

Clinical Trial Protocol: HGT-FIR-086

Study 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

Study Number: HGT-FIR-086

Study Phase: III

Product Name: Icatibant (Firazyr[®])

Indication: Hereditary angioedema

Investigators: Multicenter

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Confidentiality Statement

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Shire Human Genetic Therapies, Inc.

SYNOPSIS

Sponsor:

Shire Orphan Therapies, Inc.

Name of Finished Product:

Icatibant (Firazyr®)

Study 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

Study Number:

HGT-FIR-086

Study Phase: III

Investigational Product; Dose; and Mode of Administration:

Single dose of icatibant 0.4 mg/kg subcutaneous (SC) up to a maximal dose of 30 mg

Comparator; Dose; and Mode of Administration:

Not applicable

Study Objectives:

The objectives of this study are:

- To investigate the pharmacokinetics (PK), tolerability, and safety of a single subcutaneous (SC) dose of icatibant in children and adolescents with hereditary angioedema (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.

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.

Study Endpoints:

Primary endpoints:

- 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, electrocardiogram (ECG) recordings, physical examination, clinical laboratory parameters (serum chemistry [including liver function tests], hematology, urinalysis), reproductive hormone levels, and immunogenicity (anti-icatibant antibodies).

Secondary endpoints (only for subjects treated with icatibant during a HAE attack):

Time to onset of relief of symptoms and time to minimal symptoms, as measured by investigator- and subject-reported outcomes

- For subjects 2 to less than 18 years of age: investigator assessment and scoring of cutaneous, abdominal and laryngeal symptoms of acute HAE attacks by an investigator-rated symptom score.
- For subjects 4 years of age and older: subject self-assessment of HAE related pain using the Faces Pain Scale-Revised (FPS-R).
- For subjects less than 4 years of age: investigator assessment of HAE-related pain (cutaneous, abdominal and laryngeal) using a validated pain scale (Faces, Legs, Activity, Cry, and Consolability [FLACC]).

Incidence of rescue medication use.

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

Study Design:

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

The study will enroll 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).

At least 10 prepubertal children and at least 20 adolescents (including 10 treated during a HAE attack) must be enrolled in the study.

Study Methodology:

A subject's classification as prepubertal or pubertal/postpubertal will be determined at screening and, if appropriate, at the time of the first icatibant-treated HAE attack.

Subjects classified as pubertal/postpubertal at screening will not require further evaluation of pubertal status during the study, whereas subjects classified as prepubertal at screening will have their pubertal status reassessed at the time of their first icatibant-treated attack visit.

After a qualifying screening period, the PK, safety/tolerability, and efficacy of treatment with SC icatibant will be evaluated in at least 20 subjects (10 prepubertal and 10 pubertal/postpubertal subjects) who present with cutaneous, abdominal, or laryngeal symptoms of an acute attack of HAE. Subjects should initiate treatment with icatibant within 12 hours of the onset of symptoms; however, there are no prespecified attack severity criteria that are required for treatment. Subjects with attacks considered to be

mild, moderate, or severe are all potentially eligible to receive treatment with icatibant.

The PK and safety/tolerability of SC icatibant will be evaluated in at least 10 additional pubertal/postpubertal subjects who meet screening criteria and receive treatment with SC icatibant in the absence of a current acute HAE attack.

Initially, enrollment and dosing of pubertal/postpubertal subjects will precede that of prepubertal subjects. After the first 4 subjects in the pubertal/postpubertal group have been treated with icatibant (whether during or in the absence of attack), PK, safety/tolerability, and efficacy (as appropriate) will be reviewed by an independent Data and Safety Monitoring Board (DSMB). The DSMB review of the first 4 subjects shall be completed prior to continuing enrollment of additional pubertal/postpubertal subjects, treatment of second and third HAE attacks in pubertal/postpubertal subjects, and initiating enrollment of subjects in the prepubertal group.

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.

After having received initial treatment with icatibant, either during or in the absence of an attack, at least 10 pubertal/postpubertal subjects who subsequently experience an acute HAE attack may continue to receive treatment with icatibant as a single SC administration per attack for a total of 3 eligible icatibant-treated attacks. Further treatment with icatibant is contingent upon presentation of an acute cutaneous, abdominal, or laryngeal attack of HAE at least 7 days after prior treatment. All primary and secondary outcomes as above (including anti-icatibant antibodies and reproductive hormones) will be measured in these pubertal/postpubertal subjects after each administration. Note that for some of the pubertal/postpubertal subjects who receive further treatment, ie, those who provided PK and safety/tolerability measurements without an attack, their first icatibant-treated attack will represent their second on-study exposure to icatibant for safety analysis purposes.

The investigator will schedule a telephone contact approximately 6 months after Day 1 of each icatibant-treated attack to obtain specific updates concerning pubertal changes/milestones.

Study Population:

The study will enroll a sufficient number of children and adolescents with HAE to ensure study completion of 30 subjects. The study population to provide efficacy, PK, and safety/tolerability measurements will consist of at least 20 subjects from 2 to less than 18 years of age of whom at least 10 are prepubertal and at least 10 are pubertal/postpubertal at the time of their first icatibant-treated acute cutaneous, abdominal, or laryngeal attack of HAE. An additional 10 subjects who are pubertal/postpubertal at the time of enrollment, but who are not experiencing a current HAE attack, will provide PK and safety/tolerability measurements only.

Study Inclusion and Exclusion Criteria:

Subjects must meet all of the following criteria to be considered eligible for enrollment:

1. Two to <18 years of age (ie, from the second birthday through the day prior to the eighteenth birthday) at the time of enrollment and treatment with icatibant.
 - Prepubertal and pubertal/postpubertal subjects experiencing an acute cutaneous, abdominal, or laryngeal HAE attack treated with icatibant as part of this study.
 - Pubertal/postpubertal subjects with HAE who are treated with icatibant as part of this study, but not during an attack.
2. Documented diagnosis of HAE type I or II. Diagnosis may be on the basis of historical data: family history, characteristic attack manifestations, recurrent attacks, historical C1-INH deficiency, and exclusion of other forms of angioedema. Inclusion will be permitted initially based on medical history only if a clear diagnosis has been made based on all of the preceding criteria. However, the diagnosis must be confirmed prior to treatment by documented immunogenic and/or functional C1-INH deficiency (C1-INH protein level below the lower limit of normal and/or functional level <50% of normal) as performed by the Sponsor's central laboratory.
3. Informed consent (and subject assent as appropriate) signed by the subject's parent(s) or legal guardian(s).

Subjects who meet any of the following criteria will be excluded from the study:

1. Diagnosis of angioedema other than HAE.
2. Participation in another clinical trial that involves use of any investigational product (drug or device) within 30 days prior to study enrollment or at any time during the study.
3. Any known factor/disease that might interfere with the treatment compliance, study conduct, or result interpretation.
4. Congenital or acquired cardiac anomalies that interfere significantly with cardiac function.
5. Treatment with angiotensin converting enzyme (ACE) inhibitors within 7 days prior to treatment.
6. Use of hormonal contraception within the 90 days prior to treatment.
7. Androgen use (eg, stanozolol, danazol, oxandrolone, methyltestosterone, testosterone within the 90 days prior to treatment).
8. Pregnancy or breastfeeding.
9. A physical condition that interferes with pubertal status determination.

Study Duration:

At minimum, the duration of a subject's active participation in the study will consist of single day dosing with 90-day follow-up.

Once eligibility is established at screening, the subject will be enrolled into the study but will enter a period of inactive participation of variable duration until such time as the subject experiences an acute attack of HAE and is offered treatment. For those pubertal/postpubertal subjects who will be treated without an attack, eligibility will be established at screening and the subject will be immediately enrolled and treated with icatibant. At the time of enrollment, the subject will enter a 90-day period of active participation which will consist of treatment with a single SC administration of icatibant on Day 1 through follow-up at Day 90.

After receiving the first treatment with icatibant with or without an attack (N=20), at least 10 pubertal/postpubertal subjects who present with subsequent attacks of acute HAE will continue to receive treatment with icatibant for a total of 3 attacks each. Thus, the period of active participation in the study for prepubertal subjects will be approximately 90 days, while that for pubertal/postpubertal subjects could be a maximum of approximately 270 or 360 days (3 separate active periods of approximately 90 days for those treated with icatibant during an attack; 4 separate active periods for those treated without an attack), with each active period separated by periods of inactive participation of variable duration. The period of active participation may be shorter if pubertal/postpubertal subjects have recurrent HAE attacks in between the Day 8 and Day 90 visits for a prior icatibant-treated HAE attack. Telephone follow-up will occur approximately 6 months after each icatibant-treated attack.

Once the tenth prepubertal subject and the twentieth pubertal/postpubertal subject have completed the 6-month follow-up after the initial treatment, and the tenth pubertal/postpubertal subject has completed the 6-month follow-up after his or her third and final treatment for an attack, the study will be closed.

Pharmacokinetic Variables:

Individual patient PK variables for icatibant and major metabolites will be determined from the respective plasma concentration time profiles where appropriate, using noncompartmental methods.

A population PK model will be derived to evaluate the correlation of key covariates (ie age, body weight, gender) on the pharmacokinetic profile of icatibant.

Primary and secondary pharmacokinetic parameter estimates will be reported and include time to peak concentration (T_{max}), actual peak (C_{max}) and minimum (C_{min}) concentrations, clearance (CL/F), actual area under the plasma concentration-time curve (AUC_{0-last} and AUC_{0-inf}), mean residence time (MRT), volume of distribution at steady state (V_{ss}/F) and elimination half-life ($t_{1/2}$).

Safety Assessments:

Safety will be assessed by standard criteria including physical examination, vital signs, ECGs, clinical laboratory evaluations (clinical chemistry [including liver function tests], hematology, urinalysis), and immunogenicity (presence of anti-icatibant antibodies), recording of concomitant medications, and monitoring of adverse events. Local tolerability will be assessed by evaluation of reactions at the site of icatibant administration (injection site). Levels of reproductive hormones will be assessed in

female (follicle stimulating hormone [FSH], luteinizing hormone [LH], estradiol, progesterone) and male (FSH, LH, testosterone) subjects.

Efficacy Assessments:

Efficacy will be assessed using both investigator- and subject-reported outcomes, depending on the subject's age. Investigators will assess and score symptoms of acute cutaneous, abdominal, and laryngeal attacks of HAE for all subjects using an investigator-rated symptom score. Subjects who are 4 years of age or older will perform a self-assessment of HAE-related pain using the FPS-R instrument. Subjects who are younger than 4 years of age will have symptoms assessed by the investigator only; including an assessment of HAE-related pain (cutaneous, abdominal, and laryngeal) using the FLACC scale. The time of initial symptom relief as assessed by the investigator will be recorded for all subjects.

(Efficacy assessments will not be performed for those pubertal/postpubertal subjects treated with icatibant in the absence of an HAE attack).

Statistical Methods:

Summary statistics for continuous variables will include the number of subjects, the mean, median, standard deviation, and range. For PK parameters, the coefficient of variation and geometric mean also will be provided.

For categorical data, summaries will include counts and percentages. For time-to-event data, the median time to event and other summary statistics will be estimated using Kaplan-Meier methodology.

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
- The PK Population will consist of those subjects who were treated with icatibant and had sufficient icatibant plasma concentration time measurements to derive primary PK parameters.
- The Safety Population will consist of those subjects who were treated with icatibant at least once

Subject disposition, demographic and baseline characteristics and medical history will be summarized separately for the Efficacy Population and the Safety Population.

Efficacy analyses will be based on the Efficacy Population. Efficacy endpoints, including change from baseline when appropriate, will be summarized descriptively. The primary efficacy endpoint is the time to onset of symptom relief measured using the investigator-rated symptom score. The time to onset of symptom relief is defined as the earliest time post treatment at which there is a 20% improvement in the average post-treatment symptom score with no worsening of any single component score.

Plasma concentrations of icatibant by time point and the PK parameters will be summarized descriptively.

Safety and tolerability analyses will be based on the Safety Population. The assessment of safety will be based mainly on the frequency of adverse events. Adverse events will be

summarized by presenting the number and percentage of subjects having any adverse event, having an adverse event in each body system, and having each individual adverse event using the Medical Dictionary for Regulatory Activity (MedDRA). Adverse events also will be tabulated by severity and relationship to treatment.

Local tolerability will include symptoms at the injection site and will be assessed separately from general reports of adverse events. Local tolerability will be tabulated and summarized according to the type and severity of the injection site reaction.

The change from baseline in the secretion of reproductive hormones and the change from baseline in HAE symptoms (as reported by the investigator or subject) will be summarized descriptively.

Date of Amended Protocol: 19 June 2013

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACE	angiotensin converting enzyme
AE	adverse event
AUC	area under the curve extrapolated to zero
BMI	body mass index
BSA	body surface area
C1-INH	C1 esterase inhibitor (human)
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CL/F	total body clearance
C _{max}	maximum observed plasma concentration
C _{min}	minimum plasma drug concentration
CRF	case report form
CRO	contract research organization
CYP	cytochrome P450
DHEA	dehydroepiandrosterone
DHEA-S	dehydroepiandrosterone sulfate
DSMB	Data and Safety Monitoring Board
EC ₅₀	half maximal effective concentration
ECG	electrocardiogram
e-diary	electronic diary
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
FFP	fresh frozen plasma
FLACC	Faces, Legs, Activity, Cry, and Consolability (comportmental pain scale)
FPS-R	Faces Pain Scale-Revised
FSH	follicle stimulating hormone
GAM	general additive model
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GnRH	gonadotrophin releasing hormone
HAE	hereditary angioedema
hCG	human chorionic gonadotropin

Abbreviation	Definition
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	intravenous(ly)
kg	kilogram(s)
LBW	lean body weight
LC-MS	liquid chromatography–mass spectrometry
LH	luteinizing hormone
LOCF	last observation carried forward
LOQ	limit of quantification
MedDRA	Medical Dictionary for Regulatory Activity
mg	milligram
mL	milliliter(s)
mm	millimeters
MRT	mean residual time
ng	nanogram(s)
NSAID	non-steroidal anti-inflammatory drug
PD	pharmacodynamic
PK	pharmacokinetic(s)
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System®
SC	subcutaneous
SHBG	sex hormone binding globulin
SOC	system organ class
$t_{1/2}$	terminal elimination half-life
TBW	total body weight
T_{max}	time to maximum concentration
US	United States
VAS	visual analog scale
V_{ss}	volume of distribution at steady state
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

1.1 Disease Background

Bradykinin is responsible for the clinical symptoms of hereditary angioedema (HAE), causing increased vascular permeability, vasodilation, and contraction of visceral smooth muscle. HAE is a rare autosomal dominant disorder characterized clinically by recurrent and self-limiting attacks of edema of the skin, gastrointestinal tract, and larynx. Its prevalence is estimated at approximately 1 in 5000.

HAE is caused by either a quantitative (Type I) or qualitative (Type II) deficiency of C1 inhibitor. C1 inhibitor functions in several biochemical pathways, including inhibition of C1 complement auto-activation, inactivation of coagulation factors XIIa, XIIf, XIa, and inhibition of activated kallikrein. After a triggering event, the deficiency in C1 inhibitor results in accelerated release of bradykinin by its cleavage from high molecular weight kininogen by activated kallikrein. Bradykinin is the principal mediator of the increased vascular permeability characteristic of HAE.

Icatibant is a synthetic decapeptide with a structure similar to bradykinin that acts as an antagonist of the bradykinin B2 receptor. It is highly specific for the B2 receptor, and is characterized by high potency and a long half-life to allow systemic administration by subcutaneous injection. Inhibition of bradykinin action through use of a B2 receptor antagonist is a therapeutic strategy for treatment of clinical symptoms of HAE, and represents the rationale for use of icatibant in treatment of acute attacks of angioedema in HAE patients. In adults, SC icatibant 30 mg has been shown to produce a rapid and durable response in the treatment of cutaneous, abdominal, and laryngeal attacks of acute HAE. A single SC injection is generally sufficient for rapid relief of symptoms of acute HAE attacks irrespective of edema location. Repeated use of icatibant over time for treatment of multiple acute HAE attacks in adults produces a consistent response at each attack, with no diminution of efficacy. When self-administered by adults experiencing an acute HAE attack, icatibant also produces a rapid and safe treatment response.

The management of HAE in pediatric patients is complex. The age at onset, the frequency and duration of symptoms, as well as the severity of attacks all exhibit substantial inter-individual variation. Although acute episodes of HAE may occur at any age, the median age at first symptomatic HAE attack is estimated to range between 4 to 11 years (reviewed by Farkas^H). Subcutaneous edema of the extremities, face, neck, torso, and genitals is the most common, and usually the earliest, manifestation of HAE seen in children. In the gastrointestinal tract, submucosal edema may be associated with colicky abdominal pain, nausea, vomiting, and diarrhea. In a large pediatric cohort, increased frequency and severity of HAE symptoms were reported at between 3 and 6 years of age and at around puberty, and were attributed to physiological changes which occur during these periods of development.^H

Though infrequent compared to cutaneous and abdominal manifestations, attacks of acute HAE involving the larynx may result in submucosal edema of the upper airways and risk of death by asphyxiation if undiagnosed and/or untreated. In comparison to adults, asphyxia may ensue more rapidly in children because of smaller airway diameter.

Prompt control of attacks, short-term prophylaxis, "intermittent" prophylaxis, long-term prophylaxis and emergency therapy are recommended for the management of pediatric HAE.^H Treatment options for children with HAE according to current guidelines include antifibrinolytics, attenuated androgens, and C1 inhibitor (C1-INH) replacement therapy. Current guidelines favor antifibrinolytics for long-term prophylaxis because of their safety profile relative to attenuated androgens. The preferred antifibrinolytic agent, where approved for use, is tranexamic acid, though ϵ -aminocaproic acid is sometimes also used for this purpose. C1-INH replacement therapy has been used successfully for management of acute attacks of HAE in children; however, its use in children is associated with the same drawbacks (ie, requirement for intravenous [IV] administration, potential to elicit hypersensitivity reactions, possible transmission of blood-borne infectious agents) as in adults.

1.2 Previous Clinical Studies

1.2.1 Pharmacokinetics of Icatibant

The pharmacokinetic (PK) properties of icatibant have been characterized extensively in studies using both IV and SC administration to healthy adult subjects and adult subjects with HAE. The PK profile of icatibant in adults with HAE (JE049-2101) is similar to that in healthy adults.

After SC administration of a single 30 mg dose of icatibant to healthy adult subjects (N=96), a mean (\pm standard deviation) maximum plasma concentration (C_{max}) of 974 ± 280 ng/mL was observed after approximately 0.75 hours. The mean area under the concentration-time curve ($AUC_{0-\infty}$) after a single 30 mg dose was 2165 ± 568 ng•hr/mL, with no evidence of accumulation of icatibant after three 30 mg doses administered 6 hours apart.

Plasma clearance after SC administration of icatibant was 245 ± 58 mL/min with a mean elimination half-life of 1.4 ± 0.4 hours and volume of distribution at steady state (V_{ss}) of 29.0 ± 8.7 L. The information obtained from Phase III clinical studies clearly demonstrated that SC icatibant 30 mg is a clinically safe and effective treatment for attacks of acute angioedema across a wide range of subject demographics, including age, sex, and body weight.

Icatibant is extensively metabolized by proteolytic enzymes to inactive metabolites that are primarily excreted in the urine, with less than 10% of the dose eliminated as unchanged drug. Icatibant is not degraded by oxidative metabolic pathways, and is not an inhibitor of major cytochrome P450 (CYP) isoenzymes (CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4) and is not an inducer of CYP 1A2 and 3A4.

Clinical PK studies demonstrate that for mild to moderate impairment of renal or hepatic function no dose adjustment is necessary. In 10 subjects with hepatorenal syndrome (glomerular filtration rate (GFR) 30 to 60 mL/min), clearance of icatibant was not dependent on renal function. Icatibant clearance in subjects with a wide range of hepatic impairment (Child-Pugh score ≥ 7 and ≤ 15) was similar to that in healthy subjects.

1.2.2 Overview of the Safety and Efficacy of Sc Icatibant in Clinical Studies

Despite the rarity of HAE, a robust clinical dataset supports the safety of icatibant. As of 18 April 2013, a total of 2214 doses of SC icatibant have been administered in clinical trials. In Phase I-III studies, icatibant has been administered by a healthcare professional to 177 healthy subjects and to 269 subjects with HAE. In completed Phase III studies, the maximum number of icatibant-treated attacks in a single subject was 142 (over approximately 3 years) in JE049-2102, 22 (over approximately 1.5 years) in JE049-2103, and 34 (over approximately 3 years) in HGT-FIR-054.

Icatibant has been well tolerated in all clinical studies. Nonserious reactions (erythema, swelling, burning sensation, itching, warmth, and cutaneous pain) at the injection site were the most commonly reported adverse effects in clinical studies, and occurred transiently in almost all subjects after SC injection of icatibant. These reactions were self resolving and typically mild to moderate in severity. Icatibant was generally non-immunogenic. Over repeated treatment for multiple attacks in the 3 controlled Phase III studies, transient positivity in test results for the presence of anti-icatibant antibodies was observed in rare cases. No hypersensitivity or anaphylactic reactions were reported with use of icatibant.

Collectively, across the 3 controlled Phase III studies, subjects on icatibant had a faster median time to onset of symptom relief (2.0, 2.5, and 2.0 hours, respectively) compared to tranexamic acid (12.0 hours) and placebo (4.6 and 19.8 hours). The treatment effect of icatibant was confirmed by secondary efficacy endpoints. In subgroup analyses of data pooled across these 3 controlled Phase III studies, the time to onset of symptom relief and time to onset of primary symptom relief were similar regardless of age group, sex, race, weight or whether or not the subject used androgens or antifibrinolytic agents. A consistent treatment response was observed across repeated attacks in studies HGT-FIR-054, JE049-2102, and JE049-2103, during which a total of 237 subjects were treated with 1,383 doses of SC icatibant for 1278 acute attacks of HAE.

Thus, the clinical data supports the favorable benefit-risk profile of icatibant as a treatment for acute attacks of HAE.

The recommended dose of icatibant in adults is 1 SC injection of 3 mL (30 mg) administered in the abdominal area for the treatment of acute attacks of HAE. In case of insufficient relief or recurrence of symptoms, a second injection of icatibant can be administered after 6 hours. No more than 3 injections of icatibant should be administered in a 24-hour period. In clinical trials, a single SC injection of icatibant was generally sufficient to treat an acute HAE attack. No differences in the efficacy or safety of icatibant in clinical trials have been observed between sexes; no dose adjustments for adult males or females are necessary.

Please refer to the current edition of the Investigator's Brochure for further information concerning the safety and clinical development of icatibant.

1.2.3 Investigations of Potential Effects of Bradykinin Inhibition on Reproductive Function

In nonclinical studies performed in rat and dog, high repeated doses of icatibant have been associated with effects on sexual organs and sexual maturation. These findings are consistent with published data showing a role of bradykinin action through B2 receptors in the control of reproductive hormone release.

Completed juvenile toxicology study in sexually immature rats involving fertility assessment over the course of 7-weeks of administration of icatibant (3.0, 9.0, or 25 mg/kg/day) elicited effects on reproductive organs and impaired fertility. These findings on reproductive tissues in males to be largely expected due to the known effects of antagonizing the bradykinin B2 receptor and were seen to be partially or fully reversible during the dose-free recovery period.

Nonclinical evaluation of icatibant in rats demonstrated icatibant-related effects on hormone levels with secondary effects observed on reproductive organs in a 26-week rat toxicity study (JE049-0163) at dose levels of 3.0 and 9.0 mg/kg/day. However, these findings did not result in a functional deficit in terms of the mating performance and fertility of the male rat at doses lower than 9.0 mg/kg. Additionally, the dose regimen utilized in this study represents an exaggeration of the clinical use of icatibant, thereby minimizing the impact of the findings to what would potentially be observed in a clinical setting.

A retrospective analysis, prompted by nonclinical observations, of serum levels of gonadotrophic hormone levels (follicle-stimulating hormone [FSH] and luteinizing hormone [LH]) in 16 male and 16 female healthy volunteers in an Phase I study (JE049-1103) showed no clinically important changes from baseline in levels of FSH and LH after administration of 3 SC doses (30 mg each) of icatibant 6 hours apart on Day 1 followed by single SC doses (30 mg) on Day 8 and Day 15.

Phase 1 study (HGT-FIR-062) was a double-blind, randomized, placebo-controlled, single center study to assess the effect of icatibant on serum reproductive hormone levels in male and premenopausal female healthy adult subjects and seminal fluid analysis in healthy male adult subjects. This study was intended to definitively determine the effect of repeated administration of 3 SC doses of icatibant 30 mg on reproductive hormone levels in adults prior to any investigational use in pediatric subjects per the recommendation of the European Medicines Agency (EMA). Subjects were randomized to receive icatibant or placebo as a single SC injection at 6 hour intervals 3 times daily on Days 1, 4, and 7 of the treatment week (total 9 doses/week) with an approximately 8 week follow-up phase.

Thirty-nine adult subjects (16 females and 23 males) were enrolled and treated in Study HGT-FIR-062; 32 subjects completed the study in its entirety (7 subjects did not return for follow-up visits). No negative trends were seen with regard to the results of basal or gonadotrophin releasing hormone (GnRH)-stimulated reproductive hormone assessments in female and male subjects treated with icatibant or placebo. Though the number of subjects participating was small, and the study was not powered for statistical significance, a suppressive effect of icatibant on GnRH-stimulated reproductive hormone concentrations was not generally observed in either sex. Overall, there were no clinically significant changes from baseline in

basal and GnRH-stimulated concentrations of reproductive hormones (estradiol, progesterone, prolactin, dehydroepiandrosterone (DHEA), dehydroepiandrosterone-sulfate (DHEA-S), sex hormone binding globulin (SHBG), FSH, and LH in females and testosterone, DHEA, DHEA-S, SHBG, FSH, LH, and Inhibin-B in males) in response to treatment with icatibant. Additionally, there were no significant effects of icatibant on the concentration of luteal phase progesterone, an indicator of ovulation status and luteal function, or on menstrual cycle length in females, and there were no significant effects of icatibant on semen parameters in males.

Adrenal cortex function in male and female subjects, as assessed by serum cortisol concentrations, was unaffected by treatment with icatibant.

1.3 Rationale for Dose Selection

Icatibant has not been evaluated in clinical trial subjects below the age of 18 years. The proposed study will be the first in which icatibant is administered to pediatric subjects for treatment of acute HAE attacks. All subjects in the proposed study will receive a single, weight-adjusted dose of 0.4 mg/kg per attack as a SC injection up to a maximum dose of 30 mg.

This dose regimen was selected to target an exposure (C_{max} and area under the curve [AUC]) comparable to that observed in adults treated with icatibant. Only 1 dose of icatibant will be permitted for treatment of a single attack.

The 0.4 mg/kg dose was derived from pharmacokinetic/pharmacodynamic (PK/PD) modeling of data from a study (JE049-1001), which investigated the inhibitory potential of icatibant at various IV infusion doses and regimens after bradykinin challenge in healthy male subjects. The PK and PD data sets were used to model the PK/PD relationship of icatibant using a sigmoidal E_{max} model. A high degree of concordance of half maximal effective concentration (EC_{50}) values was obtained for each of the PD parameters studied (heart rate, blood pressure, and cutaneous blood flow) with the majority of values being between 8.54 and 9.77 ng/mL. Thus, a mean EC_{50} value of 9.5 ng/mL (7.3 nM) was used for subsequent PK/PD simulation. Based on the PK/PD modeling, IV icatibant doses of 0.4 mg/kg and 0.8 mg/kg were predicted to provide duration of therapeutic effect of as much as 9 or 13 hours, respectively, when infused over 0.5 to 1 hour. These results supported a minimum effective dose of 0.4 mg/kg to treat acute attacks of HAE. This corresponds to a dose of 30 mg of icatibant in a 75 kg subject.

A subsequent Phase II (JE049-2101) dose-ranging proof of concept efficacy study in HAE subjects was then conducted that examined the efficacy of doses ranging from 0.4 to 0.8 mg/kg IV (ie, 30 to 60 mg in a 75 kg person) and 30 to 45 mg SC. The results of this study indicated that SC administration of icatibant 30 mg produced a rapid onset of symptom relief and that 45 mg SC showed no improvement in efficacy over 30 mg SC.

As a result of clinical exploration of the efficacy, safety and exposure-response relationship of icatibant, a single SC administration of 30 mg icatibant (10 mg/mL formulation) was selected and consistently employed in the Phase III studies in adult HAE subjects. The totality of available efficacy information obtained from the Phase III clinical studies demonstrates that a single SC 30 mg dose of icatibant provides a sufficient magnitude and duration of effect to clinically manage the majority of acute attacks in adult HAE subjects across a wide range of

demographics. Therefore, 0.4 mg/kg SC is considered an appropriate dose to study the tolerability, safety and PK of icatibant in the pediatric population.

2 STUDY OBJECTIVES

2.1 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.

2.2 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.

3 STUDY ENDPOINTS

3.1 Primary Endpoints

Primary endpoints:

- 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).

3.2 Secondary Endpoints

Secondary endpoints (only for subjects treated with icatibant during a HAE attack):

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 at least 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.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

4.1.1 Study Design

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 will enroll 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).

At least 10 prepubertal children and at least 20 adolescents (including 10 treated during a HAE attack) must be enrolled in the study.

4.1.2 Study Methodology

A subject's classification as prepubertal or pubertal/postpubertal will be determined at screening and, if appropriate, at the time of the first icatibant-treated HAE attack. Subjects classified as pubertal/postpubertal at screening will not require further evaluation of pubertal status during the study, whereas subjects classified as prepubertal at screening will have their pubertal status reassessed at the time of their first icatibant-treated attack visit.

After a qualifying screening period, the PK, safety/tolerability, and efficacy of treatment with SC icatibant will be evaluated in at least 20 subjects (10 prepubertal and 10 pubertal/postpubertal subjects) who present with cutaneous, abdominal, or laryngeal symptoms of an acute attack of HAE. Subjects should initiate treatment with icatibant within 12 hours of the onset of symptoms; however, there are no prespecified attack severity criteria that are required for treatment. Subjects with attacks considered to be mild, moderate, or severe are all potentially eligible to receive treatment with icatibant.

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

Initially, enrollment and dosing of pubertal/postpubertal subjects will precede that of prepubertal subjects. After the first 4 subjects in the pubertal/postpubertal group have been treated with icatibant (whether during or in the absence of attack), PK, safety/tolerability, and efficacy (as appropriate) will be reviewed by an independent Data and Safety Monitoring Board (DSMB). The DSMB review of the first 4 subjects shall be completed prior to continuing enrollment of additional pubertal/postpubertal subjects, treatment of second and third HAE attacks in pubertal/postpubertal subjects, and initiating enrollment of subjects in the prepubertal group.

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.

After having received initial treatment with icatibant, either during or in the absence of attack, at least 10 pubertal/postpubertal subjects who subsequently experience an acute HAE attack may continue to receive treatment with icatibant as a single SC administration per attack for a total of 3 eligible icatibant-treated attacks. Further treatment with icatibant is contingent upon presentation of an acute cutaneous, abdominal, or laryngeal attack of HAE at least 7 days after prior treatment. All primary and secondary outcomes as above (including anti-icatibant antibodies and reproductive hormones) will be measured in these pubertal/postpubertal subjects after each administration. Note that for some of the pubertal/postpubertal subjects who receive further treatment, ie, those who provided PK and safety/tolerability measurements without an attack, their first icatibant-treated attack will represent their second on-study exposure to icatibant for safety analysis purposes.

The investigator will schedule a telephone contact approximately 6 months after Day 1 of each icatibant-treated attack to obtain specific updates concerning pubertal changes/milestones.

4.1.3 Study Assessments

The study will consist of the following study periods (see [Table 4-m](#)).

Table 4-1 Study Periods

Study Periods	
Screening	Day of informed consent through pretreatment on Day 1
No attack (Pubertal/postpubertal subjects only)	
Treatment	Day 1
Post Treatment	Day 1 through Day 8 (\pm 1 day)
Follow-up	Day 9 through Day 90 (\pm 7 days)
Telephone Contact	Month 6 (\pm 7 days) from Day 1

Table 4-1 Study Periods

Study Periods	
Initial icatibant-treated attack (All subjects)	
Treatment	Day 1
Post Treatment	Day 1 through Day 8 (± 1 day)
Follow-up	Day 9 through Day 90 (± 7 days)
Telephone Contact	Month 6 (± 7 days) from Day 1 of the attack
Two additional icatibant-treated attacks for a total of 3 icatibant-treated attacks (Pubertal/postpubertal subjects only)	
Treatment	Day 1
Post Treatment	Day 1 through Day 8 (± 1 day)
Follow-up	Day 9 through Day 90 (± 7 days)
Telephone Contact	Month 6 (± 7 days) from Day 1 of the attack

The study will include a screening period to determine subject eligibility. Eligibility will be evaluated after the subjects' parent(s)/legal guardian(s) and the subject (if applicable) provide informed consent/assent.

Study activities at screening will include confirmation of diagnosis of HAE type I or II by review of the subject's medical history and documentation of C1-INH deficiency indicative of HAE Type I or II. A blood sample will be collected for C1-INH testing. Other assessments performed at screening will include concomitant medication use, physical examination (including height and weight), pubertal status determination, vital signs, electrocardiogram (ECG), and a urine pregnancy test in female pubertal/postpubertal subjects.

4.1.3.1 Initial Treatment

In previously screened, eligible subjects who present with an attack of acute HAE, baseline clinical assessments for PK, safety, and efficacy will be performed on Day 1 at pretreatment. The initial severity and type of attack (ie, cutaneous, abdominal, or laryngeal) will be determined by the investigator. The investigator will complete baseline assessments at pretreatment of the symptoms of the acute HAE attack (including a separate assessment of HAE-related pain in subjects younger than 4 years of age), and adherence to inclusion/exclusion criteria will be reconfirmed. Subjects who are 4 years of age or older will perform a self-assessment of HAE-related pain. Other baseline assessments performed at pretreatment will include physical examination, pubertal status determination (only for those subjects classified as prepubertal at screening), height and weight, vital signs, collection of samples for clinical laboratory tests (serum chemistry [including liver function tests], hematology, urinalysis), urine pregnancy test for pubertal/postpubertal females, baseline PK and immunogenicity assessments, and baseline

measurement of reproductive hormones (FSH, LH, estradiol, and progesterone in females and FSH, LH, and testosterone in males).

On Day 1, subjects will be administered a single dose of icatibant as an abdominal SC injection within 12 hours after the onset of the acute attack. The time of investigational product administration on Day 1 will be designated as Time 0. All post-treatment assessments will be calculated from the time of investigational product administration. PK, safety, and efficacy assessments will be performed on Day 1 after treatment at the time points indicated in the study (dd, dx, dx, dx, dx, dx). These assessments will consist of physical examination, vital signs, ECG, clinical laboratory tests (serum chemistry [including liver function tests], hematology, urinalysis), injection site reactions, and measurement of reproductive hormones (FSH, LH, estradiol, and progesterone in females and FSH, LH, and testosterone in males) in all subjects. The investigator will complete assessments of symptoms of the acute attack of HAE for all subjects (including a separate assessment of HAE-related pain in subjects younger than 4 years of age). Subject who are 4 years of age or older will also complete a self-assessment of HAE-related pain.

Eligible pubertal/postpubertal subjects who undergo treatment with icatibant in the absence of an acute HAE attack will receive single dose of icatibant as an abdominal SC injection on Day 1 and undergo PK and safety assessments as for subjects who receive treatment with icatibant during an attack. (Efficacy assessments will not be performed for those pubertal/postpubertal subjects treated with icatibant in the absence of an HAE attack.)

A safety follow-up contact to assess the subject's condition will occur by telephone at 24 (± 4) hours and 48 (± 4) hours after treatment with icatibant (for a subject who remains hospitalized, this safety follow-up will be conducted in person).

Rescue medication use will be assessed through 48 (± 4) hours after treatment. With exception of icatibant, any medicinal product may be used as rescue medication, at the discretion of the treating physician.

Subjects will return to the hospital/study center to undergo safety assessments, including physical examination, vital signs, and clinical laboratory tests (serum chemistry [including liver function tests], hematology, urinalysis), evaluation of injection site reactions, immunogenicity, and measurement of reproductive hormones on Day 8 (± 1 day) after treatment.

Subjects will be followed over a 90-day period after initial treatment. All subjects will provide blood samples for immunogenicity testing and measurement of reproductive hormone levels at the Day 90 (± 7 days) visit and undergo safety assessments including physical examination, vital signs, and clinical laboratory tests (serum chemistry, hematology, and urinalysis). Additionally, females of childbearing potential will undergo urine pregnancy testing.

4.1.3.2 Subsequent Treatment

Subsequent treatment with icatibant may be offered to pubertal/postpubertal subjects who have received initial treatment and who present subsequently with an attack at least 7 days after prior treatment. In the event that a subsequent attack occurs at least 7 days after prior treatment, but within the window (± 1 day) allowed for performance of Day 8 assessments associated with a

prior attack, the Day 8 assessments may also serve as the pretreatment (baseline) assessments for the subsequent attack. Subjects will be eligible for treatment with icatibant until a total number of at least 10 adolescents have been treated with icatibant for a total of 3 acute attacks (ie, after the first icatibant-treated attack, only pubertal/postpubertal subjects may receive further treatment with icatibant for up to 2 subsequent attacks of acute HAE). Except for PK determinations, all primary and secondary outcomes, including immunogenicity, are to be measured after each administration. Safety, reproductive hormones, and other assessments in association with subsequent attacks of acute HAE will be performed on Day 90 (± 7 days) after treatment (each treatment for a subsequent attack will require its own Day 90 follow up visit; however, if a subsequent attack occurs within 7 days of the Day 90 follow-up visit for the previous attack, the assessments on Day 8 and Day 90 may be combined). Note that for some of the pubertal/postpubertal subjects who receive further treatment, ie, those who provide PK and safety/tolerability measurements without experiencing a current attack, their first icatibant-treated attack will represent their second on-study exposure to icatibant for safety analysis purposes.

The investigator will schedule a telephone contact approximately 6 months after Day 1 of each icatibant-treated attack to obtain updates concerning pubertal changes/milestones. If this prescheduled telephone contact date should occur within the 90-day follow-up period (ie, Day 1 through Day 90) of a subsequent attack, this prescheduled contact may be omitted.

In addition, 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.

All assessments are outlined in full in the study schedules of events i **dk** **dn** No Attack, **x** **cb**, Initial Icatibant-treated Attack, and **x** **cf**, Subsequent Icatibant-treated Attacks.

4.2 Rationale for 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 Study Duration

At minimum, the duration of a subject's active participation in the study will consist of single day dosing with 90-day follow-up.

Once eligibility is established at screening, the subject will be enrolled into the study but will enter a period of inactive participation of variable duration until such time as the subject experiences an acute attack of HAE and is offered treatment. For those pubertal/postpubertal subjects who will be treated without an attack, eligibility will be established at screening and the subject will be immediately enrolled and treated with icatibant. At the time of enrollment, the subject will enter a 90-day period of active participation which will consist of treatment with a single SC administration of icatibant on Day 1 through follow-up at Day 90.

After receiving the first treatment with icatibant with or without an attack (N=20), at least 10 pubertal/postpubertal subjects who present with subsequent attacks of acute HAE will continue to receive treatment with icatibant for a total of 3 attacks each. Thus, the period of active participation in the study for prepubertal subjects will be approximately 90 days, while that for pubertal/postpubertal subjects could be a maximum of approximately 270 or 360 days (3 separate active periods of approximately 90 days for those treated with icatibant during an attack; 4 separate active periods for those treated without an attack), with each active period separated by periods of inactive participation of variable duration. The period of active participation may be shorter if pubertal/postpubertal subjects have recurrent HAE attacks in between the Day 8 and Day 90 visits for a prior icatibant-treated HAE attack. Telephone follow-up will occur approximately 6 months after each icatibant-treated attack.

Once the tenth prepubertal subject and the twentieth pubertal/postpubertal subject have completed the 6-month follow-up after the initial treatment, and the tenth pubertal/postpubertal subject has completed the 6-month follow-up after his or her third and final treatment for an attack, the study will be closed.

5 STUDY POPULATION SELECTION

5.1 Study Population

The study will enroll a sufficient number of children and adolescents with HAE to ensure study completion of 30 subjects. The study population to provide efficacy, PK, and safety/tolerability measurements will consist of at least 20 subjects from 2 to less than 18 years of age, at least 10 of whom are prepubertal and at least 10 of whom are pubertal/postpubertal at the time of their first icatibant-treated acute cutaneous, abdominal, or laryngeal attack of HAE. An additional 10 subjects who are pubertal/postpubertal at the time of enrollment, but who are not experiencing a current HAE attack, will provide PK and safety/tolerability measurements only.

5.2 Inclusion Criteria

Subjects must meet all of the following criteria to be considered eligible for enrollment.

1. Two through <18 years of age (ie, from the second birthday until the day prior to the eighteenth birthday) at the time of the subject's first HAE attack treated with icatibant as part of this study.
 - Prepubertal and pubertal/postpubertal subjects experiencing an acute cutaneous, abdominal, or laryngeal HAE attack treated with icatibant as part of this study.
 - Pubertal/postpubertal subjects with HAE who are treated with icatibant as part of this study, but not during an attack.
2. Documented diagnosis of HAE type I or II. Diagnosis may be on the basis of historical data: family history, characteristic attack manifestations, recurrent attacks, historical C1-INH deficiency, and exclusion of other forms of angioedema. Inclusion will be permitted initially based on medical history only if a clear diagnosis has been made based on all of the preceding criteria. However, the diagnosis must be confirmed prior to treatment by documented immunogenic and/or functional C1-INH deficiency (C1-INH protein level below the lower limit of normal and/or functional level <50% of normal) as performed by the Sponsor's central laboratory.
3. Informed consent (and subject assent as appropriate) signed by the subject's parent(s) or legal guardian(s).

5.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. Diagnosis of angioedema other than HAE.
2. Participation in another clinical trial that involves use of any investigational product (drug or device) within 30 days prior to study enrollment or at any time during the study.
3. Any known factor/disease that might interfere with the treatment compliance, study conduct, or result interpretation.
4. Congenital or acquired cardiac anomalies that interfere significantly with cardiac function.
5. Treatment with angiotensin converting enzyme (ACE) inhibitors within 7 days prior to treatment.
6. Use of hormonal contraception within the 90 days prior to treatment.

7. Androgen use (eg, stanozolol, danazol, oxandrolone, methyltestosterone, testosterone) within the 90 days prior to treatment.
8. Pregnancy or breastfeeding.
9. A physical condition that interferes with pubertal status determination.

6 STUDY TREATMENT

6.1 Description of Treatment

6.1.1 Investigational Product

Icatibant is prepared as a sterile, isotonic, and acetate buffer solution containing sodium chloride, acetic acid, sodium hydroxide and water for SC injection, adjusted to pH 5.5 ±0.3. The solution does not contain any preservative.

The product is supplied as a 10 mg/mL (free base) solution in 3-mL glass syringes, with elastomeric stoppers, tip cap, plunger rod, and backstop. A fluid-dispensing connector will be used to secure a 1-mL or 3-mL syringe to the glass syringe. A syringe (H6) will be withdrawn and administered by SC injection.

6.1.2 Comparator

Not applicable to this study.

6.2 Treatment Administered

All subjects will receive treatment with icatibant as a single, weight-adjusted dose of 0.4 mg/kg up to a maximum of 30 mg administered in the abdominal region as a SC injection.

Pubertal/postpubertal subjects are potentially eligible to receive treatment with icatibant in the absence of an attack, and to receive treatment with icatibant for a total of 3 attacks of acute HAE. Thus, a maximum of 4 doses of icatibant may be administered to a pubertal/postpubertal subject in the study, while all prepubertal subjects will receive a single dose of icatibant.

6.3 Selection and Timing of Dose for Each Subject

All subjects, whether treated during or in the absence of an acute attack of HAE, will be administered a single SC injection of icatibant.

Subjects treated for an acute attack of HAE should receive icatibant within 12 hours after the onset of the attack. There are no prespecified attack severity criteria that are required for treatment. Subjects with attacks considered to be mild, moderate, or severe are all potentially eligible to receive treatment with icatibant.

Subsequent treatment with icatibant for up to 2 additional attacks of acute HAE, for a total of 3 attacks, will be offered to pubertal/postpubertal subjects contingent upon having been treated at least 7 days after prior (H7).

6.4 Method of Assigning Subjects to Treatment Groups

Not applicable to this study. All subjects will be administered icatibant at a weight-adjusted dose of 0.4 mg/kg SC up to a maximum of 30 mg per treatment.

6.5 Blinding

Not applicable to this open-label study.

6.6 Concomitant Medication Usage

All prescription and over-the-counter medications that are being taken by subjects during the study are regarded as concomitant medications and must be documented on the case report form (CRF) following informed consent.

Use of the following concomitant medications is allowed during the study:

- All chronically administered medications, except for treatments of HAE, are allowed, but the dose and regimen must have been stable for at least 1 month before the first dose of icatibant in this study.
- Prophylactic therapies for HAE (eg, anti-fibrinolytics or C1-INH) other than attenuated androgens will be allowed, but therapies known to attenuate an acute HAE attack (eg, C1-INH concentrate, fresh-frozen plasma [FFP]) must not be used during the attack being treated with icatibant unless these are required as rescue medications (see Section H). An exception is that fibrinolysis inhibitors may be given in a subject's usual, stable prophylactic regimen.

Use of the following concomitant medications is forbidden within 90 days prior to treatment, and for 90 days after receiving treatment with icatibant:

- ACE inhibitors.
- Androgens or attenuated androgens (eg, stanozolol, danazol, oxandrolone, methyltestosterone, testosterone).
- Hormonal contraceptives (acceptable contraception during the study for sexually active females will consist of abstinence or a double barrier method such as condom plus diaphragm, condom or diaphragm plus spermicide, condom or diaphragm plus intrauterine device).

6.7 Rescue Therapy

For the purposes of this protocol, 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 treatment of a single attack is not allowed in this study.

The determination of the necessity for rescue therapy will be at the discretion of the investigator. With the exception of icatibant, any medicinal product may be used as rescue medication at the discretion of the treating physician.

Rescue therapies will include agents to control the HAE attack, such as C1-INH inhibitor concentrates. C1-INH therapy has been used safely for the treatment of acute attacks in the

d 0^H If C1-INH concentrates are unavailable, FFP may be used. dA kallikrein inhibitor, ecallantide, approved only in the USA, is indicated for use in patients 16 years of age and older.

Other acceptable rescue therapies for acute attacks include palliative medications that are intended to ameliorate the symptoms (eg, pain, nausea) of angioedema rather than to control the HAE attack itself. If pain medication is required, the investigator may administer intravenous or prescription-strength non-steroidal anti-inflammatory drugs (NSAIDs) for mild to moderate pain and administer morphine sulfate (or opiate equivalent) intravenously or intramuscularly at a dose of 0.05 mg/kg (or an equivalent dose if another opiate medication is used). Anti-emetics may also be prescribed as necessary to treat nausea. Acceptable rescue therapies may also include epinephrine, intravenous fluids, or other medicinal products.

Medications provided for rescue therapy will be denoted as rescue medications on the appropriate CRF. Antihistamines (diphenhydramine, loratadine, cetirizine, etc) and glucocorticoids 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 as rescue medications.

If rescue medication is provided, the investigator will document the drug name, amount, time, route of administration, frequency, and duration administered.

6.8 Restrictions

Subjects are not to receive treatment with any investigational product(s) other than icatibant or any investigational device(s) at any point during this study.

6.8.1 Fluid and Food Intake

No specific restrictions on fluid or food intake apply for this study.

6.8.2 Subject Activity Restrictions

No specific restrictions on subject activity apply for this study.

6.9 Treatment Compliance

During this study, the investigational product will be administered at the hospital/study center under controlled conditions; therefore, full subject compliance with treatment is anticipated.

6.10 Packaging and Labeling

The investigational product will be packaged as 3-mL solution in a pre-filled 3-mL syringe made of clear type-I glass. The back stopper consists of bromobutyl coated with fluorocarbon polymer. Front closure is achieved by means of a luer-lock adaptor that allows secure attachment of the needle. Secondary packaging consists of 1 icatibant syringe, labeled in a tray with a 25-gauge needle placed inside a plain white carton, also labeled. A fluid-dispensing

adaptor will be used to secure a 1-mL or 3-mL syringe to the glass syringe for withdrawal of icatibant.

See the Pharmacy Manual for additional details.

6.11 Storage and Accountability

The following information should be considered when storing and using the investigational product.

The investigational product will be shipped at 2° to 8°C. Icatibant 10 mg/mL formulated for SC administration should be stored at or below 25°C. The syringes must not be frozen.

The disposition of all investigational product delivered to a principal investigator must be recorded on a subject-by-subject basis by completing the clinical trial material accountability log. The date and time of administration of the investigational product must be documented on the appropriate CRF.

The principal investigator, clinical research coordinator, or designee (eg, pharmacist) must ensure that all documentation regarding investigational product receipt, storage, dispensing, loss/damaged and return or destruction of used/unused product is complete, accurate, and ready for review at each monitoring visit and/or audit.

The sites must ensure that the investigational product is available for the monitor to inventory and prepare for return shipment to the sponsor or designee, if required.

6.12 Investigational Product Retention at Study Site

The process for destruction of investigational product must be determined and documented during the study start-up phase.

If the investigational product is to be destroyed by the study sites, sites must follow their own process/policy that describes such activities. All drug destruction processes will be documented and the sites must retain copies of these documents within the site regulatory binder. The sites must ensure that the clinical trial material accountability and destruction log is complete, accurate, and ready for review and/or audit at each monitoring visit.

All manifests documenting shipments of investigational product must be retained as well copies of any investigational product return forms.

See the Pharmacy Manual for additional details.

7 STUDY PROCEDURES

Detailed descriptions of subject evaluations required for this protocol are described in this section. These evaluations will be performed during the indicated days and weeks of the study (see the study schedules of events [ck](#), [dnpd](#), [ck](#), [pk](#), [cb](#), Initial Icatibant-treated Attack, and [x](#) [d7pd](#) [d](#) [d](#) -treated Attacks).

All data collected are to be recorded on the appropriate CRF or electronic diary (e-diary) page.

Details for study procedures including sample collection are described in the Operations Manual for this study.

7.1 Informed Consent

Prior to conducting any study-related procedures, written informed consent must be obtained from the subject's parent(s) or legal guardian(s) and assent from the subject (if applicable).

The nature, scope, and possible consequences, including risks and benefits, of the study will be explained to the subject, the subject's parent(s), or the subject's legal guardian(s) by the investigator or designee in accordance with the guidelines described in Section [mfj](#). Documentation and filing of informed consent documents should be completed according to Section [mfj](#).

7.2 Study Entrance Criteria

At screening, each subject will be reviewed for eligibility against the study entrance criteria. Subjects who do not meet the study entrance criteria will not be allowed to participate in the study. The reason(s) for the subject's ineligibility for the study will be documented.

7.3 Confirmation of Study Eligibility

Subject eligibility according to the study inclusion and exclusion criteria will be confirmed at the screening and pretreatment (baseline) visits on the basis of review of the study entrance criteria.

7.4 Demographics

Subject demographic information including gender, date of birth, and race will be collected prior to the subject receiving the first dose of investigational product.

7.5 Medical History

Medical history will be recorded in the CRF. Details of prior HAE attacks (eg, typical frequency, symptom duration, onset of relief, and type and frequency of medical interventions required) will be obtained at screening through pretreatment on Day 1. Other important medical events, menstrual cycle history [d](#) [cb](#) [d](#) [d](#) (H), and concomitant medication and illnesses will be recorded at other visits on the appropriate CRF pages. Any existing medical condition present prior to the time of the first dose will be reported as medical history.

7.6 Menstrual Cycle History

A menstrual cycle history will be determined historically for female subjects and will be recorded in the CRF. The timing of the blood sampling with respect to the menstrual cycle must be known to inform the interpretation of any potential changes in reproductive hormones in adolescent females, because of the normal cyclical rise and fall of reproductive hormones of the menstrual cycle.

Instructions for investigators:

To assist in this determination, investigators should obtain the following information and document in the CRF.

- Age of menarche
- Normal duration of menstrual flow
- Normal interval in between menstrual periods
- Date of last onset of bleeding
- Prospectively ask female subjects to write down subsequent dates of onset of bleeding and cessation of bleeding between Day 1 and Day 90
- Date of ovulation (sometimes called ovulation pain, mid-cycle pain or mittelschmerz) may also be documented if subjects can identify this feeling

7.7 Height and Weight

Height and weight will be recorded for all subjects.

7.8 Pubertal Status Determination

The investigator will perform an examination for all subjects to determine whether they are prepubertal or pubertal/postpubertal. A description of the sexual maturation scale described by

7.9 Investigational Product Administration

Subjects will receive treatment with icatibant as a single, weight-adjusted dose of 0.4 mg/kg administered as an abdominal SC injection up to a maximum dose of 30 mg. Treatment with icatibant should be administered within 12 hours of onset of an acute HAE attack.

Pubertal/postpubertal subjects that present with a subsequent attack at least 7 days after prior

7.10 Pharmacokinetic Assessments

7.10.1 Pharmacokinetic Variables

Individual patient PK variables for icatibant and major metabolites will be determined from the respective plasma concentration time profiles where appropriate, using noncompartmental methods.

A population PK model will be derived to evaluate the correlation of key covariates (ie, age, body weight, gender) on the PK profile of icatibant.

Pharmacokinetic variables will be determined by full sampling and noncompartmental methods where possible, and elsewhere by sparse sampling (at least 4 to 7 time points) and a population PK approach using nonlinear mixed effects modeling software.

Primary and secondary pharmacokinetic parameter estimates will be reported and include time to peak concentration (T_{max}), actual peak (C_{max}) and minimum (C_{min}) concentrations, clearance (CL/F), actual area under the plasma concentration-time curve (AUC_{0-last} and AUC_{0-inf}), mean residence time (MRT), volume of distribution at steady state (V_{ss}/F) and elimination half-life ($t_{1/2}$).

The methods to be used for estimation of PK parameter values are described in Section [7.10.0m](#)

7.10.2 Pharmacokinetic Sampling

Sampling for PK assessments will be collected according to the schedule of events provided in [x dm](#) (No Attack) and [x d](#) (Initial Icatibant-treated Attack).

The time of investigational product administration on Day 1 will be designated as Time 0. All post-treatment assessments will be calculated from the time of investigational product administration. Detailed sample collection, processing, and shipping instructions will be provided in the study Operations Manual.

Blood samples for determination of plasma concentrations of icatibant in pubertal/postpubertal subjects will be collected on Day 1 at pretreatment, and at 15 (± 5) minutes, 30 (± 5) minutes, 45 (± 5) minutes, 1 hour (± 10) minutes, 2 hours (± 10) minutes, 4 (± 0.5) hours, and 6 (± 0.5) after treatment.

Blood samples for determination of plasma concentrations of icatibant in prepubertal subjects will be collected on Day 1 at pretreatment, and at 15 (± 5) minutes, 30 (± 5) minutes, 2 hours (± 10) minutes, 4 (± 0.5) hours, and 6 (± 0.5) hours after treatment.

7.10.3 Bioanalytical Method

Plasma samples will be assayed for concentrations of icatibant and its metabolites (M1 and M2) using a validated method (see Section [, 6m](#)).

7.11 Efficacy Assessments

7.11.1 Investigator Symptom Score

The investigator will use a symptom score to assess the severities of symptoms of acute cutaneous, abdominal, and laryngeal attacks of HAE using the following 5-point scale. Symptom scores will be recorded on Day 1 at pretreatment and at predetermined time points after treatment. Results will be recorded in the CRF.

Investigator-rated Symptom Score

- 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.

7.11.2 Subject Self-assessment of Pain

Subjects who are at least 4 years of age will self-assess HAE-related pain using the FPS-R. A copy of the FPS-R is available at [www.fps-r.com](#).

FPS-R self-assessment data will be recorded in an e-diary. Subjects will record self-assessments on Day 1 at pretreatment and at predetermined time points after treatment while at the hospital/study center, and after their discharge to home. Subjects will return the e diary to the hospital/study center at the scheduled visit on Day 8.

Subjects will receive detailed instruction on when and how to use the e-diary from the investigator and/or clinical site personnel.

7.11.3 Investigator Assessment of Pain

Subjects who are below 4 years of age will undergo investigator assessment of HAE-related pain (cutaneous, abdominal, and laryngeal) using the FLACC compartmental pain scale. A copy of the FLACC scale is available at [www.flacc.com](#).

7.11.4 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.

7.12 Reproductive Hormone Assessments

Reproductive hormone levels will be measured in all subjects. Blood samples will be collected to assess FSH, LH, estradiol, and progesterone in females, and FSH, LH, and testosterone in males.

7.13 Safety Assessments

7.13.1 Physical Examination

Physical examinations will include a review of the subject's general appearance as well as evaluation of the body systems. Any clinically significant abnormal change in findings will be recorded as an adverse event (AE) on the appropriate CRF. The physical examination will include the following:

- General appearance
- Eye, ears, nose, throat
- Lymph nodes
- Cardiovascular
- Skin
- Abdomen
- Neurological
- Spine and extremities
- Lungs

7.13.2 Vital Signs

Vital signs are to be recorded for all subjects and will include pulse, blood pressure, respiration rate, and temperature.

7.13.3 Electrocardiography

A standard 12-lead ECG will be performed after 10 minutes at rest when the patient is seated or supine. ECG results will be read locally at the clinical site. Abnormalities will be recorded.

7.13.4 Clinical Laboratory Tests

Blood and urine samples will be collected as described in this section for clinical laboratory testing. The clinical laboratory d d d d d d [Table 7-m](#)

Table 7-1 List of Clinical Laboratory Tests

Hematology:	Serum Chemistry:
- Hematocrit	- Albumin
- Hemoglobin	- Alkaline phosphatase
- Mean corpuscular hemoglobin	- Alanine aminotransferase
- Mean corpuscular hemoglobin concentration	- Aspartate aminotransferase
- Mean corpuscular volume	- Calcium
- Platelet count	- Carbon dioxide
- Red blood cell count	- Chloride
- White blood cell count with differential	- Creatinine
	- Creatine kinase
	- Gamma-glutamyl transferase
	- Glucose
	- Lactate dehydrogenase
	- Phosphorus
	- Potassium
	- Sodium
	- Total bilirubin

Urinalysis:

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

7.13.5 Local Tolerability

Injection site reactions (erythema, swelling, burning sensation, itching/pruritis, warm sensation, cutaneous pain, or other) will be evaluated by the investigator or other medically qualified personnel when the subject is at the hospital/study center, and the diameter of any erythema or swelling will be measured.

After discharge, the subject (or the subject's parent/legal guardian on behalf of the subject as appropriate) will be interviewed about injection site reactions, either in person or by telephone contact.

7.13.6 Immunogenicity

The immunogenicity of icatibant will be assessed. Serum samples for immunogenicity testing will be collected for determination of anti-icatibant antibodies. Serum samples will be analyzed for anti-icatibant antibodies at Shire or at a designated laboratory. Details concerning sample collection and preparation will be provided in the study Operations Manual.

Samples will be stored frozen at -65°C or below if not shipped on the day of collection. Details for shipping will be provided in the study Operations Manual.

7.13.7 Pregnancy Testing

Female subjects of childbearing potential (ie, those who have experienced menarche) will undergo pregnancy testing at time points specified in the study schedule of events 3x dn x d, d d). All pregnancy testing will be conducted using a urine human chorionic gonadotropin (hCG) test kit. The test will be performed and interpreted by the study personnel at the hospital/study center at the time of the visit.

7.14 Sample Collection, Storage, and Shipping

Blood samples will be collected via venipuncture. Use of an indwelling catheter is encouraged for collection of serial blood samples for PK assessments when feasible. Use of a topical local anesthetic (such as EMLA or LMX) is acceptable to make the procedure more tolerable for children, provided that the timing of this application does not interfere with blood sample collection. Subjects will be in a seated or supine position during blood collection.

All samples will be stored and secured in a way that assures that unauthorized access is prohibited and the samples are not lost, allowed to deteriorate, or are accidentally or illegally destroyed. Detailed sample collection, processing, and shipping instructions will be provided in the study Operations Manual.

7.15 Recording of Concomitant Medications

All medications administered to the study subjects from the time of informed consent through the follow-up visit 90 (± 7) days after investigational product administration are regarded as concomitant and will be documented in the CRF. Concomitant medications are defined in dH

7.16 Recording of Adverse Events

Adverse events 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). Adverse event monitoring and the period of observation defined for this study d d d d m j m

7.17 Adverse Events Assessments

7.17.1 Definitions of Adverse Events and Serious Adverse Events

7.17.1.1 Adverse Event

An AE is any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in a clinical study, whether or not considered investigational product related. This includes an exacerbation of a pre-existing condition. However, any exacerbation or worsening of symptoms of an acute HAE attack treated with icatibant is considered a result of the underlying disease and will not be considered an adverse event (unless meeting the criteria for a serious adverse event, see d m m).

Adverse events include:

- Worsening (change in nature, severity, or frequency) of conditions present at the onset of the study (with the exception of HAE).
- Intercurrent illnesses.
- Drug interactions.
- Events related to or possibly related to concomitant medications.
- Clinically significant abnormal laboratory values (this includes significant shifts from baseline within the range of normal that the investigator considers to be clinically important).
- Clinically significant abnormalities in physical examination, vital signs, and weight.

The investigator must record all AEs in the CRF, regardless of the severity or relationship to investigational product. The investigator should treat subjects with AEs appropriately and observe them at suitable intervals until the events stabilize or resolve. Adverse events may be discovered through observation or examination of the subject, questioning of the subject, complaint by the subject, or by abnormal clinical laboratory values.

In addition, AEs may also include laboratory values that become clinically significantly out of range. In the event of an out-of-range value, the laboratory test should be repeated until it returns to normal or stabilizes, or can be medically explained, and the subject's safety is not at risk.

Additional illnesses present at the time when informed consent is given until the time of treatment are regarded as concomitant illnesses and will be documented on the medical history page of the CRF. Illnesses first occurring or detected on or after treatment, and worsening of a concomitant illness during the study, are to be regarded as adverse events and must be documented as such in the CRF.

The treated HAE attack is defined as any symptoms occurring in treated subjects within 48 hours of the onset of symptoms. A clinically relevant worsening of the signs and symptoms of a treated attack is considered to be related to the underlying disease of HAE, and will be collected in the appropriate CRF separately from general reports of adverse events unless meeting the criteria of a serious adverse event. Symptoms reoccurring more than 48 hours after an initial attack will be considered a new attack, and will also not be reported as AEs. Attacks not treated with icatibant will be documented in the appropriate CRF at the Day 90 visit; they are considered to be pre-existing disease and will not be documented as AEs.

Local tolerability will include symptoms at the site of icatibant administration (injection site) and will be assessed separately from general reports of AEs. Injection site reactions will be documented in the "local tolerability" page of the CRF. Injection site reactions that have been reported previously with icatibant included erythema, swelling, burning sensation, itching, warmth and pain and were generally, mild to moderate, transient, and resolved without sequelae. Injection site reactions that do not meet the criteria of a serious adverse event will not need to be additionally reported as AEs.

7.17.1.2 Serious Adverse Event

A serious adverse event (SAE) is any AE occurring at any dose that results in any of the following outcomes:

- Death.
- Is life-threatening.
- Requires hospitalization.
- Requires prolongation of existing hospitalization.
- A persistent or significant disability or incapacity.
- A congenital anomaly or birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. A life-threatening AE is defined as an AE that placed the subject, in the view of the initial reporter, at immediate risk of death from the adverse event as it occurred (ie, it does not include an AE that, had it occurred in a more severe form, might have caused death).

7.17.2 Classification of Adverse Events and Serious Adverse Events

The severity of AEs will be assessed by the investigator as mild, moderate, or severe based on the definitions shown in [Table 7-6](#). The severity of AEs and SAEs should be recorded on the appropriate CRF page as mild, moderate, or severe.

Table 7-2 Adverse Event Severity

Severity	Definition
Mild	No limitation of usual activities.
Moderate	Some limitation of usual activities.
Severe	Inability to carry out usual activities.

7.17.2.1 Clarification between Serious and Severe

The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (eg, severe headache). This is not the same as “serious,” which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) and causality serve as a guide for defining regulatory reporting obligations.

7.17.3 Relatedness of Adverse Events and Serious Adverse Events

Relationship of an AE or SAE to investigational product is to be determined by the investigator (see Table 7-7).

Table 7-3 Adverse Event Relatedness

Relationship to Product(s)	Definition
Not Related	Unrelated to investigational product
Possibly Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, but which could also be explained by concurrent disease or other drugs or chemicals.
Probably Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, unlikely to be attributable to concurrent disease or other drugs and chemicals and which follows a clinically reasonable response on de-challenge. The association of the clinical event or laboratory abnormality must also have some biologic plausibility, at least on theoretical grounds.
Definitely related	The event follows a reasonable temporal sequence from administration of the investigational product, follows a known or suspected response pattern to the investigational product, is confirmed by improvement upon stopping the investigational product (de-challenge), and reappears upon repeated exposure (re-challenge). Note that this is not to be construed as requiring re-exposure of the subject to investigational product; however, the determination of definitely related can only be used when recurrence of event is observed.

7.17.4 Procedures for Recording and Reporting Adverse Events

7.17.4.1 Adverse Event Monitoring and Period of Observation

Adverse events will be monitored continuously. For the purposes of this study, the safety observation period will extend from the time of treatment with investigational product until the subject's final evaluation after treatment. For subjects who complete the study, the final evaluation of AEs will occur at the follow-up visit performed 90 (± 7) days after treatment with investigational product.

If the investigator considers it necessary to report an AE in a subject after the end of the safety observation period, he or she should contact the sponsor to determine how the AE should be documented and reported.

7.17.4.2 Reporting Serious Adverse Events

Any 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. The SAE must be completely described on the subject's CRF, including the judgment of the investigator as to the relationship of the SAE to the investigational product.

The investigator will promptly supply all information identified and requested by the sponsor (or contract research organization [CRO]) regarding the SAE. The investigator must report the serious adverse event to the Shire Pharmacovigilance and Risk Management Department AND to the Shire Medical Monitor on an SAE form. This form must be completed and faxed or emailed within 24 hours of the investigator's learning of the event to:

Shire Pharmacovigilance and Risk Management Department:

FAX: PPD [REDACTED] (Worldwide) OR PPD [REDACTED] (North America)

Email: PPD [REDACTED]

AND

Shire Medical Monitor: PPD [REDACTED], MD, PhD

PPD [REDACTED]

FAX: PPD [REDACTED] (USA)

Any follow-up information must also be completed on an SAE form and faxed or emailed to the same numbers listed above.

In the event of a severe and unexpected, fatal, or life-threatening SAE, the clinical site must contact the Shire Medical Monitor by telephone; this is in addition to completing and transmitting the SAE form as stated above. The following provides contact information for the Shire Medical Monitor.

If an SAE is assessed as severe and unexpected, or life-threatening, contact:

If an SAE is assessed as severe and unexpected, or life-threatening, contact:
<p>PPD [REDACTED] MD, PhD PPD [REDACTED] Shire Human Genetic Therapies, Inc. 300 Shire Way Lexington, MA 02421 USA Telephone: PPD [REDACTED] Mobile: PPD [REDACTED] Fax: PPD [REDACTED] (USA) PPD [REDACTED]</p>

The investigator must promptly report all required information to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). It is the responsibility of the sponsor to ensure that each investigator receives a copy of any Council for International Organizations of Medical Sciences (CIOMS I)/MedWatch report that has been submitted to the appropriate regulatory agencies notifying them of an unexpected related SAE.

The investigator or sponsor must ensure that the IRB/IEC receives a copy of the report and that a copy is also filed within their study files.

7.18 Pregnancy

Pregnancy and lactation are exclusion criteria for this study. The sponsor must be notified in the event of a pregnancy occurring during the course of the study and through 180 days after the subject's last dose of investigational product. Pregnancy is not to be reported as an AE; the pregnancy reporting form should be used to report the pregnancy. The pregnancy will be followed up through delivery or final outcome.

7.19 Abuse, Overdose, and Medication Error

- **Abuse** – Persistent or sporadic intentional intake of investigational medicinal product at a dose higher than prescribed per protocol (but below the dose defined for overdose) or when used for non-medical purpose (eg, altering one's state of consciousness).
- **Misuse** – Intentional or unintentional use of investigational medicinal product other than as directed or indicated at any dose, which is at or below the dose defined for overdose (Note: this includes a situation where the product is not used as directed at the dose prescribed by the protocol).

- **Overdose** – No clinical information on overdose is available. A dose of 3.2 mg/kg (approximately 8 times the therapeutic dose) caused transient erythema, itching or hypotension in healthy subjects. No therapeutic intervention was necessary.
- **Medication Error** – A mistake made in prescribing, dispensing, administration and/or use of the investigational medicinal product.

7.20 Removal of Subjects from the Trial or Investigational Product

A subject's participation in the study may be discontinued at any time at the discretion of the investigator. The following may be justifiable reasons for the investigator to remove a subject from the study:

- Non-compliance, including failure to appear at one or more study visits.
- The subject was erroneously included in the study.
- The subject develops an exclusion criterion.
- The subject suffers an intolerable adverse event.
- The study is terminated by the sponsor.
- The study is closed prior to the subject's first eligible attack.

The subject, the subject's parent(s), or the subject's legal guardian(s) acting on behalf of the subject is free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment.

If a subject or the subject's parent(s) or the subject's legal guardian(s) acting on behalf of the subject, discontinues participation in the study, or the subject is discontinued by the investigator, the subject completion/discontinuation CRF describing the reason for discontinuation must be completed. Any AEs experienced up to the point of discontinuation must be documented in the CRF. If AEs are present when the subject withdraws from the study, the subject will be re-evaluated within 30 days of withdrawal. All ongoing SAEs at the time of withdrawal will be followed until resolution.

7.20.1 Safety-Related Study Stopping Rules

The Data and Safety Monitoring Board (DSMB) (a committee of independent experts in clinical research, drug safety, and disease-related or unexplained, or if there is an unexpected drug-related severe AE.

Following the review of safety data, the study will be either:

- Resumed unchanged
- Resumed with modifications to the protocol
- Terminated

Subject safety will be monitored on a continuous basis during this study until the last subject completes his or her last scheduled study visit/assessment.

Additional information on safety monitoring can be found in Section [m0U](#)

7.21 Appropriateness of Measurements

The safety assessments used in this study are standard and will provide a detailed measure of the safety of icatibant in the pediatric population.

The measures of serum reproductive hormone concentration are accepted measures for assessing the function of reproductive organs.

Plasma samples will be assayed for concentrations of icatibant and its 2 major metabolites (M1 and M2) using a validated high-performance liquid chromatography/tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification of 1 ng/mL and a range from 1 to 1000 ng/mL (Analytical Report SHR10-002). Pharmacokinetic variables will be determined by full sampling and noncompartmental methods where possible, and elsewhere by sparse sampling (at least 4 to 7 time points) and a population PK approach using non-linear mixed effects modeling software.

The symptom score used in efficacy assessments in this study is an investigator-rated measure of symptom severity based on a standard 5-point scoring system (0-absence of symptoms, 1-mild, 2-moderate, 3-severe, 4-very severe) capturing symptoms of acute attacks of HAE that have been identified and validated to assess efficacy in adults. For attacks classified as abdominal or cutaneous, investigator-rated symptom scores are 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 are collected for 13 symptoms: abdominal tenderness, nausea, vomiting, diarrhea, skin pain, erythema, skin irritation, skin swelling, dysphagia, voice change, breathing difficulties, stridor, and asphyxia.

In all pediatric subjects in the present study, irrespective of age, the investigator-rated symptom score will provide an appropriate means to measure the severity of primary symptoms (eg, cutaneous and/or abdominal pain, cutaneous swelling, or laryngeal symptoms) of acute attacks of HAE at pretreatment and the change in symptom severity, if any, after treatment with icatibant.

Though subject-reported outcomes such as the symptom score and visual analog scale (VAS) have been employed successfully as efficacy measures in clinical studies of icatibant in adults, the use of these subject-reported outcomes in children poses special challenges. The Faces Pain Scale is a validated, self-reported measure of children's pain in a wide variety of settings. The Faces Pain Scale-Revised (FPS-R) was adapted from the original FPS in order to make it possible to score pain on a widely accepted 0-to-100 mm scale. The scales are suitable for use in assessment of the intensity of children's acute pain from age 4 onward, are simple to administer, and require no specialized equipment other than the standardized images of faces. Use of the FPS-R is planned for this study, and will provide an appropriate means to measure pain associated with acute attacks of HAE in pediatric subjects who are at least 4 years of age.

Young children (ie, those below the age of 4 years) frequently lack the verbal and cognitive skills necessary to report physical discomfort and pain intensity. Behavioral cues are the primary

indicators of pain in children who are unable to report pain or follow instructions in the use of assessment tools. The FLACC instrument comprises 5 categories of behavior (face, legs, activity, cry, and consolability) to assess pain in preverbal children or children with limited verbal capability⁶⁷. Each category is scored on a 0-to-2 scale which results in a total score from 0 to 10.

Collectively, the measures employed in this study are expected to allow for assessment of the PK profile, tolerability, safety, and efficacy of icatibant in the pediatric population.

8 STUDY ACTIVITIES

8.1 Screening (Day of Informed Consent to Pretreatment on Day 1)

- Informed Consent/Assent
- Inclusion/Exclusion Criteria
- Medical History
- Documentation of HAE attack(s) not treated with icatibant*
- Confirmation of documented HAE diagnosis (via the sponsor's central laboratory)
- Measurement of C1-INH
- Pubertal status determination
- Physical examination
- Vital signs
- ECG
- Height and weight
- Urine pregnancy test (in females of childbearing potential)
- Recording of concomitant medications

*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.

8.2 Pretreatment (Baseline) Assessments (Day 1, No Attack)

The following assessments will be performed for subjects who will be treated with icatibant in the absence of a current HAE attack. All evaluations and sample collections must be performed prior to treatment.

- Medical history
- Confirm inclusion/exclusion criteria
- Pubertal status determination (only if the subject was classified as prepubertal at the time of the screening visit)
- Menstrual cycle history (in pubertal/postpubertal females only)
- Physical examination
- Vital signs
- Height and weight
- Clinical laboratory tests (serum chemistry, hematology and urinalysis)
- Urine pregnancy test (in females of childbearing potential)
- Reproductive hormone assessments
- Pharmacokinetic sampling
- Immunogenicity evaluation
- Recording of concomitant medications

8.3 Pretreatment (Baseline) Assessments (Day 1, Initial and Subsequent Attacks)

The following assessments will be performed at both initial and subsequent icatibant-treated attacks unless otherwise indicated. All evaluations and sample collections must be performed prior to treatment.

- Medical history (at initial attack only)
- Confirm inclusion/exclusion criteria
- Pubertal status determination (only if the subject was classified as prepubertal at the time of the screening visit)
- Menstrual cycle history (in pubertal/postpubertal females only)
- Physical examination
- Vital signs
- ECG (at subsequent attacks only)
- Height and weight
- Subject self-assessment of HAE-related pain (in subjects 4 years of age and older) using e-diary FPS-R
- Investigator assessment of HAE symptoms
- Investigator assessment of HAE-related pain (in subjects younger than 4 years of age only) using FLACC
- Clinical laboratory tests (serum chemistry, hematology and urinalysis)
- Urine pregnancy test (in females of childbearing potential)
- Reproductive hormone assessments
- Pharmacokinetic sampling (at pretreatment for initial attack only)
- Immunogenicity evaluation
- Recording of concomitant medications
- Assessment of adverse events (at pretreatment for subsequent attacks only)

8.4 No Attack

8.4.1 Treatment Period (Day 1 to Day 8 [± 1 Day])

- Investigational product administration (Day 1, Time 0)
- Physical examination (Day 1, 6 [±0.5] hours) (or 8 [±0.5] hours if the subject is not discharged^{***}) post dose and Day 8 [±1 day])
- Vital signs (Day 1, 1 hour [±10 minutes], 6 [±0.5] hours) (or 8 [±0.5] hours if the subject is not discharged^{***}) post dose and Day 8 [±1 day])
- ECG (Day 1, 6 [±0.5] hours (or 8 [±0.5] hours if the subject is not discharged^{***}) post dose)
- Clinical laboratory tests (Day 1, 6 [±0.5] hours post dose and Day 8 [±1 day])
- Reproductive hormone assessments (Day 1, 6 [±0.5] hours post dose and Day 8 [±1 day])
- Injection site reaction evaluation (Day 1, 1 hour [±10 minutes], 6 [±0.5] hours) (and 8 [±0.5] hours if the subject is not discharged^{**}) post dose, Day 2 (24 [±4] hours), Day 3 (48 [±4] hours), and Day 8 [±1 day])

- Sampling for PK assessments in pubertal/post pubertal subjects (Day 1, 15 [± 5] minutes, 30 [± 5] minutes, 45 [± 5] minutes, 1 hour [± 10] minutes, 2 hours [± 10] minutes, 4 [± 0.5] hours, 6 [± 0.5] hours post dose)
- Safety follow-up contact (Day 2 (24 [± 4] hours), Day 3 (48 [± 4] hours) by telephone (If a subject remains hospitalized, this safety follow-up will be conducted in person.)
- Immunogenicity evaluation (Day 8 [± 1] day)
- Menstrual cycle history (Day 8 [± 1] day) in pubertal/postpubertal females)
- Recording of concomitant medications
- Assessment of adverse events

*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.

8.5 Initial Attack

8.5.1 Treatment Period (Day 1 to Day 8 [± 1] Day)

- Investigational product administration (Day 1, Time 0)
- Physical examination (Day 1, 6 [± 0.5] hours) (or 8 [± 0.5] hours if the subject is not discharged^{***}) post dose and Day 8 [± 1] day)
- Vital signs (Day 1, 1 hour [± 10] minutes, 6 [± 0.5] hours) (or 8 (± 0.5) hours if the subject is not discharged^{***}) post dose and Day 8 [± 1] day)
- ECG (Day 1, 6 [± 0.5] hours (or 8 [± 0.5] hours if the subject is not discharged^{***}) post dose)
- Subject self-assessment of HAE-related pain (in subjects 4 years of age and older) using e-diary FPS-R (Day 1, 1 hour [± 10] minutes, 2 hours [± 10] minutes, 4 [± 0.5] hours, 6 [± 0.5] hours and 8* [± 0.5] hours post dose, Day 2 (24 [± 4] hours), Day 3 (48 [± 4] hours)
- Investigator assessment of HAE symptoms (Day 1, 1 hour [± 10] minutes, 2 hours [± 10] minutes, 4 [± 0.5] hours, 6 [± 0.5] hours (and 8 [± 0.5] hours if the subject is not discharged^{**}) post dose)
- Investigator assessment of HAE-related pain (in subjects younger than 4 of age only) using FLACC (Day 1, 1 hour [± 10] minutes, 2 hours [± 10] minutes, 4 [± 0.5] hours, 6 [± 0.5] hours (and 8 [± 0.5] hours if the subject is not discharged^{**}) post dose)
- Clinical laboratory tests (Day 1, 6 [± 0.5] hours post dose and Day 8 [± 1] day)
- Reproductive hormone assessments (Day 1, 6 [± 0.5] hours post dose and Day 8 [± 1] day)
- Injection site reaction evaluation (Day 1, 1 hour [± 10] minutes, 6 [± 0.5] hours (and 8 [± 0.5] hours if the subject is not discharged^{**}) post dose, Day 2 (24 [± 4] hours), Day 3 (48 [± 4] hours), and Day 8 [± 1] day)
- Sampling for PK assessments in pubertal/post pubertal subjects (Day 1, 15 minutes [± 5] minutes, 30 minutes [± 5] minutes, 45 minutes [± 5] minutes, 1 hour [± 10] minutes, 2 hours [± 10] minutes, 4 [± 0.5] hours, 6 [± 0.5] hours post dose at initial attack only)
- Sampling for PK assessments in prepubertal subjects (Day 1, 15 minutes [± 5] minutes, 30 minutes [± 5] minutes, 2 hours [± 10] minutes, 4 [± 0.5] hours, 6 [± 0.5] hours post dose at initial attack only)

- Safety follow-up contact (Day 2 (24 [±4] hours), Day 3 (48 [±4] hours) by telephone (If a subject remains hospitalized, this safety follow-up will be conducted in person.)
- Immunogenicity evaluation (Day 8 [±1 day])
- Menstrual cycle history (Day 8 [±1 day] in pubertal/postpubertal females)
- Recording of concomitant medications
- Assessment of adverse events

*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 e-diary FPS-R.

**If the subject's HAE symptoms have not resolved at 6 hours post treatment (the subject's investigator-rated symptom score \neq 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.

***If the subject's HAE symptoms have not resolved at 6 hours post treatment (the subject's investigator-rated symptom score \neq 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.

8.5.2 Follow-up Visit (Day 90 ±7 days)

In the event that a subject has a subsequent HAE attack within the 90 day follow-up period for the first treatment, the date of the Day 90 follow-up visit for the first treatment remains the same. Each subsequent treatment will have a corresponding Day 90 follow-up visit.

- Physical examination
- Vital signs
- Height and weight
- Clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- Urine pregnancy test (in females of childbearing potential)
- Reproductive hormone assessments
- Immunogenicity evaluation
- Menstrual cycle history (in pubertal/postpubertal females)
- Recording of concomitant medications
- Assessment of adverse events
- Documentation of HAE attack(s) not treated with icatibant

8.5.3 Telephone Contact (Month 6 ±7 days)

The scheduled telephone contact will document pubertal changes/milestones, if any.

- Pubarche
- Menarche (females only)
- Changes in menstrual cycle (females only)
- Pregnancy (females and male partner)

8.6 Subsequent Attacks (Pubertal/Postpubertal Subjects Only)

Pubertal/postpubertal subjects may receive treatment for up to 2 subsequent HAE attacks, attack of at least 7 days after prior treatment (see Section [j \(07\)](#)).

Each treatment for a subsequent attack will require a Day 90 follow up visit. If a subsequent attack occurs within 7 days of the Day 90 follow-up visit for the previous attack, the assessments on Day 8 and Day 90 will be combined.

8.6.1 Treatment Period (Day 1 to Day 8 [± 1 Day])

- Investigational product administration (Day 1, Time 0)
- Physical examination (Day 1, 6 [±0.5] hours (or 8 (±0.5) hours if the subject is not discharged^{***}) post dose and Day 8 [±1 day])
- Vital signs (Day 1, 1 hour [±10 minutes], 6 [±0.5] hours (or 8 [±0.5] hours if the subject is not discharged^{***}) post dose and Day 8 [±1 day])
- ECG (Day 1, 6 [±0.5] hours (or 8 [±0.5] hours if the subject is not discharged^{***}) post dose)
- Subject self-assessment of HAE symptoms in subjects 4 years of age and older using e-diary FPS-R (Day 1, 1 hour [±10 minutes], 2 hours [±10 minutes], 4 [±0.5] hours, 6 [±0.5] hours and 8* [±0.5] hours post dose, Day 2 (24 [±4] hours), Day 3 (48 [±4] hours))
- Investigator assessment of HAE symptoms (Day 1, 1 hour [±10 minutes], 2 hours [±10 minutes], 4 [±0.5] hours, 6 (±0.5) hours [and 8 (±0.5) hours if the subject is not discharged^{**}] post dose)
- Clinical laboratory tests (Day 1, 6 [±0.5] hours post dose and Day 8 [±1 day])
- Reproductive hormone assessments (Day 1, 6 [±0.5] hours post dose and Day 8 [±1 day])
- Injection site reaction evaluation (Day 1, 1 hour [±10 minutes], 6 [±0.5] hours (and 8 [±0.50] hours if the subject is not discharged^{**}) post dose, Day 2 (24 [± 4] hours), Day 3 (48 [±4] hours), and Day 8 [±1 day])
- Safety follow-up contact (Day 2 (24 [±4] hours), Day 3 (48 [±4] hours) by telephone (If a subject remains hospitalized, this safety follow-up will be conducted in person.))
- Immunogenicity evaluation (Day 8 [±1 day])
- Menstrual cycle history (Day 8 [±1 day] in pubertal/postpubertal females)
- Recording of concomitant medications
- Assessment of adverse events

*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 e-diary FPS-R.

**If the subject's HAE symptoms have not resolved at 6 hours post treatment (the subject's investigator-rated symptom score \neq 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.

***If the subject's HAE symptoms have not resolved at 6 hours post treatment (the subject's investigator-rated symptom score \neq 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.

8.6.2 Follow-up Visit (Day 90 \pm 7 days)

- Physical examination
- Vital signs
- Height and weight
- Clinical laboratory tests (serum chemistry, hematology, and urinalysis)
- Urine pregnancy test (in females of childbearing potential)
- Reproductive hormone assessments
- Immunogenicity evaluation
- Menstrual cycle history (in pubertal/postpubertal females)
- Recording of concomitant medications
- Assessment of adverse events
- Documentation of HAE attack(s) not treated with icatibant

8.6.3 Telephone Contact (Month 6 \pm 7 days)

The scheduled telephone contact will document pubertal changes/milestones, if any.

- Pubarche
- Menarche (females only)
- Changes in menstrual cycle (females only)
- Pregnancy (females and male partner)

9 QUALITY CONTROL AND ASSURANCE

Training will occur at an investigator meeting or at the site initiation visit or both, and instruction manuals will be provided to aid consistency in data collection and reporting across sites.

Clinical sites will be monitored by the sponsor or its designee to ensure the accuracy of data against source documents.

The required data will be captured in a validated clinical data management system that is compliant with the Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) Part 11 Guidance. The clinical trial database will include an audit trail to document any evidence of data processing or activity on each data field by each user. Users will be trained and given restricted access, based on their role(s) in the study, through a password-protected environment.

Data entered in the system will be reviewed manually for validity and completeness against the source documents by a clinical monitor from the sponsor or its designee. If necessary, the study site will be contacted for corrections or clarifications; all missing data will be accounted for.

Serious adverse event information captured in the clinical trial database will be reconciled with the information captured in the Pharmacovigilance database.

10 PLANNED STATISTICAL METHODS

10.1 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 (disposition, demographic and pretreatment characteristics, efficacy variables, and safety variables) will be detailed in the statistical analysis plan (SAP).

Data will be summarized with respect to disposition, demographic, pretreatment characteristics, PK variables, safety variables, and efficacy variables. Summary statistics for continuous variables will include the number of subjects, the mean, median, standard deviation, and range. For PK parameters, the coefficient of variation and geometric mean also will be provided. For categorical data, summaries will include counts and percentages. For time to event data, the median time to event and other summary statistics will be estimated using the method of Kaplan and Meier.

10.2 Determination of Sample Size

The study will enroll a sufficient number of children and adolescents to ensure study completion of 30 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.

10.3 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.
- The PK Population will consist of those subjects who were treated with icatibant and had sufficient icatibant plasma concentration time measurements to derive primary PK parameters.
- The Safety Population will consist of those subjects who were treated with icatibant at least once

All efficacy analyses will be performed on the Efficacy Population. The corresponding tabular summaries and listings will be presented by the subject stratification group at enrollment (ie, prepubertal group or pubertal/postpubertal group) and icatibant-treated attack number.

The PK analyses will be based on the PK Population.

Safety and tolerability analyses will be based on the Safety Population. All tabular summaries and listings within this population will be presented by the subject stratification group and icatibant exposure number.

10.4 Demographics and Baseline Characteristics

Demographic data and pretreatment characteristics will be summarized separately for the Safety Population and the Efficacy Population.

10.5 Pharmacokinetic Analysis

A primary objective of the study is to investigate the PK of a single SC injection of icatibant in pediatric subjects. All PK analyses will use the PK population.

Plasma concentrations of icatibant and metabolites (ie, M1 and M2) and actual blood sampling times will be listed by subject and sampling time. Plasma concentrations will be summarized using descriptive statistics (number, mean and standard deviation). Pharmacokinetic parameters for icatibant and metabolites will be listed by subject and will be summarized using descriptive statistics (number, mean, standard deviation, coefficient of variation, geometric mean, minimum, median, maximum). Individual and mean plasma concentrations of icatibant and metabolites versus time will be displayed on linear and semi-logarithmic axes.

10.5.1 Estimation of PK Parameters

10.5.1.1 Noncompartmental Modeling

For subjects in whom the number of samples is sufficient to permit noncompartmental modeling, individual and mean PK parameters will be computed for icatibant and metabolites (M1 and M2) using standard noncompartmental methods, where possible, using the WinNonLin software package (Pharsight Corp., Mountain View, CA). For descriptive statistical tabulation of mean plasma concentrations and graphical displays, nominal collection times will be used, while all PK analysis and parameter calculations will use actual collection times. Plasma concentrations <LOQ will be treated as 0 for the calculation of the descriptive statistics for plasma concentrations at each sampling time. For the pharmacokinetic analysis, plasma concentrations <LOQ that occurred from pre-dose to the first concentration \geq LOQ will be treated as 0 and those that occur thereafter will be treated as missing.

Pharmacokinetic parameter estimates will include, where appropriate: icatibant and metabolite concentrations at each sampling time, time to peak concentration (T_{max}), actual peak (C_{max}) and minimum (C_{min}) concentrations, CL/F , AUC_{0-last} and AUC_{0-inf} , MRT, volume of distribution at steady state (V_{ss}/F) and elimination half-life ($t_{1/2}$).

The distribution of continuous data will be evaluated using parametric tests. A transformation, such as logs, will be used where appropriate. Multiple regression analysis, with an appropriate transformation on the dependent variable, will be used to assess the contribution of potential PK covariates while controlling for demographic covariates (eg, subject's age and gender) to the inter-subject variability of icatibant PK parameters. The multivariable analysis will be

considered the primary statistical analysis. A p-value of 0.05 will be considered statistically significant for all analyses.

10.5.1.2 Compartmental Modeling Using Population Methods

Nonlinear mixed effects modeling will be used to define individual subject profiles and if possible, parameter estimates. The structural PK model will be developed and validated using PK information obtained from adult subjects and will enable delineation of the impact of age-dependent changes on icatibant disposition. Development of this model will allow for characterization and better prediction of the dose-concentration-exposure relationship for icatibant in pediatric subjects. Population PK modeling will be performed with nonlinear mixed effect modeling software (eg, NONMEM, Globomax LLC or WinNonMix, Pharsight Corp.). The program will estimate the inter- and intra-individual variability of PK parameter estimates. Both weight-normalization and allometric scaling principles will be evaluated. For selecting preliminary meaningful covariates the general additive model (GAM) analysis will be used. Variables to be considered will include (but are not limited to): age, sex, ethnicity, total and lean bodyweight (TBW, LBW), body mass index (BMI), and body surface area (BSA).

Monte Carlo simulation experiments based on the model(s) developed above may be performed by a validated simulation software program (eg, Trial Simulator, Pharsight Corp.) to assess the response patterns for various dosage regimens of icatibant treatments in the pediatric population.

10.6 Safety and Tolerability Analyses

Another key objective of the study is to investigate the safety and tolerability of a single SC dose of icatibant in pediatric subjects treated with icatibant for the first time or treated with icatibant more than once. The corresponding analyses will be based on the Safety Population.

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.

Adverse events will be categorized using MedDRA Version 8.1. The assessment of safety will be based mainly on the frequency of treatment emergent AEs. Adverse events will be summarized by system organ class (SOC) and preferred term. The number and proportion of subjects experiencing an AE will be tabulated by the stratification group and icatibant exposure number. Adverse events 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 (ie, maximum severity) will be identified for the analysis by severity and the AE that has the highest relationship to investigational product will be identified for the analysis by relationship. Serious adverse events will be provided in a data listing.

Laboratory data will be listed by subject, stratification group and icatibant exposure number. Subjects with newly occurring abnormalities outside the normal range will be flagged and listed separately. Observed values and changes from pretreatment values will be summarized by the

stratification group and icatibant exposure number. Shift tables will also be tabulated by stratification group, icatibant exposure number, and study time point.

Vital signs data will be listed by subject, stratification group, and icatibant exposure number. Furthermore, observed values and changes from baseline will be summarized by stratification group and icatibant exposure number. Shift tables may be presented, utilizing reference ranges. Subjects with notably abnormal values will be identified and listed separately along with their values.

Local tolerability will be tabulated and summarized according to the type and severity of the injection site reaction.

The impact of icatibant on the reproductive hormone levels will be assessed by presenting tabular summaries for FSH, LH, estradiol, and progesterone for females, and FSH, LH, and testosterone for males. The change from baseline values will also be summarized. Subjects with newly occurring abnormalities outside the normal range will be flagged and listed separately.

Data from other tests (eg, immunogenicity, ECG) will be listed and summarized as appropriate.

10.7 Efficacy Analyses

Efficacy analyses will be performed on the Efficacy Population. The primary efficacy endpoint is the time to onset of symptom relief measured using the investigator-reported symptom score. The investigator will report symptom scores at pretreatment and 1, 2, 4, and 6 hours post treatment, and at 8 hours post treatment for subjects who had not shown complete resolution of HAE symptoms at 6 hours. 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 earliest time post treatment at which there is a 20% improvement in the average post-treatment symptom score with no worsening of any single component score. The median time and the 95% confidence interval will be calculated using the Kaplan-Meier methodology.

A tabular summary of the average investigator-reported symptom score and the change from baseline in the average investigator-reported symptom score will be presented by the stratification group and the icatibant treated attack number. An alternative analysis will focus on the time to minimal symptoms and is defined as the time from study drug administration to the earliest time post treatment when all symptoms are either absent or mild. The median time and 95% confidence interval will be calculated using Kaplan-Meier methodology.

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. Also, for individual symptoms that are moderate or worse at pretreatment, the median and 95% confidence interval will be presented for the time to the symptom being mild or absent.

Two subsets of subjects, those 4 years of age or older and those below 4 years of age, will have assessment of pain using the FPS-R and FLACC instruments, respectively. For subjects ≥ 4 years of age, the time to onset of symptom relief is defined as the earliest time at which the post-

treatment score improves by at least one level. The time to onset of symptom relief for subjects <4 years of age is defined as the earliest time at which a 20% improvement is seen in the total post-treatment score. Additionally, time to minimal symptoms defined as the earliest time at which the post-treatment score (or total post-treatment score for FLACC) improves to zero, will be analyzed. The time to onset of symptom relief and time to minimal symptoms will be analyzed using the same methods as the primary efficacy endpoint.

10.8 Other Analyses

The number and percentage of subjects who received rescue medications before the onset of symptom relief will be summarized by the stratification group and icatibant-treated attack number. Time to first use of rescue medication prior to symptom relief will be calculated from the time of investigational product administration to the first use of rescue medication prior to the onset of symptom relief. The median time and the 95% confidence interval will be calculated using Kaplan-Meier methodology if there are at least 5 subjects for a given attack who used rescue medication prior to attaining symptom relief.

10.9 Data Monitoring and Interim Analysis

The study is a Phase II, PK, and efficacy data on an ongoing study in pediatric patients with acute pain. Its goal will be to assess the risk/benefit of icatibant treatment in this pediatric population.

An analysis of the data for DSMB review is planned after the first 4 subjects in the pubertal/postpubertal group have been treated, and will be repeated at subsequent time points as specified in the DSMB charter. Because no formal hypothesis testing is planned, multiplicity concerns regarding repeated analyses are not an issue.

Based on the anticipated sequence of data being generated in the study, an initial interim analysis of the data from pubertal/postpubertal patients (N=20) is planned. It is expected that this will be followed by an interim analysis of data from prepubertal patients (N=10), and then by a final analysis to include the data of patients treated for subsequent attacks. This sequence is based on the anticipated sequence of data being generated during the study and may be modified to fit the actual study conduct.

10.10 Handling of Missing Data

Individual pretreatment symptom scores, FPS-R scores, and FLACC scores will be assigned a value of zero. For missing post-treatment scores, imputation will be employed using the Last Observation Carried Forward (LOCF) approach. The pretreatment values may also be used in the imputation. For missing or partial rescue medication dates, the imputation will be performed such that the earliest possible time post treatment will be assigned to the rescue medication use. A similar approach will be followed to determine treatment emergent AEs in case of missing or partial AE dates.

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Investigators and Study Administrative Structure

Before initiation of the study, the investigator must provide the sponsor with a completed Form FDA 1572 or Investigator Agreement. Investigational product may be administered only under the supervision of the investigator listed on this form. Curriculum vitae must be provided for the investigator and sub-investigators listed on Form FDA 1572 or the Investigator Agreement.

The investigator should ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the study treatments, and their study related duties and functions. The investigator must maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study related duties.

11.2 Institutional Review Board or Independent Ethics Committee Approval

Before initiation of the study, the investigator must provide the sponsor with a copy of the written IRB/IEC approval of the protocol and the informed consent form. This approval must refer to the informed consent form and to the study title, study number, and version and date of issue of the study protocol, as given by the sponsor on the cover page of the protocol.

Status reports must be submitted to the IRB/IEC at least once per year. The IRB/IEC must be notified of completion of the study. Within 3 months of study completion or termination (or as required), a final report must be provided to the IRB/IEC. A copy of these reports will be sent to the study clinical monitor. The investigators must maintain an accurate and complete record of all submissions made to the IRB/IEC, including a list of all reports and documents submitted. Serious drug-related AEs which are reported to the US FDA or other Regulatory agencies (Investigational New Drug [IND] Safety Reports) must be submitted promptly to the IRB/IEC.

11.3 Ethical Conduct of the Study

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigators abide by good clinical practice (GCP) as described in the 21 CFR Parts 50, 56, and 312 and the International Conference on Harmonisation (ICH) GCP Guidelines. Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

11.4 Subject Information and Consent/Assent

Before enrolling in the clinical study, the subject and/or the subject's parent(s) or legal guardian(s) must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him or her.

An informed consent form (assent form, if applicable) that includes information about the study will be prepared and given to the subject or the subject's parent(s) or legal guardian(s).

This document will contain all FDA and ICH-required elements, as well as other elements required by ethics committees, if applicable, or as per country legal requirements. The informed consent (or assent form, if applicable) form must be in a language understandable to the subject or the subject's parent(s) or legal guardian(s) and must specify who informed the subject, the subject's parent(s), or the subject's legal guardian(s).

After reading the informed consent document, the subject or the subject's parent(s) or legal guardian(s) must give consent in writing. Consent must be confirmed at the time of consent by the personally dated signature of the subject, the subject's parent(s) or the subject's legal guardian(s) and by the personally dated signature of the person conducting the informed consent discussions.

If the subject or the subject's parent(s) or legal guardian(s) is unable to read, oral presentation and explanation of the written informed consent form and information to be supplied must take place in the presence of an impartial witness. Consent must be confirmed at the time of consent orally and by the personally dated signature of the subject or by a local legally recognized alternative (eg, the subject's thumbprint or mark) or by the personally dated signature of the subject's parent(s) or the subject's legal guardian(s). The witness and the person conducting the informed consent discussions must also sign and personally date the informed consent document. It should also be recorded and dated in the source document that consent was given.

A copy of the signed and dated consent document(s) must be given to the subject or the subject's parent(s) or the subject's legal guardian(s). The original signed and dated consent document will be retained by the investigator.

The investigator will not undertake any measures specifically required solely for the clinical study until valid consent has been obtained.

A model of the informed consent form to be used in this study will be provided to the sites separately from this protocol.

11.5 Subject Confidentiality

Subject names will not be supplied to the sponsor. Only the subject number and subject initials will be recorded in the CRF, if applicable according to local laws and regulation, and if the subject name appears on any other document, it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be told that representatives of the sponsor, a designated CRO, the IRB/IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. The investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

11.6 Study Monitoring

Monitoring procedures that comply with current GCP guidelines will be followed. Review of the CRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by the sponsor or its designee. Monitoring will be performed by a representative of the sponsor (Clinical Study Monitor) who will review the CRFs and source documents. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent site visits and communications (letter, email, telephone, and facsimile).

11.7 Case Report Forms and Study Records

Case report forms (paper or electronic) are provided for each subject. All forms must be filled out by authorized study personnel. All corrections to the original CRF entry must indicate the reason for change. The investigator is required to sign the CRF after all data have been captured for each subject. If corrections are made after review and signature by the investigator, he or she must be made aware of the changes, and his or her awareness documented by resigning the CRF.

11.7.1 Critical Documents

Before the sponsor initiates the trial (ie, obtains informed consent from the first subject), it is the responsibility of the investigator to ensure that the following documents are available to the sponsor or its designee:

- Applicable local regulatory documentation (eg, completed Form FDA 1572 [Statement of Investigator], signed, dated, and accurate).
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed within 24 months of study initiation).
- Copy of investigator(s) and sub-investigator(s) current medical license (indicating license number and expiration date).
- Signed and dated agreement of the final protocol.
- Signed and dated agreement of any amendment(s), if applicable.
- Approval/favorable opinion from the IRB/IEC clearly identifying the documents reviewed by name, number and date of approval or re approval: protocol, any amendments, Subject Information/Informed Consent Form, and any other written information to be provided regarding subjects recruitment procedures.
- Copy of IRB/IEC approved Subject Information/Informed Consent Form/any other written information/advertisement (with IRB approval stamp and date of approval).
- Current list of IRB/IEC Committee members/constitution (dated within 12 months prior to study initiation).
- Financial Disclosure Form signed by investigator(s) and sub-investigator(s).
- Current laboratory reference ranges (if applicable).
- Certification/QA scheme/other documentation (if applicable).

Regulatory approval and notification as required must also be available. The protocol will not be initiated until regulatory approval and notification are obtained; these are the responsibility of the sponsor.

11.8 Data and Safety Monitoring Board

In view of the role of bradykinin and B2 receptors in reproductive development, the study will use an external DSMB. The DSMB will provide an ongoing, independent review and assessment of the safety data to protect the interests and safety of subjects participating in the study. The DSMB will adhere to a prospectively determined charter which will be proposed by sponsor and approved by the DSMB. The charter will define the membership of the DSMB, the responsibilities of the DSMB and the sponsor, describe the conduct of meetings, and define the data to be reviewed.

Enrollment of pediatric subjects in the proposed study will be stratified into 2 groups (2 years of age to the older prepubertal children, and pubertal/postpubertal children to those less than 18 years of age). It is planned that subjects in both groups will receive an icatibant dose (0.4 mg/kg to a maximum dose of 30 mg) selected to target an exposure comparable to that observed in adults treated with icatibant. Initially, enrollment and dosing of pubertal/postpubertal subjects will precede that of prepubertal subjects. After the first 4 subjects in the pubertal/postpubertal group have been treated, icatibant concentration measurements and PK analysis, safety, tolerability, and efficacy data will be reviewed and assessed by the DSMB. This review must be completed prior to initiating enrollment of subjects in the prepubertal group. As the outcome of its review, the DSMB may make a recommendation to continue enrolling subjects in the pubertal/postpubertal group, to initiate dosing of subjects in the prepubertal group, or to administer a different dose, or to terminate the study.

11.9 Protocol Violations/Deviations

The investigator will conduct the study in compliance with the protocol. The protocol will not be initiated until the IRB/IEC and the appropriate regulatory authorities have given approval/favorable opinion. Modifications to the protocol will not be made without agreement of the sponsor. Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects. The IRB/IEC may provide, if applicable regulatory authorities permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB/IEC. The sponsor will submit all protocol modifications to the regulatory authorities in accordance with the governing regulations.

A record of subjects screened, but not entered into the study, is also to be maintained. No protocol waivers or exemptions will be considered by the sponsor during the study.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the investigator will contact the sponsor or its designee, if circumstances permit, to discuss the planned course of action.

Any departures from the protocol must be fully documented as a protocol deviation. Protocol deviations will need to be reviewed by the medical monitor and may also need to be submitted to the IRB/IEC.

Protocol modifications will only be initiated by the sponsor and must be approved by the IRB/IEC and submitted to the FDA or other applicable international regulatory authority before initiation.

11.10 Premature Closure of the Study

If the sponsor, investigator, or regulatory authorities discover conditions arising during the study which indicate that the clinical investigation should be halted due to an unacceptable risk to subjects, the study may be terminated after appropriate consultation between the sponsor and the investigator. In addition, a decision on the part of the sponsor to suspend or discontinue development of the investigational product may be made at any time. Conditions that may warrant termination of the study or site include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study
- Failure of the investigator to comply with pertinent global regulations
- Submission of knowingly false information from the study site to the sponsor or other pertinent regulatory authorities
- Insufficient adherence by the Investigator to protocol requirements

11.11 Access to Source Documentation

Regulatory authorities, the IRB/IEC, or the sponsor may request access to all source documents, CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities. Monitoring and auditing procedures that comply with current GCP guidelines will be followed. On-site review of the CRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters may be performed.

11.12 Data Generation and Analysis

The clinical database will be developed and maintained by a CRO or an electronic data capture technology provider as designated by Shire. The sponsor or its designee will be responsible for performing study data management activities.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 8.1 or higher. Concomitant medication will be coded using the World Health Organization Drug Dictionary (WHO-DD) (2004, Q4). Centralized laboratories will be employed as described in the study manual to aid in consistent measurement of efficacy and safety parameters.

11.13 Retention of Data

Essential documents should be retained until at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The sponsor will notify the investigator if these documents must be retained for a longer period of time. It is the responsibility of the sponsor to inform the Investigator or institution as to when these documents no longer need to be retained.

11.14 Financial Disclosure

The investigator should disclose any financial interests in the sponsor as described in 21 CFR Part 54 prior to beginning this study. The appropriate form will be provided to the investigator by the sponsor, which will be signed and dated by the investigator, prior to the start of the study, at the end of the study, and one year post-study (or site) closure. Changes in status concerning financial interests during the study and after its completion will be disclosed by the Investigator in accordance 21 CFR Part 54.

11.15 Publication and Disclosure Policy

All information concerning the study material, such as patent applications, manufacturing processes, basic scientific data, and formulation information supplied by the sponsor and not previously published are considered confidential and will remain the sole property of the sponsor. The investigator agrees to use this information only in accomplishing this study and will not use it for other purposes.

It is understood by the investigator that the information developed in the clinical study may be disclosed as required to the authorized regulatory authorities and governmental agencies. In order to allow for the use of the information derived from the clinical studies, it is understood that there is an obligation to provide the sponsor with complete test results and all data developed in the study in a timely manner.

The investigator and any other clinical personnel associated with this study will not publish the results of the study, in whole or in part, at any time, unless they have consulted with Shire, provided Shire a copy of the draft document intended for publication, and obtained the written consent of Shire for such publication. All information obtained during the conduct of this study will be regarded as confidential. Shire will use the information for registration purposes and for the general development of the drug.

12 LIST OF REFERENCES

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Appendix 1 Study Schedule of Events (No Attack)

(Pubertal/postpubertal subjects only)	Screening Period	Pre-treatment (Baseline)	Treatment	Post Treatment											Follow-up		
				Day 1											Day 2	Day 3	Day 8 (±1)
Study Day		Day 1	Day 1	0	0.25	0.5	0.75	1	2	4	6	8	24	48			
Time Post Treatment (hours)					(±5) min	(±5) min	(±5) min	(±10) min	(±10) min	(±0.5) hr	(±0.5) hr	(±0.5) hr	(±4) hr	(±4) hr			
Window (hours or minutes)																	
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															
Physical Examination	X	X								X	X ^e				X	X	
Pubertal Status Determination ^b	X	X															

(Pubertal/postpubertal subjects only)	Screening Period	Pre-treatment (Baseline)	Treatment	Post Treatment											Follow-up				
				Day 1											Day 2	Day 3	Day 8 (±1)	Day 90 (±7)	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																			
Menstrual Cycle History (in pubertal/postpubertal females)		X												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	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				

(Pubertal/postpubertal subjects only)	Screening Period	Pre-treatment (Baseline)	Treatment	Post Treatment											Follow-up				
				Day 1											Day 2	Day 3	Day 8 (±1)	Day 90 (±7)	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																			
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				
				Day 1											Day 2	Day 3	Day 8 (±1)	Day 90 (±7)	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.

Appendix 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		
				Day 1											Day 2	Day 3	Day 8 (±1)
Study Day		Day 1	Day 1	0	0.25	0.5	0.75	1	2	4	6	8 ^e	24	48			
Time Post Treatment (hours)					(±5) min	(±5) min	(±5) min	(±10) min	(±10) min	(±0.5) hr	(±0.5) hr	(±0.5) hr	(±4) hr	(±4) hr			
Window (hours or minutes)																	
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				
				Day 1											Day 2	Day 3	Day 8 (±1)	Day 90 (±7)	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	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 e-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				
				Day 1											Day 2	Day 3	Day 8 (±1)	Day 90 (±7)	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				
				Day 1											Day 2	Day 3	Day 8 (±1)	Day 90 (±7)	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			
				Day 1										Day 2	Day 3	Day 8 (±1)	Day 90 (±7)
Study Day		Day 1	Day 1														
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 as indicated in Section 8.5.1.
- ^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 e-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.

Appendix 3 Study Schedule of Events (Subsequent Icatibant-treated Attacks)

Subsequent Icatibant-treated Attacks (Pubertal/postpubertal subjects only)	Pre-treatment (Baseline) ^g	Treatment	Post Treatment								Follow-up	
			Day 1					Day 2	Day 3	Day 8 (±1) ^a	Day 90 (±7) ^a	Month 6 (±7 days) Telephone Contact
Study Day	Day 1	Day 1	1	2	4	6	8 ^d	24	48			
Time Post Treatment (hours)		0	1	2	4	6	8 ^d	24	48			
Window (hours or minutes)			(±10) min	(±10) min	(±0.5) hr	(±0.5) hr	(±0.5) hr	(±4) hr	(±4) hr			
Assessments												
Inclusion/Exclusion Assessment	X											
Physical Examination	X					X ^f	X ^f			X	X	
Pubertal Status Determination ^b	X											
Menstrual Cycle History (in pubertal/postpubertal females)	X									X	X	
Documentation of HAE Attack(s) Not Treated with icatibant	X ^h										X	
Documentation of Pubertal Changes/Milestones												X
Vital Signs	X		X			X ^f	X ^f			X	X	
ECG	X					X ^f	X ^f					
Height and Weight	X										X	
Subject Self-assessment of HAE-related Pain Using e-diary FPS-R (in subjects 4 years of age and older, and before blood work, if applicable)	X		X	X	X	X ^e	X ^{d,e}	X	X			

Subsequent Icatibant-treated Attacks (Pubertal/postpubertal subjects only)	Pre-treatment (Baseline) ^g	Treatment	Post Treatment								Follow-up	
			Day 1					Day 2	Day 3	Day 8 (±1) ^a	Day 90 (±7) ^a	Month 6 (±7 days) Telephone Contact
Study Day	Day 1	Day 1	Day 1					Day 2	Day 3	Day 8 (±1) ^a	Day 90 (±7) ^a	
Time Post Treatment (hours)		0	1	2	4	6	8 ^d	24	48			
Window (hours or minutes)			(±10) min	(±10) min	(±0.5) hr	(±0.5) hr	(±0.5) hr	(±4) hr	(±4) hr			
Assessments												
Investigator Assessment of HAE Symptoms	X		X	X	X	X ^e	X ^e					
Clinical Laboratory Tests (serum chemistry/hematology/urinalysis)	X					X				X	X	
Urine Pregnancy Test (in females of childbearing potential)	X										X	
Reproductive Hormone Assessments (FSH, LH, estradiol, progesterone in females; FSH, LH, testosterone in males)	X					X				X	X	
Safety Follow-up Contact								X ^c	X ^c			
Investigational Product Administration (single SC injection)		X										
Injection Site Reaction Evaluation			X			X ^e	X ^e	X ^c	X ^c	X		
Immunogenicity Evaluation	X									X	X	
Concomitant Medications	X	X	X	X	X	X ^e	X ^e	X ^c	X ^c	X	X	
Adverse Events	X	X	X	X	X	X ^e	X ^e	X ^c	X ^c	X	X	

Subsequent Icatibant-treated Attacks (Pubertal/postpubertal subjects only)	Pre-treatment (Baseline) ^g	Treatment	Post Treatment							Follow-up				
			Day 1							Day 2	Day 3	Day 8 (±1) ^a	Day 90 (±7) ^a	Month 6 (±7 days) Telephone Contact
Study Day	Day 1	Day 1	Day 1							Day 2	Day 3	Day 8 (±1) ^a	Day 90 (±7) ^a	
Time Post Treatment (hours)		0	1	2	4	6	8 ^d	24	48					
Window (hours or minutes)			(±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; SC = subcutaneous

- ^a If a subsequent attack occurs within 7 days of the Day 90 visit for the previous attack, the assessments on Day 8 and Day 90 will be combined.
- ^b A subject's classification as prepubertal or pubertal/postpubertal will be determined at the Day 1 pretreatment visit. Note that a subject classified previously as pubertal/postpubertal will not require further evaluation of pubertal status during the study.
- ^c These assessments will be conducted by telephone contact.
- ^d 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 e-diary FPS-R.
- ^e 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.
- ^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 either 6 OR 8 hours post treatment.
- ^g Subsequent treatment with icatibant for up to 2 additional attacks of acute HAE for a total of 3 attacks will be offered to pubertal/postpubertal subjects contingent upon having been treated for an initial attack and presenting with a subsequent acute attack at least 7 days after prior treatment. In the event that a subsequent attack occurs at least 7 days after prior treatment, but is within the window (±1 day) allowed for performance of Day 8 assessments associated with a prior attack, the Day 8 assessments may also serve as the pretreatment (baseline) assessments for the subsequent attack.
- ^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.

Appendix 4 Modified Sexual Maturation Scale

Stage	Female Breast Stage	Female Pubic Hair Stage ^a	Male Genital Stage	Male Pubic Hair Stage ^a
1 Preadolescent	Elevation of papilla only.	No pubic hair.	Testes, scrotum, and penis are of about the same size and proportion as in early childhood.	No pubic hair.
2	Breast bud stage; elevation of breast and papilla as a small mound, enlargement of areolar diameter.	Sparse growth of long, slightly pigmented downy hair, straight or only slightly curled, appearing on the pubis. Do not consider hair on the labia.	The scrotum and testes have enlarged and there is a change in the texture of the scrotal skin. There is also some reddening of the scrotal skin.	Sparse growth of long, slightly pigmented downy hair, straight or only slightly curled, appearing chiefly at the base of the penis.
3	Further enlargement of breast and areola, with no separation of their contours.	Considerably darker, coarser, and more curled; spreads sparsely over the conjunction of the pubes.	Growth of the penis has occurred, at first mainly in length but with some increase in breadth. There has been further growth of testes and scrotum.	Considerably darker, coarser, and more curled; spreads sparsely over the junction of the pubes.
4	Projection of areola and papilla to form a secondary mound above the level of the breast.	Hair is adult in type, but the area covered by it is still considerably smaller than in most adults. There is no spread to the medial surface of the thighs.	Penis further enlarged in length and breadth with development of glans. Testes and scrotum further enlarged. Further darkening of the scrotal skin.	Hair is adult in type, but the area covered by it is still considerably smaller than in most adults. There is no spread to the medial surface of the thighs.
5	Mature stage; projection of papilla only, owing to recession of the areola to the general contour of the breast.	Adult in quantity and type, distributed as an inverse triangle. Spread to the medial surface of the thighs, but not up the linea alba or elsewhere above the base of the inverse triangle.	Genitalia adult in size and shape. No further enlargement takes place after stage 5 is reached.	Adult in quantity and type, distributed as an inverse triangle. Spread to the medial surface of the thighs, but not up the linea alba or elsewhere above the base of the inverse triangle.
^a Pubic hair development reflects adrenal function, not hypothalamic/gonadal function. The descriptions used in this table are intended to provide guidance for the investigators and may not align with descriptions of pubic hair and pubertal stage in other sources.				

Appendix 5 Faces Pain Scale-Revised (FPS-R)

Faces Pain Scale – Revised (FPS-R)

From *Pediatric Pain Sourcebook*, www.painsourcebook.ca
Version: 7 Aug 2007 CL von Baeyer

In the following instructions, say "hurt" or "pain," whichever seems right for a particular child.

"These faces show how much something can hurt. This face [point to left-most face] shows no pain. The faces show more and more pain [point to each from left to right] up to this one [point to right-most face] – it shows very much pain. Point to the face that shows how much you hurt [right now]."

Score the chosen face 0, 2, 4, 6, 8, or 10, counting left to right, so '0' = 'no pain' and '10' = 'very much pain.' Do not use words like 'happy' and 'sad'. This scale is intended to measure how children feel inside, not how their face looks.

Permission for use. Copyright in the FPS-R is held by the International Association for the Study of Pain (IASP) © 2001. This material may be photocopied for non-commercial clinical and research use. To request permission from IASP to reproduce the FPS-R in a publication, or for any commercial use, please e-mail iaspdesk@iasp-pain.org For all other information regarding the FPS-R contact Tiina.Jaaniste@sesiahs.health.nsw.gov.au (Pain Medicine Unit, Sydney Children's Hospital, Randwick NSW 2031, Australia).

Sources. Hicks CL, von Baeyer CL, Spafford P, van Korlaar I, Goodenough B. The Faces Pain Scale – Revised: Toward a common metric in pediatric pain measurement. *Pain* 2001;93:173-183. Bieri D, Reeve R, Champion GD, Addicoat L, Ziegler J. The Faces Pain Scale for the self-assessment of the severity of pain experienced by children: Development, initial validation and preliminary investigation for ratio scale properties. *Pain* 1990;41:139-150.

----- 0 2 4 Fold here 6 8 10 -----



Appendix 6 Faces, Legs, Activity, Cry, and Consolability Scale (FLACC)

FLACC SCALE (FACE, LEGS, ACTIVITY, CRY, CONSOLABILITY)			
FACE	0 No particular expression or smile	1 Occasional grimace or frown Withdrawn Disinterested	2 Frequent to constant frown Clenched jaw Quivering chin
LEGS	0 Normal position or Relaxed	1 Uneasy Restless Tense	2 Kicking or Legs drawn up
ACTIVITY	0 Lying quietly Normal position Moves easily	1 Squirming Shifting back/forth Tense	2 Arched Rigid or Jerking
CRY	0 No cry (awake or asleep)	1 Moans or whimpers Occasional complaint	2 Crying steadily Screams or sobs Frequent complaints
CONSOLABILITY	0 Content Relaxed	1 Reassured by occasional touching, hugging, or 'talking to'. Distractible	2 Difficult to console or comfort
<p>The FLACC is a behavioral pain assessment scale suitable for use in preverbal children and children with limited verbal capability.</p> <p><u>Instructions:</u></p> <ol style="list-style-type: none"> 1. Rate patient in each of the 5 measurement categories 2. Add together. 3. Document total pain score. 			

Appendix 7 Protocol Signature Page

Study 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

Study Number: HGT-FIR-086

Original Protocol Date: 14 June 2011

Amendment 1 Date: 05 August 2011

Amendment 2 Date: 06 March 2012

Amendment 3 Date: 19 June 2013

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signatory:

Investigator

Signature

Date

Printed Name

I have read and approve the protocol described above.

Signatory:

**Shire HGT
Medical
Monitor**

PPD

Signature

PPD

Date

PPD MD, PhD

Printed Name

Appendix 8 Summary of Changes for Amendment 3

1. Amendment Summary and Rationale

Shire submitted a Paediatric Investigation Plan (PIP) modification request (EMEA-000408-PIP01-08-M04) to the Paediatric Committee (PDCO) of the European medicines Agency on 22 February 2013. Shire proposed to modify the study parameters for HGT-FIR-086 in order to facilitate enrollment and make the study less burdensome for recruitment of pediatric subjects. The request for PIP modification received a positive PDCO opinion on 17 May 2013.

The revised study design includes the following:

- Pubertal/postpubertal patients: The number of pubertal/postpubertal patients participating in the study will remain at 20 (single dose icatibant with 3-month follow-up); however, 10 patients will be treated with icatibant during an HAE attack; while the other 10 patients will be treated without an attack (ie, will be evaluated for PK, tolerability and safety, but not for efficacy).
- Prepubertal patients: The number of prepubertal patients will be reduced from 16 to 10. The Sponsor will continue to actively enroll this pediatric subset in HGT-FIR-086; however, given the significant enrolment challenges, the completion of the study in this particular subset is deferred until December 2017.
- Specific follow-up: Pubertal/postpubertal subjects, including both those treated during an attack or not, may be offered further open-label treatment with icatibant for any subsequent HAE attacks that occur at least 7 days after prior treatment. As a consequence of the difficulty in enrolling patients in the study, open-label treatment will be continued until a total number of 10 adolescents (instead of 15) have been treated with icatibant for at least 3 eligible acute attacks. The follow up phase is not part of the PIP; however, this will be a post-approval commitment.

Shire believes that the proposed study modifications will still allow for the generation of an adequate safety, PK, and efficacy dataset in pediatric subjects and therefore will continue to fulfill the overall objective of the pediatric program.

2. Detailed Summary of Changes for the Amendment

This is a section that has been updated to describe the changes from the previous protocol version. Significant changes and additions to the protocol text are captured below.

Changes in grammar, spelling, punctuation, format, minor editorial changes (including re-ordering of text or other edits for consistency and clarity), updates to the list of abbreviations and cross-references, and edits to the Introduction (Section 1) are not reflected in the change summary.

Bold text indicates new text. ~~Strikethrough~~ text indicates deleted text.

CHANGES TO TEXT

Change: Change to Medical Monitor
Section impacted by change: Cover page
Revised Text: PPD [REDACTED] MD, PhD Shire Human Genetic Therapies (HGT), Inc. Mobile: PPD [REDACTED]
Other sections impacted by change: Section 7.17.4.2 Reporting Serious Adverse Events
Change: Change to study objectives
Section impacted by change: Section 2.1 Objectives
Revised Text: <ul style="list-style-type: none"> To investigate the pharmacokinetics (PK), tolerability, and safety of a single subcutaneous (SC) dose of icatibant in children and adolescents with hereditary angioedema (HAE) during an acute HAE attack
Other sections impacted by change: Synopsis, Section 10 Planned Statistical Methods
Change: Change to study endpoints
Section impacted by change: Section 3 Endpoints
Revised Text: 3.1 Primary Endpoints Primary endpoints: <ul style="list-style-type: none"> 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). 3.2 Secondary Endpoints Secondary endpoints (only for subjects treated with icatibant during a HAE attack): Time to onset of relief of symptoms and time to minimal symptoms, as measured by investigator- and subject-reported outcomes <ul style="list-style-type: none"> For all subjects (2 to <18 47 years of age): investigator assessment and scoring of cutaneous, abdominal, and laryngeal symptoms of acute HAE attacks by an investigator-rated symptom score. <ul style="list-style-type: none"> The time to onset of relief of symptoms, defined as the earliest time at which at least 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). <ul style="list-style-type: none"> 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]). <ul style="list-style-type: none"> 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. 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.

Other sections impacted by change:	pl	dn6	Planned Statistical Methods
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Change: Change to study design

Section impacted by change:	d	dn6m	Study Design
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Revised Text:

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 ~~during an initial acute attack.~~

The study will enroll children and adolescents from 2 to **less than 18** ~~17~~ years of age, divided into 2 groups: prepubertal (Tanner stage I) and pubertal/postpubertal (Tanner stages II to V).

At least 10 prepubertal children and at least 20 adolescents (including 10 treated during a HAE attack) must be enrolled in the study.

d	d	d	d	(d
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Change: Change to study design

Section impacted by change:	d	dn6	Study Methodology
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Revised Text:

A subject's classification as prepubertal or pubertal/postpubertal will be determined **at screening and, if appropriate**, at the time of the first icatibant-treated HAE attack. Subjects classified as pubertal/postpubertal at screening will not require further evaluation of pubertal status during the study, whereas subjects classified as prepubertal at screening will have their pubertal status reassessed at the time of their first icatibant-treated attack visit.

After a qualifying screening period, the PK, safety/tolerability, and efficacy of treatment with SC icatibant will be evaluated in **at least 20 subjects (10 prepubertal and 10 pubertal/postpubertal subjects) who present with cutaneous, abdominal, or laryngeal symptoms of an acute attack of HAE. Subjects should initiate treatment with icatibant within 12 hours of the onset of symptoms; however, there are no prespecified attack severity criteria that are required for treatment. Subjects with attacks considered to be mild, moderate, or severe are all potentially eligible to receive treatment with icatibant.**

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

Initially, enrollment and dosing of pubertal/postpubertal subjects will precede that of prepubertal subjects. After the first 4 subjects in the pubertal/postpubertal group have been treated with icatibant (**whether during or in the absence of attack**), PK, safety/tolerability, and efficacy (**as appropriate**) will be reviewed by an independent Data and Safety Monitoring Board (DSMB). The DSMB review of the first 4 subjects shall be completed prior to continuing enrollment of additional pubertal/postpubertal subjects, treatment of second and third HAE attacks in pubertal/postpubertal subjects, and initiating enrollment of subjects in the prepubertal group.

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. Safety follow-up to assess the subject's condition must be conducted at 24 and 48 hours after icatibant injection, and will occur either by a telephone call from study personnel or in person at the investigator's discretion.

Subjects will return to the hospital/study center for scheduled assessments on Day 8 and for a follow-up visit on Day 90.

After having received initial treatment with icatibant, either during or in the absence of attack, at least 10 pubertal/postpubertal subjects who subsequently experience an acute HAE attack may continue to receive treatment

with icatibant as a single SC administration per attack for a total of 3 eligible icatibant-treated attacks. Further treatment with icatibant is contingent upon presentation of an acute cutaneous, abdominal, or laryngeal attack of HAE at least 7 days after prior treatment. All primary and secondary outcomes as above (including anti-icatibant antibodies and reproductive hormones) will be measured in these pubertal/postpubertal subjects after each administration. Note that for some of the pubertal/postpubertal subjects who receive further treatment, ie, those who provided PK and safety/tolerability measurements without an attack, their first icatibant-treated attack will represent their second on-study exposure to icatibant for safety analysis purposes.

The investigator will schedule a telephone contact approximately 6 months after Day 1 of each icatibant-treated attack to obtain specific updates concerning pubertal changes/milestones.

d d d d (d)

Change: Change to Study Design

Section impacted by change: [d](#) [m7](#) Study Assessments

Revised Text:

Table 4-1 Study Periods

Study Periods	
Screening	Day of informed consent through pretreatment on Day 1
No attack (Pubertal/postpubertal subjects only)	
Treatment	Day 1
Post Treatment	Day 1 through Day 8 (± 1 day)
Follow-up	Day 9 through Day 90 (±7 days)
Telephone Contact	Month 6 (± 7 days) from Day 1

Other sections impacted by change: [dJ](#) [dk](#) [pk](#) [dm](#) Schedule of Events (No Attack)

Change: Change to Study Design

Section impacted by change: [d](#) [m7](#) Study Assessments

Revised Text:

Study activities at screening will include confirmation of diagnosis of HAE type I or II by review of the subject's medical history and documentation of C1-INH deficiency (C1-INH protein level below the lower limit of normal and/or functional level <50% of normal) indicative of HAE Type I or II. Diagnosis may be supported by family history, characteristic attack manifestations, and recurrence of attacks. **A blood sample will be collected for C1-INH testing.** Other assessments performed at screening will include demography, medical history and history of HAE, concomitant medication use, physical examination (including height and weight), pubertal status determination, vital signs, ECG, **and a urine pregnancy test in female pubertal/postpubertal subjects, and blood sample collection for C1-INH testing.**

4.1.3.1 Initial Treatment

Eligible pubertal/postpubertal subjects who undergo treatment with icatibant in the absence of an acute HAE attack will receive single dose of icatibant as an abdominal SC injection on Day 1 and undergo PK and safety assessments as for subjects who receive treatment with icatibant during an attack. (Efficacy assessments will not be performed for those pubertal/postpubertal subjects treated with icatibant in the absence of an HAE attack.)

A safety follow-up contact to assess the subject's condition will occur **by telephone** at 24 (±4) hours and 48 (±4) hours after treatment with icatibant **(for a subject who remains hospitalized, this safety follow-up will be conducted in person).**

Rescue medication use will be assessed through 48 (±4) hours after treatment ~~either in person or by telephone at the discretion of the investigator.~~ **With exception of icatibant, any medicinal product may be used as rescue**

medication, at the discretion of the treating physician.

4.1.3.2 Subsequent Treatment

Subsequent treatment with icatibant may be offered to pubertal/postpubertal subjects **who have received initial treatment and who present subsequently with an** attack at least 7 days after prior treatment. In the event that a subsequent attack occurs at least 7 days after prior treatment, but within the window (± 1 day) allowed for performance of Day 8 assessments associated with a prior attack, the Day 8 assessments may also serve as the pretreatment (baseline) assessments for the subsequent attack. **Subjects will be eligible for treatment with icatibant until a total number of at least 10 ~~45~~ adolescents have been treated with icatibant for a total of 3 acute attacks (ie, after the first icatibant treated attack, only pubertal/postpubertal subjects may receive further treatment with icatibant for up to 2 subsequent attacks of acute HAE).** Except for PK determinations, all primary and secondary outcomes, including immunogenicity, are to be measured after each administration. Safety, reproductive hormones, and other assessments in association with subsequent attacks of acute HAE will be performed on Day 90 (± 7 days) after treatment (each treatment for a subsequent attack will require its own Day 90 follow up visit; however, if a subsequent attack occurs within 7 days of the Day 90 follow-up visit for the previous attack, the assessments on Day 8 and Day 90 may be combined). **Note that for some of the pubertal/postpubertal subjects who receive further treatment, ie, those who provide PK and safety/tolerability measurements without experiencing a current attack, their first icatibant-treated attack will represent their second on-study exposure to icatibant for safety analysis purposes.**

The investigator will schedule a telephone contact approximately 6 months after Day 1 of each icatibant-treated attack to obtain updates concerning pubertal changes/milestones. If this prescheduled telephone contact date should occur within the 90-day follow-up period (ie, Day 1 through Day 90) of a subsequent attack, this prescheduled contact may be omitted.

In addition, 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.

All assessments are outlined in full in the study schedules of events in **Appendix 1, No Attack, Appendix 2, Initial Icatibant treated Attack, and Appendix 3, Subsequent Icatibant-treated Attacks.**

d	d	d	d	(d	pk	dn	Schedule of Events (No Attack), x	dp	d
Icatibant treated Attack, and x				d			-treated Attacks		

Change: Change to Study Design

Section impacted by change: d 07 Study Duration

Revised Text:

At minimum, the duration of a subject’s active participation in the study will consist of single day dosing with 90-day follow-up.

Once eligibility is established at screening, the subject will be enrolled **into the study** but will enter a period of inactive participation of variable duration until such time as the subject experiences an acute attack of HAE and is offered treatment. **For those pubertal/postpubertal subjects who will be treated without an attack, eligibility will be established at screening and the subject will be immediately enrolled and treated with icatibant.** At the time of enrollment into the study, the subject will enter a 90-day period of active participation which will consist of treatment with a single SC administration of icatibant on Day 1 through follow-up at Day 90.

After receiving **the first** treatment for an initial attack of HAE with icatibant with or without an attack (N=20), at least **10 ~~45~~** pubertal/postpubertal subjects who present with subsequent attacks of acute HAE will continue to receive treatment with icatibant for a total of 3 attacks each. Thus, the period of active participation in the study for prepubertal subjects will be approximately 90 days, while that for pubertal/postpubertal subjects **could** be a maximum of approximately 270 or 360 days (3 separate active periods of approximately 90 days **for those treated with icatibant during an attack; 4 separate active periods for those treated without an attack**), with each active period separated by periods of inactive participation of variable duration. The period of active participation may be shorter if pubertal/postpubertal subjects have recurrent HAE attacks in between the Day 8 and Day 90 visits for a prior icatibant-treated HAE attack. Telephone follow-up will occur approximately 6 months after each icatibant-treated attack.

Once the **tenth ~~sixteenth~~** prepubertal subject and the **twentieth** pubertal/postpubertal subject have completed the 6-month follow-up after the initial treatment, and the **tenth** pubertal/postpubertal subject has completed the 6-month follow-up after his or her third and final treatment **for an attack**, the study will be closed.

The approximate overall duration of the study is expected to be 3 years.
d d d d (d)

Change: Change to study design
Section impacted by change: d 6 Study Population
Revised Text: The study will enroll a sufficient number of children and adolescents with HAE to ensure study completion of 30 36 evaluable subjects. The study population to provide efficacy, PK, and safety/tolerability measurements will consist of at least 20 subjects from 2 to less than 18 17 years of age, at least 10 16 of whom are prepubertal and at least 10 20 of whom are pubertal/postpubertal at the time of their first icatibant-treated acute cutaneous, abdominal, or laryngeal attack of HAE. An additional 10 subjects who are pubertal/postpubertal at the time of enrollment, but who are not experiencing a current HAE attack, will provide PK and safety/tolerability measurements only.
Other sections impacted by change: d d (d)

Change: Change to study design
Section impacted by change: d 6 Inclusion Criteria
Revised Text: 1. Two through <18 17 years of age (ie, from the second birthday until the day prior to the eighteenth birthday) at the time of the subject's first HAE attack treated with icatibant as part of this study. - Prepubertal and pubertal/postpubertal subjects experiencing an acute cutaneous, abdominal, or laryngeal HAE attack treated with icatibant as part of this study. - Pubertal/postpubertal subjects with HAE who are treated with icatibant as part of this study, but not during an attack. 2. Documented diagnosis of HAE type I or II. Diagnosis may be on the basis of historical data: family history, characteristic attack manifestations, recurrent attacks, historical C1-INH deficiency, and exclusion of other forms of angioedema. Inclusion will be permitted initially based on medical history only if a clear diagnosis has been made based on all of the preceding criteria. However, the diagnosis must be confirmed prior to treatment by documented immunogenic and/or functional C1-INH deficiency (C1-INH protein level below the lower limit of normal and/or functional C1-INH activity assayed assayed performed by the Sponsor's central laboratory.)
d d d d (d)

Change: Change to study design
Section impacted by change: d 6 Treatments Administered
Revised Text: Pubertal/postpubertal subjects are potentially eligible to receive treatment with icatibant in the absence of an attack, and to receive treatment with icatibant for a total of 3 attacks of acute HAE. Thus, a maximum of 4 doses of icatibant may be administered to a pubertal/postpubertal subject in the study, while all prepubertal subjects will receive a single dose of icatibant.
Other sections impacted by change:

Change: Change to study design
Section impacted by change: d 7 Selection and Timing of Dose for Each Subject
Revised Text: All subjects, whether treated during or in the absence of an acute attack of HAE, will be administered a single SC injection of icatibant. Subjects treated for an acute attack of HAE should receive icatibant within 12 hours after the onset of the attack. There are no prespecified attack severity criteria that are required for treatment. Subjects with attacks considered to be mild, moderate, or severe are all potentially eligible to receive treatment with icatibant.

d d d d (d)

Change: Clarification to rescue therapy
Section impacted by change: Section 4.1 Rescue Therapy
Revised Text: The determination of the necessity for rescue therapy will be at the discretion of the investigator. With the exception of icatibant, any medicinal product may be used as rescue medication at the discretion of the treating physician.
d d d d (d)

Change: Clarification to PK variables
Section impacted by change: 4.1.6 Pharmacokinetic Variables
Revised Text: Individual patient PK variables for icatibant and major metabolites will be determined from the respective plasma concentration time profiles where appropriate, using noncompartmental methods. A population PK model will be derived to evaluate the correlation of key covariates (ie age, body weight, gender) on the pharm
d d d d (d)

Change: Clarification concerning AE classification												
Section impacted by change: Section 4.1.6 Classification of Adverse Events and Serious Adverse Events												
Revised Text: The severity of adverse events will be assessed by the investigator as mild, moderate, or severe based on the severe definitions shown in Table 7-2. The severity of adverse events and serious adverse events should be recorded on the appropriate CRF page as Grade 1, 2, or 3, corresponding, respectively, to a severity of mild, moderate, or severe.												
Table 7-2 Adverse Event Severity												
<table border="1"> <thead> <tr> <th>Grade</th> <th>Severity</th> <th>Definition</th> </tr> </thead> <tbody> <tr> <td>Grade 1</td> <td>Mild</td> <td>No limitation of usual activities.</td> </tr> <tr> <td>Grade 2</td> <td>Moderate</td> <td>Some limitation of usual activities.</td> </tr> <tr> <td>Grade 3</td> <td>Severe</td> <td>Inability to carry out usual activities.</td> </tr> </tbody> </table>	Grade	Severity	Definition	Grade 1	Mild	No limitation of usual activities.	Grade 2	Moderate	Some limitation of usual activities.	Grade 3	Severe	Inability to carry out usual activities.
Grade	Severity	Definition										
Grade 1	Mild	No limitation of usual activities.										
Grade 2	Moderate	Some limitation of usual activities.										
Grade 3	Severe	Inability to carry out usual activities.										
Other sections impacted by change: None												

Change: % d d d
Section impacted by change: 4.1.7 Adverse Event Monitoring and Period of Observation
Revised Text: Adverse events will be monitored continuously. For the purposes of this study, the safety observation period will extend from the time of treatment with investigational product of the subject's acute HAE attack until the subject's final evaluation after treatment.
Other sections impacted by change: None

Change: Change to SAE reporting
Section impacted by change: 4.1.7.6 Reporting Serious Adverse Events
Revised Text: If an SAE is assessed as severe and unexpected, or life-threatening, contact:

PPD [REDACTED] MD, PhD PPD [REDACTED] Shire Human Genetic Therapies, Inc. 300 Shire Way Lexington, MA 02421 USA Telephone: PPD [REDACTED] Mobile: PPD [REDACTED] Fax: PPD [REDACTED] (USA) PPD [REDACTED]	
Other sections impacted by change: Cover page	

Change: Clarification concerning investigational product
Section impacted by change: Section 7.19 Abuse, Overdose, and Medication Error
Revised Text: <ul style="list-style-type: none"> • Misuse – Intentional or unintentional use of investigational medicinal product other than as directed or indicated at any dose, which is at or below the dose defined for overdose (Note: this includes a situation where the product test article is not used as directed at the dose prescribed by the protocol). All investigational medicinal product provided to pediatric subjects should be supervised by the parent(s)/legal guardian(s)/caregiver(s).
Other sections impacted by change: None

Change: Change to study assessments
Section impacted by change: Section 8.1 Screening (Day of Informed Consent to Pretreatment on Day 1)
Revised Text: <ul style="list-style-type: none"> • Documentation of HAE attack(s) not treated with icatibant* • Confirmation of documented HAE diagnosis (via the sponsor's central laboratory) *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.
Other sections impacted by change: Appendix 1 Schedule of Events (No Attack), Appendix 2 , Initial Icatibant-treated Attack, Appendix 3 , Subsequent Icatibant-treated Attacks

Change: Change to study assessments
Section impacted by change: Section 8.2 Pretreatment (Baseline) Assessments (Day 1, No Attack)
Revised Text: <p>The following assessments will be performed for subjects who will be treated with icatibant in the absence of a current HAE attack. All evaluations and sample collections must be performed prior to treatment.</p> <ul style="list-style-type: none"> • Medical history • Confirm inclusion/exclusion criteria • Pubertal status determination (only if the subject was classified as prepubertal at the time of the screening visit) • Menstrual cycle history (in pubertal/postpubertal females only) • Physical examination • Vital signs • Height and weight • Clinical laboratory tests (serum chemistry, hematology and urinalysis) • Urine pregnancy test (in females of childbearing potential) • Reproductive hormone assessments • Pharmacokinetic assessment • Immunogenicity assessment • Recording of concomitant medications

Change: Change to planned statistical methods
Section impacted by change: d50m General Considerations
Revised Text: 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 (disposition, demographic and pretreatment characteristics, efficacy variables, and safety variables) will be detailed in the statistical analysis plan (SAP).
Other sections impacted by change: None

Change: Change to planned statistical methods
Section impacted by change: d506 Determination of Sample Size
Revised Text: The study will enroll a sufficient number of children and adolescents to ensure study completion of 30 36 evaluable subjects. The study population is planned to consist of at least 10 16 prepubertal and 20 pubertal/postpubertal subjects from 2 to less than 18 17 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.
Other sections impacted by change:

Change: Change to planned statistical methods
Section impacted by change: d507 Analysis Populations
Revised Text: The following populations will be used in the analysis: <ul style="list-style-type: none"> • The Efficacy Population will consist of those subjects who were treated with icatibant for their first and any additional attacks. • The PK Population will consist of those subjects who were treated with icatibant and had sufficient icatibant plasma concentration time measurements to derive primary PK parameters. • The Safety Population will consist of those subjects who were treated with icatibant at least once All efficacy analyses will be performed on the Efficacy Population. The corresponding tabular summaries and listings will be presented by the subject stratification group at enrollment (ie, prepubertal group or pubertal/postpubertal group) and icatibant-treated attack number. The PK analyses will be based on the PK Population. Safety and tolerability analyses will be based on the Safety Population. All tabular summaries and listings within this population will be presented by the subject stratification group and icatibant exposure number.
Other sections impacted by change:

Change: Change to planned statistical methods
Section impacted by change: d50j Demographics and Baseline Characteristics
Revised Text: Demographic data and pretreatment characteristics will be summarized separately for the Safety Population and the Efficacy Population.
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Change: Change to planned statistical methods
Section impacted by change: d50H Safety and Tolerability Analyses
Revised Text: Another key objective of the study is to investigate the safety and tolerability of a single SC dose of icatibant in pediatric subjects treated with icatibant for the first time or treated with icatibant more than once. The

corresponding analyses will be based on the **Safety** Population.

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

Adverse events will be categorized using MedDRA Version 8.1. The assessment of safety will be based mainly on the frequency of treatment emergent adverse events. Adverse events will be summarized by system organ class (SOC) and preferred term. The number and proportion of subjects experiencing an adverse event will be tabulated by the stratification group and **icatibant exposure number**.

Laboratory data will be listed by subject, stratification group and **icatibant exposure number**. Subjects with newly occurring abnormalities outside the normal range will be flagged and listed separately. **Observed** values and **changes** from pretreatment values will be summarized by the stratification group and **icatibant exposure number**. Shift tables will also be tabulated by stratification group, icatibant exposure number, and study time point.

Vital signs data will be listed by subject, stratification group, and **icatibant exposure number**. Furthermore, **observed** values and changes from baseline will be summarized by stratification group and **icatibant exposure number**. Shift tables may be presented, utilizing reference ranges. Subjects with notably abnormal values will be identified and listed separately along with their values.

Local tolerability will be tabulated and summarized according to the type and severity of the injection site reaction.

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Change: Change to planned statistical methods

Section impacted by change: Section 10.7 Efficacy Analyses

Revised Text:

Efficacy analyses will be performed on the Efficacy Population. The primary efficacy endpoint is the time to onset of symptom relief measured using the investigator-reported symptom score. The investigator will report symptom scores at pretreatment and 1, 2, 4, and 6 hours post treatment, and at 8 hours post treatment for subjects who had not shown complete resolution of HAE symptoms at 6 hours. 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 earliest time post treatment at which there is a 20% improvement in the average post-treatment symptom score with no worsening of any single component score. The median time and the 95% confidence interval will be calculated using the Kaplan-Meier methodology.

A tabular summary of the average investigator-reported symptom score and the change from baseline in the average investigator-reported symptom score will be presented by the stratification group and the **icatibant treated attack number**. An alternative analysis will focus on the time to minimal symptoms and is defined as the **time from study drug administration to the earliest time post treatment when all symptoms are either absent or mild**.

The median time and 95% confidence interval will be calculated using Kaplan-Meier methodology.

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. Also, for individual symptoms that are moderate or worse at pretreatment, the median and 95% confidence interval will be presented for the time to the symptom being mild or absent.

Two subsets of subjects, those 4 years of age or older and those below 4 years of age, will have assessment of pain using the FPS-R and FLACC instruments, respectively. For subjects ≥ 4 years of age, the time to onset of symptom relief is defined as the earliest time at which the post-treatment score improves by at least one level. The time to onset of symptom relief for subjects < 4 years of age is defined as the earliest time at which a 20% improvement is seen in the total post-treatment score. Additionally, time to minimal symptoms defined as the earliest time at which the post-treatment score (or total post-treatment score for FLACC) improves to zero, will be analyzed. The time to onset of symptom relief and time to minimal symptoms will

ary efficacy endpoint.

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Section impacted by change: [d5U](#)Other Analyses

Revised Text:

The number and percentage of subjects who received rescue medications before the onset of symptom relief will be summarized by the stratification group and **icatibant-treated attack number**. Time to first use of rescue medication

prior to symptom relief will be calculated from the time of investigational product administration to the first use of rescue medication prior to **the onset of** symptom relief. The median time and the 95% confidence interval will be calculated using Kaplan-Meier methodology if there are at least 5 subjects **for a given attack** who used rescue medication prior to attaining symptom relief.

Other sections impacted by change: None

Change: Change to planned statistical methods

Section impacted by change: ~~dm50~~ Data Monitoring and Interim Analysis

Revised Text:

An analysis of the data for DSMB review is planned after the first 4 subjects in the pubertal/postpubertal group have been treated, and **will be repeated at subsequent time points as specified in the DSMB charter**. Because no formal hypothesis testing is planned, multiplicity concerns regarding repeated analyses are not an issue.

Based on the anticipated sequence of data being generated in the study, an initial interim analysis of the data from pubertal/postpubertal patients (N=20) is planned. It is expected that this will be followed by an interim analysis of data from prepubertal patients (N=10), and then by a final analysis to include the data of patients treated for subsequent attacks. This sequence is based on the anticipated sequence of data being generated during the study and may be modified to fit the actual study conduct.

Other sections impacted by change: None

Change: Change to planned statistical methods

Section impacted by change: ~~mf0mf~~ Handling of Missing Data

Revised Text:

Individual pretreatment symptom scores, FPS-R scores, and FLACC scores will be assigned a value of zero. For missing post-treatment scores, imputation will be employed using the Last Observation Carried Forward (LOCF) approach. The pretreatment values may also be used in the imputation. For missing or partial rescue medication dates, the imputation will be performed such that the earliest possible time post treatment will be assigned to the rescue medication use. A similar approach will be followed **to determine treatment emergent adverse events** in case of missing or partial adverse event dates.

Other sections impacted by change: None

Change: Change to administrative considerations

Section impacted by change: ~~dm0m~~ Investigators and Study Administrative Structure

Revised Text:

Before initiation of the study, the investigator must provide the sponsor with a completed Form FDA 1572 **or Investigator Agreement**. Investigational product may be administered only under the supervision of the investigator listed on this form. Curriculum vitae must be provided for the investigator and sub investigators listed on Form FDA 1572 **or the Investigator Agreement**.

Other sections impacted by change: None

Change: Change to administrative considerations

Section impacted by change: ~~dm06~~ Institutional Review Board or Independent Ethics Committee Approval

Revised Text:

Status reports must be submitted to the IRB/IEC at least once per year. The IRB/IEC must be notified of completion of the study. Within 3 months of study completion or termination (**or as required**), a final report must be provided to the IRB/IEC. A copy of these reports will be sent to the study clinical monitor. The investigators must maintain an accurate and complete record of all submissions made to the IRB/IEC, including a list of all reports and documents submitted. **Serious drug-related adverse events** which are reported to the US Food and Drug Administration (FDA) or other Regulatory agencies (Investigational New Drug [IND] Safety Reports) must be submitted promptly to the IRB/IEC.

Other sections impacted by change: None

Change: Change to administrative considerations
Section impacted by change: Section 11.7.1 Critical Documents
Revised Text: • Completed FDA Applicable local regulatory documentation (eg, completed Form FDA 1572 [Statement of Investigator], signed, dated, and accurate. Regulatory approval and notification as required must also be available. The protocol will not be initiated until regulatory approval and notification are obtained ; these are the responsibility of the sponsor.
Other sections impacted by change: None

Change: Change to administrative considerations
Section impacted by change: Section 11.14 Financial Disclosure
Revised Text: Changes in status concerning financial interests during the study and after its completion will be disclosed by the Investigator in accordance 21 CFR Part 54.
Other sections impacted by change: None

Change: Clarification to study schedule of events
Section impacted by change: Appendix 2 , Initial Icatibant treated Attack
Revised Text: Time Post Treatment (hours) 0-45 0.75 (±5) min
Other sections impacted by change: None

Change: New study schedule of events
Section impacted by change: see Appendix 1 , No Attack
Other sections impacted by change: Section 8 Study Activities