- 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:

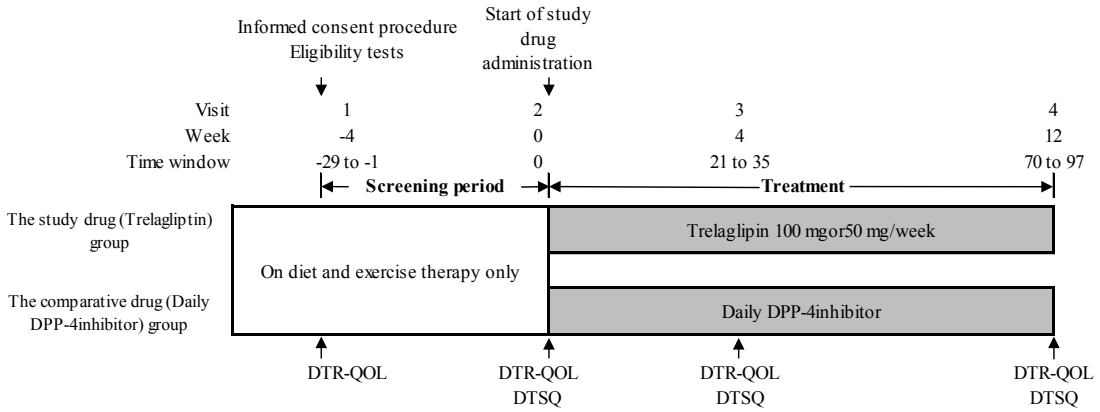
The study drug (Trelagliptin) group 120 subjects

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

- 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.

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.

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

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

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.

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.

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.

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.

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.

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)

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.