

The principal investigator or investigator shall record the main reason for discontinuation of protocol treatment on the case report form (CRF) according to the classification described below. Refer to Section 9.1.15 for study subjects who withdraw from the study before randomization.

1. Adverse events

When the study subject had an adverse event that requires withdrawal of the study subject from the study because continued participation in the study would impose an unacceptable risk to the

study subject's health, or when the study subject is unwilling to continue study participation because of the adverse event.

2. Major protocol deviation

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

3. Lost to follow-up

When the study subject failed to make visits and could not be contacted despite the attempts to contact the study subject.

4. Voluntary termination

When the study subject wishes to withdraw from the study. The reason for discontinuation shall be obtained to the extent possible.

5. Study termination

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

6. Pregnancy

When a female study subject was found to be pregnant.

Note: The study subject must discontinue the study immediately after she was found to be pregnant. Refer to Section 9.1.13 for the procedures.

7. Lack of efficacy

When efficacy of the study drug is not evident and continuation of the study may pose an unacceptable risk to the study subjects in the opinion of the principal investigator or investigator.

8. Others

When the principal investigator or investigator determined to terminate the study for other reasons.

The specific reasons should be recorded on the CRF.

7.6 Procedures for discontinuation of individual study subjects

The principal investigator or investigator shall terminate a study subject's study participation when the study subject meets the criteria described in Section 7.5. Individual study subjects may discontinue their study participation without giving a reason at any time during the study. Should a

study 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 STUDY 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 Study drug and Comparative drug

8.1.1 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

<Dose and administration method>

Trelagliptin: Trelagliptin 100 mg is orally administered once weekly. Trelagliptin 50 mg is oraly administered once weekly in patients with moderate renal impairment.

8.1.2 Comparative drug

Daily DPP-4 inhibitor: Inhibitors shown in Table 8.a are orally administered at the dosage and administration instructed in the package inserts of each drug.

Table 8.a Daily DPP-4 inhibitor

Inhibitors	Dosage and Administration
Sitagliptin: [redacted]	Take orally in accordance with the instructions in the package inserts.
Vildagliptin: [redacted]	
Alogliptin [redacted]	
Linagliptin: [redacted]	
Teneligliptin: [redacted]	
Anagliptin: [redacted]	
Saxagliptin [redacted]	

8.2 Overdose of the study drug

Overdose is defined as intentional or accidental administration of the study drug or comparative drug at a higher dose than that specified in the package inserts, either by a health professional or by the study 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 serious adverse events."

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

8.3 Medication other than the study drug and the comparative drug

Prohibited concomitant drugs (refer to Section 7.3.1) may not be used. Other treatments shall be conducted under normal medical practice.

In principle, concomitant medications cannot be added or withdrawn, and the dosages of concomitant medications cannot be changed during this clinical study period (refer to the section 7.2). However, the addition of concomitant medications will be allowed as long as the principal investigator or investigator considers its necessity due to reasons such as adverse events. The principal investigator or investigator shall provide directions to study subjects not to take any medications (including over-the-counter drugs) other than the medications instructed to use without prior consultation.

8.4 Allocation of the study drug and administration procedure

The principal investigator or the designee shall access the Case Registration Web System to allocate the study subjects. The principal investigator or the designee shall notify the information required for allocation in addition to the study subject identification (ID) code. Then, drugs that should be administered to each study subject will be notified through the Case Registration Web System. The principal investigator or investigator shall prescribe the study drug or comparative drug according to the notification, and record the drug information (the name, dose per administration, number of daily administration and number of tablets per administration) into the CRF of each research subject.

8.5 Preparation and storage of allocation list

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

Study subjects will be allocated at the Case Registration Center through the Case Registration Web System, using "the total score for the DTR-QOL Questionnaire [<80% (<168.2 as a score) or ≥80% (≥168.2 as a score※)]" and "HbA1c (<8.0% or ≥8.0%)" at the start of the screening period as stratification factors. The Case Registration Center will use the allocation list for stratification prepared by the allocation responsible person in operating the treatment allocation.

※ Refer to the section 9.1.9 for the calculation method of the total score for the DTR-QOL Questionnaire.

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 Clinical study procedures

The principal investigator or investigator shall collect data in accordance with the procedure below. In principle, all the tests, observations, and evaluations of study subjects shall be performed by the same principal investigator or investigator with the exception of the specific 20-lipoprotein fraction. The study schedule is provided in Appendix A.

9.1.1 Informed consent

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

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

A study subject ID code will be given to each study subject who provided informed consent, and then the study subject is to be de-identified. The study subject ID code shall be used throughout the study period and shall not be changed.

9.1.2 Demographic data and medical history

The following data will be collected as demographic data:

- Date of birth, sex, smoking history, alcohol intake history, the time (month and year) of diabetes onset (or a diabetes diagnosis)

As medical history, the information on clinically problematic diseases and symptoms resolved/recovered within a year before the start of the screening period will be collected. A continuous disease/symptom will be considered as a comorbidity.

9.1.3 Physical examination

The presence/absence of clinically significant abnormalities at subsequent physical examinations during the course of this study treatment will be determined compared with the baseline physical examination.

9.1.4 Body weight, height, and BMI

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

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

The sponsor will calculate BMI using the formula below, showing one decimal place.

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

9.1.5 Concomitant drugs

Concomitant drugs are all drugs to be given in addition to the study drug or comparative drug. Drugs prescribed by physicians or the over-the-counter medicines purchased by the study subjects shall be included. At every visit of the study subject, any use of drugs (name, dosage/administration, route of

administration, duration of use, and intended use) shall be investigated and recorded on the CRF from the start of the screening period to the completion of the clinical study. In addition, the followings shall be recorded on the CRF; any use of therapeutic drugs for comorbidity *; number of daily doses of therapeutic drugs for comorbidities (<2 times or ≥2 times); and total number of daily tablets of therapeutic drugs for comorbidity (<2 tablets or ≥2 tablets) from the start of the screening period to the completion of the clinical study.

* For recording of any use of therapeutic drugs for comorbidity; number of daily doses of therapeutic drugs for comorbidity (<2 times or ≥2 times); and total number of daily tablets of therapeutic drugs for comorbidity (<2 tablets or ≥2 tablets), drugs for as-needed use and topical use and supplements are not be included. For drugs for once-weekly use, the numbers shall be divided by 7 for recording.

9.1.6 Comorbidities

A comorbidity shall be defined as a disease or symptom present at the start of the screening period or observed from the start of the screening period until before the start of study drug or comparative drug administration. Clinically problematic laboratory tests and abnormal physical examination findings, etc. observed through the first tests and physical examination at the start of the screening period shall be considered as comorbidities at the discretion of the principal investigator or investigator. The details of comorbidities (diagnoses) shall be investigated.

9.1.7 Laboratory tests

The laboratories will perform the tests shown below in accordance with the Schedule for Study Procedures (Appendix A). The tests will be performed under the ≥10-hour fasting condition (excluding start of observation period). The principal investigator or investigator will retain the reported results of laboratory tests along with evaluating them..

Table 9.a Laboratory tests

Serum chemistry	
・ HbA1c	・ Glycoalbumin
・ Fasting blood glucose	・ 1,5-AG
・ Fasting insulin	・ serum creatinine
・ Fasting glucagon	
Urinalysis	
・ urinary 8-OHdG	・ Urinary creatinine

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

9.1.8 The Basic Information on Study Subject (Your Basic Profile)

Study subjects will answer the "Your Basic Profile" regarding their diabetes therapy at each assessment time point during the screening period and treatment period. The principal investigator or investigator will provide directions to the study subjects to answer all questions truthfully and recorded the answer of each question on the CRF. Of note, in the column "Other drugs than diabetic drugs (e.g., for hypertension)" in the "Your Basic Profile", drugs prescribed in a medical institution shall be recorded. (Supplements and medicines for as-needed use are not included, even though it was prescribed in a medical institution.)

9.1.9 DTR-QOL Questionnaire

Subjects will answer the DTR-QOL Questionnaire (all 29 questions) [5)] regarding the diabetes therapy being conducted at each assessment time point during the screening period and treatment period. The investigator will instruct the subjects to answer all questions truthfully and record the answer of each question of the DTR-QOL Questionnaire (29 questions in total) on the CRF.

[Calculation of the total score based on answers of the DTR-QOL Questionnaire]

・ Calculation method of the total score of Factor 1: "burden on social activities and daily activities" (13 questions in all)

  Every score of the question number 1-13 will be simply added up, and the total figure will be subsequently converted to percentage [the best (91) and worst (13) scores will be equivalent to 100% and 0%, respectively].

・ Calculation method of the total score of Factor 2: "anxiety and dissatisfaction with treatment" (8 questions in all)

Every score of the question number 14 and 19-25 will be simply added up, and the total figure will be subsequently converted to percentage [the best (56) and worst (8) scores will be equivalent to 100% and 0%, respectively].

- Calculation method of the total score of Factor 3: "hypoglycemia" (4 questions in all)

  Every score of the question number 15-18 will be simply added up, and the total figure will be subsequently converted to percentage [the best (28) and worst (4) scores will be equivalent to 100% and 0%, respectively].

- Calculation method of the total score of Factor 4: "treatment satisfaction" (4 questions in all)

  Each score of the question number 26-29 will be converted into reverse (i.e., 1 will be converted to 7, 7 will be converted to 1, and so on. The converted scores, where 7 is the best and 1 is the worst, have the opposite sequence of the original scores). Then, the converted scores will be simply added up, and the total figure will be subsequently converted to percentage [the best (28) and worst (4) scores will be equivalent to 100% and 0%, respectively].

- Calculation method of the total score of all questions

  Each score of the question number 26-29 will be converted into reverse, as described above, and then these converted scores and original scores of the question number 1-25 will be simply added up. Subsequently, the total figure will be converted to percentage [the best (203) and worst (29) scores will be equivalent to 100% and 0%, respectively].

If some answers of a questionnaire are unavailable (i.e., missing data), the scores will be handled in the manner below:

Factor 1-4: As for a factor associated with <50% missing data, the mean value calculated from available answers will be applied to cover the missing data.

The total score for a factor with ≥50% missing data should not be calculated.

The total score of whole questions should not be calculated as well, if a total score of any of the four factors is unavailable.

9.1.10 DTSQ

Subjects will answer the DTSQ (all 8 questions) [6), 7)] regarding the diabetes therapy being conducted at each assessment time point during the treatment period. The investigator will instruct the subjects to answer all questions truthfully and record the answer of each question of the DTSQ (8 questions in total) on the CRF.

9.1.11 Treatment Compliance

Throughout the study period, instructions for treatment will be given to subjects. If instructions were given for treatment incompliance, the details will be recorded on the source document. At each visit, the investigator will check with subjects the treatment compliance status with study drug or comparative drug.

The investigator will instruct the subjects to record study drug or comparative drug usage on a "Diabetes Treatment Medication Record Card*." The subjects will also be instructed to bring empty sheets allowing compliance and usage to be checked along with the "Diabetes Treatment Medication Record Card*" at each visit. The treatment compliance status with the study drug or comparative drug (administration time and quantity of the study drug or comparative drug prescribed and unused) will be recorded on the CRF throughout the study period.

*: Diabetes Treatment Medication Record Card: The card contains an electronic circuit board, and the times that medication is taken are electronically recorded by pressing a button when medication is taken.

9.1.12 Hospitalization for type 2 diabetes

The investigator will check with study subjects any hospitalization for type 2 diabetes after the first administration of the study drug or comparative drug (excluding educational hospitalization without worsening of diabetes). The admission-discharge date will be recorded on CRF.

9.1.13 Contraception

Female subjects of childbearing potential (e.g., nonsterilized or premenopausal female subjects) must use adequate contraception from signing on the informed consent throughout the study period. At the time of acquisition of informed consent from an applicable study subject, signature on the informed consent should be acquired only after explanation is made about what is the adequate contraception and that the subject must avoid to be pregnant during the study period by use of the informed consent form until the subject thoroughly understands them.

9.1.14 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.

9.1.15 Record of study subjects who are withdrawn before randomization

A CRF shall be created for all study subjects who have signed the consent form and withdrawn before randomization.

The following items are to be described on the CRF.

- Date of consent obtainment
- Date of birth
- Gender
- Eligibility
- Reason for discontinuation

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

- Not satisfying at least one of the inclusion criteria or meeting any of the exclusion criteria
- Major protocol deviation
- Lost to follow-up
- Voluntary discontinuation (specify the reason)
- Study termination
- Pregnancy
- Others (specify the reason)

Study subject ID codes assigned to study subjects withdrawn from the study before randomization shall not be reused.

9.1.16 Record of randomization

Study subjects to be randomized shall meet all of the inclusion criteria and shall not meet any of the exclusion criteria according to Section 8.4. The principal investigator or investigator shall specify the primary reason why the study subject cannot be randomized.

9.2 Implementation time point of the tests and observation

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.

9.2.1 Screening period (Week -4)

After obtaining informed consent, the physical examination and tests will be performed for the determining eligibility for study enrollment. The eligibility of a patient will be determined based on the inclusion/exclusion criteria presented in the section 7.0. Refer to the section 9.1.16 for the preparation of records on a study subject withdrawn from the study before randomization.

Tests, observations and evaluations performed at the start of the screening period (Visit 1: Day -29 to -1) are shown below.

- Informed consent
- Inclusion/ exclusion criteria
- Demographic data, medical history
- Physical examination*
- Height, body weight and BMI
- Concomitant drugs*
- Comorbidity*
- Laboratory tests (HbA1c only) *
- DTR-QOL Questionnaire*
- The Basic Information on Study Subject (Your Basic Profile)*

*: To be performed during from Day -29 until Day -14.

9.2.2 Treatment period (Week 0)

An eligible study subject in consequence of the tests, observations and evaluations before the start of the treatment period will be randomized in accordance with the section 8.4.

Tests, observations and evaluations performed at the start of the screening period (Visit 2: Week 0) are shown below.

- Inclusion/ exclusion criteria
- Physical examination
- Concomitant drugs
- Comorbidity
- Laboratory tests (blood chemistry and urinalysis)
- Prescription of the study drug/ or comparative drug
- DTR-QOL Questionnaire
- DTSQ
- The Basic Information on Study Subject (Your Basic Profile)
- Adverse event#
- Hospitalization for type 2 diabetes#

#: To be performed after the first administration (Day 1).

9.2.3 Treatment period (Week 4)

Tests, observations and evaluations performed during the treatment period (Visit 3: Week 4) are shown below.

- Physical examination
- Concomitant drugs
- Laboratory tests (blood chemistry and urinalysis)
- Prescription of the study drug/ or comparative drug
- DTR-QOL Questionnaire
- DTSQ
- The Basic Information on Study Subject (Your Basic Profile)
- Adverse event

- Treatment Compliance
- Hospitalization for type 2 diabetes

9.2.4 Treatment period (Week 12) or discontinuation

Tests, observations and evaluations performed at the end of study treatment (Visit 4: Week 12) are shown below.

- Physical examination
- body weight
- Concomitant drugs
- Laboratory tests (blood chemistry and urinalysis)
- Treatment Compliance
- DTR-QOL Questionnaire
- DTSQ
- The Basic Information on Study Subjects (Your Basic Profile)
- Adverse event
- Hospitalization for type 2 diabetes

Tests, observations and evaluations performed at the discontinuation are shown below.

- Physical examination
- Concomitant drugs
- Laboratory tests (blood chemistry and urinalysis)
- Treatment Compliance
-
- DTR-QOL Questionnaire
- DTSQ
- The Basic Information on Study Subject (Your Basic Profile)
- Adverse event evaluation
- Hospitalization for type 2 diabetes
- The reason for the discontinuation

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse events

An adverse event is defined as any untoward medical occurrence in a patient or a study subject receiving a pharmaceutical product (including the study drug or comparative drug). It does not necessarily have an apparent causal relationship with this pharmaceutical product (including study drug or comparative drug).

An adverse event can therefore be any unfavorable and unintended sign (e.g., a clinically significant laboratory abnormality), symptom, or disease temporally associated with the use of a pharmaceutical product (including the study drug or comparative drug), regardless of whether it is considered related to the pharmaceutical product (including the study drug or comparative 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 comparative 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) 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:

Abnormal laboratory values shall be recorded as adverse events when the principal investigator or the 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 study 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 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 (a disease or symptom that is present at the start of the screening period or that is observed from the start of the screening period until before the start of study drug/or comparative drug administration):
A disease or symptom that is present at the start of the screening period or that is observed from the start of the screening period until before the start of study drug/ or comparative drug administration are considered a comorbidity and not considered an adverse event. When a comorbidity 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 comorbidity (e.g., "aggravation of hypertension," etc.).

If a study 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 study 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 the investigator shall ensure that the adverse event term to be reported represents the change in the condition from baseline (e.g. "worsening of…").

Worsening of adverse events:
If a study subject experiences a worsening of the adverse event after a change of the study drug or comparative 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 the 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 study 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 treatment that were scheduled before the start of study drug or comparative drug administration 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 complication 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 study subject (cosmetic surgery, etc.) shall not be considered an adverse event; However, it shall be recorded in the source documents. Complications 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 the investigator shall make the distinction between worsening of a pre-existing condition and lack of therapeutic efficacy.

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

10.1.3 Serious adverse event

Of all the unfavorable medical events that develop with administration of a pharmaceutical product (including study drug/ or comparative 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. other medically significant condition: a medically important event that causes a risk to a study 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. In addition, 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 study 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 was 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 or comparative 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.

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 or comparative drug shall be classified and defined as shown below.

Related	An adverse event that follows a temporal sequence (including clinical course after discontinuation), or an adverse event in which there is at least a reasonable

	probability that a causal relationship to the study drug or comparative drug cannot be ruled out, although other factors such as underlying disease, complications, or concomitant drugs/treatment are also suspected.
Not related	An adverse event that does not follow a temporal sequence from administration of the study drug or comparative drug. Very likely due to other factors such as underlying disease, complications, or concomitant drugs/treatment.

10.1.7 Relationship to study procedures

The relationship shall be recorded as "Yes" if the principal investigator or the 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 event shall be determined according to the following rules:

Adverse events	Date of onset
Signs, symptoms, diseases (diagnoses)	The date on which the first signs/symptoms were noted by the study 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 complications	The date on which the first worsening of diseases/symptoms was noted by the study subject and/or the principal investigator or investigator.
Onset of a test abnormality after the start of study drug administration or comparative drug administration	The date on which a clinically significant laboratory abnormality was detected.
Worsening of a baseline test abnormality after the start of study drug administration or comparative drug administration	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 study subject recovered (including resolution with sequelae). If a study 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 study subject has not yet recovered by the end of the study.

10.1.10 Actions taken for the study drug or comparative drug

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

Drug withdrawn	The study drug or comparative drug is discontinued because of an adverse event (including withdrawal by the study subject at his/her own discretion). When the study is discontinued but administration of the study drug or comparative drug is still continued, the classification should be "Dose not changed."
Dose not changed	The dose was not changed after the onset of the adverse event. The study drug or comparative drug was discontinued, reduced, or increased because of another adverse event. The study drug was discontinued or reduced for a reason other than the adverse event, e.g., inadvertence of the study subject.
Unknown	It has not been possible to determine what action has been taken because the study subject is lost to follow-up.
Not Applicable	The administration of the study drug or comparative drug had already been completed or discontinued before the onset of the adverse event.
Dose reduced	The dose of the study drug or comparative drug is reduced because of an adverse event (including dose reduction by the study subject at his/her own discretion).
Dose increased	The dose of the study drug or comparative drug was increased because of the adverse event (including dose increase by the study subject at his/her own discretion).
Washout	If administration of the study drug or comparative drug is suspended (i.e., interrupted) (including suspension/interruption by the study subject at his/her own 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 study 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 study 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, etc. "Direct relationship" means that the concerned adverse event, etc. was the cause of death, or the concerned adverse event, etc. 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 study subject is not considered as 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 and its coverage

10.2.1.1 Adverse event collection period

Adverse events shall be collected from the start of administration with the study drug/ or comparative drug (day1) until completion of the treatment period (or discontinuation).

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 study subjects experiencing an adverse event irrespective of the causal relationship with the study drug or comparative drug, until the symptom resolve, or any clinically significant abnormal laboratory values have returned to baseline or there is a satisfactory explanation for the change (permanent and irreversible adverse events, etc.). All adverse events shall be recorded in the CRF. For the adverse event, the name, date of onset, date of resolution, category, severity, causal relationship with the study procedures (the procedure possibly having causal relationship, if applicable), causal relationship with the study drug or comparative drug (i.e. "Not related" or "Related"), action taken for the study drug or comparative drug, outcome, and seriousness shall be recorded.

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

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 after notification of the onset by the study subject, the principal investigator shall report the serious adverse event to the chief executive of the study site immediately, and the sponsor or the contract research organization (CRO) to whom the sponsor has entrusted responsibility shall notify the principal investigator of the study site.

The principal investigator shall then report the serious adverse event to the sponsor (for the contact information, refer to the attachment) within 1 working day after notification of the onset. Further, the 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
- Study subject ID code
- Name of principal investigator or the investigator
- Name of the study drug or comparative 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 Electronic Data Capture (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, principal investigator or the 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 study site (e.g., ECG charts, laboratory test values, discharge summary, postmortem results) shall be sent to the sponsor or the committee such as the Ethical Review Board 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 Ethical Review Board, etc., and regulatory authorities

When the chief executive of study site receives a report of a serious adverse event from the principal investigator, the chief executive of study site shall consult the Ethical Review Board, etc., and notify

the study sites that are conducting the clinical study through the sponsor or the CRO consigned by the sponsor.

When the principal investigator reported a serious adverse event for which a causal relationship to the study (study drug or comparative drug) cannot be ruled out and is unexpected, the chief executive of the study site 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 study sites conducting the clinical study. (The chief executive of the study site may report it to the Minister of Health, Labour and Welfare via the sponsor, and notify it to other clinical study sites via the sponsor.)

- Actions taken for serious adverse events
  (discontinuation of new enrollment, revision of informed consent form, re-consents to other study subjects, etc.)
- Date of review, summery of review, result, necessary action, etc., related to Ethical Review Board, etc.
- Notification to other collaborative study sites

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 the chief executive of study site.

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 risk-benefit of the study drug or comparative drug, continuation of administration of the study drug or comparative drug, or continuation of clinical study. The study site shall submit copies of emergency report documents to the Ethical Review Board, etc.

11.0 COMMITTEES ESTABLISHED FOR THIS STUDY

11.1 Clinical Study Steering Committee

The Clinical Study Steering Committee is composed of the chair and the sponsor. The Clinical Study Steering Committee supervise implementation and reporting of the clinical study, secure medical guidance of a high degree of professionalism and a high-level scientific quality, and revise the study protocol appropriately. The responsibilities of the committee shall be prescribed in the procedures of the Clinical Study Steering Committee.

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 comorbidities shall be coded using the MedDRA. Drugs shall be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 Case report form

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

The sponsor or the designee shall provide access rights to the EDC system to the study site. Before use of the EDC 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. CRF must be completed 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 CRF. 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 (unless recorded in the source document).

- Eligibility, completion status, reason for discontinuation, seriousness of adverse events, severity of adverse events and causal relationship between adverse events and the study drug or comparative drug or the study procedures, and outcome

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

- Laboratory test values

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; DCF) 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 the designee shall confirm that the CRFs are completed appropriately according to the procedures set by study. The sponsor or the designee shall have access to the medical records of

the study 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 the 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 EDC system

The sponsor or the designee shall request the principal investigator and investigator to promptly enter data into the EDC following enrolment of the study subject, each visit during treatment with the study drug or comparative drug, completion/discontinuation of the study, and follow-up period.

12.3 Storage of records

The principal investigator or the chief executive of the study site shall store the following materials, including those specified in Section 12.1, and study-specific documents to be investigated or audited by the regulatory authority and the sponsor or the designee. The documents include the list of study subject ID code, medical records, clinical study worksheets (if used), original signed and dated informed consent forms, the record (copy) of modification or correction on the CRF, and electric copies of EDC including audit trail. The principal investigator and the chief executive of the study site shall appropriately retain the material/information related to this study for at least 5 years from the date of reporting the end of the study 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 study site shall discuss the period and methods of storage with the sponsor.

13.0 STATISTICAL ANALYSIS METHODS

The person in charge of analysis and the designee [analysis personnel, who belongs to CRO independent from the sponsor] shall perform the statistical analysis. The sponsor will not be involved in the statistical analysis.

13.1 Statistical and analytical plans

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

13.1.1 Analysis set

Two analysis sets comprising the “Full Analysis Set (FAS)” and the “Safety Population” will be established. The FAS used as the main efficacy analysis set is defined as “randomized subjects who receive at least one dose of trelagliptin or daily DPP-4 inhibitor.” The safety population is defined as “subjects who receive at least 1 dose of trelagliptin or daily DPP-4 inhibitor.”

13.1.2 Analysis of demographic and other baseline characteristics

From “SAS” primary study subject background items will be tabulated.

13.1.3 Efficacy analysis

From FAS the following shall be analyzed.

<Primary endpoint>

Change from baseline (Week 0) in total score for all question items in the DTR-QOL Questionnaire at the end of the treatment period (Week 12).

1) A comparison between the treatment groups will be carried out based on the ANCOVA model using "the change in the total score by the end of treatment [the end of the treatment period - baseline (Week 0)]" as a dependent variable; "the total score at the baseline, the total score of the DTR-QOL Questionnaire (<80% or ≥80%) at the start of the screening period and HbA1c (<8.0% or ≥8.0%) at the start of the screening period as covariates; and "a treatment group" as an independent variable. The level of significance will be 5% (two-sided).

<Secondary endpoints>

Efficacy endpoints:

- Changes in the total score for each factor provided through the DTR-QOL Questionnaire ["Factor 1: Burden on social activities and daily activities (13 questions in all)", Factor 2: Anxiety and dissatisfaction with treatment (8 questions in all), "Factor 3; Hypoglycemia (4 questions in all)", and "Factor 4: Treatment satisfaction (4 questions in all)"] at each assessment time point.
- Change in the total score for all questions in the DTR-QOL Questionnaire at each assessment time point.
- Change in the total score for treatment satisfaction in the DTSQ (evaluated with the score of questions #1, 4, 5, 6, 7, and 8) at each assessment time point.

1) Summary statistics [sample size, mean, standard deviation (SD), maximum, minimum and quantile] and the two-sided 95% confidence interval (CI) for means per treatment group at each assessment time point will be calculated to plot the changes in means and SDs. Point estimates and the two-sided 95% CI for differences between the treatment groups will also be calculated.
2) Changes from the baseline (Week 0) to each assessment time point will be calculated to be similarly analyzed to 1) above.
3) The analyses below carried out on the total score for each factor provided through the DTR-QOL Questionnaire, and on the total score for treatment satisfaction in the DTSQ:

   A comparison between the treatment groups will be carried out based on the ANCOVA model using "the change in the total score by the end of treatment [the end of the treatment period (Week 12) - baseline (Week 0)]" as a dependent variable; the total score at the baseline (Week 0), the total score of "the DTR-QOL Questionnaire (<80% or ≥80%)" at the baseline (Week 0) and "HbA1c (<8.0% or ≥8.0%)" at the baseline (Week 0) as covariates; and "a treatment group" as an independent variable. The level of significance will be 5% (two-sided). Note that the total score for all questions in the DTR-QOL is out of the scope of the analysis.
4) To indicate the changes in the total scores for all questions in the DTR-QOL Questionnaire and the total scores for treatment satisfaction in the DTSQ, the summary statistics and two-sided 95% CI for means per treatment group will be calculated, with stratification by the following factors at the start of the treatment period (Week 0):

   - Use of medication for treatment of comorbidities
   - Number of daily doses of medication for treatment of comorbidities (<2 times or ≥2 times)

- Total number of daily tablets of medication for treatment of comorbidities (<2 tablets or ≥2 tablets)
- Number of doses of the study drug or comparative drug (once weekly, once daily or twice daily)

- Changes in the scores per question in the DTR-QOL Questionnaire at each assessment time point.
- Changes in the scores for per question in the DTSQ at each assessment time point.
  1) Summary statistics for measurements and the changes from the baseline (Week 0) will be calculated per treatment group.

<Other endpoints>

Summarizations below will be performed in the "full analysis set" (FAS).

- Laboratory tests

  Treatment compliance of each study subject will be calculated and summary statistics of compliance per treatment group will be presented.

- Treatment compliance
  Treatment compliance of each study subject will be calculated and summary statistics of compliance per treatment group will be presented.

- The Basic Information on Study Subject（Your Basic Profile）

  Frequency of answers to each question at each visit will be analyzed per treatment group.

13.1.4 Safety analysis

Frequency tables will be prepared for the incidences of adverse events, hypoglycemia, and hospitalization for type 2 diabetes (number and duration of hospitalization) after the first administration of the study drug or comparative drug administration in the “safety population” in each treatment group.

13.2 Criteria for interim analysis and premature discontinuation

No interim analysis is planned.

13.3 Determination of the number of planned study subject

In this clinical study, to discuss changes in the total score for all questions in the DTR-QOL Questionnaire from the baseline (Week 0) to the end of the treatment period, as the primary endpoint, mean changes in the daily DPP-4 inhibitor and trelagliptin groups were assumed as 14.4% and

19.0%, respectively. The mean change in the daily DPP-4 inhibitor group was assumed by reference to the data on SGLT2 inhibitor, from the previous research [4]; and that in trelagliptin group was assumed by reference to the data from the validation trial of the DTR-QOL Questionnaire [6]. The common SD was assumed as 12.1 % considering the former assumption. When 5% of significance level (two-sided) is based for the analysis of the primary endpoint, 110 subjects per group would be needed to ensure 80% power in comparisons between the trelagliptin group and daily DPP-4 inhibitor group. As this is a study on treatment for type 2 diabetes with DPP-4 inhibitors currently used in the medical setting, the number of randomized subjects was established as 120 subjects per group, for a total of 240 subjects, assuming a type 2 diabetes treatment discontinuation rate of 8%*.

*Based on the results for Topic 2 of the "Strategic Studies on the Prevention of Diabetes" (JDOIT-2), the annual discontinuation rate for the "usual care group" without intervention is approximately 8% [2].

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Monitoring of the study site

The sponsor or the designee shall perform periodic monitoring of the study site during the study to confirm that the study is conducted in accordance with all specifications in the study protocol. In the monitoring, 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 study site shall ensure that the sponsor or the designee and the Ethical Review Board, etc., have access to the source documents.

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

Detailed procedures for monitoring shall be described separately in the written procedures.

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

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

If any deviation is found, the principal investigator shall promptly notify the chief executive of the study site for the clinical study 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 study site for approval of the committee such as the Ethical Review Board.

14.3 Quality assurance audits and regulatory agency inspections

The sponsor or the designee shall perform audit at the study site as necessary. In such a case, the auditor designated by the sponsor shall contact the study site 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 study. In addition, this study 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 study site is contacted for an inspection by a regulatory body, the sponsor should be notified promptly. The

principal investigator and the chief executive of the study site shall ensure that the auditor has access to all the study-related source documents.

15.0 ETHICAL CONDUCT OF CLINICAL STUDY

This clinical study shall be conducted with the highest respect for the individual participants (i.e., study subjects) according to the study protocol, the ethical principles that have their origin in the Declaration of Helsinki, and "Ethical Guidelines for Medical and Health Research Involving Human Subjects." Each principal investigator will conduct the study according to regulatory requirements and in accordance with "Responsibilities of the Principal 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 the designee should obtain the document listing the name and title of each committee member. When a committee member directly participates in this clinical study, the document describing that he/she is not participating in deliberation or voting for the study will be obtained.

The sponsor or the designee shall supply relevant documents for submission to study site committee such as the Ethical Review Board for the protocol's review and approval. In addition to the study protocol, a copy of the informed consent form and information sheet, written materials related to study subject recruitment, advertisement, and other documents required by regulations, when necessary, shall be submitted to the central committee or a study site committee such as the Ethical Review Board to obtain approval. The sponsor or the designee must obtain written approval of the protocol and the informed consent form and information sheet from the study site committee such as the Ethical Review Board before commencement of the study. The study site committee such as the Ethical Review Board's approval must refer to the study by exact protocol title, number and version date; identify versions of other documents (e.g., informed consent form and information sheet) reviewed; and state the approval date. The sponsor shall notify the study site, the principal investigator, and investigator after confirming the validity of the regulatory documents of the study site. Protocol procedures such as obtainment of consent shall not be started until the study site, the principal investigator, and investigator receive notification.

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

15.2 Conflict of interest

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

Prior to the conduction of this clinical study, the principal investigators involved in this clinical study shall ensure appropriate management of any conflicts of interest (COI) in the conduct of the study in accordance with the rules of the study site.[9)-13)]

The study site shall observe all requirements that the Ethical Review Board, etc. prescribe. This will include self-declaration of COI, clinical study protocol, informed consent form and information sheet.

15.3 Informed consent form and information sheet, and the agreement of the study subjects

The informed consent 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 study subjects in this clinical study (both in and outside Japan: supply to a third party), and disclosure. The informed consent form will explain in detail the nature of the clinical study, its objectives, and potential risks and benefits. The informed consent form will detail the requirements of the participant and the fact that study subject is free to withdraw at any time without giving a reason and without any negative effect on 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 Ethical Review Board. The informed consent form and information sheet must be approved by the committee such as the Ethical Review Board prior to use.

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

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 study 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 study subject.

The principal investigator or investigator shall follow the same procedure as for obtaining the initial consent when newly obtaining re-consent from the concerned study subject when the informed

consent form and information sheet is revised. The date of obtaining new consent shall be recorded in the study subject's medical record, and a copy of the revised consent form shall be provided to the study subject.

15.4 Personal information of the study subjects

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

For verification of the conduct of the study 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 study sponsor's designee, representatives of regulatory authorities, designated auditors, and committees such as the Ethical Review Board direct access to study subjects' original medical records (source data or documents), including laboratory test results, admission and discharge records during a subject's study participation, and autopsy reports. The principal investigator or investigator shall obtain specific authorization of the study subject as part of the informed consent process for access to study subject's original medical records by study 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 study subject, other personal information not recorded on the CRF of the study subject).

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

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

15.6 Financial burden or reward to the study subjects

Of the expenses for this clinical study, the sponsor shall offer compensation for medical treatment not covered by health insurance as study expenses. The study 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 study to the study subjects at each visit from the research funds. Details

of the financial burden on the study subjects and rewards shall be described in the informed consent form and information sheet.

15.7 Benefits and inconveniences to the study subjects

15.7.1 Benefits to study subjects

Study subjects can deeply learn their own conditions of type 2 diabetes including such as the change in the QOL associated with the change in treatment approaches and the level of treatment satisfaction, through the study participation

15.7.2 Inconveniences to study subjects

Burdens of study subjects may be increased due to requirements of providing answers to the Basic Information on Study Subject, DTR-QOL Questionnaire and DTSQ, through the study participation.

15.8 Attribution of study results and access rights

15.8.1 Attribution of study results

The study results and data obtained from this study shall belong to the sponsor. In addition, secondary use (meta-analysis, etc.) of the data obtained in this clinical study 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 study registration policy

15.9.1 Reporting of results, publication and disclosure

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

During the study period and after the end of study, the sponsor or the 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 study (including data and information provided by the principal investigator) without obtaining agreement 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 study at an academic conference, etc.

15.9.2 Clinical study registration

To ensure that information on clinical study 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 study 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), before initiation of the clinical study. On such websites, the study location (city, country), study 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 study 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

In case of injuries, each study subject in the clinical study must be insured in accordance with the regulations applicable to the study site where the subject is participating. The sponsor or the designee shall buy an insurance policy to compensate for health injury in study subjects.

Healthy injury in a study 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 the designee.

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PROTOCOL

Study of the QOL evaluation of TRElagliptiN in patient with type 2 DiabeteS mellitus (TRENDS)

Sponsor	Takeda Pharmaceutical Company Limited 12-10 Nihonbashi 2-chome, Chuo-ku, Tokyo
Protocol number	Trelagliptin-4002
Version number/Revision number	Version 1.0
Study drug	Trelagliptin
Creation date	November 2, 2016

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1.0 STUDY ADMINISTRATIVE INFORMATION AND CLINICAL STUDY PRINCIPLES

1.1 Clinical study principles

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: International Conference on Harmonization of Technical Requirement for Registration on Pharmaceuticals for Human Use. E6)
- All applicable laws and regulations, including, without limitation, data privacy laws and conflict of interest guidelines.

1.2 Clinical study implementation system

This study will be conducted in accordance with the requirements of this clinical study protocol designed and prepared by the sponsor and also in accordance with the following. Other study administrative structures are shown in the separate documents.

Sponsor

Japan Medical Affairs, Japan Pharma Business Unit, Takeda Pharmaceutical Company Limited

The sponsor shall be responsible for matters related to planning/preparation, implementation/operation, and results/reporting in this clinical study. Methods of supervision of the contractor entrusted with the services related to this clinical study will be described in the procedure to be prepared separately.

Expenses* required for the operation of this clinical study will be paid by the sponsor.

* : Based on the "Consignment Service Contract," expenses incurred for the services of Office of Clinical Study, monitoring, registration/allocation center, and statistical processing shall be paid to the contractor entrusted with services related to this clinical study. Expenses agreed by the study site shall be paid to the site based on the "Research Expense Standard."

Chair of the Clinical Study Steering Committee:

PPD

Terms in this protocol are defined as follows:

Study site:

A corporation, governmental agency and sole proprietor conducting the study, excluding cases where only a part of the services related to storage of samples/information, statistical processing and other studies are entrusted.

Investigators:

Principal investigators and other parties involved in conduction of the study (including operations at institutions involved in collection/distribution of samples/information). Those involved only in providing existing samples/information outside the study sites and those engaged in part of the entrusted operations related to the study are excluded.

Principal Investigator:

An investigator who is engaged in implementation of the study and integrates the operations involved in this study at an affiliated study site.

Chief executive of the study site:

A representative of a corporation, head of a governmental agency, or a sole proprietor

Study subject:

A subject (including a dead subject) who meets any of the following:

1. Subjects being studied (including those who have been asked to be studied)
2. Subjects from whom existing samples/information to be used in the study have been obtained.

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2.0 STUDY SUMMARY

Sponsor: Takeda Pharmaceutical Company Limited	**Study drug:** Trelagliptin
Study title: Study of the QOL evaluation of Trelagliptin in patients with type 2 diabetes mellitus	
Protocol number: Trelagliptin-4002	
Clinical study design: This is a multi-center, randomized, open-label, parallel-group comparison study to assess the reduction in treatment burden during the administration of a DPP-4 inhibitor (trelagliptin or a daily DPP-4 inhibitor) for 12 weeks in patients with type 2 diabetes on diet and exercise therapy only. Subjects who are determined to be eligible based on the results of eligibility assessment after informed consent has been obtained will be randomized to either the study drug (trelagliptin) group or the comparative drug (daily DPP-4 inhibitor) group. Randomization was stratified by the total score (<80% (score 139.4), ≥80% (score 139.4)*)) for total score of the "Diabetes Therapy-Related QOL (DTR-QOL) Questionnaire" and "HbA1c (<8.0%, ≥8.0%)" at the start of the screening period. * A scale of 1 to 7 with 7 as the best was used for each QOL question item, and total score calculated by adding up scores of each question was expressed as a percentage of the maximum total score (i.e., the best score [203] = 100%; the worst score [29] = 0%.)	
Objectives: The objective is to assess the reduction in treatment burden during 12 weeks of trelagliptin administration in patients with type 2 diabetes on diet and exercise therapy only	
Subjects: Patients with type 2 diabetes on diet and exercise therapy alone	
Planned number of study subjects: As the number of randomized subjects: The study drug (Trelagliptin) group 120 subjects The comparative drug (daily DPP-4 inhibitor) group 120 subjects	**Number of study sites:** Approximately 15
Dose and method of administration: The study drug (Trelagliptin) group: Trelagliptin 100 mg is orally administered once weekly. Trelagliptin	**Route of administration:** Oral

50 mg is orally administered once weekly in patients with moderate renal impairment. The comparative drug (Daily DPP-4 inhibitor) group: An inhibitor is orally administered at the dosage and administration in the package inserts for each drug.	
Duration of treatment: 12 weeks	**Duration of evaluation:** 16 weeks (Screening period: 4 weeks; treatment period: 12 weeks)
Inclusion criteria: Eligibility of study subjects shall be determined in accordance with the following criteria. 1. Patients diagnosed as type 2 diabetes. 2. Patients with a stable diet and exercise therapy only for at least 12 weeks prior to the start of the screening period. 3. Patients who require a DPP-4 inhibitor treatment. 4. Patients with HbA1c ≥6.5 % and <10.0 % at the start of the screening period. 5. Patients who completed DTR-QOL questionnaire at the start of the screening period. 6. Patients who have receive less than 2 types of medication for treatment of comorbidities (such as hypertension or dyslipidemia) at the start of the screening period (any number of daily doses). 7. Patients who, in the opinion of the principal investigator or the investigator, are capable of understanding the content of the clinical study and complying with the study protocol requirements. 8. Patients who can provide the written informed consent prior to the initiation of any study procedures. 9. Patients aged ≥20 years at the time of informed consent. 10. Outpatient.	
Exclusion criteria: Study subjects meeting any of the criteria below shall not be included in this study. 1. Patients who are receiving any oral anti-diabetic medication for the treatment of type 2 diabetes at the start of the screening period. 2. Patients diagnosed as type 1 diabetes.	

3. Patients with severe renal impairment or renal failure (e.g., eGFR <30 mL/min/1.73 m^2 or on dialysis).
4. Patients with serious heart disease or cerebrovascular disorder, or serious pancreatic, blood, or other disease.
5. Patients with a history of gastrointestinal resection.
6. Patient with a proliferative diabetic retinopathy.
7. Patient with malignancy.
8. Patients with a history of hypersensitivity or allergy to DPP-4 inhibitors.
9. Pregnant, lactating or postmenopausal women.
10. Patients who may need to add or discontinue concomitant medication or change the dose during the study period.
11. Patients who will require treatment with a prohibited concomitant medication during the study period.
12. Patients participating in other clinical studies.
13. Patients assessed ineligible in the study by the principal investigator or the investigator.

ENDPOINTS:

<Primary endpoint>

Change from baseline (Week 0) in total score for all question items in the DTR-QOL Questionnaire at the end of the treatment period (Week 12).

<Secondary endpoints>

Efficacy assessment:

- Changes in the total score for each factor provided through the DTR-QOL Questionnaire [Factor 1: Burden on social activities and daily activities (13 questions in all), Factor 2: Anxiety and dissatisfaction with treatment (8 questions in all), Factor 3: Hypoglycemia (4 questions in all) and Factor 4: Treatment satisfaction (4 questions in all)] at each assessment time point.
- Change in the total score for all questions in the DTR-QOL Questionnaire at each assessment time point.
- Change in the total score for all questions in the Diabetes Treatment Satisfaction Questionnaire (DTSQ) at each assessment time point.
- Changes in the total scores for all questions in the DTR-QOL Questionnaire and DTSQ,

stratified by the following factors at the start of the treatment period (Week 0) within each treatment group.

- Use of medication for treatment of comorbidities
- Number of daily doses, including medication for treatment of comorbidities (<2 times or ≥2 times)
- Total number of daily tablets, including medication for treatment of comorbidities (<2 tablets or ≥2 tablets)
- Number of doses of the study drug or comparative drug (once weekly, once daily or twice daily)

- Changes in the scores per question in the DTR-QOL Questionnaire at each assessment time point.
- Changes in the scores per question in the DTSQ at each assessment time point.

Safety assessment:

- Adverse events
- Incidence of hypoglycemia
- Hospitalization for type 2 diabetes (duration and number, excluding educational hospitalization without worsening of diabetes)

<Other Endpoints>

- Laboratory tests [HbA1c, fasting blood glucose, fasting insulin, fasting glucagon, glycoalbumin, 1,5-AG, serum creatinine, urinary 8-OHdG (using a correction value of uric creatinine (8-OHdG/creatinine)) and urinary creatinine]
- Treatment compliance
- The Basic Information on Study Subject (Your Basic Profile)

STATISTICAL ANALYSIS METHODS:

<Analysis Sets>

Two analysis sets comprising the "Full Analysis Set (FAS)" and the "Safety Population" will be established. The FAS used as the main efficacy analysis set is defined as "randomized subjects who receive at least one dose of trelagliptin or daily DPP-4 inhibitor." The safety population is defined as "subjects who receive at least 1 dose of trelagliptin or daily DPP-4 inhibitor."

<Primary endpoint>

- Change from baseline (Week 0) in total score for all question items in the DTR-QOL Questionnaire at the end of the treatment period (Week 12).

  (1) A comparison between the treatment groups will be carried out based on the ANCOVA model using a change in the total score by the end of treatment [the end of the treatment period (Week 12) - baseline (Week 0)] as a dependent variable; the total score at the baseline (Week 0), the total score of the DTR-QOL Questionnaire (<80% or ≥80%) at the start of the screening period and HbA1c (<8.0% or ≥8.0%) at the start of the screening period as covariates; and a treatment group as an independent variable. The level of significance will be 5% (two-sided).

<Secondary endpoints>

Efficacy endpoints:

- Change in the total score for each factor provided through the DTR-QOL Questionnaire [“Factor 1: Burden on social activities and daily activities (13 questions in all)”, "Factor 2: Anxiety and dissatisfaction with treatment (8 questions in all)", “Factor 3: Hypoglycemia (4 questions in all)”, and “Factor 4: Treatment satisfaction (4 questions in all)”] at each assessment time point.
- Change in the total score for all questions in the DTR-QOL Questionnaire at each assessment time point.
- Change in the total score for all questions in the DTSQ at each assessment time point.

  (1) Summary statistics [sample size, mean, standard deviation (SD), maximum, minimum and quantile] and the two-sided 95% confidence interval (CI) for means per treatment group at each assessment time point will be calculated to plot the changes in means and SDs. Point estimates and the two-sided 95% CI for differences between the treatment groups will also be calculated.

  (2) Changes from the baseline (Week 0) to each assessment time point will be calculated to be similarly analyzed to 1) above.

  (3) The analyses below carried out on the total score for each factor provided through the DTR-QOL Questionnaire, and on the total score for DTSQ:

  A comparison between the treatment groups will be carried out based on the ANCOVA model using a change in the total score by the end of treatment [the end of the treatment period (Week 12) - baseline (Week 0)] as a dependent variable; the total score at the baseline (Week 0), the total score of "the DTR-QOL Questionnaire (<80% or ≥80%)" at the baseline (Week 0) and "HbA1c (<8.0% or ≥8.0%)" at the baseline (Week 0) as

covariates; and a treatment group as an independent variable. The level of significance will be 5% (two-sided). Note that the total score for all questions in the DTR-QOL is out of the scope of the analysis.

(4) To indicate the changes in the total scores for all questions in the DTR-QOL Questionnaire and DTSQ, the summary statistics and two-sided 95% CI for means per treatment group will be calculated, with stratification by the following factors at the start of the treatment period (Week 0):

- Use of medication for treatment of comorbidities
- Number of daily doses, including medication for treatment of comorbidities (<2 times or ≥2 times)
- Total number of daily tablets, including medication for treatment of comorbidities (<2 tablets or ≥2 tablets)
- Number of doses of the study drug or comparative drug (once weekly, once daily or twice daily)

- Changes in the scores per question in the DTR-QOL Questionnaire at each assessment time point.
- Changes in the scores for per question in the DTSQ at each assessment time point.

(1) Summary statistics for measurements and the changes from the baseline (Week 0) will be calculated per treatment group.

Safety endpoints:

Frequency tables will be prepared for the incidences of adverse events, hypoglycemia, and hospitalization (duration and number) for type 2 diabetes after the first administration of the study drug or comparative drug in the “safety population” in each treatment group.

<Other Endpoints>

Summarizations below will be performed in the "full analysis set" (FAS).

- Laboratory tests

  Summary statistics for measurements and the changes from the baseline (Week 0) will be calculated per treatment group to plot the changes in means and SDs.

- Treatment compliance

  Treatment compliance of each study subject will be calculated and summary statistics of compliance per treatment group will be presented.

- The Basic Information on Study Subject (Your Basic Profile)

Frequency of answers to each question at each visit will be analyzed per treatment group.
Rationale for the number of planned study subjects: In this clinical study, to discuss the changes in the total score for all questions in the DTR-QOL Questionnaire from the baseline (Week 0) to the end of the treatment period, as the primary endpoint, mean changes in the daily DPP-4 inhibitor and trelagliptin groups were assumed as 14.4% and 19.0%, respectively. The mean change in the daily DPP-4 inhibitor group was assumed by reference to the data on a sodium glucose transporter 2 (SGLT2) inhibitor, from the previous research; and that in trelagliptin group was assumed by reference to the data from the validation trial of the DTR-QOL Questionnaire. The common SD was assumed as 12.1 % considering the former assumption. When 5% of significance level (two-sided) is based for the analysis of the primary endpoint, 110 subjects per group would be needed to ensure 80% power in comparisons between the trelagliptin group and daily DPP-4 inhibitor group. As this is a study on treatment for type 2 diabetes with DPP-4 inhibitors currently used in the medical setting, the number of randomized subjects was established as 120 subjects per group, for a total of 240 subjects, assuming a type 2 diabetes treatment discontinuation rate of 8%*. *Based on the results for Topic 2 of the “Strategic Studies on the Prevention of Diabetes” (JDOIT-2), the annual discontinuation rate for the “usual care group” without intervention is approximately 8%.

3.0 ABBREVIATION

AE	adverse event
COI	conflict of interest
CRO	contract research organization
DTSQ	Diabetes Treatment Satisfaction Questionnaire
DTR-QOL	Diabetes Therapy-Related QOL
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization of Technical Requirement for Registration on Pharmaceuticals for Human Use
MHRA	Medicines and Healthcare Products Regulatory Agency
MedDRA	Medical Dictionary for Regulatory Activities
QOL	Quality Of Life
SAE	serious adverse event
SAP	statistical analysis plan

4.0 INTRODUCTION

4.1 Background

The aim of diabetes treatment is to maintain Quality of Life (QOL) similar to that of healthy people and continue the same QOL for life as that of healthy people [1)]. Well controlled blood glucose, lipid and blood pressure levels to prevent complications in the early stages and greatly influence the patients' QOL and prognoses. One of the characteristics of diabetes is a tendency of frequent treatment discontinuation because a patient tends to be unaware of his/her disease even after a diagnosis of diabetes due to limited subjective symptoms during the early stages without notable complications. However, in diabetes treatment, prevention of complications or slow disease progression cannot be expected unless the patient is committed to the treatment; therefore, the key point in diabetes treatment is to improve the patients' QOL to enable continued management of diabetes. On the other hand, discontinuation of diabetes treatment leads to progression of disease complications and poor QOL. Patients' understanding of the treatment and the relationship between patients and medical personnel are important [2)]. The research using an auto-recording system captured medication use reported that the level of compliance is decreased as dosing frequency increased [3)]. In this context, to minimize the dosing frequency (number of tablets) is expected to contribute to the improvement in the QOL and treatment satisfaction.

Dipeptidyl peptidase 4 (DPP-4) inhibitors inhibit degradation of gastrointestinal hormones GIP and GLP-1, and thereby, enhance incretin effects glucose-level-dependently, and consequently decrease blood glucose. In Japan, the first DPP-4 inhibitor was approved in December 2009. Since then, many "daily-dosing" DPP-4 inhibitors have been approved one after another which required to be taken every day. In March 2015, trelagliptin was approved as the world's first "weekly-dosing" DPP-4 inhibitor. In the use of trelagliptin, benefits of improving medication adherence are expected due to less frequent dosing compared with existing oral glucose-lowering medications, especially in patients who are starting oral glucose-lowering monotherapy.

4.2 Rationale for the proposed study

QOL study in patients with type 2 diabetes starting treatment with oral glucose-lowering medications can be expected to provide useful rationales in choosing a therapeutic medication corresponding to various lifestyles of patients. DPP-4 inhibitors, including "daily-dosing" products, have presented limited evidence regarding effects on the QOL of diabetes patients.

Accordingly, this study has been proposed to assess trends in the reduction of treatment burden using the Diabetes Treatment Satisfaction Questionnaire (DTSQ). Also, to assess changes and trends in the QOL at pre- and post-treatment of trelagliptin or a daily DPP-4 inhibitor in diabetes patients solely

controlled by diet/exercise therapy, comparing the "weekly-dosing" product with "daily-dosing" products, using the Diabetes Therapy-Related QOL (DTR-QOL) Questionnaire.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

The objective is to assess the reduction in treatment burden during 12 weeks of trelagliptin administration in patients with type 2 diabetes on diet and exercise therapy only.

5.2 Definition of endpoints

5.2.1 Primary endpoints

Change from baseline (Week 0) in total score for all question items in the DTR-QOL Questionnaire at the end of the treatment period (Week 12) .

5.2.2 Secondary endpoints

5.2.2.1 Efficacy assessment:

- Changes in the total score for each factor provided through the DTR-QOL Questionnaire [Factor 1: Burden on social activities and daily activities (13 questions in all), Factor 2: Anxiety and dissatisfaction with treatment (8 questions in all), Factor 3: Hypoglycemia (4 questions in all) and Factor 4: Treatment satisfaction (4 questions in all)] at each assessment time point.
- Change in the total score for all questions in the DTR-QOL Questionnaire at each assessment time point.
- Change in the total score for all questions in the Diabetes Treatment Satisfaction Questionnaire (DTSQ) at each assessment time point.
- Changes in the total scores for all questions in the DTR-QOL Questionnaire and DTSQ, stratified by the following factors at the start of the treatment period (Week 0) within each treatment group.
  - Use of medication for treatment of comorbidities
  - Number of daily doses, including medication for treatment of comorbidities (<2 times or ≥2 times)
  - Total number of daily tablets, including medications for treatment of comorbidities (<2tablets or ≥2 tablets)
  - Number of doses of the study drug or comparative drug (once weekly, once daily or twice daily)
- Changes in the score per question in the DTR-QOL Questionnaire at each assessment time point.

- Changes in the score per question in the DTSQ at each assessment time point.

5.2.2.2 Safety endpoints

- Adverse events
- Incidence of hypoglycemia
- Hospitalization for type 2 diabetes (duration and number, excluding educational hospitalization without worsening of diabetes)

5.2.3 Other Endpoints

- Laboratory tests [HbA1c, fasting blood glucose, fasting insulin, fasting glucagon, glycoalbumin, 1,5-AG, serum creatinine, urinary 8-OHdG (using a correction value of uric creatinine (8-OHdG/creatinine)) and urinary creatinine]
- Treatment compliance
- The Basic Information on Study Subject (Your Basic Profile)

6.0 CLINICAL STUDY DESIGN

6.1 Clinical study design

<Clinical study design>

This is a multi-center, randomized, open-label, parallel-group comparison study to assess the reduction in treatment burden during the administration of a DPP-4 inhibitor (trelagliptin or a daily DPP-4 inhibitor) for 12 weeks in patients with type 2 diabetes on diet and exercise therapy only.

Eligible study subjects as a result of eligibility assessment after giving informed consent will be randomized to either of the study drug (trelagliptin) group or the comparative drug (daily DPP-4 inhibitor) group as specified in Section 8.4.

< Dosage and Administration>

The study drug group: Trelagliptin 100 mg is orally administered once weekly. Trelagliptin 50 mg is orally administered once weekly in patients with moderate renal impairment.

The comparative drug group: An inhibitor is orally administered at the dosage and administration in the package inserts for each drug.

<Evaluation period and visit frequency for study subjects>

Evaluation period: 16 weeks (Screening period: 4 weeks; treatment period: 12 weeks)

Number of visits: total 4 visits

A study subject will visit to his/her study site at the start of the screening period (Visit 1; Week -4), at the start of the treatment period (Visit 2; Week 0 of the treatment period), during the treatment period (Visit 3; Week 4 of the treatment period) and at the end of the treatment period (Visit 4; Week 12 of the treatment period).

<Planned number of study subjects>

As the number of randomized subjects:

The study drug (Trelagliptin) group 120 subjects

The comparative drug (daily DPP-4 inhibitor) group 120 subjects

<Number of study sites>

Approximately 15

Figure 6 (a) shows an outline of the clinical study design. Refer to Appendix A for schedule of examinations, observations, and evaluations.

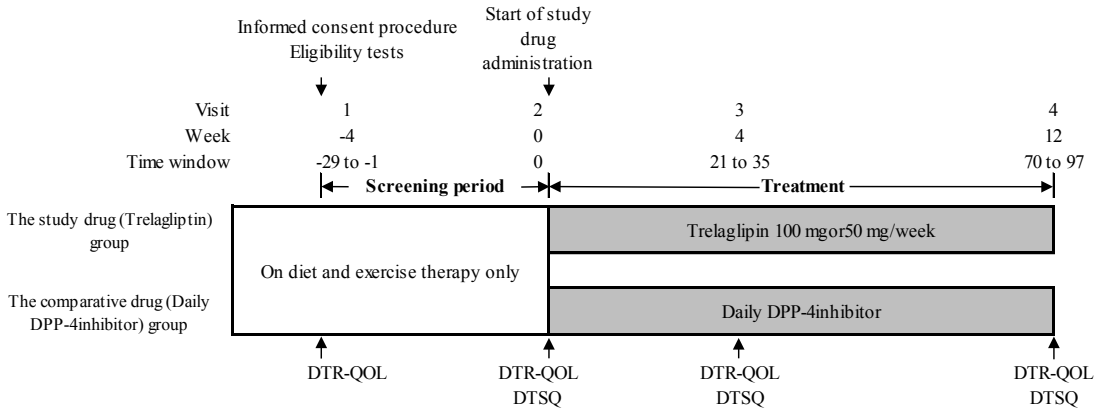
Informed consent procedure
Eligibility tests
Start of study drug administration
Visit 1 2 3 4
Week -4 0 4 12
Time window -29 to -1 0 21 to 35 70 to 97
Screening period
Treatment
The study drug (Trelagliptin) group
Trelaglipin 100 mgor50 mg/week
On diet and exercise therapy only
The comparative drug (Daily DPP-4inhibitor) group
Daily DPP-4inhibitor
DTR-QOL
DTR-QOL DTSQ
DTR-QOL DTSQ
DTR-QOL DTSQ

Figure 6.a Outline of the clinical study design

<Outline of the clinical study>

Duration of treatment: 12 weeks

Number of visits: 4 visits

6.2 Rationale for the clinical study design

(1) Rationale for the clinical study design

The study was designed as an open-label, parallel-group comparative study, to assess impact of trelagliptin on QOL of type 2 diabetes compared with Daily DPP-4 inhibitors. In conducting this parallel-group comparative study, randomization with stratification will be performed, using "the total score for all factors (1-4) in the DTR-QOL Questionnaire (<80% or ≥80%)" and "HbA1c (<8.0% or ≥8.0%)" as stratification factors, for the purpose of adjusting effects on the reduction level of diabetes treatment burdens in patients controlled by diet/exercise therapy during Visit 1.

(2) Rationale for the study period

The treatment period was designed as 12 weeks, because switch to other treatment including combination therapy with other medications is recommended for a case fails to achieve the therapeutic target following three-month continuous administration, as the evaluation on responses to treatment with oral diabetic medications [1)], and in a study which investigate changes in DTR-QOL score during treatment with sodium glucose transporter 2 (SGLT2) inhibitor, statistically significant increase in the score was observed at 12 weeks of treatment and scores at 12 weeks and 24 weeks was comparable.

(3) Rationale for the number of planned study subjects

See Section 13.3.

6.3 Premature termination of entire clinical study or premature termination of clinical study at a study site

6.3.1 Premature termination criteria of entire clinical study

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 study subject participation in the study.

- When there is serious deviation from Ethical Guidelines or ICH-GCP for medical and health study involving human subjects.

6.3.2 Criteria for premature termination of study sites

Termination of involvement of a study site in the study may be requested prematurely at the discretion of the sponsor if the entity (e.g., principal investigator) is found to have significant violation of the ethical guidelines, protocol, or contractual agreement for medical and health study involving human subjects or becomes unable to ensure proper conduct of the study, or otherwise as specified in the contractual agreement.

6.3.3 Procedures of clinical study suspension and premature termination of entire clinical study or clinical study at a study site

In the event that the sponsor or a study site committee such as an Ethical Review Board decides to prematurely suspend or terminate the entire clinical study or clinical study at a study site, a study-specific procedure shall be provided by the sponsor. The procedure shall be followed by applicable study sites 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 study site shall be informed of the details of each protocol revision. 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 study site shall submit the revised contents to committees such as the Ethical Review Board, as necessary according to institutional regulations for review, and obtain approval from the director of the entity.

7.0 SELECTION AND WITHDRAWAL CRITERIA OF STUDY SUBJECTS

The principal investigator or investigator shall check for all the inclusion/exclusion criteria including the test results prior to randomization.

7.1 Inclusion criteria

Eligibility of study subjects shall be determined in accordance with the following criteria.

1. Patients diagnosed as type 2 diabetes.
2. Patients with a stable diet and exercise therapy only for at least 12 weeks prior to the start of the screening period.
3. Patients who require a DPP-4 inhibitor treatment.
4. Patients with HbA1c ≥6.5 % and <10.0 % at the start of the screening period.
5. Patients who completed DTR-QOL questionnaire at the start of the screening period.
6. Patients who have receive less than 2 types of medication for treatment of comorbidities (such as hypertension or dyslipidemia) at the start of the screening period (any number of daily doses).
7. Patients who, in the opinion of the principal investigator or the investigator, are capable of understanding the content of the clinical study and complying with the study protocol requirements.
8. Patients who can provide the written informed consent prior to the initiation of any study procedures.
9. Patients aged ≥20 years at the time of informed consent.
10. Outpatient.

[Rationale for the inclusion criteria]

1-3: These were set to specify a study subject applicable to achieve objective of this study.

4: The lower and upper limits were set to include a study subject whom treatment with oral glucose-lowering medications is considered to require and who is suitable for glucose-lowering monotherapy.

5: This was set because total score of DTR-QOL questionnaire at the start of the screening period is stratifying factor of randomization.

6: This was set to minimize influences on drug taking behavior by medications for comorbidities in the QOL study.

7-10: These were set as fundamentals for this study.

7.2 Exclusion criteria

Study subjects meeting any of the criteria below shall not be included in this study.

1. Patients who are receiving any oral anti-diabetic medication for the treatment of type 2 diabetes at the start of the screening period.
2. Patients diagnosed as type 1 diabetes.
3. Patients with severe renal impairment or renal failure (e.g., eGFR <30 mL/min/1.73 m^2 or on dialysis).
4. Patients with serious heart disease or cerebrovascular disorder, or serious pancreatic, blood, or other disease.
5. Patients with a history of gastrointestinal resection.
6. Patient with a proliferative diabetic retinopathy.
7. Patient with malignancy.
8. Patients with a history of hypersensitivity or allergy to DPP-4 inhibitors.
9. Pregnant, lactating or postmenopausal women.
10. Patients who may need to add or discontinue concomitant medication or change the dose during the study period.
11. Patients who will require treatment with a prohibited concomitant medication during the study period.
12. Patients participating in other clinical studies.
13. Patients assessed ineligible in the study by the principal investigator or the investigator.

[Rationale for the exclusion criteria]

1, 10: These were set to exclude influences on senses of burden against treatment using concomitant medications including diabetic medications other than the allocated oral glucose-lowering medication.

2: This was set to exclude patients with type 1 diabetes, because the indications of trelagliptin and daily DPP-4 inhibitors are for "type 2 diabetes."

3: This was set to exclude patients with severe renal dysfunction or renal failure, because trelagliptin is contraindicated in such patients.

4-8, 11: These were set in consideration of patient safety.

9: This was set because trelagliptin should not be administered in pregnant or possibly pregnant females unless potential therapeutic benefits outweigh risks, and because excretion of trelagliptin and alogliptin into milk was observed in the non-clinical studies.

12, 13: These were set as fundamentals for this study.

7.3 Prohibited concomitant drugs and permitted concomitant drugs

The use of diabetic medications other than allocated oral glucose-lowering medication will be prohibited during from the start of the screening period (Week -4) until the end of the treatment period (Week 12).

<Rationale of prohibited concomitant drugs>

It was designed due to potential influences on the assessment of this clinical study.

7.4 Study 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.

(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) 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.

(4) On visit days for planned laboratory tests, give instructions for fasting ≥ 10 hours before visit.

(5) 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.

(6) 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.

(7) 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 study subject

The principal investigator or investigator shall record the main reason for discontinuation of protocol treatment on the case report form (CRF) according to the classification described below. Refer to Section 9.1.15 for study subjects who withdraw from the study before randomization.

1. Adverse events

When the study subject had an adverse event that requires withdrawal of the study subject from the study because continued participation in the study would impose an unacceptable risk to the

study subject's health, or when the study subject is unwilling to continue study participation because of the adverse event.

2. Major protocol deviation

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

3. Lost to follow-up

When the study subject failed to make visits and could not be contacted despite the attempts to contact the study subject.

4. Voluntary termination

When the study subject wishes to withdraw from the study. The reason for discontinuation shall be obtained to the extent possible.

5. Study termination

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

6. Pregnancy

When a female study subject was found to be pregnant.

Note: The study subject must discontinue the study immediately after she was found to be pregnant. Refer to Section 9.1.13 for the procedures.

7. Lack of efficacy

When efficacy of the study drug is not evident and continuation of the study may pose an unacceptable risk to the study subjects in the opinion of the principal investigator or investigator.

8. Others

When the principal investigator or investigator determined to terminate the study for other reasons.

The specific reasons should be recorded on the CRF.

7.6 Procedures for discontinuation of individual study subjects

The principal investigator or investigator shall terminate a study subject's study participation when the study subject meets the criteria described in Section 7.5. Individual study subjects may discontinue their study participation without giving a reason at any time during the study. Should a

study 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 STUDY 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 Study drug and Comparative drug

8.1.1 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

<Dose and administration method>

Trelagliptin: Trelagliptin 100 mg is orally administered once weekly. Trelagliptin 50 mg is oraly administered once weekly in patients with moderate renal impairment.

8.1.2 Comparative drug

Daily DPP-4 inhibitor: Inhibitors shown in Table 8.a are orally administered at the dosage and administration instructed in the package inserts of each drug.

Table 8.a Daily DPP-4 inhibitor

Inhibitors	Dosage and Administration
Sitagliptin: CCI Vildagliptin: CCI Alogliptin: CCI Linagliptin: CCI Teneligliptin: CCI Anagliptin: CCI Saxagliptin: CCI	Take orally in accordance with the instructions in the package inserts.

8.2 Overdose of the study drug

Overdose is defined as intentional or accidental administration of the study drug or comparative drug at a higher dose than that specified in the package inserts, either by a health professional or by the study 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 serious adverse events."

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

8.3 Medication other than the study drug and the comparative drug

Prohibited concomitant drugs (refer to Section 7.3.1) may not be used. Other treatments shall be conducted under normal medical practice.

In principle, concomitant medications cannot be added or withdrawn, and the dosages of concomitant medications cannot be changed during this clinical study period (refer to the section 7.2). However, the addition of concomitant medications will be allowed as long as the principal investigator or investigator considers its necessity due to reasons such as adverse events. The principal investigator or investigator shall provide directions to study subjects not to take any medications (including over-the-counter drugs) other than the medications instructed to use without prior consultation.

8.4 Allocation of the study drug and administration procedure

The principal investigator or the designee shall access the Case Registration Web System to allocate the study subjects. The principal investigator or the designee shall notify the information required for allocation in addition to the study subject identification (ID) code. Then, drugs that should be administered to each study subject will be notified through the Case Registration Web System. The principal investigator or investigator shall prescribe the study drug or comparative drug according to the notification, and record the drug information (the name, dose per administration, number of daily administration and number of tablets per administration) into the CRF of each research subject.

8.5 Preparation and storage of allocation list

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

Study subjects will be allocated at the Case Registration Center through the Case Registration Web System, using "the total score for the DTR-QOL Questionnaire [<80% (<168.2 as a score) or ≥80% (≥168.2 as a score※)]" and "HbA1c (<8.0% or ≥8.0%)" at the start of the screening period as stratification factors. The Case Registration Center will use the allocation list for stratification prepared by the allocation responsible person in operating the treatment allocation.

※ Refer to the section 9.1.9 for the calculation method of the total score for the DTR-QOL Questionnaire.

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 Clinical study procedures

The principal investigator or investigator shall collect data in accordance with the procedure below. In principle, all the tests, observations, and evaluations of study subjects shall be performed by the same principal investigator or investigator with the exception of the specific 20-lipoprotein fraction. The study schedule is provided in Appendix A.

9.1.1 Informed consent

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

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

A study subject ID code will be given to each study subject who provided informed consent, and then the study subject is to be de-identified. The study subject ID code shall be used throughout the study period and shall not be changed.

9.1.2 Demographic data and medical history

The following data will be collected as demographic data:

- Date of birth, sex, smoking history, alcohol intake history, the time (month and year) of diabetes onset (or a diabetes diagnosis)

As medical history, the information on clinically problematic diseases and symptoms resolved/recovered within a year before the start of the screening period will be collected. A continuous disease/symptom will be considered as a comorbidity.

9.1.3 Physical examination

The presence/absence of clinically significant abnormalities at subsequent physical examinations during the course of this study treatment will be determined compared with the baseline physical examination.

9.1.4 Body weight, height, and BMI

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

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

The sponsor will calculate BMI using the formula below, showing one decimal place.

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

9.1.5 Concomitant drugs

Concomitant drugs are all drugs to be given in addition to the study drug or comparative drug. Drugs prescribed by physicians or the over-the-counter medicines purchased by the study subjects shall be included. At every visit of the study subject, any use of drugs (name, dosage/administration, route of

administration, duration of use, and intended use) shall be investigated and recorded on the CRF from the start of the screening period to the completion of the clinical study. In addition, the followings shall be recorded on the CRF; any use of therapeutic drugs for comorbidity *; number of daily doses of drugs including therapeutic drugs for comorbidities (<2 times or ≥2 times); and total number of daily tablets including of therapeutic drugs for comorbidity (<2 tablets or ≥2 tablets) from the start of the screening period to the completion of the clinical study.

* For recording of any use of therapeutic drugs for comorbidity; number of daily doses of drugs including therapeutic drugs for comorbidity (<2 times or ≥2 times); and total number of daily tablets including of therapeutic drugs for comorbidity (<2 tablets or ≥2 tablets), drugs for as-needed use and topical use and supplements are not be included. For drugs for once-weekly use, the numbers shall be divided by 7 for recording.

9.1.6 Comorbidities

A comorbidity shall be defined as a disease or symptom present at the start of the screening period or observed from the start of the screening period until before the start of study drug or comparative drug administration. Clinically problematic laboratory tests and abnormal physical examination findings, etc. observed through the first tests and physical examination at the start of the screening period shall be considered as comorbidities at the discretion of the principal investigator or investigator. The details of comorbidities (diagnoses) shall be investigated.

9.1.7 Laboratory tests

The laboratories will perform the tests shown below in accordance with the Schedule for Study Procedures (Appendix A). The tests will be performed under the ≥10-hour fasting condition. The principal investigator or investigator will retain the reported results of laboratory tests along with evaluating them..

Table 9.a Laboratory tests

Serum chemistry	
・ HbA1c	・ Glycoalbumin
・ Fasting blood glucose	・ 1,5-AG
・ Fasting insulin	・ serum creatinine
・ Fasting glucagon	
Urinalysis	
・ urinary 8-OHdG	・ Urinary creatinine

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

9.1.8 The Basic Information on Study Subject (Your Basic Profile)

Study subjects will answer the "Your Basic Profile" regarding their diabetes therapy at each assessment time point during the screening period and treatment period. The principal investigator or investigator will provide directions to the study subjects to answer all questions truthfully, which will be recorded on the CRF. Of note, in the column "Other drugs than diabetic drugs (e.g., for hypertension)" in the "Your Basic Profile", drugs prescribed in a medical institution shall be recorded. (Supplements and medicines for as-needed use are not included, even though it was prescribed in a medical institution.)

9.1.9 DTR-QOL Questionnaire

Subjects will answer the DTR-QOL Questionnaire (all 29 questions) [5)] regarding the diabetes therapy being conducted at each assessment time point during the screening period and treatment period. The investigator will instruct the subjects to answer all questions truthfully and record the scores of each question of the DTR-QOL Questionnaire (29 questions in total) on the CRF.

[Calculation of the total score based on answers of the DTR-QOL Questionnaire]

・ Calculation method of the total score of Factor 1: "burden on social activities and daily activities" (13 questions in all)

  Every score of the question number 1-13 will be simply added up, and the total figure will be subsequently converted to percentage [the best (91) and worst (13) scores will be equivalent to 100% and 0%, respectively].

・ Calculation method of the total score of Factor 2: "anxiety and dissatisfaction with treatment" (8 questions in all)

Every score of the question number 14-21 will be simply added up, and the total figure will be subsequently converted to percentage [the best (56) and worst (8) scores will be equivalent to 100% and 0%, respectively].

- Calculation method of the total score of Factor 3: "hypoglycemia" (4 questions in all)

  Every score of the question number 22-25 will be simply added up, and the total figure will be subsequently converted to percentage [the best (28) and worst (4) scores will be equivalent to 100% and 0%, respectively].

- Calculation method of the total score of Factor 4: "treatment satisfaction" (4 questions in all)

  Each score of the question number 26-29 will be converted into reverse (i.e., 1 will be converted to 7, 7 will be converted to 1, and so on. The converted scores, where 7 is the best and 1 is the worst, have the opposite sequence of the original scores). Then, the converted scores will be simply added up, and the total figure will be subsequently converted to percentage [the best (28) and worst (4) scores will be equivalent to 100% and 0%, respectively].

- Calculation method of the total score of all questions

  Each score of the question number 26-29 will be converted into reverse, as described above, and then these converted scores and original scores of the question number 1-25 will be simply added up. Subsequently, the total figure will be converted to percentage [the best (203) and worst (29) scores will be equivalent to 100% and 0%, respectively].

If some answers of a questionnaire are unavailable (i.e., missing data), the scores will be handled in the manner below:

Factor 1-4: As for a factor associated with <50% missing data, the mean value calculated from available answers will be applied to cover the missing data.

The total score for a factor with ≥50% missing data should not be calculated.

The total score of whole questions should not be calculated as well, if a total score of any of the four factors is unavailable.

9.1.10 DTSQ

Subjects will answer the DTSQ (all 8 questions) [6), 7)] regarding the diabetes therapy being conducted at each assessment time point during the treatment period. The investigator will instruct the subjects to answer all questions truthfully and record the scores of each question of the DTSQ (8 questions in total) on the CRF.

9.1.11 Treatment Compliance

Throughout the study period, instructions for treatment will be given to subjects. If instructions were given for treatment incompliance, the details will be recorded on the source document. At each visit, the investigator will check with subjects the treatment compliance status with study drug or comparative drug.

The investigator will instruct the subjects to record study drug or comparative drug usage on a "Diabetes Treatment Medication Record Card*." The subjects will also be instructed to bring empty sheets allowing compliance and usage to be checked along with the "Diabetes Treatment Medication Record Card*" at each visit. The treatment compliance status with the study drug or comparative drug (administration time and quantity of the study drug or comparative drug prescribed and unused) will be recorded on the CRF throughout the study period.

*: Diabetes Treatment Medication Record Card: The card contains an electronic circuit board, and the times that medication is taken are electronically recorded by pressing a button when medication is taken.

9.1.12 Hospitalization for type 2 diabetes

The investigator will check with study subjects any hospitalization for type 2 diabetes after the first administration of the study drug or comparative drug (excluding educational hospitalization without worsening of diabetes). The admission-discharge date will be recorded on CRF.

9.1.13 Contraception

Female subjects of childbearing potential (e.g., nonsterilized or premenopausal female subjects) must use adequate contraception from signing on the informed consent throughout the study period. At the time of acquisition of informed consent from an applicable study subject, signature on the informed consent should be acquired only after explanation is made about what is the adequate contraception and that the subject must avoid to be pregnant during the study period by use of the informed consent form until the subject thoroughly understands them.

9.1.14 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.

9.1.15 Record of study subjects who are withdrawn before randomization

A CRF shall be created for all study subjects who have signed the consent form and withdrawn before randomization.

The following items are to be described on the CRF.

- Date of consent obtainment
- Date of birth
- Gender
- Eligibility
- Reason for discontinuation

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

- Not satisfying at least one of the inclusion criteria or meeting any of the exclusion criteria
- Major protocol deviation
- Lost to follow-up
- Voluntary discontinuation (specify the reason)
- Study termination
- Pregnancy
- Others (specify the reason)

Study subject ID codes assigned to study subjects withdrawn from the study before randomization shall not be reused.

9.1.16 Record of randomization

Study subjects to be randomized shall meet all of the inclusion criteria and shall not meet any of the exclusion criteria according to Section 8.4. The principal investigator or investigator shall specify the primary reason why the study subject cannot be randomized.

9.2 Implementation time point of the tests and observation

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.

9.2.1 Screening period (Week -4)

After obtaining informed consent, the physical examination and tests will be performed for the determining eligibility for study enrollment. The eligibility of a patient will be determined based on the inclusion/exclusion criteria presented in the section 7.0. Refer to the section 9.1.16 for the preparation of records on a study subject withdrawn from the study before randomization.

Tests, observations and evaluations performed at the start of the screening period (Visit 1: Day -29 to -1) are shown below.

- Informed consent
- Inclusion/ exclusion criteria
- Demographic data, medical history
- Physical examination*
- Height, body weight and BMI
- Concomitant drugs*
- Comorbidity*
- Laboratory tests (HbA1c only) *
- DTR-QOL Questionnaire*
- The Basic Information on Study Subject (Your Basic Profile)*

*: To be performed during from Day -29 until Day -14.

9.2.2 Treatment period (Week 0)

An eligible study subject in consequence of the tests, observations and evaluations before the start of the treatment period will be randomized in accordance with the section 8.4.

Tests, observations and evaluations performed at the start of the screening period (Visit 2: Week 0) are shown below.

- Inclusion/ exclusion criteria
- Physical examination
- Concomitant drugs
- Comorbidity
- Laboratory tests (blood chemistry and urinalysis)
- Prescription of the study drug/ or comparative drug
- DTR-QOL Questionnaire
- DTSQ
- The Basic Information on Study Subject (Your Basic Profile)
- Adverse event#
- Hospitalization for type 2 diabetes#

#: To be performed after the first administration (Day 1).

9.2.3 Treatment period (Week 4)

Tests, observations and evaluations performed during the treatment period (Visit 3: Week 4) are shown below.

- Physical examination
- Concomitant drugs
- Laboratory tests (blood chemistry and urinalysis)
- Prescription of the study drug/ or comparative drug
- DTR-QOL Questionnaire
- DTSQ
- The Basic Information on Study Subject (Your Basic Profile)
- Adverse event

- Treatment Compliance
- Hospitalization for type 2 diabetes

9.2.4 Treatment period (Week 12) or discontinuation

Tests, observations and evaluations performed at the end of study treatment (Visit 4: Week 12) are shown below.

- Physical examination
- body weight
- Concomitant drugs
- Laboratory tests (blood chemistry and urinalysis)
- Treatment Compliance
- DTR-QOL Questionnaire
- DTSQ
- The Basic Information on Study Subjects (Your Basic Profile)
- Adverse event
- Hospitalization for type 2 diabetes

Tests, observations and evaluations performed at the discontinuation are shown below.

- Physical examination
- Concomitant drugs
- Laboratory tests (blood chemistry and urinalysis)
- Treatment Compliance
-
- DTR-QOL Questionnaire
- DTSQ
- The Basic Information on Study Subject (Your Basic Profile)
- Adverse event evaluation
- Hospitalization for type 2 diabetes
- The reason for the discontinuation

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse events

An adverse event is defined as any untoward medical occurrence in a patient or a study subject receiving a pharmaceutical product (including the study drug or comparative drug). It does not necessarily have an apparent causal relationship with this pharmaceutical product (including study drug or comparative drug).

An adverse event can therefore be any unfavorable and unintended sign (e.g., a clinically significant laboratory abnormality), symptom, or disease temporally associated with the use of a pharmaceutical product (including the study drug or comparative drug), regardless of whether it is considered related to the pharmaceutical product (including the study drug or comparative 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 comparative 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) 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:

Abnormal laboratory values shall be recorded as adverse events when the principal investigator or the 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 study 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 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 (a disease or symptom that is present at the start of the screening period or that is observed from the start of the screening period until before the start of study drug/or comparative drug administration):
A disease or symptom that is present at the start of the screening period or that is observed from the start of the screening period until before the start of study drug/ or comparative drug administration are considered a comorbidity and not considered an adverse event. When a comorbidity 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 comorbidity (e.g., "aggravation of hypertension," etc.).

If a study 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 study 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 the investigator shall ensure that the adverse event term to be reported represents the change in the condition from baseline (e.g. "worsening of…").

Worsening of adverse events:
If a study subject experiences a worsening of the adverse event after a change of the study drug or comparative 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 the 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 study 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 treatment that were scheduled before the start of study drug or comparative drug administration 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 complication 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 study subject (cosmetic surgery, etc.) shall not be considered an adverse event; However, it shall be recorded in the source documents. Complications 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 the investigator shall make the distinction between worsening of a pre-existing condition and lack of therapeutic efficacy.

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

10.1.3 Serious adverse event

Of all the unfavorable medical events that develop with administration of a pharmaceutical product (including study drug/ or comparative 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. other medically significant condition: a medically important event that causes a risk to a study 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. In addition, 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 study 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 was 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 or comparative 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.

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 or comparative drug shall be classified and defined as shown below.

Related	An adverse event that follows a temporal sequence (including clinical course after discontinuation), or an adverse event in which there is at least a reasonable

	probability that a causal relationship to the study drug or comparative drug cannot be ruled out, although other factors such as underlying disease, complications, or concomitant drugs/treatment are also suspected.
Not related	An adverse event that does not follow a temporal sequence from administration of the study drug or comparative drug. Very likely due to other factors such as underlying disease, complications, or concomitant drugs/treatment.

10.1.7 Relationship to study procedures

The relationship shall be recorded as "Yes" if the principal investigator or the 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 event shall be determined according to the following rules:

Adverse events	Date of onset
Signs, symptoms, diseases (diagnoses)	The date on which the first signs/symptoms were noted by the study 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 complications	The date on which the first worsening of diseases/symptoms was noted by the study subject and/or the principal investigator or investigator.
Onset of a test abnormality after the start of study drug administration or comparative drug administration	The date on which a clinically significant laboratory abnormality was detected.
Worsening of a baseline test abnormality after the start of study drug administration or comparative drug administration	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 study subject recovered (including resolution with sequelae). If a study 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 study subject has not yet recovered by the end of the study.

10.1.10 Actions taken for the study drug or comparative drug

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

Drug withdrawn	The study drug or comparative drug is discontinued because of an adverse event (including withdrawal by the study subject at his/her own discretion). When the study is discontinued but administration of the study drug or comparative drug is still continued, the classification should be "Dose not changed."
Dose not changed	The dose was not changed after the onset of the adverse event. The study drug or comparative drug was discontinued, reduced, or increased because of another adverse event. The study drug was discontinued or reduced for a reason other than the adverse event, e.g., inadvertence of the study subject.
Unknown	It has not been possible to determine what action has been taken because the study subject is lost to follow-up.
Not Applicable	The administration of the study drug or comparative drug had already been completed or discontinued before the onset of the adverse event.
Dose reduced	The dose of the study drug or comparative drug is reduced because of an adverse event (including dose reduction by the study subject at his/her own discretion).
Dose increased	The dose of the study drug or comparative drug was increased because of the adverse event (including dose increase by the study subject at his/her own discretion).
Washout	If administration of the study drug or comparative drug is suspended (i.e., interrupted) (including suspension/interruption by the study subject at his/her own 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 study 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 study 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, etc. "Direct relationship" means that the concerned adverse event, etc. was the cause of death, or the concerned adverse event, etc. 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 study subject is not considered as 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 and its coverage

10.2.1.1 Adverse event collection period

Adverse events shall be collected from the start of administration with the study drug/ or comparative drug (day1) until completion of the treatment period (or discontinuation).

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 study subjects experiencing an adverse event irrespective of the causal relationship with the study drug or comparative drug, until the symptom resolve, or any clinically significant abnormal laboratory values have returned to baseline or there is a satisfactory explanation for the change (permanent and irreversible adverse events, etc.). All adverse events shall be recorded in the CRF. For the adverse event, the name, date of onset, date of resolution, category, severity, causal relationship with the study procedures (the procedure possibly having causal relationship, if applicable), causal relationship with the study drug or comparative drug (i.e. "Not related" or "Related"), action taken for the study drug or comparative drug, outcome, and seriousness shall be recorded.

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

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 after notification of the onset by the study subject, the principal investigator shall report the serious adverse event to the chief executive of the study site immediately, and the sponsor or the contract research organization (CRO) to whom the sponsor has entrusted responsibility shall notify the principal investigator of the study site.

The principal investigator shall then report the serious adverse event to the sponsor (for the contact information, refer to the attachment) within 1 working day after notification of the onset. Further, the 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
- Study subject ID code
- Name of principal investigator or the investigator
- Name of the study drug or comparative 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 Electronic Data Capture (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, principal investigator or the 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 study site (e.g., ECG charts, laboratory test values, discharge summary, postmortem results) shall be sent to the sponsor or the committee such as the Ethical Review Board 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 Ethical Review Board, etc., and regulatory authorities

When the chief executive of study site receives a report of a serious adverse event from the principal investigator, the chief executive of study site shall consult the Ethical Review Board, etc., and notify

the study sites that are conducting the clinical study through the sponsor or the CRO consigned by the sponsor.

When the principal investigator reported a serious adverse event for which a causal relationship to the study (study drug or comparative drug) cannot be ruled out and is unexpected, the chief executive of the study site 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 study sites conducting the clinical study. (The chief executive of the study site may report it to the Minister of Health, Labour and Welfare via the sponsor, and notify it to other clinical study sites via the sponsor.)

- Actions taken for serious adverse events
  (discontinuation of new enrollment, revision of informed consent form, re-consents to other study subjects, etc.)
- Date of review, summery of review, result, necessary action, etc., related to Ethical Review Board, etc.
- Notification to other collaborative study sites

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 the chief executive of study site.

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 risk-benefit of the study drug or comparative drug, continuation of administration of the study drug or comparative drug, or continuation of clinical study. The study site shall submit copies of emergency report documents to the Ethical Review Board, etc.

11.0 COMMITTEES ESTABLISHED FOR THIS STUDY

11.1 Clinical Study Steering Committee

The Clinical Study Steering Committee is composed of the chair and the sponsor. The Clinical Study Steering Committee supervise implementation and reporting of the clinical study, secure medical guidance of a high degree of professionalism and a high-level scientific quality, and revise the study protocol appropriately. The responsibilities of the committee shall be prescribed in the procedures of the Clinical Study Steering Committee.

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 comorbidities shall be coded using the MedDRA. Drugs shall be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 Case report form

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

The sponsor or the designee shall provide access rights to the EDC system to the study site. Before use of the EDC 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. CRF must be completed 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 CRF. 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 (unless recorded in the source document).

- Eligibility, completion status, reason for discontinuation, seriousness of adverse events, severity of adverse events and causal relationship between adverse events and the study drug or comparative drug or the study procedures, and outcome

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

- Laboratory test values

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; DCF) 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 the designee shall confirm that the CRFs are completed appropriately according to the procedures set by study. The sponsor or the designee shall have access to the medical records of

the study 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 the 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 EDC system

The sponsor or the designee shall request the principal investigator and investigator to promptly enter data into the EDC following enrolment of the study subject, each visit during treatment with the study drug or comparative drug, completion/discontinuation of the study, and follow-up period.

12.3 Storage of records

The principal investigator or the chief executive of the study site shall store the following materials, including those specified in Section 12.1, and study-specific documents to be investigated or audited by the regulatory authority and the sponsor or the designee. The documents include the list of study subject ID code, medical records, clinical study worksheets (if used), original signed and dated informed consent forms, the record (copy) of modification or correction on the CRF, and electric copies of EDC including audit trail. The principal investigator and the chief executive of the study site shall appropriately retain the material/information related to this study for at least 5 years from the date of reporting the end of the study 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 study site shall discuss the period and methods of storage with the sponsor.

13.0 STATISTICAL ANALYSIS METHODS

The person in charge of analysis and the designee [analysis personnel, who belongs to CRO independent from the sponsor] shall perform the statistical analysis. The sponsor will not be involved in the statistical analysis.

13.1 Statistical and analytical plans

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

13.1.1 Analysis set

Two analysis sets comprising the “Full Analysis Set (FAS)” and the “Safety Population” will be established. The FAS used as the main efficacy analysis set is defined as “randomized subjects who receive at least one dose of trelagliptin or daily DPP-4 inhibitor.” The safety population is defined as “subjects who receive at least 1 dose of trelagliptin or daily DPP-4 inhibitor.”

13.1.2 Analysis of demographic and other baseline characteristics

From “SAS” primary study subject background items will be tabulated.

13.1.3 Efficacy analysis

From FAS the following shall be analyzed.

<Primary endpoint>

Change from baseline (Week 0) in total score for all question items in the DTR-QOL Questionnaire at the end of the treatment period (Week 12).

1) A comparison between the treatment groups will be carried out based on the ANCOVA model using "the change in the total score by the end of treatment [the end of the treatment period - baseline (Week 0)]" as a dependent variable; "the total score at the baseline, the total score of the DTR-QOL Questionnaire (<80% or ≥80%) at the start of the screening period and HbA1c (<8.0% or ≥8.0%) at the start of the screening period as covariates; and "a treatment group" as an independent variable. The level of significance will be 5% (two-sided).

<Secondary endpoints>

Efficacy endpoints:

- Changes in the total score for each factor provided through the DTR-QOL Questionnaire ["Factor 1: Burden on social activities and daily activities (13 questions in all)", Factor 2: Anxiety and dissatisfaction with treatment (8 questions in all), "Factor 3; Hypoglycemia (4 questions in all)", and "Factor 4: Treatment satisfaction (4 questions in all)"] at each assessment time point.
- Change in the total score for all questions in the DTR-QOL Questionnaire at each assessment time point.
- Change in the total score for all questions in the DTSQ at each assessment time point.

1) Summary statistics [sample size, mean, standard deviation (SD), maximum, minimum and quantile] and the two-sided 95% confidence interval (CI) for means per treatment group at each assessment time point will be calculated to plot the changes in means and SDs. Point estimates and the two-sided 95% CI for differences between the treatment groups will also be calculated.
2) Changes from the baseline (Week 0) to each assessment time point will be calculated to be similarly analyzed to 1) above.
3) The analyses below carried out on the total score for each factor provided through the DTR-QOL Questionnaire, and on the total score for DTSQ:

   A comparison between the treatment groups will be carried out based on the ANCOVA model using "the change in the total score by the end of treatment [the end of the treatment period (Week 12) - baseline (Week 0)]" as a dependent variable; the total score at the baseline (Week 0), the total score of "the DTR-QOL Questionnaire (<80% or ≥80%)" at the baseline (Week 0) and "HbA1c (<8.0% or ≥8.0%)" at the baseline (Week 0) as covariates; and "a treatment group" as an independent variable. The level of significance will be 5% (two-sided). Note that the total score for all questions in the DTR-QOL is out of the scope of the analysis.
4) To indicate the changes in the total scores for all questions in the DTR-QOL Questionnaire and DTSQ, the summary statistics and two-sided 95% CI for means per treatment group will be calculated, with stratification by the following factors at the start of the treatment period (Week 0):

   - Use of medication for treatment of comorbidities
   - Number of daily doses, including medication for treatment of comorbidities (<2 times or ≥2 times)

- Total number of daily tablets, including medication for treatment of comorbidities (<2 tablets or ≥2 tablets)
- Number of doses of the study drug or comparative drug (once weekly, once daily or twice daily)

- Changes in the scores per question in the DTR-QOL Questionnaire at each assessment time point.
- Changes in the scores for per question in the DTSQ at each assessment time point.
  1) Summary statistics for measurements and the changes from the baseline (Week 0) will be calculated per treatment group.

<Other endpoints>

Summarizations below will be performed in the "full analysis set" (FAS).

- Laboratory tests

  Treatment compliance of each study subject will be calculated and summary statistics of compliance per treatment group will be presented.

- Treatment compliance
  Treatment compliance of each study subject will be calculated and summary statistics of compliance per treatment group will be presented.

- The Basic Information on Study Subject（Your Basic Profile）

  Frequency of answers to each question at each visit will be analyzed per treatment group.

13.1.4 Safety analysis

Frequency tables will be prepared for the incidences of adverse events, hypoglycemia, and hospitalization for type 2 diabetes (number and duration of hospitalization) after the first administration of the study drug or comparative drug administration in the “safety population” in each treatment group.

13.2 Criteria for interim analysis and premature discontinuation

No interim analysis is planned.

13.3 Determination of the number of planned study subject

In this clinical study, to discuss changes in the total score for all questions in the DTR-QOL Questionnaire from the baseline (Week 0) to the end of the treatment period, as the primary endpoint, mean changes in the daily DPP-4 inhibitor and trelagliptin groups were assumed as 14.4% and

19.0%, respectively. The mean change in the daily DPP-4 inhibitor group was assumed by reference to the data on SGLT2 inhibitor, from the previous research [4]; and that in trelagliptin group was assumed by reference to the data from the validation trial of the DTR-QOL Questionnaire [6]. The common SD was assumed as 12.1 % considering the former assumption. When 5% of significance level (two-sided) is based for the analysis of the primary endpoint, 110 subjects per group would be needed to ensure 80% power in comparisons between the trelagliptin group and daily DPP-4 inhibitor group. As this is a study on treatment for type 2 diabetes with DPP-4 inhibitors currently used in the medical setting, the number of randomized subjects was established as 120 subjects per group, for a total of 240 subjects, assuming a type 2 diabetes treatment discontinuation rate of 8%*.

*Based on the results for Topic 2 of the "Strategic Studies on the Prevention of Diabetes" (JDOIT-2), the annual discontinuation rate for the "usual care group" without intervention is approximately 8% [2].

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Monitoring of the study site

The sponsor or the designee shall perform periodic monitoring of the study site during the study to confirm that the study is conducted in accordance with all specifications in the study protocol. In the monitoring, 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 study site shall ensure that the sponsor or the designee and the Ethical Review Board, etc., have access to the source documents.

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

Detailed procedures for monitoring shall be described separately in the written procedures.

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

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

If any deviation is found, the principal investigator shall promptly notify the chief executive of the study site for the clinical study 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 study site for approval of the committee such as the Ethical Review Board.

14.3 Quality assurance audits and regulatory agency inspections

The sponsor or the designee shall perform audit at the study site as necessary. In such a case, the auditor designated by the sponsor shall contact the study site 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 study. In addition, this study 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 study site is contacted for an inspection by a regulatory body, the sponsor should be notified promptly. The

principal investigator and the chief executive of the study site shall ensure that the auditor has access to all the study-related source documents.

15.0 ETHICAL CONDUCT OF CLINICAL STUDY

This clinical study shall be conducted with the highest respect for the individual participants (i.e., study subjects) according to the study protocol, the ethical principles that have their origin in the Declaration of Helsinki, and "Ethical Guidelines for Medical and Health Research Involving Human Subjects." Each principal investigator will conduct the study according to regulatory requirements and in accordance with "Responsibilities of the Principal 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 the designee should obtain the document listing the name and title of each committee member. When a committee member directly participates in this clinical study, the document describing that he/she is not participating in deliberation or voting for the study will be obtained.

The sponsor or the designee shall supply relevant documents for submission to study site committee such as the Ethical Review Board for the protocol's review and approval. In addition to the study protocol, a copy of the informed consent form and information sheet, written materials related to study subject recruitment, advertisement, and other documents required by regulations, when necessary, shall be submitted to the central committee or a study site committee such as the Ethical Review Board to obtain approval. The sponsor or the designee must obtain written approval of the protocol and the informed consent form and information sheet from the study site committee such as the Ethical Review Board before commencement of the study. The study site committee such as the Ethical Review Board's approval must refer to the study by exact protocol title, number and version date; identify versions of other documents (e.g., informed consent form and information sheet) reviewed; and state the approval date. The sponsor shall notify the study site, the principal investigator, and investigator after confirming the validity of the regulatory documents of the study site. Protocol procedures such as obtainment of consent shall not be started until the study site, the principal investigator, and investigator receive notification.

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

15.2 Conflict of interest

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

Prior to the conduction of this clinical study, the principal investigators involved in this clinical study shall ensure appropriate management of any conflicts of interest (COI) in the conduct of the study in accordance with the rules of the study site.[9)-13)]

The study site shall observe all requirements that the Ethical Review Board, etc. prescribe. This will include self-declaration of COI, clinical study protocol, informed consent form and information sheet.

15.3 Informed consent form and information sheet, and the agreement of the study subjects

The informed consent 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 study subjects in this clinical study (both in and outside Japan: supply to a third party), and disclosure. The informed consent form will explain in detail the nature of the clinical study, its objectives, and potential risks and benefits. The informed consent form will detail the requirements of the participant and the fact that study subject is free to withdraw at any time without giving a reason and without any negative effect on 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 Ethical Review Board. The informed consent form and information sheet must be approved by the committee such as the Ethical Review Board prior to use.

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

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 study 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 study subject.

The principal investigator or investigator shall follow the same procedure as for obtaining the initial consent when newly obtaining re-consent from the concerned study subject when the informed

consent form and information sheet is revised. The date of obtaining new consent shall be recorded in the study subject's medical record, and a copy of the revised consent form shall be provided to the study subject.

15.4 Personal information of the study subjects

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

For verification of the conduct of the study 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 study sponsor's designee, representatives of regulatory authorities, designated auditors, and committees such as the Ethical Review Board direct access to study subjects' original medical records (source data or documents), including laboratory test results, admission and discharge records during a subject's study participation, and autopsy reports. The principal investigator or investigator shall obtain specific authorization of the study subject as part of the informed consent process for access to study subject's original medical records by study 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 study subject, other personal information not recorded on the CRF of the study subject).

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

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

15.6 Financial burden or reward to the study subjects

Of the expenses for this clinical study, the sponsor shall offer compensation for medical treatment not covered by health insurance as study expenses. The study 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 study to the study subjects at each visit from the research funds. Details

of the financial burden on the study subjects and rewards shall be described in the informed consent form and information sheet.

15.7 Benefits and inconveniences to the study subjects

15.7.1 Benefits to study subjects

Study subjects can deeply learn their own conditions of type 2 diabetes including such as the change in the QOL associated with the change in treatment approaches and the level of treatment satisfaction, through the study participation

15.7.2 Inconveniences to study subjects

Burdens of study subjects may be increased due to requirements of providing answers to the Basic Information on Study Subject, DTR-QOL Questionnaire and DTSQ, through the study participation.

15.8 Attribution of study results and access rights

15.8.1 Attribution of study results

The study results and data obtained from this study shall belong to the sponsor. In addition, secondary use (meta-analysis, etc.) of the data obtained in this clinical study 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 study registration policy

15.9.1 Reporting of results, publication and disclosure

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

During the study period and after the end of study, the sponsor or the 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 study (including data and information provided by the principal investigator) without obtaining agreement 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 study at an academic conference, etc.

15.9.2 Clinical study registration

To ensure that information on clinical study 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 study 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), before initiation of the clinical study. On such websites, the study location (city, country), study 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 study 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

In case of injuries, each study subject in the clinical study must be insured in accordance with the regulations applicable to the study site where the subject is participating. The sponsor or the designee shall buy an insurance policy to compensate for health injury in study subjects.

Healthy injury in a study 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 the designee.

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