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
Sponsor:	Shire Human Genetic Therapies, Inc.
Sponsor Contact:	700 Main Street Cambridge, MA 02139 USA PPD
Medical Monitor:	PPD MD, PPD Shire Human Genetic Therapies (HGT)

	Date
Original Protocol:	14 June 2011

Confidentiality Statement

SYNOPSIS

Sponsor:

Shire Human Genetic 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

Primary Objective:

The primary 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) during an acute HAE attack.

Secondary Objectives:

The secondary objectives of this study are:

- To evaluate the efficacy of a single SC dose of icatibant in children and adolescents with HAE.
- To evaluate levels of reproductive hormones after a single SC dose of icatibant in children and adolescents with HAE.

Other Objectives:

Other objectives of this study are:

- To evaluate the continued safety of icatibant in pubertal/postpubertal children after repeat exposure.
- To evaluate reproductive hormone levels in pubertal/postpubertal children after repeat exposure.
- To evaluate the efficacy of icatibant in pubertal/postpubertal children after repeat exposure.

Study Endpoints:

The primary endpoints of this study are:

- The PK profile of icatibant after a single SC injection in pediatric subjects treated for acute attacks of HAE.

- The tolerability and safety of SC icatibant as assessed by injection site reactions, adverse events (AEs), vital signs, physical examination, clinical laboratory parameters (serum chemistry [including liver function tests], hematology, urinalysis), and immunogenicity (anti-icatibant antibodies).

The secondary endpoints of this study are:

- The time to onset of relief of symptoms, measured using investigator-reported and subject-reported outcomes, defined as the earliest time at which a 20% improvement is seen in the average post-treatment score with no worsening of any single component score).
    - For all subjects (2 to 17 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 only: subject self-assessment of HAE-related pain using the Faces Pain Scale-Revised (FPS-R).
- The time to minimal symptoms, defined as all symptoms mild or absent based on the investigator-rated symptom score.
- 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.
- The levels of reproductive hormones (follicle stimulating hormone [FSH], luteinizing hormone [LH], estradiol, progesterone in females and FSH, LH, and testosterone in males).

Study Population:

The study will enroll approximately 36 pediatric subjects from 2 through 17 years of age who present with cutaneous, abdominal, or laryngeal attacks of acute HAE after a qualifying screening period.

Subject enrollment will be stratified into 2 groups based on Tanner Staging: a prepubertal group (defined as Tanner stage I) and a pubertal/postpubertal group (defined as Tanner stages II to V). A subject's classification as prepubertal or pubertal/postpubertal will be determined at the time of the subject's first attack.

Study Design:

This is an open-label, non-randomized, single-arm study to evaluate the PK, tolerability, and safety, including reproductive hormone assessments, of a single SC administration of icatibant in up to approximately 36 pediatric subjects with HAE during an initial acute attack. The study is planned to enroll up to approximately 16 prepubertal and 20 pubertal/postpubertal subjects who are from 2 through 17 years of age and who present with an acute cutaneous, abdominal, or laryngeal HAE attack.

After treatment for an initial attack, further open-label treatment with icatibant will be offered to pubertal/postpubertal subjects contingent upon having been treated previously and presenting with a subsequent acute cutaneous, abdominal, or laryngeal attack of HAE

at least 7 days after initial treatment. Open-label treatment will continue until at least 15 pubertal/postpubertal subjects have been treated with icatibant for a total of 3 attacks each. Tolerability and safety evaluations, including reproductive hormone assessments, will be performed at each subsequent icatibant-treated attack in a manner similar to that performed for the initial treated attack.

Study Duration:

Once subject eligibility is established at screening, the minimal planned duration of participation for subjects who present with an initial attack of acute HAE will be approximately 90 days and will consist of treatment with a single SC administration of icatibant on Day 1 and a 90-day follow-up period after treatment.

Subjects will be closely monitored in the hospital/study center for at least 6-8 hours after administration. Follow-up to assess the subject's condition at 24 hours and 48 hours after discharge will be conducted in person or via a telephone call by study personnel.

After receiving treatment for an initial attack, at least 15 pubertal/postpubertal subjects who present with subsequent attacks of acute HAE may continue to receive treatment with icatibant for a total of 3 attacks each.

Once the sixteenth prepubertal subject and the twentieth pubertal/postpubertal subject have completed the Day 90 follow-up after treatment for an initial attack, and the fifteenth pubertal/postpubertal subject has completed the Day 90 follow-up after the third and final treatment, the study will be closed.

Study Inclusion and Exclusion Criteria:

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

1. Two through 17 years of age, inclusive (ie, from the second birthday through the day prior to the eighteenth birthday) at the time of the subject's first attack.
2. Documented diagnosis of HAE type I or II. Diagnosis must be confirmed by documented immunogenic and/or functional C1 inhibitor (C1-INH) deficiency results (<50% of normal levels). Diagnosis may be on the basis of historic data or by diagnostic testing conducted at the time of screening.
3. Informed consent (and subject assent as appropriate) signed by the subject's parent or legal guardian.

Subjects will be excluded from the study if there is evidence of any of the following criteria at screening or at any time prior to the time of the first attack:

1. Diagnosis of angioedema other than HAE.
2. Participation in another clinical study during the 30 days prior to treatment.
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. The subject is pregnant or breastfeeding.

Pharmacokinetic Variables:

PK 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.

PK parameter estimates will include, where appropriate: actual icatibant and metabolite concentrations at each sampling time, 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 ($AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$), 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, 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 AEs. Local tolerability will be assessed by evaluation of reactions at the site of study drug administration (injection site).

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 Faces Pain Scale-Revised (FPS-R). Subjects who are below 4 years of age will have symptoms assessed by the investigator only. The time of initial symptom relief as assessed by the investigator will be recorded for all subjects.

Reproductive Hormone Assessments:

Levels of reproductive hormones will be assessed in female (FSH, LH, estradiol, progesterone) and male (FSH, LH, and testosterone) subjects.

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 Initial Non-laryngeal Treatment Population will consist of those subjects who were treated with icatibant for their initial attack and whose primary symptom was either cutaneous or abdominal.
- The Second Non-laryngeal Treatment Population will consist of those subjects who had a second icatibant-treated attack for which the primary symptom was either cutaneous or abdominal, regardless of the primary symptom for the initial attack.

- The Third Non-laryngeal Treatment Population will consist of those subjects who had a third icatibant-treated attack, for which the primary symptom was either cutaneous or abdominal, regardless of the primary symptom for the initial attack.
- The Laryngeal Population will consist of those subjects who were treated with icatibant for any attack for which the primary symptom was laryngeal.
- The PK Population will consist of those subjects who were treated with icatibant for their initial attack and who had at least 1 post-treatment icatibant concentration recorded.
- The Initial Treatment Population will consist of those subjects who were treated with icatibant for the initial attack. Safety and tolerability analyses will use this population.
- The Additional Treatment Population will consist of those pubertal/post-pubertal subjects who were treated with icatibant for more than 1 attack. Safety and tolerability analyses will use this population.

Subject disposition, demographic and baseline characteristics, medical history, and use of concomitant medications will be summarized for each analysis population.

Efficacy endpoints, including change from baseline when appropriate, will be summarized descriptively for the Initial, Second, and Third Non-laryngeal Treatment Populations. The primary efficacy endpoint is the time to onset of symptom relief measured using the investigator-rated symptom score. Time 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 efficacy data associated with the laryngeal attacks will be provided in data listings for the Laryngeal Population.

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

The assessment of safety will be based mainly on the frequency of AEs. AEs will be summarized by presenting the number and percentage of subjects having any adverse event (AE), having an AE in each body system, and having each individual AE using the Medical Dictionary for Regulatory Activity (MedDRA). The total number of AEs within each of these categories will be reported. AEs 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 AEs. Local tolerability will be tabulated and summarized according to the type and severity of attack.

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 Original Protocol: 14 June 2011

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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
DSMB	Data and Safety Monitoring Board
EC_{50}	Half maximal effective concentration
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
FFP	Fresh frozen plasma
FPS	Faces Pain Scale
FSH	Follicle stimulating hormone
GAM	General additive model
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HAE	Hereditary Angioedema
hCG	Human chorionic gonadotropin
HGT	Human Genetic Therapies
hr	Hour(s)
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	Intravenous(ly)
kg	Kilogram(s)
L	Liter(s)

LBW	Lean body weight
LH	Luteinizing hormone
LOCF	Last observation carried forward
MCB	Master Cell Bank
MedDRA	Medical Dictionary for Regulatory Activity
mg	Milligram
min	Minute(s)
mL	Milliliter(s)
mm	Millimeters
MRT	Mean residual time
n	Number
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ng	Nanogram(s)
NSAIDs	Non-steroidal anti-inflammatory drugs
PD	Pharmacodynamic
PK	Pharmacokinetic(s)
SAE	Serious adverse event
SAS	Statistical Analysis System®
SC	Subcutaneous
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

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 1:10,000 to 1:50,000.[1]

The disease is generally caused by either a quantitative (Type I) or qualitative (Type II) deficiency of C1 inhibitor. The functions of C1 inhibitor include the prevention 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, the principal mediator of the increased vascular permeability characteristic of HAE, by its cleavage from high molecular weight kininogen by dysregulated, activated kallikrein. There is a third, more rare type of HAE (Type III) which is of unknown etiology and pathophysiology and thus will not be considered further here.

Icatibant is a synthetic decapeptide with a structure similar to bradykinin that acts as an antagonist of the bradykinin B2 receptor.[2, 3] It is highly specific for the B2 receptor, and is characterized by high potency in vitro and in vivo, and sufficient biological half-life to allow systemic administration by subcutaneous (SC) injection.[4, 5] 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 accelerated 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 adult subjects 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 mean age at disease onset ranges from approximately 4 to 11 years. Subcutaneous edema of the extremities, face, neck, torso and genitals is the most common, and usually the earliest, manifestation of HAE seen in children. Analyses of the time of onset of disease symptoms have indicated an increase in the frequency and severity of manifestations between 3 and 6 years of age, as well as at around puberty, most likely related to the many physiological (endocrine, mental, and somatic) changes occurring during these periods of development. In the gastrointestinal tract, submucosal edema may be associated with colicky abdominal pain, nausea, vomiting, and diarrhea. 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.[6]

Prompt control of attacks, short-term prophylaxis, and intermittent therapy are recommended for the management of pediatric HAE.[6] Treatment options for children with HAE according to current guidelines include antifibrinolytics, attenuated androgens, and C1 inhibitor (C1-INH) replacement therapy. Antifibrinolytics are generally preferred (eg, tranexamic acid) for long-term prophylaxis because of their comparatively favorable safety profile relative to attenuated androgens; though their efficacy may be limited. 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 Clinical Study Report) 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 (± 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 Phase III Investigation of SC Icatibant

Despite the rarity of HAE, a comprehensive data set supports the efficacy and safety of SC icatibant.

In Phase I, II, and III clinical studies, SC icatibant 30 mg has been administered to 129 healthy adult subjects and to 236 adult subjects with HAE. A total of 999 acute attacks of HAE have been treated with icatibant administered by a health care provider, and an additional 56 attacks have been treated with icatibant when self administered by patients (Integrated Summary of Safety 11 January 2011).

In integrated analyses of pooled data from 3 controlled Phase III studies (HGT-FIR-054, JE049-2102, and JE049-2103), icatibant significantly decreased the time to onset of symptom relief for cutaneous and abdominal attacks relative to comparator agents (placebo, tranexamic acid) as demonstrated by the primary and key secondary endpoint analyses in subjects with non-laryngeal symptoms randomized to double-blind treatment. Moreover, the median time to onset of symptom relief after icatibant treatment was consistent across all of the controlled Phase III studies and across the 2 endpoints, ranging from 1.5 to 2.3 hours. Likewise, icatibant showed effectiveness in the treatment of laryngeal attacks.

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; therefore, dose adjustments for adult males or females are not considered necessary.

Beyond exposure in clinical studies, it is estimated that over 8000 patient exposures to Firazyr® have occurred cumulatively in the postmarketing setting from the time of European Union regulatory approval in July 2008 through January 2011.

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. Potential effects of icatibant on sexual organs and sexual maturation are being investigated further in studies in juvenile rats. These are a SC administration local tolerance study, and a 7-week toxicity study with assessment of fertility before and after recovery. The local tolerance study in juvenile rats established the doses for the 7-week toxicity study. The results will be reported in the final study reports.

A retrospective analysis, prompted by nonclinical observations, of serum levels of gonadotrophic hormone levels (follicle-stimulating hormone [FSH] and luteinizing hormone [LH]) in male and female healthy volunteers in an Phase I study (JE049-1103) showed no clinically important changes from baseline in levels of follicle-stimulating hormone [FSH] and luteinizing hormone [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) is 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 is 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 are 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 subjects have been enrolled and treated; 38 subjects have completed the study (1 subject did not return for follow-up). The results will be reported in the final clinical study report.

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 Primary Objective

The primary objective of this study is:

- To investigate the PK, tolerability, and safety of a single SC dose of icatibant in children and adolescents with HAE during an acute HAE attack.

2.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the efficacy of a single SC dose of icatibant in children and adolescents with HAE.
- To evaluate levels of reproductive hormones after a single SC dose of icatibant in children and adolescents with HAE.

2.3 Other Objectives

Other objectives of this study are:

- To evaluate the continued safety of icatibant in pubertal/postpubertal children after repeat exposure.
- To evaluate reproductive hormone levels in pubertal/postpubertal children after repeat exposure.
- To evaluate the efficacy of icatibant in pubertal/postpubertal children after repeat exposure.

3 STUDY ENDPOINTS

3.1 Primary Endpoint(s)

The primary endpoints of this study are:

- The PK profile of icatibant after a single SC injection in pediatric subjects treated for acute attacks of HAE.
- The tolerability and safety of SC icatibant as assessed by injection site reactions, adverse events, vital signs, physical examination, clinical laboratory parameters (serum chemistry [including liver function tests], hematology, urinalysis), and immunogenicity (presence of anti-icatibant antibodies).

3.2 Secondary Endpoint(s)

The secondary endpoints of this study are:

- The time to onset of relief of symptoms, measured using investigator-reported and subject-reported outcomes, defined as the earliest time at which a 20% improvement is seen in the average post-treatment score with no worsening of any single component score.
  - For all subjects (2 to 17 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 only: subject self-assessment of HAE-related pain using the Faces Pain Scale-Revised (FPS-R).
- The time to minimal symptoms, defined as all symptoms mild or absent based on the investigator-rated symptom score.
- 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.
- The levels of reproductive hormones (FSH, LH, estradiol, progesterone in females and FSH, LH, and testosterone in males).

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is an open-label, non-randomized, single-arm study to evaluate the PK, tolerability, and safety, including reproductive hormone assessments, of a single SC administration of icatibant in approximately 36 pediatric subjects with hereditary angioedema (HAE) during an initial acute attack. The study is planned to enroll approximately 16 prepubertal and 20 pubertal/postpubertal subjects who are from 2 through 17 years of age and who present with a cutaneous, abdominal, or laryngeal attack of acute HAE.

After treatment for an initial attack, further open-label treatment with icatibant will be offered to pubertal/postpubertal subjects contingent upon having been treated previously and presenting with a subsequent acute cutaneous, abdominal, or laryngeal attack of HAE at least 7 days after initial treatment. Open-label treatment will continue until at least 15 pubertal/postpubertal subjects have been treated with icatibant for a total of 3 attacks each. Tolerability and safety evaluations, including reproductive hormone assessments, will be performed at each subsequent icatibant-treated attack in a manner similar to that performed for the initial treated attack.

The study will consist of the following periods (Table 4-1).

Table 4-1 Study Periods

Study Periods	
Screening	Day of informed consent through pretreatment on Day 1 of the initial attack
Initial icatibant-treated attack (All subjects)	
Treatment	Day 1
Post-Treatment	Day 1 though Day 8
Follow-up	Day 9 through Day 90 (±7 days)
Two additional icatibant-treated attacks for a total of 3 icatibant-treated attacks (Pubertal/postpubertal subjects only)	
Treatment	Day 1
Post-Treatment	Day 1 though Day 8
Follow-up	Day 9 through Day 90 (±7 days)

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 immunogenic and/or functional C1-INH deficiency (<50% of normal levels) indicative of HAE Type I or II.

Diagnosis may be supported by family history, characteristic attack manifestations, and recurrence of attacks. Assessments performed at screening will include demography, medical history, history of HAE, concomitant medication use, physical examination (including height and weight), vital signs, urine pregnancy test in female pubertal/postpubertal subjects, and blood sample collection for C1-INH testing.

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, and adherence to inclusion/exclusion criteria will be re-confirmed. 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, height and weight, vital signs, collection of samples for clinical laboratory tests (serum chemistry [including liver function tests], hematology, and urinalysis), urine pregnancy test for pubertal/postpubertal females, baseline PK and immunogenicity evaluations, and baseline assessment of reproductive hormones (FSH, LH, estradiol, progesterone in females and FSH, LH, and testosterone in males).

On Day 1, subjects will be administered a single dose of icatibant administered as a SC injection within 12 hours after the onset of the acute attack. Subjects will be monitored closely at the hospital/study center for approximately 6 hours (prepubertal subjects) or 8 hours (pubertal/postpubertal subjects) after treatment. Subjects will be discharged after completion of scheduled assessments and when, according to the investigator's judgment, they are deemed medically stable. Follow-up to assess the subject's condition at 24 hours (±4 hours) and 48 hours (±4 hours) after discharge will be conducted in person or via a telephone call by study personnel.

The time of study drug administration on Day 1 will be designated as Time 0. All post-treatment assessments will be calculated from the time of study drug administration. Blood samples for PK evaluation in pubertal/postpubertal subjects will be collected on Day 1 at pretreatment, 15 (±5) minutes, 30 (±5) minutes, 45 (±5) minutes, 1 (±0.17) hour, 2 (±0.17) hours, 4 (±0.5) hours, 6 (±0.5), and 8 (±0.5) hours after treatment with study drug. In prepubertal subjects, blood samples for PK evaluation will be collected on Day 1 at pretreatment, 15 (±5) minutes, 30 (±5) minutes, 2 (±0.5) hours, 4 (±0.5) hours, and 6 (±0.5) hours.

Safety and efficacy assessments will be performed on Day 1 up to 6 hours after treatment. These assessments will include physical examination, vital signs, clinical laboratory tests (serum chemistry [including liver function tests], hematology, and urinalysis), and assessment of reproductive hormones (FSH, LH, estradiol, and progesterone in females and FSH, LH, and testosterone in males) in all subjects. Injection site reactions will be evaluated on Day 1 at 1 hour and at 6 hours after treatment.

The investigator will complete an assessment of symptoms of the acute attack of HAE for all subjects on Day 1 at 1, 2, 4, and 6 hours after treatment. Subject who are 4 years of age or older will also complete a self-assessment of HAE-related pain at these time points.

Rescue medication use will be assessed through 48 hours after treatment, either in person or by telephone at the discretion of the investigator.

Subjects will undergo safety assessments, including physical examination, vital signs, and clinical laboratory tests (serum chemistry, hematology, and urinalysis), evaluation of injection site reactions, immunogenicity, and measurement of reproductive hormones, as well as investigator assessments and subject self assessments (subjects ≥4 years of age only) of HAE symptoms on Day 8 after treatment.

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

Pubertal/postpubertal subjects may receive further treatment with icatibant for up to 2 additional attacks of acute HAE. Safety, reproductive hormone, and other assessments in association with subsequent attacks of acute HAE will be performed 90 days (±7 days) after treatment. 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.

Adverse events (AEs) and concomitant medication will be collected throughout the study.

All assessments are outlined in full in the Schedule of Events in Appendix 1, Initial Icatibant-treated Attack and Appendix 2, 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 being treated for an acute attack of 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, 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.

Furthermore, this study is designed to fulfill a regulatory commitment to the European Medicines Agency according to the approved pediatric investigational plan (EMEA-000408-PIP01-08-M02) for icatibant of 05 May 2010.

4.3 Study Duration

The approximate overall duration of the study will be 36 months.

Once subject eligibility is established at screening, the minimal planned duration of participation for individual subjects who present with an initial attack of acute HAE will be approximately 90 days, and will consist of a single SC dose of icatibant on Day 1 and a 90-day follow-up period after treatment.

Pubertal/postpubertal subjects, who may receive treatment for up to 2 additional attacks of acute HAE, will have a longer duration of participation. Due to the unpredictable nature of HAE attacks, the actual expected duration of these subjects is unknown. After receiving treatment for an initial attack, pubertal/postpubertal subjects who present with subsequent attacks of acute HAE may continue to receive treatment with icatibant up to a total of 3 icatibant-treated attacks.

Once the sixteenth prepubertal subject and the twentieth pubertal/postpubertal subject has completed Day 90 follow-up after treatment for an initial attack, and the fifteenth pubertal/postpubertal subject has completed the Day 90 follow-up after the third and final treatment, the study will be closed.

5 STUDY POPULATION SELECTION

5.1 Study Population

Pediatric subjects from 2 through 17 years of age who present with cutaneous, abdominal, or laryngeal attacks of acute HAE after a qualifying screening period will be eligible for enrollment in the study. Subject enrollment will be stratified into 2 groups, based on Tanner Staging,[7, 8] to consist of a prepubertal group (defined as Tanner stage I) and a pubertal/postpubertal group (defined as Tanner stages II to V).

A subject's classification as prepubertal or pubertal/postpubertal will be determined at the time of the subject's first attack.

5.2 Inclusion Criteria

Each subject must meet all of the following criteria to be enrolled in this study.

1. Two through 17 years of age, inclusive (ie, from the second birthday until the day prior to the eighteenth birthday) at the time of the subject's first attack.
2. Documented diagnosis of HAE Type I or II. Diagnosis must be confirmed by documented immunogenic and/or functional C1-INH deficiency results (<50% of normal levels). Diagnosis may be on the basis of historic data or by diagnostic testing conducted at the time of screening.
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 study during the 30 days prior to treatment.
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 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. The subject is pregnant or breastfeeding.

6 STUDY TREATMENT(S)

6.1 Description of Treatment(s)

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 single dose (see Section 6.2) will be withdrawn and administered by SC injection.

6.1.2 Comparator

Not applicable to this study.

6.2 Treatment(s) Administered

All subjects will receive treatment with icatibant for an initial acute attack of HAE as a single, weight-adjusted dose of 0.4 mg/kg up to a maximum of 30 mg administered as a SC injection.

Subsequent treatment with icatibant for up to 2 additional attacks of acute HAE will be offered to pubertal/postpubertal subjects who present with a new attack at least 7 days after prior treatment. The dosing regimen for treatment of subsequent attacks will be the same as that for treatment of the initial attack (ie, a single weight-adjusted dose of 0.4 mg/kg up to a maximum of 30 mg per attack administered as a SC injection). Thus, no more than 3 doses of icatibant will be administered to any subject during the study.

6.3 Selection and Timing of Dose for Each Subject

Each subject will be administered a single dose of icatibant as a SC injection within 12 hours after the onset of an acute HAE attack. 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 who have been previously treated and who present with another attack at least 7 days post-treatment with study drug.

6.4 Method of Assigning Subjects to Treatment Groups

Not applicable to this study. All subjects will be administered study drug 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 Medications

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 study drug.
- 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 6.7). 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 during the study:

- 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 a single attack is not allowed in this study.

The determination of the necessity for pain medication or other rescue therapy will be at the discretion of the investigator. If pain medication is required, the investigator may administer morphine sulfate at a dose of 0.05 mg/kg or an equivalent low dose narcotic. Antiemetics may also be prescribed as necessary to treat nausea. Other acceptable rescue therapies include FFP, epinephrine, C1-INH if available and intravenous or prescription-strength non-steroidal anti-inflammatory drugs (NSAIDs). Medications provided for rescue therapy will be denoted as rescue medications on the appropriate case report form (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/site 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-guage 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 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 Schedule of Events Tables in Appendix 1, Initial Icatibant-treated Attack and Appendix 2, Subsequent Icatibant-treated Attacks).

All data collected are to be recorded on the appropriate case report form (CRF) or 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 by the investigator or designee in accordance with the guidelines described in Section 11.4. Documentation and filing of informed consent documents should be completed according to Section 11.4.

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 Screening and Pretreatment 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 on 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. Other important medical events, and concomitant medication and illnesses will be recorded at other visits. Any existing medical condition present prior to the time of of the first dose will be reported as medical history.

7.6 Height and Weight

Height and weight will be recorded for all subjects.

7.7 Tanner Staging

The investigator will perform Tanner staging for all subjects to determine pubertal status.

7.8 Investigational Product Administration

All subjects will receive treatment with icatibant for an initial acute attack of HAE as a single, weight-adjusted dose of 0.4 mg/kg administered as a SC injection up to a maximum dose of 30 mg. Treatment with icatibant will be administered within 12 hours of onset of an acute HAE attack. Pubertal/postpubertal subjects who present with a subsequent attack at least 7 days post-treatment may receive further treatment with icatibant for a total of 3 attacks.

7.9 Pharmacokinetic Assessments

7.9.1 Pharmacokinetic Variables

PK 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. The methods to be used for estimation of PK parameter values are described in Section 10.5.1.

PK parameter estimates will include, where appropriate: actual icatibant and metabolite concentrations at each sampling time, 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 ($AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$), mean residence time (MRT), volume of distribution at steady state (V_{ss}/F) and elimination half-life ($t_{1/2}$).

7.9.2 Pharmacokinetic Sampling

Sampling for PK assessments will be collected according to the Schedule of Events Table in Appendix 1, Initial Icatibant-treated Attack.

The time of study drug administration on Day 1 will be designated as Time 0. All post-treatment assessments will be calculated from the time of study drug 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, 15 (±5) minutes, 30 (±5) minutes, 45 (±5) minutes, 1 (±0.17) hour, 2 (±0.17) hours, 4 (±0.5) hours, 6 (±0.5), and 8 (±0.5) hours after treatment with study drug.

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

7.9.3 Bioanalytical Method

Plasma samples will be assayed for concentrations of icatibant and its metabolites (M1 and M2) using a validated method (see Section 7.19).

7.10 Efficacy Assessments

7.10.1 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 on 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.

7.10.2 Subject Self Assessment of Pain

Subjects who are at least 4 years of age will self assess HAE-related pain using the Faces Pain Scale-Revised (FPS-R). A copy of the FPS-R is provided in Appendix 3.

Self-assessment results will be recorded in the diary. The self-assessment diaries will be provided to these subjects on Day 1 at pretreatment and at predetermined time points after treatment while at the hospital/study center and after their discharge. Subjects will return the diary at the next scheduled visit on Day 8. Subjects will receive detailed instructions on when and how to complete the diaries by the investigator and/or clinical site personnel.

7.10.3 Initial Symptom Relief

The investigator will be asked to provide the following information on the CRF:

- To record the date and time when overall subject improvement was first noted and mark the date and time accordingly.

7.11 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.

7.12 Safety Assessments

7.12.1 Physical Examination

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

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

7.12.2 Vital Signs

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

7.12.3 Clinical Laboratory Tests

Blood and urine samples will be collected as described in this section for clinical laboratory testing. All blood samples will be collected via venipuncture. Subjects will be in a seated or supine position during blood collection.

Clinical laboratory tests will include the following (See Table 7-1):

Table 7-1 List of Laboratory Tests

Hematology:	**Serum Chemistry:**
- Hematocrit - Hemoglobin - Mean corpuscular hemoglobin - Mean corpuscular hemoglobin concentration - Mean corpuscular volume - Platelet count - Red blood cell count - White blood cell count with differential	- Albumin - Alkaline phosphatase - Alanine aminotransferase) - Aspartate aminotransferase - Calcium - Carbon dioxide - Chloride - Creatinine - Creatine kinase - Gamma-glutamyl transferase - Glucose - Lactate dehydrogenase - Phosphorus - Potassium - Sodium - Total bilirubin
Urinalysis: - Appearance - Bilirubin - Color - Glucose - Ketones - Nitrite - Occult blood - pH - Protein - Specific gravity	

7.12.4 Local Tolerability

Injection site reactions (erythema, swelling, burning sensation, itching/pruritis, warm sensation, cutaneous pain, or other) will be evaluated by the investigator 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.

7.12.5 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 HGT 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.

7.12.6 Pregnancy Testing

Pubertal and postpubertal female subjects will undergo pregnancy testing at time points specified in the Schedule of Events Tables in Appendix 1 and Appendix 2. All pregnancy testing will be conducted using a urine human chorionic gonadotropin (hCG) test.

7.13 Sample Collection, Storage, and Shipping

Blood samples will be collected via venipuncture. 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.

7.14 Concomitant Medications

All medications administered to the study subjects from the time of informed consent through the Day 90 follow-up contact are regarded as concomitant and will be documented on the CRF.

7.15 Adverse Events Assessments

7.15.1 Definitions of Adverse Events and Serious Adverse Events

7.15.1.1 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 any phase of a clinical study, whether or not considered investigational product-related. This includes an exacerbation of a pre-existing condition.

AEs include:

- Worsening (change in nature, severity, or frequency) of conditions present at the onset of the study.
- Intercurrent illnesses.
- Drug interactions.
- Events related to or possibly related to concomitant medications.
- 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.

Throughout the study, the investigator must record all AEs on the AE 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 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 can be explained and the subject's safety is not at risk.

Additional illnesses present at the time when informed consent is given are regarded as concomitant illnesses and will be documented on the appropriate pages of the CRF. Illnesses first occurring or detected during the study, and worsening of a concomitant illness during the study, are to be regarded as AEs 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. Any 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 separately from general reports of AEs. 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 detail in the CRF. They are considered to be pre-existing disease and will not be documented as AEs.

Local tolerability will include symptoms at the site of study drug administration (injection site) and will be assessed separately from general reports of AEs. Local tolerability will include symptoms at the site of study drug administration (injection site) and will be assessed separately from general reports of AEs. Injection site reactions will be documented in the "local tolerability" page (or form) 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.

Though AEs will be collected throughout the study, due to the acute nature of HAE attacks and the half-life of icatibant, it is particularly important to focus on AEs which have a temporal association with treatment. Treatment-emergent AEs will be collected over a 48-hour window after the time of study drug administration.

7.15.1.2 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 AE as it occurred (ie, it does not include an AE that, had it occurred in a more severe form, might have caused death).

7.15.2 Classification of Adverse Events and Serious Adverse Events

The severity of AEs will be assessed by the investigator using the National Cancer Institute Common Terminology Criteria (NCI CTCAE) Version 4.0 grading scale. If an AE is not described in the NCI CTCAE, the severity should be recorded based on the scale below (see Table 7-2). The severity of all AEs/SAEs should be recorded on the appropriate CRF page as Grade 1, 2, 3, 4, or 5 corresponding, respectively, to a severity of mild, moderate, severe, life-threatening, or fatal.

Table 7-2 Adverse Event Severity

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 4 (Life-threatening)	Immediate risk of death.
Grade 5 (Fatal)	Death

7.15.2.1 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.

7.15.3 Relatedness of Adverse Events and Serious Adverse Events

Relationship of an AE or SAE to investigational product is to be determined by the investigator based on the following definitions (See Table 7-3).

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

Table 7-3 Adverse Event Relatedness

Relationship to Product(s)	Definition
	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.

7.15.4 Procedures for Recording and Reporting Adverse Events

7.15.4.1 Adverse Event Monitoring and Period of Observation

AEs will be monitored continuously throughout the study. For the purposes of this study, the period of observation extends from the time of informed consent until the subject's final evaluation of the study. For safety purposes, the final evaluation will be defined as the follow-up evaluation performed approximately 90 days after the last dose for subjects who complete the study.

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.

7.15.4.2 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 an SAE 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 SAE to the Shire Pharmacovigilance and Risk Management Department AND to the Shire HGT Medical Monitor on an SAE form. This form must be completed and FAXED within 24 hours of the investigator's learning of the event to:

Shire Pharmacovigilance and Risk Management Department:

International FAX: PPD **(UK) OR United States FAX:** PPD

PPD

AND

Shire HGT Medical Monitor: PPD **MD**

PPD

FAX: PPD **(USA)**

Any follow-up information must also be completed on an SAE form and faxed 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 HGT 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 HGT 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:
PPD **MD** PPD **Shire Human Genetic Therapies, Inc.** **700 Main Street** **Cambridge, MA 02139 USA** **Telephone:** PPD **Fax:** PPD **(USA)** PPD

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.

7.16 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 90 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.

7.17 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 test article 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.

All investigational medicinal product provided to pediatric subjects should be supervised by the parent(s)/legal guardian(s)/caregiver(s).

7.18 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 Case Report Form (CRF) describing the reason for discontinuation must be completed. Any AEs experienced up to the point of discontinuation must be documented on the AE 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.

7.18.1 Safety-Related Study Stopping Rules

This study will be stopped and safety data reviewed if any subject experiences a life-threatening (Grade 4) AE or a death occurs, if either is considered possibly, probably or definitely related to the investigational product.

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 11.8, Data and Safety Monitoring Board.

7.19 Appropriateness of Measurements

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

The measures of serum reproductive hormone concentration used in this study are standard validated 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).

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 used to assess the intensity of children's pain in a wide variety of clinical contexts.[9] 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-10 metric.[10] 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.

8 STUDY ACTIVITIES

8.1 Screening Period (Day of Informed Consent through Pretreatment on Day 1 of the Initial Attack)

- Inclusion/Exclusion Criteria
- Informed Consent/Assent
- Medical History
- Confirmation of documented HAE diagnosis
- Physical examination, including Tanner staging
- Vital signs
- Height and weight
- Recording of concomitant medications
- Measurement of C1-INH
- Urine pregnancy test in pubertal/postpubertal females only

8.2 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 (at initial attack only)
- Physical examination, including Tanner staging
- Vital signs
- Height and weight
- Recording of concomitant medications
- Subject self-assessment of HAE-related pain (in subjects ≥4 years of age only)
- Investigator assessment of HAE symptoms
- Clinical laboratory evaluation (serum chemistry, hematology and urinalysis)
- Urine pregnancy test (in pubertal/postpubertal females only)
- Assessment of reproductive hormones
- Pharmacokinetic evaluations (prior to treatment at initial attack only)
- Immunogenicity evaluations
- AE assessment

8.3 Initial Attack

8.3.1 Treatment Period (Day 1 to Day 8)

- Study drug administration (Day 1, Time 0)
- Physical examination (Day 1, 6 hours post-dose and Day 8)

- Vital signs (Day 1, 1 hour and 6 hours post-dose and Day 8)
- Subject self-assessment of HAE-related pain in subjects ≥4 years of age (Day 1, 1 hour, 2 hours, 4 hours, and 6 hours post-dose, Day 2 [24 hours], Day 3 [48 hours], and Day 8)
- Investigator assessment of HAE symptoms (Day 1, 1 hour, 2 hours, 4 hours, and 6 hours post-dose, Day 2 [24 hours], Day 3 [48 hours], and Day 8)
- Clinical laboratory evaluation (Day 1, 6 hours post-dose and Day 8)
- Assessment of reproductive hormones (Day 1, 6 hours post-dose and Day 8)
- Injection site reaction evaluation (Day 1, 1 hour and 6 hours post-dose, Day 2 [24 hours], Day 3 [48 hours], and Day 8)
- Sampling for PK evaluations in pubertal/post pubertal subjects (Day 1, 15 (±5) minutes, 30 (±5) minutes, 45 (±5) minutes, 1 (±0.17) hour, 2 (±0.17) hours, 4 (±0.5) hours, 6 (±0.5) hours, and 8 (±0.5) hours post-dose at initial attack only)
- Sampling for PK evaluations in prepubertal subjects (Day 1, 15 (±5) minutes, 30 (±5) minutes, 2 (±0.17) hours, 4 (±0.5) hours, and 6 (±0.5) hours post-dose at initial attack only)
- Immunogenicity evaluation (Day 8)
- Recording of concomitant medications
- Monitoring of AEs

8.3.2 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, including Tanner staging
- Vital signs
- Height and weight
- Recording of concomitant medications
- Clinical laboratory evaluation (serum chemistry, hematology, and urinalysis)
- Urine pregnancy test in pubertal/postpubertal females only
- Assessment of reproductive hormones
- Immunogenicity evaluation
- Monitoring of AEs

8.4 Subsequent Attacks (Pubertal/postpubertal Subjects Only)

Pubertal/postpupertal subjects may receive treatment for up to 2 subsequent HAE attacks. 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.

8.4.1 Treatment Period (Day 1 to Day 8)

- Study drug administration (Day 1, Time 0)

- Physical examination (Day 1, 6 hours post-dose and Day 8)
- Vital signs (Day 1, 1 hour and 6 hours post-dose and Day 8)
- Subject assessment of HAE symptoms in subjects ≥4 years of age (Day 1, 1 hour, 2 hours, 4 hours, and 6 hours post-dose, Day 2 [24 hours], Day 3 [48 hours], and Day 8)
- Investigator assessment of HAE symptoms (Day 1, 1 hour, 2 hours, 4 hours, and 6 hours post-dose, Day 2 [24 hours], Day 3 [48 hours], and Day 8)
- Clinical laboratory evaluation (Day 1, 6 hours post-dose and Day 8)
- Assessment of reproductive hormones (Day 1, 6 hours post-dose and Day 8)
- Injection site reaction evaluation (Day 1, 1 hour and 6 hours post-dose, Day 2 [24 hours], Day 3 [48 hours], and Day 8)
- Immunogenicity evaluation (Day 8)
- Recording of concomitant medications
- Monitoring of AEs

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

- Physical examination, including Tanner staging
- Vital signs
- Height and weight
- Recording of concomitant medications
- Clinical laboratory evaluation (serum chemistry, hematology, and urinalysis)
- Urine pregnancy test in pubertal/postpubertal females only
- Assessment of reproductive hormones
- Immunogenicity evaluation
- Monitoring of AEs

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.

SAE 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, NC, USA). Data will be summarized with respect to disposition, demographic, pretreatment characteristics, PK variables, safety variables, and efficacy variables. Unless stated otherwise, tabular summaries will be presented by the subject's stratification group at enrollment (ie, prepubertal group, pubertal/postpubertal group, and the overall subjects group.

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

Enrollment of approximately 16 prepubertal and 20 pubertal/postpubertal subjects, who are from 2 through 17 years of age and who present with a cutaneous, abdominal, or laryngeal attack of acute HAE, is planned. This sample size is empirically derived and not based on a formal sample size calculation. However, the inclusion of approximately 36 subjects will provide basic information for safety, tolerability, PK, and efficacy.

10.3 Analysis Populations

The following populations will be used in the analysis:

- The Initial Non-laryngeal Treatment Population will consist of those subjects who were treated with icatibant for their initial attack and whose primary symptom was either cutaneous or abdominal.
- The Second Non-laryngeal Treatment Population will consist of those subjects who had a second icatibant-treated attack for which the primary symptom was either cutaneous or abdominal, regardless of the primary symptom for the initial attack.
- The Third Non-laryngeal Treatment Population will consist of those subjects who had a third icatibant-treated attack, for which the primary symptom was either cutaneous or abdominal, regardless of the primary symptom for the initial attack.
- The Laryngeal Population will consist of those subjects who were treated with icatibant for any attack for which the primary symptom was laryngeal.
- The PK Population will consist of those subjects who were treated with icatibant for their initial attack and who had at least 1 post-treatment icatibant concentration recorded.
- The Initial Treatment Population will consist of those subjects who were treated with icatibant for the initial attack.
- The Additional Treatment Population will consist of those pubertal/post-pubertal subjects who were treated with icatibant for more than 1 attack.

All efficacy analysis will be performed on the Initial Non-laryngeal Treatment Population, the Second Non-laryngeal Treatment Population, and the Third Non-laryngeal Treatment Population. The PK analyses will be based on the PK population. Safety and tolerability analyses will be based on the Initial Treatment Population and the Additional Treatment Population. The Laryngeal Population will be used to explore the efficacy of icatibant for the treatment of laryngeal attacks. All analyses conducted with this population will be limited to data corresponding to the subject's first laryngeal attack.

10.4 Demographics and Baseline Characteristics

Demographic data and pretreatment characteristics will be summarized for each analysis 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 treated for acute attacks of HAE. 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). PK 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

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 ≥LOQ will be treated as 0 and those that occur thereafter will be treated as missing.

PK 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, clearance (CL/F), area under the plasma concentration-time curve ($AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$), mean residence time (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.

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 Analysis

Another primary objective of the study is to investigate the safety and tolerability of a single SC dose of icatibant in pediatric subjects with HAE during an acute HAE attack. The corresponding analyses will be based on the Initial Treatment Population.

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

AEs will be categorized using MedDRA Version 8.1 or higher. The assessment of safety will be based mainly on the frequency of treatment emergent AEs. AEs 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 subject stratification group and for the overall subject group. AEs by SOC and preferred term also will be tabulated by severity and by relationship to treatment. In the case of multiple occurrences of the same AEs (at the preferred term level) in an individual subject, the AE that is classified as the most severe (ie, maximum severity) will be identified for the analysis by severity and the AE that has the highest relationship to study drug will be identified for the analysis by relationship. SAEs will be provided in a data listing.

Laboratory data will be listed by subject and stratification group. Subjects with newly occurring abnormalities outside the normal range will be flagged and listed separately. Actual values and mean change from pretreatment values will be summarized by the stratification group. Shift tables will also be tabulated by stratification group and time point.

Vital signs data will be listed by subject and stratification group. Furthermore, actual values and mean changes from baseline will be summarized for each stratification group as well as the overall subject group. 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 attack

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

The assessment of safety and tolerability after repeated treatment with icatibant is also of interest. The analyses described above will be repeated using the Additional Treatment Population. The summary tables and listings will be presented by attack number (ie, Attack 1, Attack 2, and Attack 3).

10.7 Efficacy Analysis

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, 6, 24, and 48 hours post-treatment. Eight symptoms will be assessed for abdominal and cutaneous attacks, and 13 symptoms will be assessed for laryngeal attacks. Time 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 overall subjects group. An alternative analysis of time to onset of symptom relief will focus on the time to minimal symptoms. In this case, symptom relief is defined as the earliest time post-treatment when all symptoms are either absent or mild.

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.

A subset of subjects, 4 years of age or older, will assess pain using the Faces Pain Scale-Revised (FPS-R). Time to onset of symptom relief will be computed in a manner similar to that for the average investigator-reported symptom scores.

All efficacy analysis will be performed on the initial treatment population, the second treatment population, and the third treatment population. The efficacy data for subjects with laryngeal attacks will be listed. If there are at least 5 subjects with laryngeal attacks, then the average investigator-reported symptom scores and the change from baseline in the average investigator-reported symptom score will be summarized. Additionally, time to symptom relief analysis will be performed on the investigator-reported symptom scores.

10.8 Analysis of Reproductive Hormone Levels

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.

10.9 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. Time to first use of rescue medication prior to symptom relief will be calculated from the time of study drug administration to the first use of rescue medication prior to symptom relief. The median time and the 95% confidence interval will be calculated using Kaplan-Meier methodology.

10.10 Data Monitoring and Interim Analysis

A Data and Safety Monitoring Board (DSMB) will be set up to review the safety, tolerability, PK and efficacy data on an ongoing basis. The goal of the DSMB 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. Because no formal hypothesis testing is planned, multiplicity concerns regarding repeated analyses are not an issue.

10.11 Handling of Missing Data

Individual pretreatment symptom scores and FPS-R 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. Similar approach will be followed 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. 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.

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, 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. AEs 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.

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) as appropriate 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 Good Clinical Practice (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 Shire HGT 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 Shire HGT or their designee:

- Completed FDA Form 1572 (Statement of Investigator), signed, dated, and accurate.
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed within 12 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; these are the responsibility of Shire HGT.

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 Data and Safety Monitoring Board (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 Shire HGT and approved by the DSMB. The charter will define the membership of the DSMB, the responsibilities of the DSMB and Shire HGT, 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 17 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, and tolerability 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. For any subject who does not meet the inclusion or exclusion criteria a protocol exemption may be requested by the investigator. This exemption may be approved by the Shire Medical Monitor prior to enrollment and the protocol exception must be fully documented in the source documents and on the appropriate page of the CRF.

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 be required 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 contract research organization or an electronic data capture technology provider as designated by Shire HGT. Shire HGT or its designee will be responsible for performing study data management activities.

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 8.1 or higher. Concomitant medication will be coded using WHO-Drug Dictionary (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.

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 HGT, provided Shire HGT a copy of the draft document intended for publication, and obtained Shire HGT's written consent for such publication. All information obtained during the conduct of this study will be regarded as confidential. Shire HGT will use the information for registration purposes and for the general development of the drug.

12 LIST OF REFERENCES

1. Bowen T, Cicardi M, Bork K, et al. Hereditary angiodema: a current state-of-the-art review, VII: Canadian Hungarian 2007 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema. Ann Allergy Asthma Immunol 2008;100:S30-40.

2. Davis AE, 3rd. New treatments addressing the pathophysiology of hereditary angioedema. Clin Mol Allergy 2008;6:2.

3. Knolle J, Breipohl G, Henke S, Wirth K, Scholkens B. New and highly potent bradykinin antagonists. Agents Actions Suppl 1992;38 (Pt 1):559-64.

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5. Wirth K, Hock FJ, Albus U, et al. Hoe 140 a new potent and long acting bradykinin-antagonist: in vivo studies. British journal of pharmacology 1991;102:774-7.

6. Farkas H. Pediatric hereditary angioedema due to C1-inhibitor deficiency. Allergy Asthma Clin Immunol 2010;6:18.

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8. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Archives of disease in childhood 1970;45:13-23.

9. Bieri D RRACGDALZJB. 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;41:139-50.

10. Hicks CL, von Baeyer CL, Spafford PA, van Korlaar I, Goodenough B. The Faces Pain Scale-Revised: toward a common metric in pediatric pain measurement. Pain 2001;93:173-83.

Appendix 1 Study Schedule of Events (Initial Icatibant-Treated Attack)

Initial Icatibant-Treated Attack (All Subjects)	Screening Period	Pre-Treatment (Baseline)	Treatment	Post-Treatment											Follow-up
Study Day		1	1	1								2	3	8	90 ±7
Time Post-Treatment (hours)			0	0.25	0.50	0.75	1	2	4	6	8	24 ±4	48 ±4		
Assessments															
Informed Consent/Assent	X														
Medical History	X	X													
Confirm Documented Diagnosis (HAE)	X														
C1-INH assessment	X														
Inclusion/Exclusion Assessment	X	X[b]													
Physical Exam	X	X								X				X	X
Vital Signs	X	X					X			X				X	X
Height and Weight	X	X													X
Subject Self-Assessment of HAE-related Pain (in subjects ≥4 years of age and before blood work, if applicable)		X					X	X	X	X		X	X	X	
Investigator Assessment of HAE Symptoms		X					X	X	X	X		X[a]	X[a]	X	
Clinical Laboratory Tests (serum chemistry/hematology/urinalysis)		X								X				X	X
Urine Pregnancy Test (pubertal/post pubertal females)	X	X													X
Reproductive Hormones (FSH, LH, estradiol, progesterone in females) (FSH,LH testosterone in males)		X								X				X	X
Study Drug Administration (single SC dose)			X												

Initial Icatibant-Treated Attack (All Subjects)	Screening Period	Pre-Treatment (Baseline)	Treatment	Post-Treatment											Follow-up
Study Day		1	1	1								2	3	8	90 ±7
Time Post-Treatment (hours)			0	0.25	0.50	0.75	1	2	4	6	8	24 ±4	48 ±4		
Assessments															
Evaluate Injection Site Reactions							X			X		X[a]	X[a]	X	
PK Evaluations[c]		X		X	X	X	X	X	X	X	X				
Immunogenicity Evaluations		X												X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] The assessments at 24 and 48 hours (±4 hours) after study drug administration may be conducted either in person or via telephone contact.

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

[c] 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 approximately 15 minutes, 30 minutes, 2 hours, 4 hours, and 6 hours post-dose as indicated in Section 8.3.1.

Appendix 2 Study Schedule of Events (Subsequent Icatibant-Treated Attacks)

Subsequent Icatibant-Treated Attacks (Pubertal/postpubertal subjects only)	Pre-Treatment (Baseline)	Treatment	Post-Treatment							Follow-up
Study Day	1	1	1				2	3	8[b]	90 ±7[b]
Time Post-Treatment (hours)		0	1	2	4	6	24 ±4	48 ±4		
Assessments										
Physical Exam	X					X			X	X
Vital Signs	X		X			X			X	X
Height and Weight	X									X
Subject Self-Assessment of HAE-related Pain (in subjects ≥4 years of age and before blood work, if applicable)	X		X	X	X	X	X	X	X	
Investigator Assessment of HAE Symptoms	X		X	X	X	X	X[a]	X[a]	X	
Clinical Laboratory Tests (serum chemistry./hematology/urinalysis)	X					X			X	X
Urine Pregnancy Test (pubertal/post pubertal females)	X									X
Reproductive Hormones (FSH, LH, estradiol, progesterone in females; FSH, LH, testosterone in males)	X					X			X	X
Study Drug Administration (single SC dose)		X								
Evaluate Injection Site reactions			X			X	X[a]	X[a]	X	
Immunogenicity Evaluations	X								X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X

[a] The assessments at 24 and 48 hours (±4 hours) after study drug administration may be conducted either in person or via telephone contact.
[b] If a subsequent attack occurs within 7 days of the Day 90 (±7 days) follow-up visit for the previous attack, the assessments on Day 8 and Day 90 will be combined.

Appendix 3 Faces Pain Scale-Revised (FPS-R)

Pediatric Pain Sourcebook

Document information

Title:	**The Faces Pain Scale - Revised (English & French)**
Purpose:	**a scale for measurement of pain intensity in children by self-report, in both English & French**
Approval/ revision date:	**May 5, 2001**

Keywords

document type:	**protocol, guidelines, scale**
Intended audience:	**healthcare professionals**
Institution type:	**children's hospital, general hospital**
Drug type:	**N/A**
Pain type:	**disease, procedural, surgical/trauma, treatment related**
Delivery technique:	**N/A**
Nonpharmacological treatments:	**N/A**
Age:	**child, adolescent**
Disease type:	**N/A**

Submitter and institution information

Name:	**Carl L. von Baeyer, PhD**
Title:	**Professor of Psychology & Associate Member in Pediatrics**
Institution:	**University of Saskatchewan**
Location:	**Saskatoon, Saskatchewan, Canada**
Type of institution:	**N/A**
Number of beds:	**N/A**
Supervising specialist availability:	**N/A**

Submitter's commentary:

The Faces Pain Scale - Revised (FPS-R) was adapted from the Faces Pain Scale (Bieri et al, 1990) in order to make it possible to score on the widely accepted 0-to-10 metric. It shows a close linear relationship with visual analog pain scales across the age range 4 through 16 years. It is easy to administer and requires no equipment except for the photocopied faces. The absence of smiles and tears in this faces scale may be advantageous. The FPS-R is recommended for use with younger children in parallel with numerical self-rating scales (0-to-10) for older children and behavioural observation scales for those unable to provide self-report.

References:
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.

von Baeyer CL, Spafford P, van Korlaar I, Hicks CL, Goodenough B. Validation of the Faces Pain Scale - Revised (FPS-R): Pain intensity in clinical and non-clinical samples. Poster presented to Canadian Pain Society, Montreal, May 2001.

Bieri D, Reeve R, Champion GD, Addicoat L and 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.

von Baeyer CL, Hicks CL. Support for a common metric for pediatric pain intensity scales. Pain Research and Management 2000;5:157-160.

Reviewer's commentary:

published in peer-reviewed journal (see first reference above)

Reviewer: **N/A**

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.

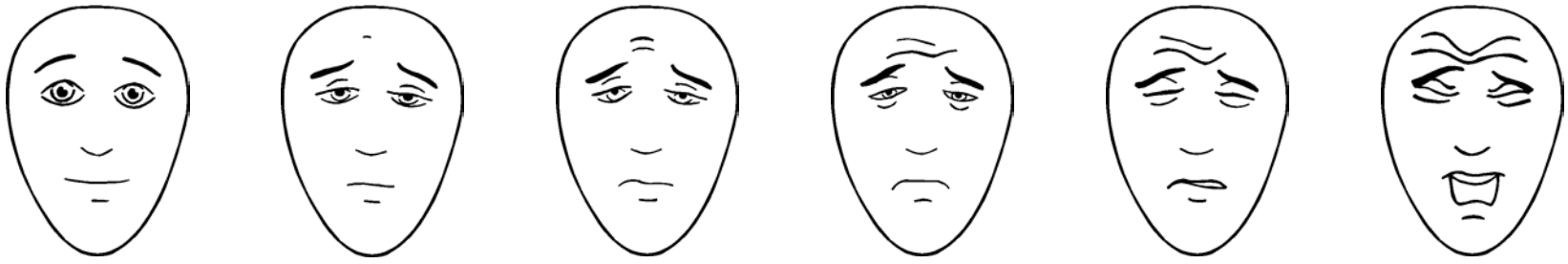
"These faces show how much something can hurt. This face *[point to left-most face]* **shows no pain. The faces show more and more pain** *[point to each from left to right]* **up to this one** *[point to right-most face]* **– it shows very much pain. Point to the face that shows how much you hurt**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

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.

Fold here

0 2 4 6 8 10



Faces Pain Scale – Revised (FPS-R)

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

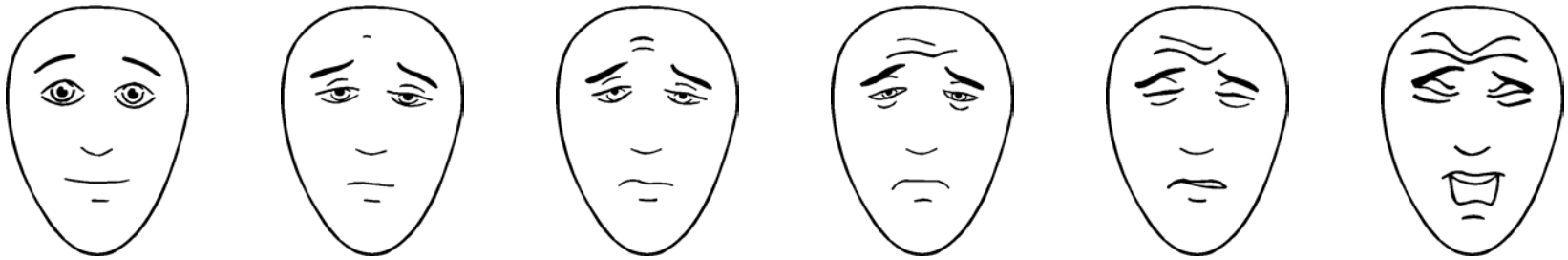
"Ces visages montrent combien on peut avoir mal. Ce visage *(montrer celui de gauche)* **montre quelqu'un qui n'a pas mal du tout. Ces visages** *(les montrer un à un de gauche à droite)* **montrent quelqu'un qui a de plus en plus mal, jusqu'à celui-ci** *(montrer celui de droite)*, **qui montre quelqu'un qui a très très mal. Montre-moi le visage qui montre combien tu as mal en ce moment."**

Les scores sont de gauche à droite : 0, 2, 4, 6, 8, 10. 0 correspond donc à "pas mal du tout" et 10 correspond à "très très mal". Exprimez clairement les limites extrêmes : "pas mal du tout" et "très très mal". N'utilisez pas les mots "triste" ou "heureux". Précisez bien qu'il s'agit de la sensation intérieure, pas de l'aspect affiché de leur visage.

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.

Plier

0 2 4 6 8 10



Appendix 4 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

Final Date: 14 June 2011

Amendment 1 Date: Original protocol, not applicable

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

_____
Signature **Date**

PPD MD
_____
Printed Name