Title: Treatment preference for weekly DPP-4 inhibitors versus daily DPP-4 inhibitors in patients with type 2 diabetes mellitus < TRINITY >

NCT Number: NCT03231709

Protocol Approve Date: 6-Jun-2017

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

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

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

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

Note; This document was translated into English as the language on original version was Japanese.

PROTOCOL

Treatment preference for weekly DPP-4 inhibitors versus daily DPP-4 inhibitors in patients with type 2 diabetes mellitus (TRINITY)

Sponsor	Takeda Pharmaceutical Company Limited 12-10, Nihonbashi 2-chome, Chuo-ku, Tokyo
Protocol number	Trelagliptin-4003
Version Number	Version 1
Study drug:	Trelagliptin and alogliptin
Creation date	June 6, 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 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).
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and conflict of interest guidelines.

1.2 Clinical Study Implementation

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

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 study. Methods of supervision of the contractor entrusted with the services related to this study will be described in the procedure to be prepared separately.
Expenses* required for the operation of this 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 study. Expenses agreed by the study site shall be paid to the site based on the "Research Expense Standard."

PPD

PPD

SIGNATURES

The signature of MACS program head, Medical Director of Japan Medical Affairs and the responsible statistician can be found on the signature page.

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2.0 STUDY SUMMARY

Name of Sponsor:	**Compounds:**
Takeda Pharmaceutical Co., Ltd.	Trelagliptin and alogliptin

Title of Protocol:

Treatment preference for weekly DPP-4 inhibitors versus daily DPP-4 inhibitors in patients with type 2 diabetes mellitus

Study Number: Trelagliptin-4003

Clinical Research Design:

This is a randomized, open-label, two-way crossover study which aims to examine the patient preference for treatment with once-weekly dosing of DPP-4 inhibitor trelagliptin versus once-daily dosing of DPP-4 inhibitor alogliptin among the patients with type 2 diabetes mellitus who are being treated with once-daily dosing of DPP-4 inhibitor.

After obtaining the consent, the subjects who are judged eligible as a result of eligibility check will be randomized either to trelagliptin preceding group (T-A group) or alogliptin preceding group (A-T group).

The outline of the clinical research design is shown in Figure 1. See the appendix for schedules of tests, observations, and assessments.

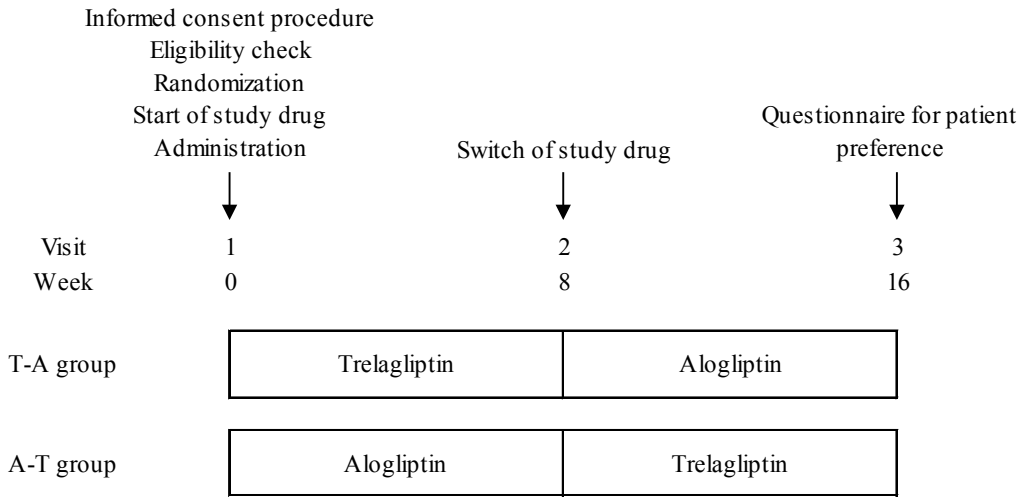

Fig. 1 Outline of Clinical Research Design

Primary Objectives:

To examine the patient preference for treatment with once-weekly dosing of DPP-4 inhibitor trelagliptin versus once-daily dosing of DPP-4 inhibitor alogliptin among the patients with type 2 diabetes mellitus.

Secondary Objective:

<table>
<tr><td colspan="2">To investigate subjects' background which affect the patient preference for treatment.</td></tr>
<tr><td colspan="2">Subject Population:
Patients with type 2 diabetes mellitus</td></tr>
<tr><td>Number of Subjects:
60 patients as randomized subjects
(T-A group: 30 subjects, A-T group: 30 subjects)</td><td>Number of Sites:
2 medical institutions</td></tr>
<tr><td>Dosage Levels:
Trelagliptin, 100 mg, once weekly.
Alogliptin, 25 mg, once daily.</td><td>Route of Administration:
Oral</td></tr>
<tr><td>Duration of administration:
16 weeks</td><td>Period of Evaluation:
16 weeks</td></tr>
<tr><td colspan="2">Criteria for Inclusion:
Subject eligibility is determined according to the following criteria prior to entry into the study.
1. Subjects who have been diagnosed with type 2 diabetes mellitus
2. Subjects who are being treated with any of the following DPP-4 inhibitors for at least 8 weeks prior to the start of treatment period (Week 0).
✓ Sitagliptin : 50 mg once daily
✓ Alogliptin : 25 mg once daily
✓ Linagliptin : 5 mg once daily
✓ Teneligliptin : 20 mg once daily
✓ Saxagliptin : 5 mg once daily
3. Subjects who were judged by the investigators possible to change the treatment from once-daily dosing of DPP-4 inhibitor shown in Inclusion Criteria 2 to study drug trelagliptin 100 mg or alogliptin 25 mg
4. Subjects whose HbA1c value measured within 8 weeks prior to the start of treatment period (Week 0) is below 10.0%
5. Subjects who responded to DTSQ (Diabetes Treatment Satisfaction Questionnaire) at the start of treatment period (Week 0)
6. Subjects who were judged by the investigators capable to understand the contents of this clinical research and comply with them
7. Subjects who are able to sign and date the Informed Consent Form before any clinical research procedure begins
8. Subjects who are at least 20 years old at the time of giving the consent
9. Subjects who are classified as outpatients</td></tr>
</table>

Criteria for Exclusion:

Subjects who correspond to any of the following criteria will not be subjects of this clinical research.

1. Subjects who have a history of taking once-weekly dosing of DPP-4 inhibitor (trelagliptin or omarigliptin)
2. Subjects who are being treated with drugs other than those for once-daily oral dosing for the purpose of treatment of chronic complication (for example, "BENET® Tablets 75 mg", a therapeutic agent for osteoporosis which is administered once monthly)
3. Subjects who are being treated with twice-daily dosing of DPP-4 inhibitor (vildagliptin or anagliptin)
4. Subjects who are being treated with anti-diabetic fixed-dose combination pill contained a DPP-4 inhibitor.
5. Subjects with moderate or severe renal impairment (for example, patients whose eGFR is below 60 mL/min/1.73m^2)
6. Subjects for whom blood sugar control by insulin preparations is desired (for example, patients with severe ketosis, diabetic coma or precoma, type 1 diabetes mellitus, severe infection, or serious trauma before or after surgery)
7. Subjects who have a history of hypersensitivity or allergy to DPP-4 inhibitor
8. Subjects with serious heart disease, cerebrovascular disorder, or patients with serious disease in the pancreas, blood, etc.
9. Subjects with unstable proliferative diabetic retinopathy
10. Subjects with malignant tumor
11. Subjects who are pregnant, breast-feeding, possibly pregnant, or planning to become pregnant.
12. Subjects participating in other clinical studies.
13. Subjects who have been determined as inappropriate subjects by the investigator.

Criteria for Evaluation and Analyses:

The primary endpoint for this study is patient preference for treatment interviewed from the subjects using the standardized questions* at the end of treatment period (treatment selection rate)

*: Questions

Regarding the drug therapy after the end of this research, which treatment do you select from the following choices from 1 to 4?
1. Either once-weekly DPP-4 inhibitor or daily DPP-4 inhibitor
2. Once-weekly DPP-4 inhibitor
3. Daily DPP-4 inhibitor
4. Neither once-weekly DPP-4 inhibitor nor daily DPP-4 inhibitor

The secondary endpoints:

- Preference for treatment (treatment selection rate) by drug (trelagliptin or alogliptin) selected by subjects at the end of treatment period and by background factor

Additional endpoints:

- Change in DTSQ treatment satisfaction* at each evaluation point
  *: Evaluated with the total points of questions 1, 4, 5, 6, 7, and 8
- Efficacy endpoint: HbA1c
- Safety endpoint: Adverse events

Statistical Consideration:

<Primary endpoint>

Patient preference for treatment interviewed from the subjects using the standardized questions at the end of treatment period (treatment selection rate)

Among the subjects who were randomized and treated with the study drugs, the treatment selection rate will be calculated by merging the subjects from whom preference for treatment was interviewed by treatment group with the treatment groups. Also, the treatment selection rates for once-weekly DPP-4 inhibitor and daily DPP-4 inhibitor are compared by applying the Mainland-Gart test.

Sample Size Justification:

By referring to the results of the questionnaire for treatment selection rate after dosing of once-weekly DPP-4 inhibitor, the treatment selection rate of once-weekly DPP-4 inhibitor is assumed to be 60%, treatment selection rate of daily DPP-4 inhibitor 20%, and rate of subjects who do not show any preference for treatment (either is fine/prefer neither) 20%, respectively.

In doing so, a total of 54 patients will be necessary in order to secure 90% power in the binomial test with two-sided significance level at 5%. With the estimated rate of discontinuation at 10%, the number of randomized subjects was set to be 30 subjects per group or 60 subjects in total.

3.0 LIST OF ABBERVIATIONS

AE	adverse event
COI	conflict of interest
CRO	contract research organization
DTSQ	Diabetes Treatment Satisfaction Questionnaire
eGFR	estimated Glomerular Filtration Rate
EDC	electronic data capture
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
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
SAE	serious adverse event

The terms used in this protocol are defined as follows:

Study site:

A corporation, a governmental agency, or a sole proprietor who is conducting the study, excluding the 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 conduct 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 investigators:

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

Subject:

A 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.

4.0 INTRODUCTION

4.1 Background

A relationship has been reported between blood glucose control and medication adherence in patients who received oral antidiabetic drugs for type 2 diabetes[1)]. Blood glucose control is crucial in preventing complication of diabetes. Poor adherence, due to miss of a dose for instance, sometimes results in poor control of blood glucose[2)], thereby increasing the risk of the complications. Hence, it is important to maintain good treatment adherence in the treatment for diabetes.

Taking many drugs every day is a burden for patients and is regarded as a reason for reduced medication adherence[3)]. A majority of patients with type 2 diabetes receive two drugs or more concomitantly once or more times daily. Many of those wish to reduce the dose frequency and/or the numbers of drugs that they are taking at a time. In particular, those who continue to work while being treated for type 2 diabetes find it difficult to take the drugs as prescribed, due to their occasional business trips or relatively irregular eating patterns[4)]. Thus, reducing dose frequency may improve medication adherence for them. Indeed, switch to weekly bisphosphonates has been reported to improve the adherence in patients with osteoporosis who had received once daily bisphosphonates[5)].

Trelagliptin is the first once-weekly oral dipeptidyl peptidase 4 (DPP-4) inhibitor. DPP-4 inhibitors increase incretin levels (GLP-1 and GIP) by blocking DPP-4-dependent their proteolytic degradation, thereby stimulating insulin secretion in a glucose-dependent manner. DPP-4 inhibitors are widely used as oral antidiabetic drugs for type 2 diabetes. Most of the DPP-4 inhibitors require once or twice daily dosing. Thus, weekly DPP-4 inhibitors may offer a novel therapeutic option for the patients who receive daily DPP-4 inhibitors. They are also expected to improve the medication adherence and prevent treatment discontinuation by relieving the burden associated with frequent dosing of the patients.

There have been several studies that compare weekly DPP-4 inhibitors with daily DPP-4 inhibitors with regard to treatment preference. Suzuki et al. reported based on the questionnaire survey that 55.3% of 170 patients taking daily DPP-4 inhibitors would like to change their daily DPP-4 inhibitors to weekly ones[6)]. Higuchi et al. reported that 61% of all the patients with type 2 diabetes treated in their clinic (364 patients) answered that weekly drugs were preferable[7)]. Uchida reported that 36 out of 38 patients showed their preference for once weekly DPP-4 inhibitors after treatment with the once-weekly DPP-4 inhibitors (trelagliptin or omarigliptin) for three or four months[8)]. Moreover, Nakamura et al. reported that 63% of 201 patients chose weekly inhibitors as a preferential treatment a few months after the treatment had been switched from their once-daily DPP-4 inhibitors to the once-weekly DPP-4 inhibitor trelagliptin[9)]. All the above reports suggest patients' interests in once-weekly DPP-4 inhibitors as well as preference for them before and after

the prescription. However, these studies cannot rule out the possible influence of the proximate medication or accustomed drug-taking behavior on preference for the subsequent treatment.

The present study is a randomized, open-label, two-way crossover study which aims to examine the patient preference for treatment with once-weekly DPP-4 inhibitor trelagliptin versus once-daily DPP-4 inhibitor alogliptin among the patients with type 2 diabetes mellitus who are being treated with once-daily DPP-4 inhibitor. Two-way crossover design enables us to reduce the possible influence of the proximate medication or drug-taking behavior on the preference. The study also includes a background research on the patients to explore the factors that influence the treatment preference. This study may bring us more information on the future antidiabetic treatment aimed at improved medication adherence as well as treatment of choice for a range of patients with individually different life-styles.

4.2 Rationale for the Proposed Study

Once-weekly DPP-4 inhibitors are expected to contribute to reducing patient burden caused by multiple dosing and thereby improve medication adherence. Several questionnaire surveys suggest preference of the patients for once-weekly DPP-4 inhibitors over daily inhibitors. However, no treatment preference study, which takes timing effects into account, has been reported for DPP-4 inhibitors. The present study is designed to examine the patient preference for once-weekly DPP-4 inhibitors versus once-daily DPP-4 inhibitors among the patients with type 2 diabetes mellitus, who receive once-daily dosing of alogliptin for 8 weeks and then once-weekly dosing of trelagliptin for another 8 weeks, or the reverse sequence.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

To examine the patient preference for treatment with once-weekly dosing of DPP-4 inhibitor trelagliptin versus daily dosing of DPP-4 inhibitor alogliptin among the patients with type 2 diabetes mellitus.

5.1.2 Secondary Objectives

To investigate subjects' background which affect the patient preference for treatment.

5.2 Endpoints

5.2.1 Primary Endpoint

Patient preference for treatment interviewed from the subjects using the standardized questions* at the end of treatment period (treatment selection rate).

*: Questions

Regarding the drug therapy after the end of this research, which treatment do you select from the following choices from 1 to 4? 1. Either once-weekly DPP-4 inhibitor or daily DPP-4 inhibitor 2. Once-weekly DPP-4 inhibitor 3. Daily DPP-4 inhibitor 4. Neither once-weekly DPP-4 inhibitor nor daily DPP-4 inhibitor

5.2.2 Secondary Endpoints

- Preference for treatment (treatment selection rate) by drug (trelagliptin or alogliptin) selected by subjects at the end of treatment period and by background factor

5.2.3 Additional Endpoints

- Change in DTSQ[10), 11)] treatment satisfaction* at each evaluation point
  *: Evaluated with the total points of questions 1, 4, 5, 6, 7, and 8
- Efficacy endpoint: HbA1c
- Safety endpoint: Adverse events

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

<Study design>

This is a randomized, open-label, two-way crossover study which aims to examine the patient preference for treatment with once-weekly dosing of DPP-4 inhibitor trelagliptin versus daily dosing of DPP-4 inhibitor alogliptin among the patients with type 2 diabetes mellitus who are being treated with daily dosing of DPP-4 inhibitor.

After obtaining the consent, the subjects who are judged eligible as a result of eligibility check will be randomized either to trelagliptin preceding group (T-A group) or alogliptin preceding group (A-T group).

Planned number of subjects is 60 in total.

<Duration>

The study period is 16 weeks. The number of visits is 3.

VISIT 1: Start of administration (week 0)

VISIT 2: Switch of study drug (week 8)

VISIT 3: End of study (week 16)

<Treatment>

Trelagliptin preceding group (T-A group):

The subjects receive 100 mg of trelagliptin once a week for 8 weeks and then 25 mg of alogliptin once a day for 8 weeks.

Alogliptin preceding group (A-T group)

The subjects receive 25 mg of alogliptin once a day for 8 weeks and then 100 mg of trelagliptin once a week for 8 weeks.

The outline of the clinical research design is shown in Figure 6.a.

See the appendix for schedules of tests, observations, and assessments.

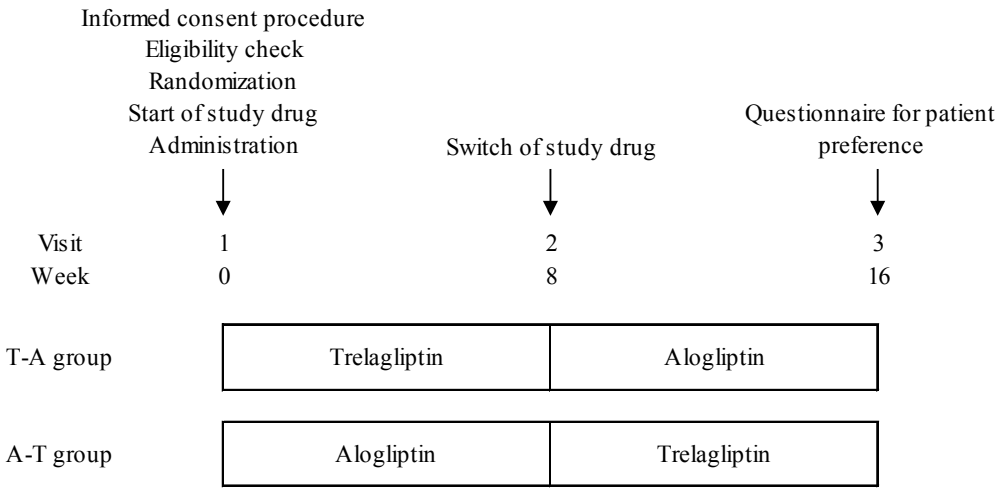

Figure 6.a Outline of Clinical Research Design

6.2 Justification for Study Design

1) Justification for study design

The primary objective of this randomized, open-label study is to evaluate treatment preference of patients with type 2 diabetes mellitus for once weekly DPP-4 inhibitors. After obtaining informed consent, the eligible subjects receive both once weekly trelagliptin and once daily alogliptin for 8 weeks each sequentially and they are then asked about their treatment preference. The study is also designed as a two-way crossover study in order to mitigate potential effects of drug sequence on treatment preference.

2) Justification for dose of the drugs

Significant change in blood glucose control during the study can affect the outcomes (treatment preference of the subjects) and should be avoided. The efficacy of trelagliptin at 100 mg in lowering blood glucose level is considered equivalent to that of alogliptin at 25 mg[12].

3) Justification for dosing period

There is a study reporting that the time it took people to form habit of doing relatively simple things in everyday life need more than 2 months[13]. In addition, a majority of patients with type 2 diabetes mellitus visit clinics once a month or once every 2 months. Therefore, 8-week is set as the dosing period.

4) Justification for the number of subjects

Refer to 13.3

6.3 Premature Termination of Study or Study Site

6.3.1 Criteria for Premature Termination of the Study

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

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the product, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises subject safety.

6.3.2 Criteria for Premature Termination of Study Sites

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

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Sites

In the event that the sponsor or a study site committee such as an independent ethics committee (IEC) elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

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. Investigators shall confirm the content of the revision of the protocol and submit an agreement form to the sponsor as evidence of agreement with the protocol revision.
[Protocol revision is required in the following cases:]

1. Change or addition of objectives
2. Change in or addition of efficacy or safety evaluation methods
3. More frequent or additional laboratory tests for which subjects incur additional expenses or changes in laboratory test methods

4. Change in dose
5. Significant change in or addition of inclusion and/or exclusion criteria
6. Change in the planned number of subjects
7. Change in plans or in description of the protocol due to serious adverse events or other reasons
8. Change which is considered as a significant change, as a result of discussion between the sponsor and the chair of the Steering Committee

Upon notification, the principal investigator at each study site shall submit the revised contents to the relevant committees (such as an institutional ethics review committee), for review and approval as necessary according to institutional regulations.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

The investigators shall confirm all the inclusion/exclusion criteria prior to enrollment.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study.

1. Subjects who have been diagnosed with type 2 diabetes mellitus
2. Subjects who are being treated with any of the following DPP-4 inhibitors for at least 8 weeks prior to the start of treatment period (Week 0).
   - ✓ Sitagliptin : 50 mg once daily
   - ✓ Alogliptin : 25 mg once daily
   - ✓ Linagliptin : 5 mg once daily
   - ✓ Teneligliptin : 20 mg once daily
   - ✓ Saxagliptin : 5 mg once daily
3. Subjects who were judged by the investigators possible to change the treatment from daily dosing of DPP-4 inhibitor shown in Inclusion Criteria 2 to study drug trelagliptin 100 mg or alogliptin 25 mg
4. Subjects whose HbA1c value measured within 8 weeks prior to the start of treatment period (Week 0) is below 10.0%
5. Subjects who responded to DTSQ (Diabetes Treatment Satisfaction Questionnaire) at the start of treatment period (Week 0)
6. Subjects who were judged by the investigators capable to understand the contents of this clinical research and comply with them
7. Subjects who are able to sign and date the Informed Consent Form before any clinical research procedure begins
8. Subjects who are at least 20 years old at the time of giving the consent
9. Subjects who are classified as outpatients

7.1.1 Justification for Inclusion Criteria

1, 4, and 5	These were set to evaluate the efficacy of the drugs in patients with type 2 diabetes mellitus.
2 and 3	These were set to include the subjects who would not have a significant change in their blood glucose control, which may affect the outcomes (treatment preference)
6 to 9	These were set as fundamental items for the study.

7.2 Exclusion Criteria

Subjects who correspond to any of the following criteria will not be subjects of this clinical research.

1. Subjects who have a history of taking once-weekly dosing of DPP-4 inhibitor (trelagliptin or omarigliptin).
2. Subjects who are being treated with drugs other than those for daily oral dosing for the purpose of treatment of chronic complication (for example, “BENET® Tablets 75 mg”, a therapeutic agent for osteoporosis which is administered once monthly).
3. Subjects who are being treated with twice-daily dosing of DPP-4 inhibitor (vildagliptin or anagliptin).
4. Subjects who are being treated with anti-diabetic fixed-dose combination pill contained a DPP-4 inhibitor.
5. Subjects with moderate or severe renal impairment (for example, subjects whose eGFR is below 60 mL/min/1.73m2).
6. Subjects for whom blood sugar control by insulin preparations is desired (for example, subjects with severe ketosis, diabetic coma or precoma, type 1 diabetes mellitus, severe infection, or serious trauma before or after surgery).
7. Subjects who have a history of hypersensitivity or allergy to DPP-4 inhibitor
8. Subjects with serious heart disease, cerebrovascular disorder, or subjects with serious disease in the pancreas, blood, etc.
9. Subjects with unstable proliferative diabetic retinopathy
10. Subjects with malignant tumor
11. Subjects who are pregnant, breast-feeding, possibly pregnant, or planning to become pregnant.
12. Subjects participating in other clinical studies.
13. Subjects who have been determined as inappropriate subjects by the investigator.

7.2.1 Justification for Exclusion Criteria

1 This was set to exclude possible effects of previous experience of taking weekly DPP-4 inhibitors on the treatment preference.

2 This was set to exclude possible effects of previous experience of taking non-daily orally available drugs on the treatment preference.

3 This was set to limit the dose frequencies as explanation factor to once daily and once weekly, since vildagliptin or anagliptin is a twice daily DPP-4 inhibitor.

4 This was set to rule out the possibility that the drug change from combination tablet to DPP-4 inhibitor only affects the subjects' blood glucose levels or the possibility that increase of the tablets affects their treatment preference.

5 to 11 These were set in consideration of safety of the subjects.

12, 13 These were set as fundamental items for the study.

7.3 Excluded Medications

Addition of drugs or changes in dose/regimen of drugs for treatment of type 2 diabetes mellitus or concurrent medical conditions such as hypertension are not allowed. However, the drugs to treat adverse events are permitted to be used.

[Justification for excluded medications]

These were set because they would affect evaluation of primary endpoint.

7.4 Subject Management

The investigators shall instruct subjects to adhere to the following throughout the study period:

1. Adhere to the instructions or restrictions prescribed in the study period.
2. Take glucose or sucrose (sugar) if hypoglycemia symptom (hunger abnormal, feeling of weakness, trembling of hands and fingers, cold sweat, palpitations, etc.) is observed, and if symptoms continue, visit the study site promptly.
3. 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.
4. Adhere to instructed prohibited concomitant drugs. When drugs are taken other than the drugs prescribed by the investigators, have the research subject report its content.
5. 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 Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the case report form (CRF) using the following categories. For subjects who withdraw from the study before administration, refer to Section 9.1.11.

1. Adverse event

   The subject has experienced an adverse event (AE) that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE.

2. Significant protocol deviation

   The discovery after the first dose of study drug that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.

3. Lost to follow-up

   The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents

4. Voluntary withdrawal

   The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the CRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).

5. Study termination

   The sponsor, IEC or regulatory authority terminates the study. Refer to Section 6.3.1 for details.

6. Pregnancy

   The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.10.

7. Lack of efficacy

   The investigator has determined that the subject is not benefiting from study treatment; and, continued participation would pose an unacceptable risk to the subject.

8. Others

   The investigator determined to terminate the study for other reasons.

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

7.6 Procedures for Discontinuation or Withdrawal of a Subjects

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit.

8.0 STUDY TREATMENT

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

8.1 Study Drug

Generic name: trelagliptin succinate

Chemical name:

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

Generic name: alogliptin benzoate

Chemical name:

2-({6[-(*3R*)-3-Aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(*2H*)-yl}m ethyl)benzonitrile monobenzoate

8.1.1 Dose and Regimen

The investigators shall administer the study drugs as shown in figure 8.a.

For trelagliptin preceding group (T-A group), trelagliptin 100 mg is orally administered once weekly for 8 weeks and then alogliptin 25 mg once daily for 8 weeks. For alogliptin preceding group (A-T group), alogliptin 25 mg is orally administered once daily for 8 weeks and then trelagliptin one weekly for 8 weeks.

Table 8.a. Dose and regimen

Treatment period		
Drug	Dose	Regimen
Trelagliptin	100 mg	Once weekly, Orally
Alogliptin	25 mg	Once daily, Orally

8.1.2 Overdose

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the CRF, in order to capture this important safety information consistently in the database. Cases of

overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE CRF according to Section 10.0.
Serious AEs (SAEs) associated with overdose should be reported according to the procedure outlined in Section 10.2.2
In the event of overdose, the subject should be treated symptomatically.

8.2 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 investigators 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.

8.3 Preparation and Storage of Allocation List

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

9.1 Clinical study procedure

The investigators 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 investigators. The study schedule is provided in Appendix A.

9.1.1 Informed Consent Procedure

The procedures for obtaining informed consent are described in Section 15.3.
Consent shall be obtained from the study subject before initiation of study.
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 Demographics and Medication History Collection Procedure

The following data will be collected as demographic data:

- Date of birth, gender, the time (month and year) of diabetes onset (or a diabetes diagnosis), work status, alcohol intake history, smoking history, experience in educational hospitalization on diabetes, presence of cohabiter, compliance with DPP-4 inhibitors for the last 4 weeks before the start of the treatment period, the number of oral drugs per day, complication of metabolic syndrome*.

  *: to be confirmed according to the following criteria:
  waist size ≥ 85 cm (for male), ≥ 90 cm (for female)
  serum triglyceride ≥ 150 mg/dl and/or HDL < 40 mg/dl
  systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg

9.1.3 Physical Examination Procedure

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 Weight, Height, and Body Mass Index (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 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. At each study visit, subjects will be asked the status of use (drug name, route of administration, treatment period, and treatment purpose) of any medication other than the study drug (including vitamin compound, over-the-counter medication, and Chinese medicine) used from signing of informed consent through the end of the study.

9.1.6 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present prior to first dose. This includes clinically significant laboratory or physical examination abnormalities noted at baseline examination, according the judgment of the investigator. The condition (ie, diagnosis) should be described.

9.1.7 Questionnaire for Patient Preference for Treatment

Patient preference for treatment interviewed from the subjects using the standardized questions* at the end of treatment period (treatment selection rate)

*: Questions

Regarding the drug therapy after the end of this research, which treatment do you select from the following choices from 1 to 4? 1. Either once-weekly DPP-4 inhibitor or daily DPP-4 inhibitor 2. Once-weekly DPP-4 inhibitor 3. Daily DPP-4 inhibitor 4. Neither once-weekly DPP-4 inhibitor nor daily DPP-4 inhibitor

9.1.8 DTSQ

Subjects will answer the DTSQ (all 8 questions) [10), 11)] 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.

9.1.9 Procedure for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. Clinical laboratory tests are listed in Table 9.a.

Table 9.a Laboratory tests

Serum chemistry
・ HbA1c

The local laboratory will perform laboratory tests. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

9.1.10 Pregnancy

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

9.1.11 Record of Subjects Who are Withdrawn Before Start of Administration

A CRF shall be created for all subjects who sign the consent form and are then withdrawn before start of administration.

The following items are to be recorded on the CRF:

- Date of informed consent signature
- Date of birth (or the age at the time of informed consent)
- Gender
- Eligibility
- Reason for withdrawal

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

- Did not meet inclusion criteria or did meet exclusion criteria
- Significant protocol deviation
- Lost to follow-up
- Voluntary withdrawal <specify reason>
- Study termination
- Pregnancy
- Others <specify the reason>

Subject identification numbers assigned to subjects withdrawn from the study before start of administration should not be reused.

9.2 Monitoring Subject Treatment Compliance

The investigator will confirm treatment compliance of study drug at every visit.

Treatment compliance will be classified into 4 categories, as follows: “took the drug properly (≥ 90%),” “usually took the drug (≥ 70%),” “took the drug more than half of the time of dosing (≥ 50%),” and “took the drug less than half of the time of dosing (< 50%).”

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time points.

9.3.1 Start of Administration（VISIT 1: Week 0）

After acquisition of informed consent, a physical examination and tests for screening will be performed. Eligibility of subjects will be determined in accordance with the inclusion and exclusion criteria as described in Section 7.0.

An eligible study subject will be randomized in accordance with section 8.2 and starts to be administered trelagliptin or alogliptin.

Tests, observations and evaluations performed at the start of the screening period (Visit 1: Week 0) are shown below.

- Informed consent*
- Inclusion/exclusion criteria
- Physical examination
- Concomitant medication (a)
- HbA1c
- Demographics, medication history
- Height / weight / BMI
- Concurrent medical conditions
- Prescription of study drug
- DTSQ

*Informed consent shall be obtained prior to any other tests, observations and evaluations.

(a) Record all concomitant medications

9.3.2 Switch of Study drug（VISIT2: Week 8）

As described in Section 8.4, the preceding drug is switched with the following drug. The study subjects then stats to be administered with the following drug.

Tests, observations and evaluations performed during the treatment period (Visit 2: Week 8) are shown below.

- Physical examination
- HbA1c
- Treatment compliance
- Concomitant medication (a)
- Prescription of study drug
- DTSQ

9.3.3 End of Study (VISIT3: Week 16)

The study subjects choose either trelagliptin or alogliptin, or neither of them. If the subjects cannot choose either of them, then the investigators choose the drug for consequent treatment upon adequate explanation.
Tests, observations and evaluations performed at the start of the screening period (Visit 3: Week 16) are shown below.

- Physical examination
- HbA1c
- DTSQ
- Concomitant medication [(a)]
- Treatment compliance
- Questionnaire for patient preference for treatment

9.3.4 Discontinuation

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

- Physical examination
- HbA1c
- DTSQ
- Concomitant medication [(a)]
- Treatment compliance
- Questionnaire for patient preference for treatment

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 AEs

An AE is defined as any untoward medical occurrence in a subject administered a pharmaceutical product (including the study drug). It does not necessarily have to have a causal relationship with this pharmaceutical product (including the study drug).
An AE can therefore be any unfavorable and unintended sign (e.g., a clinically significant abnormal laboratory value), symptom, or disease temporally associated with the use of a pharmaceutical product (including the study drug) whether or not it is considered related to the pharmaceutical product (including the study drug).

10.1.2 Additional Points to Consider for AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.).
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in the dose of the study drug, or concomitant medication.
- Be considered unfavorable by the investigator for any reason.

Diagnosis vs signs and symptoms:
Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).
Laboratory values and ECG findings:
Changes in laboratory values or ECG findings are only considered to be PTEs or AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory or ECG re-test and/or continued monitoring of an abnormal value or findings are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions (a disease or symptom that is present at the start of study drug administration):

Pre-existing conditions are considered concurrent medical conditions and should NOT be recorded as AEs. However, if the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after start of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").

If a subject has a pre-existing episodic concurrent medical condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as an AE if the condition becomes more frequent, serious or severe in nature. Investigators should ensure that the AE term recorded captures the change in the condition from baseline (eg "worsening of…").

Worsening of AEs:

If the subject experiences a worsening or complication of an AE after any change in study drug, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in intensity of AEs:

If the subject experiences changes in intensity of an AE, the event should be captured once with the maximum intensity recorded.

Preplanned procedures (surgery or interventions):

Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be recorded as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

Cases of overdose with any medication without manifested side effects are NOT considered AEs,

but instead will be documented on an Overdose page of the CRF. Any manifested side effects will be considered AEs and will be recorded on the AE page of the CRF.

10.1.3 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death,
- Is life threatening*,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Leads to a congenital anomaly/birth defect,
- Is an important medical event that may expose the subject to danger even though the event is not immediately life-threatening or fatal does not result in hospitalization, or requires intervention to prevent items 1 through 5 above. In addition, event or synonym described in the Takeda Medically Significant Adverse Event List (Table 10.a) is included in this section.

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

Table 10.a Takeda Medically Significant Adverse Event 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 Intensity of AEs

The different categories of intensity (severity) are characterized as follows.

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.

10.1.5 Causality of AEs

The relationship of each AE to the study drug will be assessed using the following categories.

Related	An AE that follows a temporal sequence (including clinical course after discontinuation), or an AE in which there is at least a reasonable probability that a causal relationship to the study drug cannot be ruled out, although other factors such as underlying disease, complications, or concomitant drugs/treatment are also suspected.
Not related	An AE 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.

10.1.6 Relationship to Study Procedures

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.7 Study Date

The start date of AEs will be determined using the following criteria.

AE	Start date
Signs, symptoms, diseases (diagnoses)	The date on which the first signs/symptoms were noted by the subject and/or the 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 comorbidities	The date on which the first worsening of diseases/symptoms was noted by the subject and/or the investigator.

Onset of a test abnormality after the start of study 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	The date on which a clear increase/decrease in a laboratory parameter was clinically confirmed based on the time profile of the parameter.

10.1.8 Stop Date

The stop date of the AE is the date at which the subject recovered, the event resolved but with sequelae or the subject died. The AE will be recorded as "ongoing" if the subject has not yet recovered by the end of the study.

10.1.9 Action Concerning Study Drug

Action concerning study drug will be classified or defined as shown below.

Drug withdrawn	The study drug is discontinued because of an AE (including withdrawal by the subject at his/her discretion). If the study drug is continued after the study termination, the action should be "Dose not changed".
Dose not changed	The dose was not changed after the onset of the AE. The study drug was discontinued, reduced, or increased because of another AE. The study drug was discontinued or reduced for a reason other than the AE, e.g., inadvertence of the subject.
Unknown	It has not been possible to determine what action has been taken because the subject is lost to follow-up.
Not Applicable	The administration of the study drug had already been completed or discontinued before the onset of the AE.
Dose reduced	The dose of the study drug was reduced because of the AE (including dose reduction by the subject at his/her discretion).
Dose Increased	The dose was increased due to the particular AE (including dose reduction by the subject at his/her discretion).
Washout	The study drug was suspended (i.e., interrupted) because of the AE (including suspension/interruption by the subject at his/her discretion), but resumed later.

10.1.10 Outcome

Outcome of AEs 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 subject died from a cause other than the concerned AE 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 subject died from another cause before resolution of the concerned AE (recording of the date of death unnecessary)
Recovered with sequelae	Disability that disturbs daily life
Death	Direct relationship between death and the concerned AE "Direct relationship" means that the concerned AE was the cause of death, or the concerned AE was clearly responsible for death. Outcome of an AE which was not determined (judged, presumed) a direct cause of death observed in the same 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 AEs

10.2.1.1 AE collection Period

Collection of AEs will commence from the time that the subject is first administered study drug (VISIT 1). Routine collection of AEs will continue until VISIT 3.

10.2.1.2 AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?". Subjects may report AEs occurring at any other time during the study.

All subjects experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed.

All AEs will be documented in the AE page of the CRF, whether or not the investigator concludes

that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date.
3. Frequency.
4. Intensity.
5. Investigator's opinion of the causal relationship between the event and administration of the study drug (related or not related),
6. Investigator's opinion of the causal relationship to study procedures, including the detail of the suspected procedure.
7. Action concerning study drug.
8. Outcome of event.
9. Seriousness.

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

If AE of Special interest (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 investigators. AESI Form should be completed and signed (or signed and sealed) by the principal investigator and reported to the sponsor within 10 business days.

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

[Hypoglycemia-related AEs]

AEs related to hypoglycemia

[Intestinal obstruction-related AEs]

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

[Acute pancreatitis-related AEs]

AEs related to pancreatitis or acute pancreatitis

[QT/QTc interval prolongation-related AEs]

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

[Liver dysfunction or jaundice-related AEs]

AEs corresponding to 'Liver dysfunction related to drug - comprehensive search' in MedDRA standard search formula.
The AESIs have to be recorded as AEs in the CRF. A report along with all other required documentation must be submitted to the sponsor.

10.2.2 Collection and Reporting of SAEs

When a SAE occurs through the AE collection period it should be reported according to the following procedure:
At the time of onset of a SAE or notification of the onset by the subject, the principal investigator shall report the SAE to the chief executive of the study site immediately, and the sponsor or the contract study organization (CRO) to whom the sponsor has entrusted responsibility shall notify the principal investigator of the study site.
A SAE should be reported by the investigator to the sponsor within 1 business day of the SAE occurrence. The investigator should submit the detailed SAE Form to the sponsor (for contact information, refer) within 10 calendar days. .
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.

- A short description of the event and the reason for why the event is categorized as serious.
- Study title.
- Subject identification number.
- Study site's name.
- Investigator's name.
- Name of the study drug.
- Causality assessment.

The investigator shall report spontaneously reported SAEs that are collected even after the AE collection period to the sponsor.

10.2.3 Reporting of Additional Information Concerning AEs

If the sponsor requests provision of additional information concerning AEs for reporting to regulatory authorities, the investigators 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 SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form (copy) or provide other written documentation

and submit it to the sponsor (for contact information, refer) within 1 working day. 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 ethics review committee upon request.
All SAEs should be followed up until resolution or permanent outcome of the event.

10.3.1 Reporting of SAEs, etc., to IECs, etc., and Regulatory Authorities

When the chief executive of study site receives a report of a SAE 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 study through the sponsor or the CRO consigned by the sponsor.
When the principal investigator reported a SAE 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 SAE 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 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 study sites via the sponsor.)

- Actions taken for SAEs
  (discontinuation of new enrollment, revision of informed consent form, re-consents from other subjects, etc.)
- Date of review, summery of review, result, necessary action, etc., related to Ethics Review Committee, etc.
- Notification to other study sites

The sponsor shall report, in accordance with regulations, unexpected serious adverse drug reactions and other SAEs that are subject to emergency reporting to regulatory authorities, the investigators, and chief executive s of study sites.
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 risks/benefits of the study drug, continuation of study drug administration, or continuation of study. The study site shall submit copies of emergency report documents to the Ethics Review Committee, etc.

11.0 STUDY-SPECIFIC COMMITTEES

11.1 Steering Committee

The Steering Committee will comprise of the chair and the sponsor. The Steering Committee will supervise implementation and reporting of the study, secure medical guidance of a high degree of professionalism and a high-level scientific quality, and revise the protocol appropriately. The responsibilities of the committee will be described in the procedures of the Steering Committee.

12.0 DATA HANDLING AND RECORDKEEPING

Data Management department of the sponsor shall be in charge of implementing data management operation according to the standard operating procedures, independently from Medical Affairs department. AEs, and concurrent conditions shall be coded using MedDRA. Drugs shall be translated using the World Health Organization (WHO) Drug Dictionary.

12.1 Case Report Forms (CRFs)

Completed CRFs are required for each subject who signs informed consent.
The sponsor or its designee will provide study sites with access authorization to the EDC system. Before use of the EDC system, the sponsor shall provide training to the investigators, and study collaborators. The CRF shall be used to report the information collected during the study period to the sponsor. The CRF shall be prepared 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 or its designee shall ensure the accuracy and completeness of the CRF, and provide an electronic signature on the relevant page of the CRF. The principal investigator bear full responsibility for the accuracy and reliability of all the data entered on the CRF.

The following data shall be recorded on the CRF directly, except for those recorded in the source documents:

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

When the investigators make a change or correction in the data entered on the CRF after fixation of clinical data base, a record (Data Clarification Form) of change or correction on the CRF provided by the sponsor shall be used. The principal investigator shall confirm that the record of change or correction on the CRF is accurate and complete, and sign or write name/ affix a seal, and date it.
The sponsor or the designee shall confirm that the CRF has been made appropriately in conformity with the procedure defined for each study. The sponsor or its designee shall have access to the medical records of the subjects and in-house records to ensure the accuracy of the CRF as necessary.
The completed CRF shall be the property of the sponsor, and the investigator shall not disclose the information to a third party without written permission from the sponsor.

12.2 Timing of Data Entry into the EDC System

The sponsor or its designee shall request the investigators to promptly enter data into the EDC system following enrollment of the subject, each visit during study treatment, and completion/discontinuation of the study.

12.3 Storage and Disposal of Specimens and Documents, etc.

The principal investigator or the chief executive of the study site shall store human-derived specimens and the following materials (information, etc.), including those specified in Section 12.1 and study-specific documents to be used by the regulatory authority and the sponsor or its designee for investigation and audit. The documents shall include, but shall not be limited to the materials related to the information used in the study such as the subject ID number list, subjects' medical records, study work sheet, original signed and dated informed consent forms, an electronic copy of the EDC system with audit trails, and the drug management records. The principal investigator and the chief executive of the study site shall appropriately retain the specimens/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. When disposing the specimens, documents, etc., the chief executive of the study site shall dispose them anonymously.

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

13.1.1 Analysis Sets

In this study, 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 study drugs". The safety population is defined as "subjects who receive at least 1 dose of study drugs".

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Using FAS, major demographic and other baseline characteristics shall be aggregated.

13.1.3 Efficacy Analysis

The primary endpoint for this study is patient preference for treatment interviewed from the subjects using the standardized questions* at the end of treatment period (treatment selection rate)

*: Questions

Regarding the drug therapy after the end of this research, which treatment do you select from the following choices from 1 to 4? 1. Either once-weekly DPP-4 inhibitor or daily DPP-4 inhibitor 2. Once-weekly DPP-4 inhibitor 3. Daily DPP-4 inhibitor 4. Neither once-weekly DPP-4 inhibitor nor daily DPP-4 inhibitor

Among the subjects who were randomized and treated with the study drugs, the treatment selection rate will be calculated by merging the subjects from whom preference for treatment was interviewed by treatment group with the treatment groups. Also, the treatment selection rates for once-weekly DPP-4 inhibitor and daily DPP-4 inhibitor are compared by applying the Mainland-Gart test.

The secondary endpoints:

- Preference for treatment (treatment selection rate) by drug (trelagliptin or alogliptin) selected by subjects at the end of treatment period and by background factor

13.1.4 Safety Analysis

- Incidence of AEs (TEAEs)

[Analytical methods]

A treatment-emergent AE (TEAE) is defined as any AE occurring after the start of study or control treatment for the healing phase. For TEAEs in the maintenance phase, the analyses listed below shall be performed for each treatment group. TEAEs shall be reported using MedDRA terminology and summarized using the Preferred Term (PT) and System Organ Class (SOC) of the MedDRA.

- Aggregation of frequencies of all TEAEs
- Aggregation of frequencies of TEAEs related to the study drug
- Aggregation of frequencies of all TEAEs by severity
- Aggregation of frequencies of TEAEs related to the study drug
- Aggregation of frequencies of TEAEs leading to discontinuation of study treatment
- Aggregation of frequencies of serious TEAEs

Frequency tables will be prepared for the incidences of adverse events and severe hypoglycemia after the first administration of the study drug or comparative drug administration in the “safety population” in each treatment group.

13.1.5 Other Analyses

Using FAS, the followings shall be analyzed.

1) Efficacy endpoint: HbA1c

   The mean and SD of HbA1c levels at each assessment time and changes in HbA1C from the baseline (Week 0) to each assessment time point will be calculated and represented in graphs.

2) Treatment compliance

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

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

60 subjects

<Rationale for the number of planned subjects>

By referring to the results of the questionnaire for treatment selection rate after dosing of once-weekly DPP-4 inhibitor, the treatment selection rate of once-weekly DPP-4 inhibitor is assumed to be 60%, treatment selection rate of daily DPP-4 inhibitor 20%, and rate of subjects who

do not show any preference for treatment (either is fine/prefer neither) 20%, respectively.

In doing so, a total of 54 subjects will be necessary in order to secure 90% power in the binomial test with two-sided significance level at 5%. With the estimated rate of discontinuation at 10%, the number of randomized subjects was set to be 30 subjects per group or 60 subjects in total.

14.0 QUALITY CONTROL AND QUALLITY ASSURANCE

14.1 Study-Site Monitoring Visits

The sponsor or its designee shall perform periodic monitoring of study sites during the study to confirm that the study is conducted in accordance with all specifications in the 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 its designee and the Ethics Review Committee, etc., have access to the source documents.

The sponsor or its designee shall access the records, including the list of subject ID codes, medical records of the subjects, and signed and dated original consent forms, to confirm that the study is appropriately conducted in compliance with the protocol. Also, confirm the consistency between CRF and the related source documents. The 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 in a procedure manual prepared separately.

14.2 Deviation from the Ethical Guideline for Clinical Research and the Protocol

The investigator shall record all deviations from the Ethical Guideline for Clinical Research and the protocol.

If any deviation is found, the principal investigator shall promptly notify the chief executive of the study site 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 study site for approval of the committee such as ethics review committee.

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 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 ASPECT OF THE STUDY

This study shall be conducted with the highest respect for the individual participants (i.e., subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the Ethical Guideline for Clinical Research. Each investigator will conduct the study according to regulatory requirements and in accordance with "Responsibilities of the Investigator" that are listed in Appendix B.

15.1 IEC Approval

The IEC, etc., shall be constituted in accordance with the regulations.
The sponsor or its designee should obtain the document listing the name and title of each committee member. When a committee member directly participates in this 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 provide related documents for review and approval of the protocol to the Ethical Review Board, etc. In addition to the protocol, a copy of the informed consent form and information sheet, written materials related to 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 Ethics Review Committee to obtain approval. The sponsor or the designee shall obtain records of approval by the Ethical Review Board, etc., for the protocol and the informed consent form and information sheet before the start of the protocol therapy. The records of approval by the Ethical Review Board, etc., shall include the study title, protocol number, preparation / revision date of the protocol, and version number and approval date of other reviewed documents (Example: informed consent and information sheet). The sponsor shall notify the study site and the 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 and investigator receive notification.
The study site shall observe all requirements that the Ethical Review Board prescribes. The requirements may include notifications to committees such as ethics review committee, for example, revision of the protocol, revision of the informed consent form and information sheet, revision of materials related to 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 Ethics Review Committee, and submission of the study completion report.
The sponsor or its designee shall obtain written approval from a study site committee such as the Ethics Review Committee related to the above mentioned items and all related materials.

15.2 Conflict of Interests

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

Prior to the initiation of this study, the investigators involved in this 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.[14)-18)]
The study site shall comply with all requirements specified by a committee such as an ethics review committee, including the COI self-statement form, the protocol, and the informed consent form and information sheet.

15.3 Informed Consent and Information Sheet, and the Agreement of the Subjects

The informed consent and information sheet form shall contain specific requirements of the Declaration of Helsinki, Ethical Guideline for Clinical Research and all applicable laws and regulations. The informed consent form and information sheet shall specify the use of personal information and medical information of subjects in this study (both in and outside Japan: supply to a third party), and disclosure. The informed consent form and the information sheet will explain in detail the nature of the study, its objectives, and potential risks and benefits. The informed consent form will detail the requirements of the participant and the fact that subject is free to withdraw at any time without giving a reason and without any negative effect on the further medical care.
The principal investigator is responsible for the preparation, contents, and approval of the informed consent form and subject information sheet by the committee such as ethics review committee. The informed consent form and information sheet must be approved by the committee prior to use.
The informed consent form and information sheet shall be written in language that can be easily understood by the potential subjects. The investigator shall be responsible for providing detailed explanation of the informed consent form and information sheet to the potential subjects.
Information should be given in both oral and written form whenever possible and in manner deemed appropriate by the committee such as ethics review committee.
The investigator shall ensure that the potential subjects have (1) an opportunity to inquire about the study and (2) sufficient time to decide on their participation. If a potential subject decides to participate in the study, then the informed consent form must be signed and dated by the potential subject prior to entering into the study as a subject. The investigator shall instruct the potential subject to sign using their legal names, not nicknames, using a blue or black ball point ink pen. Also the investigator shall sign and date the informed consent form prior to entering into the study.
Once signed, the original informed consent form shall be retained by the investigator. The investigator shall record the date that the potential 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 subject.
The investigator shall follow the same procedure as for obtaining the initial consent when newly obtaining re-consent from the concerned subject when the informed consent form is revised. The

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

15.4 Personal Information of Subjects

The sponsor or the designee shall affirm the principle of the protection of subjects' private/personal information. Throughout this 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 subjects such as gender, age, and date of birth may be used within the scope of all applicable laws and regulations for identification of subjects and confirmation of accuracy of subject ID code.

For verification of the conduct of the study in compliance with this protocol and the Ethical Guideline for Clinical Research, 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 subjects' original medical records (source data or documents), including laboratory test results, ECG results, admission and discharge records during a subject's study participation, and autopsy reports. The investigator shall obtain specific authorization of the subject as part of the informed consent process for access to 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 investigator shall delete information that may lead to identification of an individual (name and address of subject, other personal information not recorded on the CRF of the subject).

15.5 Consultation for Subjects or Persons Related to the Study

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

15.6 Financial Burden or Reward to Subjects

Regarding the expenses for this study, the sponsor shall pay for medical treatment not covered by health insurance and examinations necessary for the study as study expenses. The 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 study to the subjects at each visit from the study funds. Details of the financial burden on the subjects and rewards shall be described in the informed consent form and information sheet.

15.7 Benefits and Inconveniences to Subjects

15.7.1 Benefits to Subjects

The subjects will obtain detailed information on the status of their type 2 diabetes mellitus and their treatment satisfaction through participation in this study.

15.7.2 Inconveniences to Subjects

Participation in this study may increase burden on the subjects due to requirement for answering questionnaires and DTSQ, as compared with routine medical practice.

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 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 investigators or regulatory authorities during the study period, except when required by laws and regulations. The sponsor shall be responsible for publication of the protocol and study-related results (including the public web site) except for other cases permitted in the study contract.

During and after the study, the sponsor or its designee should promptly summarize the results and present them 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 investigators should obtain the prior written approval from the sponsor when publishing the information obtained in this study at an academic conference, etc.

The sponsor shall report to the chief executive of the study site when final publication of the study results has been made.

15.9.2 Clinical Study Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and Japan Pharmaceutical Information Center Clinical Trials Information (JAPIC) before start of study. Takeda contact information, along with investigator's city, country, and recruiting status will be registered and available for public viewing.

15.9.3 Clinical Study Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov and JAPIC, as required by applicable laws and/or regulations.

15.10 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Clinical Research Schedule

		Treatment			At discontinuation[c]
Timing of visit	Week	0	8	16	
	Day	-1[b]	56	112	
Acceptable range (days)		-1	49-63	105-119	Until 14 days after the last dose
Visit No.		1	2	3	
Informed consent		X			
Demographics and medication history		X			
Inclusion/exclusion criteria		X			
Questionnaire for patient background		X			
Physical examination		X	X	X	X
Height / weight / BMI		X			
Concomitant medications [a]		X	X	X	X
Concurrent medical condition		X			
HbA1c		X	X	X	X
Prescription of study drug		X	X		
Treatment compliance			X	X	X
DTSQ		X	X	X	X
Questionnaire for patient preference				X	
Adverse event		X→	←X→	←X	←X

(a) Record all concomitant medications.

(b) Start the dosing of the study drug from the following date after all tests at Week 0 are completed. Set the start date of dosing as Day 1 and the day before the start date of dosing as Day 0.

(c) Conduct as much as possible.