Clinical Study Protocol

NCT Number: NCT04285983

Title: Specified Drug Use Surveillance on Zafatek Tablets 25 mg−Surveillance on Long-Term Use of Trelagliptin Tablets in Type 2 Diabetes Mellitus Patients with Severe Renal Impairment or End-Stage Renal Failure−

Study Number: Trelagliptin-4004

Document Version and Date: Version 6/ 11-May-2022

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

A summary of changes to previous protocol versions is appended to the end of the document.

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

SPECIFIED DRUG USE SURVEILLANCE PROTOCOL

Specified Drug Use Surveillance on Zafatek Tablets 25 mg —Surveillance on Long-Term Use of Trelagliptin Tablets in Type 2 Diabetes Mellitus Patients with Severe Renal Impairment or End-Stage Renal Failure—

Sponsor	**Takeda Pharmaceutical Company Limited**
Protocol Number	**Trelagliptin-4004**
Version Number	**Version 6**
Prepared on	**11 May 2022**

TABLE OF CONTENTS

1.0 BACKGROUND TO THE STUDY

Zafatek Tablets—a dipeptidyl peptidase (DPP)-4 inhibitor containing trelagliptin succinate as its active ingredient—is an oral therapy for patients with type 2 diabetes mellitus (T2DM).

Following submission of the marketing authorization application (MAA) in March 2014 based on the results of clinical studies in T2DM patients, marketing authorization for Zafatek Tablets was granted in Japan in March 2015. The approved Indication is "*Type 2 diabetes mellitus*" and the approved Dosage and Administration is "*The usual adult dosage is 100 mg of trelagliptin orally administered once weekly.*"

Clinical experience with Zafatek Tablets in patients with renal impairment includes a clinical pharmacology study conducted outside Japan in this patient population. Based on the findings of this study, no dose adjustment is deemed necessary for patients with mild renal impairment whereas half the usual dose (i.e., 50 mg Q1W) is recommended for patients with moderate renal impairment. Moreover, although both the 50 mg and 100 mg Zafatek Tablets have been approved in Japan, administration is contraindicated in patients with severe renal impairment (SRI) or end-stage renal failure (ESRF) given that a quarter of the usual dose (i.e., 25 mg Q1W) is deemed to be appropriate in these patients.

However, as renal impairment is a frequent complication of T2DM, an additional study of Zafatek Tablets 25 mg (herein "Zafatek 25 mg") administered Q1W to patients with T2DM complicated by SRI or ESRF was conducted with the aim of contributing to the treatment of T2DM among patients in the severe or end stages of renal impairment. The study results demonstrated the efficacy and safety of Zafatek 25 mg, and in September 2019 this drug became available for clinical use in patients with T2DM complicated by SRI or ESRF.

Therefore, as part of Takeda Pharmaceutical's ongoing pharmacovigilance program in T2DM patients with comorbid SRI or ESRF, and following on from our supplementary pharmacovigilance and efficacy study in the form of specified drug use surveillance (SDUS) entitled "Surveillance on Long-Term Use of Trelagliptin Tablets in Patients with Type 2 Diabetes Mellitus" that has been underway since May 2016 (herein "the Long-Term Zafatek 50 mg and 100 mg SDUS on T2DM"), we are planning to conduct the SDUS entitled "Surveillance on Long-Term Use of Trelagliptin Tablets in Type 2 Diabetes Mellitus Patients with Severe Renal Impairment or End-Stage Renal Failure" (herein "the present SDUS") to gather pertinent Safety Specification data according to the Risk Management Plan (RMP) for Zafatek 25 mg—namely, important missing information on the safety of administering Zafatek 25 mg to patients with renal impairment, information on the important identified risk of hypoglycemia, and information on the important potential risk of infection.

The present SDUS will be conducted in accordance with Japan's Ministerial Ordinance on Good Postmarketing Study Practice (GPSP) and other relevant regulatory requirements.

2.0 OBJECTIVE

This Specified Drug Use Surveillance (herein "the Surveillance" or "the present SDUS") will evaluate the safety of long-term use of Zafatek Tablets 25 mg (herein "Zafatek 25 mg") in

routine clinical practice in patients with type 2 diabetes mellitus (T2DM) complicated by severe renal impairment (SRI) or end-stage renal failure (ESRF).

3.0 SAFETY SPECIFICATION

Important missing information: Safety of administering Zafatek 25 mg in patients with renal impairment

Important identified risk: Hypoglycemia

Important potential risk: Infection

4.0 PLANNED SAMPLE SIZE AND RATIONALE

4.1 Planned Sample Size

85 patients

4.2 Rationale

The Specified Drug Use Surveillance (SDUS) of Zafatek Tablets 50 mg and 100 mg entitled ”Surveillance on Long-Term Use of Trelagliptin Tablets in Patients with Type 2 Diabetes Mellitus” (herein “the Long-Term Zafatek 50 mg and 100 mg SDUS on T2DM”) is being conducted in patients with T2DM without comorbid severe or end-stage renal impairment between 1 May 2016 and 31 October 2021, with a planned sample size of 3,000 patients and observation period of 36 months. The cumulative incidence of adverse drug reactions (ADRs) in the Safety Analysis Set consisting of 1,258 enrolled patients from whom a Case Report Form (CRF) had been collected by 25 March 2019 was 2.07% (26/1,258 patients).

In a series of SDUS studies investigating the safety of once-daily (Q1D) administration of the dipeptidyl peptidase-4 (DPP-4) inhibitor Nesina Tablets (alogliptin benzoate) either alone or in combination with an alpha-glucosidase inhibitor (α-GI), in combination with a thiazolidinedione (TZD) drug, in combination with a sulfonylurea drug, in combination with a biguanide drug, and in combination with hypoglycemic drugs (insulin preparation, fast-acting insulin secretagogues, etc.) in patients with T2DM, 113 patients within the pooled Safety Analysis Set of 7,628 patients had severe or end-stage renal impairment as indicated by an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2.

In light of the findings of these previous SDUS studies, the incidences of ADRs in the present SDUS and in the Long-Term Zafatek 50 mg and 100 mg SDUS on T2DM will be compared in order to evaluate the safety of long-term Zafatek treatment of T2DM patients with severe or end-stage renal impairment (SRI or ESRF) in routine clinical practice. The present SDUS will also collect and evaluate safety information on the same number of T2DM patients with comorbid SRI or ESRF as those enrolled in the Nesina tablets SDUS studies. Specifically, the important identified risk of hypoglycemia and the important potential risk of infection will be evaluated for Zafatek 25 mg based on patient summaries including the presence/absence of these events and, if present, their time of onset and seriousness.

The planned sample size needed to perform these safety assessments was set at 85 patients based

on the number of T2DM patients with comorbid SRI or ESRF in the Nesina tablets SDUS and in consideration of study feasibility.

5.0 SURVEILLANCE POPULATION

The Surveillance will target patients with type 2 diabetes mellitus (T2DM) complicated by severe renal impairment (SRI) or end-stage renal failure (ESRF). Patients must meet all of the inclusion criteria and none of the exclusion criteria listed below. The enrollment criteria shall be based on the Zafatek Package Insert.

5.1 Inclusion Criteria

Patients with type 2 diabetes mellitus who meet the following criteria will be eligible for inclusion in the Surveillance.

Severe renal impairment (SRI) or end-stage renal failure (ESRF) with serum creatinine (mg/dL) or creatinine clearance (Ccr; mL/min) levels meeting the following criteria within 3 months of starting treatment with Zafatek 25 mg

	Serum creatinine (mg/dL)*	Creatinine clearance (Ccr; mL/min)
SRI/ ESRF	Males: >2.4 Females: >2.0	<30

In patients with ESRF, the temporal relationship between Zafatek 25 mg treatment and hemodialysis will not be taken into consideration.

*: Ccr equivalent for person aged 60 years with body weight of 65 kg

5.2 Exclusion Criteria

Patients with any of the following contraindications for treatment with Zafatek 25 mg will be excluded from the Surveillance.

Contraindications (Zafatek is contraindicated in the following patients.)

(1) Patients with severe ketosis, diabetic coma or precoma, or type 1 diabetes mellitus
(2) Patients with severe infection, patients in the perioperative period, or patients with serious trauma
(3) Patients with a history of hypersensitivity to any of the ingredients of Zafatek

6.0 DOSAGE AND ADMINISTRATION

Zafatek will be administered orally once a week (Q1W) in a single dose containing 25 mg trelagliptin.

The dosage shall be based on the Zafatek Package Insert.

Precautions Concerning Dosage and Administration:

(1) In patients with moderate or more severe renal impairment, the blood concentration of trelagliptin may be increased due to delayed excretion. Decrease the dose according to the severity of renal impairment as per the following table.

Dosage in patients with moderate or more severe renal impairment:

	Serum creatinine (mg/dL)*	Creatinine clearance (Ccr; mL/min)	Dose
Patients with moderate renal impairment	Males: 1.4–2.4 Females: 1.2–2.0	30–50	50 mg Q1W
SRI/ ESRF	Males: >2.4 Females: >2.0	<30	25 mg Q1W

In patients with ESRF, the temporal relationship between Zafatek 25 mg treatment and hemodialysis will not be taken into consideration.
*: Ccr equivalent for person aged 60 years with body weight of 65 kg

(2) The investigator will instruct the patients as follows:

1) To take Zafatek 25 mg once a week on the same day each week.

2) To take any missed doses at the prescribed dosage as soon as the patient realizes he/she has missed the dose, and to take all subsequent scheduled doses on the scheduled day.

7.0 PLANNED NUMBER OF SURVEILLANCE SITES BY DEPARTMENT

By department, approximately 30 medical institutions (herein "surveillance sites") are scheduled to be enrolled in the present SDUS, including internal medicine, nephrology and dialysis departments.

8.0 METHODS

8.1 Observation Period

12 months

8.2 Surveillance Site Recruitment and Contracting

Takeda Pharmaceutical Company Limited (herein "Takeda Pharmaceutical") will conclude a written agreement with medical institutions (herein "the surveillance sites") to conduct this Surveillance.

8.3 Patient Consent

Prior to enrollment, the surveillance site investigator (herein "the investigator") will seek the

informed consent of the patient (or their legally-authorized representative) to provide information for use in the present SDUS by way of a written or verbal explanation of the Surveillance. Patients (or their legally-authorized representative) who agree to participate in the Surveillance following the written explanation will be asked to sign and date the Informed Consent Form (ICF). The investigator will then retain the original signed ICF. For patients who agree to participate in the Surveillance following the verbal explanation, the investigator will create a record of their verbal consent.

The written explanation will contain an outline of the Surveillance, the procedure for handling the patient's personal information and personal health information throughout the Surveillance, and the fact that the patient could stop participating in the Surveillance at any time and for any reason without penalty.

The investigator will then assign an identification number ("patient ID number") to the patients who provide their informed consent.

8.4 Patient Enrollment Method

Patients will be enrolled according to a central enrollment procedure using a web-based electronic data capture system (Rave EDC). The investigator or investigator's representative (herein "the IR") will be required to enter the enrollment details (see section 10.1) of all patients who are prescribed Zafatek 25 mg on or after the start date of the surveillance site's agreement with Takeda Pharmaceutical into the Rave EDC system by 14 days after their first dose of Zafatek 25 mg (wherein the prescribing date is defined as "Day 0" and the day after the prescribing date is defined as "Day 1"), after which the investigator will attach his/her electronic signature.

8.5 Completion and Submission of Case Report Forms

Surveillance data will be collected using the Rave EDC system.

After performing the scheduled assessments and observations on all enrolled patients (see sections 10.2 through 10.6 and Appendix 1 for details), the investigator or the IR[*1] will promptly enter the surveillance data in the Rave EDC system and the investigator will then attach his/her electronic signature. If the investigator or the IR cannot confirm whether or not the patient has taken a prescribed dose of Zafatek 25 mg, the unconfirmed dosing will be recorded in the Rave EDC system (while the other relevant data elements can be left blank).

However, in patients in whom Zafatek 25 mg treatment is discontinued due to AE onset, the investigator will follow the patient after discontinuation wherever feasible until the event is either resolved or resolving, after which the investigator or the IR will enter the assessment and observation data in the Rave EDC system and the investigator will attach his/her electronic signature.

[*1]: The investigator's representative ("the IR") is defined as personnel employed at the surveillance site (including the contracted Clinical Research Coordinator (CRC) and other personnel contracted by the surveillance site). The Principal Investigator of the Surveillance

("the PI"; a single physician for the entire surveillance site or for each department who is assigned when the SDUS agreement is concluded with Takeda Pharmaceutical) is responsible for creating and signing/sealing a record of the designated IRs and submitting it to Takeda Pharmaceutical.

9.0 PLANNED DURATION OF SURVEILLANCE

Surveillance period: 1 March 2020 to 31 January 2023[*2]

Patient enrollment period: 1 March 2020 to 30 September 2021[*3]

[*2]: At completion of re-examination of all patient Case Report Forms (CRFs).

[*3]: Patients will not be enrolled (i.e., registered in the Rave EDC system) from 1 October 2021 onwards even if they have received Zafatek 25 mg on or before 30 September 2021. Furthermore, enrollment will be closed before the end of the enrollment period if the actual number of patients enrolled in the Surveillance reaches the planned sample size before 30 September 2021. If the enrollment period is shortened for this reason, the Surveillance period will be changed accordingly.

10.0 SURVEILLANCE DATA ELEMENTS

The investigator or the IR will enter the following surveillance data in the Rave EDC system. The schedule of assessments and observations in the present SDUS is shown in Appendix 1.

10.1 Patient Enrollment

1) Surveillance data elements

Zafatek 25 mg prescribing date, patient ID number, sex, age (at Zafatek 25 mg prescribing date), assessment of enrollment eligibility based on inclusion and exclusion criteria

2) Surveillance timing

At patient enrollment

10.2 Patient Demographics and Baseline Characteristics

1) Surveillance data elements

Date of T2DM diagnosis, healthcare category (at start of Zafatek 25 mg treatment), height, history of smoking, history of alcohol consumption, hypersensitivity (Y/N and description), concurrent illness (Y/N and description), previous medical history (Y/N and description)

2) Surveillance timing

At start of Zafatek 25 mg treatment

10.3 Treatment Details

1) Surveillance data elements

Zafatek 25 mg treatment details (amount per dose, dosing period, reason for any discontinuation), concomitant medication (anti-diabetic medication)*4 treatment details (Y/N, drug name, route of administration, daily dose, dosing period), concomitant medication (other than anti-diabetic medication) treatment details (Y/N, drug name, reason for use), dialysis treatment details (Y/N, type [hemodialysis/peritoneal dialysis/other], dialysis period)

*4: Includes any anti-diabetic drugs that were discontinued within the 3 months prior to initiation of Zafatek 25 mg treatment

2) Surveillance timing

The period from the start of Zafatek 25 mg treatment (Day 0) until 12 months of treatment (Day 360) (or until treatment discontinuation)

10.4 Compliance with Zafatek 25 mg Treatment and Dietary/Exercise Therapy

1) Surveillance data elements

Zafatek 25 mg treatment compliance status, description of and reason(s) for any treatment non-compliance, dietary/exercise therapy compliance status

Criteria for Assessing Zafatek 25 mg Treatment Compliance

1. Patient took the drug once weekly as prescribed at least 90% of the time
2. Patient took the drug once weekly as prescribed at least 70% of the time
3. Patient took the drug once weekly as prescribed at least 50% of the time
4. Patient took the drug once weekly as prescribed less than 50% of the time
5. Patient did not take the drug
6. Patient's treatment compliance is unknown

Description of and Reasons for Treatment Non-Compliance (only required for weeks in which the patient did not take the drug once weekly as prescribed)

a. Patient took the drug twice or more in one week.

Reasons:

A1. Patient took the drug twice in one week to make up for a previously-missed dose.

A2. Patient inadvertently took the drug twice or more in one week due to forgetting the dosing day, etc.

A3. Patient took the drug twice or more in one week due to mistaking the dosing frequency for daily dosing.

A4. Patient inadvertently took the drug twice or more in one week after taking it together with a separate daily medication.

A5. Other reason (provide details)

b. Patient took a dose exceeding the prescribed single dose.

Enter a description of and reason for the excessive dose in the Rave EDC system.

c. Patient did not take a weekly dose.

Reasons:

A1. Patient forgot to take the drug.

A2. Patient could not take the drug due to work or other circumstances.

A3. Other reason (provide details)

Criteria for Assessing Compliance with Dietary/Exercise Therapy

1. Patient followed with the therapy regimen at least 90% of the time (i.e., followed the regimen properly and as directed)
2. Patient followed with the therapy regimen at least 70% of the time (i.e., followed the regimen generally and as directed)
3. Patient followed with the therapy regimen at least 50% of the time (i.e., followed the regimen as directed at least half of the time)
4. Patient followed with the therapy regimen less than 50% of the time (i.e., did not follow the regimen as directed more than half of the time)
5. Patient did not follow the therapy regimen
6. Patient's compliance with the therapy regimen is unknown

2) Surveillance timing

At start of Zafatek 25 mg treatment (Day 0; compliance with dietary/exercise therapy only) and at 1 month (Day 30), 3 months (Day 90), 6 months (Day 180), 9 months (Day 270) and 12 months (Day 360) of treatment (or at treatment discontinuation)

10.5 Assessments and Observations

Data on each of the following assessments and observations performed at each scheduled timepoint will be entered in the Rave EDC system.

10.5.1 Vital Signs

1) Assessments and observations

Pulse rate, blood pressure (systolic/diastolic), body weight

2) Surveillance timing

Measurement timepoints at start of Zafatek 25 mg treatment (Day 0) and at 1 month (Day 30), 3 months (Day 90), 6 months (Day 180), 9 months (Day 270) and 12 months (Day 360) of treatment (or at treatment discontinuation)

10.5.2 Laboratory Tests

1) Tests/Assays

Glycated hemoglobin (HbA1c) (National Glycohemoglobin Standardization Program [NGSP] values; same hereinafter), glycoalbumin, fasting blood glucose, fasting triglyceride, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, serum creatinine, blood urea nitrogen (BUN), urine albumin (urine albumin-

creatinine ratio [uACR]), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (γ-GTP), alkaline phosphatase (ALP), total bilirubin, amylase, lipase

2) Surveillance timing

Test/assay timepoints at start of Zafatek 25 mg treatment (Day 0) and at 1 month (Day 30), 3 months (Day 90), 6 months (Day 180), 9 months (Day 270) and 12 months (Day 360) of treatment (or at treatment discontinuation)

10.5.3 Electrocardiography

1) Tests/Assays

ECG (findings and assessments)

2) Surveillance timing

Test/assay timepoints at start of Zafatek 25 mg treatment (Day 0) and at 1 month (Day 30), 3 months (Day 90), 6 months (Day 180), 9 months (Day 270) and 12 months (Day 360) of treatment (or at treatment discontinuation)

10.5.4 Other Observations

1) Observations

Pregnancy status (Y/N) during the observation period (female patients only), withdrawal of consent

If a patient is found to be pregnant during the observation period, the investigator is required to immediately contact Takeda Pharmaceutical. Pursuant to a request by Takeda Pharmaceutical, the investigator will then provide details of the pregnancy using the attached Pregnancy Form. Where possible, the submitted form will include information up to childbirth such as premature delivery or other outcomes.

2) Surveillance timing

The period from the start of Zafatek 25 mg treatment (Day 0) until 12 months of treatment (Day 360) (or until treatment discontinuation)

10.6 Adverse Events

1) Surveillance data elements

Presence or absence (Y/N) of adverse event (herein "AE"; see Table 1), AE term, date of onset, seriousness and reason for assessment as serious (see Table 2), reason for discontinuing Zafatek 25 mg, date of outcome assessment, outcome, causal relationship with Zafatek 25 mg[*5] (see Table 3)

If the AE outcome is "not recovered/not resolved" or "unknown" or if the causal relationship is deemed "not evaluable," the patient will be followed to the extent possible.

If a patient experiences an AE corresponding to the risks identified in the Safety Specification—specifically, hypoglycemia or infection—detailed information on the time of onset, seriousness and other relevant case data will be collected to the extent possible.

[*5] : If the causal relationship with Zafatek 25 mg is deemed 'not related,' the investigator will record the

rationale for this assessment. Alternatively, if the causal relationship is deemed 'not evaluable,' the investigator will provide the reason for this assessment.

N.B.) Points to consider when assessing AEs:

Abnormal worsening of the target disease (i.e., worsening beyond the expected natural course of the disease) should be assessed as an AE.

2) Surveillance timing

The period from the start of Zafatek 25 mg treatment (Day 0) until 12 months of treatment (Day 360) (or until treatment discontinuation)

Table 1 Definition of Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a patient administered a pharmaceutical product during the course of a clinical investigation, and that does not necessarily have a clear causal relationship with this pharmaceutical product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product.

Table 2 Criteria for Assessing Seriousness

AEs that meet any of the following criteria will be assessed as serious: 1. Results in death (death) 2. Is life-threatening (risk of death) The term "life-threatening" in the definition of serious refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. 3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolonged hospitalization) 4. Results in persistent or significant disability/incapacity (disability) 5. Leads to a congenital anomaly/birth defect (congenital anomaly) 6. Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent outcomes such as those listed in items 1 to 5 above.

* Any reported AE that is listed in the "Takeda Medically Significant AE List" will be handled as serious.

Table 3 Criteria for Assessing Causal Relationship of Adverse Events with Zafatek 25 mg

Assessment	Assessment Criteria
Related	A causal relationship cannot be ruled out because there is a temporal correlation between event onset and drug administration (including the course of the event after treatment is discontinued) or because it is at least plausible that the event was caused by the drug despite the possible involvement of other factors such as the underlying disease, concurrent illness or concomitant medication or procedures.
Not Related	There is no temporal correlation with the drug or there is sufficient evidence to suggest that the event was caused by other factors such as the underlying disease, concurrent illness, or concomitant medication or procedures.
Not Evaluable	There is insufficient information on the temporal relationship (including the course of the event after treatment is discontinued), underlying disease, concurrent illness, or concomitant medication or procedures to evaluate the causal relationship.

11.0 ANALYSES AND METHODS

11.1 Statistical Analysis Plan

A Statistical Analysis Plan (SAP) will be prepared prior to data lock. The SAP will contain definitions of the surveillance data elements and will describe the methods for statistical analysis.

11.2 Analysis Sets

The present SDUS is designed using the "Safety Analysis Set" as the analysis population.

11.3 Patient Disposition

Patient disposition will be tabulated for the number of enrolled patients, the number of patients for whom electronic CRFs (eCRFs) are submitted/collected, the number of patients in the Safety Analysis Set, the number of patients excluded from analysis and the reason(s) for their exclusion.

11.4 Patient Demographics and Baseline Characteristics

Demographics and baseline characteristics will be tabulated for sex, age, disease duration, concurrent illness and other relevant variables.

11.5 Treatment Details

Details of the Zafatek 25 mg treatment, treatment compliance, and use of concomitant medications will be tabulated.

11.6 Safety

The following data will be tabulated for the Safety Analysis Set. AEs will be summarized by Preferred Term (PT) and System Organ Class (SOC) using the Japanese translation of Medical Dictionary for Regulatory Activities (MedDRA/J).

11.6.1 Adverse Event Incidence Data

AE incidences during the observation period will be tabulated by category, time of onset, seriousness, causal relationship with Zafatek 25 mg and other relevant variables.

11.6.2 Factors Potentially Affecting Safety

Adverse drug reaction (ADR) incidences during the observation period will be tabulated by strata consisting of patient demographics and baseline characteristics (e.g., sex, age, concurrent illness [Y/N]) and by Zafatek 25 mg treatment details, concomitant medication (Y/N) and dialysis treatment (Y/N).

11.6.3 Time Courses of Laboratory and Other Test Values

Laboratory and other test values and absolute changes from baseline in these values (i.e., the test value at each test timepoint after starting Zafatek 25 mg minus the test value at the start of Zafatek 25 mg treatment) will be tabulated for each timepoint of the HbA1c, glycoalbumin,

fasting blood glucose and lipid tests and the kidney function tests.

11.7 Patients with Special Backgrounds

Safety data will be tabulated by strata for elderly patients and patients with hepatic impairment.

12.0 REGISTRATION OF SURVEILLANCE INFORMATION

Takeda Pharmaceutical will register information about the present SDUS on the following publicly-accessible websites prior to commencing the surveillance.

- JAPIC Clinical Trials Information website, Japan Pharmaceutical Information Center (JAPIC)
- ClinicalTrials.gov clinical trials registry, U.S. National Institutes of Health (NIH)

13.0 SURVEILLANCE ADMINISTRATIVE STRUCTURE

13.1 Administrative Structure for Postmarketing Surveillance

See attachment document.

14.0 CONTRACT RESEARCH ORGANIZATIONS

14.1 PRA Health Sciences Co., Ltd.

Address	: 4-1-3 Kyutaromachi, Chuo-ku, Osaka-shi, Osaka
Contracted operations	: Data management, electronic data capture (EDC) system development and management, retention/archiving of records, postmarketing surveillance support operations

14.2 EPS Corporation

Address	: 2-23 Shimomiyabicho, Shinjuku-ku, Tokyo
Contracted operations	: Statistical analysis

14.3 PharField Corporation

Address	: 2-8-20 Saga, Koto-ku, Tokyo
Contracted operations	: Monitoring operations

15.0 POSSIBLE FOLLOW-UP PROCEDURES BASED ON SURVEILLANCE FINDINGS AND ADOPTION CRITERIA

The Pharmaceutical Risk Management Plan (RMP) containing the following information will be revised at the relevant milestones in the present SDUS.

- If any new information or findings are obtained in relation to the Safety Specification, the need for any changes to the Package Insert's Risk Minimization Plan will be investigated.
- The need for any changes to the present SDUS Protocol, including any new items in the Safety Specification, will be investigated.

16.0 SCHEDULED MILESTONES FOR EVALUATION OF SDUS CONDUCT & RESULTS

AND PMDA REPORTING, AND RATIONALE THEREFOR

Milestone: At release of Periodic Safety Update Reports (PSURs); Rationale: To comprehensively investigate safety information.

Milestone: At creation of Final Report at 8 months after completion of the present SDUS; Rationale: To perform final tabulation of all enrolled patient data after data lock, and to then prepare and submit the Final Report.

17.0 OTHER NECESSARY MATTERS

17.1 Amendments to the Protocol

The Protocol for the present SDUS will be revised and amended during the Surveillance where required based on information obtained on the Surveillance progress, the occurrence of any ADRs or serious ADRs that are not expected based on the Zafatek Package Insert's "Precautions Concerning Use," any increases in the incidence of identified ADRs, and the appropriateness of surveillance data elements. If approval is granted for a partial change to Zafatek's authorized Dosage and Administration or Indications, the need for corresponding amendments to the Protocol will be investigated and, if deemed necessary, the Protocol will be amended accordingly during the Surveillance.

17.2 Handling of Issues and Uncertainties

If any issues are identified in relation to the safety of Zafatek 25 mg, the appropriate action will be taken based on a detailed analysis of the relevant data.

Appendix 1 Schedule of Assessments and Observations

Surveillance Timing / Surveillance Data Elements		Observation Period							
		At patient enrollment	At start of Zafatek 25 mg treatment (baseline)	1 month	3 months	6 months	9 months	12 months	At discontinuation of Zafatek 25 mg treatment
Day		-	0	30	90	180	270	360	-
Window (min–max)		-	-30–0	1–60	61–136	137–226	227–316	317–456	-
Informed consent		○							
Patient Enrollment	Zafatek 25 mg prescribing date	○							
	Patient ID No.	○							
	Sex	○							
	Age	○							
	Assessment of enrollment eligibility	○							
Patient Demographics and Baseline Characteristics	Date of T2DM diagnosis		○						
	Healthcare category		○						
	Hypersensitivity		○						
	Concurrent illnesses		○						
	Previous medical history		○						
	Height		○						
	Smoking history		○						
	Alcohol consumption history		○						
Treatment Details	Zafatek 25 mg treatment		←———	———	○	———	———	———→	○
	Concomitant medications (anti-diabetic & other medications)		←———	———	○	———	———	———→	○
	Dialysis treatment		○	←———	———	○	———	———→	○
	Zafatek 25 mg treatment compliance status, description of and reason(s) for any treatment			○	○	○	○	○	○
	Dietary/exercise therapy compliance		○	○	○	○	○	○	○
Assessments & Observations	Pulse rate, blood pressure, body weight		○	○	○	○	○	○	○
	Laboratory Tests		○	○	○	○	○	○	○
	Electrocardiography		○	○	○	○	○	○	○
	Pregnancy (Y/N) (female patients only)		←———	———	○	———	———	———→	○
	Adverse Events		←———	———	○	———	———	———→	○

○ : Performed at scheduled timepoint

←——○——→ : Perform throughout indicated period

Data from assessments and observations performed in routine clinical practice will be recorded in the Rave EDC system. Data from assessments and observations performed at discontinuation of treatment will be recorded in the Rave EDC system during the specified time window.

Document History

Version	Date	Comments
original version	2019/12/23	New document
2nd version	2020/6/12	A change in the company name of a CRO following a change in the surveillance administrative structure
3rd version	2021/1/15	The addition of a CRO
4th version	2021/6/8	Extension of the surveillance period and patient enrollment period
5th version	2021/9/6	A change in the planned sample size
6th version	2022/5/11	Addition of the Organization Structure as a Protocol attachment