Clinical Study Protocol

NCT Number: NCT04057131

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

Study Number: SHP667-401

Document Version and Date: Version 9.0 / 21-Sep-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.

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

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

For re-examination

FIRAZYR ® Subcutaneous Injection 30 mg Syringe

General use-results survey

Protocol

Date of preparation: September 21, 2023 (Ver. 9.0)

Takeda Pharmaceutical Company Limited.

1. Objectives of the survey

The main objectives of this survey are to investigate the following items in patients with hereditary angioedema (Hereditary angioedema: Hereditary angioedema) who used 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

2. Safety and efficacy specifications

(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

3. Survey implementation plan

(1) Number of patients to be surveyed and its rationale

Estimated number of patients to be surveyed: 75

Rationale for setting: There are 400 HAE patients in Japan, and approximately 2/3 of them are assumed 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) Scope of patients to be surveyed

To include HAE patients who are treated with this drug for the first time.

The indication and dosage and administration of this drug are as follows.

- Indication: Acute attack of hereditary angioedema
- Dosage and administration: The usual adult dosage is 30 mg of icatibant administered subcutaneously. Additional doses of 30 mg may be administered at intervals of at least 6

hours if response is inadequate or if symptoms recur. No more than 3 doses may be administered within any 24 hours period.

(3) Planned number of sites by clinical department to be surveyed

Targeting all medical institutions to which this drug has been delivered: Approximately 20 institutions

(4) Survey method

This surveillance will be conducted using an all-case surveillance system. Electrical Data Capture (EDC) is used as a rule and data is collected based on the following procedures. If the EDC is not acceptable at each site, an alternative method to the EDC will be used to conduct the same investigation.

1) Survey request/contract

At the time of requesting this survey, medical representatives, etc. shall request the survey at all the following institutions.

- Sites with physicians experienced in the treatment of HAE
- Sites planning to administer this drug to patients to be surveyed

If the conduct of this survey is approved, a contract will be concluded in writing with the medical institution.

2) Patient Enrollment

Patients will be enrolled via a central registration system. Physicians in charge of surveillance will register all patients who are prescribed this drug for the first time after approval in principle. The investigator will enter the following information necessary for registration in the case registration form and send it.

- Patient identification number
- Sex
- Date of birth or age
- Date this drug started or dispensed

3) Collection of survey forms and observation period

- Patients will be observed for up to 3 months after this drug administration.
  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).

Adverse events occurring after the end of the observation period will be separately reported as spontaneous reports.

- The efficacy and safety variables to be collected in the survey were those that are periodically observed in HAE patients in clinical practice.
- Since the number of registered cases has reached the planned number, a request will be made to prepare and submit CRFs for cases prescribed by June 30, 2020, and Patient registration requiring no preparation and submission of CRFs will be implemented for cases whose prescriptions have started on or after July 1, 2020, until the date of issuance of the partial revision of the "Q & A on use-results surveys by the all-case surveillance method for ethical drugs " (Administrative Notice dated August 10, 2023).

  Until the approval conditions for all-case surveillance are lifted, the system in which survey forms can be collected as necessary to obtain appropriate information will be maintained.

4) Confirmation of All-case Registration

After shifting to the patient registration only period, we will confirm with the All-Case Registration Confirmation Form that all patients for whom this drug was prescribed and who require preparation and submission of CRF are registered.

(5) Survey period

The investigation period is as follows.

- Survey period: November 2018 to April 30, 2023
- Registration period: November 2018 to August 10, 2023
- Date of completion of investigation (date of completion of final analysis): January 2024 (planned)

*The survey and registration periods for patients whose prescriptions had been started by June 30, 2020, for whom preparation and submission of survey forms are required, are until April 30, 2023. Thereafter, only registration will be performed until August 10, 2023.

(6) Items to be surveyed

1) Patient characteristics: Patient identification number, sex, date of birth or age, and race
2) Physical examination: weight, height
3) HAE diagnosis: Year of onset of first symptom, year of HAE diagnosis, HAE type (Type I, II

or III), genetic mutation, other angioedema diagnosis, family history

4) Concomitant medications and therapies
5) Past history and complications
6) History of HAE attacks in the last 12 months before treatment with this drug: number of attacks, location, treatment history
7) HAE attack status during the observation period: number of attacks, site of onset, severity of attacks, triggers of attack, prodromal symptoms, number of visits, details of treatment, etc.
8) Administration status of this drug: this drug Method of administration (self-administration or administration by healthcare professionals), dose and frequency of administration, presence or absence of other treatments, time from onset of attack to start of treatment, time to initial symptom relief, time to symptom resolution
9) Discontinued: Timing of and reason for discontinuation
10) Laboratory tests: Clinically significant abnormal changes in routine laboratory parameters arbitrarily measured at a medical institution before the start of prescription of this drug or during the observation period, if any, will be collected as adverse events along with the time course.
11) Pregnancy and lactation status
12) Adverse events: name of adverse event, date and time of onset, seriousness (classification of serious), severity, presence or absence of treatment, details of treatment, outcome, date and time of outcome, procedure, date and cause of death, presence or absence of autopsy (if applicable), causal relationship with this drug

(7) Items to be analyzed and methods

1) Analysis Items

a. Patient Population

Number of patients enrolled, number of patients from whom survey forms were collected, number of patients receiving this drug (safety analysis set), number of patients analyzed for efficacy, number of discontinued patients, details of reason for discontinuation, etc.

b. Matters concerning safety

- Adverse events/adverse drug reactions

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and the incidence and number of ADRs will be tabulated by preferred term (PT) and system organ class (SOC), by treatment for angioedema, and other stratification as needed. Serious adverse events will be tabulated in the same manner. In addition, serious hypersensitivity and severe injection site reactions during or after this drug administration,

worsening of cardiac function under ischemic conditions due to bradykinin antagonism, decreases in blood pressure, and the development of symptoms suggestive of immunogenicity will be summarized.

c. Items Related to Efficacy

To evaluate the efficacy of this drug in patients with HAE attacks.

- Time from onset of attack to start of treatment: Time from onset of attack to first dose
- Time to initial symptom relief
- Time to symptom resolution: time from first dose to complete resolution of all symptoms
- Duration of attack: time from the start of attack to resolution of all symptoms

2) Analysis Methods

Mainly, frequencies will be tabulated for categorized data such as mean and standard deviation of quantitative data and descriptive summaries. Additional details will be provided in the SAP.

(8) Organizational structure for implementation of the survey

See Attachment

(9) If part of the operations related to the study is outsourced, the name and address of the contractor of the operations and the scope of the outsourced operations

- Entrustee of the operations [1]

[redacted]

Scope of operations

Data management, statistical analysis, medical writing

- Contractor of the operations [2]

[redacted]

Scope of operations

Receipt of paper-based CRFs, etc. sent from sites, confirmation of the presence or absence of descriptions of adverse events, transfer of original CRFs, etc. to Contractor 1, storage of site contracts, etc.

- Contractor of the operations (3)

[redacted]

Scope of operations

Operations related to monitoring

4. ADDITIONAL MEASURES THAT MAY BE IMPLEMENTED BASED ON THE SURVEY RESULTS AND CRITERIA FOR DETERMINING THE INITIATION

The Risk Management Plan including the following contents will be reviewed at milestones.

- Review the necessity for changes in risk minimization activities for the current safety specifications.
- Review the necessity for changing the contents of the plan of the post-marketing surveillance (continuation of the surveillance, implementation of additional surveillance, etc.), including the presence or absence of new safety specifications.
- Review the necessity of formulating risk minimization measures for new safety specifications.

5. Scheduled timing of milestones for evaluation of the implementation status of the survey and obtained results, or reporting to the PMDA, and their rationales

- At the time of preparation of periodic safety reports and at the time of application for reexamination: To comprehensively examine safety information.
- At the time of preparation of the final report: To evaluate the safety including the comparison with the results of clinical studies and to examine the necessity of changing the plan such as adding the number of subjects to be investigated.

6. Other necessary matters

(1) Revision of the protocol

The necessity of revision will be examined based on new findings obtained as the survey progresses, and the protocol will be revised as necessary.

(2) Actions to be taken if any problem or question is observed

In cases where the onset of a serious and unknown adverse reaction is suggested, a significant increase in the frequency of adverse reactions is found, any problem is found in the efficacy and

safety compared to those until the time of approval, or the onset of a specific adverse reaction is suggested, etc., a hypothesis should be developed and implementation of a special drug use investigation to verify the hypothesis should be considered.

< Attachment >

1) Implementation guidelines
2) Registration form
3) Survey form

Document History

Version	Date	Comments
original version	2018/8/10	New document
2nd version	2018/10/23	2. Safety and efficacy specifications and 3. Survey implementation plan
3rd version	2019/3/27	3. Survey implementation plan
4th version	2020/10/1	3. Survey implementation plan
5th version	2020/11/1	3. Survey implementation plan
6th version	2021/1/15	3. Survey implementation plan
7th version	2021/11/8	3. Survey implementation plan
8th version	2022/5/12	3. Survey implementation plan
9th version	2023/9/21	3. Survey implementation plan