Statistical Analysis Plan

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Title: FIRAZYR® Subcutaneous Injection 30 mg Syringe General Drug Use-Results Survey

Study Number: SHP667-401

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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

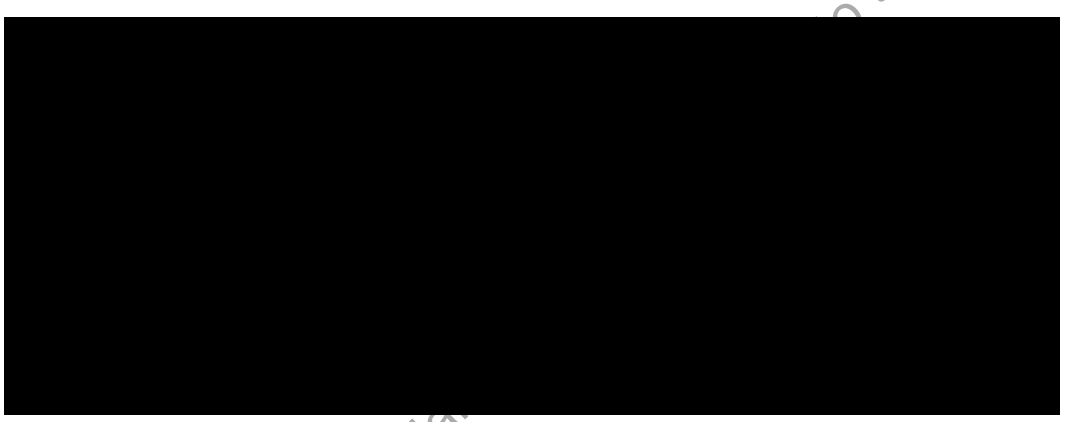
GENERAL DRUG USE-RESULTS SURVEY OF FIRAZYR ® SUBCUTANEOUS INJECTION 30 MG SYRINGE

Protocol No.: SHP667-401

Version 4.2

Date of preparation: 2024/06/18

statistical analysis plan Approver's Signature



REVISION HISTORY

Version	Date	Prepared by	Changes
1.0	2020/3/9	[redacted]	-
2.0	2020/8/13	[redacted]	Addition of the following [3.1 Patient composition] 3.2 Background Summary The following was added to "3.3.1 Occurrence Status of Adverse Events and Adverse Drug Reactions" "Occurrence Status of Adverse Events and Adverse Drug Reactions" " Occurrence of adverse reactions in the safety specifications "
3.0	2021/8/10	[redacted]	Addition of the following 3.3 Continuation or discontinuation of the survey 3.4.2 Analysis by patient characteristics The following contents were updated 3.4.1 The contents of occurrence status of adverse events and adverse reactions were updated. 3.5 List of patients
4.0	2023/7/12	[redacted]	General description adjustment Addition of the following 3.5 Efficacy
4.1	2024/2/22	[redacted]	Update below 3.1 Patient composition 3.4.1 Occurrence Status of Adverse Events and Adverse Drug Reactions
4.2	2024/6/18	[redacted]	Update below 3.2 Overview of Background

			3.4.2.4 Occurrence of ADRs by Disease Type 3.5 Efficacy

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1. Overview

This statistical analysis plan specifies the details of “analysis items and methods ” in the surveillance protocol.

1.1 Objectives

Based on the survey data collected in the survey, describe the details and methods of analysis to achieve the survey objectives.

1.2 Outline of the survey

The survey outline is shown below.

Objectives of the survey	The objective of this Surveillance is to investigate the following items in patients with hereditary angioedema (Hereditary angioedema: Hereditary angioedema) treated with FIRAZYR (hereinafter referred to as this drug) in clinical practice. (1) Unknown adverse reactions (2) Incidence of adverse reactions under the actual use status of this drug (3) Factors that may affect the safety or efficacy
Planned sample size	75 patients
Patients to be surveyed	HAE patients treated with this drug for the first time
Procedure	Central registry system
Main survey items	Patient demographics, physical examination, HAE diagnosis, concomitant medications, concomitant therapies, medical history, complications, history of HAE attacks in the last 12 months before treatment with this drug, HAE attack status during the observation period, administration status of this drug, discontinuation, laboratory tests, pregnancy and lactation status, adverse events
Collection of survey forms and observation period	Patients will be observed for up to 3 months after this drug treatment. However, as for the status of attack and its treatment status, the reporting period will be the period until 3 months after the initial attack or until disappearance of up to the fifth attack treated with this drug. The rationale for setting the observation period is set at 3 months from the prescription of this drug based on the results of a phase III clinical study (median number of months from the previous attack was 1.5 months).
Survey period	•Survey period: November 2018 to April 30, 2023 •Registration period: November 2018 to August 10, 2023

1.3 Safety specification

1) Serious hypersensitivity and severe injection site reaction
2) Aggravation of cardiac function under ischemic conditions due to bradykinin antagonistic action
3) Blood pressure decreased
4) Immunogenicity

1.4 Planned sample size of the survey and its rationale

1) Planned sample size

   75 patients

2) Rationale

   There are 400 HAE patients in Japan, and approximately 2/3 of them are estimated to receive treatment for acute attacks. Given the expected switch from existing products to the use of this drug after the launch of this drug, the number of registrable cases will be approximately 75 in 3 years. In the Japanese phase III clinical study (Study SHP FIR 301), the incidence of severe injection site reaction was 12.5% (1/8 subjects), and the sample size of 75 subjects will enable to detect at least 3 cases of severe injection site reaction with a probability of 95%. To collect 75 cases, the survey period was determined to be approximately 4 years in consideration of the registration period of 3 years and the period of 1 year until the collection of survey forms and case fixation.

2. Statistical Methods

2.1 Software Used for Statistical Analyses

SAS for Windows version: 9.4 or later (SAS Institute Japan)

Excel version for Windows: Office 365 MSO (16.0 or later)

2.2 Significance Levels for Testing and Confidence Coefficients for Interval Estimation

Unless otherwise specified, multiplicity of the tests will not be considered and the significance level will be two-sided 0.05. For interval estimation, a 2-sided confidence interval with a confidence coefficient of 0.95 will be estimated, unless otherwise specified.

2.3 Handling of missing data

Missing data will not be imputed in principle. All analyses will be performed based on the observed values.

2.4 Denominators for Percentages

Unless otherwise specified, the denominator should be the number of patients in the analysis set with non-missing data on the endpoint.

2.5 Display of calculated values

In principle, the number of digits to be displayed for statistics shall be as follows.

Item	Display digit
P value	Round off to the third decimal place.
Number of subjects	Integer number
Percentage	Round off to 2 decimal places.
Summary statistics (Mean, standard deviation, median, 14 quantiles, 34 quantiles)	Round off to the first significant digit of the target data.
Min, Max	Indicated with significant digits of target data

3. Statistical Analyses

3.1 Patient composition

Determine the numbers of registered patients, patients whose CRFs were collected, patients whose CRFs were not collected, patients whose CRFs were fixed, patients whose CRFs were not fixed, patients included in the safety analysis, and patients included in the efficacy analysis, and the numbers of sites for registered patients, patients whose CRFs were collected, patients whose CRFs were fixed, patients included in the safety analysis, and patients included in the efficacy analysis. In addition, the number of patients excluded from safety analysis and efficacy analysis will be determined according to the following table.

Evaluation excluded	Reason for exclusion (there are multiple applicable patients)	Conditions for exclusion
Excluded from safety analysis	Outside the contract period	Patients whose registration form was filled out outside the contract period
	Not registered	Patients ineligible for the registration assessment
	Outside enrollment period	Patients whose date of registration form entry is outside the period from the start date of registration to the end date of registration
	Administration of this drug outside the contract period	Cases in which the date of administration of this drug is after the contract termination date
	Duplicate case	More than one case is registered.
	This drug naïve	Patients who have not received this drug
Excluded from efficacy analysis	Efficacy indeterminate	Cases in which "Date/time of initial relief " and" Date/time of resolution " are "Unknown " in all records of the acute attack status
	Off label or unknown indication	① Patients with neither "genetic mutation" nor "family history" in patient background ② Pediatric cases (< 18 years)

Form No. T01_01 in the corresponding analysis figure/output plan

3.2 Overview of Background

- Subjects: Safety analysis set, efficacy analysis set

The number and proportion of subjects will be presented for each level of background factor. For continuous data, summary statistics will be presented.

Background factors to be tabulated by level: Sex, presence or absence of pregnancy, presence or absence of lactation, race (Japanese, others), age (in 10 year increments), age (pediatric category), age (elderly category), weight (< 50Kg, ≥ 50 to < 60Kg, ≥ 60 to < 70Kg, ≥ 70Kg), height (< 150 cm, ≥ 150 cm to < 160 cm, ≥ 160 cm to < 170 cm, ≥ 170

cm), BMI(< 18.5, ≥ 18.5 and < 25.0, ≥ 25.0), diagnosis of hereditary angioedema (HAE) (Disease duration, HAE type (disease type), genetic mutation, and family history), HAE attack within the past 12 months before treatment with this drug, presence or absence of medical history, presence or absence of allergy history, presence or absence of complications, implementation status of self-administration training, presence or absence of concomitant medications, presence or absence of concomitant therapies

Background factors included in summary statistics: Age (years), body weight (kg), height (cm), BMI (kg/m2), duration of hereditary angioedema (HAE) (years), HAE attack in the last 12 months before treatment with this drug (Number of attacks, number requiring treatment), and time from the last attack before starting this drug (months)

Form numbers in the corresponding analysis tables and figures output plan: T02_01_01, T02_01_02, T02_02_01, T02_02_02

3.3 Continuation or discontinuation of the survey

- Subjects: Safety analysis set

The number and proportion of patients who continued or discontinued the surveillance (including "reasons for discontinuation ") will be tabulated by period.

Form No.: T02_03 in the corresponding analysis figure/output plan

3.4 Status of acute attacks during the observation period

- Population: efficacy analysis population, safety analysis population

The number and proportion of patients with one dose of this drug will be tabulated (If the dose differs depending on the time of administration, create a category to understand it).

For the number of attacks per subject, the number and proportion of subjects will be presented by level (Once, twice, three times, four times, five times or more). The number and proportion of subjects will be tabulated by administration status of this drug. All attacks will be included in the summary.

Form numbers in the corresponding analysis tables and figures output plan: T03_01_01, T03_01_01_02, T03_01_01_03, T03_01_01_04

3.5 Safety

Unless otherwise specified, if multiple different events occur in the same subject, each event should be counted as 1 subject for calculation. Adverse events and adverse drug reactions will be tabulated using the Medical Dictionary for Regulatory Activities/Japanese version (Medical Dictionary for Regulatory Activities Terminology; MedDRA/J (hereinafter referred to as MedDRA/J)). In principle, events that occurred during 3 months from the onset date of an attack requiring this drug or up to 5 attacks requiring this drug, whichever is shorter, will be included in tabulation of adverse events and adverse reactions. The supplementary forms to tabulate adverse events and adverse reactions that occurred after 3 months will be separately prepared. (Analysis of forms regarding adverse events and adverse reactions that occurred after 3 months Table and table Form No.: T04_05_01_01, T04_05_01_02, T04_05_01_03,

T04_05_01_04_01, T04_05_01_04_01, T04_05_01_04_02, T04_05_01_04_03, T04_05_01_04_04, T04_05_01_05_01, T04_05_01_05_02, T04_05_01_05_03, T04_05_01_05_04, T04_05_02_01_01 to T04_05_02_01_04, T04_05_03)

3.5.1 Occurrence Status of Adverse Events and Adverse Drug Reactions

3.5.1.1 Occurrence Status of Adverse Events and Adverse Drug Reactions

- Subjects: Safety analysis set, safety analysis excluded

The number of patients with adverse events and adverse drug reactions and the incidence of adverse events and adverse drug reactions will be tabulated. Furthermore, the number of patients with adverse events and the incidence will be tabulated by system organ class and preferred term.

Serious adverse events and serious adverse drug reactions will also be tabulated in the same manner.

Form No.: T04_01_01, T04_01_01_02, T04_01_02, T04_01_02, T04_01_02_02, T04_01_03, T04_01_03_02

3.5.1.2 Occurrence Status of Adverse Events and Adverse Drug Reactions (Seriousness by gender, severity, and outcome)

- Subjects: Safety analysis set

Seriousness The number of patients with adverse events and adverse drug reactions and the incidence of adverse events and adverse drug reactions will be tabulated by sex, severity, and outcome. Furthermore, the number of patients with adverse events and the incidence will be tabulated by system organ class and preferred term. In the tabulation of adverse events by serious sex, the number of events will also be tabulated.

If different seriousness and severity occurred in the same case or event, they will be summarized as one event in each of the seriousness and severity strata.

If different outcomes occur in the same case or event, they will be summarized as one event in the final outcome.

Form numbers in the corresponding analysis tables and figures output plan: T04_01_04_01, T04_01_04_02, T04_01_04_03, T04_01_05_01, T04_01_05_02, T04_01_05_03

3.5.1.3 Occurrence of adverse reactions included in safety specifications

- Subjects: Safety analysis set

For each safety specification item, the number of patients with adverse reactions and the incidence of adverse reactions will be tabulated. Furthermore, the number of patients with adverse events and the incidence will be tabulated by system organ class and preferred term.

The safety specifications are defined in the HLT_PT list.

Form numbers in the corresponding analysis tables and figures output plan: T04_02_01_01, T04_02_01_02, T04_02_01_03, T04_02_01_04, T05_03

3.5.1.4 Occurrence Status of Adverse Events and Adverse Drug Reactions (by Treatment Form)

- Subjects: Safety analysis set

The numbers of patients with adverse events and adverse drug reactions and the incidences of adverse events and adverse drug reactions will be tabulated by treatment form (Treatment with this drug alone, combination with other drugs). Furthermore, the number of patients with adverse events and the incidence will be tabulated by system organ class and preferred term.

Form No. in the corresponding analysis figure/output plan: T04_01_04_04, T04_01_05_04

3.5.1.5 Incidence of adverse reactions/infections in post-marketing surveillance, etc. (Attached Form 2 [Attached Form 15 for application for reexamination])

- Subjects: Safety analysis set

Based on the "Periodic Safety Report Preparation Guide (September 2021 version)" and "Guidance for Application for Reexamination (October 2021 version), " the number of patients with adverse reactions and the incidence of adverse reactions in this survey will be tabulated. Furthermore, the number of patients with adverse events and the incidence will be tabulated by system organ class and preferred term.

Form No.: T05_02 in the corresponding analysis figure/output plan

3.5.2 Analysis by patient characteristics

3.5.2.1 Analysis of Adverse Reactions by Background Factors

- Subjects: Safety analysis set

For the background factors tabulated in 3.2, the number of patients with adverse reactions and the incidence will be compared between levels by background factor. For comparison, Fisher's exact test will be performed. For continuous data, summary statistics will be presented by presence/absence of adverse reactions, and Wilcoxon rank sum test will be performed. Adverse reactions will be tabulated for events that occurred during 3 months from the onset date of an attack requiring this drug treatment or until the number of attacks requiring this drug treatment reaches 5, whichever is shorter.

Form No. in the corresponding analysis figure/output plan: T04_03_01_01, T04_03_01_02

3.5.2.2 Occurrence Status of Adverse Reactions in Patients with Specific Backgrounds

- Subjects: Safety analysis set

For patients with specific backgrounds (Pediatric patients, elderly patients, pregnant and parturient women, patients with renal/hepatic impairment), the number of patients with adverse reactions and the incidence of adverse reactions will be tabulated. Furthermore, the number of patients with adverse events and the incidence will be tabulated by system organ class and preferred term.

Form numbers in the corresponding analysis tables and figures output plan: T04_03_03_01, T04_03_03_02, T04_03_03_03, T04_03_03_04, T04_03_03_05

3.5.2.3 Occurrence Status of Adverse Reactions by Background Factor

- Subjects: Safety analysis set

The number of patients with adverse reactions and the incidence of adverse reactions will be tabulated by background factor for which significant differences are confirmed in the "analysis by background factor of adverse reactions." Furthermore, the number of patients with adverse events and the incidence will be tabulated by system organ class and preferred term.

Form No. in the corresponding analysis figure/output plan: 04_03_03_xx

3.5.2.4 Occurrence of ADRs by Disease Type

- Subjects: Safety analysis set

The occurrence of adverse reactions will be tabulated by disease type (Type I or Type II/III). The tabulation method shall be the same as in 3.5.2.1 and 3.5.2.2.

Form numbers in the corresponding analysis tables and figures output plan: T04_03_01_01_02, T04_03_01_01_03, T04_03_03_07

3.6 Efficacy

3.6.1 Treatment status of acute attacks during the observation period

- Population: efficacy analysis population

For treatment status per attack, the number of events, proportion, and summary statistics will be presented by level. Data will also be tabulated by severity of attacks and treatment form. Treated attacks will be included in the tabulation. For the tabulation of the time elapsed, attacks for which all 4 of the time to onset of attack, time to start of treatment, and time to symptom relief or resolution are unknown, NK, or 0:00 will be excluded from the tabulation.

For treatment status of attacks, the following items will be tabulated.

- Time from onset of attack to start of treatment (procedure): All attacks will be summarized. Tabulation by level shall be performed at intervals of less than 30 minutes, 30 minutes to less than 1 hour, less than 1~2 hours, less than 2~4 hours, 4~8 hours, less than 8~12 hours, 12 hours to less than 24:00, and 24 hours or more.
- Time from start of treatment (procedure) to initial symptom relief: All attacks and attacks for which the last dose before symptom relief is this drug will be summarized. Tabulation by level shall be performed at intervals of less than 30 minutes, 30 minutes to less than 1 hour, less than 1~2 hours, less than 2~4 hours, 4~8 hours, less than 8~12 hours, 12 hours to less than 24:00, and 24 hours or more. For the tabulation of elapsed time, data with unknown time (data for which the calculated elapsed time becomes 0 minutes) will be excluded from the tabulation.
- Time from last treatment (procedure) to initial symptom relief: Attacks will be summarized for all attacks and for

attacks where the last dose before symptom relief is this drug. Tabulation by level shall be performed at intervals of less than 30 minutes, 30 minutes to less than 1 hour, less than 1~2 hours, less than 2~4 hours, 4~8 hours, less than 8~12 hours, 12 hours to less than 24:00, and 24 hours or more. For the tabulation of elapsed time, data with unknown time (data for which the calculated elapsed time becomes 0 minutes) will be excluded from the tabulation.

- Time from start of treatment (procedure) to symptom resolution: All attacks and attacks for which the last dose before symptom resolution is this drug will be summarized. Tabulation by level shall be performed at intervals of less than 30 minutes, 30 minutes to less than 1 hour, less than 1~2 hours, less than 2~4 hours, 4~8 hours, less than 8~12 hours, 12 hours to less than 24:00, and 24 hours or more. For the tabulation of elapsed time, data with unknown time (data for which the calculated elapsed time becomes 0 minutes) will be excluded from the tabulation.
- Time to symptom resolution since last treatment (procedure): All attacks and attacks for which the last dose before symptom resolution is this drug will be summarized. Tabulation by level shall be performed at intervals of less than 30 minutes, 30 minutes to less than 1 hour, less than 1~2 hours, less than 2~4 hours, 4~8 hours, less than 8~12 hours, 12 hours to less than 24:00, and 24 hours or more. For the tabulation of elapsed time, data with unknown time (data for which the calculated elapsed time becomes 0 minutes) will be excluded from the tabulation.
- Time from attack onset to symptom resolution: All attacks and attacks for which the last dose prior to symptom resolution is this drug will be summarized. Tabulation by level shall be performed at intervals of less than 30 minutes, 30 minutes to less than 1 hour, less than 1~2 hours, less than 2~4 hours, 4~8 hours, less than 8~12 hours, 12 hours to less than 24:00, and 24 hours or more. For the tabulation of elapsed time, data with unknown time (data for which the calculated elapsed time becomes 0 minutes) will be excluded from the tabulation.
- Time from start of treatment to latest onset of symptom relief or symptom resolution: All attacks and attacks for which the last dose before symptom relief or symptom resolution is this drug will be summarized. Tabulation by level shall be performed at intervals of less than 30 minutes, 30 minutes to less than 1 hour, less than 1~2 hours, less than 2~4 hours, 4~8 hours, less than 8~12 hours, 12 hours to less than 24:00, and 24 hours or more. For the tabulation of elapsed time, data with unknown time (data for which the calculated elapsed time becomes 0 minutes) will be excluded from the tabulation.
- Time from last treatment to latest onset of symptom relief or symptom resolution: All attacks and attacks for which the last dose prior to symptom relief or symptom resolution is this drug will be summarized. Tabulation by level shall be performed at intervals of less than 30 minutes, 30 minutes to less than 1 hour, less than 1~2 hours, less than 2~4 hours, 4~8 hours, less than 8~12 hours, 12 hours to less than 24:00, and 24 hours or more. For the tabulation of elapsed time, data with unknown time (data for which the calculated elapsed time becomes 0 minutes) will be excluded from the tabulation.
- Number of treatments per attack: The number of all treatments, the number of treatments with this drug in combination with other drugs, and the number of treatments with this drug only will be tabulated. Tabulation by

level will be performed once, twice, three times, four times, and every five times or more.

- Location of attacks: larynx, skin, abdomen, other The number and proportion of attacks will be tabulated.
- Severity of attacks: The number and proportion of mild, moderate, severe, and very severe attacks will be tabulated.
- Treatment status: The number and proportion of outpatient, inpatient, and self-administration will be tabulated.

Form No. in the corresponding analysis figure/output plan: T03_01_02_01, T03_01_03_01

3.6.2 Treatment status of acute attacks during the observation period by severity and treatment status

- Population: efficacy analysis population

The time from the last this drug treatment to symptom relief or resolution, whichever is later, will be summarized by attack severity (Mild, moderate, severe, very severe) and by treatment status (Outpatient, inpatient, self-administration). The tabulation method shall be the same as in 3.6.2.

Form No. in the corresponding analysis figure/output plan: T03_01_02_02, T03_01_03_02

3.6.3 By disease type, status of acute attacks, and treatment status of acute attacks

- Subjects: Efficacy population

Treatment status for acute attacks and treatment status for acute attacks will be tabulated by disease type (Type I or Type II/Type III). The tabulation method shall be the same as in 3.6.1 and 3.6.2.

Form No.: T03_01_02_01_02, T03_01_02_01_03, T03_01_02_02_02, T03_01_02_02, T03_01_02_02_03, T03_01_03_03_01_02, T03_01_03_03_01_01_03, T03_01_03_02_02, T03_01_03_03_02_03

3.7 List of patients

3.7.1 List of background factors

- Subjects: Subjects with locked CRFs

Form No.: L06_01 in the corresponding analysis figure/output plan

3.7.2 Adverse Event Listing

- Subjects: Safety analysis set

Form No.: L06_02 in the corresponding analysis figure/output plan

3.7.3 Listing of fatal outcomes

- Subjects: Safety analysis set

Form No.: T04_04_01 in the corresponding analysis figure/output plan

3.7.4 Case summaries from post-marketing surveillance, etc. (Attached Form 16)

- Subjects: Subjects with locked CRFs

A list of subjects will be output in accordance with the “Guidance for Application for Reexamination (10 version, 2021).”

Form No.: T05_04 in the corresponding analysis figure/output plan

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