Title: A Multicenter, Open-Label, Non-randomized Phase 3 Study to Assess the Safety, Efficacy and Pharmacokinetics of Subcutaneous Administration of Icatibant (TAK-667) in Japanese Children and Adolescents with Acute Attacks of Hereditary Angioedema

NCT Number: NCT04654351

Statistical analysis plan Approve Date: 03-SEP-2021

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This may include, but is not limited to, redaction of the following:

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If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

STATISTICAL ANALYSIS PLAN

Study Number: TAK-667-3001

Study Title: A Multicenter, Open-Label, Non-randomized Phase 3 Study to Assess the Safety, Efficacy and Pharmacokinetics of Subcutaneous Administration of Icatibant (TAK-667) in Japanese Children and Adolescents with Acute Attacks of Hereditary Angioedema

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Based on:

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[Original version]	15-Jan-2021	[Not Applicable]
[Amendment 1]	03-Sep-2021	To add listings for off-study HAE attacks in section 6.5.1.6.

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ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
BMI	body mass index
BUN	Blood urea nitrogen
COVID-19	coronavirus disease 2019
CO2	Carbon dioxide
C1-INH	C1 esterase inhibitor
ECG	electrocardiogram
FAS	full analysis set
FLACC	Faces, Legs, Activity, Cry, and Consolability
FPS-R	Faces Pain Scale-Revised
FSH	follicle stimulating hormone
GCP	good clinical practice
GGT	Gamma-Glutamyl transferase
HAE	hereditary angioedema
LDH	Lactate dehydrogenase
LH	luteinizing hormone
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetic
PT	Preferred Term (MedDRA)
PTE	pretreatment event
RBC	Red blood cells
SAE	serious adverse event
SAP	statistical analysis plan
SC	Subcutaneous
SD	Stable Disease
SOC	System Organ Class
TEAE	treatment-emergent adverse event]
WBC	White blood cells
WHO	World Health Organization

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

To evaluate the safety, efficacy and PK of Icatibant for the treatment of acute attacks in Japanese children and adolescents with type I or type II HAE.

1.2 Endpoints

1.2.1 Primary Endpoint(s)

Safety:

- *Frequency and severity of treatment-emergent adverse events (TEAEs), including injection site reactions*

1.2.2 Secondary Endpoint(s)

Safety:

- *Resting 12-lead electrocardiogram parameters in comparison to baseline*
- *Vital sign measurements in comparison to baseline*
- *Clinical laboratory parameters (serum chemistry, hematology and urinalysis) in comparison to baseline*
- *Reproductive hormone levels in comparison to baseline*
- *Immunogenicity (presence of anti-Icatibant antibodies) in comparison to baseline*

Efficacy:

- *Time to onset of symptom relief and time to minimal symptom, as measured by investigator- and subject-reported outcomes.*
  - *For all subjects (2 to <18 years of age): investigator assessment and scoring of cutaneous, abdominal, and laryngeal symptoms of acute HAE attacks by an investigator-rated symptom score.*
    - *The time to onset of symptom relief, defined as the duration of time in hours from the time of Icatibant administration to the earliest time at which at least a 20% improvement is observed in the average post-treatment score with no worsening of any single component score.*
    - *The time to minimal symptoms, defined as the duration of time in hours from the time of Icatibant administration to the earliest time post-treatment when all symptoms are either mild or absent based on the investigator-rated symptom score.*
  - *For subjects ≥4 to <18 years of age only: subject self-assessment of HAE-related pain using the Faces Pain Scale-Revised (FPS-R).*

- ✧ *The time to onset of symptom relief, defined as the duration of time in hours from the time of Icatibant administration to the earliest time at which the post-treatment score improved by at least 1 level.*
- ✧ *The time to minimal symptoms, defined as the duration of time in hours from the time of Icatibant administration to the earliest time at which the post-treatment score improved to 0.*

➢ *For subjects 2 to <4 years of age only: investigator assessment of HAE-related pain using the Faces, Legs, Activity, Cry, and Consolability (FLACC) scale.*

- ✧ *The time to onset of symptom relief, defined as the earliest time at which a 20% improvement is observed in the total post-treatment score.*
- ✧ *The time to minimal symptoms, defined as the duration of time in hours from the time of Icatibant administration to the earliest time at which the total post-treatment score improved to 0.*

- *The incidence of rescue medication use.*
- *The proportion of subjects with worsened intensity of clinical HAE symptoms between 2 and 4 hours after treatment with SC Icatibant using investigator-rated symptom scores.*
- *Time to initial symptom improvement reported by investigator or subject*
  - ✧ *Time to initial symptom improvement reported by investigator, defined as the duration of time in hours from Icatibant administration until the time when overall subject improvement was first noted by investigator.*
  - ✧ *Time to initial symptom improvement reported by subject, defined as the duration of time in hours from Icatibant administration until the time when overall subject improvement was first noted by subject, subject's parent or subject's legal guardian.*

Pharmacokinetics:

Plasma concentrations of Icatibant and its major metabolites (M-I and M-II) at 0.5, 1.0, 2.0, and 4.0 hours after the first SC injection for an initial attack.

1.3 Estimand(s)

Not applicable.

2.0 STUDY DESIGN

This is a multicenter, open-label, phase 3 study to evaluate the safety, efficacy and PK of SC administration of Icatibant in Japanese children and adolescents from 2 to less than 18 years of age with acute attacks of HAE.

Once informed consent is obtained and subject eligibility is established at screening, subjects will begin to receive treatment with Icatibant after they present with an acute attack of

cutaneous, abdominal, or laryngeal edema. The region and severity of the attack is assessed by investigators.

Subjects eligible at pre-treatment physical examination and assessment will receive treatment with single-dose SC administration of Icatibant per attack according to the subject's body weight within 12 hours after the onset of symptom. Up to 2 additional injections are permitted per attack with a time interval of at least 6 hours within 48 hours of the initial injection if there is insufficient relief or worsening of symptoms. If symptoms get worse or recur after more than 48 hours of the initial administration, it will be considered as a new attack. Icatibant will be administered by a healthcare professional, or be self-administered by the subject or the subject's caregiver, e.g. the subject's family, at the study site under the supervision of a healthcare professional. In the case that Icatibant is administered by whom other than healthcare professionals, if the subject and his/her legal guardian agree and the investigator considers it appropriate after the subject receive education and training, the subject or his/her caregiver, e.g. the subject's family, will be allowed to self-administer Icatibant under the supervision of a healthcare professional.

Subjects will be closely monitored in the hospital/study center for at least 8 hours after administration and receive physical examination and assessment to evaluate safety, efficacy and PK. Hospitalization may be prolonged until, in the opinion of the investigator, the subject is clinically stable and onset of HAE attack is completely resolved.

After discharge, follow-up to assess the subject's condition at >24-48 hours after final administration (Day 2) will be conducted via a telephone call by investigators and follow-up of safety assessment will be conducted 7 days after initial administration of Icatibant (Day 8) at the study site.

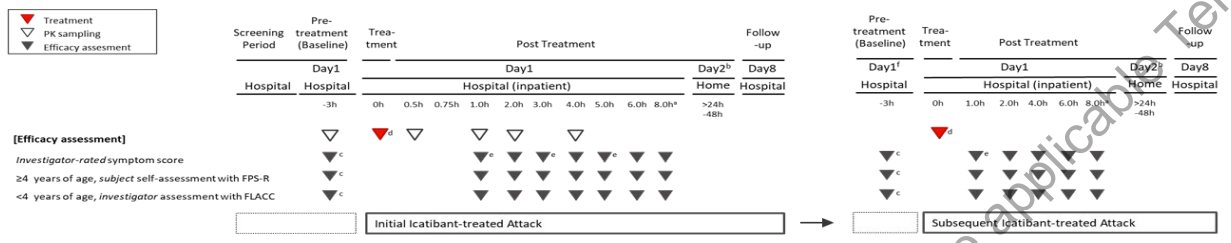
After having received initial treatment with Icatibant, subjects who subsequently experience an acute attack may continue to receive treatment with Icatibant for a total of 3 eligible Icatibant-treated attacks if the subject and the subject's parent or the subject's legal guardian consent to further treatment. Further treatment with Icatibant is contingent upon presentation of an acute cutaneous, abdominal, or laryngeal edema attack of HAE at least 7 days after first treatment for a prior attack. The new attack of within less than 7 days after first treatment for a prior attack should be treated in accordance with standard of care for HAE without being administrated Icatibant. Except for PK assessment, all outcomes are to be measured after each attack as with the initial attack.

The period of active participation in the study may depend on the number of subsequent treatment and could be a maximum of approximately 25 days.

Sites will employ all efforts to see subjects in the hospital/study center for assessments. In unavoidable circumstances (eg, a widespread disease outbreak such as the coronavirus disease 2019 (COVID-19) pandemic or natural disaster), exceptions may be consulted for alternative visits or assessments for conducting subject visits with approval by the Medical Monitor and/or sponsor. Such instances will be documented in the study records as related to COVID-19.

A schematic of the study design is included as Figure 1. A schedule of assessments is listed in Appendix A in the protocol.

Figure 1 Schematic of Study Design



a) *Hospitalization may be prolonged until the investigator determines that the clinical condition is stable and the subject's HAE symptoms is resolved. In this case, as a general rule, the efficacy evaluation (investigator-rated symptom score, FPS-R, FLACC scale) and injection site reaction evaluation are performed every 2 hours including 8 hours after administration, until discharge. Initial symptom improvement (investigator and subject), adverse events, and concomitant medications will be continuously evaluated until discharge. Physical examination, vital signs, ECG, clinical laboratory tests and reproductive hormone assessments are performed only at discharge.*
b) *A contact via telephone is scheduled at >24-48 hours after final administration. If hospitalization continues 48 hours after the last dose, assessments are performed at the hospital.*
c) *Investigator-rated symptom score, FPS-R, FLACC scale will be performed within 1 hour prior to treatment. Other assessments are performed within the acceptable range up to 3 hours before administration.*
d) *Administration of Icatibant will consist of 1 SC injection of Icatibant. However, a maximum of 3 SC injections of Icatibant with at least 6 hours intervals can be given for treatment of an attack if, within 48 hours of the initial injection, there is insufficient relief or worsening of symptoms.*
e) *The vomiting and diarrhea assessments will be performed every 2 hours and, therefore, are excluded from the investigator-rated symptom score at the time points indicated.*
f) *In the event that a subsequent attack occurs at least 7 days after first treatment for a prior attack, but within the window (+1 day) allowed for performance of follow-up (Day 8) assessments associated with a prior attack, the follow-up (Day 8) assessments may also serve as the pretreatment (baseline) assessments for the subsequent attack.*

3.0 THESES AND DECISION RULES

Not applicable.

3.1 Multiplicity Adjustment

Not applicable.

4.0 SAMPLE-SIZE DETERMINATION

*Total of at least 3 subjects**

** The enrollment will be continued until the end of the enrollment period and the sample size may exceed 3 subjects.*

[Justification for Determination of Sample Size]

The planned sample size chosen of 3 subjects administered Icatibant in this study is based on the feasibility and is not statistically determined.

Although there have been no accurate reports regarding the number of pediatric HAE patients in Japan, it is estimated approximately 30 to 50 patients based on the population estimate and the percentage of children among Japanese HAE patients confirmed in the latest Japanese HAE survey. However, comprehensivefeasibility assessment for medical institutions across Japan found much less candidate subjects and only few clinical sites possible to conduct the study due to some hurdles in implementation. In addition, considering a difficulty to obtain informed consent in a pediatric study, the number of patients to be enrolled was assumed to be 3.

5.0 ANALYSIS SETS

5.1 Safety Analysis Set

The safety analysis set will be defined as all subjects who received at least 1 dose of study drug.

5.2 Full Analysis Set

The full analysis set will be defined as all subjects who received at least 1 dose of study drug. The definition of full analysis set is the same as the safety analysis set in this study.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

In case of 2 subjects who received at least 1 dose of study drug, no tables and figures will be produced except for 6.5.1.2 (2), 6.6.1.1, 6.6.1.2 (1), and 6.6.2.1. In case of only one subject who received at least 1 dose of study drug, no tables and figures will be produced.

6.1.1 Analysis Approach for Continuous Variables

Continuous variables will be summarized using the descriptive statistics (n, mean, standard deviation [SD], minimum, median, and maximum) unless stated otherwise in the section specific to an endpoint.

6.1.2 Analysis Approach for Binary Variables

Binary and categorical variables will be summarized using the number and percentage of subjects unless stated otherwise in the section specific to an endpoint

6.2 Disposition of Subjects

6.2.1 Study Information

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variables:

Date of First Subject Signed Informed Consent Form

Date of Last Subject's Last Visit/Contact

MedDRA Version

WHO Drug Version

SAS Version Used for Creating the Datasets

Analytical Methods:

(1) Study Information

Study information shown in the analysis variables section will be provided.

6.2.2 Screen Failures

Analysis Set:

All Subjects Who Did Not Enter the Treatment Period

Analysis Variables:

Age (years)[<6 years, 6-11 years, >11 years]

Gender [Male, Female]

Analytical Methods:

(1) Screen Failures

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

6.2.3 Subject Eligibility

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variables:

Eligibility Status [Eligible for Entrance into the Treatment Period, Not Eligible for Entrance into the Treatment Period]

Primary Reason for Subject Not Being Eligible [Death, Adverse Event, Screen Failure, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Withdrawal by Parent or Guardian, Study Terminated by Sponsor, Pregnancy, The study is closed prior to the subject's eligible attack, Other]

Analytical Methods:

(1) Eligibility for Entrance into the Treatment Period

Frequency distributions will be provided. When calculating percentages for the primary reasons for subject not being eligible, the total number of ineligible subjects will be used as the denominator.

6.2.4 Number of Subjects Who Entered the Treatment Period by Site

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variables:

Status of Entrance into the Treatment Period [Entered]

Category:

Site [Site numbers will be used as categories]

Analytical Methods:

(1) Number of Subjects Who Entered the Treatment Period by Site

Frequency distribution will be provided by site.

6.2.5 Disposition of Subjects

Analysis Set:

All Subjects Who administered the Study Drug

Analysis Variables:

Study Status [Completed, Discontinued]

Reason for Discontinuation of Study [Death, Adverse Event, Significant Protocol Deviation, Lost to Follow-up, Voluntary Withdrawal by the Subject, Voluntary

Withdrawal by Subject's Parent/Subject's Legal Guardian, Study Termination, Pregnancy, Lack of Efficacy, Other]

Analytical Methods:

(1) Disposition of Subjects

Frequency distributions will be provided. When calculating percentages for the reasons for not being treated, the total number of subjects not treated by the study drug will be used as the denominator. When calculating percentages for the reasons for discontinuation, the total number of subjects who prematurely discontinued will be used as the denominator.

6.2.6 Protocol Deviations and Analysis Sets

6.2.6.1 Protocol Deviations

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variables:

Significant Protocol Deviation [Entry Criteria, Concomitant Medication, Procedure Not Performed Per Protocol, Study Medication, Withdrawal Criteria, Major GCP Violations]

Analytical Methods:

(1) Protocol Deviations

Frequency distribution will be provided for each deviation category. A subject who has several deviations will be counted once in each appropriate category. A subject who has several deviations that can be classified into the same category will be counted only once.

6.2.6.2 Analysis Sets

Analysis Set:

All Subjects Who Administered the Study Drug

Analysis Variables:

Handling of Subjects	[Subject Evaluability List]	
Analysis Sets	Full Analysis Set	[Included]
	Safety Analysis Set	[Included]

Analytical Methods:

(1) Subjects Excluded from Analysis Sets

(2) Analysis Sets

Frequency distributions will be provided. For (1), a subject who has several reasons for exclusion will be counted once in each appropriate category. A subject who has several reasons for exclusion that can be classified into the same category will be counted only once.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics and Other Baseline Characteristics

Analysis Set:

Safety Analysis Set

Analysis Variables:

Age at Informed Consent (years) [<6 years, 6-11 years, >11 years]

Age at First Treatment (years) [<6 years, 6-11 years, >11 years]

Gender [Male, Female]

Height at First Treatment (cm)

Height Percentile at First Treatment

Weight at First Treatment (kg)

Weight Percentile at First Treatment

BMI at First Treatment (kg/m2)

BMI Percentile at First Treatment

Pubertal Status [Prepubertal, Pubertal/Postpubertal]

Prior Icatibant Treatment [Yes, No]

Time Since Diagnosis at First Treatment (years)

Time Since First Symptom at First Treatment (years)

Type of HAE [I, II, Unclassified]

Amount of C1-INH protein (mg/dL)

Activity of C1-INH (%)

Genetic Mutation [Yes, No]

Family history of HAE [Yes, No, No Answer]

Number of Attacks During Last 12 Months

Number of Attacks with Any Medical Intervention During Last 12 Months

Number of Attacks with Icatibant Treatment During Last 12 Months

Number of Abdominal Attacks During Last 12 Months

Number of Cutaneous Attacks During Last 12 Months

Number of Cutaneous and Abdominal Attacks During Last 12 Months

Number of Laryngeal Attacks During Last 12 Months

Time Since Last Attack at First Treatment (months)

Type of Last Attack [Cutaneous, Abdominal, Cutaneous and Abdominal, Laryngeal]

Existence of Trigger of Last Attack [Yes, No]

Prodromal Symptoms of Last Attack [Yes, No]

Severity of Last Attack [Mild, Moderate, Severe, Very Severe]

Time to Onset of Relief from Last Attack (hours)

Time to Complete Relief from Last Attack (hours)

Medical Intervention [Yes, No]

HAE Medication [Yes]

Intubation [Yes]

Other [Yes]

Analytical Methods:

(1) Summary of Demographics

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

For weight percentile and height percentile, a category which apply to the sex and age (year and month) of a subject will be identified based on the attached table 2 in the Japanese Society for Pediatric Endocrinology[1], such as "3 -< 10 percentile".

Below variables will be derived and listed.

Average Time from HAE Onset to Relief for Cutaneous Attacks (hours)

Average Time from HAE Onset to Relief for Abdominal Attacks (hours)

[1] http://jspe.umin.jp/medical/taikaku.html

Average Time from HAE Onset to Relief for Cutaneous and Abdominal Attacks (hours)

Average Time from HAE Onset to Relief for Laryngeal Attacks (hours)

Most Frequent Severity for Previous Cutaneous Attacks [Mild, Moderate, Severe, Very Severe]

Most Frequent Severity for Previous Abdominal Attacks [Mild, Moderate, Severe, Very Severe]

Most Frequent Severity for Previous Cutaneous and Abdominal Attacks [Mild, Moderate, Severe, Very Severe]

Most Frequent Severity for Previous Laryngeal Attacks [Mild, Moderate, Severe, Very Severe]

6.3.2 Medical History and Concurrent Medical Conditions

Analysis Set:

Safety Analysis Set

Analysis Variables:

Medical History

Concurrent Medical Conditions

Analytical Methods:

Medical History and Concurrent Medical Conditions coded by MedDRA dictionary will be listed.

6.4 Medication History and Concomitant Medications

6.4.1 Prior Medications

Analysis Set:

Safety Analysis Set

Analysis Variables:

Prior HAE Medications

Analytical Methods:

(1) Prior HAE Medications by Preferred Medication Name

Frequency distributions will be provided. WHO Drug dictionary will be used for coding. Summaries will be provided using preferred medication name and sorted in decreasing frequency based on the number of reports. A subject who has been

administered several medications with the same preferred medication name will be counted only once for that preferred medication name.

6.4.2 Concomitant Medications

Analysis Set:

Safety Analysis Set

Analysis Variables:

Concomitant HAE Medications

Rescue Medications

Analytical Methods:

(1) Concomitant HAE Medications by Preferred Medication Name

(2) Rescue Medications by Preferred Medication Name

Frequency distributions will be provided. WHO Drug dictionary will be used for coding. Summaries will be provided using preferred medication names and sorted in decreasing frequency based on the number of reports. A subject who has been administered several medications with the same preferred medication name will be counted only once for that preferred medication name.

6.5 Efficacy Analysis

Due to the small sample size, no statistical inferences (statistical test nor confidence interval) will be performed.

6.5.1 Secondary Endpoint(s) Analysis

6.5.1.1 Derivation of Endpoint(s)

The definitions of the events of time-to-event endpoints are referred to 1.2.2. The definitions of the censors are the duration of time in hours from the time of Icatibant administration to the latest observed time in the score or the record in subjects without events.

Composite investigator-assessed symptom score is calculated by taking an average of 8 (abdominal or cutaneous attack) or 13 (laryngeal attack) individual symptom scores (0=None, 1=Mild, 2=Moderate, 3=Severe, 4=Very Severe), excluding missing scores. Assessments on vomiting and diarrhea symptom severity follow a less frequent schedule than the other symptoms. On time points that these two symptom scores were not assessed, the composite symptom scores will be calculated by taking the average of the other symptom scores.

The subjects with worsened intensity of clinical HAE symptoms between 2 and 4 hours after treatment with SC Icatibant using investigator-rated symptom scores is defined as subjects

who one or more symptom score(s) in 4 hours after treatment worsen from 2 hours after treatment.

FLACC total score is calculated by sum of all FLACC scores.

6.5.1.2 Main Analytical Approach for Time-to-Event Variables

Analysis Set:

Full Analysis Set

Analysis Variables:

Time to onset of symptom relief by an investigator-rated symptom score

Time to minimal symptoms by an investigator-rated symptom score

Time to onset of symptom relief by FPS-R for subjects ≥4 to <18 years of age only

Time to minimal symptoms by FPS-R for subjects ≥4 to <18 years of age only

Time to onset of symptom relief by FLACC scale for subjects 2 to <4 years of age only

Time to minimal symptoms by FLACC scale for subjects 2 to <4 years of age only

Time to initial symptom improvement reported by investigator

Time to initial symptom improvement reported by subject

Analytical Methods:

(1) The survival function (e.g. proportion of subjects not achieving symptom relief) for each assessment time will be calculate by Kaplan-Meier method using the first Icatibant-treated attacks within each subject. In case of 2 or less subjects in an analysis variable, no tables and figures will be produced for the analysis variable.

(2) Assuming independency in recurrent events within a subject, the survival function for each assessment time will be also calculated by Kaplan-Meier method using all Icatibant-treated attacks. In case of 2 or less events of Icatibant-treated attacks in an analysis variable, no tables and figures will be produced for the analysis variable.

Analysis variables in the second and third Icatibant-treated attacks will be listed.

6.5.1.3 Main Analytical Approach for Other Variables

Analysis Set:

Full Analysis Set

Analysis Variables:

The incidence of rescue medication use

The proportion of subjects with worsened intensity of clinical HAE symptoms between 2 and 4 hours after treatment with SC Icatibant using investigator-rated symptom scores

Categories:

Icatibant Exposure [#1, #2, #3]

Analytical Methods:

(1) The incidence of rescue medication use

Refer to 6.4.2 (2).

(2) The proportion of subjects with worsened intensity of clinical HAE symptoms between 2 and 4 hours after treatment with SC Icatibant using investigator-rated symptom scores by Icatibant exposure.

Frequency distributions will be provided by Icatibant exposure

6.5.1.4 Supplementary Analyses 1

Analysis Set:

Full Analysis Set

Analysis Variables:

Composite investigator-assessed symptom score

FPS-R

FLACC total score

Categories:

Icatibant Exposure [#1, #2, #3]

Visit:

Pretreatment (0 Hour), 1, 2, 3, 4, 6, 8 Hour Post-treatment in Icatibant exposure #1

Pretreatment (0 Hour), 1, 2, 4, 6, 8 Hour Post-treatment in Icatibant exposure #2 and #3

Analytical Methods:

(1) Composite investigator-assessed symptom score by visit in each Icatibant Exposure

Descriptive statistics for composite investigator-assessed symptom score and changes from pretreatment will be provided by visit in each Icatibant exposure. The changes from pretreatment will be calculated in each Icatibant exposure.

Plots of composite investigator-assessed symptom score and subscores over time in each Icatibant exposure for each subject will be presented.

(2) FPS-R by visit in each Icatibant Exposure

Descriptive statistics for FPS-R and changes from pretreatment will be provided by visit in each Icatibant exposure. The changes from pretreatment will be calculated in each Icatibant exposure.

Plots of FPS-R over time in each Icatibant exposure for each subject will be presented.

(3) FLACC total score by visit in each Icatibant Exposure

Descriptive statistics for FLACC total score and changes from pretreatment will be provided by visit in each Icatibant exposure. The changes from pretreatment will be calculated in each Icatibant exposure.

Plots of FLACC total score over time in each Icatibant exposure for each subject will be presented.

6.5.1.5 Supplementary Analyses 2

Analysis Set:

Full Analysis Set

Analysis Variables:

Type of On-study HAE Attack [Cutaneous, Abdominal, Cutaneous and Abdominal, Laryngeal]

Time from On-study HAE Attack to Study Drug Administration (hours)

Categories:

Icatibant Exposure [#1, #2, #3]

Analytical Methods:

(1) Type of On-study HAE Attack by Icatibant Exposure

Frequency distributions will be provided by Icatibant exposure.

(2) Time from On-study HAE Attack to Study Drug Administration (hours) by Icatibant Exposure

Descriptive statistics will be provided by Icatibant exposure.

6.5.1.6 Supplementary Analyses 3

Analysis Set:

Full Analysis Set

Analysis Variables:

Time to onset of relief from HAE medication in off-study HAE attack

Time to complete relief from HAE medication in off-study HAE attack

Analytical Methods:

Time to onset of relief and complete relief from HAE medication in off-study HAE attack will be listed.

6.6 Safety Analysis

6.6.1 Adverse Events

6.6.1.1 Overview of Treatment-Emergent Adverse Events

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE

Categories:

Relationship to Study Drug [Related, Not Related]

Intensity [Mild, Moderate, Severe]

Analytical Methods:

TEAE is defined as an AE that occurs on or after administration of Icatibant for each attack and until the end of follow-up period (Day 8).

The following summaries will be provided.

Overview of Treatment-Emergent Adverse Events

1) All Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
2) Relationship of Treatment-Emergent Adverse Events to study drug (number of events, number and percentage of subjects)
3) Intensity of Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
4) Treatment-Emergent Adverse Events leading to study drug discontinuation (number of events, number and percentage of subjects)
5) Serious Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
6) Relationship of Serious Treatment-Emergent Adverse Events to study drug (number of events, number and percentage of subjects)

7) Serious Treatment-Emergent Adverse Events leading to study drug discontinuation (number of events, number and percentage of subjects)
8) Treatment-Emergent Adverse Events resulting in death (number of events, number and percentage of subjects)
9) Injection Site Reaction Meeting SAE Criteria

TEAEs will be counted according to the rules below.

Number of subjects

- Summaries for 2) and 6)

  A subject with occurrences of TEAE in both categories (i.e., Related and Not Related) will be counted once in the Related category.

- Summary for 3)

  A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum toxicity grade.

- Summaries other than 2) , 3) , and 6)

  A subject with multiple occurrences of TEAE will be counted only once.

Number of events

For each summary, the total number of events will be calculated.

6.6.1.2 Displays of Treatment-Emergent Adverse events

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE

Categories:

Intensity	[Mild, Moderate, Severe]
Icatibant Exposure	[#1, #2, #3]

Analytical Methods:

The following summaries will be provided using frequency distribution.

TEAEs will be coded using the MedDRA and will be summarized using SOC and PT.

SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by System Organ Class only or PT only.

(1) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(2) Treatment-Emergent Adverse Events by System Organ Class

(3) Treatment-Emergent Adverse Events by Preferred Term

(4) Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(5) Intensity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(6) Intensity of Drug-Related Treatment-Emergent Adverse Events by System Organ Class, and Preferred Term

(7) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term

(8) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(9) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Icatibant Exposure

The frequency distribution will be provided according to the rules below.

Number of subjects

- Summary tables other than (5) and (6)

  A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT. Percentages will be based on the number of subjects in the safety analysis set.

- Summary tables for (5), (6) and (9)

  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum intensity. Percentages will be based on the number of subjects in the safety analysis set.

- Summary table for (9)

  TEAEs in Icatibant Exposure #1 are defined as TEAEs occurred on or after administration of the first Icatibant (until administration of the second Icatibant if the subject received the second Icatibant treatment).

  TEAEs in Icatibant Exposure #2 are defined as TEAEs occurred on or after administration of the second Icatibant (until administration of the third Icatibant if the subject received the third Icatibant treatment).

  TEAEs in Icatibant Exposure #3 are defined as TEAEs occurred on or after administration of the third Icatibant.

A subject with a TEAE that occurs in more than one category (#1, #2, #3) is counted in all the intervals that the TEAE occurs. For each category, a subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once in that SOC or PT.
When calculating percentages for each category, the number of subjects at risk (i.e., subjects who received the number of Icatibant) will be used as the denominator. The number of subjects whose onset of any one of the TEAEs is within the category will be used as the numerator.

6.6.1.3 Displays of Pretreatment Events

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variables:

PTE

Analytical Methods:

PTE is defined as an AE that occurs before the first administration of Icatibant.

The following summaries will be provided using frequency distribution.

PTEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.

(1) Pretreatment Events by System Organ Class and Preferred Term

(2) Serious Pretreatment Events by System Organ Class and Preferred Term

The frequency distribution will be provided according to the rules below.

Number of subjects

A subject with multiple occurrences of PTE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of PTE within a PT will be counted only once in that PT.

<Number of events

For each summary, the total number of events will be calculated.>

6.6.2 Adverse Events of Special Interest

6.6.2.1 Injection Site Reaction

Analysis Set:

Safety Analysis Set

Analysis Variables:

Erythema [Absent, Mild, Moderate, Severe]

Swelling [Absent, Mild, Moderate, Severe]

Cutaneous Pain [Absent, Mild, Moderate, Severe]

Burning Sensation [Absent, Mild, Moderate, Severe]

Itching/Pruritis [Absent, Mild, Moderate, Severe]

Warm Sensation [Absent, Mild, Moderate, Severe]

Categories:

Icatibant Exposure [#1, #2, #3]

Visit:

At Any Time Point1 hour Post Treatment, 4 hours Post Treatment, 8 hours Post Treatment, Day 2, Follow-up

Analytical Methods:

(1) Proportion of Subjects with Any Injection Site Reaction by each Icatibant Exposure

Frequency distributions will be provided by each Icatibant exposure.

(2) Proportion of Subjects with Severe Injection Site Reaction by each Icatibant Exposure

Frequency distributions will be provided by each Icatibant exposure.

(3) Summary of Injection Site Reaction by Severity by Visit in each Icatibant Exposure

Frequency distributions will be provided by visit in each Icatibant exposure.

6.6.3 Clinical Laboratory Evaluations

6.6.3.1 Hematology and Serum Chemistry

Analysis Set:

Safety Analysis Set

Analysis Variables:

Hematology

Red blood cells (RBC), White blood cells (WBC) count with differential (%) (neutrophil, basophil, eosinophil, lymphocyte, monocyte), Hemoglobin, Hematocrit, Platelets, Mean corpuscular hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC), Mean corpuscular volume (MCV)

Serum Chemistry

ALT, Albumin, Alkaline phosphatase, AST, Total bilirubin, Creatinine, Creatine kinase, Gamma-Glutamyl transferase (GGT), Chloride, Potassium, Sodium, Calcium, Glucose, Lactate dehydrogenase (LDH), Carbon dioxide (CO2), Phosphorus, Blood urea nitrogen (BUN), Magnesium, Total protein, Uric acid

Categories:

Icatibant Exposure [#1, #2, #3]

Results of determination based on normal reference range [Low, Normal, High]

Visit:

Baseline, Post Treatment, Follow-up

Analytical Methods:

The following summaries will be provided.

(1) Summary of Laboratory Test Results and Change from Baseline by Visit in each Icatibant Exposure

Descriptive statistics for observed values and changes from baseline will be provided by visit in each Icatibant Exposure. The changes from baseline will be calculated in each Icatibant Exposure.

Values below the lower limit of quantification will be treated as zero when calculating the descriptive statistics. Values above the upper limit of quantification will be treated as the upper limit value when calculating the descriptive statistics.

(2) Summary of Shifts of Laboratory Test Results by Visit in each Icatibant Exposure

Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

For each laboratory test, the laboratory values will be classified as “Low”, “Normal” or “High” relative to the normal reference range. The shift tables will be based on these classifications.

6.6.3.2 Urinalysis

Analysis Set:

Safety Analysis Set

Analysis Variables:

Specific gravity

Glucose [-, +-, 1+, 2+, 3+, 4+, 5+]

pH [Min <= - <= 8.0, 8.0 < - <= Max]

Protein [-, +-, 1+, 2+, 3+, 4+, 5+]

Occult blood [-, +-, 1+, 2+, 3+, 4+, 5+]

Ketones [-, +-, 1+, 2+, 3+, 4+, 5+]

Bilirubin [-, +-, 1+, 2+, 3+, 4+, 5+]

Nitrites [-, +-, 1+, 2+, 3+, 4+, 5+]

Categories:

Icatibant Exposure [#1, #2, #3]

Visit:

Baseline, Post Treatment, Follow-up

Analytical Methods:

For specific gravity, summaries (1) and (2) will be provided.

For each variable other than specific gravity, summaries (3) will be provided.

(1) Summary of Laboratory Test Results and Change from Baseline by Visit in each Icatibant Exposure

Descriptive statistics for observed values and changes from baseline will be provided by visit in each Icatibant Exposure. The changes from baseline will be calculated in each Icatibant Exposure.

(2) Summary of Shifts of Laboratory Test Results by Visit in each Icatibant Exposure

Shift tables showing the number of subjects in each category at baseline and each post-baseline visit in each Icatibant exposure will be provided.

For each laboratory test, the laboratory values will be classified as “Low”, “Normal” or “High” relative to the normal reference range. The shift tables will be based on these classifications.

(3) Number of Subjects in Categories of Urine Laboratory Test Results by Visit in each Icatibant Exposure

Shift tables showing the number of subjects in each category at baseline and each post-baseline visit in each Icatibant exposure will be provided.

6.6.4 Vital Signs

Analysis Set:

Safety Analysis Set

Analysis Variables:

Body Temperature

Respiratory Rate

Sitting Systolic Blood Pressure

Sitting Diastolic Blood Pressure

Pulse Rate

Categories:

Icatibant Exposure [#1, #2, #3]

Visit:

Baseline, 0.5 hour Post Treatment, 1 hour Post Treatment, 8 hours Post Treatment, Follow-up in Icatibant Exposure #1

Baseline, 1 hour Post Treatment, 8 hours Post Treatment, Follow-up in Icatibant Exposure #2 and #3

Analytical Methods:

The following summaries will be provided.

(1) Summary of Vital Signs and Change from Baseline by Visit in each Icatibant Exposure

Descriptive statistics for observed values and changes from baseline will be provided by visit in each Icatibant Exposure. The changes from baseline will be calculated in each Icatibant exposure.

6.6.5 12-Lead ECGs

Analysis Set:

Safety Analysis Set

Analysis Variables:

Heart Rate

RR Interval

PR Interval

QT Interval

QRS Interval

QTcF Interval

Interpretation [Within Normal Limits, Abnormal but not Clinically Significant, Abnormal and Clinically Significant]

Categories:

Icatibant Exposure [#1, #2, #3]

Visit:

Baseline, 0.75 hour Post Treatment, 8 hours Post Treatment, Follow-up in Icatibant Exposure #1

Baseline, 1 hour Post Treatment, 8 hours Post Treatment, Follow-up in Icatibant Exposure #2 and #3

Analytical Methods:

For each variable other than 12-lead ECG interpretations, summaries (1) and (2) will be provided.

For 12-lead ECG interpretation, summary (3) will be provided.

(1) Summary of ECG Parameters and Change from Baseline by Visit in each Icatibant Exposure

Descriptive statistics for observed values and changes from baseline will be provided by visit in each Icatibant Exposure. The changes from baseline will be calculated in each Icatibant exposure.

(2) Summary of Shift of 12-lead ECG Interpretation by Visit in each Icatibant Exposure

Shift table showing the number of subjects in each category at baseline and each post-baseline visit in each Icatibant exposure will be provided.

6.6.6 Other Safety Analysis

6.6.6.1 Reproductive hormone levels

Analysis Set:

Safety Analysis Set

Analysis Variables:

Reproductive hormone levels

FSH, LH, estradiol, and progesterone in females

FSH, LH, and testosterone in males

Categories:

Icatibant Exposure [#1, #2, #3]

Results of determination based on normal reference range [Low, Normal, High]

Visit:

Baseline, Post Treatment, Follow-up

Analytical Methods:

Reproductive hormone levels and classified values as "Low", "Normal" or "High" relative to the normal reference range will be listed.

6.6.6.2 Immunogenicity (presence of anti-Icatibant antibodies)

Analysis Set:

Safety Analysis Set

Analysis Variables:

Immunogenicity (presence of anti-Icatibant antibodies)

Categories:

Icatibant Exposure [#1, #2, #3]

Anti-Icatibant Antibody [Positive, Negative]

Visit:

Baseline, Follow-up

Analytical Methods:

The following summaries will be provided.

(1) Frequency Distributions by Visit in each Icatibant Exposure

Frequency distributions of Anti-Icatibant Antibody by visit in each Icatibant exposure will be provided.

6.6.7 Extent of Exposure and Compliance

Analysis Set:

Safety Analysis Set

Analysis Variables:

Number of Icatibant Exposure [1, 2, 3]

Analytical Methods:

(1) Study Drug Exposure and Compliance

Frequency distributions for categorical variables will be provided.

6.7 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

6.7.1 Pharmacokinetic Analysis

Analysis Set:

Safety Analysis Set

Analysis Variable(s):

Plasma Concentrations of Icatibant Analyte (Icatibant, M-I and M-II)

Visit:

Predose, 0.5, 1.0, 2.0, and 4.0 hours after the first Icatibant administration

Analytical Method(s):

The following summaries will be provided.

(1) Summary of Plasma Concentrations by Visit

Descriptive statistics will be provided by visit.

6.8 Other Analyses

6.8.1 Self-administration Assessment

Analysis Set:

Safety Analysis Set

Analysis Variable(s):

Do you consider the training materials sufficient to explain the method of self-administration? [1 - not at all sufficient, 2 - not sufficient, 3 - neither sufficient nor insufficient, 4 - sufficient, 5 - very sufficient]

How stressful did you find the idea of self-injecting this medication during an HAE attack? [1 - very stressful, 2 - stressful, 3 - indifferent, 4 - not stressful, 5 - not at all stressful]

Was it difficult to prepare the injection site before self-injection?[1 - very difficult, 2 - difficult, 3 - neither difficult nor easy, 4 - easy, 5 - very easy]

Was it difficult to adjust the dose using a graduated syringe and connector? [1 - very difficult, 2 - difficult, 3 - neither difficult nor easy, 4 - easy, 5 - very easy]

Did you find it difficult to assemble and handle the syringe? [1 - very difficult, 2 - difficult, 3 - neither difficult nor easy, 4 - easy, 5 - very easy]

How difficult was it to actually self-inject the study medication? [1 - very difficult, 2 - difficult, 3 - neither difficult nor easy, 4 - easy, 5 - very easy]

Visit:

Icatibant Exposure [#1, #2, #3]

Analytical Method(s):

The frequency distributions by Icatibant exposure will be provided.

6.9 Interim Analyses

Not applicable.

7.0 REFERENCES

Not applicable.

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

Not applicable.

9.0 APPENDIX

9.1 Changes From the Previous Version of the SAP

Original version in section 6.1

In case of 2 subjects who received at least 1 dose of study drug, no tables and figures will be produced except for 6.5.1.2 (2), 6.6.1.1, 6.6.1.2 (1), and 6.6.2.1.

Amendment 1

In case of 2 subjects who received at least 1 dose of study drug, no tables and figures will be produced except for 6.6.1.1, 6.6.1.2 (1), and 6.6.2.1.

Reason for the amendment

Correction, to follow the specification in 6.5.1.2 (2), “In case of 2 or less events of Icatibant-treated attacks in an analysis variable, no tables and figures will be produced for the analysis variable.”

Original version in section 6.2.5.1

6.2.5.1 Treatment of Subjects

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variables:

Study Drug Administration Status [Eligible but Not Treated]

Reason for Not Being Treated [Death, Adverse Event, Significant Protocol Deviation, Lost to Follow-up, Voluntary Withdrawal by the Subject, Voluntary Withdrawal by Subject's Parent/Subject's Legal Guardian, Study Termination, Pregnancy, Other]

Analytical Methods:

(1) Disposition of Subjects

Frequency distributions will be provided. When calculating percentages for the reasons for not being treated, the total number of subjects not treated by the study drug will be used as the denominator. When calculating percentages for the reasons for discontinuation, the total number of subjects who prematurely discontinued will be used as the denominator.

Amendment 1

Deleting this section.

Reason for the amendment

The same results will be obtained as the analysis of 6.2.5.2.

Original version in section 6.3.1

Age (years) [<6 years, 6-11 years, >11 years]

Gender[Male, Female]

Height (cm)

Height percentile

Weight (kg)

Weight percentile

BMI (kg/m2)

BMI percentile

Amendment 1

Age at Informed Consent (years) [<6 years, 6-11 years, >11 years]

Age at First Treatment (years) [<6 years, 6-11 years, >11 years]

Gender[Male, Female]

Height at First Treatment (cm)

Height Percentile at First Treatment

Weight at First Treatment (kg)

Weight Percentile at First Treatment

BMI at First Treatment (kg/m2)

BMI Percentile at First Treatment

Reason for the amendment

To ad age at informed consent and to clarify the timing of analyses.

Original version in section 6.3.1

Average Duration of Previous Cutaneous Attacks (days)

Average Duration of Previous Abdominal Attacks (days)

Average Duration of Previous Cutaneous and Abdominal Attacks (days)

Average Duration of Previous Laryngeal Attacks (days)

Amendment 1

Deleting above them.

Reason for the amendment

These cannot be calculated.

Original version in section 6.3.1

Most Frequent Severity for Previous Cutaneous Attacks [Mild, Moderate, Severe]

Most Frequent Severity for Previous Abdominal Attacks [Mild, Moderate, Severe]

Most Frequent Severity for Previous Cutaneous and Abdominal Attacks [Mild, Moderate, Severe]

Most Frequent Severity for Previous Laryngeal Attacks [Mild, Moderate, Severe]

Amendment 1

Most Frequent Severity for Previous Cutaneous Attacks [Mild, Moderate, Severe, Very Severe]

Most Frequent Severity for Previous Abdominal Attacks [Mild, Moderate, Severe, Very Severe]

Most Frequent Severity for Previous Cutaneous and Abdominal Attacks [Mild, Moderate, Severe, Very Severe]

Most Frequent Severity for Previous Laryngeal Attacks [Mild, Moderate, Severe, Very Severe]

Reason for the amendment

To add "Very Severe" per CRF.

Original version

None

Amendment 1

6.5.1.6 Supplementary Analyses 3

Analysis Set:

Full Analysis Set

Analysis Variables:

Time to onset of relief from HAE medication in off-study HAE attack

Time to complete relief from HAE medication in off-study HAE attack

Analytical Methods:

Time to onset of relief and complete relief from HAE medication in off-study HAE attack will be listed.

Reason for the amendment

To add this listing.

Original version in section 6.6.2

Visit:

Baseline, 1 hour Post Treatment, 4 hours Post Treatment, 8 hours Post Treatment, Day 2, Follow-up

Amendment 1

Visit:

At Any Time Point, 1 hour Post Treatment, 4 hours Post Treatment, 8 hours Post Treatment, Day 2, Follow-up

Reason for the amendment

Correction

Original version in section 6.6.3.2

Glucose [-, +-, 1+, 2+, 3+, 4+]

pH [Min <= - <= 8.0, 8.0 < - <= Max]

Protein [-, +-, 1+, 2+, 3+, 4+]

Occult blood [-, +-, 1+, 2+, 3+, 4+]

Ketones [-, +-, 1+, 2+, 3+, 4+]

Bilirubin [-, +-, 1+, 2+, 3+, 4+]

Nitrites [-, +-, 1+, 2+, 3+, 4+]

Amendment 1

Glucose [-, +-, 1+, 2+, 3+, 4+, 5+]

pH [Min <= - <= 8.0, 8.0 < - <= Max]

Protein [-, +-, 1+, 2+, 3+, 4+, 5+]

Occult blood [-, +-, 1+, 2+, 3+, 4+, 5+]

Ketones [-, +-, 1+, 2+, 3+, 4+, 5+]

Bilirubin [-, +-, 1+, 2+, 3+, 4+, 5+]

Nitrites [-, +-, 1+, 2+, 3+, 4+, 5+]

Reason for the amendment

Correction

Original version in section 6.6.5

Visit:

Baseline, 0.75 hour Post Treatment, 1 hour Post Treatment, 8 hours Post Treatment, Follow-up in Icatibant Exposure #1

Amendment 1

Visit:

Baseline, 0.75 hour Post Treatment, 8 hours Post Treatment, Follow-up in Icatibant Exposure #1

Reason for the amendment

Correction

9.2 Data Handling Conventions

9.2.1 Definition of Visit Windows

No windowing of visits and time points will be done for data obtained at the scheduled visits and time points.

9.3 Analysis Software

Statistical analyses will be performed using [redacted] on a suitably qualified environment.