Statistical Analysis Plan

NCT Number: NCT02415712

Title: Drug Use Surveillance of Fomepizole Intravenous Infusion "Takeda" (All-Case Surveillance)

Study Number: Fomepizole-5001

Document Version and Date: Version 2.1/ 01-Aug-2022

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

STATISTICAL ANALYSIS PLAN

(FINAL ANALYSIS)

P R O D U C T N A M E : fomepizole

S T U D Y T I T L E : Drug Use Surveillance of Fomepizole Intravenous Infusion "Takeda" (All-Case Surveillance)

PROTOCOL NUMBER :Fomepizole-5001

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

[redacted]

Version 2.1: Prepared on 1 August 2022

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LIST OF TERMS AND ABBREVIATIONS

- Fomepizole IV: The study drug Fomepizole Intravenous Infusion “Takeda” shall be abbreviated as “fomepizole IV”
- AE: Adverse event occurring after administration of fomepizole IV
- ADRs, etc.: An abbreviation for "adverse drug reactions/infections” that refers to AEs other than those with a causal relationship to fomepizole IV 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: Adverse event assessed as "serious" by the investigator. Any event listed in the MedDRA code list (PT code) of the Important Medical Events List provided under the title “Takeda Medically Significant AE List” is to be handled as serious even if said event was assessed by the investigator as "not serious.”
- "Related": AEs with a causal relationship with fomepizole IV that is assessed as either “related” or “not evaluable” by the investigator will be handled as "related" AEs.
- Summary statistics: A term that collectively refers to the number of patients, mean value, standard deviation, maximum value, minimum value, and quartile value.
- Number of days after fomepizole IV dosing: The day before the start of fomepizole IV dosing is referred to as Day -1, while the day on which fomepizole IV dosing is commenced is referred to as Day 1.
- Duration of fomepizole IV treatment (days): Final day of fomepizole IV dosing − start date of fomepizole IV dosing + 1.
- Time & date of completion of fomepizole IV treatment: The time and date at completion of the final infusion of fomepizole IV as recorded in the CRF.
- Patients with faxed Contact Forms: Refers to the patients for whom a completed Contact Form has been transmitted by fax and received by the Central Enrollment Center.
- Enrolled patients: Patients whose enrollment was approved by the PMS system.
- Unenrolled patients: Patients with faxed/received Contact Forms whom the PMS system has not approved for enrollment.
- 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 a CRF has been submitted/collected.

- Time of onset of AEs (or ADRs, etc.): Calculated by subtracting the start date of fomepizole IV treatment from the date of onset of the AE (or ADR, etc.) and adding 1 (i.e., adding 1 day).
- Patients with concurrent diabetes mellitus: Patients for whom the box for "Diabetes mellitus" in the "Concurrent (coexisting) disease" section of the CRF has been checked. Or other disease: Refers to patients with a concurrent disease recorded in the disease name field of the CRF that corresponds to standardized MedDRA query (herein "SMQ") code 20000041 (Hyperglycaemia/new onset diabetes mellitus SMQ [scope: narrow]).
- Patients with concurrent hypertension: Patients for whom the box for "Hypertension" in the "Concurrent (coexisting) disease" section of the CRF has been checked. Or other disease: Refers to patients with a concurrent disease recorded in the disease name field of the CRF that corresponds to SMQ code 20000147 (Hypertension SMQ [scope: narrow]).
- Patients with concurrent dyslipidaemia: Patients for whom the box for "Dyslipidaemia" in the "Concurrent (coexisting) disease" section of the CRF has been checked. Or other disease: Refers to patients with a concurrent disease recorded in the disease name field of the CRF that corresponds to SMQ code 20000026 (Dyslipidaemia SMQ [scope: narrow]).
- Patients with concurrent hyperuricaemia: Patients for whom the box for "Hyperuricaemia" in the "Concurrent (coexisting) disease" section of the CRF has been checked. Or other disease: Refers to patients with a concurrent disease recorded in the disease name field of the CRF that corresponds to MedDRA PT code 10020903 (Hyperuricaemia).
- Patients with concurrent liver disorder: Patients for whom any of the boxes for "Fatty liver," "Alcoholic hepatitis," "Chronic hepatitis," or "liver cirrhosis" in the "Concurrent (coexisting) disease" section of the CRF has been checked. Or other disease: Refers to patients with a concurrent disease recorded in the disease name field of the CRF that corresponds to SMQ code 20000005 (Hepatic disorders SMQ [scope: narrow]).
- Patients with concurrent renal disorder: Patients for whom the box for "Chronic renal disorder" in the "Concurrent (coexisting) disease" section of the CRF has been checked. Or other disease: Refers to patients with a concurrent disease recorded in the disease name field of the CRF that corresponds to the Takeda MedDRA query (herein "TMQ") (Renal Disease) or TMQ (Renal Impairment).
- Patients with other concurrent diseases: Patients whose concurrent disease does not fall under the above-listed categories of (i.e., concurrent diabetes mellitus, concurrent hypertension, concurrent dyslipidaemia, concurrent hyperuricaemia, concurrent liver disorder or concurrent renal disorder).

- GCS: The sum of Glasgow Coma Scale (GCS) scores will be calculated for 3 items: eye opening (E), best verbal response (V), and best motor response (M).
- 3-3-9 rating system (JCS) : When expressing the Japan Coma Scale (JCS) score numerically, the following categories are used.
    - Score of 0 is recorded as “0 (Alert)”
    - Scores of 1, 2 and 3 are recorded as “I”
    - Scores of 10, 20 and 30 are recorded as “II”
    - Scores of 100, 200 and 300 are recorded as “III”
- Time from ingestion of toxic substance to start of fomepizole IV treatment:
    - Calculated by subtracting the time/date of ingestion (confirmed or estimated) recorded in the Toxic Symptoms column of the CRF from the time/date of starting treatment with fomepizole IV. Estimated times for “time X” will be expressed as X hr:00mins. Any missing data for time or date will be handled as “unknown.”
- Ethanol: Drugs with a medicinal product code starting with 2615702 or 2615704.
- Vitamin B6 preparations: Drugs with a medicinal product code starting with 3134001, 3134002, 3134003, 3134004, 3134400 or 3134402.
- Vitamin B1 preparations: Drugs with a medicinal product code starting with 3121001 or 3121400.
- Folic acid preparations: Drugs with a medicinal product code starting with 3135.
- Sodium bicarbonate preparations: Drugs with a medicinal product code starting with 2344004, 2344005 or 3929400.
- Potassium chloride preparations: Drugs with a medicinal product code starting with 3229001, 3229002 or 3229400.

ANALYSIS SETS

The DUS all-case surveillance was designed with a "Safety Analysis Set" and an "Efficacy Analysis Set." These analysis sets are defined below.

- Safety Analysis Set

The Safety Analysis Set is defined as "the set of patients who received fomepizole IV, who did not commit any significant breaches of the DUS Protocol, and in whom the safety of fomepizole IV could be evaluated." Patients for whom CRFs were submitted/collected and who met any of the following criteria were excluded from the Safety Analysis Set.

- Patients who did not receive treatment with fomepizole IV
- Patients in whom the presence or absence of AEs could not be determined (i.e, was "unknown")

- Efficacy Analysis Set

The Efficacy Analysis Set is defined as "the Safety Analysis Set patients who did not commit any significant breaches of the DUS Protocol and in whom the efficacy of fomepizole IV could be evaluated." The Efficacy Analysis Set consisted of the patients in the Safety Analysis Set after excluding the following patients.

- Patients who did not meet the indication for treatment with fomepizole IV
- Patients for whom there is no efficacy data: Patients who met all of the following criteria are regarded as having no efficacy data.
  - There is no available data for arterial blood pH at the start of fomepizole IV dosing (i.e., at baseline), and there is no available data for arterial blood pH from at least one assessment timepoint from 30 minutes (herein denoted as "0.5 hr") after starting fomepizole IV dosing up to 24 hours after completing the final fomepizole IV infusion.
  - There is no available data for at least one of the poisoning/toxicity test parameters ($PaCO_2$, PaO_2, bicarbonate ion, BE, anion gap, blood ethylene glycol concentration, blood glycolic acid concentration, blood methanol concentration, blood formic acid concentration, and osmotic pressure gap) at baseline, and there is no available data for at least one of these parameters from at least one assessment timepoint from 0.5 hr after starting fomepizole IV dosing up to 24 hours after completing the final infusion.
  - There is no available data for at least one toxic symptom parameter at baseline nor at completion of the final fomepizole IV infusion.
  - Outcome has not been documented.

IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS AND IMPORTANT MISSING INFORMATION

- Important Identified Risks
    - Anaphylaxis: Events that fall under the MedDRA PT codes 10002198 (anaphylactic reaction), 10002199 (anaphylactic shock), 10002216 (anaphylactoid reaction), and 10063119 (anaphylactoid shock).
- Important Potential Risks
    - Central nervous system disorder: An event that meets the MedDRA SOC Code 10029205 (nervous system disorders).
    - Fetal disorder due to drug exposure during pregnancy: An event that corresponds to SMQ Code 20000185 (Pregnancy and neonatal topics) (broad).
- Important Missing Information
    - Clinical experience in Japanese patients: Events that occurred in patients within Japan. All patients enrolled in this DUS are located within Japan and are therefore within the scope of "Clinical experience in Japanese patients" so no additional tabulations will be performed for this variable.

HANDLING OF TIME WINDOWS

Evaluable test parameter data (i.e., data deemed not to be missing any elements and able to be used in the statistical analyses) shall be handled as described below.

Evaluable data that was collected within the relevant time window will be used. If multiple elements of evaluable data exist within the same time window, the data obtained from the test performed closest to the reference time/date will be used. If the time elapsed from the reference time/date is identical or if no reference time/date has been stipulated, the subsequently-obtained data will be used. The amount of time elapsed from the reference time/date shall be determined based on the time elapsed from dosing. If data for the time/date of the test is missing or incomplete, the test timing printed on the CRF shall be used. (As this data is obtained at the time of hospitalization due to poisoning, the integrity/reliability of the test timepoints recorded in the CRF are deemed to be greater than those of other data elements and will therefore be used for the analysis.) If there is a mix of both missing and available data for the time/date of tests at the same assessment timepoint, the data that actually contains the test time/date will be used.

Test Parameters for Vital Signs, Laboratory Tests and Toxic Symptoms

Assessment time point	Reference time/date	Time window Time after dosing
Start of fomepizole IV treatment −108 hr after start of fomepizole IV treatment		
At start of fomepizole IV treatment	At start of fomepizole IV treatment	-48 hr ≤ fomepizole IV infusion start time/date ≤ 0 hr
0.5 hr after starting fomepizole IV treatment	Fomepizole IV infusion start time/date + 0.5 hr	0 hr < fomepizole IV infusion start time/date ≤ 2 hr
4 hr after starting fomepizole IV treatment	Fomepizole IV infusion start time/date + 4 hr	2 hr < fomepizole IV infusion start time/date ≤ 6 hr
8 hr after starting fomepizole IV treatment	Fomepizole IV infusion start time/date + 8 hr	6 hr < fomepizole IV infusion start time/date ≤ 10 hr
12 hr after starting fomepizole IV treatment	Fomepizole IV infusion start time/date + 12 hr	10 hr < fomepizole IV infusion start time/date ≤ 14 hr
16 hr after starting fomepizole IV treatment	Fomepizole IV infusion start time/date + 16 hr	14 hr < fomepizole IV infusion start time/date ≤ 18 hr
20 hr after starting fomepizole IV treatment	Fomepizole IV infusion start time/date + 20 hr	18 hr < fomepizole IV infusion start time/date ≤ 22 hr
24 hr after starting fomepizole IV treatment	Fomepizole IV infusion start time/date + 24 hr	22 hr < fomepizole IV infusion start time/date ≤ 30 hr
36 hr after starting fomepizole IV treatment	Fomepizole IV infusion start time/date + 36 hr	30 hr < fomepizole IV infusion start time/date ≤ 42 hr

Assessment time point	Reference time/date	Time window Time after dosing
48 hr after starting fomepizole IV treatment	Fomepizole IV infusion start time/date + 48 hr	42 hr < fomepizole IV infusion start time/date ≤ 54 hr
60 hr after starting fomepizole IV treatment	Fomepizole IV infusion start time/date + 60 hr	54 hr < fomepizole IV infusion start time/date ≤ 66 hr
72 hr after starting fomepizole IV treatment	Fomepizole IV infusion start time/date + 72 hr	66 hr < fomepizole IV infusion start time/date ≤ 78 hr
84 hr after starting fomepizole IV treatment	Fomepizole IV infusion start time/date + 84 hr	78 hr < fomepizole IV infusion start time/date ≤ 90 hr
96 hr after starting fomepizole IV treatment	Fomepizole IV infusion start time/date + 96 hr	90 hr < fomepizole IV infusion start time/date ≤ 102 hr
108 hr after starting fomepizole IV treatment	Fomepizole IV infusion start time/date + 108 hr	102 hr < fomepizole IV infusion start time/date ≤ 114 hr
From end of final infusion until 24 hours after end of final infusion of fomepizole IV		
At completion of final fomepizole IV infusion	Time/date of final fomepizole IV infusion	-0.5 hr ≤ end time/date of final fomepizole IV infusion ≤ 6 hr
12 hr after completing final fomepizole IV infusion	Time/date of final fomepizole IV infusion + 12 hr	6 hr < end time/date of final fomepizole IV infusion ≤ 18 hr
24 hr after completing final fomepizole IV infusion	Time/date of final fomepizole IV infusion + 24 hr	18 hr < end time/date of final fomepizole IV infusion ≤ 30 hr
Final assessment timepoint		
Final assessment timepoint		0 hr < fomepizole IV infusion start time/date ≤ 114 hr; or -0.5 hr ≤ end time/date of final fomepizole IV infusion ≤ 30 hr; whichever assessment timepoint is sooner

OTHER DATA HANDLING METHODS

- Displayed decimals/numerical data will be handled according to the following rules.
    - Percentages (%):
        - Incidences of AEs or ADRs, etc.: Round percentage to the second decimal place and display up to the second decimal place.
        - Other data elements: Round percentage to the first decimal place and display up to the first decimal place.
    - Summary statistics:
        - Means: 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 this data using the same method as that for raw data.
        - First quartile, median, third quartile: Display raw data up to single digits.
    - P values: Round down (i.e., truncate) to the third decimal place and display up to the third decimal place. When the P value truncated to the third decimal place is <0.001, display as P<0.001.
- Use a two-sided significance level of 5%.
- Missing data for the date (i.e., day, month and year) of AE onset will be handled as follows.
    - If the day of onset is the only data that is missing, and if the month and year of AE onset is identical to those of the initial fomepizole IV treatment, the day of onset shall be regarded as the day on which fomepizole IV dosing commenced (i.e., the event shall be regarded as having occurred on the day of initial fomepizole IV dosing). In all other situations, the day of onset shall be regarded as the first day (i.e. the 1st) of the month.
    - If data for both the day and month are missing, and if the year of AE onset is identical to that of the initial fomepizole IV treatment, the day of onset shall be regarded as the day on which fomepizole IV dosing commenced (i.e., the event shall be regarded as having occurred on the day of initial fomepizole IV dosing). In all other situations, the day and month of onset shall be regarded as the 1st of January.
    - If data on the day, month and year are all missing, the AE onset date will be regarded as missing data.

- If the same patient has been treated on multiple occasions (e.g., if the patient has attempted suicide on multiple occasions), said patient shall be handled as a separate patient on the second and subsequent occasions. Such patients will also be specified in the Patient Disposition diagram.

1 NUMBER OF SURVEILLANCE SITES & ENROLLED PATIENTS AND PATIENT DISPOSITION

1.1 Breakdown of Patients (Patient Disposition)

Analysis set:	All-Case (enrolled patients)
Data element analyzed:	Number of patients enrolled
	Number of sites where patients are enrolled
	Patients for whom CRFs were not submitted/collected
	Patients for whom CRFs were submitted/collected
	Patients excluded from Safety Analysis Set*
	Reason for exclusion (duplicate count) — Patients who did not receive fomepizole IV, patients whom presence or absence of AEs is unknown:
	Safety Analysis Set
	Patients excluded from Efficacy Analysis Set*
	Reason for exclusion (duplicate count) — [Did not meet fomepizole IV indication, no efficacy data]
	Efficacy Analysis Set
Analysis method:	The following analyses will be performed and the Patient Disposition diagram will be prepared for the above-mentioned data elements.
	The number of surveillance sites will also be shown for patients for whom the Contact Form was transmitted/received by fax and for enrolled patients. 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". The numbers of patients excluded from the Safety Analysis Set and from the Efficacy Analysis Set will be tabulated and listed along with the reasons for exclusion.
	* "Patients excluded from the Safety Analysis Set" refers to the patients for whom CRFs were submitted/collected and were also excluded from the Safety Analysis Set. * Similarly, "patients excluded from the Efficacy Analysis Set" refers to the patients for whom CRFs were submitted/collected and were also excluded from the Efficacy Analysis Set.

- Frequency tables

2 PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

2.1 Patient Demographics and Baseline Characteristics

Analysis set:	Safety Analysis Set	
Data element analyzed:	Sex	[male, female]
	Age (years)	[Min <= - < 65, 65 <= - <= Max, Unknown] [Min <= - < 65, 65 <= - <= 74, 75 <= - <= Max, Unknown] [Min <= - < 20, 20 <= - <= 29, 30 <= - <= 39, 40 <= - <= 49, 50 <= - <= 59, 60 <= - <= 69, 70 <= - <= 79, 80 <= - <= Max, Unknown]
	Diagnosis (final diagnosis)	[Ethylene glycol poisoning, suspected ethylene glycol poisoning, methanol poisoning, suspected methanol poisoning, other disease, unknown]
	Hypersensitivity	[no, yes, unknown]
	Concurrent (coexisting) disease	[no, yes, unknown]
	Details of any concurrent (coexisting) disease (duplicate count)	[Diabetes mellitus, hypertension, dyslipidaemia, hyperuricaemia, liver disorder, renal disorder, other]
	Previous medical history	[no, yes, unknown]
	Height (cm)	[Min <= - < 150, 150 <= - < 160, 160 <= - < 170, 170 <= - <= Max, Not measured]
	Body weight (kg)	[Min <= - < 50.0, 50.0 <= - < 60.0, 60.0 <= - < 70.0, 70.0 <= - < 80.0, 80.0 <= - <= Max, Not measured]
	BMI (kg/m^2)	[Min <= - < 18.5, 18.5 <= - < 25.0, 25.0 <= - < 30.0, 30.0 <= - <= Max, Not measured]
	Alcohol consumption (at time of poisoning)	[no, yes, unknown]
	Pregnancy (females only)	[no, yes, unknown]
	Level of consciousness (duplicate count)	[GCS, 3-3-9 rating system (JCS), unknown]
	Level of consciousness details	
	GCS	[minor (14/15), moderate (9–13), severe (3–8)]

3-3-9 rating system (JCS)	[0 (alert), I, II, III]
Circumstances of poisoning	
Ingested substance (duplicate count)	[ethylene glycol, methanol, other, unknown]
Data available on time from ingestion of toxic substance to start of fomepizole IV treatment (Yes/No)	[yes, unknown]
Details of "Yes" for data available on time from ingestion of toxic substance to start of fomepizole IV	[Min <= - < 6, 6 <= - < 12, 12 <= - < 24, 24 <= - <= Max]
Route of ingestion	[oral, inhalation, dermal, other, unknown]
Reason ingested	[accidental ingestion, suicide attempt, other, unknown]

Analysis method: Frequency tables of calculated values and summary statistics of measured values will be prepared for the above-mentioned data elements.
Listings will be prepared for details of concurrent (coexisting) diseases (other diseases) and circumstances of poisoning (ingested substance and amount, time and date ingested, route of ingestion, reason ingested).

3 TREATMENT DETAILS

3.1 Administration of Fomepizole IV

Analysis set:	Safety Analysis Set	
Data element analyzed:	Initial dose of fomepizole IV (mg)	
	Fomepizole IV treatment duration (days)	
	Fomepizole IV cumulative dose (mg)	
	Maximum number of infusions	[1, 2, 3, 4, 5, 6, 7, 8, 9, 10, ≥11]
	Mean duration of single infusion (min)	[Min <= - < 30, 30 <= - < 60, 60 <= - < 90, 90 <= - <= Max]
	Infusion dose per body weight	[15 mg/kg, 10 mg/kg, Other]
	Reason for discontinuation of fomepizole IV (duplicate count)	[Therapeutic objective achieved, occurrence of AE, inadequate response, other]
Analysis method:	Frequency tables of calculated values and summary statistics of measured values will be prepared for the above-mentioned data elements.	

3.2 Interventions/Procedures (Other Than Pharmacotherapy)

Analysis set:	Safety Analysis Set	
Data element analyzed:	Acute blood purification therapy	[no, yes]
	Details of any (i.e., "Yes") acute blood purification therapy (duplicate count)	[continuous renal replacement therapy , plasma exchange, adsorption, intermittent renal replacement therapy , other]
	Respiratory management (mechanical ventilation)	[no, yes]
	GI decontamination	[no, yes]
	Details of any (i.e., "Yes") GI decontamination therapy (duplicate count)	[gastrolavage, induced emesis, other]
Analysis method:	Frequency tables will be prepared for the above-mentioned data elements.	

3.3 Administration of Medications (Other than Fomepizole IV)

Analysis set:	Safety Analysis Set

Data element analyzed:	Administration of medication (other than fomepizole IV)	[no, yes]
	Details of administered medication (other than fomepizole IV)	
	Medication name (duplicate count)	[ethanol, vitamin B6, vitamin B1, folic acid preparations, sodium bicarbonate preparations, potassium chloride preparations, others]
	No. of medications used	
	Reason for use (duplicate count)	[treatment of AE, treatment of concurrent (coexisting) disease, treatment of underlying disease (poisoning), other (prophylaxis, etc.)]
Analysis method:	Frequency tables of calculated values and summary statistics of measured values will be prepared for the above-mentioned data elements. Reason for use will be calculated by the number of occasions used and number of patients treated.	

4 SAFETY ANALYSES

4.1 Incidences of Adverse Events and Adverse Drug Reactions/Infections

4.1.1 Incidences of Adverse Events

Analysis set: Safety Analysis Set

Data element analyzed: AEs

Analysis method: AEs will be analyzed as follows.

(1) No. of patients with AEs
(2) No. of AEs
(3) Incidence rate 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 rate of AEs:

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

AE category:

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

4.1.2 Incidences of Adverse Drug Reactions/Infections

Analysis set: Safety Analysis Set

Data element analyzed: ADRs, etc.

Analysis method: AEs will be analyzed as follows.

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

(2) No. of occurrences of ADRs, etc.

(3) Incidence rate 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.

Number of occurrences of ADRs, etc.:

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

Incidence rate of ADRs, etc.:

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

Category of ADRs, etc.:

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

4.1.3 Incidences of Adverse Events and Adverse Drug Reactions/Infections Identified in the Safety Specification

4.1.3.1 Incidences of Adverse Events Identified in the Safety Specification (Tabulated By Risk)

Analysis set: Safety Analysis Set

Data element analyzed:	AEs identified in the Safety Specification (important identified risks and important potential risks)
Stratification variable:	Seriousness [serious, not serious]
Analysis method:	The above-mentioned data elements will be analyzed by risk using the same method described in section 4.1.1 for each stratum of the stratification variables. Patients with multiple occurrences of the same SOC/PT will be counted as a single patient within said SOC/PT. However, patients who experience multiple AEs of varying seriousness will be separately counted as a single patient for the serious event and the non-serious event. Risks to be analyzed shall adhere to the definitions outlined in the Important Identified Risks, Important Potential Risks, and Important Missing Information.

4.1.3.2 Incidences of Adverse Drug Reactions/Infections Identified in the Safety Specification (Tabulated By Risk)

Analysis set:	Safety Analysis Set
Data element analyzed:	ADRs, etc. in the Safety Specification (important identified risks and important potential risks)
Stratification variable:	Seriousness [serious, not serious]
Analysis method:	The above-mentioned data elements will be analyzed by risk using the same method described in section 4.1.2 for each stratum of the stratification variables. Patients with multiple occurrences of the same SOC/PT will be counted as a single patient within said SOC/PT. However, patients who experience multiple AEs of varying seriousness will be separately counted as a single patient for the serious event and the non-serious event. Risks to be analyzed shall adhere to the definitions outlined in the Important Identified Risks, Important Potential Risks, and Important Missing Information.

4.2 Incidences of Adverse Events and Adverse Drug Reactions/Infections in Patients Excluded from the Safety Analysis Set

4.2.1 Incidences of Adverse Events in Patients Excluded from the Safety Analysis Set

Analysis set:	Patients excluded from the Safety Analysis Set
Data element analyzed:	AEs
Analysis method:	The above-mentioned data element will be analyzed using the same method described in section 4.1.1.

4.2.2 Incidences of Adverse Drug Reactions/Infections in Patients Excluded from the Safety Analysis Set

Analysis set:	Patients excluded from the Safety Analysis Set
Data element analyzed:	ADRs, etc.
Analysis method:	The above-mentioned data element will be analyzed using the same method described in section 4.1.2.

4.3 Incidences of Adverse Events and Adverse Drug Reactions/Infections by Seriousness, Time of Onset, Outcome, and Causal Relationship with Fomepizole IV

4.3.1 Incidences of Adverse Events by Seriousness, Time of Onset, Outcome, and Causal Relationship with Fomepizole IV

Analysis set:	Safety Analysis Set	
Data element analyzed:	AEs	
Stratification variable:	Total	
	Seriousness	[serious, not serious]
	Time of onset (time)	[Min <= - < 24, 24 <= - < 48, 48 <= - < 72, 72 <= - < 96, 96 <= - < 120, 120 <= - <= Max]
	Outcome	[recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, death (due to this event), unknown]
	Causal relationship to fomepizole IV	[related, not related]
Analysis method:	The above-mentioned data elements will be analyzed using the same method described in section 4.1.1 for each stratum of the stratification variables. Patients with multiple occurrences of the same SOC/PT will be counted as a single patient within said SOC/PT. Events in the same SOC will be analyzed as single events according to the priority described below, whereas events with the same PT will be analyzed as single events according to the priority described below based on the details of the stratification variable. Seriousness: Serious→Not serious Time of onset: <24 hr → 24-<48 hr → 48-<72 hr → 72-<96 hr → 96-<120 hr → ≥120 hr	

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

Causal relationship with fomepizole IV: Related→ Not related

4.3.2 Incidences of Adverse Drug Reactions/Infections By Seriousness, Time of Onset, and Outcome

Analysis set:	Safety Analysis Set	
Data element analyzed:	ADRs, etc.	
Stratification variable:	Total	
	Seriousness	[serious, not serious]
	Time of onset (time)	[Min <= - < 24, 24 <= - < 48, 48 <= - < 72, 72 <= - < 96, 96 <= - < 120, 120 <= - <= Max]
	Outcome	[recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, death (due to this event), unknown]

Analysis method: The above-mentioned data elements will be analyzed using the same method described in section 4.1.2 for each stratum of the stratification variables. Patients with multiple occurrences of the same SOC/PT will be counted as a single patient within said SOC/PT. Events in the same SOC will be analyzed as single events according to the priority described below, whereas events with the same PT will be analyzed as single events according to the priority described below based on the details of the stratification variable.

Seriousness: Serious→Not serious

Time of onset: <24 hr → 24-<48 hr → 48-<72 hr → 72-<96 hr → 96-<120 hr → ≥120 hr

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

4.4 Incidences of Serious Adverse Events and Adverse Drug Reactions/Infections

4.4.1 Incidences of Serious Adverse Events

Analysis set: Safety Analysis Set

Data element analyzed:	SAEs
Analysis method:	The above-mentioned data element will be analyzed using the same method described in section 4.1.1.

4.4.2 Incidences of Serious Adverse Drug Reactions/Infections

Analysis set:	Safety Analysis Set
Data element analyzed:	Serious ADRs, etc.
Analysis method:	The above-mentioned data element will be analyzed using the same method described in section 4.1.2.

4.5 Factors Potentially Affecting Safety

4.5.1 Incidences of Adverse Drug Reactions/Infections by Patient Demographics & Baseline Characteristics and Treatment Details

Analysis set:	Safety Analysis Set	
Data element analyzed:	ADRs, etc.	
Stratification variable:	Sex	[male, female]
	Age (years)	[Min <= - < 65, 65 <= - <= Max, Unknown] [Min <= - < 65, 65 <= - <= 74, 75 <= - <= Max, Unknown] [Min <= - < 20, 20 <= - <= 29, 30 <= - <= 39, 40 <= - <= 49, 50 <= - <= 59, 60 <= - <= 69, 70 <= - <= 79, 80 <= - <= Max, Unknown]
	Alcohol consumption (at time of poisoning)	[no, yes, unknown]
	Infusion dose per body weight	[15 mg/kg, 10 mg/kg, Other]
	Acute blood purification therapy	[no, yes]
	Respiratory management (mechanical ventilation)	[no, yes]
	GI decontamination	[no, yes]
	Administration of medication (other than fomepizole IV)	[no, yes]

	Toxic symptoms (at start of fomepizole IV dosing)	[no, yes]

Analysis method: The above-mentioned data elements will be analyzed for each stratum of the stratification variables as follows.

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

(2) No. of occurrences of ADRs, etc.

(3) Incidence rate 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.

Number of occurrences of ADRs, etc.:

- The number of times that ADRS, etc. occur.

Incidence rate of ADRs, etc.:

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

4.5.2 Incidences of Adverse Drug Reactions/Infections by Seriousness, Deaths, Patient Demographics & Baseline Characteristics and Treatment Details

Analysis set:	Safety Analysis Set	
Data element analyzed:	ADRs, etc.	
Stratification variable 1:	Seriousness	[serious, not serious]
	Death	
Stratification variable 2:	Sex	[male, female]
	Age (years)	[Min <= - < 65, 65 <= - <= Max, Unknown] [Min <= - < 65, 65 <= - <= 74, 75 <= - <= Max, Unknown] [Min <= - < 20, 20 <= - <= 29, 30 <= - <= 39, 40 <= - <= 49, 50 <= - <= 59, 60 <= - <= 69, 70 <= - <= 79, 80 <= - <= Max, Unknown]
	Alcohol consumption (at time of poisoning)	[no, yes, unknown]
	Infusion dose per body weight	[15 mg/kg, 10 mg/kg, Other]

	Acute blood purification therapy	[no, yes]
	Respiratory management (mechanical ventilation)	[no, yes]
	GI decontamination	[no, yes]
	Administration of medication (other than fomepizole IV)	[no, yes]
	Toxic symptoms (at start of fomepizole IV dosing)	[no, yes]
Analysis method:	The dual stratification variables 1 and 2 for the above-mentioned data elements will be analyzed using the same method described in section 4.5.1.	

4.5.3 Incidences of Adverse Drug Reactions/Infections by Sex

Analysis set:	Safety Analysis Set	
Data element analyzed:	ADRs, etc.	
Stratification variable:	Sex	[male, female]
Analysis method:	The above-mentioned data elements will be analyzed using the same method described in section 4.1.2 for each stratum of the stratification variables.	

4.5.4 Incidences of Adverse Drug Reactions/Infections by Age Bracket

Analysis set:	Safety Analysis Set	
Data element analyzed:	ADRs, etc.	
Stratification variable:	Age (years)	[Min <= - < 65, 65 <= - <= Max, Unknown]
		[Min <= - < 65, 65 <= - <= 74, 75 <= - <= Max, Unknown]
		[Min <= - < 20, 20 <= - <= 29, 30 <= - <= 39, 40 <= - <= 49, 50 <= - <= 59, 60 <= - <= 69, 70 <= - <= 79, 80 <= - <= Max, Unknown]
Analysis method:	The above-mentioned data elements will be analyzed using the same method described in section 4.1.2 for each stratum of the stratification variables.	

4.5.5 Incidences of Adverse Drug Reactions/Infections by Alcohol Consumption (Y/N)

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

Stratification variable:	Alcohol consumption (at time of poisoning)	[no, yes, unknown]
Analysis method:	The above-mentioned data elements will be analyzed using the same method described in section 4.1.2 for each stratum of the stratification variables.	

4.5.6 Incidences of Adverse Drug Reactions/Infections by Administration of Fomepizole IV

Analysis set:	Safety Analysis Set	
Data element analyzed:	ADRs, etc.	
Stratification variable:	Infusion dose per body weight	[15 mg/kg, 10 mg/kg, Other]
Analysis method:	The above-mentioned data elements will be analyzed using the same method described in section 4.1.2 for each stratum of the stratification variables.	

4.5.7 Incidences of Adverse Drug Reactions/Infections by Intervention/Procedure (Other than Pharmacotherapy)

Analysis set:	Safety Analysis Set	
Data element analyzed:	ADRs, etc.	
Stratification variable:	Acute blood purification therapy	[no, yes]
	Respiratory management (mechanical ventilation)	[no, yes]
	GI decontamination	[no, yes]
Analysis method:	The above-mentioned data elements will be analyzed using the same method described in section 4.1.2 for each stratum of the stratification variables.	

4.5.8 Incidences of Adverse Drug Reactions/Infections by Administration of Medications (Other than Fomepizole IV)

Analysis set:	Safety Analysis Set	
Data element analyzed:	ADRs, etc.	
Stratification variable:	Administration of medication (other than fomepizole IV)	[no, yes]
Analysis method:	The above-mentioned data elements will be analyzed using the same method described in section 4.1.2 for each stratum of the stratification variables.	

4.5.9 Incidences of Adverse Drug Reactions/Infections by Presence or Absence (Y/N) of Toxic Symptoms

Analysis set:	Safety Analysis Set	
Data element analyzed:	ADRs, etc.	
Stratification variable:	Toxic symptoms	[no, yes]
Analysis method:	The above-mentioned data elements will be analyzed using the same method described in section 4.1.2 for each stratum of the stratification variables.	

4.6 Time Courses of Test and Measurement Data

4.6.1 Time Courses of Vital Signs

Analysis set:	Safety Analysis Set
Data element analyzed:	Pulse rate, systolic blood pressure, diastolic blood pressure, respiratory rate, body temperature
Assessment timepoints:	At start of fomepizole IV dosing (i.e., baseline), 0.5 hr after start of fomepizole IV dosing, 4 hr after start of fomepizole IV dosing, 8 hr after start of fomepizole IV dosing, 12 hr after start of fomepizole IV dosing, 16 hr after start of fomepizole IV dosing, 20 hr after start of fomepizole IV dosing, 24 hr after start of fomepizole IV dosing, 36 hr after start of fomepizole IV dosing, 48 hr after start of fomepizole IV dosing, 60 hr after start of fomepizole IV dosing, 72 hr after start of fomepizole IV dosing, 84 hr after start of fomepizole IV dosing, 96 hr after start of fomepizole IV dosing, 108 hr after start of fomepizole IV dosing, at completion of final fomepizole IV infusion, 12 hr after completion of final fomepizole IV infusion, 24 hr after completion of final fomepizole IV infusion, at final assessment
Analysis method:	Summary statistics of the above-mentioned data elements will be presented for measured values and absolute changes from baseline (obtained by subtracting the measured values at the start of fomepizole IV dosing [i.e., at baseline] from the measured value at each assessment timepoint after starting fomepizole IV dosing), and the 95% CI of the mean will be presented for said absolute changes from baseline. Spaghetti graphs will also be prepared for the measured values of all patients.

4.6.2 Time Courses of Laboratory Test Parameters

Analysis set:	Safety Analysis Set

Data element analyzed:	RBC count, WBC count, platelet count, AST, ALT, gamma-GTP, serum creatinine, BUN
Assessment timepoints:	At start of fomepizole IV dosing (i.e., baseline), 0.5 hr after start of fomepizole IV dosing, 4 hr after start of fomepizole IV dosing, 8 hr after start of fomepizole IV dosing, 12 hr after start of fomepizole IV dosing, 16 hr after start of fomepizole IV dosing, 20 hr after start of fomepizole IV dosing, 24 hr after start of fomepizole IV dosing, 36 hr after start of fomepizole IV dosing, 48 hr after start of fomepizole IV dosing, 60 hr after start of fomepizole IV dosing, 72 hr after start of fomepizole IV dosing, 84 hr after start of fomepizole IV dosing, 96 hr after start of fomepizole IV dosing, 108 hr after start of fomepizole IV dosing, at completion of final fomepizole IV infusion, 12 hr after completion of final fomepizole IV infusion, 24 hr after completion of final fomepizole IV infusion, , at final assessment
Analysis method:	Summary statistics of the above-mentioned data elements will be presented for test values and absolute changes from baseline (obtained by subtracting the test values at the start of fomepizole IV dosing [i.e., at baseline] from the test value at each assessment timepoint after starting fomepizole IV dosing), and the 95% CI of the mean will be presented for said absolute changes from baseline. Spaghetti graphs will also be prepared for the test values of all patients.

5 EFFICACY ANALYSES

5.1 Time Course of Arterial Blood pH

Analysis set:	Patients in the Efficacy Analysis Set for whom test value/s from at least one assessment time point is/are available from both before (i.e., at baseline) and after the start of fomepizole IV dosing.
Data element analyzed:	Arterial blood gas analysis (arterial blood pH)
Assessment timepoints:	At start of fomepizole IV dosing (i.e., baseline), 0.5 hr after start of fomepizole IV dosing, 4 hr after start of fomepizole IV dosing, 8 hr after start of fomepizole IV dosing, 12 hr after start of fomepizole IV dosing, 16 hr after start of fomepizole IV dosing, 20 hr after start of fomepizole IV dosing, 24 hr after start of fomepizole IV dosing, 36 hr after start of fomepizole IV dosing, 48 hr after start of fomepizole IV dosing, 60 hr after start of fomepizole IV dosing, 72 hr after start of fomepizole IV dosing, 84 hr after start of fomepizole IV dosing, 96 hr after start of fomepizole IV dosing, 108 hr after start of fomepizole IV dosing, at completion of final fomepizole IV infusion, 12 hr after completion of final fomepizole IV infusion, 24 hr after completion of final fomepizole IV infusion, at final assessment
Analysis method:	Summary statistics of the above-mentioned data elements will be presented for test values and absolute changes from baseline (obtained by subtracting the test values at the start of fomepizole IV dosing [i.e., at baseline] from the test value at each assessment timepoint after starting fomepizole IV dosing). The 95% CI of the mean will also be presented and a paired Student's t-test will be performed for absolute changes from baseline. Furthermore, line graphs will be prepared by plotting the mean±SD of test values on the Y-axis and the test timepoints on the X-axis, while bar graphs will be prepared by plotting absolute changes from baseline on the Y-axis and the test timepoints on the X-axis. The results of the paired Student's t-test will be denoted within the graph with an asterisk (*).

5.2 Time Courses of Poisoning/Toxicity Test Parameters

Analysis set:	Patients in the Efficacy Analysis Set for whom test value/s from at least one assessment time point is/are available from both before (i.e., at baseline) and after the start of fomepizole IV dosing.
Data element analyzed:	Arterial blood gas analyses (arterial carbon dioxide partial pressure [$PaCO_2$], arterial oxygen partial pressure [PaO_2], bicarbonate ion, base excess [BE], anion

	gap, blood ethylene glycol concentration, blood glycolic acid concentration, blood methanol concentration, blood formic acid concentration, osmotic pressure gap)
Assessment timepoints:	At start of fomepizole IV dosing (i.e., baseline), 0.5 hr after start of fomepizole IV dosing, 4 hr after start of fomepizole IV dosing, 8 hr after start of fomepizole IV dosing, 12 hr after start of fomepizole IV dosing, 16 hr after start of fomepizole IV dosing, 20 hr after start of fomepizole IV dosing, 24 hr after start of fomepizole IV dosing, 36 hr after start of fomepizole IV dosing, 48 hr after start of fomepizole IV dosing, 60 hr after start of fomepizole IV dosing, 72 hr after start of fomepizole IV dosing, 84 hr after start of fomepizole IV dosing, 96 hr after start of fomepizole IV dosing, 108 hr after start of fomepizole IV dosing, at completion of final fomepizole IV infusion, 12 hr after completion of final fomepizole IV infusion, 24 hr after completion of final fomepizole IV infusion, at final assessment
Analysis method:	Summary statistics of the above-mentioned data elements will be presented for test values and absolute changes from baseline (obtained by subtracting the test values at the start of fomepizole IV dosing [i.e., at baseline] from the test value at each assessment timepoint after starting fomepizole IV dosing). The 95% CI of the mean will also be presented and a paired Student's t-test will be performed for absolute changes from baseline. Furthermore, line graphs will be prepared by plotting the mean±SD of test values on the Y-axis and the test timepoints on the X-axis, while bar graphs will be prepared by plotting absolute changes from baseline on the Y-axis and the test timepoints on the X-axis. The results of the paired Student's t-test will be denoted within the graph with an asterisk (*).

5.3 Time Courses of Toxic Symptoms

Analysis set:	Patients in the Efficacy Analysis Set for whom data is available for at least one toxic symptom parameter both at baseline and at completion of the final fomepizole IV infusion.
Data element analyzed:	Respiratory symptoms (tachypnea, respiratory failure, laboured breathing) Cardiovascular symptoms (cardiovascular irritation, tachycardia, bradycardia, arrhythmias, hypertension, heart failure) GI symptoms (nausea, vomiting, abdominal pain) Neurologic or psychiatric symptoms (nervous system irritation, consciousness disturbed, convulsions, ataxia)

	Renal and urinary symptoms (renal failure, hematuria) Eye symptoms (visual impairment, nystagmus) Abnormal test values (renal function test abnormal, liver function test abnormal, electrolytes abnormal (sodium abnormal, potassium abnormal, calcium abnormal, phosphorus abnormal, magnesium abnormal), metabolic acidosis (examination finding), urine sediment abnormal, osmotic pressure gap abnormal, chest X-ray abnormal, electrocardiography abnormal, cranial CT abnormal, brain edema on MRI, fundus examination abnormal).
Assessment timepoints:	At the start of fomepizole IV dosing (i.e., at baseline) and at completion of the final fomepizole IV infusion
Analysis method:	The numbers and proportions of patients with or without each toxic symptom at each assessment timepoint will be presented for each of the above-mentioned data elements. Presence or absence of toxic symptoms at baseline will also be cross-tabulated against those at completion of the final fomepizole IV infusion.

5.4 Outcome

Analysis set:	Patients in the Efficacy Analysis Set and patients in the Safety Analysis Set for whom outcome was recorded in the CRF.	
Data element analyzed:	Outcome	[survived without sequelae, survived with sequelae, death]
	Sequelae details * Only if the outcome is “survived with sequelae”	
Analysis method:	Frequency tables will be prepared for each outcome in the above-mentioned data elements in both the Efficacy Analysis Set and in the Safety Analysis Set. Listings will also be prepared for the Safety Analysis Set and Efficacy Analysis Set categories, outcomes and details of sequelae.	

5.5 Factors Potentially Affecting Efficacy

Analysis set:	Patients in the Efficacy Analysis Set for whom test value/s from at least one assessment time point is/are available from both before (i.e., at baseline) and after the start of fomepizole IV dosing.
Data element analyzed:	Arterial blood gas analysis (arterial blood pH)
Assessment timepoints:	At start of fomepizole IV dosing (i.e., baseline), 0.5 hr after start of fomepizole IV dosing, 4 hr after start of fomepizole IV dosing, 8 hr after start of fomepizole

	IV dosing, 12 hr after start of fomepizole IV dosing, 16 hr after start of fomepizole IV dosing, 20 hr after start of fomepizole IV dosing, 24 hr after start of fomepizole IV dosing, 36 hr after start of fomepizole IV dosing, 48 hr after start of fomepizole IV dosing, 60 hr after start of fomepizole IV dosing, 72 hr after start of fomepizole IV dosing, 84 hr after start of fomepizole IV dosing, 96 hr after start of fomepizole IV dosing, 108 hr after start of fomepizole IV dosing, at completion of final fomepizole IV infusion, 12 hr after completion of final fomepizole IV infusion, 24 hr after completion of final fomepizole IV infusion, at final assessment	
Stratification variable:	Sex	[male, female]
	Age (years)	[Min <= - < 65, 65 <= - <= Max, Unknown] [Min <= - < 65, 65 <= - <= 74, 75 <= - <= Max, Unknown] [Min <= - < 20, 20 <= - <= 29, 30 <= - <= 39, 40 <= - <= 49, 50 <= - <= 59, 60 <= - <= 69, 70 <= - <= 79, 80 <= - <= Max, Unknown]
	Alcohol consumption (at time of poisoning)	[no, yes, unknown]
	Infusion dose per body weight	[15 mg/kg, 10 mg/kg, Other]
	Acute blood purification therapy	[no, yes]
	Respiratory management (mechanical ventilation)	[no, yes]
	GI decontamination	[no, yes]
	Administration of medication (other than fomepizole IV)	[no, yes]
	Toxic symptoms	[no, yes]
Analysis method:	Summary statistics for test values at each assessment timepoint will be calculated for each stratum of the stratification variable of the data elements listed above.	

6 INCIDENCE OF ADVERSE DRUG REACTIONS/INFECTIONS IN THE SUPPLEMENTARY PHARMACOVIGILANCE PLAN

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

Analysis set:	Safety Analysis Set
Data element analyzed:	ADRs, etc. in the Safety Specification (important identified risks, important potential risks, and important missing information)
Stratification variable:	Seriousness [serious, not serious]
Analysis method:	Analysis of the above-mentioned data elements will be performed for each stratum of the stratification variables as follows according to Attached Form 12 (Notes) items 1 through 4 stipulated in Re-Examination Notification No. 0325-10 issued on 25 March 2020 by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare (herein "MHLW/PSEHB/PED"). (1) Numbers and incidence rates of patients with ADRs, etc. The names of risks and the order of describing these risks shall adhere to the definitions outlined in the Important Identified Risks, Important Potential Risks, and Important Missing Information.

7 SUMMARY OF PATIENTS IN POSTMARKETING SURVEILLANCE

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

Analysis set:	Patients for whom CRFs were submitted/collected
Data element analyzed:	Patient No. Site name Sex Age Reason for use (disease code, disease name) Concomitant disease (disease code, disease name) Route of administration Maximum dose Mean dose Units Period used (duration of fomepizole IV treatment) Concomitant medications (drug code, drug name) Extent of response ADRs (disease code, disease name, outcome) CRF number Dropouts Reason for dropout
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.

Document History (Version Control)

Version	Date	Created or modified by	Comments
Original version	2015.10.23	[redacted]	New document
2nd version	2022.6.23	[redacted]	The tabulated data was revised in accordance with the SAP standardized template.
Version 2.1	2022.8.1	[redacted]	Version 2.1 created All changes from Version 2 are described in Attachment 1.

[Attachment 1] Amendment Comparison Table

Statistical Analysis Plan (Version 2: Prepared on 23 June 2022 → Version 2.1: Prepared on 1 August 2022)

Page No.	Before amendment	After amendment	Reason for amendment
13	Description of level of consciousness assessment: 3-3-9 rating system (JCS): [I, II, III]	Description of level of consciousness assessment: 3-3-9 rating system (JCS): [0 (alert), I, II, III]	Due to a change in the method of analysis, the 3-3-9 rating system (JCS) category “0 (alert)” was added to the analyzed data element “Level of consciousness details” in section 2.1 “Patient Demographics and Baseline Characteristics.”