Statistical Analysis Plan

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: Original Version/ 26-Jan-2023

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.

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

STATISTICAL ANALYSIS PLAN

(FINAL REPORT)

P R O D U C T N A M E Zafatek Tablets

S T U D Y T I T L E : Specified Drug Use Surveillance—Surveillance on Long-Term Use of Trelagliptin Tablets in Type 2 Diabetes Mellitus Patients with Severe Renal Impairment or End-Stage Renal Failure—

PROTOCOL NUMBER : Trelagliptin-4004

S P O N S O R : Takeda Pharmaceutical Company Limited

Director, Office of Biostatistics, Takeda Pharmaceutical Company Limited

Original Version: Created on 26 January 2023

1 DEFINITIONS OF TERMS

1.1 List of Terms and Abbreviations

- Zafatek 25 mg: The abbreviated name of the drug product "Zafatek Tablets 25 mg" of this Surveillance.
- ADRs, etc.: An abbreviation for "adverse drug reactions/infections" that refers to AEs other than those with a causal relationship to Zafatek 25 mg as assessed by the investigator as "not related." In this SAP, the term is denoted using the full wording "Adverse Drug Reactions/Infections" in titles and is abbreviated as "ADRs, etc." in the text and tables.
- SAE:
  - An AE that is assessed as "serious" by the investigator. Any AE listed in the MedDRA code list (PT code) of the Important Medical Events List is to be handled as serious even if it was assessed by the investigator as "not serious."
- "Related": AEs other than those assessed as not causally related to Zafatek 25 mg will be handled as "related," whereas AEs assessed as not causally related to Zafatek 25 mg will be handled as "not related."
- Summary statistics: A term that collectively refers to the number of patients, mean value, standard deviation, maximum value, minimum value, and quartile value.
- Patients without submitted CRFs: Refers to enrolled patients for whom a CRF has not been submitted/collected.
- Patients with submitted CRFs: Refers to enrolled patients for whom CRFs has been submitted/collected.
- Number of days after Zafatek 25 mg dosing: The day before the start of Zafatek 25 mg dosing is referred to as Day -1, while the day on which Zafatek 25 mg dosing is commenced is referred to as Day 1.
- Duration of Zafatek 25 mg treatment (days): Final day of Zafatek 25 mg dosing − start date of Zafatek 25 mg dosing + 1.
- Patients with hepatic impairment: Patients with a concurrent illness classified as "hepatic impairment" using the broad SMQ.
- Severity of hepatic impairment: Severity will be defined using the most severe hepatic impairment assessment based on the laboratory values for total bilirubin, AST, ALT, and symptoms (concurrent illness).
  - Severity of hepatic impairment (total bilirubin)

Mild: 1.6<= – <3.0

Moderate: 3.0<= – <10

Severe: 10<=

- Severity of hepatic impairment (AST or ALT)

Mild: 50<= – <100

Moderate: 100<= – <500

Severe: 500<=

- Severity of hepatic impairment (symptoms [concurrent illness])

Preferred Term (PT)	Severity
Hepatic cirrhosis	Severe
Hepatocellular carcinoma	Severe
Metastases to liver	Severe
Hepatomegaly	Moderate
Hepatic mass	Moderate
Hepatic steatosis	Moderate
Autoimmune hepatitis	Moderate
Non-alcoholic steatohepatitis	Moderate
Non-alcoholic fatty liver disease	Moderate

- Elderly: Patients aged ≥65 years
- Duration of type 2 diabetes mellitus (years):
  - Actual duration (years) = Date of initial dose of Zafatek 25 mg - Date of type 2 diabetes mellitus (T2DM) diagnosis + 1

    If the month of the patient's T2DM diagnosis is not known, use the month of January.
- Overdosage/Overdose: A determination of overdosage/overdose will apply to patients whose reason for non-compliance with Zafatek 25 mg treatment listed under "Description of and Reasons for Treatment Non-Compliance" was "*Patient took the drug twice or more in one week*" and "*Patient took the drug twice or more in one week due to mistaking the dosing frequency for daily dosing*" or "*Patient inadvertently took the drug twice or more in one week after taking it together with a separate daily medication*" on at least one occasion, or to patients whose recorded description of non-compliance was *"Patient took a dose exceeding the prescribed single dose"* on at least one occasion.

- Anti-diabetic medications other than Zafatek 25 mg
    - Alpha-glucosidase inhibitors: Drugs with a medicinal product code starting with 3969003, 3969004, 3969009, or 3969102.
    - Thiazolidines: Drugs with a medicinal product code starting with 3969005, 3969007, 3969100, 3969101, or 3969103.
    - Sulfonylureas: Drugs with a medicinal product code starting with 3961 or 3969101.
    - Biguanides: Drugs with a medicinal product code starting with 3962, 3969100, 3969104, or 3969105.
    - Fast-acting insulin secretagogues: Drugs with a medicinal product code starting with 3969006, 3969008, 3969013, or 3969102.
    - Insulin preparations: Drugs with a medicinal product code starting with 2492.
    - DPP-4 inhibitors: Drugs with a medicinal product code starting with 3969010, 3969011, 3969012, 3969014, 3969015, 3969016, 3969017, 3969024, or 3969025.
    - GLP-1 receptor agonists: Drugs with a medicinal product code starting with 2499410, 2499411, 2499415, or 2499416.
    - SGLT2 inhibitors: Drugs with a medicinal product code starting with 3969018, 3969019, 3969020, 3969021, 3969022, or 3969023.
    - Anti-diabetic combination drugs: Drugs with a medicinal product code starting with 3969100, 3969101, 3969102, 3969103, 3969104, 3969105, 3969106, 3969107, or 3969108.

1.2 Analysis Sets

The present SDUS will be designed using the "Safety Analysis Set" as the analysis population. It is defined as follows.

Safety Analysis Set

The Safety Analysis Set is defined as "the set of patients for whom CRFs were submitted/collected, who received at least one dose of Zafatek 25 mg and in whom the safety of Zafatek 25 mg could be evaluated." Patients who met any of the following criteria were excluded from the Safety Analysis Set.

- Patients who did not receive treatment with Zafatek 25 mg
- Patients who had received treatment with Zafatek 25 mg before the contracted Surveillance period
- Patients who were enrolled in the Surveillance 15 or more days after Zafatek 25 mg was prescribed
- Patients who withdrew their consent to participate in the Surveillance

1.3 Presentation of Numerical Data

- Percentages (%)
  Incidence proportions or incidence rates of AEs or ADRs, etc.:
  Round to the second decimal place and display up to the second decimal place.
  Other data elements:
  Round to the first decimal place and display up to the first decimal place.

- Summary statistics
  Means, medians, and first & third quartiles:
  Round off raw data in the double digits and display up to single digit.
  Standard deviations:
  Round off raw data in the triple digits and display up to double digits.
  Minimum and maximum values:
  Display the actual number of digits of the data element without rounding.

1.4 Important Identified Risks, Important Potential Risks, and Important Missing Information

- Important identified risks
  - Hypoglycemia: Events classified as the PT “hypoglycemia”
- Important potential risks
  - Infections: Events classified within the SOC “Infections and infestations”
- Important missing information
  - Safety of administering Zafatek 25 mg in patients with renal impairment: Safety Analysis Set*

    *As the present SDUS is targeting patients with T2DM complicated by severe renal impairment (SRI) or end-stage renal failure (ESRF).

1.5 Handling of Time Windows

Data obtained from each test, observation and assessment that are evaluable (i.e., data that is not missing and is available for analysis) and that are within their respective time windows will be used for statistical analysis. If multiple evaluable data points exist within the same time window, the data obtained from the test/observation/assessment performed closest to the reference date (herein "reference day") will be used. If the time elapsed from the reference day is identical or if no reference day has been stipulated, the subsequently-obtained data will be used. The amount of time elapsed from the reference day shall be determined based on the number of days elapsed from dosing.

Vital Signs, Laboratory Tests, and Electrocardiography

Assessment timepoint	Reference day	Time window
		No. of days post-dosing
Start of Zafatek 25 mg treatment	No. of days post-dosing: -1	-30 – 1
1 mo after starting Zafatek 25 mg treatment	No. of days post-dosing: 30	2 – 60
3 mo after starting Zafatek 25 mg treatment	No. of days post-dosing: 90	61 – 135
6 mo after starting Zafatek 25 mg treatment	No. of days post-dosing: 180	136 – 225
9 mo after starting Zafatek 25 mg treatment	No. of days post-dosing: 270	226 – 315
12 mo after starting Zafatek 25 mg treatment	No. of days post-dosing: 360	316 – 456

1.6 Other Data Handling Methods

- Time of onset of AEs or ADRs, etc.: Time of onset will be calculated using the formula [Date of onset – Start date of Zafatek 25 mg treatment + 1] AEs or ADRs, etc. for which the date of onset is unknown will be calculated as having occurred on Day 1. However, if the month and year in which Zafatek 25 mg treatment is started match the month and year on which the AE or ADR, etc. occurred, the time of onset will be calculated as the day on which Zafatek 25 mg treatment was started.

2 NUMBER OF SURVEILLANCE SITES & ENROLLED PATIENTS AND PATIENT DISPOSITION

2.1 Disposition of Patients

Analysis set:	All-Case (enrolled patients)	
Data elements analyzed:	Enrolled patients	
	Surveillance sites	
	Patients for whom CRFs were not submitted/collected	
	Patients for whom CRFs were submitted/collected	
	Patients excluded from safety assessments*	
	Reason for exclusion (duplicate count)	[Patients not treated with Zafatek 25 mg, patients treated with Zafatek 25 mg before start of contracted Surveillance period, patients enrolled 15 or more days after Zafatek 25 mg was prescribed, patients who withdrew consent]
	Patients assessed for safety	
	Surveillance completion status	[completed, discontinued]

Analysis method: The following analyses will be performed and the Patient Disposition diagram will be prepared for the above-mentioned data elements.

Analysis of the data element 'enrolled patients' will also include computation of the number of surveillance sites. If the Surveillance is conducted in different departments at the same site, the site shall be counted only once (i.e., as a single site).

If no patients meet the criteria for exclusion, said number of patients shall be listed as 0.

Analysis of the data element 'patients excluded from safety assessments' will include tabulation and listing of patients with each reason for exclusion.

*The data element 'patients assessed for safety' is synonymous with the Safety Analysis Set, whereas 'patients excluded from safety assessments' refers to the patients who were excluded from the Safety Analysis Set.

(1) Frequency tables

3 PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

3.1 Patient Demographics and Baseline Characteristics

Analysis set:	Safety Analysis Set	
Data elements analyzed:	Sex	[male, female]
	Age (years)	[Min<= – <65, 65<= – <=Max]
		[Min<= – <75, 75<= – <=Max]
	Duration of T2DM (years)	[Min<= – <2, 2<= – <5, 5<= – <10, 10<= – <=Max]
	Body weight (kg)	
	BMI (kg/m^2)	[Min<= – <18.5, 18.5<= – <25.0, 25.0<= – <30.0, 30.0<= – <=Max]
	Height (cm)	
	Healthcare category	[outpatient, inpatient]
	Dialysis before starting Zafatek 25 mg treatment	[no, yes]
	Type of dialysis	[hemodialysis, peritoneal dialysis, other]
	Hypersensitivity	[no, yes, unknown]
	Concurrent illness	[no, yes]
	Breakdown of concurrent illness (duplicate count)	[diabetic nephropathy, diabetic retinopathy, diabetic neuropathy]
	Diabetic complications	[hypertension, dyslipidemia, hyperuricemia]
	Lifestyle diseases	[pancreatitis, calculus of gallbladder]
	Pancreas & biliary tract diseases	[hepatic steatosis, alcoholic hepatitis, chronic hepatitis, hepatic cirrhosis]
	Liver diseases	[nephrotic syndrome, glomerulonephritis, chronic renal failure]
	Kidney diseases	[cardiac failure, myocardial infarction, angina pectoris, cerebral infarction (including late effects of cerebral infarction)]
	Heart & cerebrovascular diseases	[gastric cancer, lung cancer, colorectal cancer, pancreatic cancer]
	Malignancies	[no, yes, unknown]
	Previous medical history	

	Smoking history	[never smoker, current smoker, former smoker, unknown]
	Alcohol consumption history	[yes, no, unknown]
	Severity of renal impairment	[severe renal impairment, end-stage renal failure]
	Presence/absence of hepatic impairment	[no, yes]
	Severity of hepatic impairment	[normal, mild, moderate, severe]
	HbA1c (NGSP value) (%)	[<6.0%, 6.0% – <7.0%, 7.0% – <8.0%, ≥8.0%, unknown]
	Fasting blood glucose (mg/dL)	
	Serum creatinine within 3 months before starting Zafatek 25 mg treatment (mg/dL)	
	Creatinine clearance within 3 months before starting Zafatek 25 mg treatment (mL/min)	
Analysis method:	The following analyses will be performed on the above-mentioned data elements. Data will be tabulated for the entire Safety Analysis Set ("overall") and for the hepatic impairment and elderly patient subsets.	
	(1) Frequency tables of discrete data and summary statistics of continuous data	

4 TREATMENT DETAILS

4.1 Duration and Completion of Zafatek 25 mg Treatment

Analysis set:	Safety Analysis Set	
Data elements analyzed:	Zafatek 25 mg treatment duration	
	Completion status	[completed, discontinued]
	Reason for Zafatek 25 mg treatment discontinuation (duplicate count)	[therapeutic objective achieved, occurrence of AE, patient stopped visiting site due to hospital transfer, etc., pregnancy, inadequate response, other]
Analysis method:	The following analyses will be performed on the above-mentioned data elements. Data will be tabulated for the entire Safety Analysis Set ("overall") and for the hepatic impairment and elderly patient subsets. (1) Frequency tables of discrete data and summary statistics of continuous data	

4.2 Previous and Concomitant Medications (Anti-Diabetic Medications)

Analysis set:	Safety Analysis Set	
Data elements analyzed:	Previous treatment with anti-diabetic medications	[no, yes]
	Breakdown of previous anti-diabetic medications (duplicate count)	[alpha-glucosidase inhibitors, thiazolidines, sulfonylureas, biguanides, fast-acting insulin secretagogues, insulin preparations, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, combination anti-diabetics] Proportions of patients previously treated with each type of anti-diabetic medication will be calculated using the total number of 'yes' patients as the denominator.
	Concomitant treatment with anti-diabetic medications	[no, yes]
	Breakdown of concomitant anti-diabetic medications	[alpha-glucosidase inhibitors, thiazolidines, sulfonylureas,

	(duplicate count)	biguanides, fast-acting insulin secretagogues, insulin preparations, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, combination anti-diabetics]
		Proportions of patients concomitantly treated with each type of anti-diabetic medication will be calculated using the total number of 'yes' patients as the denominator.
Analysis method:	The following analyses will be performed on the above-mentioned data elements. Data will be tabulated for the entire Safety Analysis Set ("overall") and for the hepatic impairment and elderly patient subsets. (1) Frequency tables	

4.3 Concomitant Medications (Other Than Anti-Diabetic Medications)

Analysis set:	Safety Analysis Set	
Data elements analyzed:	Concomitant treatment with other (non-anti-diabetic) medications	[no, yes]
Analysis method:	The following analyses will be performed on the above-mentioned data elements. Data will be tabulated for the entire Safety Analysis Set ("overall") and for the hepatic impairment and elderly patient subsets. (1) Frequency tables	

4.4 Zafatek 25 mg Treatment Compliance

Analysis set:	Safety Analysis Set	
Data elements analyzed:	Zafatek 25 mg treatment compliance	[patient took the drug once weekly as prescribed at least 90% of the time, patient took the drug once weekly as prescribed at least 70% of the time, patient took the drug once weekly as prescribed at least 50% of the time, patient took the drug once weekly as prescribed less than 50% of the time, patient did not take the drug, patient's treatment compliance is unknown]
Analysis method:	Frequency tables will be prepared for each assessment timepoint (i.e., 1 month [Day 30], 3 months [Day 90], 6 months [Day 180], 9 months [Day 270], and 12 months [Day 360] after starting Zafatek 25 mg treatment). Data	

will be tabulated for the entire Safety Analysis Set ("overall") and for the hepatic impairment and elderly patient subsets.

4.5 Overdosage/Overdose

Analysis set:	Safety Analysis Set	
Data elements analyzed:	Overdosage/Overdose	[no, yes]
Analysis method:	The following analyses will be performed on the above-mentioned data elements. Data will be tabulated for the entire Safety Analysis Set ("overall") and for the hepatic impairment and elderly patient subsets. (1) Frequency tables	

4.6 Dialysis Treatment

Analysis set:	Safety Analysis Set	
Data elements analyzed:	Dialysis treatment/non-treatment	[no, yes]
	Type of dialysis	[hemodialysis, peritoneal dialysis, other]
Analysis method:	The following analyses will be performed on the above-mentioned data elements. Data will be tabulated for the entire Safety Analysis Set ("overall") and for the hepatic impairment and elderly patient subsets. (1) Frequency tables	

5 SAFETY

5.1 Incidences of Adverse Events and Adverse Drug Reactions/Infections

5.1.1 Incidences of Adverse Events

Analysis set: Safety Analysis Set

Data elements analyzed: AEs

Analysis method: The following analyses will be performed on the above-mentioned data elements. Data will be tabulated for the entire Safety Analysis Set ("overall") and for the hepatic impairment and elderly patient subsets.

(1) No. of patients with AEs

(2) No. of AEs

(3) Incidence proportion of AEs

(4) AE category

Each of these data elements will be determined as follows.

No. of patients with AEs:

- The number of patients who develop an AE.

No. of AEs:

- The number of AEs that occur. If the same AE occurs multiple times in the same patient, the total number of occurrences will be tabulated.

Incidence proportion of AEs:

- Calculated as follows: No. of patients with AEs ÷ No. of patients in Safety Analysis Set × 100

AE category:

- AEs will be coded using the MedDRA/J terms, and will be broadly classified into SOC and tabulated according to PT. AEs belonging to the SOC "Investigations" will be summarized by HLGT (listed in ascending order of HLGT code but not output) and tabulated by PT.
- At the SOC level, the numbers and incidence proportions of AEs will be described according to the internationally-recognized SOC order. Patients with multiple AEs within the same SOC will be counted as a single patient within said SOC.
- At the PT level, the numbers and incidence proportions of AEs will be presented by PT code in ascending order. Patients with multiple AEs with the same PT will be counted as a single patient for said PT.

5.1.2 Incidences of Adverse Drug Reactions/Infections

Analysis set: Safety Analysis Set

Data elements analyzed: ADRs, etc.

Analysis method: The following analyses will be performed on the above-mentioned data elements. Data will be tabulated for the entire Safety Analysis Set ("overall") and for the hepatic impairment and elderly patient subsets.

(1) No. of patients with ADRs, etc.

(2) No. of ADRs, etc.

(3) Incidence proportion of ADRs, etc.

(4) Category of ADRs, etc.

Each of these data elements will be determined as follows.

No. of patients with ADRs, etc.:

- The number of patients who develop ADRs, etc.

No. of ADRs, etc.:

- The number of ADRs, etc. that occur. If the same ADR, etc. occurs multiple times in the same patient, the total number of occurrences will be tabulated.

Incidence proportion of ADRs, etc.

- Calculated as follows: No. of patients with ADRs, etc. ÷ No. of patients in Safety Analysis Set × 100

Category of ADRs, etc.:

- ADRs, etc. will be coded using the MedDRA/J terms, and will be broadly classified into SOC and tabulated according to PT. AEs belonging to the SOC "Investigations" will be summarized by HLGT (listed in ascending order of HLGT code but not output) and tabulated by PT.
  - At the SOC level, the numbers and incidence proportions of ADRs, etc. will be described according to the internationally-recognized SOC order. Patients with multiple AEs within the same SOC will be counted as a single patient within said SOC.
- At the PT level, the numbers and incidence proportions of ADRs, etc. will be presented by PT code in ascending order. Patients with multiple AEs with the same PT will be counted as a single patient for said PT.

5.2 Incidences of Adverse Events Identified in the Safety Specification (Risk-Based Tabulation)

Analysis set: Safety Analysis Set

Data elements analyzed: AEs assessed as an important identified risk (hypoglycemia) and AEs assessed as an important potential risk (infections)

Analysis method: The following analyses will be performed on the above-mentioned data elements. Each of these identified risks shall adhere to the respective definitions of important identified risks and important potential risks in section 1.4. Data will be tabulated for the entire Safety Analysis Set ("overall") and for the hepatic impairment and elderly patient subsets.

(1) No. of patients with AEs
(2) No. of AEs
(3) Incidence proportion of AEs
(4) AE category

Each of these data elements will be determined as follows.

No. of patients with AEs:

- The number of patients who develop an AE.

No. of AEs:

- The number of AEs that occur. If the same AE occurs multiple times in the same patient, the total number of occurrences will be tabulated.

Incidence proportion of AEs:

- Calculated as follows: No. of patients with AEs ÷ No. of patients in Safety Analysis Set × 100

AE category:

- AEs will be coded using the MedDRA/J terms, and will be broadly classified into SOC and tabulated according to PT. AEs belonging to the SOC "Investigations" will be summarized by HLGT (listed in ascending order of HLGT code but not output) and tabulated by PT.
- At the SOC level, the numbers and incidence proportions of AEs will be described according to the internationally-recognized SOC order. Patients with multiple AEs within the same SOC will be counted as a single patient within said SOC.
- At the PT level, the numbers and incidence proportions of AEs will be presented by PT code in ascending order. Patients with multiple AEs with the same PT will be counted as a single patient for said PT.

5.3 Incidences of Adverse Drug Reactions/Infections Identified in the Safety Specification (Risk-Based Tabulation)

Analysis set: Safety Analysis Set

Data elements analyzed: ADRs, etc. assessed as an important identified risk (hypoglycemia) and ADRs, etc. assessed as an important potential risk (infections)

Analysis method: The following analyses will be performed on the above-mentioned data elements. Each of these identified risks shall adhere to the respective definitions of important identified risks and important potential risks in section 1.4. Data will be tabulated for the entire Safety Analysis Set ("overall") and for the hepatic impairment and elderly patient subsets.

(1) No. of patients with ADRs, etc.

(2) No. of ADRs, etc.

(3) Incidence proportion of ADRs, etc.

(4) Category of ADRs, etc.

Each of these data elements will be determined as follows.

No. of patients with ADRs, etc.:

- The number of patients who develop ADRs, etc.

No. of ADRs, etc.:

- The number of ADRs, etc. that occur. If the same ADR, etc. occurs multiple times in the same patient, the total number of occurrences will be tabulated.

Incidence proportion of ADRs, etc.

- Calculated as follows: No. of patients with ADRs, etc. ÷ No. of patients in Safety Analysis Set × 100

Category of ADRs, etc.:

- ADRs, etc. will be coded using the MedDRA/J terms, and will be broadly classified into SOC and tabulated according to PT. AEs belonging to the SOC "Investigations" will be summarized by HLGT (listed in ascending order of HLGT code but not output) and tabulated by PT.
- At the SOC level, the numbers and incidence proportions of ADRs, etc. will be described according to the internationally-recognized SOC order. Patients with multiple AEs within the same SOC will be counted as a single patient within said SOC.
- At the PT level, the numbers and incidence proportions of ADRs, etc. will be presented by PT code in ascending order. Patients with multiple AEs with the same PT will be counted as a single patient for said PT.

5.4 Incidences of Adverse Drug Reactions/Infections Identified in the Safety Specification by Seriousness (Risk-Based Tabulation)

Analysis set:	Safety Analysis Set
Data elements analyzed:	ADRs, etc. assessed as an important identified risk (hypoglycemia) and ADRs, etc. assessed as an important potential risk (infections)
Stratification variables:	Seriousness [serious, not serious]
Analysis method:	The following analyses will be performed on the above-mentioned data elements for each risk-based stratum. Each of these identified risks shall adhere to the respective definitions of important identified risks and important potential risks in section 1.4. Data will be tabulated for the entire Safety Analysis Set ("overall") and for the hepatic impairment and elderly patient subsets.

Category of ADRs, etc.:

- ADRs, etc. will be coded using the MedDRA/J terms, and will be broadly classified into SOC and tabulated according to PT. AEs belonging to the SOC "Investigations" will be summarized by HLGT (listed in ascending order of HLGT code but not output) and tabulated by PT.
- At the SOC level, the numbers and incidence proportions of ADRs, etc. will be described according to the internationally-recognized SOC order. Patients with multiple AEs within the same SOC will be counted as a single patient within said SOC. However, ADRs, etc. with different types of seriousness will be counted as a single patient for the serious events and as a single patient for the non-serious events.
- At the PT level, the numbers and incidence proportions of ADRs, etc. will be presented by PT code in ascending order. Patients with multiple AEs with the same PT will be counted as a single patient for said PT. However, ADRs, etc. with different types of seriousness will be counted as a single patient for the serious events and as a single patient for the non-serious events.

5.5 Incidences of Adverse Events and Adverse Drug Reactions/Infections in Patients Excluded from Safety Assessments

5.5.1 Incidences of Adverse Events

Analysis set: The set of patients excluded from safety assessments

Data elements analyzed: AEs

Analysis method: The following analyses will be performed on the above-mentioned data elements.

(1) No. of patients with AEs
(2) No. of AEs
(3) Incidence proportion of AEs
(4) AE category

Each of these data elements will be determined as follows.

No. of patients with AEs:

- The number of patients who develop an AE.

No. of AEs:

- The number of AEs that occur. If the same AE occurs multiple times in the same patient, the total number of occurrences will be tabulated.

Incidence proportion of AEs:

- Calculated as follows: No. of patients with AEs ÷ No. of patients in Safety Analysis Set × 100

AE category:

- AEs will be coded using the MedDRA/J terms, and will be broadly classified into SOC and tabulated according to PT. AEs belonging to the SOC "Investigations" will be summarized by HLGT (listed in ascending order of HLGT code but not output) and tabulated by PT.
- At the SOC level, the numbers and incidence proportions of AEs will be described according to the internationally-recognized SOC order. Patients with multiple AEs within the same SOC will be counted as a single patient within said SOC.
- At the PT level, the numbers and incidence proportions of AEs will be presented by PT code in ascending order. Patients with multiple AEs with the same PT will be counted as a single patient for said PT.

5.5.2 Incidences of Adverse Drug Reactions/Infections

Analysis set: The set of patients excluded from safety assessments

Data elements analyzed: ADRs, etc.

Analysis method: The following analyses will be performed on the above-mentioned data elements.

(1) No. of patients with ADRs, etc.

(2) No. of ADRs, etc.

(3) Incidence proportion of ADRs, etc.

(4) Category of ADRs, etc.

Each of these data elements will be determined as follows.

No. of patients with ADRs, etc.:

- The number of patients who develop ADRs, etc.

No. of ADRs, etc.:

- The number of ADRs, etc. that occur. If the same ADR, etc. occurs multiple times in the same patient, the total number of occurrences will be tabulated.

Incidence proportion of ADRs, etc.

- Calculated as follows: No. of patients with ADRs, etc. ÷ No. of patients in Safety Analysis Set × 100

Category of ADRs, etc.:

- ADRs, etc. will be coded using the MedDRA/J terms, and will be broadly classified into SOC and tabulated according to PT. AEs belonging to the SOC "Investigations" will be summarized by HLGT (listed in ascending order of HLGT code but not output) and tabulated by PT.
- At the SOC level, the numbers and incidence proportions of ADRs, etc. will be described according to the internationally-recognized SOC order. Patients with multiple AEs within the same SOC will be counted as a single patient within said SOC.
- At the PT level, the numbers and incidence proportions of ADRs, etc. will be presented by PT code in ascending order. Patients with multiple AEs with the same PT will be counted as a single patient for said PT.

5.6 Incidences of Adverse Events and Adverse Drug Reactions/Infections by Seriousness, Time of Onset, and Outcome

5.6.1 Incidences of Adverse Events by Seriousness, Time of Onset, and Outcome

Analysis set:	Safety Analysis Set	
Data elements analyzed:	AEs	
Stratification variables:	Seriousness	[serious, not serious]
	Time of onset	[1–14 days, 15–28 days, 29–84 days, 85–168 days, 169–336 days, ≥337 days]
	Outcome	[recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, death (due to event), unknown]

Analysis method: The following analyses will be performed on the above-mentioned data elements for each stratum. Data will be tabulated for the entire Safety Analysis Set ("overall") and for the hepatic impairment and elderly patient subsets.

(1) No. of patients with AEs
(2) No. of AEs
(3) Incidence proportion of AEs
(4) AE category

Each of these data elements will be determined as follows.

No. of patients with AEs:

- The number of patients who develop an AE.

No. of AEs:

- The number of AEs that occur. If the same AE occurs multiple times in the same patient, the total number of occurrences will be tabulated.

Incidence proportion of AEs:

- Calculated as follows: No. of patients with AEs ÷ No. of patients in Safety Analysis Set × 100

AE category:

- AEs will be coded using the MedDRA/J terms, and will be broadly classified into SOC and tabulated according to PT. AEs belonging to the SOC "Investigations" will be summarized by HLGT (listed in ascending order of HLGT code but not output) and tabulated by PT.

- At the SOC level, the numbers and incidence proportions of AEs will be described according to the internationally-recognized SOC order. Patients with multiple AEs within the same SOC will be counted as a single patient within said SOC. However, AEs within the same SOC will be determined as a single event according to the orders of precedence listed at the end of this section.
- At the PT level, the numbers and incidence proportions of AEs will be presented by PT code in ascending order. Patients with multiple AEs with the same PT will be counted as a single patient for said PT. However, AEs with the same PT will be determined as a single event according to the following orders of precedence.
  Seriousness: Serious → Non-serious
  Time of onset: The earliest event to occur after administration of Zafatek 25 mg
  Outcome: Death (due to event) → Recovered/resolved with sequelae → Not recovered/not resolved → Recovering/resolving → Recovered/resolved → Unknown

5.6.2 Incidences of Adverse Drug Reactions/Infections by Seriousness, Time of Onset, and Outcome

Analysis set:	Safety Analysis Set	
Data elements analyzed:	ADRs, etc.	
Stratification variables:	Seriousness	[serious, not serious]
	Time of onset	[1–14 days, 15–28 days, 29–84 days, 85–168 days, 169–336 days, ≥337 days]
	Outcome	[recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, death (due to event), unknown]

Analysis method: The following analyses will be performed on the above-mentioned data elements for each stratum. Data will be tabulated for the entire Safety Analysis Set ("overall") and for the hepatic impairment and elderly patient subsets.

(1) No. of patients with ADRs, etc.

(2) No. of ADRs, etc.

(3) Incidence proportion of ADRs, etc.

(4) Category of ADRs, etc.

Each of these data elements will be determined as follows.

No. of patients with ADRs, etc.:

- The number of patients who develop ADRs, etc.

No. of ADRs, etc.:

- The number of ADRs, etc. that occur. If the same ADR, etc. occurs multiple times in the same patient, the total number of occurrences will be tabulated.

Incidence proportion of ADRs, etc.

- Calculated as follows: No. of patients with ADRs, etc. ÷ No. of patients in Safety Analysis Set × 100

Category of ADRs, etc.:

- ADRs, etc. will be coded using the MedDRA/J terms, and will be broadly classified into SOC and tabulated according to PT. AEs belonging to the SOC "Investigations" will be summarized by HLGT (listed in ascending order of HLGT code but not output) and tabulated by PT.
- At the SOC level, the numbers and incidence proportions of ADRs, etc. will be described according to the internationally-recognized SOC order. Patients with multiple AEs within the same SOC will be counted as a single patient within said SOC. However, AEs within the same SOC will be determined as a single event according to the orders of precedence listed at the end of this section.
- At the PT level, the numbers and incidence proportions of ADRs, etc. will be presented by PT code in ascending order. Patients with multiple AEs with the same PT will be counted as a single patient for said PT. However, AEs with the same PT will be determined as a single event according to the following orders of precedence.

  Seriousness: Serious → Non-serious

  Time of onset: The earliest event to occur after administration of Zafatek 25 mg

  Outcome: Death (due to event) → Recovered/resolved with sequelae → Not recovered/not resolved → Recovering/resolving → Recovered/resolved → Unknown

5.6.3 Incidences of Adverse Events Identified in the Safety Specification by Seriousness, Time of Onset, and Outcome

Analysis set:	Safety Analysis Set	
Data elements analyzed:	AEs assessed as an important identified risk (hypoglycemia) and AEs assessed as an important potential risk (infections)	
Stratification variables:	Seriousness	[serious, not serious]
	Time of onset	[1–14 days, 15–28 days, 29–84 days, 85–168 days, 169–336 days, ≥337 days]
	Outcome	[recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, death (due to event), unknown]

Analysis method: The following analyses will be performed on the above-mentioned data elements for each stratum. These identified risks shall adhere to the respective definitions of important identified risks and important potential risks in section 1.4. Data will be tabulated for the entire Safety Analysis Set ("overall") and for the hepatic impairment and elderly patient subsets.

AE category:

- AEs will be coded using the MedDRA/J terms, and will be broadly classified into SOC and tabulated according to PT. AEs belonging to the SOC "Investigations" will be summarized by HLGT (listed in ascending order of HLGT code but not output) and tabulated by PT.
  - At the SOC level, the numbers and incidence proportions of AEs will be described according to the internationally-recognized SOC order. Patients with multiple AEs within the same SOC will be counted as a single patient within said SOC. However, AEs within the same SOC will be determined as a single event according to the orders of precedence listed at the end of this section.
- At the PT level, the numbers and incidence proportions of AEs will be presented by PT code in ascending order. Patients with multiple AEs with the same PT will be counted as a single patient for said PT. However, AEs with the same PT will be determined as a single event according to the following orders of precedence.

  Seriousness: Serious → Non-serious

Time of onset: The earliest event to occur after administration of Zafatek 25 mg

Outcome: Death (due to event) → Recovered/resolved with sequelae → Not recovered/not resolved → Recovering/resolving → Recovered/resolved → Unknown

5.6.4 Incidences of Adverse Drug Reactions/Infections Identified in the Safety Specification by Seriousness, Time of Onset, and Outcome

Analysis set:	Safety Analysis Set	
Data elements analyzed:	ADRs, etc. assessed as an important identified risk (hypoglycemia) and ADRs, etc. assessed as an important potential risk (infections)	
Stratification variables:	Seriousness	[serious, not serious]
	Time of onset	[1–14 days, 15–28 days, 29–84 days, 85–168 days, 169–336 days, ≥337 days]
	Outcome	[recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, death (due to event), unknown]

Analysis method: The following analyses will be performed on the above-mentioned data elements for each stratum. These identified risks shall adhere to the respective definitions of important identified risks and important potential risks in section 1.4. Data will be tabulated for the entire Safety Analysis Set ("overall") and for the hepatic impairment and elderly patient subsets.

Category of ADRs, etc.:

- ADRs, etc. will be coded using the MedDRA/J terms, and will be broadly classified into SOC and tabulated according to PT. AEs belonging to the SOC "Investigations" will be summarized by HLGT (listed in ascending order of HLGT code but not output) and tabulated by PT.
- At the SOC level, the numbers and incidence proportions of ADRs, etc. will be described according to the internationally-recognized SOC order. Patients with multiple AEs within the same SOC will be counted as a single patient within said SOC. However, AEs within the same SOC will be determined as a single event according to the orders of precedence listed at the end of this section.

- At the PT level, the numbers and incidence proportions of ADRs, etc. will be presented by PT code in ascending order. Patients with multiple AEs with the same PT will be counted as a single patient for said PT. However, AEs with the same PT will be determined as a single event according to the following orders of precedence.
  Seriousness: Serious → Non-serious
  Time of onset: The earliest event to occur after administration of Zafatek 25 mg
  Outcome: Death (due to event) → Recovered/resolved with sequelae → Not recovered/not resolved → Recovering/resolving → Recovered/resolved → Unknown

5.7 Incidences of Adverse Drug Reactions/Infections by Patient Demographics & Baseline Characteristics and Treatment Factors

5.7.1 Incidences of Adverse Drug Reactions/Infections by Patient Demographics & Baseline Characteristics and Treatment Factors

Analysis set:	Safety Analysis Set	
Data elements analyzed:	ADRs, etc.	
Stratification variables:	Sex	[male, female]
	Age (years)	[Min<= – <65, 65<= – <=Max] [Min<= – <75, 75<= – <=Max]
	Duration of T2DM (years)	[Min<= – <2, 2<= – <5, 5<= – <10, 10<= – <=Max]
	BMI (kg/m^2)	[Min<= – <18.5, 18.5<= – <25.0, 25.0<= – <30.0, 30.0<= – <=Max]
	Severity of renal impairment	[severe renal impairment, end-stage renal failure]
	Presence/absence of hepatic impairment	[no, yes]
	Severity of hepatic impairment	[normal, mild, moderate, severe]
	Concomitant anti-diabetic medication	[no, yes]
	Type of concomitant anti-diabetic medication (duplicate count)	[alpha-glucosidase inhibitors, thiazolidines, sulfonylureas, biguanides, fast-acting insulin secretagogues, insulin preparations, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, combination anti-diabetics]
	Concurrent illness	[no, yes]
	Dialysis treatment/non-treatment	[no, yes]

Analysis method: The following analyses will be performed on the above-mentioned data elements for each stratum. Data will be tabulated for the entire Safety Analysis Set ("overall") and for the hepatic impairment and elderly patient subsets.

(1) No. of patients with ADRs, etc.

(2) Incidence proportion of ADRs, etc.

Each of these data elements will be determined as follows.

No. of patients with ADRs, etc.:

- The number of patients who develop ADRs, etc.

Incidence proportion of ADRs, etc.

- Calculated as follows: No. of patients with ADRs, etc. ÷ No. of patients in Safety Analysis Set × 100

5.7.2 Incidences of Adverse Drugs Reactions/Infections by Sex

Analysis set:	Safety Analysis Set	
Data elements analyzed:	ADRs, etc.	
Stratification variables:	Sex	[male, female]

Analysis method: The following analyses will be performed on the above-mentioned data elements for each stratum. Data will be tabulated for the entire Safety Analysis Set ("overall") and for the hepatic impairment and elderly patient subsets.

(1) No. of patients with ADRs, etc.
(2) No. of ADRs, etc.
(3) Incidence proportion of ADRs, etc.
(4) Category of ADRs, etc.

The tabulation method for each analyzed data element is the same as that described in section 5.1.2.

5.7.3 Incidences of Adverse Drug Reactions/Infections by Age Bracket

Analysis set:	Safety Analysis Set	
Data elements analyzed:	ADRs, etc.	
Stratification variables:	Age (years)	[Min<= – <65, 65<= – <=Max] [Min<= – <75, 75<= – <=Max]

Analysis method: The following analyses will be performed on the above-mentioned data elements for each stratum. Data will be tabulated for the entire Safety Analysis Set ("overall") and for the hepatic impairment patient subset.

(1) No. of patients with ADRs, etc.
(2) No. of ADRs, etc.
(3) Incidence proportion of ADRs, etc.
(4) Category of ADRs, etc.

The tabulation method for each analyzed data element is the same as that described in section 5.1.2.

5.7.4 Incidences of Adverse Drug Reactions/Infections by Severity of Renal Impairment

Analysis set:	Safety Analysis Set
Data elements analyzed:	ADRs, etc.

Stratification variables:	Severity of renal impairment	[severe renal impairment, end-stage renal failure]

Analysis method: The following analyses will be performed on the above-mentioned data elements for each stratum. Data will be analyzed for the entire Safety Analysis Set ("overall") and the hepatic impairment and elderly patient subsets.

(1) No. of patients with ADRs, etc.
(2) No. of ADRs, etc.
(3) Incidence proportion of ADRs, etc.
(4) Category of ADRs, etc.

The tabulation method for each analyzed data element is the same as that described in section 5.1.2.

5.7.5 Incidences of Adverse Drug Reactions/Infections by Presence/Absence and Severity of Hepatic Impairment

Analysis set:	Safety Analysis Set	
Data elements analyzed:	ADRs, etc.	
Stratification variables:	Presence/absence of hepatic impairment	[no, yes]
	Severity of hepatic impairment	[normal, mild, moderate, severe]

Analysis method: The following analyses will be performed on the above-mentioned data elements for each stratum. Data will be analyzed for the entire Safety Analysis Set ("overall") and the elderly patient subset.

(1) No. of patients with ADRs, etc.
(2) No. of ADRs, etc.
(3) Incidence proportion of ADRs, etc.
(4) Category of ADRs, etc.

The tabulation method for each analyzed data element is the same as that described in section 5.1.2.

5.7.6 Incidences of Adverse Drug Reactions/Infections by Administration of Concomitant Anti-Diabetic Medication

Analysis set:	Safety Analysis Set
Data elements analyzed:	ADRs, etc.

Stratification variables:	Concomitant anti-diabetic medication	[no, yes]

Analysis method: The following analyses will be performed on the above-mentioned data elements for each stratum. Data will be tabulated for the entire Safety Analysis Set ("overall") and for the hepatic impairment and elderly patient subsets.

(1) No. of patients with ADRs, etc.
(2) No. of ADRs, etc.
(3) Incidence proportion of ADRs, etc.
(4) Category of ADRs, etc.

The tabulation method for each analyzed data element is the same as that described in section 5.1.2.

5.7.7 Incidences of Adverse Drug Reactions/Infections by Type of Concomitant Anti-Diabetic Medication

Analysis set:	Safety Analysis Set	
Data elements analyzed:	ADRs, etc.	
Stratification variables:	Type of concomitant anti-diabetic medication	[alpha-glucosidase inhibitors, thiazolidines, sulfonylureas, biguanides, fast-acting insulin secretagogues, insulin preparations, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, combination anti-diabetics]

Analysis method: The following analyses will be performed on the above-mentioned data elements for each stratum. Data will be tabulated for the entire Safety Analysis Set ("overall") and for the hepatic impairment and elderly patient subsets.

(1) No. of patients with ADRs, etc.
(2) No. of ADRs, etc.
(3) Incidence proportion of ADRs, etc.
(4) Category of ADRs, etc.

The tabulation method for each analyzed data element is the same as that described in section 5.1.2.

5.7.8 Incidences of Adverse Drug Reactions/Infections by Presence/Absence of Concurrent Illness

Analysis set:	Safety Analysis Set	
Data elements analyzed:	ADRs, etc.	
Stratification variables:	Concurrent illness	[no, yes]

Analysis method: The following analyses will be performed on the above-mentioned data elements for each stratum. Data will be tabulated for the entire Safety Analysis Set ("overall") and for the hepatic impairment and elderly patient subsets.

(1) No. of patients with ADRs, etc.
(2) No. of ADRs, etc.
(3) Incidence proportion of ADRs, etc.
(4) Category of ADRs, etc.

The tabulation method for each analyzed data element is the same as that described in section 5.1.2.

5.7.9 Incidences of Adverse Drug Reactions/Infections by Dialysis Treatment/Non-Treatment

Analysis set:	Safety Analysis Set	
Data elements analyzed:	ADRs, etc.	
Stratification variables:	Dialysis treatment/non-treatment	[no, yes]

Analysis method: The following analyses will be performed on the above-mentioned data elements for each stratum. Data will be tabulated for the entire Safety Analysis Set ("overall") and for the hepatic impairment and elderly patient subsets.

(1) No. of patients with ADRs, etc.
(2) No. of ADRs, etc.
(3) Incidence proportion of ADRs, etc.
(4) Category of ADRs, etc.

The tabulation method for each analyzed data element is the same as that described in section 5.1.2.

5.8 Time Courses of Test/Measurement Data

5.8.1 Vital Signs

Analysis set:	Safety Analysis Set
Data elements analyzed:	Systolic blood pressure, diastolic blood pressure, body weight, pulse rate
Analysis method:	Summary statistics for the above-mentioned data elements will be calculated for the Safety Analysis Set at each assessment timepoint (i.e., start of Zafatek 25 mg treatment [Day 0] and 1 month [Day 30], 3 months [Day 90], 6 months [Day 180], 9 months [Day 270], and 12 months [Day 360] after starting Zafatek 25 mg treatment). Moreover, summary statistics will be calculated for the absolute change from baseline (calculated by subtracting the test value at the start of Zafatek 25 mg treatment [i.e., at baseline] from the test value at each assessment timepoint after baseline). Data will be tabulated for the entire Safety Analysis Set ("overall") and for the hepatic impairment and elderly patient subsets.

5.8.2 Laboratory Tests

Analysis set:	Safety Analysis Set
Data elements analyzed:	HbA1c, glycoalbumin, fasting blood glucose, fasting triglyceride, total cholesterol, HDL cholesterol, LDL cholesterol, serum creatinine, BUN, urine albumin (urine albumin-creatinine ratio), AST, ALT, γ-GTP, ALP, total bilirubin, amylase, lipase
Analysis method:	Summary statistics for the above-mentioned data elements will be calculated for the Safety Analysis Set at each assessment timepoint (i.e., start of Zafatek 25 mg treatment [Day 0] and 1 month [Day 30], 3 months [Day 90], 6 months [Day 180], 9 months [Day 270], and 12 months [Day 360] after starting Zafatek 25 mg treatment). Moreover, summary statistics will be calculated for the absolute change from baseline (calculated by subtracting the test value at the start of Zafatek 25 mg treatment [i.e., at baseline] from the test value at each assessment timepoint after baseline). Data will be tabulated for the entire Safety Analysis Set ("overall") and for the hepatic impairment and elderly patient subsets.

5.8.3 Electrocardiography

Analysis set:	Safety Analysis Set
Data elements analyzed:	Electrocardiography [no abnormal ECG findings, abnormal ECG findings]
Analysis method:	ECG assessment frequency tables will be calculated for the Safety Analysis Set at each assessment timepoint (i.e., start of Zafatek 25 mg treatment [Day 0] and 1 month [Day 30], 3 months [Day 90], 6 months [Day 180], 9 months [Day 270] and

12 months [Day 360] after starting Zafatek 25 mg treatment). Data will be tabulated for the entire Safety Analysis Set ("overall") and for the hepatic impairment and elderly patient subsets.

6 INCIDENCES OF ADVERSE DRUG REACTIONS/INFECTIONS IN POSTMARKETING SURVEILLANCE

6.1 Incidences of Adverse Drug Reactions/Infections in Postmarketing Surveillance (Attached Form 15)

Analysis set: Patients assessed for safety

Data elements analyzed: ADRs, etc.

Analysis method: The following analyses will be performed on the above-mentioned data elements.

(1) Postmarketing surveillance status
   1) No. of patients assessed for safety
   2) No. of patients with ADRs, etc.
   3) Incidence proportion of ADRs, etc.

(2) Category of ADRs, etc.
   1) Total number and proportion of patients with ADRs, etc. (by SOC)
   2) Total number and proportion of patients with ADRs, etc. (by PT)

ADRs, etc. will be coded using the MedDRA/J terms. At the SOC level, ADRs, etc. will be presented according to the internationally-recognized SOC order. At the PT level, ADRs, etc. belonging to the SOC "Investigations" will be shown by HLGT code and PT code in their respective ascending orders. ADRs, etc. belonging to all other SOCs will be shown by PT code in ascending order.
The events for each of these analyzed data elements will be computed as follows.
Number and proportion of patients with ADRs, etc. by category:

- When calculating frequency tables, patients with multiple ADRs, etc. within the same SOC or with the same PT will be counted as a single patient for said SOC or PT. When calculating incidence proportions, the number of patients assessed for safety (i.e., the Safety Analysis Set) will be used as the denominator.

7 INCIDENCES OF ADVERSE DRUG REACTIONS/INFECTIONS IN THE SUPPLEMENTARY PHARMACOVIGILANCE PLAN

7.1 Incidences of Adverse Drug Reactions/Infections in the Supplementary Pharmacovigilance Plan (Attached Form 12)

Analysis set:	Safety Analysis Set
Data elements analyzed:	Important identified risks Hypoglycemia Important potential risks Infections Important missing information Safety of administering Zafatek 25 mg in patients with renal impairment
Stratification variables:	Seriousness [serious, not serious]
Analysis method:	The following analyses will be performed on the above-mentioned data elements for each stratification variable in accordance with Notes 1 through 4 of Attached Form 12 of Re-Examination Notification No. 1128-2 issued by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare (MHLW/PSEHB/PEB) on 28 November 2017. (1) Number and proportion of patients with important identified risks (2) Number and proportion of patients with important potential risks (3) Number and proportion of patients with important missing information The definition and descriptive order of risks shall adhere to section 1.4 "Important Identified Risks, Important Potential Risks, and Important Missing Information."

8 SUMMARY OF PATIENTS IN POSTMARKETING SURVEILLANCE

8.1 Summary of Patients in Postmarketing Surveillance (Attached Form 16)

Analysis set:	Patients for whom CRFs were submitted/collected
Data elements analyzed:	Patient ID number Site name Sex Date of birth Reason for use (disease code, disease name) Concurrent illness (disease code, disease name) Route of administration Maximum dose Mean dose Units Duration of use Concomitant medications (medicinal product code and name) Effectiveness ADRs (disease code & name, outcome) CRF No. Dropouts Reason for dropout Overdosage/Overdose
Analysis method:	Listings of the above-mentioned data elements will be prepared in accordance with the "Procedures for Preparing Reexamination Data Entry Files" stipulated in MHLW/PSEHB/PEB Re-Examination Notification No. 1119-3 issued on 19 November 2020. Patients in whom overdosage/overdose is deemed to have occurred will be indicated using the letter "Y."

Creation History (Version Control)

Version	Date	Author/Reviser	Remarks
Original Version	26 January 2023	[redacted]	Author of original version