STATISTICAL ANALYSIS PLAN

Protocol Title:	A Multicenter, Open-Label, Non-Randomized Study to Assess the Pharmacokinetics, Tolerability, and Safety of a Single Subcutaneous Administration of Icatibant in Children and Adolescents with Hereditary Angioedema	
Protocol Number:	HGT-FIR-086	
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Study Phase	III	
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1. LIST OF ABBREVIATIONS AND DEFINITIONS

1.1 Abbreviations

AE	Adverse Event
BMI	Body Mass Index
C1-INH	C1 inhibitor
CRF	Case Report Form
ECG	Electrocardiogram
FLACC	Faces, Legs, Activity, Cry, and Consolability
FPS-R	Faces Pain Scale – Revised
HAE	Hereditary Angioedema
ITT	Intent To Treat
IV	Intravenous
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
PD	Protocol Deviation
PK	Pharmacokinetic
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SOC	System Organ Class
SOP	Standard Operating Procedure
WHO	World Health Organization
WHO-DD	World Health Organization-Drug Dictionary

2. INTRODUCTION

2.1 Purpose of the Statistical Analysis Plan

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the planned statistical analyses on safety and efficacy endpoints for protocol HGT-FIR-086, a multicenter, open-label, non-randomized study to assess the pharmacokinetics (PK), tolerability, and safety of a single subcutaneous (SC) administration of icatibant in children and adolescents with hereditary angioedema. SAP for PK endpoints will be provided in a separate document.

This study evaluated the effect of a single administration of icatibant in children and adolescents with hereditary angioedema (HAE). It also examined the effect of repeated exposures of icatibant in adolescents. This SAP presents the statistical analysis methods on complete safety and efficacy results for single administration of icatibant in at least 10 prepubertal children and at least 20 adolescents with HAE treated once with icatibant and repeated exposure of icatibant during subsequent HAE attacks in adolescents.

2.2 Background

This is an open-label, non-randomized, single-arm study to evaluate the PK, tolerability, safety including reproductive hormone assessments, and efficacy of a single SC administration of icatibant in approximately 30 pediatric subjects with HAE during an initial acute attack. Details of the study design, rationale, and procedures are documented in Protocol HGT-FIR-086.

2.3 Study Rationale

Three controlled Phase III studies established the safety and efficacy of icatibant as a treatment for acute attacks of HAE. Icatibant has not been evaluated in clinical trial subjects below the age of 18 years. This study was designed to evaluate the PK, tolerability, safety including reproductive hormone assessments, and efficacy of a single SC administration of icatibant in subjects from 2 to less than 18 years of age.

3. STUDY OBJECTIVES

The study objectives are listed below.

3.1 Objectives

The objectives of this study are:

- To investigate the PK, tolerability, and safety of a single SC dose of icatibant in children and adolescents with HAE.
- To evaluate the efficacy of a single SC dose of icatibant in children and adolescents with HAE.
- To evaluate the effect on reproductive hormone levels after a single SC dose of icatibant in children and adolescents with HAE.

3.2 Other Objectives

Other objectives of this study are:

- To evaluate the continued safety of icatibant in pubertal/postpubertal children after repeated exposures.
- To evaluate the efficacy of icatibant in the treatment of acute HAE attacks in pubertal/postpubertal children after repeated exposures.
- To evaluate the effect on reproductive hormone levels in pubertal/postpubertal children after repeated exposures.

4. STUDY DESIGN

4.1 General Description

This is an open-label, non-randomized, single-arm study to evaluate the PK, tolerability, and safety, including effects on reproductive hormones, of a single SC administration of icatibant in pediatric subjects with HAE.

The study enrolled children and adolescents from 2 to less than 18 years of age, divided into 2 groups: prepubertal (Tanner stage I) and pubertal/postpubertal (Tanner stages II to V).

After a qualifying screening period, the PK, safety/tolerability, and efficacy of treatment with SC icatibant was evaluated in at least 20 subjects (10 prepubertal and 10 pubertal/postpubertal subjects) who presented with cutaneous, abdominal, or laryngeal symptoms of an acute attack of HAE.

The PK and safety/tolerability of SC icatibant was evaluated in at least 10 additional pubertal/postpubertal subjects who met screening criteria, but received treatment with SC icatibant in the absence of a current acute HAE attack.

Subjects will receive treatment with a single SC administration of icatibant on Day 1 and will be monitored closely in the hospital/study center for at least 6 to 8 hours after treatment. Subjects will undergo PK and safety assessments; efficacy assessments will be performed if treatment occurs during an acute HAE attack. All subjects will have serum reproductive hormone measurements.

A subject may be discharged after completion of assessments at 6 hours post treatment, if deemed medically stable in the investigator's clinical judgment and, if applicable, the subject's HAE symptoms have resolved (the subject's investigator-rated symptom score must be zero, denoting the absence of symptoms). If HAE symptoms have not completely resolved at 6 hours (ie, the investigator-rated symptom score is >0), the subject shall remain in the hospital/study center for at least 8 hours after icatibant administration for further evaluation. Telephone follow-up will occur at both 24 and 48 hours after treatment. Subjects will return to the hospital/study center for scheduled assessments on Day 8 and for a follow-up visit on Day 90.

A table showing the Schedule of Events for the study is provided in Appendix III: Schedule of Events.

4.2 Discussion of Study Design

This study has an open-label, single arm design.

The study is intended to determine the PK profile of SC icatibant when administered to children and adolescents with HAE and to identify an optimal pediatric dosing regimen.

In addition, the study is intended to establish the tolerability and safety of icatibant in children and adolescents, particularly with respect to potential effects on reproductive development, and to demonstrate the effectiveness of icatibant in relieving the symptoms of acute HAE attacks. Therefore, this study will help determine whether icatibant can address an unmet medical need for a safe and effective treatment for acute attacks of HAE in pediatric patients.

4.3 Method of Assigning Subjects to Treatment Group

Not applicable to this single arm study.

4.4 Blinding

Not applicable to this open-label study.

4.5 Determination of Sample Size

The study will enroll a sufficient number of children and adolescents to ensure study completion of 30 evaluable subjects. The study population is planned to consist of at least 10 prepubertal and 20 pubertal/postpubertal subjects from 2 to less than 18 years of age. Though empirically derived and not based on a formal sample size calculation, this sample size will provide basic information concerning the PK, tolerability and safety, and efficacy of icatibant in children and adolescents with HAE.

5. STUDY ENDPOINTS

The primary endpoints of this study are:

- The PK profile of icatibant after a single SC injection in pediatric subjects (in prepubertal children with an acute attack of HAE and pubertal/postpubertal children with or without an acute attack of HAE).
- The tolerability and safety of SC icatibant as assessed by injection site reactions, adverse events, vital signs, ECG recordings, physical examination, clinical laboratory parameters (serum chemistry [including liver function tests], hematology, urinalysis), reproductive hormone levels, and immunogenicity (presence of anti-icatibant antibodies).

The secondary endpoints (only for subjects treated with icatibant during a HAE attack) of this study are:

Time to onset of relief of symptoms and time to minimal symptoms, 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 relief of symptoms, defined as the earliest time at which a 20% improvement is seen in the average post-treatment score with no worsening of any single component score.
    - The time to minimal symptoms, defined as the earliest time post-treatment when all symptoms are either mild or absent based on the investigator-rated symptom score.

- For subjects ≥4 years of age only: subject self-assessment of HAE-related pain using the Faces Pain Scale-Revised (FPS-R).
    - The time to onset of relief of symptoms, defined as the earliest time at which the post-treatment score improves by at least one level.
    - The time to minimal symptoms, defined as the earliest time at which the post-treatment score improves to zero (or no pain).

- For subjects <4 years of age only: investigator assessment of HAE-related pain (cutaneous, abdominal, and laryngeal) using a validated pain scale (Faces, Legs, Activity, Cry, and Consolability [FLACC]).
    - The time to onset of relief of symptoms, defined as the earliest time at which a 20% improvement is seen in the total post-treatment score.
    - The time to minimal symptoms, defined as the earliest time at which the total post-treatment score improves to zero.

- Incidence of rescue medication use.

- Proportion of subjects with worsened intensity of clinical HAE symptoms between 2 and 4 hours after treatment with icatibant.

6. EFFICACY AND SAFETY VARIABLES

6.1 Schedule of Evaluations

Please refer to Appendix III: Schedule of Events for details of assessments performed at each visit.

6.2 Safety Assessments

The safety and tolerability parameters include AEs, vital signs, ECG, local tolerability at the injection site, reproductive hormone levels, immunogenicity, and standard hematology, serum chemistry, and urinalysis.

6.3 Efficacy Assessments

6.3.1 Investigator Symptom Score

The investigator will use a symptom score to assess the severity of symptoms of acute cutaneous, abdominal, and laryngeal attacks of HAE using the following 5-point scale.

0 = none; absence of symptoms

1 = mild (no to mild interference with daily activities)

2 = moderate (moderate interference with daily activities)

3 = severe (severe interference with daily activities)

4 = very severe (very severe interference with daily activities)

For attacks classified as cutaneous and/or abdominal, investigator-rated symptom scores will be collected for 8 symptoms: abdominal tenderness, nausea, vomiting, diarrhea, skin pain, erythema, skin irritation, and skin swelling.

For attacks classified as laryngeal, investigator-assessed symptom scores will be collected for 13 symptoms: abdominal tenderness, nausea, vomiting, diarrhea, skin pain, erythema, skin irritation, skin swelling, dysphagia, voice change, breathing difficulties, stridor, and asphyxia.

6.3.2 FPS-R

The Faces Pain Scale – Revised (FPS-R) is a self-reported measure used to assess the intensity of children's pain and it is scored using a 0 to 10 scale (‘0’=’no pain’ and ‘10’=’very much pain’). Subjects who are at least 4 years of age will self-assess HAE-related pain using the FPS-R.

6.3.3 FLACC

Subjects who are below 4 years of age will undergo investigator assessment of HAE-related symptoms using the Faces, Legs, Activity, Cry, and Consolability (FLACC) comportmental

pain scale. The FLACC is a behavior pain assessment scale for use in preverbal children or children with limited verbal capability who are unable to provide reports of pain. Each of the five categories (F) Face; (L) Legs; (A) Activity; (C) Cry; (C) Consolability is scored from 0-2, which results in a total score between zero and ten.

7. STATISTICAL ANALYSES

7.1 General Considerations

All statistical analyses will be performed using SAS® statistical software (SAS Institute, North Carolina, USA) except for the population PK modeling which will be performed with nonlinear mixed effect modeling software (eg, Phoenix NLME module, Pharsight Corp.). A separate analytic plan will be developed to support the analysis of PK data. The analysis methods for all other study data (demographic and pretreatment characteristics, efficacy variables, and safety variables) will be detailed in the SAP.

Data will be summarized with respect to disposition, demographic, pre-treatment characteristics, safety variables, and efficacy variables. Summary statistics for continuous variables will include the number of subjects, the mean, median, standard deviation, and range. For categorical data, summaries will include counts and percentages. Time-to-event data will be summarized using Kaplan-Meier estimates of the 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals, as well as percentage of censored observations. Plots of the Kaplan-Meier curves and supporting data listings detailing each subject's contribution to the analysis will be provided.

7.2 Analysis Populations

The following populations will be used in the analysis:

- The Efficacy Population will consist of those subjects who were treated with icatibant for their first and any additional attacks during the study.
- The Safety Population will consist of those subjects who were treated with icatibant at least once during the study (irrespective of the presence of an HAE attack).

All efficacy analyses will be performed on the Efficacy Population. The corresponding tabular summaries will be presented by the icatibant exposure number. For the initial icatibant exposure, the analyses will be presented by the pubertal status (Pre-pubertal vs. Pubertal/Post-pubertal) and overall; for the subsequent icatibant exposures, the analyses will be presented by the administration type (Study Site Personnel (HCP Administration) vs. Home Healthcare Providers/Patient/Parent/Legal Guardian/Caregiver (Caregiver Administration)) and overall.

Safety and tolerability analyses will be based on the Safety Population. All tabular summaries within this population will be presented by the icatibant exposure number. For the initial icatibant exposure, the analyses will be presented by the pubertal status (Pre-pubertal vs. Pubertal/Post-pubertal) and overall; for the subsequent icatibant exposures, the analyses will be presented by the administration type (HCP Administration vs. Caregiver Administration) and overall.

7.3 **Subject Disposition**

The number and percentage of subjects who completed assessments (complete assessments up to Day 8 and complete assessment up to Day 90) and discontinued prematurely by reason will be summarized separately for the Efficacy Population and the Safety Population, by the icatibant exposure number. For the initial icatibant exposure, the analyses will be presented by the pubertal status and overall; for the subsequent icatibant exposures, the analyses will be presented by the administration type (HCP Administration vs. Caregiver Administration) and overall.

The number and percentage of subjects who completed assessments and discontinued prematurely by reason will be summarized separately for the Efficacy Population and the Safety Population by pubertal status stratification level.

7.4 **Demographics and Pre-treatment Characteristics**

Demographic and pre-treatment characteristics (age at screening [years], age at exposure [years], age group at exposure [<6 years, 6-11 years, >11 years], sex [male, female], race [American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Other], ethnicity [Hispanic or Latino, Not Hispanic or Latino], weight at exposure [kg], weight group at exposure [<75 kg, ≥75 kg], weight percentile at exposure, height at exposure [cm], height percentile at exposure [cm], BMI [kg/m^2] at exposure, BMI percentile at exposure, and country) will be summarized separately for the Efficacy Population and the Safety Population, and by icatibant exposure number. For the initial icatibant exposure, the analyses will be presented by the pubertal status and overall; for the subsequent icatibant exposures, the analyses will be presented by the administration type (HCP Administration vs. Caregiver Administration) and overall.

7.5 **Medical and HAE History**

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.0 and summarized by system organ class (SOC) and preferred term (PT) for the Efficacy Population and the Safety Population, and by icatibant exposure number. For the initial icatibant exposure, the analyses will be presented by the pubertal status and overall; for the subsequent icatibant exposures, the analyses will be presented by the administration type (HCP Administration vs. Caregiver Administration) and overall.

History of HAE (family history [yes, no], time since diagnosis at first treatment [years], type of last attack[cutaneous, abdominal, cutaneous and abdominal, or laryngeal], and time since last attack at first treatment [months]) and details on previous HAE attacks (number of attacks in last 12 months, average duration of attacks [days], average time between onset of symptoms and relief [days], and most frequent severity of attacks [mild, moderate, or severe]) for each attack type (cutaneous, abdominal, cutaneous and abdominal, and laryngeal) will be summarized separately for the Efficacy Population and the Safety Population, and by icatibant exposure number. For the initial icatibant exposure, the analyses will be presented by the pubertal status and overall; for the subsequent icatibant exposures, the analyses will be presented by the administration type (HCP Administration vs. Caregiver Administration) and overall.

Medical history and HAE history will also be provided in listings.

7.6 On-Study HAE Attacks and Drug Exposure

Type of attack (cutaneous, abdominal, laryngeal) and time from attack onset to study drug administration (hours) will be summarized for the Efficacy Population, by icatibant exposure number. For the initial icatibant exposure, the analyses will be presented by the pubertal status and overall; for the subsequent icatibant exposures, the analyses will be presented by the administration type (HCP Administration vs. Caregiver Administration) and overall.

Number of injections will be summarized for the Efficacy Population and Safety Population, by icatibant exposure number. For the initial icatibant exposure, the analyses will be presented by the pubertal status and overall; for the subsequent icatibant exposures, the analyses will be presented by the administration type (HCP Administration vs. Caregiver Administration) and overall.

The exposure information for all icatibant administrations given as part of the study will also be presented in a listing.

7.7 Protocol Deviations

Prior to the interim data cut, protocol deviations will be reviewed by the study team and the subset of protocol deviations that may have significantly impacted the completeness, accuracy, and/or reliability of the study data or that may significantly affected a subject's rights, safety, or well-being will be identified as significant protocol deviations.

A listing of the protocol deviations will be provided for each subject.

7.8 Efficacy Analysis

Efficacy will be assessed using data from the investigator symptom score, FPS-R and FLACC. The corresponding analyses will be based on the Efficacy Population. All efficacy summaries will be presented by icatibant exposure number. For the initial icatibant exposure, the analyses will be presented by the pubertal status and overall; for the subsequent icatibant exposures, the analyses will be presented by the administration type (HCP Administration vs. Caregiver Administration) and overall.

All efficacy results will be listed by subject.

7.8.1 Investigator Symptom Score

The primary efficacy endpoint is the time to onset of symptom relief measured using the investigator-reported symptom score. Eight symptoms will be assessed for abdominal and cutaneous attacks, and 13 symptoms will be assessed for laryngeal attacks. Time to onset of symptom relief is defined as the duration of time in hours from study drug administration to the earliest time post-treatment at which there is at least a 20% improvement in the composite (or average) post-treatment symptom score with no worsening of any single component score.

Subjects not achieving the onset of symptom relief will be censored at the time of their last symptom assessment. Time to onset of symptom relief will be summarized using the Kaplan-Meier method.

An alternative efficacy endpoint is the time to minimum symptoms measured using the investigator-reported symptom score. It is defined as the earliest time post-treatment when all symptoms are either mild or absent. Subjects not achieving the minimum symptom criteria will be censored at the time of their last symptom assessment. Time to minimum symptoms will be summarized using the Kaplan-Meier method. Subjects with all symptoms as mild or absent at pretreatment will be excluded from this analysis.

The composite investigator-reported symptom score and the change from pre-treatment in the composite investigator-reported symptom score will be summarized by study time-point. Furthermore, the symptom scores associated with individual symptoms will be summarized by study time-point. The mean composite investigator-assessed symptom score will be plotted by study time-point by pubertal status stratification group.

For individual investigator-reported symptom scores, a shift table from baseline will be presented for each post-treatment time point. The analysis will be repeated to assess shift in the individual symptom scores from the 2 hour time-point.

Time to onset of symptom relief for individual symptom is defined as duration of time in hours from study drug administration to the earliest time post-treatment when the specific symptom is either mild or absent. Subjects not achieving the relief for individual symptom criteria will be censored at the time of their last symptom assessment. Time to onset of symptom relief for individual symptoms will be summarized using the Kaplan-Meier method. Subjects with the individual symptom as mild or absent at pretreatment will be excluded from the analysis on that symptom.

Analyses on investigator symptom score will be performed for the initial icatibant exposure and both subsequent exposures.

7.8.2 **FPS-R**

Pain will be assessed in subjects 4 years of age or older using the FPS-R. Time to onset of symptom relief in this case will be defined as the duration of time in hours from the time of study drug administration to the earliest time at which the post-treatment score improves by at least one level. Subjects not achieving the onset of symptom relief for FPS-R will be censored at the time of their last FPS-R assessment. Time to onset of symptom relief will be summarized using the Kaplan-Meier method. Subjects with pretreatment value of zero will be excluded from this analysis.

Time to minimum symptom for FPS-R is defined as the duration of time in hours from the time of study drug administration to the earliest time at which the post-treatment score improves to zero (or no pain). Subjects not achieving minimum symptom for FPS-R will be censored at the time of their last FPS-R assessment. Time to minimum symptom for FPS-R

will be summarized using the Kaplan-Meier method. Subjects with pretreatment value of zero will be excluded from this analysis.

The observed values and change from pre-treatment in the FPS-R score will be summarized by study time-point.

Analyses on the FPS-R will be performed for the initial icatibant exposure and both subsequent icatibant exposures.

7.8.3 **FLACC**

For subjects less than 4 years of age, the investigator will assess HAE-related pain (cutaneous, abdominal, and laryngeal) using FLACC. Time to onset of symptom relief will be calculated from the time of study drug administration to the earliest time at least a 20% improvement is seen in the total post-treatment pain score. Subjects not achieving the onset of symptom relief for FLACC will be censored at the time of their last FLACC assessment. Time to onset of symptom relief will be summarized using the Kaplan-Meier method. Subjects with pretreatment value of zero will be excluded from this analysis.

Time to minimum symptom for FLACC is defined as the duration of time in hours from the time of study drug administration to the earliest time at which the post-treatment total score improves to zero (or no pain). Subjects not achieving minimum symptom for FLACC will be censored at the time of their last FLACC assessment. Time to minimum symptom for FLACC will be summarized using the Kaplan-Meier method. Subjects with pretreatment value of zero will be excluded from this analysis.

The observed values and changes from pre-treatment in the total pain score will be summarized by study time-point. Similarly, the scores in each of the five domains will be summarized by the study time-point.

Analyses on FLACC will be performed for the initial icatibant exposure only.

7.8.4 **Other Efficacy Analyses**

Time to First Use of Rescue Medication

The number and percentage of subjects who received rescue medications before the onset of symptom relief will be summarized. Time to first use of rescue medication prior to onset of symptom relief will be calculated from the time of study drug administration to the first use of rescue medication prior to the onset of symptom relief. Subjects not using rescue medication prior to the onset of symptom relief will be censored at the time of their onset of symptom relief. Time to first use of rescue medication will be summarized using the Kaplan-Meier method. This analysis will only be performed if there are at least 5 subjects for a given attack who used rescue medication prior to attaining symptom relief.

Subjects who received rescue medication before the onset of symptom relief will be denoted in the listing on rescue medication for the efficacy population.

Analyses on time to first use of rescue medication will be performed for the initial icatibant exposure and both subsequent icatibant exposures.

Time to Initial Symptom Relief

The investigator will be asked to record the date and time when overall subject improvement was first noted and mark the date and time accordingly in the CRF. The time to initial symptom relief will be defined as the duration of time in hours from study drug administration until the time when overall subject improvement was first noted. Subjects not achieving the initial symptom relief will be censored at the time of their last assessment. Time to initial symptom relief will be summarized using the Kaplan-Meier method.

Analyses on time to initial symptom relief will be performed for the initial icatibant exposure and both subsequent icatibant exposures.

7.9 Safety Analyses

All safety summaries will be presented by icatibant exposure number, if not otherwise specified. For the initial icatibant exposure, the analyses will be presented by the pubertal status and overall; for the subsequent icatibant exposures, the analyses will be presented by the administration type (HCP Administration vs. Caregiver Administration) and overall.

All safety summaries will be presented for the initial icatibant exposure and both subsequent icatibant exposures.

All safety outcomes will be listed by subject.

7.9.1 Adverse Events

Adverse events (AE) will be collected over an observation period from the time of treatment until the follow-up visit 90 (±7) days after investigational product administration (or until the event has resolved/stabilized or an outcome is reached, whichever comes first). Any serious adverse events (SAE), regardless of relationship to investigational product, which occurs in a subject after informed consent, should be recorded by the clinical site on a serious adverse event form.

AEs will be coded using MedDRA Version 16.0. A summary of subjects with treatment-emergent adverse events defined as AEs which occurred or worsened on or after the time of the first study drug administration will be presented. The summary will include the number and percentage of subjects who experience any AEs, any related AE, any severe AE, any related severe AE, any SAE, any related SAE, and any injection site reaction which was deemed an SAE; as well as the number of events in each category. Additionally, the summary table will include the number and percentage of subjects with AEs result in death.

Related AEs are AEs assessed as possibly, probably, or definitely related to the study treatment.

Treatment emergent AEs will be summarized by system organ class (SOC) and preferred term by pubertal status stratification level and icatibant exposure number. Tabulations will be presented sorted by SOC in alphabetical order and by PT within each SOC by descending frequency. The number and percentage of subjects experiencing an AE, as well as total number of AEs, will be tabulated. Treatment emergent AEs by SOC and preferred term also will be tabulated by severity and by relationship to treatment. In the case of multiple occurrences of the same AEs (at the preferred term level) in an individual subject, the AE that is classified as the most severe (i.e., maximum severity) will be identified for the analysis by severity and the AE that has the closest relationship to study drug will be identified for the analysis by relationship. Treatment emergent SAEs will be tabulated according to SOC and preferred term and provided in a data listing.

For analyses on treatment emergent AEs, in addition to summaries by icatibant exposure number, the analyses on all treatment emergent AEs by pubertal status stratification level and overall will be performed as well.

Pre-treatment AEs will be presented in a listing.

7.9.2 **Symptoms at Injection Site**

Injection site reactions (erythema, swelling, burning sensation, itching/pruritus, warm sensation, cutaneous pain) will be evaluated by the investigator or home healthcare provider/parent/legal guardian/caregiver when the subject is at the hospital/study center.

The number and percentage of subjects with any injection site reactions, and any severe reactions, will be summarized by type of reaction.

The number and percentage of subjects with injection site reactions will be summarized by maximum severity at any time point and for each study time point.

7.9.3 **Immunogenicity**

Serum samples for immunogenicity testing for determination of anti-icatibant antibodies will be collected pre-treatment and 8 and 90 days post-treatment. A subject will be considered as anti-icatibant antibody positive if he/she has at least 1 positive antibody result after the pre-treatment visit.

The number and percentage of subjects with a positive post-treatment antibody test result will be summarized.

For analyses on immunogenicity, in addition to summaries by icatibant exposure number, the analyses on all immunogenicity measurements by pubertal status stratification level and overall will be performed as well.

7.9.4 **Laboratory Results**

Laboratory test results will be presented in conventional units. Serum chemistry, hematology, and urinalysis parameters will be collected at pre-treatment, 6 hours post-treatment and at 8 and 90 days post-treatment for the initial icatibant treatment.

Observed values and changes from pre-treatment will be summarized by study time-point. Laboratory test results will be classified according to the reference ranges and clinical significance as determined by the investigator. The number of subjects with a non-missing result, and the number and percentage of subjects with a clinically significant result less than the lower limit of normal, non-clinically significant result less than the lower limit of normal, within the normal range, non-clinically significant result more than the upper limit of normal, and clinically significant result more than the upper limit of normal will be summarized by study time point. If more than one laboratory result is reported per study time point per parameter, the result yielding the most severe classification will be selected for analysis. Listings of abnormal results and records with missing reference ranges (eliminated from the summary analysis), as well as results of the same laboratory parameter for the subject across all study time points, will be presented.

Laboratory parameters collected are listed below.

Serum Chemistry:

Albumin, Alkaline phosphatase, Alanine aminotransferase, Aspartate aminotransferase, Calcium, Carbon dioxide, Chloride, Creatinine, Creatine kinase, Gamma-glutamyl transferase, Glucose, Lactate dehydrogenase, Phosphorus, Potassium, Sodium, Total bilirubin.

Hematology:

Hematocrit, Hemoglobin, Mean corpuscular hemoglobin, Mean corpuscular hemoglobin concentration, Mean corpuscular volume, Platelet count, Red blood cell count, White blood cell count with differential.

Urinalysis:

Appearance, Bilirubin, Color, Glucose, Ketones, Nitrite, Occult blood, pH, Protein, Specific gravity.

7.9.5 **Electrocardiogram (ECG)**

ECGs will be performed at screening and at 6 hours (or 8 hours for subjects who did not have complete resolution of HAE symptoms at 6 hours) post-treatment for the initial icatibant treatment. ECG results (abnormal or normal) will be summarized by study time point. Listings of treatment-emergent abnormalities, as well as results for the subject across all study time points, will be presented.

7.9.6 **Vital Signs**

Vital signs (temperature [°C], pulse [bpm], blood pressure [systolic and diastolic, mmHg], and respiration [per min]) will be collected at screening, pre-treatment, and 1 hour, 6 hours (or 8 hours for subjects who did not have complete resolution of HAE symptoms at 6 hours), 8 days and 90 days post-treatment for the initial icatibant treatment; and at pretreatment, 8 days and 90 days post-treatment for subsequent icatibant-treated attacks. Observed values and changes from pre-treatment will be summarized by study time-point.

7.9.7 **Reproductive Hormone Assessments**

Reproductive hormone levels will be measured in all subjects at pre-treatment, and 6 hours, 8 days and 90 days post-treatment for the initial icatibant treatment, and pretreatment, 8 days and 90 days post-treatment for subsequent icatibant-treated attacks. FSH, LH, estradiol, and progesterone will be summarized for females, and FSH, LH, and testosterone will be summarized for males. Observed values and changes from pre-treatment will be summarized by study time-point. The number and percentage of subjects with levels outside the normal range defined for their sex and pubertal status will be summarized by study time-point. Observations below the limit of detection will be considered abnormal if the lower limit of normal is not zero.

7.9.8 **Pregnancy Test Results**

Female subjects of childbearing potential will undergo pregnancy testing at screening, pre-treatment and 90 days post-treatment. A listing of pregnancy test results will be presented by site number, subject number, icatibant exposure number, and study time point.

7.9.9 **Concomitant Medication**

Concomitant medications will be coded using the WHO Drug Dictionary (Version 2011, Q4).

Concomitant medications administered after the treatment start and within 5 days from the treatment start will be summarized by icatibant exposure number, therapeutic class, and preferred term for the Efficacy Population and the Safety Population. For medications with partial onset times, non-missing date parts will be used to determine if the medication qualifies as concomitant. If it cannot be definitively determined that a concomitant medication was used within 5 days from treatment start then it will be included in the summary.

7.9.10 **Rescue Medication**

Rescue medications will be coded using the WHO Drug Dictionary (Version 2011, Q4).

Rescue therapy is any medication used after the administration of icatibant which, in the opinion of the investigator, is immediately necessary to alleviate acute symptoms which are judged by the investigator as resultant from the current HAE attack.

Repeat administration of icatibant for the treatment of a single attack is not allowed in this study.

Antihistamines and corticosteroids are considered ineffective for the alleviation of an acute HAE attack. If administered during an acute attack that occurs during the study, they should be recorded as concomitant medications but will not be considered rescue medications.

Rescue medications administered after the treatment start and within 48+4 hours after the treatment start will be summarized by icatibant exposure number, therapeutic class, and preferred term for the Efficacy Population and the Safety Population. For medications with partial onset times, non-missing date parts will be used to determine if the rescue medication was used within 3 days of treatment. If it cannot be definitely determined that the rescue medication was used within 3 days of treatment, the rescue medication will be excluded from the summary. See Section 10.2.14 for the detailed definition of rescue medication.

8. CHANGES IN THE CONDUCT OF THE STUDY OR PLANED ANALYSES

8.1 Changes in the Conduct of the Study

There was no change in the conduct of the study.

8.2 Changes from the Analyses Planned in the Protocol

There was no change from the analyses planned in the protocol.

9. STATISTICAL/ANALYTIC ISSUES

9.1 Adjustment for Covariates

Given the small number of subjects treated in the study, no modelling approach will be performed to analyze the study data. Therefore, adjustment for covariates is not necessary.

9.2 Handling of Dropouts or Missing Data

9.2.1 Handling of Missing Data in Efficacy Assessments

In general, a conservative approach that is unlikely to bias the results will be used to deal with missing data. Individual missing pretreatment scores, when the assessment was performed (i.e., other instrument-specific pretreatment scores are non-missing), will be assigned a value of mean value from the other available symptom scores when calculating the composite symptom scores at baseline.

Individual missing post-treatment scores, when the assessment was performed (i.e., other instrument-specific scores are non-missing), will be assigned the last non-missing value using last observation carried forward (LOCF). If the baseline observation is the last non-missing value it will be carried forward as well. This imputation method assumes that if an investigator did not rate a symptom at a particular assessment, then there was no change from the previous assessment.

9.2.2 Handling of Missing Start Dates for Adverse Event Reporting

For AEs with partial onset times, non-missing date parts will be used to determine if the AE is treatment-emergent or not. If a determination cannot be made using the non-missing date parts as to when the AE occurred relative to study drug administration then the AE will be classified as treatment-emergent.

9.3 Interim Analyses and Data Monitoring

An interim analysis was performed when at least 10 prepubertal children and at least 20 adolescents have been enrolled in the study to support a regulatory filing fulfilling Shire's commitment in the Paediatric Investigation Plan (PIP) for Firazyr (EMEA-000408-PIP01-08-M05). Also, an independent DSMB was established to provide ongoing, independent review and assessment of the safety data, and to safeguard the interests and safety of the participating subjects in the study. Analysis of the data for DSMB review was conducted according to the DSMB Charter and DSMB SAP. Because no formal hypothesis testing was planned, multiplicity concerns regarding repeated analyses were not an issue.

9.4 Multicenter Studies

Data from all centers that participate in this protocol will be combined so that an adequate number of subjects will be available for analysis. Given the small number of subjects treated at each study site, no analysis on study center effects is planned.

9.5 Multiple Comparisons/Multiplicity

Given the small number of subjects treated in the study, no modelling approach will be performed to analyze the study data. Therefore, adjustment for multiple testing is not necessary.

9.6 Examination of Subgroups and Interactions

Given the small sample size of this study, no analysis is planned to examine subgroups.

9.7 Sensitivity Analyses

No sensitivity analysis is planned for this study.

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10.2 APPENDIX II: Definitions and Programming Conventions

10.2.1 Age Calculation

Age will be calculated as the date of study drug administration minus the date of birth and displayed rounded to one decimal place.

If the date of birth is not complete (i.e., contains only partial information such as month and year or only year), then the non-missing date parts will be used to calculate the subject's age. If the date of birth is completely missing, then the age reported in the clinical database will be used as the subject's age.

10.2.2 BMI Calculation

BMI will be calculated using the standard formula (below) and displayed rounded to one decimal place.

$$\text{BMI (kg/m}^2\text{)} = \text{(body weight in kilograms) / (height in meters)}^2$$

10.2.3 Weight and Height Percentile Calculation

Weight and height will be converted to percentiles using CDC growth charts based on the subject's sex and age.

10.2.4 Time-to-Event Endpoints

Time-to-event endpoints will be calculated from the time of study drug administration to the earliest time point at which endpoint is achieved. The actual study drug administration date and time, and the first assessment date and time at which at the endpoint criteria is satisfied will be used for this calculation.

10.2.5 Study Day of an Event

Study day is calculated as the date of event of interest – date of treatment + 1 for dates on or after treatment, and date of event of interest – date of treatment for dates prior to treatment.

10.2.6 Duration of an Event

The duration of an event is calculated as the event stop date/time – event start date/time if time is not missing, and event stop date – event start date + 1 if either the start or stop time is missing.

10.2.7 Attribution of Concomitant Medications

For subjects treated with study drug for more than once during the study, concomitant medications will be programmatically assigned to the appropriate attack(s) by comparing the reported dates and times of study drug administration for all exposures with that of start and

end dates and times of concomitant medication. Medications will be assigned to the study drug administration(s) for which the concomitant medication was administered during the 5-day interval after the study drug administration.

If the concomitant medication start time is missing, but the concomitant medication start date is the same as a dosing date, then the concomitant medication will be attributed to the attack that was dosed on that day.

10.2.8 Calculating Years since Diagnosis and Months since Last Attack with Partial Dates

For the calculation of durations using dates with a missing day component, but non-missing month and year components, the date will be assumed to occur at the first of the month. For the calculation of durations using dates with missing day and month components, but a non-missing year component, the date will be assumed to occur at the first of the year. If the year component is missing the duration will be missing.

10.2.9 Handling of Missing Individual Symptom Assessment at Baseline

If an individual symptom assessment was missing at baseline before an on-study icatibant exposure, then the missing symptom assessment will be considered as the mean of other individual symptom severity in the calculation of the composite symptom severity at baseline.

10.2.10 Deriving Time to First Use of Rescue Medication for Subjects with Missing Time to Onset of Symptom Relief

Subjects with missing pretreatment symptom assessments would be excluded from the time to onset of symptom relief analysis. If a subject was excluded from the time to onset of symptom relief analysis, but received a rescue medication within 48+4 hours after an on-study icatibant exposure, then the time between the icatibant treatment and the first rescue treatment use would be considered as time to first use of rescue medication.

10.2.11 Attribution of AEs

For subjects treated with study drug for more than one attack during the study, adverse events will be programmatically assigned to the appropriate attack by comparing the reported dates and times of first study drug administration for all attacks with that of AE onset. Events will be assigned to the latest attack for which the study drug administration preceded the AE onset. If the adverse event start time is missing, but the adverse event start date is the same as a dosing date, then the adverse event will be attributed to the attack that was dosed on that day.

10.2.12 Handling of Missing Data for Adverse Events

For the analysis of AEs, the following assumptions will be applied.

- If the AE severity is missing, it will be assumed that the AE was severe.
- If the AE relationship is missing, it will be assumed that the AE was definitely related to study drug.

10.2.13 **Handling of Immunogenicity Data for the Second and Third Study Drug Exposure**

Combined Visits

In case of combined study visits according to scheduled visit dataset, immunogenicity data supporting two combined visits will be programmatically copied to both visits.

Baseline

The baseline measurements for immunogenicity data for the subsequent exposures were collected every six months, regardless of the dates of icatibant exposures. Therefore, the last non-missing baseline immunogenicity measurement that was prior to a post-baseline measurement will be considered as the baseline measurement for that post-baseline measurement.

10.2.14 **Defining Rescue Medications**

Rescue medications are the medications that were

1. Recorded as rescue medication in the CRF form, started within 48+4 hours (or 3 days where the time is missing) of a study drug exposure for an HAE attack,

or,

2. Recorded as concomitant medication in the CRF form, started within 48+4 hours (or 3 days where the time is missing) after a study drug exposure, is not ongoing, and had an indication that include ‘HAE’ or ‘Swelling’.

10.3 Appendix III: Schedule of Events

10.3.1 Study Schedule of Events (No Attack)

(Pubertal/postpubertal subjects only)	Screening Period	Pre-treatment (Baseline)	Treatment	Post Treatment											Follow-up	
																Month 6 (±7 days) Telephone Contact
Study Day		**Day 1**	**Day 1**	**Day 1**									**Day 2**	**Day 3**	**Day 8 (±1)**	**Day 90 (±7)**	
Time Post Treatment (hours)			**0**	**0.25**	**0.5**	**0.75**	**1**	**2**	**4**	**6**	**8**	**24**	**48**			
Window (hours or minutes)				**(±5) min**	**(±5) min**	**(±5) min**	**(±10) min**	**(±10) min**	**(±0.5) hr**	**(±0.5) hr**	**(±0.5) hr**	**(±4) hr**	**(±4) hr**			
Assessments																
Informed Consent/Assent	X															
Medical History	X	X														
Documentation of HAE Attack(s) Not Treated with icatibant	X[f]														X	
Documentation of Pubertal Changes/Milestones																X
Confirm Documented HAE Diagnosis (via Sponsor's central lab)	X															
C1-INH Assessment	X															
Inclusion/Exclusion Assessment	X	X[a]														

(Pubertal/postpubertal subjects only)	Screening Period	Pre-treatment (Baseline)	Treatment	Post Treatment											Follow-up	
																Month 6 (±7 days) Telephone Contact
Study Day		**Day 1**	**Day 1**	**Day 1**									**Day 2**	**Day 3**	**Day 8 (±1)**	**Day 90 (±7)**	
Time Post Treatment (hours)			**0**	**0.25**	**0.5**	**0.75**	**1**	**2**	**4**	**6**	**8**	**24**	**48**			
Window (hours or minutes)				**(±5) min**	**(±5) min**	**(±5) min**	**(±10) min**	**(±10) min**	**(±0.5) hr**	**(±0.5) hr**	**(±0.5) hr**	**(±4) hr**	**(±4) hr**			
Assessments																
Physical Examination	X	X								X	X[e]			X	X	
Pubertal Status Determination[b]	X	X														
Menstrual Cycle History (in pubertal/postpubertal females)		X													X	
Vital Signs	X	X					X			X	X[e]			X	X	
ECG	X									X	X[e]					
Height and Weight	X	X													X	
Clinical Laboratory Tests (serum chemistry, hematology, urinalysis)		X								X				X	X	
Urine Pregnancy Test (in females of childbearing potential)	X	X													X	

(Pubertal/postpubertal subjects only)	Screening Period	Pre-treatment (Baseline)	Treatment	Post Treatment											Follow-up	
																Month 6 (±7 days) Telephone Contact
Study Day		**Day 1**	**Day 1**	**Day 1**									**Day 2**	**Day 3**	**Day 8 (±1)**	**Day 90 (±7)**	
Time Post Treatment (hours)			**0**	**0.25**	**0.5**	**0.75**	**1**	**2**	**4**	**6**	**8**		**24**	**48**			
Window (hours or minutes)				**(±5) min**	**(±5) min**	**(±5) min**	**(±10) min**	**(±10) min**	**(±0.5) hr**	**(±0.5) hr**	**(±0.5) hr**		**(±4) hr**	**(±4) hr**			
Assessments																	
Reproductive Hormone Assessments (FSH, LH, estradiol, progesterone in females; FSH, LH, testosterone in males)		X								X					X	X	
Investigational Product Administration (single SC dose)			X														
Safety Follow-up Contact													X[c]	X[c]			
Injection Site Reaction Evaluation							X			X	X[e]		X[c]	X[c]	X		
PK Sampling[d]		X		X	X	X	X	X	X	X							
Immunogenicity Evaluation		X													X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X[e]		X[c]	X[c]	X	X	
Adverse Events			X	X	X	X	X	X	X	X	X[e]		X[c]	X[c]	X	X	

(Pubertal/postpubertal subjects only)	Screening Period	Pre-treatment (Baseline)	Treatment	Post Treatment										Follow-up	
															Month 6 (±7 days) Telephone Contact
Study Day		**Day 1**	**Day 1**	**Day 1**								**Day 2**	**Day 3**	**Day 8 (±1)**	**Day 90 (±7)**	
Time Post Treatment (hours)			**0**	**0.25**	**0.5**	**0.75**	**1**	**2**	**4**	**6**	**8**	**24**	**48**			
Window (hours or minutes)				**(±5) min**	**(±5) min**	**(±5) min**	**(±10) min**	**(±10) min**	**(±0.5) hr**	**(±0.5) hr**	**(±0.5) hr**	**(±4) hr**	**(±4) hr**			
Assessments																

Abbreviations: FLACC = Faces, Legs, Activity, Cry, and Consolability (comportmental pain scale); FPS-R = Faces Pain Scale-Revised; FSH = follicle stimulating hormone; HAE = hereditary angioedema; hr = hour; LH = luteinizing hormone min = minute; PK = pharmacokinetic; SC = subcutaneous

[a] The inclusion/exclusion criteria will be confirmed at the Pretreatment (Baseline) Visit.

[b] A subject's classification as prepubertal or pubertal/postpubertal will be determined at the Day 1 pretreatment visit. Note that a subject classified as pubertal/postpubertal at screening will not require further evaluation of pubertal status during the study.

[c] These assessments may be conducted by telephone contact.

[d] The PK sampling times shown are for pubertal/postpubertal subjects.

[e] A subject may be discharged after completion of all assessments at 6 hours post treatment, if deemed medically stable in the investigator's clinical judgment. If this is the case, the assessments scheduled for 8 hours post treatment will be omitted.

[f] For all subjects who remain enrolled in the study for longer than 6 months, a telephone contact will be scheduled every 6 months to collect information concerning HAE attacks not treated with icatibant in the study.

10.3.2 Study Schedule of Events (Initial Icatibant-treated Attack)

Initial Icatibant-treated Attack (All Subjects)	**Screening Period**	**Pre-treatment (Baseline)**	**Treatment**	**Post Treatment**											**Follow-up**	
																Month 6 (±7 days) Telephone Contact
Study Day		**Day 1**	**Day 1**	**Day 1**									**Day 2**	**Day 3**	**Day 8 (±1)**	**Day 90 (±7)**	
Time Post Treatment (hours)			**0**	**0.25**	**0.5**	**0.75**	**1**	**2**	**4**	**6**	**8[e]**	**24**	**48**			
Window (hours or minutes)				**(±5) min**	**(±5) min**	**(±5) min**	**(±10) min**	**(±10) min**	**(±0.5) hr**	**(±0.5) hr**	**(±0.5) hr**	**(±4) hr**	**(±4) hr**			
Assessments																
Informed Consent/Assent	X															
Medical History	X	X														
Documentation of HAE Attack(s) Not Treated with icatibant	X[h]														X	
Documentation of Pubertal Changes/Milestones																X
Confirm Documented HAE Diagnosis (via Sponsor's Central Laboratory)	X															
C1-INH Assessment	X															
Inclusion/Exclusion Assessment	X	X[a]														
Physical Examination	X	X								X[g]	X[g]			X	X	

Initial Icatibant-treated Attack (All Subjects)	**Screening Period**	**Pre-treatment (Baseline)**	**Treatment**	**Post Treatment**											**Follow-up**	
																Month 6 (±7 days) Telephone Contact
Study Day		**Day 1**	**Day 1**	**Day 1**								**Day 2**	**Day 3**	**Day 8 (±1)**	**Day 90 (±7)**	
Time Post Treatment (hours)			**0**	**0.25**	**0.5**	**0.75**	**1**	**2**	**4**	**6**	**8[e]**	**24**	**48**			
Window (hours or minutes)				**(±5) min**	**(±5) min**	**(±5) min**	**(±10) min**	**(±10) min**	**(±0.5) hr**	**(±0.5) hr**	**(±0.5) hr**	**(±4) hr**	**(±4) hr**			
Assessments																
Pubertal Status Determination[b]	X	X														
Menstrual Cycle History (in pubertal/postpubertal females)		X													X	
Vital Signs	X	X					X			X[g]	X[g]			X	X	
ECG	X									X[g]	X[g]					
Height and Weight	X	X													X	
Subject Self-assessment of HAE-related Pain Using diary FPS-R (in subjects 4 years of age and older, and before blood work, if applicable)		X					X	X	X	X[f]	X[e,f]	X	X			
Investigator Assessment of HAE Symptoms		X					X	X	X	X[f]	X[f]					

Initial Icatibant-treated Attack (All Subjects)	**Screening Period**	**Pre-treatment (Baseline)**	**Treatment**	**Post Treatment**											**Follow-up**	
																Month 6 (±7 days) Telephone Contact
Study Day		**Day 1**	**Day 1**	**Day 1**									**Day 2**	**Day 3**	**Day 8 (±1)**	**Day 90 (±7)**	
Time Post Treatment (hours)			**0**	**0.25**	**0.5**	**0.75**	**1**	**2**	**4**	**6**	**8[e]**	**24**	**48**			
Window (hours or minutes)				**(±5) min**	**(±5) min**	**(±5) min**	**(±10) min**	**(±10) min**	**(±0.5) hr**	**(±0.5) hr**	**(±0.5) hr**	**(±4) hr**	**(±4) hr**			
Assessments																
Investigator Assessment of HAE-related Pain Using FLACC (in subjects younger than 4 years of age, and before blood work, if applicable)		X					X	X	X	X[f]	X[f]					
Clinical Laboratory Tests (serum chemistry, hematology, urinalysis)		X								X				X	X	
Urine Pregnancy Test (in females of childbearing potential)	X	X													X	
Reproductive Hormone Assessments (FSH, LH, estradiol, progesterone in females; FSH, LH, testosterone in males)		X								X				X	X	

Initial Icatibant-treated Attack (All Subjects)	**Screening Period**	**Pre-treatment (Baseline)**	**Treatment**	**Post Treatment**											**Follow-up**	
																Month 6 (±7 days) Telephone Contact
Study Day		**Day 1**	**Day 1**	**Day 1**									**Day 2**	**Day 3**	**Day 8 (±1)**	**Day 90 (±7)**	
Time Post Treatment (hours)			**0**	**0.25**	**0.5**	**0.75**	**1**	**2**	**4**	**6**	**8[e]**	**24**	**48**			
Window (hours or minutes)				**(±5) min**	**(±5) min**	**(±5) min**	**(±10) min**	**(±10) min**	**(±0.5) hr**	**(±0.5) hr**	**(±0.5) hr**	**(±4) hr**	**(±4) hr**			
Assessments																
Investigational Product Administration (single SC dose)			X													
Safety Follow-up Contact												X[c]	X[c]			
Injection Site Reaction Evaluation							X			X[f]	X[f]	X[c]	X[c]	X		
PK Sampling[d]		X		X	X	X	X	X	X	X						
Immunogenicity Evaluation		X												X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X[f]	X[f]	X[c]	X[c]	X	X	
Adverse Events			X	X	X	X	X	X	X	X[f]	X[f]	X[c]	X[c]	X	X	

Initial Icatibant-treated Attack (All Subjects)	Screening Period	Pre-treatment (Baseline)	Treatment	Post Treatment											Follow-up	
																Month 6 (±7 days) Telephone Contact
Study Day		**Day 1**	**Day 1**	**Day 1**									**Day 2**	**Day 3**	**Day 8 (±1)**	**Day 90 (±7)**	
Time Post Treatment (hours)			**0**	**0.25**	**0.5**	**0.75**	**1**	**2**	**4**	**6**	**8[e]**	**24**	**48**			
Window (hours or minutes)				**(±5) min**	**(±5) min**	**(±5) min**	**(±10) min**	**(±10) min**	**(±0.5) hr**	**(±0.5) hr**	**(±0.5) hr**	**(±4) hr**	**(±4) hr**			
Assessments																

Abbreviations: FLACC = Faces, Legs, Activity, Cry, and Consolability (comportmental pain scale); FPS-R = Faces Pain Scale-Revised; FSH = follicle stimulating hormone; HAE = hereditary angioedema; hr = hour; LH = luteinizing hormone min = minute; PK = pharmacokinetic; SC = subcutaneous

[a] The inclusion/exclusion criteria will be confirmed at the Pretreatment (Baseline) Visit.

[b] A subject's classification as prepubertal or pubertal/postpubertal will be determined at the Day 1 pretreatment visit. Note that a subject classified as pubertal/postpubertal at screening will not require further evaluation of pubertal status during the study.

[c] These assessments may be conducted by telephone contact.

[d] The PK sampling times shown are for pubertal/postpubertal subjects. Prepubertal subjects will have blood samples drawn on Day 1 prior to dosing and at 15 (±5) minutes, 30 (±5) minutes, 2 hours (±10 minutes), 4 (±0.5) hours, and 6 (±0.5) hours post dose.

[e] A subject may be discharged after completion of all assessments at 6 hours post treatment, if deemed medically stable in the investigator's clinical judgment and the subject's HAE symptoms have resolved (the subject's investigator-rated symptom score = zero, denoting the absence of symptoms). If this is the case, the assessments scheduled for 8 hours post treatment will be omitted with the exception of subject self-assessment of HAE-related pain using the diary FPS-R.

[f] If the subject's HAE symptoms have not resolved at 6 hours post treatment (the subject's investigator-rated symptom score ≠ zero) and the subject is not to be discharged after completion of assessments at the 6-hour time point, the assessments indicated will be performed at both 6 AND 8 hours post treatment.

[g] If the subject's HAE symptoms have not resolved at 6 hours post treatment (the subject's investigator-rated symptom score ≠ zero) and the subject is not to be discharged after completion of assessments at the 6-hour time point, the assessments indicated will be performed at either 6 OR 8 hours post treatment.

[h] For all subjects who remain enrolled in the study for longer than 6 months, a telephone contact will be scheduled every 6 months to collect information concerning HAE attacks not treated with icatibant in the study.

10.3.3 Study Schedule of Events (Subsequent Icatibant-treated Attacks)

	Subsequent Icatibant-Treated Attack Baseline [a] (Site)	Every Month after Baseline (Home)[b]	Treatment						Post Treatment	
			Day 1 (Site or Home)					Day 2 (Home)	Day 8 (±1)[c] (Site)	Day 90 (±7)[c] (Site)
Time Post Treatment (hours)			**Prior to Dosing**	**0**	**1**	**2**	**6-8**	**24**		
Window (hours or minutes)					**(±10) min**	**(±10) min**	**(±4) hr**	**(±4) hr**		
Assessments										
Inclusion/Exclusion Assessment	X	X								
Menstrual Cycle History	X									X
Documentation of HAE Attack(s) Not Treated with icatibant	X	X								X
Physical Examination	X									X
Vital Signs	X								X	X
Height and Weight	X									X
Clinical Laboratory Tests (serum chemistry/hematology)	X									X
Urine Pregnancy Test (in females of childbearing potential)	X		X							X
Reproductive Hormone Assessments (FSH, LH, estradiol, progesterone in females; FSH, LH, testosterone in males)	X								X	X
Immunogenicity Evaluation	X								X	X
Training on icatibant administration [d]	X									
Training on how to assess HAE symptoms, time to initial symptom relief, and injection site reactions [d]	X									
Dispense 1 syringe of icatibant [d]	X									
Contact investigator with weight to confirm dose [d]		X								
Contact investigator in the event of an HAE attack			X[b]							
Investigational Product Administration (single SC dose)				X[e]						
Subject Self-assessment of HAE-related Pain Using FPS-R			X		X	X[f]	X[f]	X		
Investigator Assessment of HAE Symptoms			X[g]		X[g,h]	X[g,h]	X[g,h]			

	Subsequent Icatibant-Treated Attack Baseline [a] (Site)	**Every Month after Baseline (Home)[b]**	**Treatment**						**Post Treatment**	
			Day 1 (Site or Home)					**Day 2 (Home)**	**Day 8 (±1)[c] (Site)**	**Day 90 (±7)[c] (Site)**
Time Post Treatment (hours)			**Prior to Dosing**	**0**	**1**	**2**	**6-8**	**24**		
Window (hours or minutes)					**(±10) min**	**(±10) min**	**(±4) hr**	**(±4) hr**		
Assessments										
Home Healthcare Provider or Parent/Legal Guardian/Caregiver Assessment of HAE Symptoms			X		X[h]	X[h]	X[h]			
Record Injection Site Reactions					X[b, i]	X[b, i]	X[b, i]	X[e]	X	
Safety Follow-up Contact							X[b]			
Concomitant Medications	X	X	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X	X
Adverse Events	X	X	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X	X
Return study drug[d]									X	

Abbreviations: FPS-R=Faces Pain Scale-Revised; FSH=follicle stimulating hormone; HAE=hereditary angioedema; LH=luteinizing hormone; SC = subcutaneous

[a] All evaluations and sample collections must be performed at the hospital/study center within 6 months prior to treatment if a repeat attack does not occur within 6 months. If a second "baseline" visit is conducted due to lack of repeat attacks, one of the monthly phone calls may overlap with the onsite visit. In this case, a monthly call would not be necessary.

[b] These assessments may be conducted by telephone contact.

[c] If a subsequent attack occurs within 3 days of the Day 8 follow-up visit for the previous attack, the visits for Day 1 (of the subsequent icatibant-treated attack) and Day 8 (of the prior icatibant-treated attack) will be combined. If a subsequent attack occurs within 7 days of the Day 90 follow-up visit for the previous attack, the visits for Day 8 (of the subsequent icatibant-treated attack) and Day 90 (of the prior icatibant-treated attack) will be combined.

[d] For subjects who have expressed an interest in self-administering or having a parent/legal guardian/caregiver administer icatibant in the home.

[e] For subsequent attacks, study drug may be administered by study site personnel at the hospital/study center or by qualified home healthcare personnel at the subject's home. Alternatively, a parent/legal guardian/caregiver will be allowed to administer or the subject (under the supervision of a parent/legal guardian/caregiver) will be allowed to self-administer the investigational product after having received appropriate training. For all subsequent laryngeal attacks, subjects should be advised to seek medical attention in an appropriate healthcare facility immediately following treatment with icatibant.

[f] If after the completion of the assessments scheduled for 2 hours post-treatment, the subject's pain is absent, no further Day 1 assessments are required. If the subject's pain at 2 hours post-treatment is NOT absent, the subject will be assessed every 2 hours until pain is absent.

[g] For subjects treated at the hospital/study center only.

[h] The subject will be observed for a minimum of 2 hours after icatibant administration. If after the completion of the assessments scheduled for 2 hours post-treatment, the subject's symptoms are absent or mild, no further Day 1 assessments are required. If the subject's symptoms at 2 hours post-treatment are moderate, severe, or very severe, the subject will be assessed every 2 hours until the subject's symptoms are absent or mild.

[i] Injection site reaction will be recorded (1 hour [±10 minutes] post dose and 2 [±0.5] hours post dose, and every 2 [±0.5] hours until injection site reaction is mild or absent (if the subject's injection site reaction is not mild or absent at 2 hours post dose)