# PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE MEETING
# June 23, 2011

## Hilton Washington DC/
## Silver Spring (Colesville Road)
## Silver Spring, MD

## NDA 022-150: Firazyr (icatibant) injection for the treatment of acute attacks of hereditary angioedema (HAE) in patients 18 years of age and older

**Disclaimer Statement**

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the new drug application, NDA 022-150 for Firazyr (icatibant) by Jerini U.S. Inc., a subsidiary of Shire HGT, for the treatment of acute attacks of hereditary angioedema (HAE) in patients 18 years of age and older to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

# FDA Briefing Package

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# I. Division Memorandum

**Division Memorandum**

Date: May 25, 2011

From: Susan Limb, MD
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To: Members, Pulmonary-Allergy Drugs Advisory Committee

Subject: Overview of the FDA background materials for New Drug Application (NDA) 22-150, Firazyr (icatibant), at a dose of 30 mg subcutaneously for the treatment of acute attacks of hereditary angioedema (HAE) in patients 18 years of age and older

## Introduction

Thank you for your participation in the Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting to be held on June 23, 2011. As members of the PADAC, you provide important expert scientific advice and recommendations to the US Food and Drug Administration (the Agency) on the regulatory decision-making process related to the approval of a drug or biologic product for marketing in the United States. The upcoming meeting is to discuss New Drug Application (NDA) 22-150 from Jerini US, Inc. for Firazyr (icatibant), at a dose of 30 mg subcutaneously for the treatment of acute attacks of hereditary angioedema (HAE) in patients 18 years of age and older. The applicant, Jerini US, Inc., is a subsidiary of Shire Human Genetic Therapies (HGT) and is referred to as Jerini in this document.

HAE is a rare, inherited condition characterized by intermittent, unpredictable attacks of angioedema in various parts of the body, including the airway, face, intestinal wall, and extremities.[1] [2] [3] The condition is associated with a defect in the C1-esterase inhibitor protein, resulting in low or absent functional protein. HAE is estimated to affect 1 in 10,000 to 50,000 individuals worldwide and is categorized as an orphan disease. The acute attacks of HAE are potentially life-threatening, particularly in cases of airway compromise. Attacks at other anatomic sites can cause disabling pain and significant morbidity. These attacks are highly variable in frequency and location among individuals and even within a given individual. Currently, there are two products approved for the treatment of acute attacks of HAE in the US. The first product is a plasma-derived C1 inhibitor replacement product (Berinert®)[4] that is administered intravenously. The other product is ecallantide (Kalbitor®),[5] a kallikrein inhibitor delivered via subcutaneous injection. Both products require administration by a healthcare professional and carry a

[1] Zuraw B. Hereditary angioedema. N Engl J Med 2008; 359:1027-1036
[2] Frank MM. Hereditary angioedema. J Allergy Clin Immunol. 2008 Feb;121(2 Suppl):S398-401
[3] Bowen T et al. 2010 International consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema. Allergy Asthma Clin Immunol. 2010; 6(1):24
[4] US Professional drug label for Berinert (human C1 esterase inhibitor)
[5] US Professional drug label for Kalbitor (ecallantide)

risk of hypersensitivity reactions, including anaphylaxis. Several other products are available for prophylaxis, but acute HAE attacks can still occur.

Icatibant is a new molecular entity, a novel decapeptide antagonist directed against the bradykinin type-2 receptor. Bradykinin is thought to be the major downstream mediator that increases vascular permeability and inflammation, leading to the swelling and pain characteristic of HAE.[6] Icatibant is supplied as a pre-filled syringe containing 30 mg icatibant acetate in 3 mL solution. The proposed trade name is Firazyr.

Jerini originally submitted this application to the Agency on October 22, 2007, for the same dose and indication. A Not Approvable action was taken on April 28, 2008, due to clinical deficiencies. The Not Approvable letter cited a lack of substantial evidence of efficacy to support the proposed indication. The original submission included the results of two Phase 3 clinical trials in patients with HAE. One clinical trial had a placebo control while the second clinical trial used an active comparator, tranexamic acid. The placebo-controlled trial did not show a statistically significant difference between icatibant and placebo for the primary efficacy endpoint, time to onset of symptom relief. The second trial did demonstrate a statistically significant difference between icatibant and tranexamic acid. However, tranexamic acid is not approved for the treatment of HAE in the US, and there is limited data to support the efficacy of tranexamic acid for the treatment of acute HAE attacks. The uncertain efficacy of this active comparator complicated the interpretation of the results from the second trial. As a result, Jerini was asked to conduct an additional controlled trial to confirm the efficacy of icatibant for the proposed indication. The Agency also requested that Jerini provide data to support the potential self-administration of icatibant by patients as had been proposed.

Jerini submitted a Complete Response on February 25, 2011, with results from another placebo-controlled trial and an open-label self-administration trial to address these deficiencies. The proposed dose remains 30 mg of icatibant administered subcutaneously, with the option of two additional 30-mg doses administered at intervals of no less than 6 hours for cases of insufficient relief or relapse. A total of 3 doses in a 24-hour period may be administered.

Major issues highlighted for discussion at the PADAC meeting include whether the totality of the data support: 1) the efficacy of icatibant; 2) the safety of icatibant; 3) approval for the proposed indication; and 4) the appropriateness of patient self-administration.

This memorandum provides an overview of the original submission and the subsequent Complete Response. The materials prepared by the Agency contain findings and opinions based on reviews of information submitted by Jerini. These materials reflect preliminary findings and do not represent the final position of the Agency. The opinions and input provided by you at this PADAC meeting will be an important factor in our decision on this application.

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[6] Frank MM. Complement disorders and hereditary angioedema. J Allergy Clin Immunol. 2010 Feb;125(2 Suppl 2):S262-71

The clinical and statistical issues related to the icatibant clinical trial results are the primary focus of this PADAC meeting. In determining approvability of a product, the Agency takes into consideration other factors in the regulatory decision-making process, including the manufacturing and controls of a product and preclinical data. These will not be the focus of this PADAC meeting.

Attached are the background materials for this meeting. In addition to this memorandum, the FDA background materials include the following: Clinical Briefing Document, Statistical Briefing Document, a brief summary of the clinical pharmacology program, the product labels of other products approved the same indication, and reference articles.

## Background

### Relevant Regulatory History for Icatibant

Jerini met with the Agency for a Pre-IND meeting on February 6, 2004, to discuss the requirement for replicate, well-controlled trials to support the indication as well as the selection and validation of symptom-based endpoints for HAE. On June 11, 2004, Jerini submitted a protocol for a Special Protocol Assessment (SPA) for a randomized, double-blind, placebo-controlled efficacy trial. The Agency at the time agreed in principle with the proposed endpoints and sample size but added the caveat that the treatment difference should be clinically meaningful. The Agency later raised concerns about support for selection of the proposed 30 mg dose at a pre-NDA meeting on March 1, 2005. Subsequently, a second pre-NDA meeting was held on January 24, 2007, which highlighted several major issues: 1) the lack of replicate efficacy findings; 2) the need for validation of the patient-reported outcomes instrument, the Visual Analogue Scale (VAS), used in the Phase 3 program; and 3) the need for additional data to support self-administration.

Jerini submitted an NDA on October 22, 2007, for icatibant 30 mg SC for the treatment of acute attacks of HAE. A Not Approvable action was taken on April 28, 2008, due to the lack of replicate evidence of efficacy described in the Introduction section.

Jerini met with the Agency on December 15, 2008, to clarify the clinical deficiencies outlined in the Not Approvable letter for the original NDA submission. Jerini agreed to conduct a third, controlled trial in patients with HAE to confirm the efficacy results of the earlier trials. Subsequently, Jerini submitted a request on February 12, 2009, for a Special Protocol Assessment for the confirmatory third trial. Although no agreement was reached, the Agency informed Jerini that a trial that was generally similar in design to FAST-1 and FAST-2 would be acceptable for addressing the clinical deficiencies.

Subsequently, Jerini submitted a Complete Response on February 25, 2011, with results from another placebo-controlled trial and an open-label self-administration trial to address these deficiencies. The Complete Response also included the results of a thorough QT trial to evaluate the effects of icatibant on various ECG parameters as well as additional pharmacokinetic data to support dose selection.

**Product Information**
Icatibant is a synthetic decapeptide antagonist directed against the bradykinin type-2 receptor. Icatibant is structurally similar to bradykinin with the ecveption of 5 non-proteinogenic amino acids. It is supplied as a single-use, pre-filled 25-gauge syringe containing 30 mg icatibant acetate in 3 mL solution. In addition to the active ingredient, the sterile, acetate buffer solution contains 7.45 mg sodium chloride, 1.32 mg acetic acid, and 0.64 mg sodium hydroxide/ml and water for injection adjusted to pH 5.5±0.3. The solution contains no preservatives. The recommended storage conditions are at <25ºC and protected from light. The proposed dose of icatibant is 30 mg administered by slow SC injection in the abdominal area for the treatment of an acute HAE attack. In cases of insufficient relief or recurrence of symptoms, two additional doses may be administered at intervals of ≥6 hours, not to exceed 3 doses in a 24-hour period.

**Nonclinical Pharmacology and Toxicology**
Jerini submitted a complete pharmacology/toxicology program to support the chronic, intermittent use of icatibant. The program included a 6-month repeat dose toxicology studs in rats and a 9-month study in dogs as well as other short-term toxicology studies. Reproductive toxicology assessment included a fertility study in mice and rats, teratology studies in rats and rabbits, and a perinatal/postnatal study in rats. Other toxicology studies included a juvenile rat toxicology study and an ongoing carcinogenicity study. Completed genotoxicity testing of icatibant did not suggest genotoxic potential.

The animal studies were notable for injection site reactions at higher doses in dogs, which appear to be mediated by histamine in a dose-related manner. In addition, dose-schedule-dependent effects on male and female reproductive organs were observed. Testicular and uterine atrophy were observed in rats and dogs, and a reversible delay in sexual maturation was observed in sexually immature dogs. No teratogenicity was observed, but icatibant appears to affect the uterine implantation process and is associated with delayed parturition in late pregnancy. While the reproductive toxicities raise concerns, the findings in animals should be considered in the context of the disease being treated as well as the fact that the animals were dosed daily, while patients will receive icatibant intermittently. A clinical trial to evaluate icatibant effects on reproductive hormones is currently ongoing.

**Clinical Pharmacology**
Jerini submitted results from a comprehensive clinical pharmacology program, which included studies to assess protein binding and metabolism in vitro, single- and multiple-dose pharmacokinetics, effect of hepatic impairment, the effect of renal impairment in hepatorenal syndrome, QTc effect, and effect on CYP540 isoenzymes.

Icatibant has linear pharmacokinetics, with a dose-proportional increase in mean Cmax and mean $AUC_{0-\infty}$. The elimination profile is triphasic, with the majority of the drug eliminated with a half-life of ~1 hour. Multiple dose administration does not lead to accumulation of icatibant. During the review of the original submission, the Agency noted a difference in systemic exposure by gender and age that was not readily explained

by body weight differences, with women and patients >65 years of age achieving higher plasma levels of drug. The Agency requested that Jerini justify why dose adjustments for gender and age were not necessary. In the Complete Response, Jerini provided population PK analysis to address the issue. While acknowledging that systemic exposure does vary somewhat with age, gender, and body weight, Jerini has concluded that these pharmacokinetic differences are not clinically significant based on the results of pivotal Phase 3 trials.

A possible QTc effect was noted in a trial conducted in healthy volunteers who received 5 doses of icatibant 30 mg SC on 3 separate days. Subsequent evaluation in a dedicated thorough QTc trial with an active control does not appear to indicate a QTc effect.

Additional details regarding the clinical pharmacology assessment for icatibant can be found in the clinical pharmacology summary document included in these briefing materials.

**Clinical Program**

Jerini completed three Phase 3 efficacy and safety trials (FAST-1, FAST-2, and FAST-3) to support the use of icatibant in the treatment of acute attacks of HAE in patients 18 years of age and older. FAST-1 and FAST-2 were included in the original application; FAST-3 was included in the Complete Response. FAST-1 was a randomized, double-blind, placebo-controlled trial in 64 adult patients; FAST-2 (n=77) was similar in design to FAST-1 but included tranexamic acid as an active control instead of placebo. The third confirmatory trial, FAST-3 (n=98), was a placebo-controlled trial similar to FAST-1. All of these trials included an open-label extension phase where patients could continue to receive intermittent treatment as needed for subsequent acute HAE attacks. In addition to these pivotal efficacy and safety trials, Jerini conducted a Phase 2 proof-of-concept/dose-ranging trial, a Phase 3 self-administration trial, and an observational study to evaluate the patient-reported instrument used to score symptoms, the VAS. Table 1 summarizes the key icatibant studies conducted in HAE patients.

| Table 1 Clinical trials conducted in HAE patients for icatibant | | | | | |
|---|---|---|---|---|---|
| **Study** [year][a] | **Study type** | **N**[b] ***N***[c] **(n)**[d] | **Dose** | **Endpoint** | **Study sites** |
| **Phase 2 trial** | | | | | |
| 2101 [2004] | Proof-of-concept, dose-ranging | 15[e] | • 0.4mg/kg IV over 30 min<br>• 0.8mg/kg IV over 30 min<br>• 0.4mg/kg IV over hours<br>• 30 mg SC icatibant<br>• 45 mg SC icatibant | • PK<br>• Symptom score | • Germany |
| **Pivotal Phase 3 efficacy and safety trials** | | | | | |
| 2102 (FAST-2) [2006] | Efficacy and safety | 74<br>*3*<br>(39) | • 30 mg SC icatibant<br>• Tranexamic acid (3 x 1g for 2 days) | • time to onset of symptom relief (single symptom VAS) | • W. and E. Europe<br>• Israel |
| | Open-label extension | 54[f] | | | |
| 2103 (FAST-1) [2006] | Efficacy and safety | 56<br>*8*<br>(36) | • 30 mg SC icatibant<br>• Placebo | • time to onset of symptom relief (single symptom VAS) | • N. America<br>• Australia<br>• Argentina |
| | Open-label extension | 72[f] | | | |
| 054 (FAST-3) [2010] | Efficacy and safety | 93<br>*5*<br>(53) | • 30 mg SC icatibant<br>• Placebo | • Time to onset of symptoms relief (3-symptom composite VAS) | • N. America<br>• Australia<br>• E. Europe<br>• Mexico<br>• S. Africa<br>• Turkey<br>• Israel |
| | Open-label extension (ongoing) | 76[f] as of Sep 2010 | | | |
| **Additional studies** | | | | | |
| 4102 [2007] | Observational patient-reported outcome validation study | 60 | • No intervention | • Correlation of VDS to VAS to calculate MCSD | • W. and E. Europe<br>• N. America<br>• Argentina |
| 3101 (EASSI) [2010] | Open-label self-administration trial (ongoing) | 56 as of Oct 2010 | • 30 mg SC icatibant | • Safety | • W. Europe<br>• Israel |

[a] Year enrollment completed
[b] Number of patients randomized (FAST-1 and FAST-2: abdominal and cutaneous attacks; FAST-3: abdominal, cutaneous, and mild to moderate laryngeal attacks)
[c] Number treated with open-label icatibant for laryngeal attacks
[d] Number of patients treated with at least 1 dose of icatibant during controlled portion of trial, including patients treated with open-label icatibant for laryngeal attacks or for rescue
[e] A total of 15 patients enrolled.
[f] Number of patients enrolled in open-label extension phase, including patients who rolled over from the preceding controlled phase of the trial.
Source: Individual study reports, Jerini

## Efficacy variables

The unpredictable, fluctuating nature of HAE attacks complicates the conduct of clinical trials for HAE, and there is limited regulatory precedent in terms of drug development programs for HAE. In the absence of an accepted standard endpoint, Jerini developed new patient self-assessment and investigator assessment tools for use in the icatibant efficacy trials. A description of the efficacy variables is provided here, followed by a discussion of the pivotal trials and the major efficacy results.

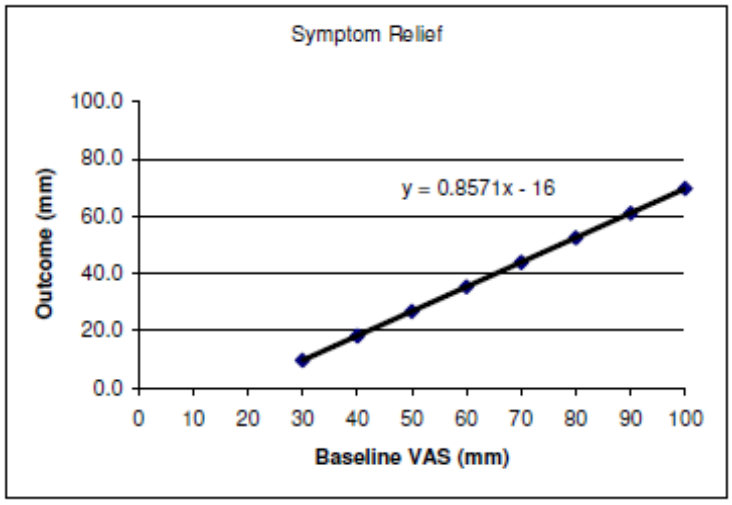
- ***Patient-reported outcome instrument: Visual Analog Scale (VAS)***

Jerini used a patient reported outcome instrument called the Visual Analog Scale (VAS) to measure patient symptoms as the primary efficacy variable. While the VAS has been used in clinical trials of chronic pain, the use of a VAS in HAE is novel. The VAS is a 100 mm horizontal line with 0 mm = no symptoms and 100 mm = worst possible symptom. Patients mark on the line to rate the intensity of each symptoms of at baseline and pre-determined time points throughout the treatment period. The symptoms rated include the following: cutaneous swelling, cutaneous pain, abdominal pain and nausea. For cutaneous attacks, the time to onset of symptom relief was defined by a single symptom of "swelling" or "pain," whichever was the most severe presenting symptom. If both were equally severe, "pain" was used as the primary endpoint. For abdominal attack patients, abdominal pain was used as the primary symptom to assess onset of symptom relief.

In FAST-1 and FAST-2, the primary efficacy endpoint was the median time to onset of relief for the primary symptom as defined by the following Figure 1:

- A response to the right and below a line Y = 6/7 X - 16 with X≥30mm.
  - X = pre-treatment VAS in mm
  - Y = post-treatment VAS in mm
- Corresponds to a reduction by 30 mm at a baseline VAS = 100 mm and by 21 mm at a baseline VAS = 30 mm.

**Figure 1: Definition of onset of symptom relief by VAS in FAST-1 and FAST-2**




Source: je049-2102-statistical.pdf, Section 3

To support the use of the VAS in the original application, Jerini conducted Study 4102, an observational, non-interventional study in 80 adult HAE patients presenting with an acute abdominal and/or cutaneous HAE attack of at least moderate severity. The objective of the study was to identify the minimum clinically important difference (MCID) for the VAS instrument. Patients received the standard of care as determined by the physician and were asked to complete patient diaries, the VAS, and a five-category Verbal Descriptor Scale (VDS), where patients categorized changes in skin swelling, skin

pain, and abdominal pain from baseline ("much more," "a little more," "about the same," "a little less," and "much less"). Based on comparison to the VDS, a 9 mm change in VAS was proposed as the MCID for "onset of symptom relief" and a cut-off of a change of ≥20 mm was defined as a responder. Changes in the VAS corresponded to changes in the VDS ($r=0.7576$; $p<0.0001$), as well as to patient diary data and physician assessments. Despite these validation studies, the Agency expressed uncertainty regarding the clinical meaning of the VAS due to discrepancies noted between the VAS-based time to onset of symptom relief and the separate patient-reported start of improvement that were observed in the two efficacy trials submitted in the original NDA. The Agency requested additional validation of the instrument in the Not Approvable letter. To address these concerns, Jerini conducted patient cognitive debriefing interviews, literature review, and sought additional expert input to support the instrument.

As a result of these additional validation studies, Jerini proposed a modified, composite symptom VAS endpoint in the third confirmatory Phase 3 trial, FAST-3. The time to symptom relief was defined as the first documented time point when the patient experiences a 50% reduction in the 3-symptom composite VAS from the pretreatment composite score. For cutaneous and abdominal attacks, the 3 components of the composite VAS (VAS-3) were abdominal pain, skin pain, and skin swelling. (For laryngeal attacks, the composite VAS (VAS-5) included these three symptom components plus the symptoms of difficulty swallowing and voice change. Laryngeal attack VAS scores were collected but were not included in the calculation of the primary efficacy endpoint.) Based on a receiver operating characteristics (ROC) curve analysis, Jerini has proposed a MCID value of 5-6mm in patients with a baseline VAS-3 score of ≥30 mm for at least one symptom.

The validity of the proposed minimally important differences in the VAS and the VAS-3 are integral to the discussion of efficacy. While the validation studies appear supportive, changes in the single-symptom VAS or the composite VAS are not entirely intuitive, and their clinical significance is open to interpretation. Given the lack of regulatory experience with the primary efficacy variable, the Agency also recommended the assessment of a range of secondary efficacy variables that were independent of the VAS as additional measures of efficacy.

- ***Secondary efficacy variables***

Secondary endpoints in the pivotal trials included the time to relief of each symptom present in pre-dose VAS other than the primary symptom, time to almost complete symptom relief (0-10 mm on VAS), response rate at 4 hours, regression of symptoms (start of improvement), and individual symptom severity scoring on a 5-point scale of none to very severe. Investigators scored specific symptoms as well as performing global assessments of patient improvement or worsening. Laryngeal attacks were analyzed separately from abdominal and cutaneous attacks. Patients and investigators scored symptoms on a similar 5-point severity scale, rating dysphagia and voice change. Investigators made additional assessments of breathing difficulties, stridor, and asphyxia.

Rescue medication use was not assessed formally as a secondary endpoint, but information was provided as an additional indicator of efficacy.

As mentioned in the preceding section, the secondary efficacy variables were needed to support the proposed primary endpoint, with which the Agency did not have prior regulatory experience. The secondary variables were also important due to concerns regarding adequate blinding. Icatibant causes local injection site reactions in nearly all patients, making it difficult to blind. For this reason, rescue medication use was of particular interest, since this variable did not rely directly on subjective patient- or investigator-based symptom scoring.

**Proof-of-concept and dose selection**

Study 2101 was an open-label, multi-center, single dose trial in HAE patients, divided into 5 sequential dose groups. A total of 15 patients presenting with 20 unique cutaneous or gastrointestinal HAE attacks received a single dose of icatibant in one of 5 possible dosing IV or SC dosing regimens: 0.4mg/kg IV over 2 hours; 0.4mg/kg IV over 30 minutes; 0.8mg/kg IV over 30 minutes; 30mg SC; or 45mg SC. These doses were selected on the basis of pharmacokinetic/pharmacodynamic data obtained in previous trials which evaluated the inhibitory profile of icatibant following bradykinin challenge. Five patients were treated twice for separate HAE attacks. Patients completed symptom scores, visual analog scales (VAS), and diaries. Symptom relief was defined by an absolute reduction of ≥20 mm if baseline ≥ 30 mm and ≤ 50 mm or ≥30 mm if baseline > 50 mm. Attacks with VAS <30 mm were not assessed by this evaluation.

**Table 2 Study 2101: Median time to symptom relief by patient report and Visual Analogue Scale (VAS)**

| Treatment Group | Onset of symptoms to treatment (h:min) | Change in VAS (cm) at 4 h | Onset of relief as reported by patient (h:min) | Onset of relief by VAS (h:min) | Time to complete relief by VAS |
|---|---|---|---|---|---|
| **0.4mg/kg IV (2 hours)** | 8:22 | 5.31 | 1:30 | 2:00 | 50:00 |
| **0.4 mg/kg IV (30 min)** | 9:05 | 1.92 | 1:25 | 3:30 | 34:30 |
| **0.8 mg/kg IV (30 min)** | 9:50 | 5.61 | 1:08 | 3:30 | 20:30 |
| **30mg SC** | 7:20 | 3.15 | 0:35 | 3:00 | 34:00 |
| **45mg SC** | 6:07 | 4.31 | 0:27 | 5:00 | 60:00 |

Overall, shorter times to onset of relief were reported for subcutaneous icatibant compared to intravenous icatibant. The patient-reported times for onset of relief were discordant with the onset of relief as identified by the VAS, underscoring some of the clinical uncertainty regarding the VAS instrument. In the absence of clear clinical dose separation between the 30 mg and 45 mg SC dose, Jerini relied on pharmacokinetic/pharmacodynamic (PK/PD) data to guide dose selection. No changes in C1 INH, C4, or C1q were observed over time. Reduction of bradykinin levels from baseline was observed at 4 hours post-dose for both the 30 mg and 45 mg SC doses. In the 30 mg dose group, mean bradykinin decreased from 63 to 38 pmol/L. In the 45 mg dose group, bradykinin decreased from 82 to 71 pmol/L. PK/PD modeling suggested that higher doses were unlikely to have increased efficacy. Furthermore, higher doses administered subcutaneously were more likely to elicit stronger injection site reactions.

Based on these results, the 30 mg SC dose was selected for evaluation in the Phase 3 trials.

Aside from Study 2101, no formal clinical dose-ranging trial in HAE patients was performed. Given the unpredictable nature of the attacks and the subjectivity of the efficacy measurements, establishing a true dose-response curve for icatibant may not be feasible. However, it is unclear whether the pharmacodynamic modeling of HAE attacks is truly representative.

**Efficacy**

The robustness of the efficacy findings varied among the 3 pivotal efficacy trials. Since the primary efficacy endpoint used in FAST-1 and FAST-2 differs from the endpoint used in FAST-3, efficacy results for both the single symptom VAS and the 3-symptom composite VAS (VAS-3) are presented for comparison. These results are shown with the caveat that the VAS-3 results for FAST-1 and FAST-2 reflect post hoc analyses. Efficacy data for laryngeal attacks and subsequent repeat attacks are presented separately, since these types of attacks were not included in the calculation of the primary endpoint in any of the 3 trials.

- ***Original NDA : FAST-1 and FAST-2***

The general trial design was similar for FAST-1 and FAST-2. FAST-1 and FAST-2 were randomized, double-blind, multicenter safety and efficacy studies. The key difference between the studies was the controls used. FAST-1 used a placebo control, while FAST-2 used an active control, oral tranexamic acid. The efficacy of tranexamic acid, a synthetic antifibrinolytic related to epsilon-aminocaproic acid, for treatment of acute HAE attacks is not established. Currently, tranexamic acid is not approved for HAE treatment in the US. It is marketed in the US under the trade name, Cyklokapron®, for the prophylaxis and treatment of hemorrhage in hemophiliac patients undergoing tooth extraction. Tranexamic acid is approved in other countries for other indications related to its antifibrinolytic properties, such as dysfunctional uterine bleeding. Tranexamic acid is approved in a few countries, including the European Union and South Africa, for hereditary angioedema. The foreign package inserts do not specify whether the indication is for chronic or acute treatment of HAE. In general, the literature to support the use of tranexamic acid for acute intervention is very limited.

In both trials, patients 18 years of age and older presenting with an acute abdominal or cutaneous HAE attack of at least moderate severity within 6 hours of onset of symptoms were randomized to icatibant or the other treatment group. Patients were then observed for up to 48 hours, during which time clinical assessments were made at regular intervals. Patients presenting with a laryngeal edema attack were not randomized but were eligible to receive a single dose of icatibant 30 mg SC. Patients who participated in the double-blind treatment phase or received open-label treatment for a laryngeal attack were then eligible to participate in an open-label extension (OLE) phase. For the OLE, any attack severe enough to warrant treatment qualified for treatment with icatibant 30 mg SC. If

the attack worsened within 48 hours of initial treatment, additional injections were permitted (maximum of 3 injections per attack at least 6 hours apart). The OLE was later further modified to enroll patients who met original study criteria but who had not participated in the double-blind phase or who did not have an attack sufficiently severe to qualify during the double-blind phase.

The prespecified primary efficacy endpoint was the median time to onset of symptom relief as measured by the single-symptom VAS. The results for FAST-1 and FAST 2 are shown below in Table 3.

**Table 3 Median time to onset of symptom relief (hours) based on the primary single symptom VAS**

| | Icatibant 30mg SC | | Tranexamic acid | | Placebo | | P value |
|---|---|---|---|---|---|---|---|
| | N† | Time (h) | N† | Time (h) | N† | Time (h) | |
| **Study 2102 (FAST-2)** | | | | | | | |
| All attacks | 36 | 2.0 | 38 | 12.0 | | | <0.001 |
| *Cutaneous* | 24 | 2.5 | 23 | 18.2 | | | <0.001 |
| *Abdominal* | 12 | 1.6 | 15 | 3.5 | | | 0.026 |
| **Study 2103 (FAST-1)** | | | | | | | |
| All attacks | 27 | 2.5 | | | 29 | 4.6 | 0.142 |
| *Cutaneous* | 14 | 3.4 | | | 13 | 10.0 | 0.221 |
| *Abdominal* | 13 | 2.0 | | | 16 | 6.0 | 0.159 |
| **FAST-3*** | | | | | | | |
| All attacks | 43 | 1.5 | | | 45 | 18.5 | <0.001 |
| *Cutaneous* | 26 | 2.0 | | | 26 | 22.5 | <0.001 |
| *Abdominal* | 17 | 1.0 | | | 19 | 3.6 | 0.002 |

† Patients who did not achieve symptom relief within the observation period were censored at the last observation time.

* Designated as key secondary endpoint in FAST-3 and shown for comparison. The FAST-3 primary endpoint was the median time to onset of symptom relief based on the 3-symptom VAS.

Although numerically supportive, FAST-1 did not show a statistically significant benefit for icatibant over placebo (2.5 vs. 4.6 hours, respectively; p=0.142). Jerini has reasoned that the failure to show a statistically significant difference can be attributed in part to the number of patients in FAST-1 compared to FAST-2 who presented with abdominal pain as the primary symptom assessed by the VAS. The Applicant states that abdominal pain symptoms are more likely to respond to placebo treatments; hence a robust placebo effect in this study minimized the treatment difference. Review of cutaneous pain VAS scores do not show a placebo effect of the same magnitude, but the assertion of a more robust placebo effect for abdominal symptoms is somewhat difficult to verify. At the very least, this explanation indicates a potential shortcoming of the VAS-based primary efficacy endpoint.

Secondary endpoints in FAST-1 showed variable support for efficacy. Of particular concern was the durability of response, defined as the onset of symptom relief for the primary symptom within 8 hours after treatment that lasted for at least 24 hours. There appeared to be no differences between icatibant and placebo. In the icatibant group, 52% reported a durable response, similar to the 50% in the placebo group (p=1.0). When examining attacks by anatomic sites, the results for abdominal attacks were unfavorable. For abdominal attacks, 46% of icatibant patients reported a durable response compared to

60% of placebo patients (p=0.705). For cutaneous attacks, 57% of icatibant patients compared to 39% of placebo patients reported a durable response (p=0.449). Other secondary endpoints were generally more supportive. For example, icatibant patients reported a time to start of improvement of 0.8 hours, compared to 16.9 hours for placebo patients (p<0.001; based on patients' self-reported, non-VAS, regression of symptoms). In terms of rescue medications, 22% of patients in the icatibant group (n=6) received rescue medication on the day of study drug administration compared to 52% (n=15) of placebo patients.

In contrast, FAST-2 met the prespecified primary efficacy endpoint, the time to onset of relief as assessed by the single-symptom VAS. Patients in the icatibant arm reported a median time of 2.5 hours compared to 12.0 hours for the active control, tranexamic acid (p<0.001). Although the treatment difference was not as robust for the subset of patients with abdominal attacks, statistically significant differences were observed for both cutaneous and abdominal attacks. Secondary endpoints were also supportive of icatibant compared to tranexamic acid. Icatibant patients self-reported a median time to start of improvement of 1.7 hours, compared to 8.0 hours for tranexamic acid patients (p<0.001; based on patients' self-reported, non-VAS, regression of symptoms). In the icatibant group, 69% (n=24) reported a durable response, compared to 39% (n=14) in the tranexamic acid group (p=0.017), although minimal difference was observed for the subset of patients with abdominal pain attacks (75% vs. 69%, respectively; p=1.0). In terms of rescue medication use, no patients in the icatibant group required rescue treatment during the first 12 hours after administration of study drug, compared to 5 patients in the tranexamic acid group.

However, as discussed above, the efficacy of tranexamic acid for the treatment of acute HAE attacks is not established. Jerini has argued that use of tranexamic acid is likely to be no worse than placebo, even if the benefit of tranexamic acid is uncertain. This assertion is not supported by cross-study comparison, which shows that icatibant performed similarly in both Phase 3 trials (median time to onset of symptom relief of 2-2.5 hours), but the comparator groups performed differently. Tranexamic acid had a much longer time to onset of symptom relief (12.0 hrs) compared to placebo (4.6 hrs). Although cross-study comparison has limitations, this difference in the comparators' performance makes it difficult to rely on the results of FAST-2 without confirmatory support from other well-controlled trials.

In the absence of a conclusive trial in the original clinical program, the Agency requested that Jerini conduct at least one additional well-controlled trial to confirm efficacy findings. In response, Jerini initially provided a post-hoc analysis of FAST-1 and FAST-2 data using the modified composite VAS (VAS-3) endpoint, which shows statistically significant findings for both FAST-1 and FAST-2 (Table 4). While these data provided some support for efficacy, the Agency declined to accept the post-hoc analysis as the basis for approval. The Agency advised Jerini to conduct another placebo-controlled study with a comparable sample size to confirm efficacy findings. Also, given that icatibant was administered by healthcare professionals in both FAST-1 and FAST-2, the

Agency requested that Jerini provide data to support the proposed self-administration of icatibant by patients.

- ***Complete Response: FAST-3***

FAST-3 (n=98) was the third trial conducted in response to the clinical deficiency identified in the review of the original submission. Like FAST-1, FAST-3 utilized a placebo control. However, in contrast to the preceding trials, FAST-3 assessed a new primary endpoint based on a 3-symptom composite VAS (VAS-3) that is described in the preceding section. The primary endpoint was the time to onset of symptom relief for the first cutaneous and/or abdominal attack as defined by a 50% reduction in the composite endpoint. The key secondary endpoint was the time to onset of symptom relief as defined by a 50% reduction for the primary single-symptom VAS score as assessed in FAST-1 and FAST-2. FAST-3 also assessed mild-moderate laryngeal attacks in a double-blind fashion with a 5-symptom composite VAS, but the laryngeal assessments were not included in the primary endpoint analysis. Severe laryngeal attacks were treated in an open-label fashion as in FAST-1 and FAST-2. After the first attack, patients were eligible to continue to receive open-label icatibant for subsequent attacks.

As shown in Table 4, a statistically significant different was shown between the icatibant and placebo groups for the median time to onset of symptom relief based on the new 3-symptom composite VAS in FAST-3 (2.0 versus 19.8 hours; $p<0.001$). As in FAST-2, the treatment difference for abdominal attacks was smaller compared to cutaneous attacks, but statistically significant results were observed for both anatomic sites. Similar results were observed in the key secondary endpoint analysis based on the single-symptom VAS shown in Table 3 (1.5 versus 18.5 hours; $p<0.001$). The single-symptom VAS was the basis for the prespecified primary endpoint in FAST-1 and FAST-2.

**Table 4 Median time to onset of symptom relief (hours) based on 3-symptom composite VAS (VAS-3)**

| | Icatibant 30mg SC | | Tranexamic acid | | Placebo | | P value |
|---|---|---|---|---|---|---|---|
| | N† | Time (h) | N† | Time (h) | N† | Time (h) | |
| **Study 2102 (FAST-2)*** | | | | | | | |
| All attacks | 35 | 2.0 | 38 | 12.0 | | | <0.001 |
| *Cutaneous* | 22 | 3.5 | 20 | 22.3 | | | <0.001 |
| *Abdominal* | 11 | 1.6 | 14 | 2.3 | | | 0.216 |
| **Study 2103 (FAST-1)*** | | | | | | | |
| All attacks | 26 | 2.3 | | | 27 | 7.9 | 0.014 |
| *Cutaneous* | 13 | 5.1 | | | 12 | 23.0 | 0.047 |
| *Abdominal* | 13 | 2.0 | | | 15 | 6.0 | 0.103 |
| **FAST-3** | | | | | | | |
| All attacks | 43 | 2.0 | | | 45 | 19.8 | <0.001 |
| *Cutaneous* | 26 | 2.0 | | | 26 | 23.9 | 0.001 |
| *Abdominal* | 17 | 1.5 | | | 19 | 4.0 | 0.003 |

† Patients who did not achieve symptom relief within the observation period were censored at the last observation time.

* Post-hoc analyses shown for comparison. The FAST-1 and FAST-2 primary endpoint was the median time to onset of symptom relief based on the single symptom VAS as shown in Table 2. Patient numbers vary slightly from the original pre-specified primary endpoint results shown in Table 3 due to reassignment of a patient from each trial as a laryngeal attack patient.

The treatment difference was nearly 18 hours ($p<0.001$), which markedly exceeded the treatment differences observed in FAST-2 versus tranexamic acid (10 hours, $p<0.001$ by post-hoc analysis) and in FAST-1 versus placebo (6 hours, $p=0.014$ by post-hoc analysis). In all three trials, it appears that icatibant performed similarly, with a median onset of symptom relief of approximately 2 hours. Much greater variability was observed in the comparator groups. The source for this variable comparator/placebo response is uncertain, but it appears that the anatomic site of attack at baseline may be a factor. Across the three pivotal trials, cutaneous attacks appeared to resolve much more slowly than abdominal attacks. In turn, the proportion of patients presenting with cutaneous versus abdominal attacks correlated with the magnitude of the treatment difference observed. In other words, FAST-2 and FAST-3 had a greater proportion of patients in the comparator arm present with a cutaneous attack (58% and 53%, respectively), compared to FAST-1 (44%). Jerini has hypothesized that greater placebo effects are observed with pain symptoms like abdominal pain versus other symptoms such as cutaneous swelling. Alternatively, the natural course of abdominal attacks may differ from the course of cutaneous attacks. A similar pattern is observed in the analysis based on the single symptom VAS endpoint prespecified as shown in Table 3. While the inconsistent performance of the comparator arms remains unexplained, the consistent performance of icatibant in all 3 trials supports icatibant's efficacy for the proposed indication, with a more prominent treatment benefit observed for cutaneous attacks.

Secondary endpoints in FAST-3 were also generally supportive of icatibant's efficacy. Based on non-VAS assessments, patient self-reported time of initial improvement was 0.8 hours versus 3.5 hours in the icatibant and placebo groups, respectively ($p<0.001$). The majority of patients in the icatibant group (35 of 43, 81%) also reported a durable response compared to 38% (16 of 45) in placebo. Durability of response was demonstrated for both cutaneous (77%) and abdominal (88%) attacks treated with icatibant. These data help to counter the inconsistent responses observed in FAST-1 and confirm the durability of response findings of FAST-2. In terms of rescue medication use, three of 43 (7%) patients in the icatibant group used rescue medication (up to 120 hours post-treatment) compared to 18 of 45 (40%) patients in the placebo group. Sensitivity analysis which censored all patients who required rescue medications showed similar results as the primary analysis for the median time to onset of symptom relief.

- ***Laryngeal attacks***

In both FAST-1 and FAST-2, the data to support icatibant's efficacy in laryngeal attacks was limited by the small number of subjects and the open-label nature of the assessments (all laryngeal attack patients received icatibant). In FAST-1, 8 patients were treated with open-label icatibant during the controlled phase, and the median time to regression of symptoms as reported by the patients was 0.6 hours. In FAST-2, 3 patients presented with laryngeal attacks during the controlled phase of the study. In this study, 2 of the 3 patients self-reported a regression of symptoms by 0.3 and 1 hour post-icatibant. The third patient was intubated and unable to complete symptoms scoring during the acute attack, but was successfully extubated 8 hours later and reported regression of symptoms

24 hours after icatibant administration. Time to onset of symptom relief as assessed by the VAS was not reported in either trial.

In FAST-3, all 10 patients presenting with laryngeal attacks were treated with icatibant during the double-blind treatment portion of the trial. The two patients who were originally randomized to placebo developed symptoms that were considered severe enough by the investigators to warrant treatment with open-label icatibant. As a result, there is no true placebo group for comparison. However, the median time to onset of symptom relief using the 5-symptom laryngeal VAS composite scoring was 2.5 hours, which is comparable to the reported onset of symptom relief for attacks at other anatomical sites.

Overall, a total of 60 patients experienced a laryngeal attack during the conduct of FAST-1, FAST-2, and FAST-3 and the corresponding open-label extension trials. Patients' self-reported time to initial symptom improvement was consistent across the 3 trials, ranging from 0.6 to 0.8 hours. Additional assessments based on the VAS collected in FAST-3 showed that efficacy for laryngeal and non-laryngeal attacks was similar.

In summary, despite the small sample size and the lack of a placebo control for comparison, the results generally support the efficacy of icatibant for the treatment of laryngeal HAE attacks.

- ***Efficacy with repeat use***

The double-blind portion of each of the three pivotal trials assessed efficacy for a single HAE attack; subsequent attacks were treated in the open-label extension phase. In the pivotal Phase 3 trials, a total of 225 patients were treated for a total of 987 attacks with 1076 doses of icatibant. The mean number of icatibant-treated HAE attacks for all patients in the Phase 3 trials was 3.7 attacks (range 0 to 142 attacks). For the first 5 attacks experienced by the 225 icatibant-treated patients, a single injection was used to treat 546 attacks, a second injection was administered in 33 attacks, and a third injection was given in only 3 attacks. Similar changes in VAS and VAS-3 were reported for subsequent multiple attacks, suggesting that icatibant remains effective with intermittent, repeat use.

- ***Efficacy findings for population subgroups***

As mentioned previously, systemic exposure varied by age and gender, raising concern that the differential exposure may impact efficacy. In terms of gender, males tended to have a numerically slower onset to symptom relief compared to females. However, the slowed response was most prominent for males allocated to placebo or tranexamic acid, while male patients who received icatibant had similar results as their female counterparts (2.5 and 2.0 hours, respectively, in the pooled Phase 3 analysis). There was no apparent correlation between gender and the baseline severity of attack, and the anatomic sites of attack were fairly equally distributed among males and females. The cause for the observed gender differences in the comparator arms is uncertain, but the pattern of results suggests that icatibant was efficacious in both males and females. Likewise, pooled

analysis of patients treated with icatibant across different age brackets did not show any clear correlation with age. Furthermore, nearly 90% of all HAE attacks in the Phase 3 program were treated with a single 30 mg injection and did not require an additional icatibant injection as was permitted by the study protocols. Of the minority of patients who received a second and/or third icatibant injection, there was no predominant gender or age bracket. While the small size of the clinical trials limits such subgroup analyses, the results are reassuring and provide support for the proposed 30 mg dose without adjustment for gender or age.

## Safety

The safety database for icatibant includes a total of 236 unique HAE patients who received at least one dose of 30 mg icatibant SC in the Phase 2 and Phase 3 program. The safety review focuses on the 225 patients who participated in the three controlled Phase 3 trials, with additional information obtained from the open-label extensions which included patients rolled over from the controlled portion and new patients enrolled after completion of the double-blind portion. As stated above, 225 patients were treated for a total of 987 attacks with 1076 doses of icatibant, with the majority of attacks treated with a single injection.

### Safety findings

Safety was assessed in the clinical trials with reports of adverse events, laboratory values, vital signs, and physical exams. No deaths were reported in patients treated with icatibant. A total of 27 icatibant-treated patients were reported to have a serious adverse event (SAE).[7] The SAEs covered a range of conditions, and causality cannot be refuted or confirmed. A total of 4 icatibant-treated patients discontinued due to an AE. The AEs cited for discontinuation included pregnancy (n=2), vomiting (n=1), and coronary artery disease (n=1).

The safety data shows that the most common adverse reactions were local injection site reactions. Local injection site reactions occurred in nearly all patients who received icatibant by subcutaneous injection, characterized predominantly by erythema and local swelling. These reactions appeared self-limited and generally resolved within a few hours of treatment. More serious adverse events were not associated with these reactions. These reactions appear to be irritant in nature rather than mediated by a specific immune response. The second most common AE was HAE attack (worsening of HAE symptoms). HAE was to be reported as an AE only in the event of a new attack during treatment or significant worsening of an attack during treatment; however, these distinctions are difficult to make clinically during an acute attack. The reporting of HAE attacks as an AE is difficult to interpret, but is more likely a reflection of limited efficacy

[7] Serious Adverse Drug Experience is defined in 21 CFR 312.32 as any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience (defined in the same regulation as any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

and the fluctuating course of the underlying condition rather than a treatment-related exacerbation of symptoms.

Nonclinical studies in dogs and rabbits have raised concerns of reproductive toxicities. While the clinical safety database has not confirmed these toxicities in humans, the limitations of a small database based on intermittent use make it impossible to exclude this as a risk of the drug. Of eight medically confirmed cases of icatibant exposure during pregnancy to date, three resulted in full-term healthy infants and two were electively aborted. No follow-up information is available for the remaining three cases. Other reproductive adverse events were not reported in the HAE program. As mentioned previously in the summary of nonclinincal information, a clinical trial to evaluate icatibant's effects on reproductive hormones is currently ongoing, which may provide additional insight into this potential risk.

An earlier clinical pharmacology trial showed several examples of transient ST/T wave changes and/or QT prolongation in healthy patients receiving 5 doses of icatibant 30 mg SC on 3 separate days. However, a subsequent formal QT prolongation trial with moxifloxacin as a positive control does not appear to show evidence of clinically relevant prolongation of the QT interval at icatibant doses up to 90 mg SC upon preliminary review.

Other safety assessments included laboratory, vital signs, and immunogenicity testing, the results of which do not suggest a safety signal with icatibant 30mg. As a decapeptide, icatibant is not anticipated to be particularly immunogenic. In vitro antibody testing and the adverse event profile to date support this assertion.

**Self-administration**

JE049-3101B (EASSI) was an open-label, multicenter trial to evaluation the efficacy and safety of patient self-administration of icatibant in acute HAE attacks in 56 patients 18 years of age and older. All patients were trained in the method of self-administration at enrollment. Patients who had previously received icatibant (n=48) were given 1 pre-filled syringe for self-treatment. Icatibant-naïve patients (n=8) were to present to a clinical site for the treatment of the first attack before a single dose of icatibant for self-treatment was dispensed. The main objective was the clinical safety of self-treatment, assessed through the reporting of adverse events (AEs) and grading of local injection site reactions. In addition, patients recorded VAS scores for skin swelling, skin pain, and abdominal pain pre-dose and at interval times up to 48 hours post-dose. Other assessments included a physician Global Assessment at 48 hours after self-treatment and a patient questionnaire to evaluate satisfaction with self-administration.

Overall, the results of EASSI support the self-administration of icatibant. The majority of patients reported ease and a preference for self-administration. The frequency and nature of the reported adverse events, including local injection site reactions, were similar to those observed for the injections administered by a healthcare professional. In terms of efficacy, the median time to onset of symptom relief based on the VAS-3 was 2.6 hours; for the single-symptom VAS, the median time was 2.0 hours. These times are

consistent with the times observed in the pivotal efficacy trials and do not indicate any diminished efficacy with self-administration.

**Benefit-risk assessment**

Statistically significant evidence of efficacy has been demonstrated in one active-controlled trial (FAST-2) and one placebo-controlled trial (FAST-3) for icatibant in the treatment of acute HAE attacks. Results from an additional placebo-controlled trial (FAST-1) were not statistically significant, and the secondary efficacy results from this trial were variable. While the overall results from the clinical program appear supportive of efficacy, the clinical meaning of the treatment differences observed remains somewhat unclear. The VAS-based efficacy endpoint is not completely intuitive, and given the subjective nature of the patient-reported symptom scoring, the adequacy of blinding is also an issue. In the absence of a gold standard, the validity of the VAS instrument in HAE and the clinical meaning of the efficacy results are topics for discussion. In terms of safety, local injection site reactions appear to be the most common adverse event attributable to icatibant. Patient self-administration of icatibant does not appear to pose any additional safety concerns. No other major safety concerns have been identified, but this statement is made with the caveat that the overall safety database was small and based on relatively limited, intermittent use of icatibant.

**Summary**

The purpose of the PADAC meeting is to discuss the adequacy of the efficacy and safety data submitted by Jerini to support the approval of icatibant 30 mg subcutaneous injection for the treatment of acute attacks of hereditary angioedema (HAE). Icatibant is a new molecular entity, and there are limited therapeutic options currently available for the treatment of acute HAE attacks. The major issues for discussion are whether the totality of the data support: 1) the efficacy of icatibant; 2) the safety of icatibant; 3) approval for the proposed indication; and 4) the appropriateness of patient self-administration.

At the PADAC meeting, Jerini will present an overview of the clinical program, which will be followed by the Agency's presentation of the efficacy and safety data. Please keep in mind the following questions that will be posed to the committee following the presentations and discussion.

**Draft Questions to the Committee**

1. Does the data provide substantial and convincing evidence of a clinically meaningful benefit for icatibant in the treatment of acute attacks of hereditary angioedema? **(Voting Question)**
    - *If not, what further data should be obtained?*

2. Has the safety of icatibant been adequately assessed for the treatment of acute attacks of hereditary angioedema? **(Voting Question)**
    - *If not, what further data should be obtained?*

3. Do the efficacy and safety data provide substantial evidence to support approval of icatibant for the treatment of acute attacks of hereditary angioedema in patients 18 years of age and older? **(Voting Question)**
    - *If not, what further data should be obtained?*

4. Does the committee have recommendations regarding the following:
    - Patient self-administration
    - Other

# II. Clinical Briefing Document

# Pulmonary-Allergy Drugs Advisory Committee Meeting

**June 23, 2011**

# Clinical Briefing Document

Complete Response: NDA 22-150

Firazyr (icatibant) 30 mg SC for the treatment of acute attacks of hereditary angioedema

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# 1 Executive Summary

## 1.1 Brief Overview of Clinical Program

Shire Human Genetic Therapies (Shire HGT) for Jerini US, Inc. has submitted a Complete Response to a Not Approvable action letter issued on April 23, 2008, for New Drug Application (NDA) 22-150 for icatibant (Firazyr) injectable solution in pre-filled syringe for the treatment of acute attacks of hereditary angioedema (HAE) in adults. HAE is a rare, autosomal dominant, inheritable disease caused by a quantitative or qualitative functional deficiency in C1 esterase inhibitor (C1-INH), which leads to dysregulated accumulation of the potent vasodilator bradykinin. This results in recurrent, intermittent attacks of potentially life-threatening mucosal edema at various bodily sites, most commonly the skin, abdomen, and upper respiratory tract. In addition to causing physical disfigurement and severe pain, acute HAE attacks may compromise the upper airway and cause significant hypotension, both of which can be fatal. Two products are currently approved and marketed in the U.S. for the prophylaxis of HAE attacks: Cinryze (a recombinant C1 esterase inhibitor) and danazol (a synthetic androgenic steroid). There are also only two products currently approved and marketed to treat acute HAE attacks: Berinert (a human C1-INH replacement product administered intravenously) and Kalbitor (ecallantide: a plasma kallikrein inhibitor injected subcutaneously). Both Berinert and ecallantide have been associated with potentially severe hypersensitivity reactions, including anaphylaxis.

Icatibant is a new molecular entity and is the first drug in its class. Unlike the other agents approved for the treatment of acute HAE attacks, icatibant has been developed specifically to target the receptor-ligand interactions of the bradykinin receptor pathway, as a treatment for acute HAE attacks in adults. Icatibant is a decapeptide antagonist of the bradykinin type 2 receptor that is designed for subcutaneous administration from a pre-filled syringe, which contains 30 mg of icatibant acetate in a 3 mL solution. In addition to the active ingredient, the sterile, preservative-free acetate buffer solution also contains 7.45 mg sodium chloride, 1.32 mg acetic acid, 0.64 mg sodium hydroxide/ml, and water for injection adjusted to pH 5.5 ±0.3. The proposed dose of icatibant is 30 mg delivered by subcutaneous (SC) injection, with repeat 30 mg doses as needed up to every six hours, not to exceed three doses (90 mg total) within a 24-hour period.

Icatibant dose-selection was based on several Phase 1 clinical pharmacology studies in healthy adults, a Phase 2 proof-of-concept pharmacokinetic trial in HAE patients that included IV and SC dose-ranging, data generated from a human IV bradykinin challenge model, and additional pharmacokinetic and pharmacodynamic modeling. An integrated analysis of these data (JE049-5108) was submitted in the Complete

Response, in which the Applicant states that the 30 mg SC dose of icatibant carried forward into the three pivotal Phase 3 efficacy trials is safe and effective for the proposed indication and, therefore, no further dose definition is necessary. The Applicant also describes findings from an additional pharmacokinetic trial of repeat SC icatibant dosing in healthy adults (HGT-FIR-065) that was conducted since the original NDA was denied approval, which the Applicant feels further supports the selected dose.

The safety and efficacy assessments of icatibant are based primarily on results generated from three pivotal Phase 3 safety and efficacy trials: FAST-1, FAST-2, and FAST-3. Each of these trials was a randomized, controlled, double-blind, prospective, parallel-group trial in adult Type I or Type II HAE patients ≥ 18 years of age. Upon presentation of their first on-study moderate to severe cutaneous or abdominal HAE attack, subjects were randomized 1:1 to receive either a single dose of icatibant 30 mg SC versus matched placebo (buffered solution without active drug) in FAST-1 and FAST-3 or tranexamic acid (1000 mg of an oral tablet formulation every 6-8 hours for up to six doses over two days) in FAST-2, in double-blind, double-dummy (for FAST-2) fashion. In contrast to FAST-1 and FAST-2, subjects in FAST-3 with mild to moderate laryngeal HAE attacks were similarly randomized to blinded treatment with icatibant 30 mg SC versus placebo, whereas all other laryngeal HAE attacks across all three trials were treated with open-label icatibant 30 mg SC at the same dose. Each trial was followed by an open-label extension phase, which subjects automatically entered following blinded study treatment for their initial qualifying HAE attack. During the extension phases, subjects received open-label icatibant 30 mg SC for all subsequent HAE attacks of sufficient severity to warrant treatment and could potentially be re-dosed up to two more times for persistent HAE symptoms, for a maximum of three injections over a 24-hour period, with at least six hours between doses.

These Phase 3 trials all utilized a novel patient-reported outcome (PRO) measure, the Visual Analog Scale (VAS), to quantify self-reported patient-assessed symptomatology. Validation studies of this outcome measure were submitted to the Division following issuance of the Not Approvable action letter. FAST-1 and FAST-2 both designated time to onset of primary symptom relief based on VAS assessments as the primary efficacy endpoint. In contrast, FAST-3 designated the primary efficacy endpoint as time to onset of symptom relief based on a composite VAS-based symptom score encompassing both cutaneous and abdominal HAE symptoms (VAS-3: abdominal pain, skin pain, skin swelling). However, the same endpoint designated as the primary efficacy endpoint in FAST-1 and FAST-2 was retained as the key secondary efficacy endpoint in FAST-3.

Safety and tolerability of icatibant were assessed in these trials through reports of AEs/SAEs, clinical laboratory tests (including immunogenicity), physical examination, vital signs assessments, and 12-lead ECG testing. The clinical program did not include a placebo-controlled evaluation of repeat icatibant dosing, although the open-label extension phases of each of the pivotal Phase 3 efficacy trials allowed for long-term

follow-up of subjects repeatedly exposed to intermittent icatibant dosing for recurrent HAE attacks.

Icatibant has been developed for SC injection from a pre-filled syringe containing a single 30 mg dose, which the Applicant also proposes for self-administration by patients during acute HAE attacks. Thus, the Applicant also conducted an additional open-label, uncontrolled Phase 3 trial, FAST-4, which specifically evaluated the safety and efficacy of icatibant self-administration by non-healthcare workers in nonclinical settings. Both FAST-3 and FAST-4 were conducted in response to deficiencies cited in the Not Approvable action letter that was issued following review of the original icatibant NDA submission.

## 1.2 Summary of Efficacy

The Applicant has presented results from three randomized, controlled, double-blind Phase 3 efficacy trials (FAST-1, FAST-2, and FAST-3, as described in Section 1.1 Brief Overview of Clinical Program) to support the proposed indication of icatibant for the treatment of acute HAE attacks in adults. The primary efficacy analysis in these trials was based on subjects with an initial moderate to severe cutaneous or abdominal HAE attack who were randomized to icatibant (FAST-1: 27 icatibant-recipients; FAST-2: 36 icatibant-recipients; FAST-3: 43 icatibant-recipients) versus placebo in FAST-1 (29 control subjects) and FAST-3 (45 control subjects) or tranexamic acid in FAST-2 (38 control subjects). Secondary efficacy data were generated from subjects treated with open-label icatibant for both initial laryngeal HAE attacks and recurrent HAE attacks occurring during the extension phases of each trial. The Applicant also submitted data from an additional Phase 3 trial, FAST-4, which specifically evaluated the safety and efficacy of icatibant self-administration by non-healthcare workers in nonclinical settings for urgent treatment of acute HAE attacks.

The primary efficacy analyses in these pivotal Phase 3 trials were based on time to onset of symptom relief, as determined by subject-assessed VAS symptom ratings. The VAS is a 100 mm linear scale anchored by the extreme values of 0 mm = no symptom and 100 mm = worst possible symptom, which subjects used to rate the intensity of each HAE symptom at baseline and at predetermined post-dosing time points. The primary efficacy endpoint for FAST-1 and FAST-2 was designated as time to onset of primary symptom relief, defined graphically as a response to the right and below a line determined by the function $Y = 6/7X - 16$ mm, where $X \geq 30$ mm, X = pre-treatment VAS in mm, and Y = post-treatment VAS in mm. In contrast, although this endpoint was prespecified in FAST-3 as the key secondary efficacy endpoint, the primary efficacy endpoint in FAST-3 was time to symptom relief onset based on a 50% reduction from baseline in VAS-3, the mean score of abdominal pain, skin pain, and skin swelling. This composite score was developed in response to the Division's recommendations to explore icatibant efficacy using composite symptom measures, in

addition to the primary VAS symptom score, as discussed at an End of Review Meeting on December 15, 2008, following issuance of the Not Approvable action letter. The 50% reduction threshold was considered by the Applicant to be clinically significant and more appropriate for a composite symptom score than the graphically defined threshold level for primary VAS symptom score, based on feedback from study investigators, as well as a receiver-operator curve and comparative validation analysis of VAS-3 against the Visual Descriptor Scale (a 5-point rating scale used as a comparative standard to the VAS in evaluating symptom change over time). Thus, time to onset of symptom relief based on VAS-3 was calculated as a *post hoc* analysis for FAST-1 and FAST-2 for this Complete Response submission.

Collectively, the findings from the Phase 3 clinical program support the efficacy of icatibant for the proposed indication, as shown in Table 1. However, the results were not consistent across the three trials, with FAST-1 failing to demonstrate a statistically significant difference favoring icatibant in the primary efficacy endpoint of time to onset of primary symptom relief. Moreover, as FAST-2 utilized tranexamic acid as a control treatment, which is unapproved for the treatment of acute HAE attacks in the U.S., the clinical significance of the shorter time to primary symptom relief onset observed in icatibant-recipients (2.0 hrs) versus control subjects (12.0 hrs) in this trial was unclear. As the effects of tranexamic acid on acute HAE manifestations are not fully characterized, the positive treatment effect of icatibant observed in FAST-2 may have been inflated by a potentially negative therapeutic effect of tranexamic acid on HAE symptomatology. Thus, upon review of the original NDA, data from FAST-1 and FAST-2 were considered by the Division to be insufficient to establish the efficacy of icatibant for the proposed indication. However, data from FAST-3 submitted in this Complete Response, demonstrated a statistically significant decrease in time to primary symptom relief onset (prespecified as the key secondary efficacy endpoint in FAST-3) in icatibant (1.5 hrs) versus placebo-recipients (18.5 hrs). In addition, time to symptom relief onset based on VAS-3 (the primary efficacy endpoint) was also significantly decreased in icatibant (2.0 hrs) versus placebo-recipients (19.8 hrs) in FAST-3. *Post hoc* efficacy analyses of time to symptom relief onset based on VAS-3 for FAST-1 and FAST-2 (with slightly decreased sample sizes, due to the exclusion of one icatibant-recipient from each trial, due to the emergence of post-randomization laryngeal HAE symptoms) revealed statistically significant differences in favor of icatibant treatment for both trials.

**Table 1: Median time to onset of symptom relief based on primary and composite VAS symptom scores in pivotal Phase 3 efficacy trials**

| **Clinical Trial** | **FAST-1** | | **FAST-2** | | **FAST-3** | |
|---|---|---|---|---|---|---|
| **Treatment Group** | **Icatibant** | **Placebo** | **Icatibant** | **Tranexamic Acid** | **Icatibant** | **Placebo** |
| **All non-laryngeal HAE attacks (n)** | 27 | 29 | 36 | 38 | 43 | 45 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Primary: Time to symptom relief onset (hrs)** | 2.5 | 4.6 | 2.0** | 12.0 | 1.5** | 18.5 |
| ***VAS-3: Time to symptom relief onset (hrs)** | 2.3*** | 7.9 | 2.0** | 12.0 | 2.0** | 19.8 |

**Sample sizes of icatibant-recipients are decreased to 26 for FAST-1 and 35 for FAST-2 in these post hoc analyses, due to exclusion of one subject from each trial for the emergence of laryngeal symptoms post-randomization; **p < 0.001 versus control; *** p = 0.014 versus control*
*Source: Clinical Study Report for FAST-1, Table 22; Clinical Study Report for FAST-2, Table 22; Clinical Study Report for FAST-3, Table 7-8, Table 7-9; Integrated Summary of Efficacy, Table 3-17*

To assess the efficacy of intermittent icatibant dosing over time for repeated HAE attacks, efficacy analyses were compiled for the entire study population exposed to icatibant treatment for any qualifying HAE attack either during the blinded treatment or open-label extension phases (N = 225). Efficacy data summarized for the first five sequential icatibant-treated HAE attacks in this population did not suggest the development of tolerance, as median time to onset of primary and composite symptom relief remained similar across all five HAE attacks (range: 1.5-2.4 hrs). Moreover, although FAST-4 was not a placebo-controlled trial, efficacy results based on the self-administration of icatibant for acute HAE attacks were generally consistent with those from the three pivotal Phase 3 efficacy trials, with regard to time to onset of primary and composite symptom relief.

Stratified efficacy analyses based on HAE attack location indicated the largest treatment difference between icatibant and control arms was seen in cutaneous HAE attacks (FAST-1: icatibant = 3.4 hrs, placebo = 10.0 hrs, non-significant; FAST-2: icatibant = 2.5 hrs, tranexamic acid = 18.2 hrs, $p < 0.001$; FAST-3: icatibant = 2.0 hrs, placebo = 22.5 hrs, $p < 0.001$), although a statistically significant treatment effect in abdominal HAE attacks was observed in FAST-3 (FAST-1: icatibant = 2.0 hrs, placebo = 6.0 hrs, non-significant; FAST-2: icatibant = 1.6 hrs, tranexamic acid = 3.5 hrs, $p = 0.026$; FAST-3: icatibant = 1.0 hrs, placebo = 3.6 hrs, $p = 0.002$). As time to symptom relief onset in icatibant-recipients was similar in cutaneous and abdominal HAE attacks, these treatment differences largely resulted from differential placebo responses. The efficacy assessment of icatibant in laryngeal HAE attacks was complicated by the lack of control subjects with laryngeal HAE attacks in FAST-1 and FAST-2. Although subjects with mild to moderate laryngeal attacks were randomized to blinded treatment in FAST-3, this constituted only five subjects. Thus, efficacy data were also compiled for all subjects treated with blinded or open-label icatibant for an initial laryngeal HAE attack, demonstrating similar times to symptom relief onset based on primary symptom VAS (2.2 hrs) and composite VAS score (2.2 hrs), as well as progressive reductions in laryngeal symptomatology, which suggest a clinically significant treatment effect of icatibant in laryngeal HAE attacks.

## 1.3 Summary of Safety

The Applicant reports that across the icatibant clinical development program (Phase 2-3), a total of 999 HAE attacks in 236 HAE patients have been treated with icatibant 30 mg SC administered by healthcare workers. In addition, a single 30 mg SC dose of icatibant was self-administered in 56 subjects with HAE in FAST-4. In turn, safety analyses were reviewed from a pooled database of all subjects administered blinded study treatment for an initial qualifying HAE attack during the randomized treatment phases of the three pivotal Phase 3 efficacy trials (FAST-1, FAST-2, and FAST-3), including 113 icatibant-recipients, 38 tranexamic acid-recipients, and 75 placebo-recipients. Major safety findings (e.g., deaths, SAEs, AE-related discontinuations) were also reviewed for icatibant-recipients in the open-label extension phases of each trial, including 72 subjects from FAST-1 who were treated up to 32 times for a total of 340 recurrent HAE attacks, 54 subjects from FAST-2 who were treated up to 141 times for a total of 374 recurrent HAE attacks, and 96 subjects from FAST-3 who are currently enrolled in the ongoing extension phase of this trial. Approximately 90% of subjects across these trials were managed with only a single dose of icatibant 30 mg SC for each acute HAE attack. Thus, this safety database is less informative with regard to larger overall icatibant doses for a single HAE attack, as it is for recurrent, intermittent icatibant dosing for recurrent HAE attacks.

No deaths were noted in any icatibant-recipients in the overall clinical program, although several SAEs in icatibant-recipients were noted during the blinded treatment phase of FAST-2 and in the open-label extension phases of all three trials. Many of these were coded as HAE events (defined, per protocol, as worsening or recurrent HAE symptoms within 48 hours of initial study treatment), however, and are difficult to distinguish from the natural progression of HAE attacks. In addition, many of these SAEs were greatly separated in time from last icatibant dosing, making a causal relationship less likely. Overall, no pattern in SAEs emerged across the three trials, which appeared attributable to the effects of icatibant. The most common AEs noted in icatibant-recipients were HAE, which was reported equally in icatibant-recipients and control subjects, and local injection site reactions (erythema, swelling, pruritus, burning sensation, warm sensation), which occurred in some form in nearly all icatibant-recipients soon after injection. In general, however, these local reactions were self-limited and resolved without sequelae within 24 hours.

No other treatment-emergent AEs were clearly attributable to icatibant, as most of the AEs seen disproportionately in icatibant-recipients were noted in only 1-2 subjects (versus 0-1 control subjects). With regard to clinical laboratory tests, elevations in hepatic transaminases (AST and ALT) above the upper limit of normal (ULN = 35 U/L) were noted more frequently in icatibant-recipients versus control subjects, but the majority of these elevations were mild ($\leq$ 2.5 times ULN). Rare elevations of creatine kinase and uric acid were also noted, although these were typically preceded by

elevated pretreatment values and returned to baseline. Of note, no hypersensitivity reactions were observed following icatibant treatment, and only one incidence of post-treatment icatibant-specific antibodies was noted in a subject who also had anti-drug antibodies at baseline (pretreatment) of similar titer, suggesting this was a nonspecific background finding.

Safety data from FAST-4 were reviewed separately in this safety review, as they focus specifically on the safety and tolerability of self-administered icatibant by non-healthcare workers in nonclinical settings. Thus, assessment measures included not only safety endpoints, but also efficacy indices and measures of perceived convenience that support the use of self-administered icatibant in HAE patients. In general, the safety findings in FAST-4 were similar to those of the pivotal Phase 3 efficacy trials, and no additional safety signals related to icatibant self-administration were noted.

# 2 Introduction and Regulatory Background

## 2.1 Product Information

Icatibant (Firazyr) is a new molecular entity developed for the treatment of acute attacks of HAE in adults. HAE is a rare (prevalence of 1 in 10,000 to 1 in 50,000), inheritable, autosomal dominant disease characterized by recurrent episodes of angioedema of the skin and mucosal surfaces due to uncontrolled bradykinin-mediated vasodilation, which commonly involve the head and neck, bowel, and respiratory tract. Acute HAE attacks may be life-threatening, particularly if they involve upper airway edema and/or severe hypotension due to vasodilation. Icatibant is a decapeptide antagonist of the bradykinin type 2 receptor that is designed for subcutaneous administration from a pre-filled syringe, which contains 30 mg of icatibant acetate in a 3 mL solution. In addition to the active ingredient, the sterile, preservative-free acetate buffer solution also contains 7.45 mg sodium chloride, 1.32 mg acetic acid, 0.64 mg sodium hydroxide/ml, and water for injection adjusted to pH 5.5 ± 0.3. By directly inhibiting receptor-ligand interaction and antagonizing bradykinin receptor function, icatibant counters the predominant symptoms of acute HAE attacks that are mediated by dysregulated bradykinin accumulation, including bradykinin-mediated vasodilation, skin swelling, mucosal swelling, laryngeal edema, skin pain, abdominal pain, and hypotension. The proposed dose of icatibant is 30 mg delivered by subcutaneous (SC) injection, with repeat 30 mg doses as needed up to every six hours, not to exceed three doses (90 mg total) within a 24-hour period.

## 2.2 Table of Currently Available Treatments for Proposed Indications

As summarized in the follow table, there are currently two other approved products indicated for the treatment of acute attacks of HAE (Berinert, a human C1 esterase

inhibitor replacement product, and Kalbitor, a plasma kallikrein inhibitor), as well as two products approved for the prophylaxis of HAE attacks (Cinryze, a recombinant C1 esterase inhibitor, and danazol, a synthetic androgenic steroid). Not listed in this table are two additional androgenic steroids originally approved for HAE prophylaxis, stanozolol and oxymetholone, as these agents are no longer marketed in the U.S. Also not included in this table are epsilon aminocaproic acid and tranexamic acid, which are used as chronic treatments for HAE in some foreign countries but are not approved for this indication in the U.S. Fresh frozen plasma (FFP) has also been used off-label in the U.S. as acute treatment or short-term prophylaxis of HAE attacks, although its efficacy is controversial.

## Table 2: Alternative approved treatments currently available in the U.S. for the treatment of HAE

| Product | Trade Name | Mechanism | Approval Date | Indication and Age Group | Recommended Dose |
|---|---|---|---|---|---|
| **BLA 125-287** Human C1 esterase inhibitor | Berinert | Plasma-derived enzyme replacement product | 10/09/09 | Treatment of acute abdominal or facial attacks of HAE in adults and adolescents* | 20 U/kg IV |
| **BLA 125-277** Ecallantide | Kalbitor | Plasma kallikrein inhibitor | 12/01/09 | Treatment of acute attacks of HAE in patients ≥ 16 years | 30 mg SC (3 injections of 10 mg) with an additional 30 mg dose as needed within 24 hrs |
| **BLA 125-267** Recombinant human C1 esterase inhibitor | Cinryze | Recombinant enzyme replacement product | 10/10/08 | Routine prophylaxis against attacks of angioedema in adolescent and adult HAE patients** | 1000 U IV every 3-4 days |
| **NDA 017-557** Danazol | Danocrine | Androgenic steroid | 06/21/76 | HAE: Prevention of angioedema attacks of all types in males and females | Individualized: Start 200 mg 2-3 times/day, then decrease by ≤ 50% every ≥ 1-3 month (may increase by ≤ 200 mg if attack occurs) |

**Labeling states safety and efficacy in children 0 to 12 years of age have not been established; **Labeling states safety and effectiveness not established in neonates, infants, or children, with three subjects studied under the age of 18 years in single efficacy trial; IV = intravenous; SC = subcutaneous*

Of note, severe hypersensitivity reactions, including anaphylaxis, are listed in the Warnings and Precautions section of the Berinert Prescribing Information (PI), while the PI for Kalbitor contains a boxed warning for anaphylaxis, indicating Kalbitor should only be administered by a healthcare professional capable of managing anaphylaxis and

HAE. Similarly, severe hypersensitivity reactions, including anaphylaxis, are also listed in the Warnings and Precautions section of the Cinryze PI, which further indicates that epinephrine should be available for the immediate treatment of acute severe hypersensitivity reactions. Allergic reactions (urticaria, pruritus, nasal congestion) have also been reported for danazol, although a causal relationship to the drug has not been established. Of note, danazol carries a boxed warning emphasizing its contraindication in pregnancy, as well as reports of thromboembolic events, peliosis hepatis, benign hepatic adenomas, and benign intracranial hypertension.

## 2.3 Availability of Proposed Active Ingredient in the United States

Icatibant is a new molecular entity and is not approved in the U.S. for any indication. However, icatibant was approved for use in the European Union on July 11, 2008.

## 2.4 Important Safety Issues with Consideration to Related Drugs

There are no other members of this pharmacologic class (bradykinin type 2 receptor antagonist) currently approved in the U.S. or any other country for HAE treatment or any other indication. Although the risk of severe hypersensitivity reactions has been associated with other agents approved for the treatment of acute HAE attacks (Berinert and Kalbitor), these products are of a different pharmacologic class.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

Jerini US, Inc. originally submitted NDA 22-150 on October 22, 2007, to seek approval for icatibant for the treatment of HAE, later revising this indication to the treatment of acute attacks of HAE. As summarized in Table 3, the original NDA submission consisted of data from seven clinical trials: three Phase 1 trials evaluating safety, tolerability, pharmacokinetics, and QTc effects in healthy volunteers (JE049-1101, JE049-1102, JE049-1103), a single open-label proof-of-concept Phase 2 safety, tolerability, and pharmacokinetic trial in adult HAE patients (JE049-2101), an observational PRO validation study in adult HAE patients (JE049-4102) that characterized the minimum clinically significant difference in Visual Analog Scale (VAS), and two Phase 3 safety and efficacy trials: JE049-2103 (FAST-1), which compared the effectiveness of icatibant versus placebo in the treatment of acute HAE attacks, and JE049-2102 (FAST-2), which compared the effectiveness of icatibant versus a control agent with unclear activity in HAE (tranexamic acid, which is unapproved in the U.S. for the treatment of acute HAE attacks). In addition to the randomized blinded treatment of initial cutaneous and/or abdominal HAE attacks, FAST-1 and FAST-2 both allowed for open-label icatibant treatment of initial laryngeal HAE attacks, as well as recurrent HAE attacks of any type that occurred during an open-label extension period, into which all subjects from the blinded treatment phase were automatically enrolled (regardless of

initial treatment assignment). A smaller number of patients who met trial participation criteria but did not experience an initial HAE attack prior to the close of enrollment were also allowed to enter the extension phase and receive open-label icatibant as needed for any subsequent HAE attack. For completeness sake, Table 3 also lists in italics the third similarly designed pivotal Phase 3 efficacy trial (FAST-3), as well as a fourth Phase 3 trial (FAST-4) that evaluated icatibant self-administration, neither of which were included in the original NDA submission.

## Table 3: Clinical development program supporting original submission of NDA 22-150 for icatibant

| Trial | Phase | Subjects | Design | Treatment Arms | Duration | Relevance |
|---|---|---|---|---|---|---|
| JE049-1101 | I | Healthy subjects, (10) | R, PC, DB | Icatibant 0.4 mg/kg IV (0.25 hr infusion)<br>Icatibant 0.4 mg/kg IV (0.5 hr infusion)<br>Icatibant 8 mg/kg IV (1 hr infusion)<br>Placebo | Single dose on three occasions | Safety, tolerability, PK |
| JE049-1102 | I | Part I:<br>Healthy<br>(16)<br><br>Part II:<br>Healthy<br>(24) | Part I:<br>DB, PC, AD<br><br>Part II:<br>R, OL, XO | Part I:<br>Icatibant 0.05 mg/kg SC (40 mg/mL)<br>Icatibant 0.2 mg/kg SC (40 mg/mL)<br>Icatibant 0.2 and 0.4 mg/kg SC (20 mg/mL)<br><br>Part II:<br>Icatibant 0.4 mg/kg SC (10 or 20 mg/mL)<br>Icatibant 0.4 mg/kg IV | Part I:<br>Single ascending dose<br><br>Part II:<br>Single dose | Bioavailability of SC versus IV delivery |
| JE049-1103 | I | Healthy<br>(32) | DB, PC | Icatibant 30 mg SC<br>(3 doses every 6 hours on Day 1 and a single dose on Days 8 and 15) | 5 doses over 15 days | PK, safety (including QT effects) in young and elderly subjects |
| JE049-2101 | II | Adults with HAE,<br>18 to ≤65 yrs<br>(15) | OL, POC, RD | Icatibant 0.4 mg/kg IV (0.5 hr infusion)<br>Icatibant 0.4 mg/kg IV (2 hr infusion)<br>Icatibant 8 mg/kg IV (0.5 hr infusion)<br>Icatibant 30 mg SC<br>Icatibant 45 mg SC | Sequential dosing over 5 days | Efficacy, safety and tolerability, PK, PD |
| JE049-4102 | --- | Adults with HAE<br>(80) | Observa-tional | No intervention | PRO validation study | Correlation of VDS to VAS to establish the minimum clinically significant difference in VAS rating |

| | | | | | | |
|---|---|---|---|---|---|---|
| **JE049-2103 (FAST-1)** | **III** | **Adults with HAE (64, including 56 randomized & 8 open-label)** | **R, DB, PC *24-wk OL Ext (72)** | **Icatibant 30 mg SC Placebo** | **Single dose, with 14-day observation period** | **Efficacy versus placebo on time to onset of symptom relief (primary symptom VAS rating)** |
| **JE049-2102 (FAST-2)** | **III** | **Adults with HAE (77, including 74 randomized & 3 open-label)** | **R, DB, DD, AC *24-wk OL Ext (54)** | **Icatibant 30 mg SC Tranexamic acid 1000 mg PO every 6 to 8hr for 2 days (up to 6 doses)** | **Single dose, with 14-day observation period** | **Efficacy versus tranexamic acid on time to onset of symptom relief (primary symptom VAS rating)** |
| ***HGT-FIR-054 (FAST-3)** | ***III*** | ***Adults with HAE (98, including 88 randomized abdominal & cutaneous, 5 randomized laryngeal, & 5 open-label)*** | ***R, DB, PC *OL EXT (96)*** | ***Icatibant 30 mg SC Placebo*** | ***Single dose, with 14-day observation period (EXT ongoing)*** | ***Efficacy versus placebo on time to onset of symptom relief (composite symptom VAS rating)*** |
| ***JE049-3101 (FAST-4)** | ***III*** | ***Adults with HAE (150; 56 completed)*** | ***OL*** | ***Icatibant 30 mg SC*** | ***Single dose (2 days non-naïve and 2 days naïve)*** | ***Safety of self-administration of SC drug*** |

**Not included in the original NDA submission (submitted in the Complete Response)*
*R = randomized, PC = placebo-controlled, DB = double-blind, SC = subcutaneous, AD = ascending-dose, OL = open-label, XO = cross-over, IV = intravenous, POC = proof-of-concept, RD = repeat-dose, PRO = patient-reported outcome, VDS = verbal descriptor scale, VAS = visual analog scale, Ext = extension phase, DD = double-dummy*

Following a review of the trials included in the original NDA submission, the Division issued a Not Approvable action letter on April 23, 2008, which cited multiple CMC deficiencies, the lack of long-term nonclinical toxicity studies, incomplete characterization of age and gender effects on icatibant pharmacokinetics (as discussed in the Clinical Pharmacology Summary of this Advisory Committee (AC) Background Package), as well as the following clinical deficiencies in the icatibant development program:

1. The submitted data from your clinical program do not provide substantial evidence that icatibant is sufficiently safe and effective for the proposed indication of the treatment of acute attacks of hereditary angioedema (HAE). The uncertain efficacy of the comparator drug, tranexamic acid, in the treatment of acute attacks of HAE complicates interpretation of the results of Study JE049-2102 (FAST-2). Study JE049-2103 (FAST-1) failed to demonstrate a statistically significant treatment difference between placebo and icatibant. In addition, there are concerns regarding the validity of the primary endpoint used in both studies (time to onset of symptom relief using the Visual Analog Scale). Without

substantial evidence of the efficacy of the proposed dose of icatibant, we cannot evaluate if there is appropriate safety. Before icatibant may be approved, you must submit sufficient evidence of the efficacy of icatibant for the treatment of patients with acute attacks of HAE. This evidence must be generated by using a reliable instrument to assess efficacy and an appropriate control arm. You will need to demonstrate appropriate safety for the dose shown to be efficacious.

2. Firazyr injection is likely to be used in settings outside the usual healthcare delivery environment, such as self-injection by patients. Submit data to show that Firazyr can be safely used in such settings.

3. Dose-selection should be further defined in sufficient patients based on the clinical endpoint or other biomarkers that are validated to be related to the clinical endpoint.

On February 25, 2011, Shire HGT for Jerini US, Inc. submitted a Complete Response to this Not Approvable action letter. In addition to information submitted to address the nonclinical and CMC deficiencies, the Applicant submitted the following information to address each of the clinical deficiencies:

**Demonstration of Clinical Efficacy**

Only two pivotal Phase 3 efficacy trials were included in the original NDA submission, which produced inconsistent efficacy results that did not support drug approval. FAST-1 consisted of 56 patients randomized to icatibant (30 mg SC) versus placebo for an initial moderate to severe cutaneous or abdominal HAE attack, eight patients treated with open-label icatibant for an initial laryngeal HAE attack, and 42 subjects treated during the open-label extension phase with a total of 128 icatibant doses for a total of 109 HAE attacks. FAST-2 consisted of 74 patients similarly randomized to icatibant versus tranexamic acid (1000 mg taken orally every 6-8 hours up to 6 doses over 2 days) for an initial cutaneous or abdominal HAE attack, three patients treated with open-label icatibant for an initial laryngeal HAE attack, and 35 subjects treated during the open-label extension phase with a total of 131 icatibant doses for a total of 122 HAE attacks. A statistically significant difference was not observed in FAST-1 for the primary efficacy endpoint of time to onset of primary symptom relief, as determined by self-reported Visual Analogue Scale (VAS) ratings of the predominant symptom manifestation based on HAE attack location (e.g., skin, abdomen). In contrast, FAST-2 demonstrated a statistically significant decrease in time to onset of primary symptom relief in the icatibant arm versus the control tranexamic acid arm, which the Applicant felt supported the proposed indication. However, the Division questioned the validity of this interpretation, given that tranexamic acid is not approved in the U.S. to treat acute HAE attacks. Therefore, it was unclear whether tranexamic acid could potentially have lengthened time to symptom relief onset in the control arm, if it conferred a negative effect on HAE manifestations, thereby inflating any positive treatment effect seen with

icatibant. For these reasons, the original Phase 3 program was considered insufficient to establish the efficacy of icatibant for the proposed indication.

As noted in the Not Approvable action letter, the Division recommended the Applicant conduct an additional placebo-controlled trial of icatibant of similar scope as FAST-1 and FAST-2, in order to establish replicate efficacy results in support of the proposed indication. The Applicant responded by completing HGT-FIR-054 (FAST-3), which was a placebo-controlled trial conducted in 98 subjects, similar in design to FAST-1, with the main difference being the designated primary efficacy endpoint of time to symptom relief onset based on a mean composite VAS rating (VAS-3), which included skin pain, skin swelling, and abdominal pain as symptom components. Given the Division's recommendation during an End of Review Meeting on December 15, 2008, to use the same primary efficacy endpoint in FAST-3 as was used in FAST-1 and FAST-2, the Applicant designated time to onset of primary symptom relief as the key secondary endpoint in FAST-3, and a Special Protocol Assessment (SPA) for this trial was submitted by the Applicant on February 13, 2009. However, in a No Agreement SPA letter dated April 2, 2009, the Division stated the design and planned analysis of FAST-3 did not adequately address the objectives required to support a marketing submission, given concerns over the proposed primary endpoint analyses based on VAS-3 and the proposed secondary efficacy endpoint analyses. Despite this, the Applicant completed the trial and submitted a Clinical Study Report for FAST-3 in this Complete Response.

Concerns were also raised by the Division in the Not Approvable action letter for the original NDA over the validity of the VAS rating scale. The VAS is defined as a 100 mm horizontal line, with the right-most extreme value equal to 100 mm connoting the worst possible symptoms, whereas the left-most extreme (0 mm) indicates no symptoms. Subjects are asked to rate their symptoms by physically marking this line somewhere along its continuum, with reference to the two extremes. The Applicant addressed concerns over its validity by completing a series of PRO validation studies evaluating the face, content, and clinical validity of the VAS, as well as characterizing its minimum clinically significant difference by correlating VAS ratings with ratings on the Verbal Descriptor Scale, a 5-point scale that the Applicant considered to be the standard comparison for self-reported symptom assessments. Results of these PRO validation studies were submitted in the SPA for FAST-3. Although a No Agreement SPA letter was issued by the Division over disagreements with certain design and analysis aspects of the FAST-3 protocol, the Division also indicated in this letter that these validation studies were consistent with recommendations made in the Agency's *Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009). However, the validity of the VAS as an acceptable PRO remains under review.

**Safety and Efficacy of Icatibant Self-administration**

With regard to demonstrating the safety of icatibant for self-administration in emergency settings, the Applicant conducted an additional Phase 3 clinical trial (JE049-3101 or FAST-4) in 56 subjects to assess the safety, tolerability, and perceived convenience of self-administered icatibant outside of a medical setting. This multicenter, open-label, uncontrolled trial of single-dose icatibant 30 mg SC also assessed efficacy as a secondary endpoint. At the outset of the trial, patients with documented Type I or Type II HAE (eight icatibant-naïve subjects and 48 subjects previously treated with icatibant) were trained in the self-administration of icatibant using a placebo-filled syringe. Immediately following training, icatibant-experienced subjects were given a single icatibant syringe for self-administration and a symptom diary and were instructed to self-administer this dose at the outset of their next HAE attack of qualifying severity. In contrast, icatibant-naïve subjects were treated at the investigator's medical institution at the time of their first post-enrollment HAE attack, where icatibant was administered by a healthcare professional. Following resolution of this initial attack, these subjects were similarly given a single icatibant syringe for self-administration and a new symptom diary and were then allowed to self-administer icatibant at the onset of a second HAE attack, followed by evaluation at the clinical site within 48 hours of treatment (where up to two more injections of icatibant could be administered every 6 hours, as needed). One subject was lost to follow-up after completing icatibant self-treatment, and another 95 subjects were enrolled in the trial, trained in the use of icatibant, but never experienced an HAE attack during the course of the trial and, therefore, did not self-administer icatibant. The Applicant suggests that the nature and severity of adverse events (AEs) documented in this trial following icatibant self-administration were similar to what was observed in prior clinical trials of icatibant administered in medical settings by healthcare workers and identified no new safety signals.

**Dose-selection based on Clinical Endpoint or Biomarkers**

The Applicant states that icatibant dose-selection was originally based on several Phase 1 clinical pharmacology studies, a Phase 2 repeat-dose proof-of-concept trial that included IV and SC dose-ranging (JE049-2101), data generated from a human bradykinin challenge model, and additional pharmacokinetic and pharmacodynamic modeling. An integrated analysis of these data (JE049-5108) was submitted in this Complete Response, in which the Applicant argues that the 30 mg SC dose of icatibant carried forward into the three pivotal Phase 3 efficacy trials is safe and effective for the proposed indication and, therefore, no further dose definition is necessary. The Applicant also submitted a Complete Study Report for an additional pharmacokinetic trial of repeat icatibant dosing in healthy adults (HGT-FIR-065) that was conducted since the original NDA was denied approval, which the Applicant feels further supports the selected dose.

### 2.6 Other Relevant Background Information

Icatibant is approved and marketed in the European Union (37 countries), and the Applicant has indicated that an estimated 5,379 patient exposures to Firazyr have occurred cumulatively in the postmarketing setting between July 11, 2008 (time of EU approval) and July 11, 2010. Safety data from this postmarketing exposure is discussed in Section 8 Postmarketing Experience.

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

A review of the ethical and clinical research practices utilized for the clinical trials newly submitted with this Complete Response submission (FAST-3 and FAST-4) revealed no deficiencies which compromised the validity of the data collected. In particular, data from FAST-3 were obtained from 67 study sites in the United States and 10 foreign countries (Australia, Canada, Hungary, Israel, Mexico, Romania, Russia, South Africa, Turkey, Ukraine), with the majority of subjects recruited domestically (219 out of 369 screened subjects for a total of 65 enrollees). Of the foreign study sites, the greatest number of subjects were enrolled in Israel (n = 10), whereas 0 to 5 subjects were enrolled in each of the other countries. As icatibant is a new molecular entity, an audit by the Division of Scientific Investigations (DSI) was already conducted for the original NDA submission in which those study sites that enrolled the highest number of subjects for FAST-1 and FAST-2 were evaluated for scientific integrity and adherence to Good Clinical Practices. In contrast to the original application, however, the majority of study sites for FAST-3 were located domestically. In addition, a statistical review of efficacy data from FAST-3 by the Biometrics Review Team did not detect any outliers in performance by individual study site, which would require an additional DSI audit. Moreover, the Applicant states that no debarred investigators participated in these trials. Thus, no additional DSI audit for this Complete Response was requested.

### 3.2 Compliance with Good Clinical Practices

The Applicant has certified that all clinical trials were conducted under Good Clinical Practices (GCP). However, the original NDA review noted that several GCP violations were identified for FAST-1 (two subjects with missing source data from one study site) and FAST-2 (one subject with retrospectively entered data and two subjects with lost source documents and informed consent forms signed after the screening visit). In addition, two protocol violations were noted in the randomized treatment phase of FAST-3: one subject who was randomly assigned to placebo treatment subsequently

developed laryngeal symptoms that were treated with open-label icatibant and was assigned to the laryngeal population; one placebo-recipient was enrolled in the trial, despite not meeting the inclusion criterion of having at least one VAS score ≥ 30 mm. These violations do not appear to reflect systemic bias in the underlying samples, however, and are not suspected to have markedly affect data analysis or interpretation.

### 3.3 Financial Disclosures

No investigators associated with FAST-1, FAST-2, or FAST-3 were listed as having any financial conflicts of interest. One financial disclosure was made for a German-based investigator who involved in FAST-4, who had received research funding (37,000 euros in 2010) from the Applicant for a separate single investigator-initiated study regarding HAE classification in clinical practice. This investigator certified that she had no other financial interests related to the Applicant prior to the initiation of FAST-4. The Applicant certifies that the data obtained from this clinical site was unbiased, with protocol adherence and source documentation monitored by a contract research organization on an ongoing basis during the trial.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Clinical Pharmacology

A summary of the pharmacokinetic characteristics of icatibant is provided in the Clinical Pharmacology Summary document of this AC background package. For this Complete Response submission, the Applicant has submitted two new Phase 1 clinical pharmacology trials (HGT-FIR-061, a thorough QT prolongation study that is also being reviewed by the Agency's QT-Interdisciplinary Review Team for safety purposes, and HGT-FIR-065, a pharmacokinetic trial in healthy adults), a population pharmacokinetic analysis encompassing all pharmacokinetic data, and a pooled data analysis for HGT-FIR-061 and HGT-FIR-065 evaluating the effects of age and gender on icatibant pharmacokinetics. Both age and gender effects were noted in the Phase 1 program, with respect to rates of icatibant clearance in clinical pharmacology trials of healthy subjects. While elderly subjects (> 65 years) had similar Cmax values as younger adults (18-45 years), AUC values were increased by approximately 66-116%, with longer half-lives in elderly subjects. Decreased rates of icatibant clearance were also noted in females compared to males, with 2.3-fold increases in both Cmax and AUC noted for young females. In elderly females, Cmax was similarly increased 2.3-fold compared to elderly males, whereas AUC was increased 1.8-fold. Increases in clearance rates were also noted as body weight increased. Thus, when clearance data

for age-matched females and males were corrected for body weight (which is generally lower in females compared to males), clearance rates by gender were more comparable. This Clinical Review addresses whether these subgroup effects on drug clearance may have had any demonstrable impact on the clinical efficacy (Section 6 Review of Efficacy, Section 6.1.7 Subpopulations) or safety (Section 7 Review of Safety, Section 7.5.3 Drug-Demographic Interactions) of icatibant.

### 4.1.1 Mechanism of Action

HAE is a rare inheritable autosomal dominant disease resulting from a quantitative (Type I HAE) or qualitative functional (Type II HAE) deficiency in complement 1 (C1) esterase inhibitor (C1-INH) due to mutations in the C1-INH gene. A third form of HAE (Type III) with an indistinguishable clinical phenotype from Type I and Type II HAE also exists due to an unknown genetic defect that is unrelated to C1-INH deficiency. C1-INH is a serine protease inhibitor that irreversibly complexes with its target serine proteases, preventing C1 complement autoactivation and inactivating several coagulation factors, including XIIa (activated Hageman factor), XIIf, Xia, as well as plasma kallikrein. In HAE, the increased activity of plasma kallikrein results in dysregulated release of bradykinin from high molecular weight kininogen. It is this accumulation of bradykinin during acute HAE attacks that is thought to result in the predominant clinical signs and symptoms of HAE, resulting from increased vascular permeability, vasodilation, and visceral smooth muscle contraction. In turn, the clinical presentation of HAE is characterized by recurrent spontaneous attacks of varying frequency, involving cutaneous, abdominal, and/or laryngeal edema of variable duration, which may be disfiguring, extremely painful, and life-threatening (particularly related to airway compromise and hypotension). Icatibant is a synthetic decapeptide, which is similar in structure to bradykinin and acts as a direct antagonist of the bradykinin type 2 receptor, thereby counteracting the pathophysiologic effects of uncontrolled bradykinin production that result from C1-INH deficiency during acute HAE attacks.

### 4.1.2 Pharmacodynamics

Multiple trials were conducted to assess pharmacodynamic biomarkers in the original NDA submission in support of dose-selection. These characterized the dose-dependent inhibition of bradykinin effects by icatibant on blood pressure and heart rate in healthy volunteers (JE049-1001, JE049-1102, JE049-1103). In brief, an exogenous IV bradykinin challenge model was used as a pharmacological tool in healthy subjects to investigate the dose range and regimen for later clinical trials of icatibant. Intravenous dosing was utilized in these studies in order to minimize variability in the exposure-time profile of the drug. These studies were designed to determine the dose of icatibant that would provide near complete inhibition of exogenously administered bradykinin in healthy adults, given the hypothesis that this would correlate to improvement in bradykinin-mediated symptoms of acute HAE attacks. Thus, the dose of icatibant selected for exploration in Phase 3 trials was determined not through dose-ranging trials

that assessed the impact of icatibant on clinical efficacy endpoints or validated clinical surrogates, but rather on the plasma levels of bradykinin expected to occur in acute HAE attacks and the plasma levels of icatibant needed to completely antagonize bradykinin effects, as assessed in the human bradykinin challenge model. A Phase 2 proof-of-concept trial (JE049-2101) suggested the comparability of the pharmacokinetic and pharmacodynamic profile of icatibant in HAE patients versus healthy volunteers at equivalent doses. These trials were all reviewed previously with the original NDA submission.

Newly presented in this Complete Response submission are pharmacokinetic and pharmacodynamic modeling data (JE049-5108) in healthy subjects and HAE patients, which the Applicant feels support Phase 3 dose-selection. A review of these data is provided in the Clinical Pharmacology Summary included in this AC background package. In addition, a Clinical Study Report for an additional Phase 1 pharmacodynamic trial (HGT-FIR-061) examining the effects of icatibant on QT prolongation that was conducted after the original NDA submission was also included with this Complete Response. This thorough QT prolongation study is briefly summarized below.

**Protocol Title: HGT-FIR-061—**The Effect of Icatibant on QT and QTc Intervals: A Randomized, Placebo Controlled, Active Comparator, Crossover Study in Healthy Adult Volunteers

Enrollment Initiation Date: February 16, 2010

Enrollment Completion Date: August 12, 2010

Design and Methods: HGT-FIR-061 was a Phase 1 randomized, placebo- and active-controlled, open-label crossover trial whose primary objective was to assess whether a single 30 mg or 90 mg SC dose of icatibant caused QT interval prolongation in healthy male and female adults. Subjects were randomized to variable sequences of four treatment periods, each consisting of a 24-hour ECG assessment prior to a 24-hour treatment period in which subjects received either placebo, a single 3 mL SC injection of 30 mg icatibant, three SC injections of 30 mg icatibant for a total dose of 90 mg, or a single oral dose of moxifloxacin 400 mg. This was then followed by a minimum 2-day wash-out period, prior to advancement to the next subsequent treatment period. A total of 82 subjects were enrolled in the trial and received at least one dose of study drug, with 71 subjects completing all four treatment periods. ECG acquisition and interpretation was done by blinded investigators who were unaware of subjects' treatment assignment and treatment period sequence. The primary analysis consisted of determining the largest upper 1-sided 95% confidence limit for QTcL for icatibant 30 mg and 90 mg relative to placebo at the same nominal time, using a linear mixed model with fixed effects for baseline QTc, treatment, period, sequence, schedule time, and treatment by time interaction as a repeated measure within subject by treatment. A

determination of no effect on QT prolongation was concluded if the maximum of this upper confidence limit fell below 10 msec.

Summary Results

No subject had a maximum QTcL, QTcF, or QTcB value of greater than 480 msec or a change from baseline of greater than 60 msec following receipt of icatibant at either dose. All placebo-corrected change from baseline mean values for QTcL were below 1.7 msec for both icatibant 30 mg and icatibant 90 mg, with the upper limit of all 2-sided 90% confidence intervals below 10 msec at all time points. Results based on QTcF and QTcB were similar to those for the primary QTcL analysis. In addition, results for the moxifloxacin positive control indicated that the lower limit of the 2-sided 99% confidence interval for placebo-corrected change from baseline mean values for QTcL was greater than 5 msec from 1-3 hours post-dose. The Applicant states that these control findings were consistent with typical values established for moxifloxacin when used as a positive control agent in QT prolongation studies, thereby establishing assay sensitivity in this study. The Applicant states that there was no evidence of icatibant-mediated QT prolongation in either males or females at the proposed treatment doses (30-90 mg SC). No deaths, SAEs, or severe AEs reported during the study, and most AEs were mild in severity and resolved without specific intervention. No clinically significant changes in laboratory tests, vital sign assessments, or ECG findings were reported in icatibant-recipients.

### 4.1.3 Pharmacokinetics

A review of data establishing the pharmacokinetic profile of icatibant is discussed in the Clinical Pharmacology Summary document included in this backgrounder package. These data were generated from Phase 1 clinical pharmacology trials and a Phase 2 proof-of-concept trial with IV and SC dose-ranging information that were submitted with the original NDA. In this Complete Response submission, both population pharmacokinetic data and pharmacokinetic/pharmacodynamic modeling data have been included, as discussed above in Section 4.4 Clinical Pharmacology and Section 4.4.2 Pharmacodynamics. In addition, the Applicant has submitted a Clinical Study Report for a Phase 1 pharmacokinetic trial (HGT-FIR-065) in healthy adults that was conducted since the original NDA submission, which is summarized briefly below. Further details may be found in the Clinical Pharmacology Summary of this AC background document.

**Protocol Title: HGT-FIR-065—**An Open-label, Phase I, Single-center Study to Determine the Pharmacokinetics and Safety of Multiple Doses of Subcutaneously Administered Icatibant in Healthy Adult Male and Female Subjects

Enrollment Initiation Date: March 30, 2010

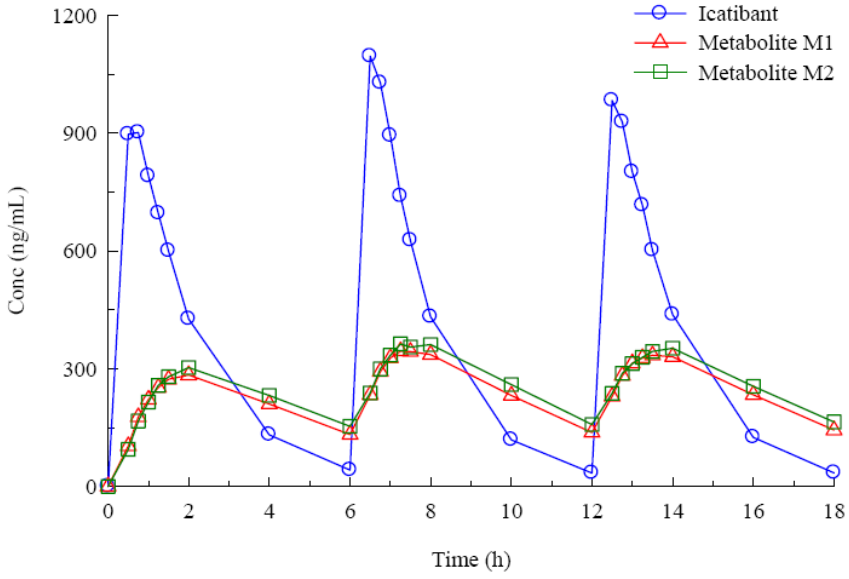
Enrollment Completion Date: May 16, 2010

Design and Methods: HGT-FIR-065 was a Phase 1 open-label, single-center trial to assess the pharmacokinetics, tolerability, and safety of multiple doses of icatibant 30 mg SC in healthy male and female adults (18-45 years, BMI = 18-30 kg/$m^2$ inclusive, weight > 50 kg). Subjects received three individual doses of icatibant 30 mg/3 mL SC, each separated six hours apart, with pharmacokinetic (plasma concentrations of icatibant, M1 metabolite, and M2 metabolite, in order to determine Cmax, tmax, $t_{1/2}$, $AUC_{last}$, $AUC_{\infty}$) and safety parameters (AEs, injection site reactions, clinical laboratory tests [hematology, serum chemistry, urinalysis], vital signs, physical examination, 12-lead ECG) assessed throughout the 2-day post-dosing inpatient observation period. A total of 21 subjects received all planned doses of study drug and completed all planned assessments with no major protocol violations.

Summary Results

The overall mean values for Cmax and $AUC_{0\text{-}6hr}$ were comparable for all three doses of icatibant, suggesting no drug accumulation. Mean $t_{1/2}$ was estimated to range from 1.06-1.16 hrs following SC administration and did not vary across doses. Of note, both the M1 and M2 metabolites showed approximately a 25% increase between the first two icatibant doses but were comparable between the second and third, with an estimated $t_{1/2}$ of 3.19-3.53 hrs for M1 and 3.47-3.67 hrs for M2, achieving steady state by 12 hours post-dosing. Thus, although icatibant was not shown to accumulate, levels of M1 and M2 accumulated between the first and second doses, as shown in Figure 1, which was constructed by the Applicant.

**Figure 1: Mean plasma concentrations of icatibant, M1, and M2 after icatibant 30 mg SC every 6 hours for 3 doses in healthy adults**




*Source: HGT-FIR-065 Clinical Study Report, Appendix 12.2.6.2*

No new safety signals emerged from this study, with no deaths, SAEs, or AE-related discontinuations.

# 5 Sources of Clinical Data

## 5.1 Tables of Studies/Clinical Trials

In addition to the two Phase 3 clinical efficacy trials (FAST-1 and FAST-2) that were submitted and reviewed with the original NDA submission, this Complete Response includes one additional Phase 3 placebo-controlled clinical efficacy trial (HGT-FIR-054 or FAST-3), which is reviewed herein within the context of FAST-1 and FAST-2. Both clinical efficacy and safety data were obtained from all three of these pivotal Phase 3 trials. Comparative efficacy analyses from these trials are reviewed in Section 6 Review of Efficacy, while pooled safety data are discussed in Section 7 Review of Safety. The Applicant also conducted an additional Phase 3 trial to evaluate the safety of icatibant for self-administration in nonclinical settings by non-healthcare workers, as shown in Table 4 (the first two pivotal Phase 3 efficacy trials included in the original NDA submission are listed in italics).

**Table 4: Phase III clinical development program for icatibant**

| Trial | Phase | Subjects | Design | Treatment Arms | Duration | Relevance |
|---|---|---|---|---|---|---|
| ***JE049-2103 (FAST-1)** | ***III*** | ***Adults with HAE (64, including 56 randomized & 8 open-label)*** | ***R, DB, PC *24-wk OL Ext (72)*** | ***Icatibant 30 mg SC Placebo*** | ***Single dose, with 14-day observation period*** | ***Efficacy versus placebo on time to onset of symptom relief (primary symptom VAS rating)*** |
| ***JE049-2102 (FAST-2)** | ***III*** | ***Adults with HAE (77, including 74 randomized & 3 open-label)*** | ***R, DB, DD, AC *24-wk OL Ext (54)*** | ***Icatibant 30 mg SC Tranexamic acid 1000 mg PO every 6-8hr for 2 days (up to 6 doses)*** | ***Single dose, with 14-day observation period*** | ***Efficacy versus tranexamic acid on time to onset of symptom relief (primary symptom VAS rating)*** |
| **HGT-FIR-054 (FAST-3)** | **III** | **Adults with HAE (98, including 88 randomized abdominal & cutaneous, 5 randomized laryngeal, & 5 open-label)** | **R, DB, PC *OL EXT (96)** | **Icatibant 30 mg SC Placebo** | **Single dose, with 14-day observation period (EXT ongoing)** | **Efficacy versus placebo on time to onset of symptom relief (composite symptom VAS rating)** |

| | | | | | | |
|---|---|---|---|---|---|---|
| **JE049-3101 (FAST-4) | III | Adults with HAE (150; 56 completed) | OL | Icatibant 30 mg SC | Single dose (2 days non-naïve and 2 days naïve) | Safety of self-administration of SC drug |

**Included in the original NDA submission; **Included in the Complete Response submission*
*R = randomized, DB = double-blind, PC = placebo-controlled, OL =open-label, EXT = extension, SC = subcutaneous, VAS = visual analog scale*

## 5.2 Review Strategy

This Clinical Review presents a review of efficacy and safety data from the Phase 3 icatibant development program, emphasizing data from two new trials, FAST-3 and FAST-4. A review of the methodology and safety data for FAST-3 is presented in Appendix Section 9.2 Detailed Reviews of Individual Study Reports. Efficacy analyses for FAST-3 are discussed individually, within the context of the previous two Phase 3 clinical trials, FAST-1 and FAST-2, in Section 6 Review of Efficacy. As FAST-1 and FAST-2 were reviewed in detail with the original NDA submission, individual study report reviews for these trials are not provided in this Clinical Review, although separate efficacy analyses for FAST-1 and FAST-2 are presented in Section 6 Review of Efficacy. In contrast to the review of Phase 3 efficacy results, the safety data for the Phase 3 development program are pooled for FAST-1, FAST-2, and FAST-3 and are reviewed collectively in Section 7 Review of Safety, as a comparison of icatibant-recipients versus control subjects (placebo or tranexamic acid-recipients). The methodology, major safety data, and secondary efficacy results from FAST-4 are reviewed separately in Section 7.4.5 Special Safety Studies/Clinical Trials, as this trial focused primarily on the safety of icatibant self-administration by non-healthcare workers in nonclinical settings.

Validation studies supporting the use of the VAS as a PRO efficacy measure were submitted by the Applicant following issuance of the Not Approvable action letter for the original NDA submission. These studies were reviewed previously by the Division, although the Division's final determination regarding the validity of the VAS as an acceptable PRO measure is pending. Neither the non-interventional VAS validation study, JE049-4102 (which the Applicant used to define the proposed minimum clinically significant difference that defined treatment responders in the Phase 3 icatibant program), nor earlier Phase 1 and 2 clinical pharmacology trials of icatibant are reviewed in this document, as they were reviewed with the original NDA submission.

## 5.3 Discussion of Individual Studies/Clinical Trials

**Key Design Aspects of Pivotal Phase 3 Efficacy Trials**

The general trial designs for FAST-1, FAST-2, and FAST-3 were similar, with each being randomized, controlled, double-blind, parallel-group, multicenter trials. Randomization was stratified in all three trials: FAST-1 and FAST-2 by cutaneous or abdominal edema location; FAST-3 by cutaneous, abdominal, or laryngeal edema location and previous use of C1-INH replacement therapy. The primary difference in these trials was in choice of control treatment arms, as FAST-1 and FAST-3 were both placebo-controlled, whereas FAST-2 was active-controlled, utilizing tranexamic acid as a comparator. Although not approved for the treatment of HAE in the U.S., tranexamic acid holds an indication for HAE in Europe and South Africa. In addition, tranexamic acid is marketed as Cyklokapron in the U.S. and is approved for the prophylaxis and treatment of hemorrhage in hemophiliac patients undergoing tooth extraction. Prior review of FAST-2 by the Division in the original NDA submission concluded that there were insufficient data in the medical literature to support tranexamic acid as an effective treatment for acute HAE attacks.

All three trials studied adults (≥ 18 years old) with Type I or Type II HAE (confirmed by quantitative or functional C1-INH results from a central laboratory or by medical history alone if subjects had an established family history, characteristic recurrent HAE attacks, historical C1-INH function < 50%, and an exclusion of other forms of angioedema including acquired angioedema with normal C1q levels), who presented with moderate to severe abdominal or cutaneous acute HAE attacks within 6 hours of symptom onset. These patients were randomized to treatment with either icatibant 30 mg SC or placebo no more than 12 hours after the onset of symptoms and were then observed for up to 48 hours as inpatients, during which time self-reported (VAS scores and symptom ratings) and investigator-based (physical examination and symptom ratings) clinical assessments were completed at regular intervals. Subjects were excluded from these trials if they had evidence of coronary artery disease or congestive heart failure, were on ACE-inhibitor therapy, had received C1-INH replacement therapy within 3 days of onset of the acute HAE attack, or had taken pain medication since the onset of the HAE attack. In addition, subjects in FAST-3 were not permitted to have received icatibant in the past. Of note, blinding of the randomized treatment phase in all three trials may have been compromised due to the emergence of local injection site reactions almost exclusively in the active treatment arms versus placebo groups. In addition, although a double-dummy design with placebo injections and placebo tablets was utilized in FAST-2 to mask randomized treatment assignment, in contrast to icatibant, tranexamic acid is known to cause significant gastrointestinal side effects (e.g., nausea, vomiting, and diarrhea), which may also have compromised blinding of both subjects and investigators.

Patients with laryngeal attacks were treated with open-label icatibant 30 mg SC in FAST-1 and FAST-2, whereas patients with mild to moderate laryngeal attacks were randomized to icatibant versus placebo treatment in FAST-3, while severe laryngeal attacks were treated with open-label icatibant in FAST-3. All three trials were followed by an open-label extension period in which all enrollees were treated with open-label icatibant 30 mg SC up to every 6 hours (but no more than 3 doses within 24 hours) for any subsequent HAE attack severe enough to warrant treatment. Additional enrollees who did not have an initial attack during the randomized treatment phase, as well as other subjects who met trial entry criteria but were not enrolled during the randomized treatment phase, were also allowed to join the open-label extension phase. At the time of this review, the open-label extension phases of FAST-1 and FAST-2 were complete, whereas the extension phase of FAST-3 was ongoing.

# 6 Review of Efficacy

## 6.1 Indication

- Treatment of acute attacks of hereditary angioedema (HAE) in adults

### 6.1.1 Methods

This clinical efficacy review is based on the three pivotal Phase 3 trials, FAST-1, FAST-2, and FAST-3, as well as a fourth Phase 3 trial, FAST-4, which evaluated self-administered icatibant in non-medical settings by non-healthcare workers. FAST-1 was a randomized, double-blind, placebo-controlled trial evaluating the treatment of patients presenting with acute cutaneous and abdominal HAE attacks with icatibant 30 mg SC versus placebo injection. FAST-2 had a similar trial design as FAST-1 but utilized a double-blind, double-dummy control agent (tranexamic acid) that is not approved in the U.S. for the treatment of acute HAE attacks. FAST-3 was newly submitted as part of this Complete Response and was similar in design to FAST-1 as a randomized placebo-controlled trial. Thus, the ITT population used for primary efficacy analyses in each of these Phase 3 trials consisted only of subjects with moderate to severe abdominal and/or cutaneous HAE attacks, who received double-blind, randomized study treatment. Of note, all three of these trials provided open-label icatibant treatment to patients presenting with laryngeal HAE attacks, although in FAST-3, open-label icatibant was only given to patients with severe laryngeal HAE attacks. In contrast to FAST-1 and FAST-2, following a protocol amendment to FAST-3, subjects with mild to moderate laryngeal attacks were randomized to icatibant versus placebo treatment in FAST-3, allowing for a placebo-controlled efficacy assessment of icatibant treatment in laryngeal HAE attacks in this trial. All three of these pivotal efficacy trials were also followed by open-label extension phases in which all subjects received icatibant 30 mg SC at up to

three doses, each separated by at least 6 hours, for any additional HAE attack. This integrated review of efficacy presents a comparison of efficacy findings from FAST-1, FAST-2, and FAST-3 in parallel fashion, organized by common efficacy endpoints. Although the Applicant conducted a pooled efficacy analysis across these three trials of blinded icatibant versus control treatments, this presentation of the data is not an effective means of demonstrating replicate evidence of efficacy for the proposed indication. Thus, pooled efficacy analyses are not reviewed here, other than for the laryngeal HAE attack population that consisted primarily of subjects treated with open-label icatibant, as well as for a sequential analysis of total icatibant-recipients who were evaluated for each of their first five sequential icatibant-treated HAE attacks.

**Primary Efficacy Endpoints**

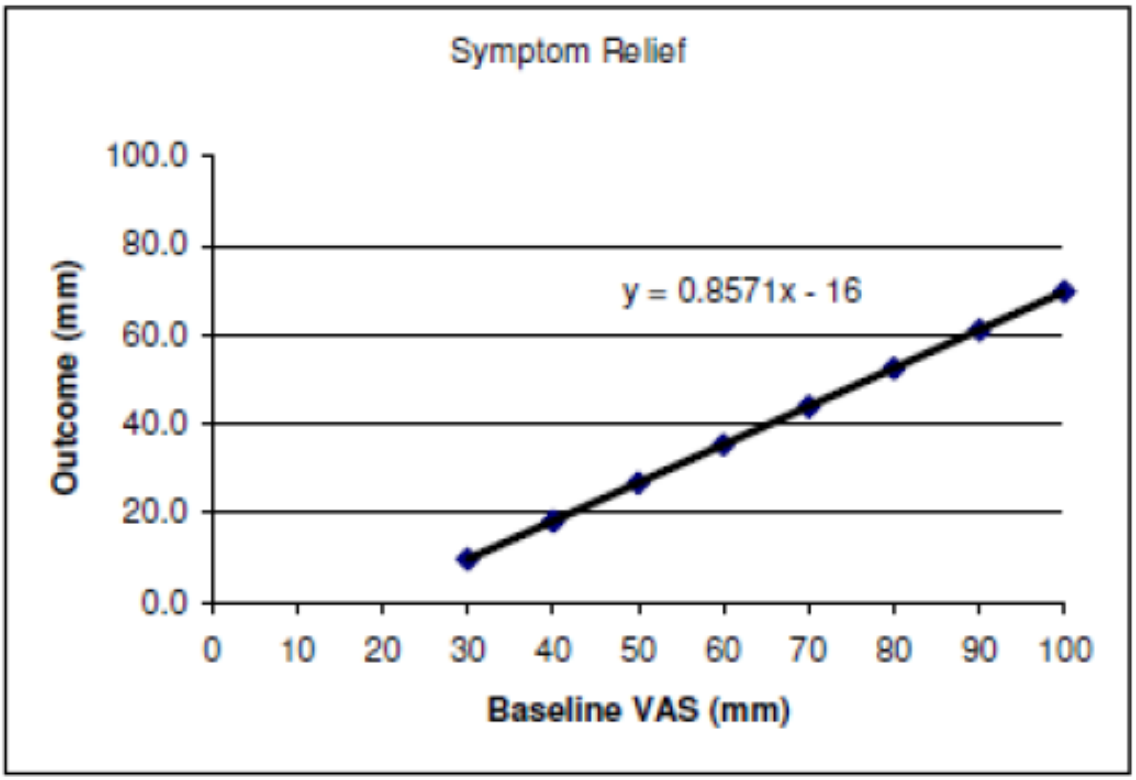
The primary efficacy endpoint in FAST-3 differed from that of FAST-1 and FAST-2. The two initial trials utilized the same primary efficacy endpoint of median time to onset of primary symptom improvement, based on Visual Analog Scale (VAS) score for the single most severe presenting symptom. The VAS is a 100 mm linear scale anchored by the extreme values of 0 mm = no symptom and 100 mm = worst possible symptom, which subjects used to rate the intensity of each HAE symptom at baseline and at predetermined time points post-dosing. A series of validation studies establishing the utility of the VAS as a PRO included a non-interventional PRO validation study (JE049-4102) to establish the minimum clinically significant difference for the VAS, in comparison to the Visual Descriptor Scale, a 5-point rating scale used as a comparative standard to the VAS in evaluating symptom change over time.

Symptoms rated with the VAS included cutaneous swelling, cutaneous pain, abdominal pain, and nausea. For cutaneous HAE attacks, the time to onset of symptom relief was defined by the more severe presenting symptom of either skin swelling or skin pain, with skin pain designated as the primary symptom if both were equally severe. For abdominal attack patients, abdominal pain ratings were used to assess onset of primary symptom relief. For subjects with both cutaneous and abdominal manifestations, HAE attacks were only classified as cutaneous if abdominal symptoms were no worse than mild and cutaneous symptoms were at least moderate to severe; otherwise, attacks were classified as abdominal HAE attacks. For the purposes of analysis in this Complete Response submission, any subject presenting with laryngeal HAE symptoms during an acute attack (even if not as severe as concurrent cutaneous or abdominal symptoms) was classified as having a laryngeal attack. These laryngeal attack subjects were not included in the ITT analysis for the primary efficacy endpoints, which consisted only of subjects with moderate to severe cutaneous and/or abdominal HAE attacks with at least one baseline VAS symptom rating of ≥ 30 mm.

Time to onset of symptom relief was defined as the time between initial injection and the first documentation of symptom relief as evidenced in the earliest of three consecutive non-missing VAS assessments. Subjects with no documented symptom relief were

censored at the time of their last symptom assessment. Symptom relief based on the VAS was originally defined as an absolute reduction from pretreatment VAS of ≥ 20 mm if pre-dose VAS ≥ 30 and ≤ 50 mm, or of ≥ 30 mm if VAS > 50 mm. However, this algorithm was modified in the Statistical Analysis Plan for FAST-1 and FAST-2 to define the onset of symptom relief based on VAS score graphically, as a response to the right and below a line defined by the function Y = 6/7X - 16 mm, where X ≥ 30 mm, X = pre-treatment VAS in mm, and Y = post-treatment VAS in mm. This corresponds to a reduction of 30 mm for a baseline VAS = 100 mm and by 21 mm for a baseline VAS = 30 mm, as shown in the following figure provided by the Applicant:

**Figure 2: Definition of onset of symptom relief by VAS as presented in the statistical analysis plan for the icatibant Phase 3 clinical program**




*Source: JE049-2102-statistical.pdf, Section 3*

Although FAST-3 also utilized VAS assessments to define symptom improvement, rather than using the primary symptom rating to define the primary efficacy endpoint, FAST-3 used time to onset of symptom relief based on a composite symptom score (VAS-3) calculated as the mean of individual VAS scores for three major symptom domains: abdominal pain, skin edema, and skin pain. Subjects without documented symptom relief were censored at the time of their last VAS-3 assessment. Missing data were imputed for VAS-3 but not for primary symptom VAS scores. In further contrast to FAST-1 and FAST-2, symptom improvement in FAST-3 based on VAS-3 was defined

as a reduction of ≥ 50% of baseline VAS-3 score. However, despite this difference in the designated primary efficacy endpoint, the key secondary efficacy endpoint in FAST-3 was identical to the primary efficacy endpoint in FAST-1 and FAST-2 (i.e., time to onset of primary symptom relief based on graphically defined reduction in VAS), allowing for efficacy comparisons across all three Phase 3 trials.

**Secondary Clinical Efficacy Endpoints**

Secondary endpoints in these three Phase 3 trials included the following:

- Time to relief of each non-primary symptom
- Time to almost complete symptom relief, defined as all individual VAS scores being $\leq$ 10 mm
- Response rate at 4 hours, defined as the proportion of subjects with onset of symptom relief with 4 hours post-dosing
- Durability of response to study drug, defined as a 50% reduction from baseline composite VAS score within 8 hours of study drug administration that is maintained for ≥ 24 hours
- Use of rescue therapy (up to within 120 hours of initial treatment with study drug)
- Safety and efficacy of icatibant treatment specifically in laryngeal HAE attacks
- Assessed in FAST-3 only: Time to onset of symptom relief based on of a composite 5-domain symptom score (VAS-5) for subjects with laryngeal HAE attacks, with or without concurrent HAE manifestations in other bodily sites (skin swelling, skin pain, abdominal pain, difficulty swallowing, voice change)
- Patient-based and investigator-based assessments of symptom regression (time to initial symptom improvement)
- Patient-based assessments of individual symptom severity on a 5-point ordinal scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe): skin swelling, erythema/redness, skin irritation, skin pain, abdominal pain/tenderness, nausea, vomiting, diarrhea, and for laryngeal attacks, difficulty swallowing and voice change
- Investigator-based assessments of individual symptom severity on a 5-point ordinal rating scale of the same 10 patient-assessed symptom domains, as well as breathing difficulties, stridor and asphyxia

Composite symptom severity scores based on the average of these individual symptom severity ratings were prespecified endpoints for FAST-3. These included mean composite symptom severity scores based on the eight non-laryngeal symptom domains (either patient-based or investigator-based), as well as scores based on the 10 patient-based and 13 investigator-based non-laryngeal plus laryngeal symptom domains. These composite symptom severity scores are distinct from the VAS-based composite symptom scores, VAS-3 and VAS-5. As these composite symptom severity scores and composite VAS-based symptom scores were prespecified endpoints only for FAST-3, *post hoc* analyses of these endpoints were conducted for FAST-1 and FAST-2. Thus, these secondary efficacy analyses were presented in comparison to FAST-3 in this Complete Response only, and not in the Clinical Study Reports for FAST-1 or FAST-2.

Additional investigator-based secondary endpoint assessments included the following:

- Clinical Global Assessment in which cutaneous, abdominal, and laryngeal symptoms were rated on the same 5-point ordinal rating scale, as described above

- Clinical Global Impression/Improvement in which post-treatment change in clinical status was rated on a 7-point ordinal scale (1 = very much improved, 2 = much improved, 3 = minimal improvement, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse)

**Key Statistical Approaches**

For demographic and safety outcome data, tabular summaries, descriptive statistics, and frequency distributions were presented by treatment group, without inferential statistics. In contrast, for the primary efficacy analysis, time to onset of symptom relief was summarized using the Kaplan-Meier method, characterizing median values and sign test-based 2-sided 95% confidence intervals, as well as the number of subjects censored and achieving symptom relief. A comparison of hazard rates for icatibant-recipients versus control subjects was analyzed using the Peto-Peto Wilcoxon test with a 2-sided significance level of 5%, as well as a Cox proportional hazards model that included treatment and stratification factors as covariates (edema location and prior use of C1-INH replacement therapy, as applicable). Time to symptom relief was also analyzed using 30%, 40%, 60%, and 70% reductions from pretreatment composite VAS score via the Kaplan-Meier method, sign test-based 2-sided 95% confidence intervals, and Peto-Peto Wilcoxon test. Time to symptom onset in subgroups was similarly analyzed in the non-laryngeal ITT population only.

Other time-based secondary efficacy endpoints were analyzed in like fashion via the Kaplan-Meier method and the comparative Peto-Peto Wilcoxon test. For the evaluation

of individual and composite VAS scores and both patient and investigator-assessed symptom scores, change from pretreatment and AUC from pretreatment to 2, 4, and 8 hours post-treatment were analyzed using a non-parametric Wilcoxon rank-sum test without covariate adjustment, as well as an ANCOVA model with type of attack and baseline score as covariates, only if assumptions of homogeneity of variance and normality were satisfied. Global assessments, individual symptom assessments, and the proportion of subjects receiving rescue medications were analyzed via the Fisher's exact test for categorical data.

### 6.1.2 Demographics

Table 5 summarizes patient demographics for the three Phase 3 efficacy trials. Female subjects predominated in each trial, which is in contrast to the equal gender distribution of this autosomal dominant condition in the general population. The Applicant does not offer any explanation for this unequal gender distribution, although male to female ratios were similar between the randomized treatment groups within each trial. Of note, all three trials consisted largely of Caucasian participants (86-100%), with a range in mean age from 34.8-41.9 years. With regard to the initial treated on-study HAE attack, subjects in FAST-2 and FAST-3 experienced a predominance of cutaneous HAE attacks (consistent with their recent previous history of pre-enrollment HAE attacks), whereas cutaneous and abdominal HAE attacks were balanced in FAST-1. Of note, across all three trials, all randomized icatibant-recipients received only a single dose of icatibant for their initial HAE attack, whereas one placebo recipient each in FAST-1 and FAST-3 ultimately received a single dose of icatibant as rescue medication for persistent HAE symptoms. While the demographic distribution between active treatment and control groups in these three trials is sufficient to allow for statistical comparisons to assess treatment effect, the preponderance of white subjects in the Phase 3 clinical program calls into question the generalizability of these findings to patients of different ethnicities not reflected in this racial classification. This is particularly relevant, given that HAE has been documented in all major ethnic groups.

**Table 5: Patient demographics and baseline characteristics for non-laryngeal ITT population in pivotal Phase 3 efficacy trials**

| Clinical Trial | FAST-1 | | FAST-2 | | FAST-3 | |
|---|---|---|---|---|---|---|
| **Treatment Group** | **Icatibant** | **Placebo** | **Icatibant** | **Tranexamic Acid** | **Icatibant** | **Placebo** |
| **Non-laryngeal ITT population (n)** | 27 | 29 | 36 | 38 | 43 | 45 |
| **Sex (n, %)** | | | | | | |
| *Female* | 16 (59.3) | 21 (72.4) | 24 (66.7) | 23 (60.5) | 27 (62.8) | 29 (64.4) |
| *Male* | 11 (40.7) | 8 (27.6) | 12 (33.3) | 15 (39.5) | 16 (37.2) | 16 (35.6) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Race (n, %)** | | | | | | |
| *Caucasian* | 25 (92.6) | 25 (86.2) | 36 (100) | 38 (100) | 38 (88.4) | 40 (88.9) |
| *Black* | 0 | 0 | 0 | 0 | 3 (7.0) | 0 |
| *Asian* | 0 | 1 (3.4) | 0 | 0 | 0 | 0 |
| *Multiracial* | 0 | 1 (3.4) | 0 | 0 | 0 | 0 |
| *Other* | 2 (7.4) | 2 (6.9) | 0 | 0 | 2 (4.7) | 5 (11.1) |
| **Age (years)** | | | | | | |
| *Mean* | 34.8 | 34.9 | 40.4 | 41.9 | 36.1 | 36.6 |
| *Median* | 35.0 | 34.0 | 38.0 | 42.0 | 36.0 | 36.0 |
| *Range* | 20-54 | 18-58 | 20-68 | 19-66 | 19-83 | 18-66 |
| **Mean number of HAE attacks over previous 6 mon** | | | | | | |
| *Cutaneous* | 8.6 | 9.9 | 7.4 | 7.9 | 6.7 | 7.3 |
| *Abdominal* | 5.1 | 6.8 | 4.2 | 8.7 | 4.2 | 3.8 |
| *Cutaneous/Abdominal* | 7.3 | 4.9 | 6.5 | 2.4 | 3.6 | 3.8 |
| *Laryngeal* | 1.7 | 2.8 | 2.4 | 1.0 | 1.0 | 0.7 |
| **On-study HAE attacks (n,%)** | | | | | | |
| *Cutaneous* | 14 (51.9) | 13 (44.8) | 24 (66.7) | 23 (60.5) | 26 (60.5) | 26 (57.8) |
| *Abdominal* | 13 (48.1) | 16 (55.2) | 12 (33.3) | 15 (39.5) | 17 (39.5) | 19 (42.2) |

*Source: Clinical Study Report for FAST-1, Section 10.5; Clinical Study Report for FAST-2, Section 10.5, Section 10.8, and Tables 10, 11, 12, and 17; Clinical Study Report for FAST-3, Table 7-1, Section 7.2.4.1.1.1*

Demographic data were also summarized for the entire population of 225 icatibant-recipients across the blinded and open-label treatment phases of all three pivotal efficacy trials. This study population was used to determine the safety and efficacy of repeated icatibant dosing (albeit in open-label fashion) for recurrent HAE attacks, with data summarized for the first five sequential icatibant-treated HAE attacks (including unblinded data for icatibant-recipients from the randomized treatment phase). The median age of this recurrent icatibant dosing group was 37.0 years, with the majority of this population being female (65.8%) and nearly all identified as white (93.8%). Thus, this combined extension phase population was comparable demographically to the blinded treatment populations in each of the pivotal Phase 3 efficacy trials.

With regard to patients treated for an initial laryngeal HAE attack during the primary treatment phases of these efficacy trials (i.e., not including recurrent laryngeal HAE attacks), 28 of 30 subjects across the three trials were treated with a single dose of icatibant, whereas two subjects in FAST-3 were randomized to placebo (following implementation of FAST-3 Amendment 1, as shown in Table 6, which summarizes individual trial level data, as well as pooled data for the 28 icatibant-recipients. In general, the demographic distribution of this initial laryngeal attack population was similar to that of the non-laryngeal ITT population, although the smaller sample sizes contributed to greater variability.

**Table 6: Demographic and baseline characteristics of patients treated for initial laryngeal HAE attacks during the primary treatment phases of pivotal Phase 3 efficacy trials**

| Clinical Trial | FAST-1 | FAST-2 | FAST-3 | | Pooled |
|---|---|---|---|---|---|
| **Treatment Group** | **Icatibant (N = 15)** | **Icatibant (N = 5)** | **Icatibant (N = 8)** | **Placebo (N = 2)** | **Icatibant (N = 28)** |
| **Sex (n, %)** | | | | | |
| *Female* | 10 (66.7) | 3 (60.0) | 4 (50.0) | 1 (50.0) | 17 (60.7) |
| *Male* | 5 (33.3) | 2 (40.0) | 4 (50.0) | 1 (50.0) | 11 (39.3) |
| **Race (n, %)** | | | | | |
| *White* | 13 (86.7) | 5 (100.0) | 7 (87.5) | 2 (100.0) | 25 (89.3) |
| *Non-White* | 2 (13.3) | 0 | 1 (12.5) | 0 | 3 (10.7) |
| **Age (n, %)** | | | | | |
| *≤ 30 years* | 4 (26.7) | 2 (40.0) | 1 (12.5) | 0 | 7 (25.0) |
| *> 30 to ≤ 40 years* | 1 (6.7) | 0 | 4 (50.0) | 1 (50.0) | 5 (17.9) |
| *> 40 to ≤ 50 years* | 6 (40.0) | 1 (20.0) | 2 (25.0) | 0 | 9 (32.1) |
| *> 50 years* | 4 (26.7) | 2 (40.0) | 1 (12.5) | 1 (50.0) | 7 (25.0) |
| **Weight group (n, %)** | | | | | |
| *≤ 50 kg* | 0 | 0 | 0 | 0 | 0 |
| *> 50 to ≤ 75 kg* | 5 (33.3) | 2 (40.0) | 1 (12.5) | 2 (100.0) | 8 (28.6) |
| *> 75 to ≤ 100 kg* | 6 (40.0) | 2 (40.0) | 5 (50.0) | 0 | 12 (42.9) |
| *> 100 kg* | 3 (20.0) | 0 | 3 (37.5) | 0 | 6 (21.4) |

*Source: Integrated Summary of Efficacy, Table 3-2*

Demographic data were also compiled for the full population of 60 icatibant-recipients across the blinded and open-label treatment phases of all three pivotal efficacy trials (FAST-1: 27 subjects, FAST-2: 12 subjects, FAST-3: 21 subjects), who were treated with icatibant for laryngeal HAE attacks at any point, primarily in open-label fashion. This study population was used to determine the safety and efficacy of icatibant dosing for laryngeal HAE attacks, regardless of prior icatibant treatment for previous cutaneous or abdominal HAE attacks, with analysis focused on the first icatibant-treated laryngeal attack, regardless of its sequence in relation to other HAE attacks. The median age of this group was 38.5 years, with the majority of this population being female (63.3%) and white (85.0%), which was similar to the demographics of the blinded treatment populations in each of the pivotal Phase 3 efficacy trials.

### 6.1.3 Subject Disposition

Table 7 summarizes the disposition of the 794 subjects who were screened for the three pivotal Phase 3 efficacy trials, of whom 69.9% (n = 555) were screening failures, due either to a violation of trial participation criteria (n = 86) or a failure to develop a

qualifying HAE attack of sufficient severity to warrant treatment (n = 469). Thus, 28.1% (n = 223) of these subjects were randomized to blinded treatment for an initial HAE attack, while 2.0% (n = 16) were treated with open-label icatibant for qualifying laryngeal HAE attacks during the primary treatment phases of each trial. Specifically, eight subjects in FAST-1 and three subjects in FAST-2 received open-label icatibant for initial laryngeal HAE attacks of mild to severe severity, while five subjects in FAST-3 received open-label icatibant for severe laryngeal attacks.

### Table 7: Disposition of screened subjects during primary treatment phase of pivotal Phase 3 efficacy trials

| Clinical Trial | FAST-1 | FAST-2 | FAST-3 |
|---|---|---|---|
| **Screened (n)** | 178 | 247 | 369 |
| **Failed Screening (n, %*)** | 114 (64.0) | 170 (68.8) | 271 (73.4) |
| Violated inclusion/exclusion criteria (n) | 21 | 23 | 42 |
| Did not develop qualifying HAE attack (n) | 93 | 147 | 229 |
| **Randomized to treatment (n, %*)** | 56 (31.5) | 74 (30.0) | 93 (25.2) |
| Initial non-laryngeal HAE attack (n) | 56 | 74 | 88 |
| Initial laryngeal HAE attack (n) | 0 | 0 | 5 |
| **Received open-label icatibant treatment (n, %*)** | 8 (4.5) | 3 (1.2) | 5 (1.4) |

**Percentages are out of total number of screened subjects*
*Source: Clinical Study Report for FAST-1, Section 10.1, Table 7; Clinical Study Report for FAST-2, Section 10.1, Table 7; Clinical Study Report for FAST-3, Section 6.1*

As detailed in Table 8, the randomized treatment population across all three trials was comprised of 218 subjects who received blinded treatment for an initial moderate to severe non-laryngeal HAE attack (i.e., the non-laryngeal ITT population) and five subjects (all from FAST-3) who received randomized treatment for an initial mild to moderate laryngeal HAE attack (three icatibant-recipients and two placebo-recipients). Thus, the non-laryngeal ITT population consisted of 106 subjects randomized to icatibant 30 mg SC, 38 subjects randomized to tranexamic acid, and 74 subjects randomized to placebo. All randomized subjects received their assigned double-blind treatment. In turn, all subjects who received blinded treatment for an initial non-laryngeal HAE attack were included in the primary efficacy endpoint analysis.

### Table 8: Subject disposition for randomized treatment population in pivotal Phase 3 efficacy trials

| Clinical Trial | FAST-1 | | FAST-2 | | FAST-3 | |
|---|---|---|---|---|---|---|
| **Treatment Group** | **Icatibant** | **Placebo** | **Icatibant** | **Tranexamic Acid** | **Icatibant** | **Placebo** |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Randomized** | 27 | 29 | 36 | 38 | 46 | 47 |
| **Received treatment** | 27 | 29 | 36 | 38 | 46 | 47 |
| **Discontinuations** | 1 (3.7) | 0 | 1 (2.8) | 3 (7.9) | 0 | 1 (1.1) |
| Other | 1 (3.7) | 0 | 1 (2.8) | 1 (2.6) | 0 | 0 |
| Withdrawn consent | 0 | 0 | 0 | 0 | 0 | 0 |
| Adverse event | 0 | 0 | 0 | 0 | 0 | 0 |
| Lost to follow-up | 0 | 0 | 0 | 1 (2.6) | 0 | 0 |
| Death | 0 | 0 | 0 | 1 (2.6) | 0 | 1 (1.1) |
| **Excluded from analysis*** | 0 | 0 | 0 | 0 | 3 | 2 |
| **Analyzed for efficacy**** | 27 | 29 | 36 | 38 | 43 | 45 |

**Randomized laryngeal HAE attacks; **Included in the non-laryngeal ITT population analyzed for primary efficacy endpoint*
*Source: Clinical Study Report for FAST-1, Table 7, Table 9; Clinical Study Report for FAST-2, Table 7, Table 9; Clinical Study Report for FAST-3, Table 6-4*

### 6.1.4 Analysis of Primary Endpoint(s)

As discussed in Section 6.1.1 Methods, the primary efficacy endpoint for FAST-1 and FAST-2 was time to onset of primary symptom relief, whereas the primary endpoint for FAST-3 was time to onset of symptom relief based on the mean composite endpoint VAS-3. For the purposes of comparison across clinical trials, Table 9 summarizes the time to onset of primary symptom relief for all three pivotal efficacy trials. Censored patients are those who did not experience symptom relief within the defined observation period (by Day 14), who were censored at their last recorded observation time.

## Table 9: Median time to onset of primary symptom relief based on VAS score in pivotal Phase 3 efficacy trials

| **Clinical Trial** | **FAST-1** | | **FAST-2** | | **FAST-3** | |
|---|---|---|---|---|---|---|
| **Treatment Group** | **Icatibant** | **Placebo** | **Icatibant** | **Tranexamic Acid** | **Icatibant** | **Placebo** |
| **All non-laryngeal HAE attacks (n)** | 27 | 29 | 36 | 38 | 43 | 45 |
| **Patients with baseline VAS ≥ 30 mm (n)** | 27 | 28 | 35 | 36 | 43 | 45 |
| **Censored patients (n)** | 1 | 1 | 0 | 2 | 0 | 4 |
| **Median time to symptom relief onset (hrs)** | 2.5 | 4.6 | 2.0* | 12.0 | 1.5* | 18.5 |
| | | | | | | |
| **Cutaneous HAE attacks (n)** | 14 | 13 | 24 | 23 | 26 | 26 |
| **Patients with baseline VAS ≥ 30 mm (n)** | 14 | 13 | 23 | 23 | 26 | 26 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Censored patients (n)** | 0 | 1 | 0 | 2 | 0 | 4 |
| **Median time to symptom relief onset (hrs)** | 3.4 | 10.0 | 2.5* | 18.2 | 2.0* | 22.5 |
| | | | | | | |
| **Abdominal HAE attacks (n)** | 13 | 16 | 12 | 15 | 17 | 19 |
| **Patients with baseline VAS ≥ 30 mm (n)** | 13 | 15 | 12 | 13 | 17 | 19 |
| **Censored patients (n)** | 1 | 0 | 0 | 0 | 0 | 0 |
| **Median time to symptom relief onset (hrs)** | 2.0 | 3.0 | 1.6** | 3.5 | 1.0*** | 3.6 |

*Versus control group: *p < 0.001, **p = 0.026, ***p = 0.002*
*Source: Clinical Study Report for FAST-1, Section 11.4.1, Tables 22, 23, and 24; Clinical Study Report for FAST-2, Table 22, Table 23, Table 24; Clinical Study Report for FAST-3, Section 7.4.1.1.3.1, Table 7-8, Table 7-9, Section 7.4.2.8.1, Table 10.2.2.1.3; Integrated Summary of Efficacy, Table 3-17*

In the integrated efficacy analyses submitted by the Applicant in this Complete Response, one icatibant-recipient each in FAST-1 (Subject 022-001, with moderate cutaneous symptoms and mild laryngeal symptoms) and FAST-2 (Subject 078-009, with severe cutaneous symptoms and mild laryngeal symptoms) was reclassified as having had a laryngeal HAE attack for analysis purposes, given concurrent laryngeal symptoms. Thus, efficacy endpoints from FAST-1 and FAST-2 were reanalyzed without these subjects considered as part of the blinded treatment phase for the intent-to-treat analysis (which included only subjects with moderate to severe cutaneous and abdominal HAE attacks in FAST-1 and FAST-2). However, no significant differences in treatment effect or statistical significance were noted in these revised analyses for this Complete Response submission, compared to the analyses compiled for the individual Clinical Study Reports for FAST-1 and FAST-2.

As noted in the Not Approvable action letter to the original NDA submission, although a numerical trend in favor of icatibant toward a shorter time to symptom relief onset was noted in FAST-1, this difference was non-significant in this well-designed, randomized Phase 3 trial and was therefore insufficient to establish the efficacy of icatibant for the proposed indication. Moreover, although the statistically significant difference in primary efficacy endpoint that was observed in FAST-2 favored icatibant-recipients over the control group, the uncharacterized effects of tranexamic acid on acute HAE attacks complicated the interpretation of these data. As an unapproved agent for this indication, it could not be ruled-out that tranexamic acid could potentially have a negative treatment effect on HAE attacks and, thus, artificially inflate the magnitude of the positive treatment effect of icatibant observed in FAST-2. Thus, a final determination of the efficacy of icatibant strongly rested on the outcome of FAST-3. In turn, the corresponding key secondary endpoint analysis of FAST-3 demonstrated a statistically

significant treatment effect of icatibant versus placebo, which was observed for the overall non-laryngeal ITT population, as well as for subjects stratified by HAE attack location.

Of note, all three trials demonstrated larger group differences in cutaneous versus abdominal HAE attacks for time to primary symptom relief onset between icatibant and control groups (either placebo or tranexamic acid). The Applicant suggests that this was because pain symptoms (which predominated in abdominal HAE attacks) were more likely to improve following treatment with either icatibant or control agents, compared to edema symptoms, regardless of location. In turn, abdominal pain was the primary symptom used to assess clinical efficacy for abdominal HAE attacks, which the Applicant feels accounts for the smaller treatment differences between icatibant and control-recipients in these trials. However, skin pain did not appear to have the same degree of response to treatment as did abdominal pain, as shown later in Table 11 in Section 6.1.5 Analysis of Secondary Endpoint(s). Moreover, the current understanding of HAE pathophysiology does not suggest any differences that would lead to a differential treatment response in pain symptoms by HAE attack site, based on inhibition of the bradykinin pathway. However, from the data generated in placebo-recipients across all three trials, it is evident that abdominal pain symptoms had a faster onset of spontaneous relief than cutaneous pain symptoms, regardless of whether or not pain was designated the primary HAE symptom. This difference was particularly marked for FAST-2. Thus, although icatibant treatment shortened times to symptom relief onset for both abdominal and cutaneous attacks, the difference in placebo-effect seen for cutaneous versus abdominal pain symptoms largely accounted for the treatment difference in time to onset of primary symptom relief between cutaneous and abdominal laryngeal attacks.

Table 10 summarizes the time to onset of symptom relief based on composite VAS-3 score (abdominal pain, skin pain, skin edema), as well as each individual symptom domain, for the non-laryngeal ITT population for all three pivotal Phase 3 efficacy trials. As discussed earlier, efficacy endpoints based on VAS-3 were prespecified endpoints in FAST-3, but for FAST-1 and FAST-2, all VAS-3-based assessments were *post hoc* analyses. In FAST-1, icatibant-recipients had a decreased and significantly different time to symptom relief onset based on VAS-3, in contrast to the non-significant findings for the primary efficacy endpoint based on primary VAS-based symptom score. Of note, however, time to onset of symptom relief for each of the component symptom domains did not differ between the treatment groups in FAST-1, as shown later in Table 11 in Section 6.1.5 Analysis of Secondary Endpoint(s).

**Table 10: Median time to onset of symptom relief based on composite VAS-3 score in pivotal Phase 3 efficacy trials**

| Clinical Trial | FAST-1 | | FAST-2 | | FAST-3 | |
|---|---|---|---|---|---|---|
| **Treatment Group** | **Icatibant** | **Placebo** | **Icatibant** | **Tranexamic Acid** | **Icatibant** | **Placebo** |
| **Non-laryngeal ITT Population (n)** | 26 | 29 | 35 | 38 | 43 | 45 |
| **VAS-3: Median time to symptom relief onset (hrs)** | 2.3* | 7.9 | 2.0** | 12.0 | 2.0** | 19.8 |

*Versus control group: *0.01 < p ≤ 0.05, **p ≤ 0.001, ***0.001 < p ≤ 0.01*
*Source: Summary of Clinical Efficacy, Table 2.7.3-20*

Sensitivity analyses were conducted on the primary (VAS-3-based) and key secondary (primary symptom VAS-based) efficacy endpoints for each trial individually, using either the Peto-Peto Wilcoxon test or Cox proportional hazards model fitted on the protocol-specific randomization stratification factors (edema location for FAST-1, FAST-2, and FAST-3; prior C1-INH replacement for FAST-3 only). These stratified analyses produced findings consistent with the primary analyses, with regard to statistically significant differences between icatibant and placebo-recipients for the VAS-3-based endpoint in all three trials and the primary symptom-based endpoint in FAST-2 and FAST-3. An additional sensitivity analysis was also performed to assess the effects of rescue medication use by censoring all subjects who used rescue medications before the onset of VAS-3-based and primary symptom-based relief from the randomized treatment analysis of each trial. This resulted in the censoring of 12, 11, and 16 control subjects from FAST-1, FAST-2, and FAST-3, respectively, as well as one icatibant-recipient from FAST-1. Similar to the other sensitivity analyses, median time to onset of VAS-3-based symptom relief remained statistically lower in icatibant versus placebo-recipients for all three trials. In addition, statistically significant group differences remained in time to onset of primary symptom relief, which favored icatibant in FAST-2 and FAST-3. Collectively, these data support the efficacy of icatibant for the proposed indication of the treatment of acute HAE attacks in adults.

### 6.1.5 Analysis of Secondary Endpoints(s)

## Detailed Analysis of Non-laryngeal HAE Attacks

Time to Symptom Relief for Individual VAS Symptom Domains

Median time to onset of symptom relief for each individual symptom domain (i.e., skin swelling, skin pain, abdominal pain) was determined in each trial for all subjects who displayed the symptom at baseline (i.e., VAS ≥ 30 mm). For FAST-1 and FAST-2, individual symptom relief based on VAS was defined by the same graphic line equation

as primary VAS symptom relief. In contrast, for FAST-3, individual symptom relief was defined as a 50% reduction from baseline VAS score. Statistically lower median times to symptom relief onset were noted across all three trials in the icatibant versus control groups for each individual symptom, except for abdominal pain in FAST-1, as shown in Table 11.

**Table 11: Median time to onset of symptom relief based on individual VAS symptom scores in pivotal Phase 3 efficacy trials**

| Clinical Trial | FAST-1 | | FAST-2 | | FAST-3 | |
|---|---|---|---|---|---|---|
| **Treatment Group** | **Icatibant** | **Placebo** | **Icatibant** | **Tranexamic Acid** | **Icatibant** | **Placebo** |
| **Total non-laryngeal ITT Population (n)** | 27 | 29 | 36 | 38 | 43 | 45 |
| **Time to onset of relief: Skin swelling (hrs)** | 3.1* | 10.2 | 2.6** | 18.1 | 3.0** | 22.3 |
| **Time to onset of relief: Skin pain (hrs)** | 1.6*** | 9.0 | 1.5*** | 12.0 | 2.0* | 8.0 |
| **Time to onset of relief: Abdominal pain (hrs)** | 2.0 | 3.3 | 1.6* | 3.5 | 1.8*** | 3.5 |

*Versus control group: *p = 0.01 < p ≤ 0.05, **p ≤ 0.001, ***p = 0.001 < p ≤ 0.01*
*Source: Clinical Study Report for FAST-1, Table 32; Clinical Study Report for FAST-2, Table 41; Clinical Study Report for FAST-3, Table 10.5.2.1*

These results generally support the proposed indication, as statistically significant differences were observed in favor of icatibant treatment for nearly all symptom domains across all three trials.

Time to Almost Complete Symptom Relief

Median time to near complete symptom relief, defined as having all VAS scores ≤ 10 mm, was statistically lower for the icatibant versus control group in FAST-2 and FAST-3 but not FAST-1, as shown in Table 12. Similar to other secondary efficacy endpoint findings, however, the results of FAST-1 reflected a numerical trend favoring icatibant.

**Table 12: Median time to almost complete symptom relief (all VAS scores ≤ 10 mm) in pivotal Phase 3 efficacy trials**

| Clinical Trial | FAST-1 | | FAST-2 | | FAST-3 | |
|---|---|---|---|---|---|---|
| **Treatment Group** | **Icatibant** | **Placebo** | **Icatibant** | **Tranexamic Acid** | **Icatibant** | **Placebo** |
| **Non-laryngeal ITT Population (n)** | 27 | 29 | 36 | 38 | 43 | 45 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Time to almost complete symptom relief (hrs)** | 8.5 | 23.3 | 10.0* | 51.0 | 8.0** | 36.0 |

*Versus control group: *p ≤ 0.001, **p = 0.012*
*Source: Clinical Study Report for FAST-1, Table 33; Clinical Study Report for FAST-2, Table 42; Clinical Study Report for FAST-3, Table 7-10*

Use of Rescue Medications

Rates of rescue medication use at any point during the initial HAE attack consistently favored icatibant-treatment across the randomized treatment phases of all three pivotal Phase 3 efficacy trials, as 14 of 29 (48.3%), 12 of 38 (31.6%), and 18 of 45 (40.0%) control subjects used rescue medications in FAST-1, FAST-2, and FAST-3, respectively, whereas rescue medications were used by only 6 of 27 (22.2%), 7 of 36 (19.4%), and 3 of 43 (7.0%) icatibant-recipients in each of the three trials. The most commonly administered rescue medications across the three trials were C1-INH replacement therapy and opioids for pain relief. Other rescue medications administered included anti-emetic agents, NSAIDs, and glucocorticoids.

Response Rate at 4-hours Post-dosing

In FAST-1 and FAST-2, response rates at 4 hours post-dosing were originally defined as the proportion of subjects with pretreatment VAS scores ≥ 30 mm who experienced an onset of primary symptom relief within 4 hours of study drug administration [FAST-1: icatibant = 18 of 27 (66.7%), control = 13 of 28 (46.4%), non-significant; FAST-2: icatibant = 28 of 35 (80.0%), control = 11 of 36 (30.6%), $p \leq 0.001$]. Given its different primary efficacy endpoint, this specific analysis was not conducted for FAST-3. Rather, response rate in FAST-3 was prespecified as the proportion of subjects with a 50% reduction in baseline VAS-3 score at 4 hours post-dosing. For the purposes of comparison, *post hoc* analyses for FAST-1 and FAST-2 of response rates based on VAS-3 were provided in this Complete Response submission, in which one subject from the non-laryngeal ITT population for each trial was excluded, due to reclassification for the emergence of post-randomization laryngeal HAE symptoms. As shown in Table 13, response rates based on VAS-3 were statistically different and higher in icatibant-recipients versus control subjects in FAST-2 and FAST-3, but not in FAST-1, which was consistent with the prespecified response rate analyses for FAST-1 and FAST-2, based on primary symptom relief. Of note, regardless of whether response rate was a function of primary symptom VAS or composite VAS-3 score, this definition of treatment response is based on a relative reduction in symptoms, rather than on an absence or near-resolution of symptoms. Thus, although this analysis documents a positive treatment effect of icatibant, subjects with severe HAE symptoms at initial onset would still be considered to be treatment responders, even if moderate to mild symptoms persisted post-dosing.

**Table 13: Response rates based on 50% decrease from pretreatment level in VAS-3 in pivotal Phase 3 efficacy trials**

| Clinical Trial | FAST-1 | | FAST-2 | | FAST-3 | |
|---|---|---|---|---|---|---|
| **Treatment Group** | **Icatibant** | **Placebo** | **Icatibant** | **Tranexamic Acid** | **Icatibant** | **Placebo** |
| **Non-laryngeal ITT population (n)** | 26 | 29 | 35 | 38 | 43 | 45 |
| **Responder (n, %)** | | | | | | |
| Yes | 15 (57.7) | 10 (34.5) | 24 (68.6)* | 12 (31.6) | 32 (74.4)** | 14 (31.1) |
| No | 9 (34.6) | 19 (65.5) | 8 (22.9) | 24 (63.2) | 11 (25.6) | 31 (68.9) |

*Versus control group: *p < 0.001, **p < 0.0001*
*Source: Integrated Summary of Efficacy, Table 13.1*

Durability of Response

In FAST-1 and FAST-2, durability of response was originally defined as experiencing an onset of primary symptom relief within eight hours of study drug administration (regardless of rescue medication use), which lasted for at least 24 hours. These rates were determined only among subjects with baseline VAS scores ≥ 30 mm at baseline (pretreatment). Durability of response was not a designated efficacy endpoint for FAST-3, and this type of analysis was not included in the original Clinical Study Report for FAST-3. However, in response to a request for information from the Division dated May 6, 2011, the Applicant provided *post hoc* durability analyses for FAST-3 based on primary VAS symptom score, as defined in FAST-1 and FAST-2. In addition, similar durable response analyses stratified by HAE attack site (cutaneous versus abdominal) were provided, which had also been calculated for FAST-1 and FAST-2 in their original Clinical Study Reports. These results are summarized in Table 14 for all three pivotal efficacy trials. In line with primary efficacy endpoint analyses, no proportional differences in durable response rates were noted in FAST-1 (either for the entire study population or stratified by HAE attack location), while in FAST-2 and FAST-3, durability of response favored icatibant for cutaneous and overall HAE attacks only, but not for abdominal HAE attacks.

**Table 14: Durable response rates in subjects with baseline VAS ≥ 30 mm based on primary VAS symptom score in pivotal Phase 3 efficacy trials (number of subjects, %)**

| Clinical Trial | FAST-1 | | FAST-2 | | FAST-3 | |
|---|---|---|---|---|---|---|
| **Treatment Group** | **Icatibant** | **Placebo** | **Icatibant** | **Tranexamic Acid** | **Icatibant** | **Placebo** |

| | | | | | | |
|---|---|---|---|---|---|---|
| **All non-laryngeal HAE attack subjects** | 27 | 28 | 35 | 36 | 43 | 45 |
| Durable Response | 14 (51.9) | 14 (50.0) | 24 (68.6)* | 14 (38.9) | 37 (86.0)*** | 19 (42.2) |
| **Cutaneous HAE attack subjects** | 14 | 13 | 23 | 23 | 26 | 26 |
| Durable Response | 8 (57.1) | 5 (38.5) | 15 (65.2)** | 5 (21.7) | 22 (84.6)*** | 7 (26.9) |
| **Abdominal HAE attack subjects** | 13 | 15 | 12 | 13 | 17 | 19 |
| Durable Response | 6 (46.2) | 9 (60.0) | 9 (75.9) | 9 (69.2) | 15 (88.2) | 12 (63.2) |

*Versus control group: *0.01 < p < 0.05, **0.001 < p < 0.01, ***p < 0.0001*

*Source: Clinical Study Report for FAST-1, Table 5.3.1.1, Table 5.3.1.2, Table 5.3.1.3; Clinical Study Report for FAST-2, Table 36, Table 37, Table 5.3.1.3; Response to Clinical Information Request dated May 17, 2011, Table 1.1, Table 1.2*

Of note, the Applicant also submitted *post hoc* durability of response analyses for all three trials based on composite VAS-3 symptom score, with a durable response defined as a 50% reduction from pretreatment composite VAS-3 score that began within eight hours post-dosing and was maintained for ≥ 24 hours. Different versions of these analyses are presented in the Complete Response submission, as well as in the Response to Clinical Information Request (communicated by the Applicant on May 17, 2011). These analyses used several variants of the underlying study population as the rate denominator, which differ from the original durability of response analyses provided in the Clinical Study Reports for FAST-1 and FAST-2, including total randomized subjects, subjects with documented onset of symptom relief, classification of rescue medication-recipients as treatment failures, and exclusion of two placebo-recipients from FAST-1 and FAST-2 who were reclassified as laryngeal HAE attack subjects in *post hoc* analyses in the Complete Response submission. Results of these alternative durability of response analyses, did not differ substantially from the original statistical analyses prespecified for all three trials, which are shown in Table 14.

Regression of Symptoms

Both patients and investigators were asked to document the time at which they initially perceived an improvement in symptoms, as summarized in Table 15. Across all three trials, icatibant-recipients reported a median time to initial symptom improvement within the first hour, versus control subjects who had approximately 4-20 fold greater lag times prior to symptom improvement. Interestingly, although investigator assessments of time to initial symptom improvement favored icatibant-recipients across all three trials, investigator assessments were consistently longer than patient assessments with respect to symptom improvement in icatibant-recipients, except in FAST-3. In fact, in FAST-1, only patient assessments, but not investigator assessments, were statistically

lower for icatibant versus control-recipients. Thus, in each of these trials, patients appeared to have a more favorable view of the treatment effect of icatibant than investigators.

## Table 15: Median time to initial symptom improvement in pivotal Phase 3 efficacy trials

| Clinical Trial | FAST-1 | | FAST-2 | | FAST-3 | |
|---|---|---|---|---|---|---|
| **Treatment Group** | **Icatibant** | **Placebo** | **Icatibant** | **Tranexamic Acid** | **Icatibant** | **Placebo** |
| **Non-laryngeal ITT Population (n)** | 27 | 29 | 36 | 38 | 43 | 45 |
| **Patient-assessed (hrs)** | 0.8* | 16.9 | 0.8* | 7.9 | 0.8* | 3.5 |
| **Investigator-assessed (hrs)** | 6.5 | 14.0 | 1.7* | 8.0 | 0.8* | 3.4 |

*Versus control group: *p ≤ 0.001, *p < 0.0001, **p = 0.0001*
*Source: Clinical Study Report for FAST-1, Table 38; Table 40; Clinical Study Report for FAST-2, Table 49, Table 50; Clinical Study Report for FAST-3, Table 7-11*

Patient-based Symptom Severity Scores

Individual symptom severity scores (on a 5-point ordinal scale) were prespecified endpoints in all three pivotal Phase 3 efficacy trials. However, analyses of composite indices based on averages of these symptom severity scores grouped by HAE attack location (non-laryngeal: skin swelling, erythema/redness, skin irritation, skin pain, abdominal pain/tenderness, nausea, vomiting, diarrhea; laryngeal: difficulty swallowing and voice change, in addition to these eight symptom domains) were only determined for FAST-1 and FAST-2 as *post hoc* analyses in the Complete Response submission. These analyses were thus based on adjusted sample sizes that excluded two icatibant-recipients from these trials, who had developed laryngeal symptoms during their initial HAE attack post-randomization and were, therefore, excluded from the non-laryngeal ITT population in this retrospective analysis of FAST-1 and FAST-2 data. However, a comparison of individual symptom score analyses from the original Clinical Study Reports for FAST-1 and FAST-2 and analyses in the Complete Response submission based on these slightly adjusted sample sizes did not substantially impact these findings. As shown in Table 16, greater decreases in patient-assessed 8-domain composite symptom severity scores were noted in icatibant-recipients versus control subjects by 1 hour post-dose across all three trials. By 12 hours post-dose, these group differences were negligible in FAST-1 but had increased in FAST-2 and FAST-3. Thus, overall these self-reported symptom severity assessments reflected an early treatment effect of icatibant versus control treatments.

**Table 16: Median baseline and post-dosing (Hours 1 and 12) changes in patient-based composite symptom severity scores for non-laryngeal HAE attacks in pivotal Phase 3 efficacy trials**

| Clinical Trial | FAST-1 | | FAST-2 | | FAST-3 | |
|---|---|---|---|---|---|---|
| **Treatment Group** | **Icatibant** | **Placebo** | **Icatibant** | **Tranexamic Acid** | **Icatibant** | **Placebo** |
| **Non-laryngeal ITT Population (n)** | 26 | 29 | 35 | 38 | 43 | 45 |
| **Pretreatment Symptom Severity Score** | 0.94 | 1.00 | 0.75 | 0.88 | 1.00 | 0.88 |
| **Change at Hour 1 post-dosing** | -0.38* | -0.13 | -0.13** | 0 | -0.25** | 0 |
| **Change at Hour 12 post-dosing** | -0.63 | -0.63 | -0.63** | -0.38 | -0.69** | -0.06 |

*Versus control group: *p < 0.05, **p < 0.01*
*Source: Integrated Summary of Efficacy, Table 17.1*

Investigator-based Symptom Severity Scores

Similarly, composite investigator-assessed symptom severity scores were not calculated for the original Clinical Study Reports of FAST-1 or FAST-2. However, these composite endpoint analyses were conducted as *post hoc* analyses for these earlier efficacy trials (with slightly reduced sample sizes) in the Complete Response submission and were presented in comparison to similar prespecified analyses for FAST-3, as shown in Table 17. Greater decreases in investigator-assessed 8-domain composite symptom severity scores were noted in icatibant-recipients versus control subjects at 1 hour post-dose. By 12 hours post-dose, group differences were negligible in FAST-1 (albeit statistically significant) and FAST-2 (although favoring icatibant-recipients), with a marked decrease noted only in FAST-3. Thus, collectively, these results were also supportive of an early treatment effect of icatibant versus control treatments, as recognized by investigators.

**Table 17: Median baseline and post-dosing (Hours 1 and 12) changes in investigator-based composite symptom severity scores for non-laryngeal HAE attacks in pivotal Phase 3 efficacy trials**

| Clinical Trial | FAST-1 | | FAST-2 | | FAST-3 | |
|---|---|---|---|---|---|---|
| **Treatment Group** | **Icatibant** | **Placebo** | **Icatibant** | **Tranexamic Acid** | **Icatibant** | **Placebo** |
| **Non-laryngeal ITT Population (n)** | 26 | 29 | 35 | 38 | 43 | 45 |
| **Pretreatment Symptom Severity Score** | 0.81 | 0.88 | 0.88 | 0.88 | 0.63 | 0.69 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Change at Hour 1 post-dosing** | -0.25* | 0 | -0.25* | 0 | -0.25* | 0 |
| **Change at Hour 12 post-dosing** | -0.56** | -0.50 | -0.75 | -0.50 | -1.0* | 0 |

*Versus control group: *p ≤ 0.01, **0.01 < p < 0.05*
*Source: Integrated Summary of Efficacy, Table 21.1*

Investigator-based Clinical Global Assessment

Global investigator-based assessments that took into account abdominal, cutaneous, and laryngeal symptoms for all HAE attacks were graded on a 5-point ordinal scale ranging from 0 = absence of symptoms to 4 = very severe. The distribution of cutaneous symptom severity ratings at 4 hours post-dosing statistically differed between icatibant-recipients and control subjects in FAST-2 and FAST-3, with a greater proportion of lower ratings noted in the icatibant group. However, this finding was not observed in FAST-1. Differences in global assessments of abdominal symptoms were less disparate between icatibant and control groups, although symptom improvement based on clinical global assessment occurred more rapidly in icatibant-recipients in FAST-2 and FAST-3, with a statistical difference in rating distribution noted in FAST-1 to favor icatibant at Hour 24 post-dosing. However, interpretation of the global assessment endpoint is complicated by an imbalance noted pretreatment in which icatibant-recipients in all three trials had a greater proportion (albeit not statistically different) of severe cutaneous symptoms at baseline, compared to their respective control groups.

Investigator-based Clinical Global Improvement

Global investigator-based impressions of symptom improvement were made periodically throughout the 14-day observation period, using a 7-point ordinal rating scale from 1 = normal, not ill to 7 = among the most extremely ill. Statistically greater symptom improvements were noted by 4 hours post-dose in the icatibant versus control groups in all three trials.

## Detailed Analysis of Laryngeal HAE Attacks

The relatively small number of subjects experiencing laryngeal HAE attacks during the primary treatment phase of the three pivotal Phase 3 efficacy trials limits the generalizability of these data, as does the limited number of subjects treated with placebo for laryngeal HAE attacks (occurring only after protocol Amendment 1 in FAST-3). The Applicant has submitted an analysis of all subjects treated for a first laryngeal HAE attack, with either blinded or open-label treatment, in the Integrated Summary of Efficacy by individual pivotal efficacy trial, as well as pooled total icatibant-recipients.

These *post hoc* analyses included two subjects from FAST-1 and FAST-2 who were reclassified as having had laryngeal HAE attacks, although these subjects were not grouped in the original laryngeal HAE attack population identified in the Clinical Study Reports for FAST-1 and FAST-2. Overall, however, reclassification of these two subjects did not appear to result in marked differences in the overall conclusions drawn from this laryngeal HAE attack population.

Patient-based Symptom Severity Scores

Over time, progressively greater decreases in patient-assessed 10-domain composite symptom severity scores were noted in icatibant-recipients treated for an initial laryngeal HAE attack, as shown in Table 18. It is unclear, however, whether these trends may reflect a treatment effect of icatibant or the rate of spontaneous resolution of laryngeal HAE attacks in this study population. Of note, there was a greater decrease in self-reported symptoms for placebo-recipients in FAST-3 (who had been randomized to blinded treatment with placebo), but this median value was based on only two subjects at Hour 4 post-dosing, while no placebo-recipients had data available for Hour 12. Thus, the utility of this randomized comparison is limited.

**Table 18: Median baseline and post-dosing (Hours 4 and 12) changes in patient-based composite symptom severity scores for laryngeal HAE attacks in pivotal Phase 3 efficacy trials**

| Clinical Trial | FAST-1 | FAST-2 | FAST-3 | | Pooled |
|---|---|---|---|---|---|
| **Treatment Group** | **Icatibant (N = 15)** | **Icatibant (N = 5)** | **Icatibant (N = 8)** | **Placebo (N = 2)** | **Icatibant (N = 28)** |
| **Pretreatment Symptom Severity Score** | 0.80 | 0.65 | 0.80 | 0.95 | 0.80 |
| **Change at Hour 4 post-dosing** | -0.50 | -0.50 | -0.50 | -1.50 | -0.50 |
| **Change at Hour 12 post-dosing** | -0.80 | -0.85 | -0.80 | --- | -0.80 |

*Source: Integrated Summary of Efficacy, Table 17.3*

A review of individual patient-reported symptom severity scores indicated that 17 of 25 subjects (68.0%) with available data from an initial laryngeal HAE attack had difficulty swallowing of moderate to worse severity at baseline. By 12 hours post-dosing, however, all but one subject reported absent or mild difficulty swallowing. Similarly, 60.0% of these subjects had voice change of moderate or worse severity at baseline, and all but one reported absent or mild voice change by 12 hours post-dose.

Median composite patient-reported symptom severity scores were also reported for the 60 subjects who experienced a laryngeal attack at any point in the three trials (FAST-1: 27 subjects, FAST-2: 12 subjects, FAST-3: 21 subjects). Baseline scores were similar among these trials (FAST-1: 0.80, FAST-2: 0.60, FAST-3: 0.60), with slightly greater decreases in FAST-2 at 2 hours post-dose (FAST-1: -0.10, FAST-2: -0.40, FAST-3: -0.25) but similar reductions observed at 12 hours post-dose (FAST-1: -0.85, FAST-2: -0.80, FAST-3: -0.70). The distribution of individual symptom severity ratings for the 10 component symptom domains demonstrated similar patterns, with steady improvement from baseline over the 12 hours post-dosing. Although it also improved, skin swelling appeared to be the most recalcitrant symptom, although no moderate or severe symptoms were reported at 12 hours.

Investigator-based Symptom Severity Scores

Progressively greater decreases in investigator-assessed 13-domain composite symptom severity scores were noted in icatibant-recipients in all three trials over time (data for Hour 1 and Hour 8 are shown, as subjects in FAST-3 were not assessed for this endpoint at Hour 12), as summarized in Table 19.

**Table 19: Median baseline and post-dosing (Hours 1 and 8) changes in investigator-based composite symptom severity scores for laryngeal HAE attacks in pivotal Phase 3 efficacy trials**

| Clinical Trial | FAST-1 | FAST-2 | FAST-3 | | Pooled |
|---|---|---|---|---|---|
| **Treatment Group** | **Icatibant (N = 15)** | **Icatibant (N = 5)** | **Icatibant (N = 8)** | **Placebo (N = 2)** | **Icatibant (N = 28)** |
| **Pretreatment Symptom Severity Score** | 0.46 | 0.85 | 0.54 | 0.81 | 0.62 |
| **Change at Hour 1 post-dosing** | -0.15 | -0.58 | -0.23 | -0.54 | -0.23 |
| **Change at Hour 8 post-dosing** | -0.46 | -0.85 | -0.46 | -0.23 | -0.54 |

*Source: Integrated Summary of Efficacy, Table 21.3*

A review of individual investigator-reported symptom severity scores indicated that at baseline, 9 of 21 subjects (42.9%) with available data had dysphagia of moderate or worse severity, 52.4% had voice change of moderate or worse severity, 23.8% had breathing difficulties of moderate or worse severity, and 19.0% had stridor of moderate or worse severity. However, by 12 hours post-dose, only a single patient still reported dysphagia, voice change, or breathing difficulties, while no patients reported stridor by 5 hours post-dose. Although the lack of a randomized placebo-control group of sufficient

size complicates the interpretation of these findings, symptom improvements in laryngeal symptoms are highly clinically relevant, given the significant intubation risk and mortality associated with acute laryngeal HAE attacks.

Regression of Symptoms

Both patients and investigators were asked to document the time in hours from initial study drug dosing at which they initially perceived an improvement in laryngeal HAE attack symptoms, as summarized in Table 20. This table includes data from all subjects treated for a laryngeal HAE attack at any point in the three trials (i.e., including both the primary treatment and open-label extension phases), as opposed to only those experiencing an initial laryngeal HAE attack. Patient assessments were similar across all three trials (0.6-0.8 hrs). Of note, investigator assessments were not collected during the open-label extension phases of FAST-1 and FAST-2, complicating the interpretation of data from the pooled analysis of icatibant-recipients. However, similar to the patient-based assessments, the median time to investigator-assessed initial symptom improvement in FAST-3 was also 0.8 hrs (95% CI: 0.5-1.1 hrs). Thus, based on this limited, largely open-label treated sample, post-icatibant symptom improvement times appeared shorter for laryngeal versus non-laryngeal HAE attacks.

**Table 20: Median time to patient-based initial symptom improvement for all icatibant-treated laryngeal HAE attacks from pivotal Phase 3 efficacy trials (both primary treatment and open-label extension phases)**

| Clinical Trial | FAST-1 | FAST-2 | FAST-3 | Pooled |
|---|---|---|---|---|
| **Treatment Group** | **Icatibant** | **Icatibant** | **Icatibant** | **Icatibant** |
| **Total Laryngeal Population (n)** | 12 | 27 | 21 | 60 |
| **Patient-assessed (hrs)** | 0.6 | 0.8 | 0.8 | 0.6 |
| ***Investigator-assessed (hrs)** | --- | --- | 0.8 | 2.3 |

**Investigator-assessments were not done during the extension phases of FAST-1 and FAST-2*
*Source: Integrated Summary of Efficacy, Table 3-35*

Investigator-based Clinical Global Assessment

Global investigator-based assessments of laryngeal HAE attacks that took into account all abdominal, cutaneous, and laryngeal symptoms were graded on a 5-point ordinal scale ranging from 0 = absence of symptoms to 4 = very severe. Similar to ratings for initial non-laryngeal HAE attacks, the proportion of subjects with icatibant-treated initial laryngeal HAE attacks with moderate or severe symptoms was consistently decreased

at 4 hours post-dose compared to baseline for all three types of symptoms, with no subjects reporting severe symptoms at 4 hours post-dose. This was observed both for pooled analyses of all initial laryngeal attacks during the primary treatment phase, as well as separately within each individual trial.

Similar results were also seen for the overall laryngeal attack population comprised of the 60 subjects that experienced laryngeal HAE attacks, regardless of order. Despite severe and very severe laryngeal and concurrent cutaneous symptoms being noted in this population at baseline, none were observed by 4 hours post-dose. Concurrent abdominal symptoms were not as severe as cutaneous symptoms at baseline, with only 1 subject in FAST-3 rated as severe. However, by 4 hours post-dose, no subjects were noted to have any abdominal symptoms rated more than mild.

Clinical Global Improvement

Across all three trials, all subjects with laryngeal attacks were noted to have overall clinical improvement by the investigator at 4 hours post-dosing, except for one subject who was judged to be minimally worse. All other subjects were noted to be either much improved or very much improved, with only one subject rated as having minimal improvement. Subjects in FAST-3 only were similarly asked to assess their symptom improvement using a 7-point ordinal rating scale. At 4 hours post-dose 18 of 21 subjects (90.0%) rated their symptoms as much improved or very much improved, with one subject (5.0%) rated as minimally improved and one subject rated as minimally worse.

Use of Rescue Medications

No subject treated for a laryngeal attack with icatibant in any of the three trials used rescue medications prior to the onset of symptom relief, although 5 of 23 subjects (17.9%) with available data used rescue medications within five days of the onset of the acute HAE attack. Rates of rescue medication use in icatibant-recipients at any time during the attack were similar across the three trials (FAST-1: 3 of 15 subjects (20.0%); FAST-2: 1 of 5 subjects (20.0%); FAST-3: 1 of 8 subjects (12.5%). These data are difficult to interpret without a randomized placebo comparator.

Time to VAS-based Symptom Relief: Primary Symptom and VAS-5

Symptom scores during laryngeal attacks based on VAS ratings were only collected for FAST-3, and analyses of these endpoints reflect the 21 subjects who experienced laryngeal attacks from this trial only. VAS-5 is a 5-component composite symptom score based on mean VAS ratings for skin swelling, skin pain, abdominal pain, difficulty swallowing, and voice change, with time to symptom relief defined as a 50% reduction from baseline VAS-5. The median time to symptom onset based on VAS-5 was 2.2

hours (95% CI: 1.5-3.5 hrs). By 2 hours post-dosing, 9 of 20 subjects (45%) with available data had a reduction in VAS-5 to below 50% of baseline. Similar rates of improvement at this time point to below 50% of baseline were also observed for the laryngeal-specific symptom domains comprising VAS-5 (difficulty swallowing: 47.6%; voice change: 42.9%).

The primary symptom rating for acute laryngeal attacks was based on the most severe symptom at baseline of either difficulty swallowing or voice change, with the former selected if both symptoms were equal in severity. Onset of primary symptom relief was defined as for non-laryngeal attacks, using the same graphic algorithm based on a line defined as Y = 6/7 X –16 mm with X ≥ 30 mm, where X = pre-treatment (baseline) VAS in mm and Y = post-treatment VAS in mm). Median time to primary symptom relief was 2.2 hours (95% CI: 1.5-3.0 hours), similar to that for non-laryngeal attacks in the blinded treatment phases of the three pivotal efficacy trials. The median time to near complete symptom relief based on all VAS scores being ≤ 10 mm was 6.2 hours (95% CI: 3.2-24.3 hours), which was faster than that observed for non-laryngeal HAE attacks.

### 6.1.6 Other Endpoints

Exploratory *post hoc* analyses were submitted for the three pivotal efficacy trials for time to symptom relief based on 30%, 40%, 60%, and 70% reductions from pretreatment composite VAS-3 score (thus excluding the two subjects from FAST-1 and FAST-2 who were reclassified as having had laryngeal HAE attacks). As shown in Table 21, median times to VAS-3-based symptom relief were consistently lower in the icatibant versus placebo groups and statistical significance was observed in group differences in all alternative cut-off analyses, except when the 70% cut-off was applied to FAST-1 data, thus supporting the primary analysis of response rates based on a 50% cut-off.

**Table 21: Exploratory analyses of alternative cut-offs for median time to symptom relief based on VAS-3 in pivotal Phase 3 efficacy trials**

| Clinical Trial | FAST-1 | | FAST-2 | | FAST-3 | |
|---|---|---|---|---|---|---|
| **Treatment Group** | **Icatibant** | **Placebo** | **Icatibant** | **Tranexamic Acid** | **Icatibant** | **Placebo** |
| **Non-laryngeal ITT Population (n)** | 26 | 29 | 35 | 38 | 43 | 45 |
| **Time to onset of symptom relief: 30% cut-off (hrs)** | 1.8* | 4.0 | 1.5** | 10.0 | 1.5** | 8.0 |
| **Time to onset of symptom relief: 40% cut-off (hrs)** | 1.8* | 6.0 | 1.6** | 11.0 | 1.5** | 16.3 |
| **Time to onset of symptom relief: 60% cut-off (hrs)** | 2.3* | 8.0 | 2.0** | 16.3 | 2.5** | 23.8 |
| **Time to onset of symptom relief: 70% cut-off (hrs)** | 2.5 | 12.0 | 5.0** | 26.0 | 3.7** | 29.5 |

*Versus control group: *p 0.01 < p < 0.05, **p < 0.0001*
*Source: Integrated Summary of Efficacy, Table 3-20*

### 6.1.7 Subpopulations

The primary and key secondary efficacy endpoints were analyzed by subgroups for each of the pivotal Phase 3 efficacy trials: time to onset of symptom relief based on composite VAS-3 score and time to onset of primary symptom relief. Table 22 summarizes the median times to onset of symptom relief for each of these variables by specific demographic subgroups. Although these trials were not designed to evaluate demographic associations from a statistical perspective, there appears to be a trend toward delayed response times to icatibant in male subjects relative to female subjects. This was seen across all three trials, suggesting a consistent effect, which may relate to higher systemic levels of icatibant observed in females in the Phase 2 clinical pharmacology trial JE049-2101. However, the times to onset of symptom relief were lower in both male and female icatibant-recipients compared to control subjects, thus establishing the efficacy of icatibant in both genders. In addition, the same pattern of delayed symptom improvement in male subjects was also seen in the placebo and tranexamic acid groups, suggesting that HAE symptoms are more recalcitrant in males versus females in general. Interestingly, longer times to symptom onset relief were also evident for increasing weight groups in icatibant-recipients in FAST-2. This trend was not evident in control subjects in FAST-2, or in either icatibant or placebo-recipients in FAST-1 or FAST-3. Given these limited stratified sample sizes, it is difficult to assess the clinical significance and generalizability of these findings. As placebo-recipients still experienced longer times to symptom relief onset than icatibant-recipients in each weight stratum in FAST-2, icatibant appeared effective across all weight categories.

**Table 22: Median time to onset of composite (VAS-3) and primary symptom relief in pivotal Phase 3 efficacy trials, stratified by selected demographic factors (hrs)**

| Clinical Trial | FAST-1 | | | | FAST-2 | | | | FAST-3 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Time to Onset of Symptom Relief | VAS-3 | | Primary | | VAS-3 | | Primary | | VAS-3 | | Primary | |
| Treatment Group | I | P | I | P | I | T | I | T | I | P | I | P |
| N (per Tx group) | 26 | 29 | 26 | 29 | 35 | 38 | 35 | 38 | 43 | 45 | 43 | 45 |
| **Age** | | | | | | | | | | | | |
| *≤ 30 yrs* | 2.3 | 7.9 | 3.0 | 5.0 | 2.8 | 13.1 | 2.8 | 8.0 | 2.0 | 16.2 | 2.0 | 16.2 |
| *> 30 to ≤ 40 yrs* | 1.5 | 8.0 | 1.0 | 4.8 | 1.5 | 14.0 | 1.5 | 13.0 | 2.0 | 24.5 | 1.5 | 21.9 |
| *> 40 to ≤ 50 yrs* | 5.1 | 13.9 | 2.7 | 6.1 | 1.3 | 12.0 | 1.8 | 18.5 | 2.1 | 19.8 | 1.6 | 19.8 |
| *> 50 yrs* | 3.5 | 1.0 | 3.8 | 1.0 | 3.5 | 10.0 | 2.6 | 10.0 | 2.5 | 23.8 | 1.3 | 2.0 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Gender** | | | | | | | | | | | | |
| *Male* | 5.1 | 32.8 | 2.7 | 23.0 | 4.7 | 17.1 | 4.4 | 13.0 | 2.3 | 27.8 | 1.8 | 27.8 |
| *Female* | 2.0 | 6.0 | 2.0 | 3.5 | 1.6 | 9.0 | 1.6 | 7.0 | 2.0 | 8.0 | 1.5 | 8.0 |
| **Race** | | | | | | | | | | | | |
| *White* | 2.3 | 7.9 | 2.3 | 5.0 | 2.0 | 12.0 | 2.0 | 10.1 | 2.0 | 20.1 | 1.6 | 19.1 |
| *Non-white* | --- | --- | --- | --- | --- | --- | --- | --- | 1.5 | 8.0 | 1.0 | 2.5 |
| **Weight** | | | | | | | | | | | | |
| *≤ 50 kg* | 6.8 | 2.0 | 3.5 | 1.5 | 1.0 | 1.5 | 1.0 | 3.5 | 3.2 | 4.0 | 1.5 | 4.5 |
| *> 50 to ≤ 75 kg* | 2.0 | 4.6 | 2.0 | 3.3 | 1.5 | 10.0 | 2.0 | 8.0 | 2.0 | 21.8 | 1.8 | 11.1 |
| *> 75 to ≤ 100 kg* | 5.1 | 32.8 | 5.0 | 23.0 | 3.5 | 17.1 | 2.0 | 14.0 | 1.5 | 23.9 | 1.0 | 30.6 |
| *> 100 kg* | 1.5 | 13.9 | 2.0 | 3.3 | 5.0 | 6.5 | 4.0 | 6.5 | 4.0 | 11.1 | 3.5 | 11.1 |

*I = icatibant-recipient, P = placebo-recipient, T = tranexamic acid, Tx = treatment*
*Source: Integrated Summary of Efficacy, Table 7.1.1, Table 7.1.2, Table 7.1.3, Table 7.1.4, Table 9.1.1, Table 9.1.2, Table 9.1.3, Table 9.1.4*

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

As discussed in Section 4.4.2 Pharmacodynamics, formal dose-ranging trials were not conducted in the icatibant clinical development program. Rather, dose-selection was based on the levels of bradykinin expected to occur in acute HAE attacks and the levels of icatibant needed to nearly completely antagonize the effects of bradykinin, as determined in studies utilizing an IV bradykinin challenge model in healthy adults. In addition, supportive data suggesting the comparability of the pharmacokinetic profile of icatibant in HAE patients and healthy adults were generated in the Phase 2 trial JE049-2101, in which HAE patients received a single dose of either IV or SC icatibant for an acute cutaneous or abdominal HAE attack. Likewise, efficacy data in support of dose-selection were also generated in this trial for three IV dosing regimens (0.4 mg/kg IV over 2 hrs; 0.4 mg/kg IV over 30 min; 0.8 mg/kg IV over 30 min) and two SC dose levels (30 mg SC; 45 mg SC) of icatibant. Based on these data, the Applicant chose to evaluate only a single dose level of icatibant (30 mg SC) in the Phase 3 development program. As noted in the Not Approvable action letter issued for the original NDA submission, the Applicant was instructed to address this deficiency by further defining dose-selection in a sufficient number of patients, based on clinical endpoints or another validated related biomarker. The Applicant has not submitted additional dose-ranging data in this Complete Response based on clinical endpoints or validated biomarkers. However, a population pharmacokinetic analysis and pharmacokinetic-pharmacodynamic modeling data were newly submitted in this Complete Response, as well as an additional clinical pharmacology trial (HGT-FIR-065). Review of these newly submitted data by the Clinical Pharmacology Review Team is ongoing.

Given the rarity of HAE, the Division recognizes that there are significant challenges to enrolling a sufficient number of HAE patients in dose-ranging trials of adequate size to evaluate multiple dose levels and dosing regimens of novel therapies for the treatment of acute HAE attacks. Thus, the Applicant's pharmacodynamic-based approach to dose-selection is generally acceptable, as the pathophysiologic symptoms of HAE are

generally believed to be mediated by dysregulated bradykinin accumulation. Thus, the nominal dose of icatibant that was selected for evaluation in Phase 3 clinical trials is supported by the additional pharmacokinetic and pharmacodynamic analyses and clinical efficacy and safety data submitted in this Complete Response. In addition, the capacity of the 30 mg SC dose to confer a significant treatment benefit versus placebo for the proposed indication, within the context of an acceptable safety and tolerability profile, was confirmed by the results of FAST-3, with the findings from FAST-1 and FAST-2 serving as supportive data.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Time to onset of symptom relief was analyzed as the primary efficacy variable in all Phase 3 trials and has already been discussed in Section 6.1.4 Analysis of Primary Endpoint(s). Persistence of effect was assessed in FAST-4 by evaluating clinical status at the 48-hour post-dosing time point, as well as by monitoring mean VAS scores throughout this period. These findings were discussed in Section 7.4.5 Special Safety Studies/Clinical Trials. Given the intermittent nature of acute HAE attacks, their variability of duration, and their tendency for spontaneous resolution in the absence of specific therapy, it was difficult to assess the persistence of effect of icatibant beyond the defined 14-day post-dosing observation period. In fact, by the nature of the trial design of the Phase 3 program, HAE symptoms that occurred more than 48 hours after initial study drug dosing were considered to constitute a new acute HAE attack for which a subject could receive additional doses of icatibant during an open-label extension phase. Thus, the clinical program was not designed to evaluate the potential prophylactic effects of icatibant treatment in preventing subsequent HAE attacks.

On the other hand, the recurrent nature of HAE attacks allowed for an assessment of the development of tolerance to icatibant during the open-label extension phase of the pivotal Phase 3 efficacy trials, given that subjects were treated with open-label icatibant for all subsequent acute HAE attacks. Summary efficacy data are presented for the first five acute HAE attacks, which demonstrated similar requirements for total number of icatibant doses (one, two, or three), as well as similar times to onset of symptom relief based on both primary symptom score and VAS-3, as shown in Table 23. Thus, the development of tolerance to icatibant does not appear to be a concern.

**Table 23: Summary of pooled icatibant treatment efficacy results for recurrent non-laryngeal HAE attacks across all pivotal Phase 3 efficacy trials, including open-label extension phases**

| HAE Attack Number | Attack 1 (N = 225) | Attack 2 (N = 146) | Attack 3 (N = 96) | Attack 4 (N = 67) | Attack 5 (N = 48) |
|---|---|---|---|---|---|
| **Number of Injections** | | | | | |
| *One (n, %)* | 217 (96.4) | 137 (93.8) | 86 (89.6) | 65 (97.0) | 41 (85.4) |
| *Two (n, %)* | 8 (3.6) | 7 (4.8) | 10 (10.4) | 1 (1.5) | 7 (14.6) |
| *Three (n, %)* | 0 | 2 (1.4) | 0 | 1 (1.5) | 0 |

| | | | | | |
|---|---|---|---|---|---|
| **Time to onset of symptom relief:** *Primary symptom (median, 95% CI)* | 2.0 (1.5 - 2.0) | 1.6 (1.5 - 2.0) | 2.0 (1.5 - 2.5) | 1.5 (1.3 - 2.5) | 1.3 (1.0 - 2.0) |
| **Time to onset of symptom relief:** *VAS-3 (median, 95% CI)* | 2.0 (1.6 - 2.5) | 2.0 (1.6 - 2.1) | 2.4 (2.0 - 2.5) | 2.0 (1.5 - 3.0) | 1.5 (1.4 - 2.1) |

*CI = confidence interval*
*Source: Summary of Clinical Efficacy, Table 2.7.3-19*

# 7 Review of Safety

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The focus of this integrated review of safety is a pooled analysis of the 225 adults who were treated with a single injection of icatibant 30 mg SC for an initial moderate to severe cutaneous and/or abdominal acute HAE attack during the randomized, controlled treatment phases of FAST-1, FAST-2, and FAST-3. A detailed discussion of safety data from FAST-3 may be found in Appendix Section 9.2 Detailed Reviews of Individual Study Reports. As the individual safety data from FAST-1 and FAST-2 were reviewed in detail in the original NDA submission, they are not discussed separately in this review. Collectively, the safety and tolerability of icatibant was assessed in these trials through reports of AEs/SAEs, clinical laboratory tests, physical examination, vital signs assessments, and 12-lead ECG testing. Safety information is also reviewed from an analysis of the first five icatibant-treated HAE attacks (cutaneous, abdominal, or laryngeal) experienced by these 225 subjects, across both the primary treatment and open-label extension phases of these three pivotal efficacy trials. Safety data from FAST-4, which specifically pertain to the self-administration of icatibant by non-healthcare workers in nonclinical settings are reviewed and discussed separately in Section 7.4.5 Special Safety Studies/Clinical Trials.

### 7.1.2 Categorization of Adverse Events

AEs were categorized using terminology specified in MedDRA version 8.1. AE data are coded in an acceptable manner for analysis and review.

### 7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

For the purposes of this integrated safety review, pooled safety data are presented for the non-laryngeal ITT population from the randomized treatment phases of all three pivotal Phase 3 efficacy trials: FAST-1, FAST-2, and FAST-3. Data are presented by treatment group, with separate categories for icatibant-treated subjects (from FAST-1, FAST-2, and FAST-3), placebo-treated subjects (from FAST-1 and FAST-3), and tranexamic acid-treated subjects (from FAST-2). Data presented for sequential HAE attacks combine blinded treatment phase and open-label extension phase data from all three pivotal Phase 3 efficacy trials, as well.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The Applicant reports that across the icatibant clinical development program (Phase 2-3), a total of 999 HAE attacks in 236 HAE patients have been treated with icatibant 30 mg SC administered by healthcare workers. In addition, a single 30 mg SC dose of icatibant was self-administered in 56 subjects with HAE in FAST-4, with one subject receiving an additional dose from a healthcare worker for the same attack. An additional four subjects with HAE each received a single dose of icatibant 30 mg SC in the only Phase 2 trial (JE049-2101) conducted in the icatibant program, while 129 healthy subjects were exposed to icatibant 30 mg SC in Phase 1 trials. These earlier Phase 1-2 trials were reviewed in the original NDA submission.

Exposure data for the overall Phase 3 safety population is presented in Table 24, summarizing the total number of HAE attacks treated and SC icatibant doses administered for the three pivotal Phase 3 efficacy trials pooled for this integrated safety analysis: FAST-1, FAST-2, and FAST-3. Across the randomized treatment phases of these trials in which subjects received treatment for their initial qualifying HAE attack, a total of 113 subjects received icatibant, 38 subjects received tranexamic acid, and 75 subjects received placebo. During the open-label extension phases of these trials, recurrence rates of HAE attacks were highly variable, ranging from 0 to 141 repeat HAE attacks per patient, although most subjects were treated for $\leq$ 5 recurrent HAE attacks. Specifically, in the open-label extension phase of FAST-1, 72 subjects were treated up to 32 times for a total of 340 recurrent HAE attacks, with a second icatibant injection given in 10.8% of patients and a third injection administered in 1.2% of patients. In the open-label extension phase of FAST-2, 54 subjects were treated up to 141 times for a total of 374 recurrent HAE attacks, with similar rates of additional icatibant doses for individual attacks: a second injection given in 10.2% of patients and a third injection

given in 0.3% of patients. The open-label extension phase of FAST-3 is ongoing, with 96 of 98 subjects actively enrolled at the time of the Complete Response submission (one placebo-recipient having died and one open-label icatibant-recipient having been lost to follow-up during the blinded treatment phase). However, summary data available in this Complete Response for all three pivotal efficacy trials indicate that approximately 90% of HAE patients across these trials were managed with only a single dose of icatibant 30 mg SC for each acute HAE attack.

Thus, if the entire duration of the Phase 3 program is considered, including the open-label extension phases for each trial in which patients received open-label icatibant for all subsequent HAE attacks (ranging from 55-71% of subjects across the three treatment groups), a total of 225 subjects received treatment at some point with icatibant for 987 HAE attacks with a total of 1076 doses of icatibant 30 mg SC. Of these icatibant-recipients, 76 received icatibant once, while 41 received more than five doses of icatibant across all treated HAE attacks. The number of patients treated with one, two, or three sequential 30 mg SC doses of icatibant for each of the first five sequential HAE attacks is also shown. Only a limited number of subjects were treated during the open-label extension phase with two or three 30 mg doses of icatibant for a single HAE attack, as the majority of subjects received only one injection per HAE attack. Thus, this safety database is less informative with regard to larger overall icatibant doses for a single HAE attack, as it is for recurrent, intermittent icatibant dosing for recurrent HAE attacks.

**Table 24: Summary of all icatibant exposures and acute HAE attacks treated with icatibant in pivotal Phase 3 efficacy trials**

| **Number of total icatibant exposures across all sequential HAE attacks** | |
|---|---|
| 0 | 42 |
| 1 | 76 |
| 2 | 50 |
| 3 | 28 |
| 4 | 20 |
| 5 | 10 |
| >5 | 41 |

| **Doses given per acute HAE attack** | **Attack 1 (N = 225)** | **Attack 2 (N = 146)** | **Attack 3 (N = 96)** | **Attack 4 (N = 67)** | **Attack 5 (N = 48)** |
|---|---|---|---|---|---|
| 1 SC dose (30 mg) | 217 (96.4) | 137 (93.8) | 86 (89.6) | 65 (97.) | 41 (85.4) |
| 2 SC doses (60 mg) | 8 (3.6) | 7 (4.8) | 10 (10.4) | 1 (1.5) | 7 (14.6) |
| 3 SC doses (90 mg) | 0 | 2 (1.4) | 0 | 1 (1.5) | 0 |

*Source: Integrated Summary of Safety, Table 1-3; Integrated Summary of Efficacy, Table 3-13*

A demographic description of the Phase 3 safety population (subjects treated with randomized blinded treatment for their initial qualifying non-laryngeal HAE attack) by individual clinical trial is provided in Table 5 in Section 6.1.2 Demographics. However, Table 25 summarizes key demographic characteristics and baseline traits for this pooled safety population by treatment group. With the addition of FAST-3, the pooled safety database has adequate representation from domestic study sites within the U.S.

## Table 25: Demographic and baseline characteristics of pooled Phase 3 safety population

| Characteristic | Icatibant (N = 113) | Tranexamic Acid (N = 38) | Placebo (N = 75) |
|---|---|---|---|
| **Sex (n, %)** | | | |
| *Female* | 71 (62.8) | 23 (60.5) | 51 (68.0) |
| *Male* | 42 (37.2) | 15 (39.5) | 24 (32.0) |
| **Race (n, %)** | | | |
| *White* | 105 (92.9) | 38 (100) | 66 (88.0) |
| *Non-White* | 8 (7.1) | 0 | 9 (12.0) |
| **Age (years)** | | | |
| *Mean* | 37.6 | 41.9 | 35.9 |
| *Median* | 36.0 | 42.0 | 35.0 |
| *Range* | 19-83 | 19-66 | 18-66 |
| **BMI (kg/cm$^2$)** | | | |
| *Mean* | 27.9 | 25.3 | 27.9 |
| *Median* | 26.3 | 24.05 | 26.6 |
| *Range* | 15.8-49.7 | 17.7-35.1 | 18.0-44.7 |
| **Geographic Region** | | | |
| *North America* | 51 (45.1) | 0 | 51 (68.0) |
| *(United States)* | 48 (42.5) | 0 | 47 (62.7) |
| *Western Europe* | 27 (23.9) | 27 (71.1) | 0 |
| *Eastern Europe* | 14 (12.4) | 7 (18.4) | 4 (5.3) |
| *Other* | 21 (18.6) | 4 (10.5) | 20 (26.7) |
| **Initial HAE attack** | | | |
| *Cutaneous* | 64 (56.6) | 23 (60.5) | 39 (52.0) |
| *Abdominal* | 42 (47.2) | 15 (39.5) | 35 (46.7) |
| *Laryngeal* | 7 (6.2) | 0 | 1 (1.3) |

*Source: Integrated Summary of Safety, Table 4-5*

### 7.2.2 Explorations for Dose Response

Formal dose-response trials were not conducted in the icatibant Phase 3 clinical program. Moreover, the subjects in the pivotal efficacy trials received only one dose of blinded treatment (icatibant versus control) to treat a single HAE attack during the

randomized treatment phase. However, as shown in Table 24, throughout the entire open-label extension phases of the three trials, a limited number of subjects were administered more than one dose of icatibant to treat subsequent HAE attacks. .

### 7.2.3 Special Animal and/or In Vitro Testing

No special animal or *in vitro* testing was conducted.

### 7.2.4 Routine Clinical Testing

Routine clinical laboratory testing in the icatibant Phase 3 program consisted of serum chemistry assessments (glucose, AST, ALT, albumin, total bilirubin, creatinine, creatine kinase, C1-INH level and function, C4, C1q, uric acid, BUN), hematology (hemoglobin, hematocrit, MCH, MCHC, platelet count, RBC count, WBC count with differential, PT, aPTT), and urinalysis (appearance, pH, protein, glucose, bilirubin, nitrite, ketone, urobilinogen, blood, leukocytes, pregnancy testing). In addition, the immunogenicity of icatibant was also assessed. These laboratory assessments appeared adequate as safety screening measures.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

Metabolic and pharmacokinetic analyses are discussed under Section 4.4 Clinical Pharmacology. No drug interaction data were submitted with this application, although the Applicant discusses the potential for antagonistic effects of icatibant on ACE-inhibitor therapy. Given the intermittent and limited nature of icatibant dosing for highly variable and unpredictable recurrent HAE attacks, clinical practice patterns of icatibant usage are unlikely to result in significant drug interactions, as might be expected for chronic medications indicated for HAE prophylaxis.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There are no other members of this pharmacologic class (bradykinin type 2 receptor antagonist). As with other subcutaneously administered therapies, however, safety and tolerability data were collected regarding local injection site reactions to icatibant.

## 7.3 Major Safety Results

### 7.3.1 Deaths

No deaths were reported in any subject who received icatibant in the HAE development program. One death (Subject 096-001) was reported for FAST-2 in a 53 year-old man randomized to tranexamic acid: 41 days after receiving blinded treatment, this subject

collapsed and died and was subsequently shown to have coronary artery disease and aortic sclerosis upon autopsy. A second death (Subject 320-010) was reported for FAST-3 in a 44 year-old man who was randomized to placebo and died from a myocardial infarction 10 days after blinded treatment for an acute HAE attack. The investigator considered this death unrelated to study treatment, although this subject had no cardiac history, cardiac symptoms, clinically significant ECG findings, or abnormal laboratory results prior to his death.

### 7.3.2 Nonfatal Serious Adverse Events

Blinded Treatment Phase

No SAEs were noted in icatibant-recipients during the controlled treatment phase of FAST-1 or FAST-3. However, a total of seven SAEs were recorded in five subjects in FAST-2 during the double-blind treatment phase (two of which were pregnancies, which by definition were considered SAEs):

- Subject 016-005: Viral gastroenteritis and hypertensive crisis requiring hospitalization, which developed three months after last receipt of icatibant

- Subject 075-013: Severe laryngeal HAE attack requiring tracheostomy five months after last receipt of icatibant

- Subject 075-014: Laryngeal HAE attack considered severe enough to warrant open-label treatment with icatibant (subject added to laryngeal HAE attack population for analysis purposes)

- Subject 090-004: Abdominal HAE attack two weeks after initial treatment with icatibant, accompanied by hypotension, pyuria, and microhematuria (moderate cystitis); subject fully recovered five days after treatment with C1-INH replacement, volume resuscitation, and antibiotics (without additional icatibant); subject also became pregnant 638 days after last icatibant-administration (pregnancy ongoing at the time of Complete Response submission)

- Subject 070-013: Pregnancy (defined as SAE) that developed 206 days after icatibant treatment for initial HAE attack, which resolved without sequelae but resulted in discontinuation from trial

Open-label Extension Phase

Multiple SAEs were noted in several patients following icatibant administration during the extension phases of all three trials in patients who were treated with open-label icatibant for all subsequent HAE attacks, as well as during longer term follow-up for

patients who received icatibant for a single HAE attack during the randomized treatment phase:

FAST-1

- Subject 15-007: Pancreatitis that developed 1.5 weeks after second icatibant-treated HAE attack
- Subject 18-002: Atypical chest pain that occurred five days after second icatibant-treated HAE attack
- Subject 026-001: Atypical chest pain occurring 335 days after icatibant administration for initial icatibant-treated HAE attack
- Subject 40-010: Pregnancy that occurred 69 days after treatment for second icatibant-treated attack, which resolved without sequelae

FAST-2

- Subject 16-005: Abdominal HAE symptoms and pre-renal insufficiency related to diuretic use that occurred 4 months after last icatibant administration during the second HAE attack treated with icatibant
- Subject 20-001: Bacterial urinary tract infection with microhematuria that developed after treatment of third icatibant-treated HAE attack
- Subject 20-005: Dental extraction that occurred after last icatibant dose given for third icatibant-treated HAE attack
- Subject 21-002: Worsening HAE symptoms during the third, fourth, and fifth icatibant-treated HAE attacks
- Subject 40-001: Head injury associated with a motor vehicle crash, which occurred two days after last icatibant dose for second icatibant-treated HAE attack
- Subject 70-004: Rotavirus-associated diarrhea and increased pancreatic enzymes requiring hospitalization three months following last icatibant dose for a fourth icatibant-treated HAE attack
- Subjects 78-001: Laryngeal HAE symptoms during fourth icatibant-treated HAE attack

- Subject 90-008: Suicide attempt 205 days after last icatibant dose for fourth icatibant-treated HAE attack

- Subject 81-002: HAE attack and cholelithiasis developing 303 days and 350 days after icatibant administration for initial HAE attack, respectively

- Subject 70-006: Carcinoma *in situ* of the cervix that was noted 809 days after initial icatibant-treated attack

- Subject 78-006: Pregnancy (defined as SAE) after third icatibant-treated HAE attack that resolved without sequelae but resulted in discontinuation from trial

FAST-3

- Subject 316-003: Pulmonary embolism after fourth icatibant-treated HAE attack

- Subject 359-002: Cholecystitis and pneumonia (recorded as separate SAEs) that developed after the third icatibant-treated HAE attack

- Subject 320-001: Severe laryngeal edema that developed 61 days after open-label icatibant treatment for second HAE attack

- Subject 320-003: Severe life-threatening laryngeal edema that developed 49 days after open-label icatibant treatment for second HAE attack

As noted, many of these SAEs were widely separated in time from last administration of icatibant and were less likely to have had a causal relationship to study drug compared to acute post-treatment events.

### 7.3.3 Dropouts and/or Discontinuations

To compare relative dropout and discontinuation rates between treatment groups, subject disposition data are summarized in Table 26 for the randomized, non-laryngeal HAE attack population in each of the three pivotal efficacy trials. In addition, discontinuations among subjects treated for non-laryngeal HAE attacks during the open-label extension phase of each trial are also listed. For clarity, this table does not include discontinuations by subjects who experienced an initial laryngeal HAE attack during the primary treatment phases of these trials. The differences in dropout rates between treatment groups during the randomized treatment phases of each trial did not reveal a safety signal associated with icatibant exposure.

**Table 26: Subject disposition in pivotal Phase 3 efficacy trials**

| Clinical Trial | FAST-1 | | FAST-2 | | FAST-3 | |
|---|---|---|---|---|---|---|
| **Treatment Group** | **Icatibant** | **Placebo** | **Icatibant** | **Tranexamic Acid** | **Icatibant** | **Placebo** |
| **Non-laryngeal ITT Population (n)** | 27 | 29 | 36 | 38 | 43 | 45 |
| Randomized Treatment Phase | | | | | | |
| **Discontinuations** | 1 (3.7) | 0 | 1 (2.8) | 3 (7.9) | 0 | 1 (1.1) |
| Other | 1 (3.7) | 0 | 1 (2.8) | 1 (2.6) | 0 | 0 |
| Withdrawn consent | 0 | 0 | 0 | 0 | 0 | 0 |
| Adverse event | 0 | 0 | 0 | 0 | 0 | 0 |
| Lost to follow-up | 0 | 0 | 0 | 1 (2.6) | 0 | 0 |
| Death | 0 | 0 | 0 | 1 (2.6) | 0 | 1 (1.1) |
| Open-label Extension Phase | | | | | | |
| **Discontinuations** | 3 (11.1) | 5 (17.2) | 1 (2.8) | 0 | | |
| Other | 3 (11.1) | 2 (6.9) | 1 (2.8) | 0 | | |
| Withdrawn consent | 0 | 3 (10.3) | 0 | 0 | No discontinuations reported | |
| Adverse event | 0 | 0 | 0 | 0 | | |
| Lost to follow-up | 0 | 0 | 0 | 0 | | |
| Death | 0 | 0 | 0 | 0 | | |

Source: Clinical Study Report for FAST-1, Table 9, Table 6.22.1, Table 6.23.1.1; Clinical Study Report for FAST-2, Table 9, Table 6.22.1, Table 6.23.1.1; Clinical Study Report for FAST-3, Table 6-4, Table 10.1.2.1

### 7.3.4 Significant Adverse Events

All severe AEs observed within the 2-week observation period following study treatment were more frequent in control subjects versus icatibant-recipients, except for a single case of severe dyspepsia and a single case of severe headache seen in icatibant-recipients. Neither of these AEs were experienced by any placebo or tranexamic acid-recipient as a severe AE. However, dyspepsia was a rare AE, with only two events reported (one in the aforementioned icatibant-recipient and one in a placebo-recipient). In addition, headache was reported less frequently in icatibant-recipients compared to either placebo or tranexamic acid-recipients. Thus, these isolated cases of severe AEs do not appear to represent a significant safety risk attributable to icatibant.

Of note, as shown later in Table 29, HAE was the most commonly reported AE, although its incidence in icatibant-recipients was similar to or lower than that in control subjects. Per protocol, worsening or recurrent HAE symptoms that occurred within 48 hours after study drug administration were to be reported as AEs. In contrast, HAE symptoms developing more than 48 hours later were to be considered new HAE attacks and were not to be classified as AEs. However, the Applicant acknowledges that some

investigators may have mistakenly reported new HAE attacks as AEs, leading to potential over-reporting. In addition, it is difficult to discern whether these AE rates of worsening or recurrent HAE symptoms reflect a lack of efficacy or potential negative effect of study treatment on the underlying condition or simply the variable natural progression of acute HAE attacks. Regardless, despite the high incidence of reports, icatibant was not disproportionately associated with HAE symptoms defined as AEs.

### 7.3.5 Submission Specific Primary Safety Concerns

In the Phase 3 program, injection sites were specifically assessed for erythema, swelling, burning sensation, pruritus, warmth, and pain during the observation period at 0.5, 1, 2, 4, 8, 12, and 24 hours, and again at Day 14. These reactions were graded as mild, moderate, or severe by the investigator and summarized separately from general reporting for AEs (accounting for the differences in reported rates). Multiple types of local injection site reactions and/or complications were documented following SC icatibant administration that were observed at lower levels in one or both control groups. Overall, injection site reactions were observed in 110 of 113 (97.3%) icatibant-recipients, 10 of 38 (26.3%) tranexamic acid-recipients, and 25 of 75 (33.3%) placebo-recipients. Table 27 lists the local injection site reactions that occurred at a greater rate in icatibant-recipients than in one or both of the control groups. As shown, local injection site reactions were far more common in icatibant-recipients. Thus, this imbalance could have affected the quality of blinding in these trials.

**Table 27: Local injection site reactions occurring in pooled Phase 3 safety population (n, %)**

| Treatment Group | Icatibant 30 mg N = 113 | Tranexamic Acid N = 38 | Placebo N = 75 |
|---|---|---|---|
| **Any injection site reaction:** | **110 (97.3)** | **10 (26.3)** | **25 (33.3)** |
| Erythema | 108 (95.6) | 4 (10.5) | 15 (20.0) |
| Swelling | 93 (82.3) | 6 (15.8) | 12 (16.0) |
| Burning | 41 (36.3) | 2 (5.3) | 3 (4.0) |
| Itching | 35 (31.0) | 0 | 0 |
| Warm sensation | 60 (53.1) | 1 (2.6) | 3 (2.7) |
| Cutaneous (skin) pain | 29 (25.7) | 0 | 3 (4.0) |
| **Severe injection site reaction:** | **30 (26.5)** | **0** | **2 (2.7)** |
| Erythema | 28 (24.8) | 0 | 0 |
| Swelling | 7 (6.2) | 0 | 0 |
| Burning | 5 (4.4) | 0 | 1 (1.3) |
| Itching | 3 (2.7) | 0 | 0 |
| Cutaneous (skin) pain | 2 (1.8) | 0 | 1 (1.3) |

*Source: Summary of Clinical Safety, Table 2.7.4-23*

Of note, there were no hypersensitivity reactions reported following icatibant administration. Within 2 hours of dosing, most cases of erythema (the most common type of localized injection site reaction, which occurred in nearly all icatibant-recipients) were mild in intensity, while approximately 85% of cases had resolved within 8 hours of icatibant-dosing.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

AEs were defined as any untoward medical occurrence or clinical investigation in a patient administered a pharmaceutical product, regardless of causality association with this treatment. Pre-existing medical conditions were documented at baseline and events related to these conditions were only considered to be AEs if they reflected a worsening of these conditions. Formal checklists were not utilized, and all AEs that occurred from randomization to the final telephone follow-up contact were recorded in CRFs, regardless of their relatedness to study drug. Treatment-emergent AEs (TEAEs) were defined as AEs that occurred or worsened after first study drug treatment and were possibly, probably, or definitely related to study drug, per investigator. For subjects who experienced more than one on-study HAE attack or were treated with more than one study drug for a single HAE attack, AEs were assigned to the most recent HAE attack and the study drug which most recently preceded the event. Given the acute nature of HAE attacks and the half-life of icatibant, AEs were characterized as acute (occurring within 24 hours of study drug administration) or occurring during the observation period (between Days 1 and 14 post-study drug treatment). Worsening or recurrent HAE symptoms that occurred within 48 hours after study drug administration were reported as AEs, whereas HAE symptoms developing more than 48 hours later were considered new HAE attacks. As with all *de novo* HAE attacks, these new HAE attacks were not to be reported as AEs, per protocol; however, the Applicant acknowledges that some individual investigators may have mistakenly reported new HAE attacks as AEs, leading to potential over-reporting.

Acute AEs in icatibant-recipients occurred at a similar rate as in tranexamic acid-recipients and at a lower rate than in placebo-recipients: 31 of 113 (27.4%) icatibant-recipients, 10 of 38 (26.3%) tranexamic acid-recipients, and 31 of 75 (41.3%) placebo-recipients. No severe AEs occurred more frequently in icatibant-recipients, compared to control subjects. Table 28 summarizes all acute AEs (within 24 hours of study drug dosing) for the pooled safety population that occurred at a greater frequency in the icatibant treatment group versus either control group (placebo or tranexamic acid), based on MedDRA preferred term (System Organ Class is included for reference). Except for pyrexia, which was observed in three icatibant-recipients but no control subjects, all other AEs observed at greater rates in icatibant-recipients occurred in only one to two subjects. In addition, many of these AEs were consistent with symptoms of

acute HAE attacks. Thus, these findings do not appear to represent a clinically significant imbalance of AEs in icatibant-recipients.

**Table 28: Acute adverse events (within 24 hours post-dose) occurring at greater rates in icatibant versus control-recipients in pooled Phase 3 safety population (reported as number of subjects)**

| System Organ Class<br>Preferred Term (n, %) | Treatment Group | | |
|---|---|---|---|
| | **Icatibant 30 mg N = 113** | **Tranexamic Acid N = 38** | **Placebo N = 75** |
| **Gastrointestinal disorders** | 4 (3.5) | 1 (2.6) | 6 (8.0) |
| Abdominal distension | 1 (0.9) | 0 | 0 |
| Abdominal pain | 2 (1.8) | 0 | 0 |
| Diarrhea | 1 (0.9) | 0 | 0 |
| Nausea | 2 (1.8) | 0 | 2 (2.7) |
| **General disorders and administration site conditions** | 8 (7.1) | 2 (5.3) | 4 (5.3) |
| Asthenia | 1 (0.9) | 0 | 0 |
| Chills | 1 (0.9) | 0 | 0 |
| Injection site pain | 2 (1.8) | 0 | 0 |
| Injection site reaction | 2 (1.8) | 0 | 0 |
| Pyrexia | 3 (2.7) | 0 | 0 |
| **Infections and infestations** | 1 (0.9) | 0 | 1 (1.3) |
| Urinary tract infection | 1 (0.9) | 0 | 0 |
| **Investigations** | 3 (2.7) | 0 | 0 |
| Blood urine present | 1 (0.9) | 0 | 0 |
| Liver function test abnormal | 1 (0.9) | 0 | 0 |
| WBC urine positive | 1 (0.9) | 0 | 0 |
| **Musculoskeletal and connective tissue disorders** | 1 (0.9) | 0 | 0 |
| Chest wall pain | 1 (0.9) | 0 | 0 |
| **Nervous system disorders** | 3 (2.7) | 2 (5.3) | 6 (8.0) |
| Dizziness | 1 (0.9) | 0 | 1 (1.3) |
| **Renal and urinary disorders** | 1 (0.9) | 0 | 0 |
| Dysuria | 1 (0.9) | 0 | 0 |

| | | | |
|---|---|---|---|
| **Respiratory, thoracic, and mediastinal disorders** | 3 (2.7) | 1 (2.6) | 1 (1.3) |
| Nasal congestion | 2 (1.8) | 0 | 0 |
| Throat irritation | 1 (0.9) | 0 | 0 |
| **Skin and subcutaneous tissue disorders** | 2 (1.8) | 0 | 2 (2.7) |
| Rash | 2 (1.8) | 0 | 0 |

*Source: Integrated Summary of Safety, Table 17.1*

Table 29 summarizes all AEs occurring during the observation period (between Days 1 and 14 post-dosing) for the pooled safety population that occurred at a greater frequency in the icatibant treatment group versus either control group (placebo or tranexamic acid) based on MedDRA preferred term (System Organ Class is included for reference). On average, the icatibant group had a similar duration of treatment exposure per subject, quantified as person-time in months, with regard to AEs occurring during the post-dose observation period,: icatibant = 52.0 months (average of 0.46 months per patient), tranexamic acid = 18.3 months (average of 0.46 months per patient), placebo = 32.5 months (average of 0.43 months per patient). Overall, AEs during the observation period were reported in 48 of 113 (42.5%) icatibant-recipients, 13 of 38 (34.2%) tranexamic acid-recipients, and 41 of 75 (54.7%) placebo-recipients.

## Table 29: Adverse events during post-dosing observation period (Days 1 to 14) occurring at greater rates in icatibant versus control-recipients in pooled Phase 3 safety population (reported as number of subjects)

| **System Organ Class** Preferred Term (n, %) | **Treatment Group** | | |
|---|---|---|---|
| | **Icatibant 30 mg N = 113** | **Tranexamic Acid N = 38** | **Placebo N = 75** |
| **Congenital, familial, and genetic disorders** | 18 (15.9) | 6 (15.8) | 15 (20.0) |
| HAE | 18 (15.9) | 6 (15.8) | 15 (20.0) |
| **Gastrointestinal disorders** | 7 (6.2) | 1 (2.6) | 7 (9.3) |
| Abdominal distension | 2 (1.8) | 0 | 0 |
| Abdominal pain | 3 (2.7) | 0 | 0 |
| Diarrhea | 2 (1.8) | 0 | 0 |
| Dyspepsia | 1 (0.9) | 0 | 1 (1.3) |
| Nausea | 2 (1.8) | 0 | 3 (4.0) |

| | | | |
|---|---|---|---|
| **General disorders and administration site conditions** | 12 (10.6) | 2 (5.3) | 4 (5.3) |
| Asthenia | 1 (0.9) | 0 | 0 |
| Chills | 1 (0.9) | 0 | 0 |
| Injection site erythema | 1 (0.9) | 0 | 1 (1.3) |
| Injection site pain | 2 (1.8) | 0 | 0 |
| Injection site reaction | 2 (1.8) | 0 | 0 |
| Injection site swelling | 1 (0.9) | 0 | 1 (1.3) |
| Edema | 1 (0.9) | 0 | 0 |
| Pyrexia | 4 (3.5) | 0 | 0 |
| **Infections and infestations** | 11 (9.7) | 2 (5.3) | 7 (9.3) |
| Cystitis | 1 (0.9) | 0 | 0 |
| Herpes simplex | 1 (0.9) | 0 | 1 (1.3) |
| Influenza | 1 (0.9) | 0 | 0 |
| Nasopharyngitis | 2 (1.8) | 1 (2.6) | 0 |
| Pharyngitis | 1 (0.9) | 0 | 2 (2.7) |
| Sinusitis | 3 (2.7) | 0 | 1 (1.3) |
| Urinary tract infection | 2 (1.8) | 0 | 1 (1.3) |
| **Injury, poisoning, and procedural complications** | 2 (1.8) | 0 | 0 |
| Fall | 1 (0.9) | 0 | 0 |
| Joint aspiration | 1 (0.9) | 0 | 0 |
| **Investigations** | 5 (4.4) | 0 | 2 (2.7) |
| ALT increased | 1 (0.9) | 0 | 0 |
| AST increased | 1 (0.9) | 0 | 0 |
| Blood bilirubin increased | 1 (0.9) | 0 | 0 |
| Blood CPK increased | 1 (0.9) | 0 | 1 (1.3) |
| Blood urine present | 1 (0.9) | 0 | 0 |
| Liver function test abnormal | 1 (0.9) | 0 | 0 |
| WBC urine positive | 1 (0.9) | 0 | 0 |
| **Musculoskeletal and connective tissue disorders** | 1 (0.9) | 0 | 0 |
| Chest wall pain | 1 (0.9) | 0 | 0 |
| **Nervous system disorders** | 6 (5.3) | 2 (5.3) | 7 (9.3) |
| Dizziness | 2 (1.8) | 0 | 1 (1.3) |
| **Renal and urinary disorders** | 1 (1.8) | 0 | 1 (1.3) |
| Dysuria | 1 (0.9) | 0 | 0 |
| Nephrolithiasis | 1 (0.9) | 0 | 0 |

| | | | |
|---|---|---|---|
| **Respiratory, thoracic, and mediastinal disorders** | 3 (2.7) | 1 (2.6) | 2 (2.7) |
| Nasal congestion | 2 (1.8) | 0 | 0 |
| Throat irritation | 1 (0.9) | 0 | 0 |
| **Skin and subcutaneous tissue disorders** | 2 (1.8) | 0 | 4 (5.3) |
| Rash | 2 (1.8) | 0 | 0 |

*Source: Integrated Summary of Safety, Table 10.1*

As with AEs observed during the acute post-dosing period, AEs during the observation period were similarly noted in only a limited number of icatibant-recipients (typically 1-2 patients, except for abdominal pain, which was observed in three subjects, and pyrexia, which was seen in four subjects). All severe AEs observed during the observation period were more frequent in tranexamic acid or placebo-recipients versus icatibant-recipients, except for a single case of severe dyspepsia (0.9%) and a single case of severe headache (0.9%) in icatibant-recipients. Although neither of these AEs was experienced by any placebo or tranexamic acid-recipient as a severe AE, dyspepsia was a rare event reported in only one icatibant-recipient and one placebo-recipient, while the overall incidence of headache was lower in the icatibant group (4 subjects or 3.5%), compared to either the tranexamic acid (2 subjects or 5.3%) or placebo (4 subjects or 5.3%) groups. Of note, HAE was cited most frequently as an AE at a relatively high rate (15.9%), but its incidence in icatibant-recipients was similar to or lower than that in control subjects, as discussed in Section 7.3.4 Significant Adverse Events. Thus, overall, these AE findings do not appear to reflect any systematic safety risks associated disproportionately with icatibant-dosing, other than local injection site reactions.

### 7.4.2 Laboratory Findings

Clinical laboratory values were assessed at each individual study site and then converted into Standard International (SI) units to allow for integrated comparisons within the pooled Phase 3 safety population. Out of range laboratory values were determined with reference to normal ranges established for each individual study site, and abnormalities were graded according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v 3.0). No clinically significant changes in laboratory values from baseline (pretreatment) to the end of the 14-day observation period were observed for hematology, clinical chemistry, or urinalysis parameters.

Table 30 summarizes the median change from baseline values in hematologic laboratory parameters for each pooled treatment group at the end of the post-dose observation period (Day 14). The sample sizes indicated are the total number of

subjects in the different treatment groups at baseline. All median changes from baseline at Day 14 in the icatibant group were similar to or less extreme than those seen in the placebo group.

**Table 30: Median baseline and end-of-observation (Day 14) values for hematologic laboratory parameters by treatment group in pooled Phase 3 safety population**

| Treatment | Icatibant 30 mg N = 113 | | Tranexamic Acid N = 38 | | Placebo N = 75 | |
|---|---|---|---|---|---|---|
| **Laboratory Parameter** | **Baseline** | **Day 14** | **Baseline** | **Day 14** | **Baseline** | **Day 14** |
| Hgb (g/L) | 144.0 | -4.7 | 146.8 | -8.1 | 150.2 | -7.8 |
| Hct (%) | 41.1 | -1.3 | 41.4 | -2.0 | 42.8 | -2.9 |
| MCH (pg) | 30.3 | 0 | 30.6 | -0.229 | 29.9 | 0 |
| MCHC (g/L) | 347.0 | 0.9 | --- | --- | 346.5 | 1.0 |
| MCV (fL) | 88.0 | 0.5 | 90.2 | -0.5 | 87.3 | 0.5 |
| RBC ($10^{12}$/L) | 4.6 | -0.20 | 4.9 | -0.23 | 4.9 | -0.35 |
| WBC ($10^3$/mcL) | 7.8 | -1.4 | 7.6 | -2.2 | 8.2 | -2.5 |
| Platelets ($10^9$/L) | 265.0 | 4.2 | 234.9 | -15.2 | 259.7 | 0 |
| Neutrophils ($10^6$/L) | 4817.6 | -499.1 | 4544.7 | -502.9 | 4981.2 | -835.1 |
| Lymphocytes ($10^6$/L) | 1926.4 | 10.3 | 1868.3 | 11.7 | 1990.8 | 81.8 |
| Monocytes ($10^6$/L) | 370.7 | -8.4 | 367.9 | -19.3 | 380.6 | -11.5 |
| Eosinophils ($10^6$/L) | 100.0 | 0 | 92.4 | 2.3 | 92.9 | 0.4 |
| Basophils ($10^6$/L) | 18.1 | 0 | 21.7 | 0 | 18.5 | 0 |
| PT (sec) | 10.4 | -0.15 | 10.8 | 0 | 9.9 | 0.1 |
| aPTT (sec) | 23.4 | 0.2 | 22.0 | 0 | 23.2 | 0 |

*Source: Integrated Summary of Safety, Table 30.1*

Table 31 summarizes the median change from baseline values in chemistry laboratory parameters for each pooled treatment group at the end of the post-dose observation period (Day 14). The sample sizes indicated are the total number of subjects in the different treatment groups at baseline. All median changes from baseline at Day 14 in the icatibant group were similar to or less extreme than those seen in the placebo group.

**Table 31: Median baseline and end-of-observation (Day 14) values for chemistry laboratory parameters by treatment group in pooled Phase 3 safety population**

| Treatment | Icatibant 30 mg N = 113 | | Tranexamic Acid N = 38 | | Placebo N = 75 | |
|---|---|---|---|---|---|---|
| **Laboratory Parameter** | **Baseline** | **Day 14** | **Baseline** | **Day 14** | **Baseline** | **Day 14** |
| BUN (mmol/L) | 3.7 | 0 | 4.1 | -0.3 | 3.5 | -0.5 |
| Creatinine (mg/dL) | 81.3 | 0 | -3.4 | 0.90 | 0 | 0.80 |
| Glucose (mmol/L) | 5.27 | -0.13 | 5.41 | -0.36 | 5.38 | -0.20 |
| AST (U/L) | 20.1 | 0 | 20.1 | -0.9 | 21.0 | -1.2 |
| ALT (U/L) | 20.5 | -0.3 | 19.7 | 0 | 17.7 | -0.9 |
| GGT (U/L) | 14.4 | 0 | 12.9 | -0.6 | 15.6 | 1.0 |
| Total Bilirubin (mcmol/L) | 7.5 | -0.8 | 8.4 | -0.5 | 7.2 | 0 |
| Albumin (g/L) | 48.2 | 0 | --- | --- | 50.6 | 0 |
| Creatine kinase (U/L) | 75.7 | 2.1 | 78.5 | -0.4 | 68.5 | 0.2 |
| Uric Acid (mcmol/L) | 315.0 | -15.4 | 324.8 | -7.4 | 308.0 | -13.5 |

*Source: Integrated Summary of Safety, Table 27.1*

Elevations in hepatic transaminases (AST and ALT) above the upper limit of normal (ULN = 35 U/L) were noted more frequently in icatibant-recipients versus control subjects, but the majority of these elevations were mild ($\leq$ 2.5 times ULN). The Applicant reports one subject (Subject 321-005) who developed clinically relevant elevations in AST (without pretreatment elevations) to $\geq$ 5 times ULN (ALT = 354 U/L; AST = 303 U/L) that occurred two days after each of two different treatments with

icatibant. A review of the line listing data for this subject, who was reported to have concurrent cholelithiasis, indicated that hepatic transaminases decreased by Day 14, as well as prior to a subsequent HAE attack. Another subject (Subject 022-003) was reported as having developed a clinically relevant elevation in creatine kinase to 2107 U/L at 14 days post-icatibant-dosing for a second HAE attack. This subject experienced back pain and a fall around this time, which may have contributed to this increase, as creatine kinase was noted to be normal during two subsequent HAE attacks. Rare elevations of uric acid were noted in the icatibant group, but none of these were considered clinically relevant by the Applicant. In addition, with one exception (Subject 001-004), hyperuricemia was also noted at baseline. Thus, these laboratory abnormalities do not appear to represent significant safety risks attributable to icatibant.

Table 32 summarizes the proportion of subjects at baseline and end-of-observation (Day 14) with abnormal urinalysis values for each pooled treatment group. The sample sizes indicated are the total number of subjects in the different treatment groups at baseline. Although several urine abnormalities were noted at follow-up in the icatibant group, similar abnormal findings were also observed at pretreatment. In addition, rates of abnormal findings at Day 14 in icatibant-recipients were similar or lower that the rates seen in control subjects.

**Table 32: Baseline and end-of-observation (Day 14) abnormal urinalysis laboratory parameters by treatment group in pooled Phase 3 safety population (n, %)**

| Treatment | Icatibant 30 mg N = 113 | | Tranexamic Acid N = 38 | | Placebo N = 75 | |
|---|---|---|---|---|---|---|
| Laboratory Parameter* | Baseline | Day 14 | Baseline | Day 14 | Baseline | Day 14 |
| pH* | 5.8 | 5.5 | 5.5 | 6.0 | 5.8 | 6.0 |
| Protein | 17 (15) | 10 (8.8) | 4 (10.5) | 2 (5.3) | 15 (20.0) | 7 (9.3) |
| Glucose | 3 (2.7) | 0 | 1 (2.6) | 1 (2.6) | 0 | 0 |
| Ketones | 13 (11.5) | 0 | 2 (5.3) | 0 | 12 (16.0) | 5 (6.7) |
| Bilirubin | 3 (2.7) | 2 (1.8) | 1 (2.6) | 1 (2.6) | 4 (5.3) | 1 (1.3) |
| Blood | 21 (18.6) | 11 (9.7) | 11 (28.9) | 5 (13.2) | 14 (18.7) | 9 (12.0) |
| Urobilinogen | 4 (3.5) | 3 (2.7) | 2 (5.3) | 2 (5.3) | 1 (1.3) | 1 (1.3) |
| Leukocytes | 24 (21.2) | 21 (18.6) | 7 (18.4) | 6 (15.8) | 18 (24.0) | 16 (21.3) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Nitrites | 4 (3.5) | 1 (0.9) | 0 | 0 | 1 (1.3) | 0 |

**Data presented in pH units; all other results presented as number and percent of subjects with abnormal (positive) results*
*Source: Integrated Summary of Safety, Table 33.1, Table 34.1*

In this Complete Response submission, the Applicant did not provide laboratory data summarized as shift changes from normal to abnormal values over time. However, Table 33 summarizes the number and percentage of subjects whose hematologic laboratory values at the end of the 14-day observation period fell outside of the normal range (either above or below), as established by the clinical laboratory at each study site. Although the proportion of out of range values for some tests were higher in the icatibant group compared to placebo-recipients, a review of individual laboratory values did not reveal any clinically significant abnormalities.

**Table 33: Frequency and percent of subjects with abnormal (L = low or H = high) hematologic laboratory values at end-of-study (Day 14) by treatment group in pooled Phase 3 safety population**

| Treatment | Icatibant 30 mg | | | Tranexamic Acid | | | Placebo | | |
|---|---|---|---|---|---|---|---|---|---|
| Laboratory Parameter | Total N | Freq | % | Total N | Freq | % | Total N | Freq | % |
| Hgb-L | 86 | 7 | 8.1 | 30 | 2 | 6.6 | 60 | 4 | 6.6 |
| Hgb-H | | 1 | 1.2 | | 0 | 0 | | 5 | 8.4 |
| Hct-L | 83 | 10 | 12.0 | 27 | 5 | 18.5 | 60 | 4 | 6.7 |
| Hct-H | | 0 | 0 | | 1 | 3.7 | | 6 | 10 |
| MCH-L | 81 | 7 | 8.6 | 28 | 0 | 0 | 56 | 4 | 7.1 |
| MCH-H | | 7 | 8.6 | | 3 | 10.7 | | 0 | 0 |
| MCHC-L | 37 | 1 | 2.7 | -- | -- | -- | 30 | 0 | 0 |
| MCHC-H | | 0 | 0 | | -- | -- | | 0 | 0 |
| MCV-L | 48 | 2 | 4.2 | 30 | 1 | 3.3 | 26 | 1 | 3.8 |
| MCV-H | | 1 | 2.1 | | 4 | 13.3 | | 0 | 0 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| RBC-L | 86 | 4 | 4.7 | 30 | 1 | 3.3 | 60 | 3 | 5.0 |
| RBC-H | | 1 | 1.2 | | 0 | 0 | | 4 | 6.7 |
| WBC-L | 86 | 0 | 0 | 30 | 2 | 6.7 | 60 | 0 | 0 |
| WBC-H | | 8 | 9.3 | | 1 | 3.3 | | 4 | 6.7 |
| PLT-L | 86 | 1 | 1.2 | 30 | 0 | 0 | 59 | 0 | 0 |
| PLT-H | | 3 | 3.5 | | 0 | 0 | | 2 | 3.4 |
| Neutrophils-L | 75 | 0 | 0 | 29 | 2 | 6.9 | 53 | 0 | 0 |
| Neutrophils-H | | 7 | 9.3 | | 1 | 3.4 | | 3 | 5.7 |
| Lymphocytes-L | 76 | 1 | 1.3 | 29 | 3 | 10.3 | 53 | 0 | 0 |
| Lymphocytes-H | | 2 | 2.6 | | 0 | 0 | | 0 | 0 |
| Monocytes-L | 76 | 1 | 1.3 | 28 | 1 | 3.6 | 53 | 2 | 3.8 |
| Monocytes-H | | 1 | 1.3 | | 1 | 3.6 | | 0 | 0 |
| Eosinophils-L | 76 | 0 | 0 | 28 | 0 | 0 | 52 | 1 | 1.9 |
| Eosinophils-H | | 5 | 6.6 | | 1 | 3.6 | | 2 | 3.8 |
| Basophils-L | 76 | 1 | 1.3 | 28 | 0 | 0 | 52 | 0 | 0 |
| Basophils-H | | 1 | 1.3 | | 1 | 3.6 | | 1 | 1.9 |
| Prothrombin Time-L | 38 | 3 | 7.9 | 5 | 2 | 40.0 | 30 | 3 | 10.0 |
| Prothrombin Time-H | | 0 | 0 | | 0 | 0 | | 3 | 10.0 |
| aPTT-L | 73 | 19 | 26.1 | 28 | 9 | 32.1 | 47 | 14 | 29.8 |
| aPTT-H | | 3 | 4.1 | | 3 | 10.7 | | 0 | 0 |

*Source: Integrated Summary of Safety, Table 31.1*

Table 34 summarizes the number and percentage of patients whose chemistry laboratory values at the end of the 14-day observation period fell outside of the normal range (either above or below), as established by the clinical laboratory at each study site. The proportion of out-of-range values for some tests was higher in the icatibant group compared to placebo-recipients, such as for ALT and creatinine elevations. However, as discussed previously for the data presented in Table 31, transaminemia did not appear to reflect functional hepatic damage.

**Table 34: Frequency and percent of subjects with abnormal (L = low or H = high) chemistry laboratory values at end-of-observation (Day 14) by treatment group in pooled Phase 3 safety population**

| Treatment | Icatibant 30 mg | | | Tranexamic Acid | | | Placebo | | |
|---|---|---|---|---|---|---|---|---|---|
| Laboratory Parameter | Total N | Freq | % | Total N | Freq | % | Total N | Freq | % |
| Glucose-L | 84 | 6 | 7.2 | 30 | 1 | 3.3 | 58 | 7 | 12.1 |
| Glucose-H | | 15 | 17.9 | | 2 | 6.7 | | 10 | 17.2 |
| AST-L | 86 | 0 | 0 | 30 | 0 | 0 | 60 | 0 | 0 |
| AST-H | | 5 | 5.9 | | 1 | 3.3 | | 2 | 3.4 |
| ALT-L | 85 | 3 | 3.5 | 29 | 0 | 0 | 61 | 2 | 3.3 |
| ALT-H | | 11 | 13.0 | | 3 | 10.3 | | 2 | 3.3 |
| GGT-L | 44 | 1 | 2.3 | 29 | 1 | 3.4 | 25 | 0 | 0 |
| GGT-H | | 4 | 9.1 | | 2 | 6.9 | | 3 | 12.0 |
| BUN-L | 84 | 2 | 2.4 | 28 | 1 | 3.6 | 57 | 0 | 0 |
| BUN-H | | 3 | 3.6 | | 1 | 3.6 | | 0 | 0 |
| Creatinine-L | 87 | 3 | 3.4 | 29 | 1 | 3.4 | 61 | 4 | 6.6 |
| Creatinine-H | | 6 | 6.9 | | 2 | 6.8 | | 1 | 1.6 |
| Total Bilirubin-L | 84 | 0 | 0 | 27 | 0 | 0 | 61 | 1 | 1.6 |
| Total Bilirubin-L | | 2 | 2.4 | | 0 | 0 | | 2 | 3.3 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Albumin-L | 38 | 1 | 2.6 | --- | --- | --- | 35 | 1 | 2.9 |
| Albumin-H | | 1 | 2.6 | | --- | --- | | 0 | 0 |
| Creatine Kinase-L | 73 | 0 | 0 | 30 | 0 | 0 | 47 | 0 | 0 |
| Creatine Kinase-H | | 9 | 12.4 | | 3 | 10.0 | | 6 | 12.7 |
| Uric Acid-L | 77 | 5 | 6.5 | 28 | 5 | 17.9 | 51 | 2 | 3.9 |
| Uric Acid-H | | 4 | 5.2 | | 2 | 7.1 | | 1 | 2.0 |

*Source: Integrated Summary of Safety, Table 28.1*

Overall, very few icatibant-recipients had post-treatment laboratory abnormalities that were classified as severe (Grade 3) or life-threatening/disabling (Grade 4) by CTCAE (v 3.0) criteria during the randomized treatment phase at the end of the observation period on Day 14 [Grade 3 glucose elevation > 250-500 mg/dL (n = 1)] or during the open-label extension phase [Grade 3 platelet decrease < 50,000 – 25,000/mcL (n = 1), Grade 3 glucose elevation 250-500 mg/dL (n = 2), Grade 4 creatine kinase elevation > 5-10 times ULN (n = 1), Grade 4 uric acid elevation > 10 mg/dL (n = 3)]. The Applicant did not indicate that these laboratory abnormalities were accompanied by clinical signs or symptoms reflective of underlying pathology. Given that these post-treatment laboratory abnormalities reversed over time and were most often preceded by out-of-range levels at baseline (pretreatment), these data not appear to reflect significant safety risks specifically attributable to icatibant.

### 7.4.3 Vital Signs

Vital sign assessments for systolic (normal range: 90-140 mmHg) and diastolic (normal range: 60-90 mmHg) blood pressure, heart rate (normal range = 60-100 beats per minute), and temperature (normal range = 36.5-37.2 $^{o}$C) were done at baseline and at 0.5 hr, 12 hr, 2 days, and 14 days post-dosing. Table 35 summarizes the median change from baseline values in vital sign assessments for each pooled treatment group at Day 2 and Day 14. The sample sizes indicated are the total number of subjects in the different treatment groups at baseline. Changes from baseline at both Day 2 and Day 14 were negligible and did not appear to be clinically significant.

## Table 35: Median baseline and end-of-observation (Day 14) values for vital sign assessments by treatment group in pooled Phase 3 safety population

| Treatment | Icatibant 30 mg N = 113 | | | Tranexamic Acid N = 38 | | | Placebo N = 75 | | |
|---|---|---|---|---|---|---|---|---|---|
| **Laboratory Parameter** | **Baseline** | **Day 2** | **Day 14** | **Baseline** | **Day 2** | **Day 14** | **Baseline** | **Day 2** | **Day 14** |
| **Temperature (°C)** | 36.6 | 0 | -0.1 | 36.5 | 0 | 0 | 36.6 | 0 | 0 |
| **Heart Rate (beats/min)** | 80.0 | -2.0 | -1.5 | 76.0 | -4.0 | -4.0 | 80.0 | -4.0 | -4.0 |
| **Systolic BP (mmHg)** | 122.0 | -2.0 | -1.0 | 125.0 | -2.5 | -5.0 | 120.0 | -2.5 | -1.5 |
| **Diastolic BP (mmHg)** | 78.0 | -1.0 | -0.5 | 80.0 | -3.5 | 0 | 75.0 | -2.0 | 0 |

*BP = blood pressure*
*Source: Integrated Summary of Safety, Table 36.1*

As the Applicant did not summarize vital sign data in terms of shift changes from normal baseline values to abnormal follow-up values, Table 36 summarizes the number and percentage of subjects whose vital sign readings fell outside of the normal range at the end of the 14-day observation period, defined by the Applicant as either abnormal or borderline abnormal, per the normal limit ranges given above.

## Table 36: Frequency and percent of subjects with abnormal (L = low or H = high) vital sign readings at end-of-study (Day 14) by treatment group in pooled Phase 3 safety population

| Treatment | Icatibant 30 mg | | | Tranexamic Acid | | | Placebo | | |
|---|---|---|---|---|---|---|---|---|---|
| **Vital Sign Parameter** | **Total N** | **Freq** | % | **Total N** | **Freq** | % | **Total N** | **Freq** | % |
| Temperature-L | 85 | 32 | 37.6 | 28 | 9 | 32.2 | 61 | 21 | 34.4 |
| Temperature -H | | 1 | 1.2 | | 1 | 3.6 | | 0 | 0 |
| Heart Rate-L | 88 | 5 | 5.7 | 29 | 1 | 3.4 | 62 | 8 | 12.9 |
| Heart Rate-H | | 1 | 1.1 | | 0 | 0 | | 1 | 1.6 |
| Systolic BP-L | 88 | 4 | 4.5 | 30 | 2 | 6.7 | 62 | 2 | 3.2 |
| Systolic BP-H | | 6 | 6.8 | | 3 | 10.0 | | 8 | 12.9 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Diastolic BP-L | 88 | 5 | 5.6 | 30 | 0 | 0 | 62 | 1 | 1.6 |
| Diastolic BP-H | | 9 | 10.2 | | 2 | 6.7 | | 1 | 1.6 |

*BP = blood pressure*
*Source: Integrated Summary of Safety, Table 37.1*

Although diastolic blood pressure readings appeared to fall out of range more frequently in the icatibant group versus placebo-recipients, the median change from baseline in these measures at both Day 2 and Day 14 suggests that these changes were not clinically significant. In addition, the proportion of abnormal physical examination results by organ system across the three treatment groups was similarly distributed, other than the occurrence of local cutaneous findings at drug injection sites, which were more common in icatibant-recipients, as noted in Table 27.

### 7.4.4 Electrocardiograms (ECGs)

Concerns over the potential for icatibant to affect QT interval prolongation were raised in Study JE049-1103, a Phase 1 pharmacokinetic and safety trial conducted in healthy adults, including both young (19-40 years) and elderly (> 65 years) subjects, who received five doses of icatibant 30 mg SC on three separate days. While the Applicant concluded that no consistent relationship between icatibant and QT prolongation was observed in this trial, a review of the 12-lead ECG and Holter monitoring data by the Agency's identified several instances of ST/T wave changes and QT prolongation. Given this evidence of QT prolongation by icatibant, the Agency concluded that a thorough QT study was not warranted. However, the Applicant chose to evaluate this effect further in an additional trial (HGT-FIR-061). In addition, ECG testing was incorporated into each of the pivotal Phase 3 efficacy trials.

Overall ECG readings were characterized as either normal or abnormal at baseline and were then repeated at 0.5 hr and 2 days post-dosing in all three trials. As shown in Table 37, abnormal ECG findings were detected at lower rates in icatibant-recipients versus placebo-recipients at all time points, albeit at higher rates than seen in tranexamic acid-recipients. These data will be considered within the context of the pending review of HGT-FIR-061 by the QT-Interdisciplinary Review Team.

## Table 37: Longitudinal ECG results by treatment group in pooled Phase 3 safety population (n, %)

| Treatment | Icatibant 30 mg N = 113 | | | Tranexamic Acid N = 38 | | | Placebo N = 75 | | |
|---|---|---|---|---|---|---|---|---|---|
| **ECG Reading** | **Baseline** | **0.5 hr** | **Day 2** | **Baseline** | **0.5 hr** | **Day 2** | **Baseline** | **0.5 hr** | **Day 2** |
| **Normal** | 97 (85.8) | 94 (83.2) | 94 (83.2) | 36 (94.7) | 36 (94.7) | 34 (89.5) | 62 (82.7) | 59 (78.7) | 61 (81.3) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Abnormal** | 13 (11.5) | 16 (14.2) | 13 (11.5) | 2 (5.3) | 2 (5.3) | 1 (2.6) | 13 (17.3) | 14 (18.7) | 10 (13.3) |

*Source: Integrated Summary of Safety, Table 35.1*

### 7.4.5 Special Safety Studies/Clinical Trials

**Self-administration of Icatibant**

Given the unpredictable and often spontaneous nature of acute HAE attacks, the Applicant proposes the use of pre-filled syringes containing icatibant for self-administration by non-healthcare workers outside of the clinical setting, i.e., self-injection by patients at home, at work, etc. In response to a clinical deficiency cited in the Not Approvable action letter issued for the original NDA submission, the Applicant conducted FAST-4, a Phase 3 trial that specifically assessed the safety of icatibant self-administration. A detailed discussion of the methodology, major safety results, and secondary efficacy endpoints from FAST-4 is provided in this section.

**Protocol Title:** JE049-3101 (FAST-4): Open-Label, Multicenter Study to Evaluate Safety, Local Tolerability, Convenience, and Efficacy of a Self-administered Subcutaneous Formulation of Icatibant for the Treatment of Acute Attacks of Hereditary Angioedema

**Original Protocol Date:** July 7, 2009

**Amendment Dates:** July 20, 2010 (Amendment 1)

**Trial Initiation and Completion Dates:** September 25, 2009 to October 16, 2010

**Final Report Date:** December 20, 2010

**Study Sites:** 15 study sites in six countries in Europe (Austria, Germany, United Kingdom, Spain), Asia (Israel), and South America (Argentina).

**Primary Objective:** To explore clinical safety of self-treatment of acute HAE attacks with SC injections of icatibant

**Key Secondary Objective:** To determine local tolerability, convenience, and clinical efficacy of self-treatment of HAE attacks with SC injections of icatibant

**Study Rationale:** Given the life-threatening nature of HAE and rapid onset of symptoms, there is a recognized need for treatments with the capacity for self-administration in non-healthcare settings. Immediate self-administration of icatibant 30

mg SC (3 mL) in a pre-filled syringe with a 25 gauge needle may provide an essential bridge to emergency medical care.

**Study Design Overview:** FAST-4 was a multicenter, open-label, uncontrolled, single-dose Phase 3b trial in which 56 subjects were trained at the time of enrollment in icatibant self-administration using a placebo-filled syringe and the completion of symptom diaries, with additional information on the self-diagnosis of acute HAE attacks and severity assessment. After this training, icatibant-experienced subjects were given a single icatibant syringe for self-administration, along with a symptom diary, and were given permission to self-administer this dose at the outset of their next HAE attack of sufficient severity to warrant treatment. Icatibant-naïve subjects were treated at the investigator's medical institution at the time of their first on-study HAE attack, where icatibant was administered by a healthcare professional. Following resolution of this initial attack, these subjects were then given a single icatibant syringe for self-administration and a new symptom diary and were also instructed to self-administer icatibant at the onset of a second HAE attack of sufficient severity to warrant treatment, followed by evaluation at the clinic site within 48 hours of treatment (where up to two more injections of icatibant, each separated by 6 hours, could be administered as needed). Icatibant-naïve subjects who did not experience an acute HAE attack within two months of enrollment were given refresher training on icatibant self-administration at the follow-up visit following their initial on-study HAE attack. All subjects were instructed to return to the clinic following self-administration of icatibant within a specified timeframe based on symptom manifestations.

**Study Population:** A total of 56 subjects with either Type I or Type II HAE were evaluated, 8 of whom were icatibant-naïve at baseline and 48 of whom had been previously treated with icatibant for a previous HAE attack.

**Pertinent Inclusion Criteria**

- Males or females aged ≥ 18 years
- Documented diagnosis of Type I or II HAE, based on family and/or medical history, characteristic attack manifestations and recurrent attacks, historical C1-INH < 50% of normal levels by functional or qualitative assay
- Women of childbearing potential must agree to highly effective pregnancy prevention (annual failure rate < 1%) throughout the trial
- Mental or physical condition that allows for completion of study procedures
- Ability to provide signed informed consent following complete discussion of all aspects of the trial

**Pertinent Exclusion Criteria**

- Previous participation in clinical trial with receipt of investigational product other than icatibant within the past month
- Angioedema diagnosis other than Type I or Type II HAE
- History of symptomatic coronary artery disease (e.g., unstable angina, severe coronary heart disease, congestive heart failure NYHA Class 3 or 4)
- Stroke within the past 6 months
- Treatment with angiotensin converting enzyme (ACE) inhibitor therapy
- Pregnancy or breastfeeding
- Mental condition rendering subject unable to understand the nature and consequences of protocol or manage study medication (i.e., self-administration of injection)
- Per investigator, unlikely to comply with assessments or follow-up visits for any reason, including uncooperative attitude

**Study Treatments:** This trial involved self-treatment of only a single HAE attack with icatibant 30 mg SC (3 mL). Symptoms that persisted beyond 48 hours were considered an additional HAE attack for the purposes of this trial. All subjects could receive up to two additional icatibant doses administered by a healthcare worker for persistent HAE symptoms, provided that all injections were separated by at least six hours, and no more than three doses were given per attack.

**Study Procedures:** Following training in the self-administration of icatibant and self-assessment of acute HAE attacks, icatibant-naïve subjects were treated for a total of two HAE attacks, the first with icatibant administered by a healthcare professional and the second through self-administration of icatibant. In contrast, icatibant-experienced subjects were treated for only one HAE attack through the self-administration of drug.

Following self-injection at the first eligible attack, subjects were instructed to return to the clinic for evaluation as follows:

- Immediately after self-injection for laryngeal HAE attacks or cutaneous attacks affecting the face or neck

- Within 48 hours for all other HAE attacks
- Within seven days for close-out (when the symptom diary was collected)
- For persistent, worsening, or new HAE symptoms, given that up to two additional icatibant doses were permitted per attack (as delivered by a healthcare worker in a medical setting)
- Within 10 months of enrollment for close-out, if no HAE attacks occurred

A schedule of key trial procedures and assessments is presented in the following table:

## Table 38: Timetable of assessments and procedures for FAST-4

| **Visit** | **Screen** | **HCW-Tx for Naïve** | **Additional Doses for Naive** | **48-hr F-U for Naive** | **Self-Tx for All** | **Direct Obs. for All** | **Additional Doses for All** | **48-hr F-U for All** | **Close-out for All** |
|---|---|---|---|---|---|---|---|---|---|
| **Procedure** | | | | | | | | | |
| Trial Overview | X | | | | | | | | |
| Informed Consent | X | | | | | | | | |
| Demography Data | X | | | | | | | | |
| Physical Exam | X | | | | | | | | X |
| Medical History | X | | | | | | | | |
| History of HAE I or II | X | | | | | | | | |
| Inc/Exc Criteria | X | X | | | | | | | |
| Documented prior icatibant (Non-naïve) | X | | | | | | | | |
| Documented training | X | | | | | | | | |
| Syx Diary and TSQM to Non-naive | X | | | | | | | | |
| Symptom Diary to naïve | | X | | X | | | | | |
| TSQM to naïve | | | | X | | | | | |
| Icatibant to | X | | | | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Non-naïve | | | | | | | | | |
| Icatibant to naïve | | | | X | | | | | |
| Vital Signs Assessment | X | X | X | X | | X | X | X | |
| Icatibant by HCW (Naïve) | | X | X | | | | X | | |
| Icatibant self-administration | | | | | X | | | | |
| Patient symptom VAS | | X | | X | X | X | | X | |
| Patient Local Tolerability | | X | | X | X | X | | X | |
| Patient-based convenience and TSQM | | | | | X | | | | |
| Global Assessment | | X | X | X | | X | X | X | |
| Physician symptom score | | X | X | | | X | X | | |
| Physician global impression | | X | X | | | X | X | | |
| Physician Local Tolerability | | X | X | X | | X | X | X | |
| Concomitant medications | X | X | X | X | X | X | X | X | X |
| Adverse Events | X | X | X | X | X | X | X | X | X |
| Rescue medications | X | X | X | X | X | X | X | X | X |
| Collect Symptom Diary | | | | X | | | | X | |
| Collect TSQM | | | | | | | | X | |
| Final Assessment | | | | | | | | | X |

*Screen = screening visit, Tx = treatment, F-U = follow-up, Obs = observation, Inc/Exc = inclusion/exclusion, Syx = symptom, TSQM = Treatment Satisfaction Questionnaire for Medication*
*Source: FAST-4 Clinical Study Report, Table 5-2*

**Safety Assessments:** As noted in Table 38, the safety and tolerability of self-administered icatibant was assessed through AEs/SAEs (coded using MedDRA v. 8.1), local injection site reactions (reddening, swelling, burning, itching, warm sensation, skin pain), and physical examination including vital sign assessments. AEs were monitored continuously from the time of enrollment through the end of study and were classified as mild, moderate, or severe and not related, possibly related, probably related, or definitely related. All events of study drug abuse, misuse, overdose, or medication error were reported regardless of classification as an AE.

**Efficacy Assessments:** All efficacy endpoints were considered secondary study endpoints in this trial:

- Time to onset of symptom relief, defined as at least 50% reduction from baseline in VAS-3 score
- Time to onset of primary symptom relief defined as Y = 6/7 X –16 mm with X ≥ 30 mm, where X = pre-treatment (baseline) VAS in mm and Y = post-treatment VAS in mm
- Change from pre-dose in individual symptom (skin swelling, skin pain, abdominal pain), single primary symptom, and VAS-3 scores in both self-treated and healthcare worker-treated HAE attacks
- Subject Assessment of Symptoms at 48 hours post-dose
- Investigator Global Assessment of skin edema, abdominal symptoms, and laryngeal edema on a 5-point scale from 0 = absent symptoms to 4 = very severe.
- Subject assessment of convenience of self-administration and satisfaction with study medication
- Investigator Symptom Score for laryngeal symptoms or cutaneous swellings of the face or neck
- Investigator Clinical Global Impression for laryngeal symptoms or cutaneous swellings of the face or neck

**Statistical Analysis Plan:** Statistical analyses were conducted separately for the initial HAE attack in icatibant-naïve subjects treated by a healthcare worker and the initial treatment in all subjects of an HAE attack with self-administered icatibant—the latter representing the primary safety analysis population for this trial. Data were also analyzed collectively for all subjects who received icatibant treatment in any form (i.e.,

self-administered or healthcare worker-administered). AE data were presented as tabulated summaries of incidences among each treatment group (self-administered versus healthcare worker-administered icatibant). Secondary efficacy endpoints based on VAS score were analyzed using Kaplan-Meier methodology for median time to onset of symptom relief, including estimates of 95% confidence intervals. Last observation carried forward methodology was used to impute missing data values for the analysis of VAS-3 only. Of note, as this trial is currently ongoing, an additional final analysis is planned.

**Sample Size Calculation:** Formal sample size calculations were not performed. A goal of 150 enrolled subjects was planned to obtain at least 25 unsupervised, evaluable, self-administered injections for the treatment of acute HAE attacks in at least 25 subjects. Thus, the reported sample size of 56 treated subjects surpassed this goal.

**Summary of Amendment Changes:** Amendment 1 (dated July 20, 2010) increased the number of study sites from 30 to 40, altered the inclusion criteria to require a historical C1-INH value < 50% of normal by functional or quantitative assay, added the Treatment Satisfaction Questionnaire for Medication (TSQM) as an additional assessment, and changed the Study Director. All but one subject (55 of 56) enrolled in the trial prior to Amendment 1.

**Subject Disposition:** A total of 56 subjects received self-administered icatibant in this trial, 48 of whom had previously received icatibant and eight of whom were icatibant-naïve prior to enrollment. Thus, these eight subjects received their initial treatment with icatibant from a healthcare worker for their first post-enrollment HAE attack, whereas icatibant was self-administered at the onset of their second on-study HAE attack. All subjects completed the trial except for one icatibant-experienced patient who self-administered icatibant for an initial HAE attack as planned, but then did not complete the follow-up clinic visit and was ultimately lost to follow-up.

**Protocol Violations:** Nine subjects were noted to have protocol violations, five of whom were icatibant-experienced patients whose violations occurred during the self-administration phase of the trial (three subjects failed to return a used medication syringe as documentation of medication adherence; two subjects violated post-dose data collection procedures and/or schedules), while the other four were icatibant-naïve subjects whose violations occurred during the naïve treatment phase (one subject did not return a completed patient symptom diary; three subjects violated data collection procedures and/or schedules). Violations in which used icatibant syringes were not returned were considered to be major protocol violations with the potential to affect study outcomes, given the potential for group misclassification. In turn, the potential impact of these violations was explored in sensitivity analyses.

**Demographics:** Although the goal of this trial was not to compare outcomes in icatibant-naïve versus non-naïve subjects, the demographic and baseline

characteristics of these two subsets were comparable, as shown in Table 39. Of note, none of these subjects were recruited from the U.S., as subjects were enrolled primarily from Europe (Austria = 12, Germany = 9, Spain = 7, United Kingdom = 7), as well as from Israel (n = 11) and Argentina (n = 10). In turn, the sample consisted nearly exclusively of whites. While this may not have significant implications for endpoints focused primarily on assessing the safety and convenience of icatibant self-administration, the generalizability of safety and efficacy results related to the drug itself may be limited by this homogeneous sample.

**Table 39: Demographic and baseline characteristics by subject cohort in FAST-4**

| Characteristic | Icatibant-experienced (N = 48) | Icatibant-naive (N = 8) | Overall (N = 56) |
|---|---|---|---|
| **Sex (n, %)** | | | |
| *Female* | 32 (66.7) | 6 (75.0) | 38 (67.9) |
| *Male* | 16 (33.3) | 2 (25.0) | 18 (32.1) |
| **Race (n, %)** | | | |
| *White* | 47 (97.9) | 8 (100.0) | 55 (98.2) |
| *Non-White* | 1 (2.1) | 0 | 1 (1.8) |
| **Age (years)** | | | |
| *Mean* | 39.2 | 40.9 | 39.4 |
| *Median* | 37.5 | 39.0 | 37.5 |
| *Standard Deviation* | 12.5 | 15.0 | 12.7 |
| **Weight (kg)** | | | |
| *Mean* | 73.1 | 77.5 | 73.7 |
| *Median* | 69.3 | 68.5 | 69.3 |
| *Standard Deviation* | 18.4 | 23.7 | 19.1 |
| **Height (kg)** | | | |
| *Mean* | 169.5 | 166.8 | 169.1 |
| *Median* | 168.5 | 168.0 | 168.5 |
| *Standard Deviation* | 10.0 | 6.6 | 9.6 |

*Source: FAST-4 Clinical Study Report, Table 7-2*

**Major Safety Results**

**Adverse Events:** No deaths or SAEs were reported in FAST-4. In addition, no AE-related trial discontinuations were recorded. No clinical laboratory assessments were conducted in FAST-4, and no clinically significant changes from baseline in vital signs or physical examination findings were noted. At least one AE was experienced by nearly 32.1% of the sample (18 subjects) during the self-administration phase, with 4 subjects (7.1%) developing severe AEs (2 subjects with HAE, 1 subject with abdominal pain, 1 subject with gastrointestinal pain, and 1 subject with headache). HAE AEs were defined as worsening or recurrent HAE symptoms; however, these symptoms were typically less severe than the original HAE attack. Rescue medications (primarily palliative medications for pain and gastrointestinal symptoms and C1-INH replacement therapy) were used by 9 of 13 subjects (69.2%) reporting worsening or recurrent HAE symptoms, regardless of AE designation. Table 40 summarizes the AEs that occurred in more than 1 subject during the self-administration phase of FAST-4. Worsening and recurrence of HAE was the only AE (classified by MedDRA preferred term) observed in more than two subjects.

## Table 40: Adverse events occurring in more than 1 subject during the self-administration phase of FAST-4, grouped by pre-enrollment icatibant exposure

| **System Organ Class**<br>Preferred Term (n, %) | **Icatibant-experienced N = 48** | **Icatibant-naïve N = 8** | **Overall N = 56** |
|---|---|---|---|
| **Congenital, familial, and genetic disorders** | 12 (25.0) | 1 (12.5) | 13 (23.2) |
| HAE | 12 (25.0) | 1 (12.5) | 13 (23.2) |
| **Gastrointestinal disorders** | 3 (6.3) | 0 | 3 (5.4) |
| Abdominal pain | 2 (4.2) | 0 | 2 (3.6) |
| **Nervous system disorders** | 2 (4.2) | 1 (12.5) | 3 (5.4) |
| Headache | 1 (2.1) | 1 (12.5) | 2 (3.6) |

*Source: FAST-4 Clinical Study Report, Table 8-2*

During the naïve treatment phase, 4 of 8 subjects (50%) experienced at least one AE, with three reports of HAE and one report of facial swelling. Although FAST-4 was not a placebo-controlled trial, the reported AE rates are consistent with those observed in icatibant-recipients in the pivotal Phase 3 efficacy trials and did not identify any additional safety signals for icatibant.

**Local Injection Site Reactions**: As in other pivotal Phase 3 efficacy trials, one or more local injection site reactions were noted in nearly all subjects in FAST-4 within 48 hours of icatibant dosing. Most reactions were reported as mild to moderate, with the following exceptions: 2 subjects with severe skin redness, 2 subjects with severe swelling, 1 subject with severe itching, and 1 subject with a severe warm sensation. However, no severe symptoms were noted by 10 hours post-dosing, although 2 subjects had a recurrence of burning and itching at 36 hours post-dose.

## Table 41: Local injection site reactions occurring in FAST-4 (n, %)

| **Self-administration Phase** | **N = 56** |
|---|---|
| Skin redness | 50 (89.3) |
| Swelling | 39 (69.6) |
| Burning | 26 (46.4) |
| Itching | 16 (28.6) |
| Warm sensation | 23 (41.1) |
| Skin pain | 19 (33.9) |
| **Naïve Treatment Phase** | **N = 8** |
| Skin redness | 7 (87.5) |
| Swelling | 3 (37.5) |
| Burning | 2 (25.0) |
| Itching | 2 (25.0) |
| Warm sensation | 2 (25.0) |
| Skin pain | 0 |

*Source: FAST-4 Clinical Study Report, Listing 12.2.7.2.1, Listing 12.2.7.2.2*

Despite nearly universal occurrence following icatibant-administration, these local injection site reactions had largely abated by 48 hours post-dosing, as determined by a review of individual patient line listing data. Thus, rates of investigator-assessed injection site reactions made at the 48-hour post-dosing follow-up clinic visit were far lower than self-reported assessments recorded during the self-administration phase (as determined from a review of individual patient line data in Listing 12.2.7.2.3 and Listing 12.2.7.2.4 from the Clinical Study Report of FAST-4: erythema = 8 subjects (14.3%), swelling = 4 subjects (7.1%), burning sensation = 4 subjects (7.1%), itching/pruritus = 4 subjects (7.1%), warm sensation = 5 subjects (8.9%), skin pain = 2 subjects (4.2%). During the naïve-treatment phase, investigators determined that injection site reactions were resolved by the 48-hour follow-up clinic visit in all subjects except for erythema, burning sensation, and warm sensation, which were each observed in a single subject (12.5%). These data were all consistent with local tolerability data generated from the pivotal Phase 3 efficacy trials and did not indicate an increase rate of local injection site reactions associated with icatibant self-administration.

**Adverse Events by Subgroups:** Similar numbers of male (5 of 18 = 33.3%) and female (12 of 38 = 31.6%) subjects experienced AEs during the self-administration phase of FAST-4, whereas one male (5.6%) and three female (7.9%) subjects experienced a severe AE. When stratified by rescue medication use, all of the 11 subjects who used rescue medications experienced an AE (nine with worsening or recurrence of HAE, two with abdominal pain, and one each with gastrointestinal pain, headache, and dizziness). In contrast, only 7 of 45 subjects (15.6%) who did not take rescue medications experienced an AE (4 subjects with worsening or recurrence of HAE, and one each with headache, migraine, rhinitis, back pain, and skin swelling). These differences in AE rates were not surprising, as subjects who used rescue medications could be expected to have HAE symptoms of greater severity than those who did not require additional medications.

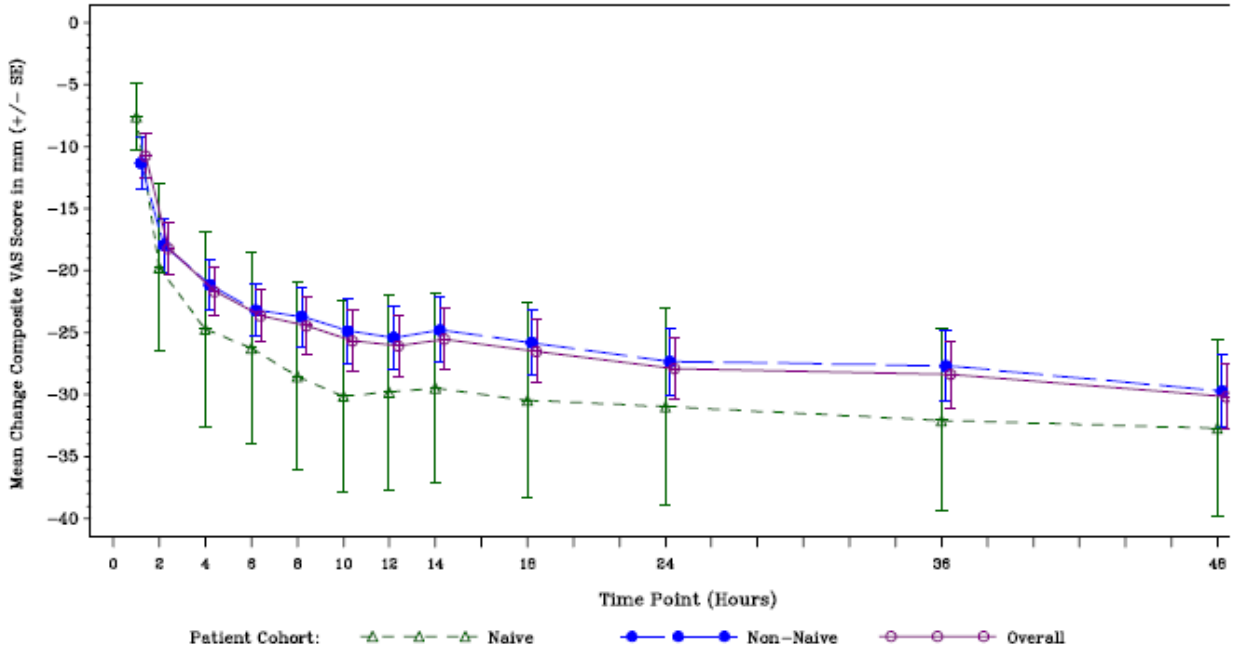
**Secondary Efficacy Results**

The efficacy of self-administered icatibant was evaluated as a secondary study endpoint in FAST-4. Efficacy analyses from this trial were based primarily on the self-administration phase involving all 56 subjects in the trial. Data from the subset of eight icatibant-naïve patients in this trial who participated in the naïve-treatment phase in which icatibant was initially administered by a healthcare worker were also analyzed. Of note, given that FAST-4 was an uncontrolled trial, a statistical comparison of self-administered icatibant to healthcare worker-administered icatibant cannot be made, although data for the eight subjects involved in the naïve-treatment phase of this trial are provided for trend comparisons.

**Time to Onset of Symptom Relief:** Based on symptom ratings during the self-administration phase of FAST-4, the median time to symptom relief based on a 50% reduction in composite VAS-3 score was 2.6 hrs for the entire sample (95% CI: 2.0-4.0 hrs), 2.0 hrs (95% CI: 1.8-4.0 hrs) for the 44 evaluable icatibant-experienced subjects (two icatibant-experienced subjects without documented symptom relief were censored from the analysis), and 4.0 hrs (95% CI: 2.0-6.2 hrs) for the eight evaluable icatibant-naïve subjects. Median time to primary symptom relief (defined as in FAST-1, FAST-2, and FAST-3) was noted to be even shorter: 2.0 hrs for the entire sample, 2.0 hrs (95% CI: 1.3-2.0 hrs) for 43 evaluable icatibant-experienced subjects, and 2.1 hrs (95% CI: 2.0-4.0 hrs) for seven evaluable icatibant-naïve patients. Consistent with the efficacy results generated during the self-administration phase, results from the naïve-treatment phase in which eight icatibant-naïve patients were administered icatibant by healthcare workers, the median time to onset of symptom relief based on VAS-3 was 2.0 hrs (95% CI: 1.9-5.9 hrs) in seven evaluable subjects, and the median time to onset of primary symptom relief was 4.2 hrs (95% CI: 2.0-24.0 hrs) in five evaluable subjects. These findings were generally consistent with response times observed in the pivotal Phase 3 efficacy trials.

**Change in Mean VAS Symptom Scores:** An examination of mean VAS scores over time for the composite symptom measure (VAS-3) and individual symptom domains during both the self-administration and naïve treatment phases of FAST-4 revealed similar patterns for both icatibant-naïve and icatibant-experienced subjects with regard to the timing of symptom relief, consisting of a rapid fall in symptom scores over the first 4 hours post-dosing, followed by a slower but persistent decline over the next 48 hours. A representative graph of these data generated by the Applicant is shown in Figure 3.

## Figure 3: Mean change in VAS-3 score over time during icatibant self-administration phase of FAST-4




*Source: Figure 10.2.1.2.1.1*

**Self-described Clinical Status at 48 hours Post-dosing:** The majority of HAE attacks were considered resolved by 48 hours post-dosing, as reported in 41 of 48 (85.4%) icatibant-experienced subjects and 7 of 8 (87.5%) icatibant-naïve subjects. Of note, a slightly lower percentage of icatibant-experienced subjects considered their HAE attack to be satisfactorily resolved by 48 hours (37 of 48 subjects = 77.1%). During the naïve-treatment phase, only 5 of 8 subjects (62.5%) reported their attack as resolved at this time point, although a higher percentage (7 of 8 subjects = 87.5%) considered their attack to be satisfactorily resolved. Of note, although subjects were instructed to return to the clinic site for persistent symptoms within 6-48 hours of icatibant self-administration for additional healthcare worker-administered doses if needed, only one subject returned to receive an additional dose of icatibant. Other subjects preferred to self-manage any persistent symptoms independently.

**Convenience of Icatibant Self-Administration:** An 8-item questionnaire designed to assess the convenience of icatibant self-administration was completed by all 56 subjects in the study; of note, the psychometric properties of this instrument (e.g., validity, reliability) are not described by the Applicant. While all subjects reported that the training materials were sufficient or very sufficient to explain self-administration, 11 subjects (19.7%) felt the idea of self-injection was stressful or very stressful. Interestingly, however, 53 subjects (94.6%) indicated that self-administration of icatibant was preferable or very preferable to clinic-based administration. Nearly the entire sample (55 subjects = 98.3%) considered assembly and handling of the pre-filled syringe to be easy or very easy, with 49 subjects (87.5%) stating it was easy or very easy to self-inject icatibant and 46 subjects (82.1%) indicating it was convenient or very convenient to carry the medication for self-injection. Finally, 49 subjects (87.5%) reported that they were satisfied or very satisfied with how icatibant relieved their symptoms compared to their usual treatment. In general, the results of this unvalidated questionnaire support the convenience of self-administered icatibant.

**Investigator Global Assessment of Symptoms:** Investigator-based symptom assessments at the 48-hour post-icatibant follow-up clinic visit were consistent and slightly lower in severity ratings, compared to self-assessments by patients. Complete resolution of skin edema was noted by investigators in 49 subjects (87.5%), while 48 subjects (85.7%) were considered to have no abdominal symptoms at 48 hours post-dosing. Only two subjects were felt to have persistent severe abdominal symptoms at 48 hours post-dosing. Of those subjects judged by investigators to have persistent mild to moderate symptoms, approximately half of these patients felt their attacks had resolved or improved to a satisfactory degree by this time point. During the naïve-treatment phase, only one subject was felt to have persistent symptoms at the 48-hour follow-up (moderate skin edema).

Although no symptoms of laryngeal edema were recorded at 48 hours post-dosing, only a single subject reported laryngeal symptoms during their self-treated attack. This subject was a 59 year-old man with Type II HAE who was instructed to come to the clinic for physician-directed treatment after the initial reporting of his laryngeal symptoms, but he refused due to his distance from the clinic site. Although he agreed to seek medical care at a closer facility following icatibant self-administration, he did not do this, noting that his symptoms began to improve at 4 hours following this single icatibant dose and were completely resolved by 14 hours post-dose, with no symptom recurrence noted at the 48-hour time point.

**Sensitivity Analyses for Main Efficacy Measures:** Sensitivity analyses were conducted to assess the potential effects of rescue medication use on the main efficacy measures in FAST-4. Rescue medication use was reported in 11 subjects (19.6%), consisting primarily of analgesics (e.g., ibuprofen, acetaminophen, diclofenac), gastrointestinal medications (e.g., metoclopramide, hyoscine, buscopan), and other treatments for HAE (e.g., C1-INH replacement, tranexamic acid, commercial Firazyr).

Rescue medication use did not appear to impact self-reported time to onset of symptom relief based on VAS-3 score (2.0 hrs, 95% CI: 1.8-10.0 hrs) or primary symptom score (3.5 hrs, 95% CI: 2.0-6.3 hrs). Subjects who reported no rescue medication use (45 subjects = 80.4%) had a median time to onset of symptom relief based on VAS-3 of 3.4 hrs (95% CI: 2.0-4.0 hrs), with 97.6% reporting symptom relief, and 2.0 hrs (95% CI: 1.3-2.0) based on primary symptom score, with 97.5% reporting symptom relief. In addition, when subjects who received rescue medications were censored from the efficacy analysis at the time of their rescue medication use, the median time to primary symptom relief remained similar to that of the main efficacy analysis: 2.0 hrs, with 92% of subjects reporting symptom relief. These censored analyses were similar for time frames based on VAS-3: 2.3 hrs, with 90.4% reporting symptom relief.

Sensitivity analyses were also performed to evaluate the potential impact on the primary efficacy endpoints of major protocol violations, which may have lead to subject misclassification. The exclusion of three subjects who failed to return used icatibant syringes to the study site (as a confirmation of medication compliance) from the analyses of data generated during the self-administration phase of the trial did not significantly impact time to onset of symptom relief or summary VAS symptom scores.

**Gender Subgroup Analyses:** Time to onset of symptom relief based on VAS-3 was the same for icatibant-experienced male subjects (2.0 hrs, 95% CI: 1.1-4.0) and female subjects (2.0 hrs, 95% CI: 1.8-4.0), in contrast to the gender subgroup findings noted in the pivotal Phase 3 efficacy trials. Time to onset of symptom relief was longer in the icatibant-naïve group for both genders, particularly for males (male subjects: 5.1 hrs, 95% CI: 4.0-6.2 hrs; female subjects: 3.5 hrs, 95% CI: 2.0-6.0 hrs). This contributed to longer lag times noted in the overall samples for male (4.0 hrs, 95% CI: 1.1-6.0 hrs) versus female (2.3 hrs, 95% CI: 2.0-4.0 hrs) subjects, which was consistent with overall findings from the other Phase 3 trials.

### 7.4.6 Immunogenicity

Immunogenicity assessments were conducted across the three pivotal Phase 3 efficacy trials. Serum samples from FAST-1 and FAST-2 were analyzed by both screening and confirmatory ELISA for icatibant-specific IgG and IgE, whereas samples from FAST-3 were analyzed using screening ELISA only (given the absence of positive screening results in FAST-3). Samples drawn both pretreatment and post-treatment (at Day 14 post-doing for the initial HAE attack) were tested and considered positive only if evidence of either drug-specific IgG or IgE was detected by both screening and confirmatory ELISA.

Across all three trials, a total of 121 icatibant-recipients (with 192 pretreatment and 214 post-treatment samples) and 108 placebo or tranexamic acid-recipients (with 163 pretreatment and 189 post-treatment samples) were evaluated. As expected, no placebo or tranexamic acid-recipients had positive icatibant-specific antibody results at

either time point. In contrast, two icatibant-recipients were noted to be antibody positive at baseline, although only one of these subjects was antibody positive at post-treatment. However, this subject did not have a detectable increase in drug-specific antibody titer post-dosing, and follow-up immunogenicity samples over the next 5 months were all negative. Thus, the Applicant suggests these positive findings were related to nonspecific background noise for both subjects, which appears to be a reasonable hypothesis. Of note, no anaphylactic or otherwise significant hypersensitivity reactions were noted for any subject. Therefore, icatibant appears to have a low likelihood of immunogenicity.

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

Dose explorations were limited in the icatibant development program to Phase 1 and 2, with only the 30 mg SC dose evaluated in the randomized treatment portion of the pivotal Phase 3 safety and efficacy trials. Although during the open-label extension phases of all three pivotal efficacy trials, up to three 30 mg icatibant injections were allowed within a 24-hour period (each separated by at least 6 hours) for persistent signs and symptoms of HAE, relatively few patients were treated with more than one dose of icatibant for any given HAE attack in the Phase 3 program. Thus, it is difficult to evaluate AE data for dose dependency. However, from the limited safety data available, no dose-dependent patterns emerged.

### 7.5.2 Time Dependency for Adverse Events

From the safety data presented, rates for the majority of AEs do not appear to be time-dependent. However, local injection site reactions (regardless of AE designation) appeared to occur immediately or soon after subcutaneous icatibant dosing.

### 7.5.3 Drug-Demographic Interactions

Incidences of total and severe AEs recorded during the 14-day post-dosing observation period for initial HAE attacks are shown within key demographic strata in Table 42. When safety data were stratified by age group or gender, AE rates in icatibant-recipients were similar across all strata and were noted to be lower than in placebo-recipients for each subgroup. In contrast, a higher rate of AEs were observed in subjects classified as white versus non-white, although the number of non-white subjects was limited in the pooled safety population (icatibant = 6 subjects, tranexamic acid = 0 subjects, placebo = 7 subjects). Similarly, when AE rates were stratified by weight groups, there appeared to be an increase in AE rates as weight categories increased. However, in all subgroups defined by race or weight, AE rates within each

stratum were similar to or lower than rates in the corresponding subgroup of placebo-recipients. Therefore, overall icatibant does not appear to induce disproportionate rates of AEs in specific demographic subgroups at rates greater than observed with placebo treatment.

**Table 42: Observation period AE rates by treatment group in pooled Phase 3 safety population, stratified by selected demographic factors (number and percentage of subjects within each specific stratum)**

| Treatment Group | Icatibant 30 mg N = 113 | | Tranexamic Acid N = 38 | | Placebo N = 75 | |
|---|---|---|---|---|---|---|
| n, % | Any AE | Any severe AE | Any AE | Any severe AE | Any AE | Any severe AE |
| **Age** | | | | | | |
| ≤ 30 yrs | 15 (44.1) | 2 (5.9) | 6 (60.0) | 2 (20.0) | 11 (45.8) | 4 (16.7) |
| > 30 to ≤ 40 yrs | 15 (38.5) | 4 (10.3) | 1 (16.7) | 0 | 14 (56.0) | 4 (16.0) |
| > 40 to ≤ 50 yrs | 11 (47.8) | 0 | 5 (41.7) | 2 (16.7) | 12 (63.2) | 5 (26.3) |
| > 50 yrs | 7 (41.2) | 1 (5.9) | 1 (10.0) | 0 | 4 (57.1) | 1 (14.3) |
| **Gender** | | | | | | |
| Male | 17 (40.5) | 5 (11.9) | 6 (40.0) | 2 (13.3) | 13 (54.2) | 5 (20.8) |
| Female | 31 (43.7) | 2 (2.8) | 7 (30.4) | 2 (8.7) | 28 (54.9) | 9 (17.6) |
| **Race** | | | | | | |
| *White* | 47 (43.9) | 7 (6.5) | 13 (34.2) | 4 (10.5) | 35 (51.5) | 12 (17.6) |
| *Non-white* | 1 (16.7) | 0 | 0 | 0 | 6 (85.7) | 2 (28.6) |
| **Weight** | | | | | | |
| *≤ 50 kg* | 2 (28.6) | 0 | 0 | 0 | 1 (25.0) | 0 |
| *> 50 to ≤ 75 kg* | 17 (38.6) | 3 (6.8) | 7 (33.3) | 3 (14.3) | 23 (65.7) | 9 (25.7) |
| *> 75 to ≤ 100 kg* | 19 (43.2) | 4 (9.1) | 5 (35.7) | 1 (7.1) | 8 (36.4) | 3 (13.6) |
| *> 100 kg* | 10 (55.6) | 0 | 1 (50.0) | 0 | 9 (64.3) | 2 (14.3) |

*Source: Integrated Summary of Safety, Table 9.1.1, Table 9.1.2, Table 9.1.3, Table 9.1.4*

### 7.5.4 Drug-Disease Interactions

The Applicant seeks an indication for the treatment of acute HAE attacks in adults, without specific reference to severity or edema location, which is generally supported by results of the Phase 3 clinical program. Across the three pivotal Phase 3 efficacy trials, HAE attacks ranging from mild to severe were treated with blinded study treatment, with moderate to severe cutaneous and/or abdominal HAE attacks randomly in all three trials and mild to moderate laryngeal HAE attacks randomly treated in FAST-3 only. Thus, the distribution of blinded treatments by severity of HAE attacks was largely limited to moderate to severe HAE attacks: icatibant (N = 113): mild = 1.8%, moderate = 46.9%, severe = 51.3%; tranexamic acid (N = 38): mild = 0%, moderate = 28.9%, severe =

71.1%; placebo (N = 75): mild = 0%, moderate = 54.7%, severe = 45.3%. Safety data from these clinical trials do not suggest an attack-severity dependency for AEs, with similar or lower AE rates observed in icatibant versus placebo-recipients within each severity grade stratum.

In terms of edema location, a range of cutaneous, abdominal, and laryngeal HAE attacks was treated across the three trials, with the majority being cutaneous and abdominal HAE attacks: icatibant: cutaneous = 56.6%, abdominal = 37.2%, laryngeal = 6.2%; tranexamic acid: cutaneous = 60.5%, abdominal = 39.5%, laryngeal = 0%; placebo: cutaneous = 52.0%, abdominal = 46.7%, laryngeal = 1.3%. An attack-site dependency was not noted for AE data in these trials, other than an expected preponderance of specific System Organ Class AEs associated with the different edema sites, e.g., gastrointestinal AEs noted more frequently in abdominal HAE attacks (7.1%) versus cutaneous attacks (1.6%). Of note, acute AE rates were higher with abdominal HAE attacks (acute = 42.9%; observation period = 45.2%) compared to cutaneous attacks (acute = 18.8%; observation period = 40.6%) in the icatibant group. Although the underlying pathophysiology of a potential association is unclear, this pattern may reflect a drug-disease interaction specific to icatibant, as a preponderance of abdominal attack-associated AEs was not observed in placebo-recipients, for whom AEs were more common with cutaneous attacks (acute = 48.7%; observation period = 66.7%) compared to abdominal attacks (acute = 31.4%; observation period = 45.2%). Overall, however, it is difficult to draw conclusions regarding the clinical significance of differences in AE rates by edema location, given the limited sample size of the Phase 3 program. This is particularly true of laryngeal HAE attacks, which were much lower in number in the icatibant development program, compared to other edema sites.

Icatibant was also studied in patients with mild to moderate hepatic and renal impairment in pharmacokinetic trials. Although a formal renal impairment study was not conducted as part of the clinical program, an earlier trial previously reviewed in the original NDA submission (JE049-2002) studied the pharmacokinetics of intravenously administered icatibant in 10 of 37 subjects with hepatorenal syndrome and glomerular filtration rates below 60 mL/min. Another trial (JE049-2001) evaluated the pharmacokinetics of icatibant in eight subjects with hepatic insufficiency compared to eight healthy volunteers. Based on the findings from these trials, no significant accumulation of icatibant or its principal metabolites (M1 and M2) was noted in patients with renal or hepatic impairment, and no distinct AE patterns related to renal or hepatic impairment were observed.

### 7.5.5 Drug-Drug Interactions

Formal drug-drug interaction studies were not performed in the icatibant Phase 3 clinical program; however, nonclinical *in vitro* studies did not reveal significant inhibition (e.g., 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4) or induction (e.g., 1A2 or 3A4) of CYP450 enzymes by icatibant. Of note, the Applicant recognizes the theoretical

potential for icatibant to attenuate the antihypertensive effects of ACE-inhibitors via antagonism of bradykinin, which is known to accumulate as a result of ACE-inhibitor therapy, thereby leading to vasodilation and antihypertensive effects. Given that ACE-inhibitors are known to induce angioedema in idiosyncratic fashion, however, their use is generally contraindicated in HAE patients. Therefore, this theoretical interaction is unlikely to pose significant risk in clinical practice, given expected prescribing patterns for the two drugs.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

The Applicant acknowledges a theoretical risk of induction or worsening of malignancies with icatibant, based on the *in vitro* mitogenic potential of icatibant-mediated bradykinin inhibition observed in nonclinical studies. However, this safety signal has not emerged in the icatibant clinical program or in reports from the medical literature. Moreover, the expected infrequent and intermittent use of icatibant would presumably lessen a risk of human carcinogenesis in most HAE patients. Of note, however, one subject in FAST-2 received a total of 142 doses of icatibant for 142 separate HAE attacks, reflecting the striking variability in the clinical presentation of HAE. Thus, long-term (2-year) carcinogenicity studies in rats are currently ongoing.

### 7.6.2 Human Reproduction and Pregnancy Data

No formal studies of icatibant in pregnancy have been conducted. Active pregnancy and breastfeeding were exclusion criteria in the icatibant Phase 3 program. However, five medically confirmed pregnancies have occurred to date in clinical trial participants, who had received icatibant prior to being withdrawn from their respective trials. Three of these pregnancies resolved without complication or sequelae. One was terminated in an elective abortion in the eighth week of pregnancy, and follow-up information was not available for the fifth. A sixth pregnancy in an icatibant-recipient was described in a spontaneous report to the Applicant, but follow-up information was unavailable.

Nonclinical studies in rats and dogs demonstrated delayed maturation of reproductive organs following icatibant treatment, with decreased testosterone levels but no clinically significant effects on luteinizing hormone levels. A Phase 1 clinical trial (HGT-FIR-062) is currently ongoing to evaluate the effects of icatibant on reproductive hormone levels in 10 male and 10 premenopausal female subjects.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

Icatibant was not evaluated in subjects less than 18 years of age, and the Applicant is not currently seeking an indication for pediatric use in the treatment of acute HAE attacks.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Nonclinical studies of icatibant indicated that it does not distribute to brain tissue and does not display pharmacologic attributes of drugs prone to overuse, abuse, or withdrawal syndromes. The Applicant states that icatibant has no addictive potential, and intentional overdose is unexpected. In turn, withdrawal phenomena have not been evaluated for icatibant. However, with regard to potential effects of icatibant overdose, one spontaneous postmarketing report from the European Union (where icatibant is currently approved for the treatment of HAE attacks) documented an extreme elevation in hepatic enzymes in a 23 year-old man who received a total of eight icatibant injections (two of which were 60 mg in dose) for a presumed laryngeal HAE attack on a background of multi-organ failure secondary to septic shock. Although this particular patient received an icatibant overdose totaling 300 mg over 5 days, the clinical context of this case suggests the ultimate outcome of death (and possibly the extreme elevation in hepatic enzymes) was related to the underlying condition of septic shock and multi-organ failure, rather than icatibant overdose. This case is discussed in detail in Section 8 Postmarket Experience.

# 8 Postmarket Experience

The Applicant based a postmarketing safety review on information submitted to the Shire Global Safety Systems (SGSS) database, as monitored by Shire's Global Pharmacovigilance and Risk Management Department. This review included all serious and non-serious cases (other than non-serious cases from clinical trials) entered into the SGSS for the first two years of postmarketing experience in the European Union through July 11, 2010, where the Applicant estimates that 5,379 patient exposures to Firazyr have occurred cumulatively since the time of EU approval on July 11, 2008. From the Applicant's postmarket review, a total of 21 cases were identified, with 11 from spontaneous reporting and ten drawn from the literature. These accounted for 37 adverse drug reactions (ADRs), seven of which were unlisted, with two of these seven ADRs considered serious. Per the MedDRA classification system, the majority of these ADRs fell under the General Disorders and Administration Site Conditions System Organ Class, which primary included local injection site reactions (erythema, irritation, pruritus, pain, and swelling) that were also commonly reported in the icatibant clinical program, as well as one non-serious unlisted report of polyuria.

Serious and Unlisted ADRs

Two serious and unlisted ADRs have been reported:

1) Extremely elevated hepatic enzymes and eventual death in a 23 year-old man following icatibant use at greater than recommended doses. Patient first presented for surgical resection of tonsillar abscess, which was followed by severe throat and facial swelling that required fasciotomy and tracheotomy two days later. HAE was suspected and patient received C1-INH replacement therapy (1000 U Berinert) but required repeat fasciotomy for persistent throat abscess. Hepatic enzymes noted to be elevated at that time (AST = 63 U/L, NML: 0-35 U/L; GGT = 74 U/L, NML: 0-55 U/L), with abnormal platelets, aPTT, and D-dimer levels. Septic shock subsequently diagnosed with multi-organ failure (including renal failure) and intracranial ischemia. Subjects received first dose of icatibant 30 mg SC at this time for a presumed laryngeal HAE attack, with only minor, transient improvement in throat edema. Second, third, and fourth doses of icatibant 30 mg SC were subsequently given, as well as another 1000 U of C1-INH, along with vancomycin and metoclopramide, with additional elevations observed in hepatic function tests (AST = 86 U/L; ALT = 42 U/L, NML: not reported; GGT = 378 U/L; ALK Phos = 199 U/L, NML: 35-130 U/L; LDH = 491 U/L, NML: 0-248 U/L). Over two more days, several additional doses of icatibant were given, including fifth and sixth doses of 60 mg each and seventh and eighth doses of 30 mg each, for a total dose of 300 mg SC icatibant administered over 5 days. Hepatic enzymes rose sharply over this period and peaked after the seventh dose of icatibant (AST = 13,780 U/L; ALT = 4,477 U/L), with abdominal CT scanning revealing multiple areas of hepatic ischemia. After the eighth and final dose of icatibant, hepatic enzymes began to decrease, although multi-organ failure continued to progress, and the patient eventually died with evidence of widespread brain, liver, and spleen infarctions, thrombosis of the hepatic vein and inferior vena cava, and severe transverse and ascending colitis, with suspected abdominal perforation. The Applicant has suggested that these hepatic enzyme elevations were due to the patient's underlying septic shock and malperfusion of the liver, rather than from acute drug toxicity, despite icatibant dosing beyond current recommendations.

2) Life-threatening acute myocardial infarction in a 23 year-old man with hypertension, significant adiposity, and a family history of coronary artery disease, which occurred one day after receipt of icatibant for an acute HAE attack. Patient had received an initial dose of icatibant one month prior for an acute HAE attack without adverse reaction. Following this episode, patient received a cardiac stent and beta blocker, clopidogrel, statin, and ACE inhibitor therapy, prior to starting rehabilitation. Although this patient had several cardiac risk factors, his young age and the temporal relationship of icatibant administration to the myocardial infarction raise the possibility of a causal relationship.

A Firazyr Patient Registry (Icatibant Outcomes Survey) has also been initiated that is open to all patients receiving icatibant treatment, which focuses on the safety of long-term icatibant treatment, with special attention to cardiac ischemic events, generalized reactions (hypotension, mucosal edema, bronchoconstriction, and aggravation of pain), effects on sexual maturation in adolescents, potential hypersensitivity reactions, and the safety and effectiveness of icatibant in laryngeal HAE attacks. Although outcome data from this registry are not included in this Complete Response submission, a total of 250 patients have been registered from eight countries, as of December 2010.

# 9 Appendices

## 9.1 Literature Review/References

A literature review was provided by the Applicant of icatibant-related safety data documented in the MEDLINE database, which spans the period from 1950 to November 2010. Details of the search process, as provided by the Applicant, included the drug-specific terms “icatibant,” “firazyr,” and “HOE 140” paired with the following search terms for safety-related topics pertaining to human drug exposure: abnormalities, drug induced; breast feeding; breast milk; congenital malformation (exploded); death (exploded); Adverse drug interactions (exploded); drug interaction (exploded); drug overdose; drug toxicity (exploded); lactation (exploded); milk, human; overdose; pregnancy (exploded); pregnancy complications (exploded); pregnant women; side effect (exploded); substance abuse (exploded); drug abuse (exploded); substance-related disorders (exploded); teratogens; teratogenicity; treatment failure; drug treatment failure. A total of 128 publications were identified by these search terms, including journal articles, commercial reports, letters, editorials, short surveys, notes, trade journals, and documentation of U.S. government and non-government research support. The Applicant identified eight of these publications as containing relevant safety data, but only five of these publications reported AE data in human recipients of icatibant outside of the icatibant development program.

The five publications identified described the following adverse drug reactions in humans related to icatibant (*in vitro* and nonclinical effects are not described here): 1) local injection site reactions (erythema, pruritus) noted in a series of eight emergency department patients treated with icatibant 30 mg SC for ACE-inhibitor-induced angioedema; 2) local injection site reaction (erythema, edema, burning sensation) following icatibant treatment in a 49 year-old man with acquired C1-INH deficiency or acquired angioedema who had also received treatment with C1-INH replacement therapy; 3) attenuation of the hypotensive effect of ACE-inhibitor therapy as studied in 20 normotensive and seven hypertensive patients who were co-administered icatibant and captopril; 4) reduction in arterial flow dependent dilation noted in 10 healthy

volunteers treated with icatibant; and 5) resolution of acute HAE symptoms in six patients, with subsequent local injection site reactions (erythema, burning sensation, swelling) in all patients, as well as severe dizziness in one patient. Other than the single report of dizziness, these post-dosing reactions are all consistent with the adverse effect profile and known physiologic effects of icatibant described in the Phase 3 clinical program.

**Key References Provided by the Applicant:**

1) Bas, M., et al. "Therapeutic efficacy of icatibant in angioedema induced by angiotensin-converting enzyme inhibitors: A case series." *Ann Emerg Med*. 2010; 56(3):278-282.

2) Bright, P., et al. "Successful treatment of acquired C1 inhibitor deficiency with icatibant." *Clin Exp Derm*. 2010; 35(5):553.

3) Gainer, J., et al. "Effect of bradykinin-receptor blockade on the response to angiotensin-converting enzyme inhibitor in normotensive and hypertensive subjects." *New Eng J Med.* 1998; 339(18):1285-1292.

4) Hornig B., et al. "Role of bradykinin in mediating vascular effects of angiotensin-converting enzyme inhibitors in humans." *Circulation*. 1997; 95(5):1115-1118.

5) Krause K., et al. "Successful treatment of hereditary angioedema with bradykinin B2-receptor antagonist icatibant." *J Germ Soc Derm*. 2009; 8(4):272-274.

A separate literature review of the PubMed database from January 1, 1977, through January 1, 2011, was conducted as part of this Clinical Review to search for additional reports of complications or adverse events related to icatibant exposure in humans. For this search, the following terms were pooled into two separate searches:

1) icatibant OR firazyr OR HOE 140 (1418 citations)

2) adverse event OR adverse effect OR complication OR sequela OR sequella OR sequelae OR sequellae (2,324,830 citations) [incorrect spelling variants included to capture additional citations]

These searches were then combined to identify overlapping citations, which limited to references in humans, produced a final tally of 17 references. A review of the available abstracts for these citations identified no additional descriptions of adverse events associated with icatibant exposure in humans that were not already referenced in the Applicant's literature review or the safety data submitted for this Complete Response. Of note, one manuscript not produced by the Applicant's literature review (Pretorius,

M., et al. “A pilot study indicating that bradykinin B2 receptor antagonism attenuates protamine-related hypotension after cardiopulmonary bypass.” *Clin Pharmacol Ther.* 2005; 78(5):477-485) detailed the use of intravenous icatibant (HOE 140) after cardiopulmonary bypass, in order to minimize the potential hypotensive complications associated with protamine reversal of heparin-induced anticoagulation. This small trial of 16 adult male patients noted a decrease in the activity of tissue plasminogen activator following administration of icatibant versus saline placebo, as well as a reduction in protamine-induced hypotension. No complications associated with bleeding or fibrinolytic imbalance were noted in this trial. Thus, no clinical correlates of this finding were identified, although this result raises the hypothesis of potential thrombotic complications associated with bradykinin receptor blockade.

## 9.2 Detailed Reviews of Individual Study Reports

## FAST-3

**Protocol Title:** HGT-FIR-054 (FAST-3): A Phase III Randomized Double-blind, Placebo-controlled Multicenter Study of Icatibant for Subcutaneous Injection in Patients with Acute Attacks of Hereditary Angioedema

**Original Protocol Date:** February 12, 2009

**Amendment Dates:** August 6, 2009 (Amendment 1)
January 25, 2010 (Amendment 2)

**Trial Initiation and Completion Dates:** July 16, 2009 to October 1, 2010

**Final Report Date:** December 20, 2010

**Study Sites:** 67 study sites in 11 countries in North America (United States, Canada, Mexico), Europe (Hungary, Romania, Ukraine), Asia (Turkey, Israel, Russia), Africa (South Africa), and Australia

**Primary Objective:** To compare the efficacy of icatibant with placebo on the time to symptom relief using a composite VAS during moderate to very severe acute cutaneous and/or abdominal attacks in patients with Type I or Type II HAE

**Key Secondary Objective:** To compare the efficacy of icatibant with placebo on the time to onset of symptom relief using the VAS score for a single primary symptom (defined as a reduction in VAS score to any value to the right and below the line defined as $Y = 6/7\ X - 16$ mm with $X \geq 30$ mm, where X = pre-treatment (baseline) VAS in mm and Y = post-treatment VAS in mm)

**Other Secondary Objectives:**

- To compare the efficacy of icatibant with placebo on time to symptom relief using a composite VAS score during moderate to very severe acute cutaneous and/or abdominal HAE attacks and mild to moderate laryngeal HAE attacks

- To compare the global outcome following treatment with icatibant versus placebo using patient-reported and physician-reported outcome measures

- To compare the time to almost complete symptom relief following treatment with icatibant versus placebo during moderate to very severe acute cutaneous and/or abdominal attacks

- To assess the safety and tolerability of icatibant compared with placebo

- To assess the efficacy and safety of icatibant treatment in patients experiencing laryngeal HAE attacks

- To compare the time to symptom relief in icatibant- and placebo-treated patients for each individual component in the 5-symptom composite VAS during moderate to very severe acute cutaneous and/or abdominal HAE attacks and mild to moderate laryngeal HAE attacks

- To evaluate the impact of icatibant treatment compared with placebo on the use of rescue medication during acute HAE attacks

**Study Rationale:** As a direct inhibitor of the bradykinin type 2 receptor, icatibant is expected by the Applicant to directly counter the pathophysiologic effects of dysregulated bradykinin production during acute attacks of HAE.

**Study Design Overview:** FAST-3 was a randomized, double-blind, placebo-controlled, parallel-group Phase 3 trial in which 88 subjects were randomized 1:1 to treatment with a single dose of icatibant 30 mg SC versus placebo for the initial post-enrollment acute HAE attack of moderate to severe cutaneous and/or abdominal edema. An additional five subjects were similarly randomized for initial HAE attacks of mild to moderate laryngeal edema. Finally, another five subjects who presented with initial laryngeal HAE attacks during the primary treatment phase were treated with open-label icatibant either due to severe laryngeal symptoms or because they were enrolled prior to protocol Amendment 1 (dated August 6, 2009), which allowed for randomized blinded treatment of laryngeal HAE attacks.

**Study Population:** 98 adults with either Type I or Type II HAE were randomized to active treatment with icatibant versus placebo, according to the following participation criteria:

**Pertinent Inclusion Criteria**

- Males or females aged ≥ 18 years
- Documented diagnosis of Type I or II HAE, confirmed by decreased C4 levels and/or immunogenic or functional C1-INH deficiency (< 50% of normal levels) consistent with Type I or II HAE or by medical history; medical history alone was sufficient for inclusion if the subject also presented a consistent family history, characteristic recurrent attacks, historical functional C1-INH deficiency (< 50% of normal), and exclusion of other forms of angioedema including acquired angioedema with normal C1q levels
- Current HAE attack in cutaneous, abdominal, and/or laryngeal/pharyngeal areas
- Cutaneous or abdominal HAE attacks must have been moderate to severe, as determined by investigator global assessment at baseline
- Patient reported at least one VAS score ≥ 30 mm
- Patient commenced treatment within 6 hours of attack becoming at least mild (for laryngeal attacks) or moderate (for abdominal and cutaneous attacks) in severity, but not more than 12 hours after onset
- Voluntary signing of IRB-approved informed consent following complete discussion of all relevant aspects of the trial
- Women of childbearing potential must have a negative urinary pregnancy test and must have used appropriate pregnancy prevention method during trial

**Pertinent Exclusion Criteria**

- Angioedema diagnosis other than HAE
- Previous icatibant treatment
- Previous participation in clinical trial with receipt of other investigational product within past 30 days

- Treatment with any pain medication since onset of current angioedema attack
- Treatment with angiotensin converting enzyme (ACE) inhibitor
- History of coronary artery disease at baseline (e.g., unstable angina, severe coronary heart disease and congestive heart failure NYHA Class 3 or 4)
- Serious concomitant illness or condition that (per investigator) would contraindicate trial participation
- Pregnancy or breastfeeding
- Inability to understand nature and consequences of protocol or unlikely to comply with assessments or follow-up visits for any reason

**Study Treatments:** Patients were enrolled upon presentation with an initial cutaneous or abdominal HAE attack of at least moderate severity or an initial laryngeal attack of mild to moderate severity and were randomized (stratified by attack location and previous use of C1-INH replacement therapy) to a single injection into the abdomen of either 30 mg SC icatibant or placebo of equal volume (3 mL of sterile, isotonic, buffered acetate solution). Randomized treatments were given within 6 hours of symptoms becoming at least mild (laryngeal) or moderate (abdominal or cutaneous), but no more than 12 hours after symptom onset. Patients with severe laryngeal HAE symptoms were treated with open-label icatibant 30 mg SC; prior to Amendment 1 of the protocol, all laryngeal attacks of any severity were treated with open-label icatibant.

All subsequent attacks could be treated with open-label icatibant 30 mg SC during an extension phase. Repeat injections of icatibant separated by at least six hours each (up to a total icatibant dose of 90 mg within a 24 hour period for a single HAE attack) were permitted within 48 hours of symptom onset for all subsequent HAE attacks experienced during this extension phase. Symptoms that worsened at greater than 48 hours after initial study treatment were considered to constitute a new HAE attack. No more than 8 injections of icatibant were permitted within any 4-week period, although patients could be re-treated for any number of recurrent qualifying HAE attacks during the extension phase.

Concomitant therapy with attenuated androgens used as prophylactic treatment for HAE was allowed, provided that the dose was stable or decreased during the trial. Recent C1-INH replacement therapy (e.g., C1-INH replacement products, fresh frozen plasma) was also allowed, per Amendment 2 of the protocol (prior to Amendment 2, subjects receiving such treatments within 5 days of the current HAE attack were ineligible). Although rescue therapies for acute HAE attacks were permitted at the discretion of the investigator (e.g., fresh frozen plasma, epinephrine, C1-INH replacement, NSAIDs),

such therapies were to be delayed as long as possible, ideally for the first nine hours after injection of randomized treatment. Antihistamines and glucocorticoids were also permitted as concurrent medications, although these were not considered to be rescue medications, given their lack of efficacy in the treatment of acute HAE attacks. Morphine sulfate 0.05 mg/kg or an equivalent low-dose narcotic were allowed for analgesia, and anti-emetics were permitted for nausea.

**Study Procedures:** Following randomized treatment, subjects were hospitalized and observed for at least eight hours post-dosing, prior to discharge home if deemed clinically stable by the investigator. Two follow-up visits were then conducted, once between Days 2 to 5 and again at Day 14 (± 2 days).

A schedule of key trial procedures and assessments is presented in the following tables for both the blinded treatment phase, as well as the open-label extension period.

## Table 43: Timetable of assessments during blinded treatment phase of FAST-3

| Visit | Scr | Pre-Tx | Tx | 2 | | | | | | | | | | | | 3 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day/Week | | 1 | 1 | 1 (post-Tx) | | | | | | | | | | | | 2 | 3-5 |
| Hour | | | 0 | 0.5 | 1.0 | 1.5 | 2.0 | 2.5 | 3.0 | 3.5 | 4.0 | 5.0 | 6.0 | 8.0 | 12 | 24-28 | 48-120 |
| **Procedure** | | | | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | | | | |
| Inc/Exc Criteria | X | X | | | | | | | | | | | | | | | |
| Demog. | X | | | | | | | | | | | | | | | | |
| Medical History | X | X | | | | | | | | | | | | | | | |
| Concom. Meds | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Phys. Exam | X | X | | | | | | | | | | | | | | X | |
| Vital Signs | X | X | | | | | | | | | | | | | X | X | |
| ECG | | X | | X | | | | | | | | | | | | X | |
| Inpatient Observ. | | | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Syx Diary | X | X | | | | | | | | | | | | X | X | X | |
| VAS: Pt | | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Symptom Score: Pt | | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Patient Global | | X | | | | | | | | | X | | | X | X | | |

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Impression | | | | | | | | | | | | | | | | | |
| Symptom Score: Inv. | | X | | | X | X | X | X | X | X | X | X | X | X | X | X | |
| Inv. Global Assessment | | X | | | | | X | | | | X | | | X | X | X | |
| Inv. Global Impression | | X | | | | | | | | | X | | | X | X | | |
| Study Drug | | | X | | | | | | | | | | | | | | |
| Local Tolerability | | | | X | X | | X | | | | X | | | X | X | X | X |
| Symptom Relief: Pt | | | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Symptom Relief: Inv | | | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Final attack assessment | | | | | | | | | | | | | | | | | |
| Adverse Events | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| C1-INH, C4, C1q | X | | | | | | | | | | | | | | | | |
| Anti-drug antibodies | | X | | | | | | | | | | | | | | | |
| Labs: heme & chem. | | X | | | | | | | | | | | | | | X | |
| Urine preg. | | X | | | | | | | | | | | | | | | |
| U/A | | X | | | | | | | | | | | | | | X | |

| **Visit** | **4** | **5** | **Phone F-U** | **F-U** |
|---|---|---|---|---|
| **Day/Week** | **14 (± 2)** | **Week 5 ± 1** | **Every 12 weeks** | **Every 6 months** |
| **Procedure** | | | | |
| Informed Consent | | | | |
| Inc/Exc Criteria | | | | |
| Demog. | | | | |
| Medical History | | | | |
| Concom. Meds | X | X | X | X |
| Phys. Exam | X | | | X |
| Vital Signs | X | | | X |
| ECG | | | | |
| Inpatient | | | | |

| | | | | |
|---|---|---|---|---|
| Observ. | | | | |
| Syx Diary | X | | | |
| VAS: Pt | | | | |
| Symptom Score: Pt | X | | | |
| Patient Global Impression | | | | |
| Symptom Score: Inv. | X | | | |
| Inv. Global Assessment | X | | | |
| Inv. Global Impression | | | | |
| Study Drug | | | | |
| Local Tolerability | | | | |
| Symptom Relief: Pt | | | | |
| Symptom Relief: Inv | | | | |
| Final attack assessment | X | | | |
| Adverse Events | X | X | X | X |
| C1-INH, C4, C1q | | | | |
| Anti-drug antibodies | X | X | | X |
| Labs: heme & chem. | X | | | |
| Urine preg. | X | | | |
| U/A | X | | | |

*Scr = screening visit, Tx = treatment, F-U = follow-up, Inc/Exc = inclusion/exclusion, Demog = demographics, Concom = concomitant, Phys = physical, Observ = observation, Syx = symptom, Pt = patient, Inv = investigator, heme = hematology, chem = chemistry, preg = pregnancy, U/A = urinalysis*
*Source: FAST-3 Clinical Study Report, Table 5-5*

## Table 44: Timetable of assessments during open-label extension phase of FAST-3

| **Visit** | **Pre-Tx** | **Tx** | **2** | **3** | | **4** |
|---|---|---|---|---|---|---|
| **Day** | **1** | **1** | **1** | **2** | **3-5** | **14 (±2)** |

| Hour | | 0 | 0.5 | 1.0 | 1.5 | 2.0 | 2.5 | 3.0 | 3.5 | 4.0 | 5.0 | 6.0 | 8.0 | 12 | 24-28 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Procedure** | | | | | | | | | | | | | | | | | |
| Phys Exam | X | | | | | | | | | | | | | | | | X |
| Vital Signs | X | | | | | | | | | | | | | | | | X |
| ECG | | | X | | | | | | | | | | | | | | |
| Inpatient Observ. | | | X | X | X | X | X | X | X | X | X | | | | | | |
| Syx Diary | X | | | | | | | | | | | | | | X | | X |
| VAS: Pt | X | | | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Symptom Score: Pt | X | | | | | X | | | | X | | X | X | X | X | X | |
| Patient Global Impression | X | | | | | | | | | X | | | X | | | | |
| Symptom Score: Inv. | X | | | | | X | | | | X | | | | | X | | X |
| Inv. Global Assessment | X | | | | | X | | | | X | | | X | | X | | X |
| Inv. Global Impression | X | | | | | | | | | X | | | X | | | | |
| Study Drug | | X | | | | | | | | | | | | | | | |
| Local Tolerability | | | X | | | | | | | X | | | | | X | X | |
| Symptom Relief: Pt | | X | X | X | X | X | X | X | X | X | X | X | X | X | | | |
| Symptom Relief: Inv | | X | X | X | X | X | X | X | X | X | X | X | X | X | | | |
| Final attack assessment | | | | | | | | | | | | | | | | | X |
| Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concom. Meds | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Anti-drug antibodies | X | | | | | | | | | | | | | | | | X |
| Labs: heme & chem | X | | | | | | | | | | | | | | | | X |
| Urine preg. | X | | | | | | | | | | | | | | | | X |
| U/A | X | | | | | | | | | | | | | | | | X |

*Tx = treatment, Phys = physical, Observ = observation, Syx = symptom, Pt = patient, Inv = investigator, Concom = concomitant, heme = hematology, chem = chemistry, preg = pregnancy, U/A = urinalysis*
*Source: FAST-3 Clinical Study Report, Table 5-6*

**Safety Assessments:** The safety and tolerability of icatibant were assessed in FAST-3 in the same manner as for the other pivotal Phase 3 efficacy trials (FAST-1 and FAST-2), including AEs, injection site reactions, immunogenicity (anti-drug antibody formation post-dosing), clinical laboratory results (serum chemistry: glucose, AST, ALT, albumin, total bilirubin, creatinine, creatine kinase, C1-INH level and function, C4, C1q, uric acid, BUN; hematology: hemoglobin, hematocrit, MCH, MCHC, platelet count, RBC count, WBC count with differential, PT, aPTT; and urinalysis: appearance, pH, protein, glucose, bilirubin, nitrite, ketone, urobilinogen, blood, WBCs, pregnancy testing), physical examination and vital signs (heart rate, blood pressure, respiratory rate, and temperature), and 12-lead ECG. AEs were monitored continuously from the time of randomization through Day 14 ± 2 days after last dose of study drug or until resolution. AEs were classified as mild, moderate, or severe and not related, possibly related, probably related, and definitely related.

**Efficacy Assessments:** Despite recommendations by the Division that FAST-3 utilize the same primary efficacy endpoint as FAST-1 and FAST-2, this trial designated the primary efficacy endpoint as time from blinded treatment administration to the onset of symptom relief defined as a 50% reduction from pretreatment in the mean composite VAS score consisting of three symptom domains (abdominal pain, skin pain, skin swelling). Time to onset of primary symptom relief determined by edema location (the designated primary efficacy endpoint in FAST-1 and FAST-2), was designated the key secondary efficacy endpoint in FAST-3 and defined as in FAST-1 and FAST-2.

Other secondary efficacy endpoints based on either patient or investigator assessments included the following:

- Time from treatment to almost complete symptom relief, defined as all VAS symptom scores < 10 mm
- Time from treatment to subject-assessed initial symptom improvement
- Time from treatment to investigator-assessed initial symptom improvement
- Composite VAS-3 scores for non-laryngeal HAE attacks, change from pretreatment, and AUC at 2, 4, and 8 hours post-treatment
- Composite VAS-5 scores for laryngeal HAE attacks (abdominal pain, skin pain, skin swelling, difficulty swallowing, voice change), change from pretreatment, and AUC at 2, 4, and 8 hours post-treatment
- Individual VAS scores, change from pretreatment, and AUC at 2, 4, and 8 hours post-treatment

- Composite and individual subject-assessed symptom scores (abdominal pain, nausea, vomiting, diarrhea, skin pain, erythema, skin irritation, skin swelling, dysphagia, voice change), change from pretreatment, and AUC at 2, 4, and 8 hours posttreatment.

- Composite and individual investigator-assessed symptom scores (as above), change from pretreatment, and AUC at 2, 4, and 8 hours posttreatment.

- Investigator Global Assessment at 2, 4, and 8 hours posttreatment

- Investigator Clinical Global Impression/Improvement at 4 and 8 hours post-treatment.

- Time from treatment administration to any reduction in subject-assessed laryngeal symptom scores (difficulty swallowing and voice change) for laryngeal attacks

- Time from treatment administration to any reduction in investigator-assessed laryngeal symptom scores (difficulty swallowing, voice change, breathing difficulties, stridor, and asphyxia) for laryngeal attacks

- Time from treatment administration to onset of symptom relief for composite subject-assessed symptom score, where symptom relief is defined as a 50% reduction in composite subject-assessed symptom scores from pretreatment

- Time from treatment administration to onset of symptom relief for composite investigator-assessed symptom score, where symptom relief is defined as a 50% reduction in composite investigator-assessed symptom scores from pretreatment

- Time from treatment administration to onset of symptom relief for each VAS symptom, where symptom relief is defined as a 50% reduction from pretreatment in individual VAS scores

- Time from treatment administration to any reduction in laryngeal VAS symptoms (difficulty swallowing and voice change) for laryngeal attacks

- Occurrence of rescue medication use posttreatment

**Statistical Analysis Plan:** Statistical analyses were based primarily on data generated from the double-blind phase of randomized treatment for moderate to severe abdominal or cutaneous HAE attacks with a cut-off date of September 29, 2010, immediately following randomization of the 89$^{th}$ subject in the trial. The primary efficacy analysis population was the non-laryngeal intent-to-treat (ITT) population that received

randomized treatment for an initial qualifying abdominal or cutaneous HAE attack. Exploratory subgroup analyses were performed for this population only. A per-protocol (PP) non-laryngeal population was also analyzed as a sensitivity measure for the primary and key secondary endpoints. Total ITT and PP populations that also included subjects who received randomized treatment for their initial mild to moderate laryngeal HAE attacks were also analyzed, as well as a laryngeal population that included all subjects treated for an initial laryngeal attack with either randomized blinded treatment or open-label icatibant. For the safety analysis, all subjects who received study drug (either as randomized or open-label treatment) were analyzed collectively as the primary safety population. Data from the open-label extension phase were further collected for the first five icatibant-treated attacks of any type (including subjects originally randomized to receive placebo treatment for their initial HAE attack). Safety and efficacy analyses were performed on this total treated population to analyze the effects of repeated treatment with icatibant.

For demographic and safety outcome data, tabular summaries, descriptive statistics, and frequency distributions were presented by treatment group, without inferential statistics. In contrast, for the primary efficacy analysis, time to onset of symptom relief was summarized using the Kaplan-Meier method, characterizing median values and sign test-based 2-sided 95% confidence intervals, as well as the number of subjects censored and achieving symptom relief. A comparison of hazard rates for icatibant- versus placebo-recipients was analyzed using the Peto-Peto Wilcoxon test with a 2-sided significance level of 5% and a Cox proportional hazards model that included treatment and stratification factors as covariates (edema location and prior use of C1-INH replacement). Time to symptom relief was also similarly analyzed using 30%, 40%, 60%, and 70% reductions from pretreatment composite VAS score via the Kaplan-Meier method, sign test-based 2-sided 95% confidence intervals, and Peto-Peto Wilcoxon test. Time to symptom onset in subgroups was similarly analyzed in the non-laryngeal ITT population only.

Other time-based secondary efficacy endpoints were analyzed in similar fashion via the Kaplan-Meier method and comparative Peto-Peto Wilcoxon test. For the evaluation of individual and composite VAS scores and both patient- and investigator-assessed symptom scores, change from pretreatment and AUC from pretreatment to 2, 4, and 8 hours post-treatment were analyzed using a non-parametric Wilcoxon rank-sum test without covariate adjustment, as well as an ANCOVA model with type of attack and baseline score as covariates (if assumptions of homogeneity of variance and normality were satisfied). Investigator Global Assessment, individual symptom assessments, and the proportion of subjects receiving additional rescue medications were analyzed via Fisher's exact test for categorical data.

**Sample Size Calculation:** Assuming a 10% non-evaluable rate, a total of 88 subjects with moderate to severe abdominal or cutaneous HAE attacks were planned to be randomized to study treatment (with 40 completed subjects per treatment group) in

order to provide 80% power, assuming a 2-sided significance level of 0.05. Subjects were considered evaluable if they had a VAS score ≥ 30 mm at baseline and completed the 8-hour assessment post-dose or reached the predefined criterion for symptom relief (i.e., reduction by 50% from baseline in composite VAS-3 score). Subjects with mild to moderate laryngeal HAE attacks were considered evaluated if they completed the 8-hour assessment time point or achieved the primary endpoint, although there was no requirement for a pre-treatment VAS score ≥ 30 mm. In addition, subjects with laryngeal attacks were not considered to contribute to the planned sample size. Likewise, open-label treated subjects (i.e., with severe laryngeal HAE attacks) did not contribute to the planned sample size.

**Summary of Amendment Changes:** In consideration of discussions regarding a Special Protocol Assessment agreement for FAST-3 that was not reached between the Applicant and the Division, Amendment 1 (dated August 6, 2009) allowed for subjects experiencing an initial mild to moderate laryngeal HAE attack to be randomized to blinded treatment with either icatibant 30 mg SC versus placebo (severe laryngeal HAE attacks were still treated with open-label icatibant). In addition, this amendment updated secondary efficacy endpoints to include time to onset of symptom relief in all patients randomized to study treatment regardless of location of HAE attack. In addition, time to onset of primary symptom relief was designated as the key secondary efficacy endpoint (defined as in FAST-1 and FAST-2), in order to facilitate a comparison with the primary efficacy analyses of FAST-1 and FAST-2. Amendment 1 further clarified several secondary endpoints (adding additional secondary endpoints based on the 5-symptom composite VAS-5 score for laryngeal HAE attacks), inclusion and exclusion criteria (specifying HAE diagnostic requirements based on complement levels and clarifying the need for pregnancy prevention methods throughout the trial), statistical methods, and study procedures, including instructions for study drug abuse, misuse, overdose, and other medication errors. Amendment 2 (dated January 25, 2010) eliminated the exclusion criterion for patients receiving replacement therapy (FFP or C1-INH products) less than 5 days from the onset of the current HAE attack, in order to expand enrollment to patients who may have had breakthrough attacks on C1-INH prophylaxis or had new attacks despite recent treatment with C1-INH replacement therapy.

**Efficacy Results:** Individual efficacy data for FAST-3 are reviewed and discussed in Section 6 Review of Efficacy, within the context of the larger icatibant Phase 3 program, in comparison to the efficacy results of FAST-1 and FAST-2.

**Safety Results:** Safety data for FAST-3 pooled with the safety results for FAST-1 and FAST-2 and are discussed in Section 7 Review of Safety, whereas individual safety results for FAST-3 are reviewed and discussed here. The primary safety population described for FAST-3 consisted of 98 subjects, 46 of whom were randomized to icatibant and 46 to placebo treatment, with 6 additional subjects treated with open-label icatibant for laryngeal HAE attacks. The safety findings presented for this population

are limited to the initial treated on-study acute HAE attack. Additional analyses were conducted on the complete treated population, which included subjects treated with open-label icatibant for all subsequent HAE attacks, in order to characterize the safety of repeated intermittent icatibant treatment. Table 45 summarizes the characteristics of the initial HAE attack treated with blinded or open-label study treatment, which appear well-balanced between treatment groups.

**Table 45: Initial HAE attack and study drug exposure in FAST-3 by treatment group**

| Treatment Group | Blinded Icatibant (N = 46) | Blinded Placebo (N = 46) | Open-label Icatibant (N = 6) |
|---|---|---|---|
| **Type of HAE attack (n, %)** | | | |
| Cutaneous | 26 (56.5) | 26 (55.3) | 0 |
| Abdominal | 17 (37.0) | 19 (41.3) | 0 |
| Laryngeal | 3 (6.5) | 1 (2.2) | 6 (100.0) |
| **Time from onset of HAE attack to study treatment** median (range) in hours | 6.3 (2.2 – 12.4) | 5.5 (2.4 – 14.0) | 3.6 (1.0 – 14.0) |
| **Number of injections** | | | |
| One | 46 (100.0) | 46 (100.0) | 6 (100.0) |
| Two | 0 | 0 | 0 |

*Source: FAST-3 Clinical Study Report, Table 8-1*

During the open-label extension phase, only one subject received a total of two injections for a subsequent HAE attack. All other HAE attacks were treated with only a single injection of icatibant.

Deaths

No deaths occurred in the icatibant group, although one death was reported in a 44 year-old man randomized to placebo, who died of a myocardial infarction 10 days after blinded treatment for his initial on-study acute HAE attack. The investigator considered this death unrelated to study drug, although this subject had no cardiac history, cardiac symptoms, clinically significant ECG findings, or abnormal laboratory results prior to his death.

Serious Adverse Events

No SAEs were noted in any icatibant-recipients during the blinded treatment phase of FAST-3, although three placebo-recipients experienced SAEs: one death due to myocardial infarction (described above), one severe laryngeal HAE attack, and one

episode of moderate, acute gastroenteritis. In addition, two other placebo-recipients experienced SAEs outside of the post-treatment observation window: an acute myocardial infarction 27 days after placebo treatment and a case of severe diverticulitis 23 days after placebo treatment.

During the open-label extension phase, one subject developed cholecystitis and pneumonia (recorded as separate SAEs) 4 days and 8 days, respectively, after the third HAE attack treated with icatibant, while one subject developed pulmonary embolism 10 days after the fourth HAE attack treated with icatibant. Severe laryngeal edema classified as SAEs that occurred outside the post-treatment observation window were also noted in two subjects, which developed at 61 days and 49 days, respectively, after open-label icatibant treatment for their second acute HAE attack.

No pregnancies were reported for any subject in FAST-3.

Common Adverse Events

Summary AE data were presented for all AEs recorded within 16 days of study drug treatment. All HAE symptoms that worsened or recurred following study drug treatment were reported as AEs, whereas symptoms recurring more than 48 hours after onset of the initial attack were considered a new HAE attack, which could be treated with open-label icatibant treatment. Overall, 46 icatibant-recipients (41.3%) and 24 placebo-recipients (52.2%) experienced one or more AE. Three subjects in the placebo group experienced at least one SAE, with one of these subjects dying due to an acute myocardial infarction. No deaths or SAEs were attributed to receipt of icatibant, however. Severe AEs were observed in 2 of 46 (4.3%) icatibant-recipients (single cases each of headache and dyspepsia, both of which were deemed to be drug-related by the investigator), compared to 10 of 46 (21.7%) placebo-recipients.

Table 46 summarizes all AEs observed at greater rates in icatibant-recipients versus placebo-recipients within 24 hours of randomized study treatment. Many of these preferred terms are also consistent with worsening HAE symptoms, which were classified as AEs. While these signs and symptoms would be expected in the placebo group, it is notable that none of the listed preferred term AEs occurred in more than 2 icatibant-recipients. Thus, these safety data do not reflect a clear pattern of drug-related AEs.

**Table 46: Acute adverse events (within 24 hours post-dose) occurring at greater rates in icatibant versus control recipients in FAST-3 (reported as number of subjects)**

| System Organ Class<br>Preferred Term (n, %) | Icatibant 30 mg<br>N = 46 | Placebo<br>N = 46 |
|---|---|---|
| **Gastrointestinal disorders** | 6 (13.0) | 2 (4.3) |
| Abdominal distension | 2 (4.3) | 0 |
| Abdominal pain | 2 (4.3) | 0 |
| Diarrhea | 2 (4.3) | 0 |
| Nausea | 2 (4.3) | 0 |
| Dyspepsia | 1 (2.2) | 0 |
| Vomiting | 1 (2.2) | 0 |
| **General disorders and administration site conditions** | 4 (8.7) | 1 (2.2) |
| Pyrexia | 2 (4.3) | 0 |
| Chills | 1 (2.2) | 0 |
| Injection site erythema | 1 (2.2) | 0 |
| Edema | 1 (2.2) | 0 |
| **Infections and infestations** | 6 (13.0) | 5 (10.7) |
| Sinusitis | 2 (4.3) | 1 (2.2) |
| Urinary tract infection | 2 (4.3) | 1 (2.2) |
| Nasopharyngitis | 2 (4.3) | 0 |
| **Investigations** | 1 (2.2) | 2 (4.3) |
| Alanine aminotransferase increased | 1 (2.2) | 0 |
| **Nervous system disorders** | 3 (6.5) | 4 (8.7) |
| Dizziness | 1 (2.2) | 0 |
| **Renal and urinary disorders** | 1 (2.2) | 0 |
| Dysuria | 1 (2.2) | 0 |

*Source: FAST-3 Clinical Study Report, Table 8-4*

Treatment-emergent AEs related to clinical laboratory evaluations were reported in three subjects following blinded treatment for the initial HAE attack, only one of whom received icatibant:

- Elevated creatine phosphokinase to 314 U/L (NML: 38-190 U/L), decreased hemoglobin to 129 g/L (NML: 135-175 g/L), and decreased RBC count to 4.45 x $10^{12}$ cells/L (NML: 4.5-6.5 x $10^{12}$ cells/L) in a placebo-recipient

- Elevated serum calcium in a placebo-recipient

- Elevated ALT to 223 U/L (NML: 0-40 U/L) in an icatibant-recipient, which ultimately resolved without sequelae (Subject 427-002, discussed further in the Clinical Laboratory Results section below)

Adverse Events with Repeated Icatibant treatment

Treatment-emergent AEs reported with recurrent icatibant dosing during the open-label extension phase of FAST-3 were similar to those observed during the blinded treatment phase. When AE data for all subjects were summarized according to the first five icatibant-treated HAE attacks (regardless of original blinded or open-label treatment assignment), AE rates were generally similar for each attack, although sample sizes progressively decreased, as expected: Attack 1 = 30 of 75 subjects (40.0%); Attack 2 = 18 of 48 subjects (37.5%); Attack 3 = 11 of 27 subjects (40.7%); Attack 4 = 5 of 17 subjects (29.4%); Attack 5 = 2 of 11 subjects (18.2%). Severe AEs were experienced in a limited number of these patients following icatibant treatment: Attack 1 = 4 subjects (5.3%); Attack 2 = 1 subject (2.1%); Attack 3 = 4 subjects (14.8%); Attack 4 = none; Attack 5 = 1 subject (9.1%).

As seen in the blinded treatment phase, the most common AE across sequential HAE attacks was worsening or recurrent HAE manifestations, as defined per protocol: Attack 1 = 6 of 75 subjects (8.0%); Attack 2 = 2 of 48 subjects (4.2%); Attack 3 = 3 of 27 subjects (11.1%). Other common AEs in the recurrent treatment phase included abdominal pain (Attack 1 = 4 of 75 subjects [5.3%]; Attack 2 = 1 of 48 subjects [2.1%]), headache (Attack 1 = 5 of 75 subjects [6.7%]; Attack 2 = 2 of 48 subjects [4.2%]; Attack 3 = 2 of 27 subjects [7.4%]), and nasopharyngitis (Attack 1 = 2 of 75 subjects [2.7%]; Attack 2 = 3 of 48 subjects [6.3%]). In contrast, laboratory abnormalities were rarely reported as AEs during the recurrent treatment phase:

- Elevated ALT to 291 U/L (NML: 0-40 U/L) and AST to 126 U/L (NML: 0-40 U/L), and decreased RBC count to 4.45 x 1012 cells/L (NML: 4.5-6.5 x 1012 cells/L) in one subject (Subject 356-003) prior to treatment of a second HAE attack, which resolved by Day 14 post-dosing without intervention

- Elevated creatine phosphokinase to 287 U/L (NML: 15-195 U/L) two weeks after treatment for a third HAE attack (Subject 411-004), which resolved without intervention by the time of the subject's next subsequent HAE attack

- Elevated WBC count to 18.5 x $10^9$ cells/L (NML: 4-11 x $10^9$ cells/L) in an icatibant-recipient (Subject 411-003) following open-label treatment for an initial HAE attack, which resolved without intervention by the time of the subject's next subsequent HAE attack

Of note, the elevations noted in hepatic transaminases during both the blinded and open-label treatment phases were not accompanied by increases in bilirubin or other markers of impaired hepatic function. In addition, the temporal separation between all these laboratory abnormalities and last icatibant dosing makes a causal association with icatibant less clear.

Injection Site Reactions

Consistent with other Phase 3 trials of icatibant, all 46 icatibant-recipients in FAST-3 experienced one or more local injection site reactions, which were repeatedly assessed at 0.5 hrs, 1 hr, 2 hrs, 4 hrs, 8 hrs, 12 hrs, Day 3, Day 4, and Day 5 post-treatment: erythema in 45 subjects (97.8%); swelling in 42 subjects (91.3%); burning sensation in 20 subjects (43.5%); itching in 19 subjects (41.3); warm sensation in 24 subjects (52.2%); skin pain in 15 subjects (32.6%). In contrast, only 19 placebo-recipients (41.3%) developed such reactions, with individual rates lower for each type of localized reaction. Most injection site reactions were mild to moderate, although severe erythema developed in 6 (13.0%) icatibant-recipients but only 1 (2.2%) placebo-recipient, with severe local swelling noted in 3 (6.5%) icatibant-recipients but no placebo-recipients. No severe local injection site reactions were observed in icatibant-recipients by 4 hours post-doing, while most mild to moderate reactions had resolved by this time. These local reactions appear to be related to the irritant nature of icatibant, as far lower rates were observed with SC injection of the identical placebo formulation that differed only in drug content. However, in comparison with the potentially severe manifestations of HAE, these local reactions appear far more tolerable and would not preclude the use of an effective agent to treat acute HAE attacks.

Clinical Laboratory Results

Serum chemistry, hematology, and urinalysis parameters were assessed during the blinded treatment phase at Day 2 and Day 14 post-dosing. As noted earlier, few laboratory abnormalities qualified as AEs. On average, only minor changes from baseline in these parameters were observed during the blinded treatment phase, as noted in Table 47, with similar findings in the open-label extension phase. Thus, no safety signals related to laboratory findings were noted.

## Table 47: Median baseline values and end-of-observation period (Day 14) changes in clinical laboratory parameters by treatment group in FAST-3

| Treatment Group | Icatibant 30 mg (N = 46) | | Placebo (N = 46) | |
|---|---|---|---|---|
| **Laboratory Parameter** | **Baseline** | **Day 14** | **Baseline** | **Day 14** |
| Hgb | 143.0 | -3.0 | 148.4 | -8.7 |

| | | | | |
|---|---|---|---|---|
| (g/L) | | | | |
| Hct (%) | 40.6 | -0.010 | 42.5 | -0.031 |
| MCH (pg) | 30.4 | 0.1 | 29.8 | 0 |
| MCHC (g/L) | 347.0 | 0.8 | 346.5 | 1.2 |
| RBC ($10^{12}$/L) | 4.6 | -0.2 | 4.9 | -0.4 |
| WBC ($10^{9}$/L) | 7.2 | -1.1 | 7.9 | -2.0 |
| Platelets ($10^{9}$/L) | 282.7 | -3.0 | 259.8 | -4.3 |
| Neutrophils ($10^{6}$/L) | 4415.4 | -411.8 | 4919.2 | -760.3 |
| Lymphocytes ($10^{6}$/L) | 1896.0 | 25.7 | 1993.8 | 43.4 |
| Monocytes ($10^{6}$/L) | 369.9 | 0 | 378.2 | -12.5 |
| Eosinophils ($10^{6}$/L) | 103.2 | 10.9 | 88.6 | 5.0 |
| Basophils ($10^{6}$/L) | 20.0 | 0 | 19.6 | 0 |
| PT (sec) | 10.4 | -0.2 | 10.2 | -0.1 |
| aPTT (sec) | 24.7 | 0 | 23.7 | 0 |
| BUN (mmol/L) | 3.5 | 0.3 | 3.4 | -0.5 |
| Creatinine (mg/dL) | 81.0 | 0 | 83.3 | -1.8 |
| Glucose (mmol/L) | 5.4 | 0.3 | 5.6 | -0.5 |
| AST (U/L) | 17.8 | 1.8 | 21.0 | -1.8 |
| ALT (U/L) | 15.8 | 0 | 11.4 | -0.6 |
| Total Bili (mcmol/L) | 7.5 | -1.4 | 6.9 | 0 |
| Albumin (g/L) | 48.2 | 0 | 50.6 | 0 |
| Creatine Kinase (U/L) | 78.3 | 1.3 | 72.4 | -1.5 |

| | | | | |
|---|---|---|---|---|
| Uric Acid (mcmol/L) | 313.2 | -5.3 | 311.0 | -13.5 |

*Source: FAST-3 Clinical Study Report, Table 10.3.9.1, Table 10.3.12.1*

Median changes in post-dosing laboratory values during the blinded treatment phase did not reveal any potential safety signals. Thus, laboratory safety data were also examined for potentially significant outliers. Of note, only one subject (Subject 427-002) in the icatibant group had evidence of elevated hepatic transaminases following blinded icatibant-treatment, with an ALT value of 223 U/L (NML: 0-40 U/L) detected prior to open-label icatibant treatment for this subject's next subsequent HAE attack. This result was not deemed clinically significant by the investigator and was reported as a mild AE. By Day 14 post-dosing, ALT had decreased to 67 U/L. In addition, this subject also had an elevated ALT level prior to icatibant treatment for the initial HAE attack (ALT = 72 U/L). Thus, this result does not appear to reflect a significant safety risk attributable to icatibant.

Several elevations in creatine kinase were also noted during the blinded treatment phase at Day 2 post-dosing, but in equal numbers in icatibant and placebo-recipients (4 of 46 subjects = 8.7% in each group). These results were not considered clinically relevant by the investigator, except for one placebo-recipient (Subject 409-002), who had a persistently elevated creatine kinase level at Day 14, as well. Of note, one icatibant-recipient (Subject 310-001) had an elevated creatine kinase level of 362 U/L (NML: 20-200 U/L) at Day 2, but this value was actually a decrease from an elevated pretreatment level of 697 U/L and ultimately resolved by Day 14. Only one icatibant-recipient (Subject 348-001) had an elevated creatine kinase level at Day 14 of 325 U/L (NML: 25-190 U/L) without a pretreatment elevation, which was considered clinically significant by the Applicant (follow-up creatine kinase data are not provided for this patient in the subject line listings). Overall, however, given the nonspecific nature of creatine kinase elevations, the rarity of these findings, and their equal distribution among icatibant-recipients and control subjects, these results do not appear to reflect a significant risk attributable to icatibant.

During the FAST-3 extension phase, one subject was noted to have elevated values of ALT (291 U/L) and AST (126 U/L) prior to open-label icatibant treatment for a second HAE attack, although these increases resolved by the next visit. Another two subjects had clinically significant elevations in creatine kinase: 1) 287 U/L at Day 14 following open-label icatibant treatment for a third HAE attack, and 2) persistent elevation from 246 U/L prior to open-label icatibant treatment for a second HAE attack to 431 U/L at Day 2 and 302 U/L at Day 14, which normalized prior to treatment for the next subsequent HAE attack.

Summary urinalysis results are presented in Table 48, which shows the proportion of subjects with abnormal urine tests at baseline and at Day 14 follow-up. All abnormal findings were similar or reduced in rate in icatibant versus placebo-recipients. In

particular, the relatively high rates of abnormal protein, blood, and leukocytes noted at Day 14 post-icatibant treatment were preceded by even higher rates at baseline, as well as higher or similar rates in placebo-recipients.

**Table 48: Baseline and end-of-observation (Day 14) abnormal urinalysis laboratory parameters by treatment group in FAST-3 (n, %)**

| Treatment Group | Icatibant 30 mg N = 46 | | Placebo N = 46 | |
|---|---|---|---|---|
| **Laboratory Parameter** | **Baseline** | **Day 14** | **Baseline** | **Day 14** |
| pH* (hydronium units) | 6.0 | 6.0 | 6.0 | 6.0 |
| Protein (% present) | 6 (13.0) | 5 (10.9) | 5 (10.9) | 4 (8.7) |
| Glucose (% present) | 2 (4.3) | 0 | 0 | 0 |
| Ketones (% present) | 2 (4.3) | 0 | 5 (10.9) | 5 (10.9) |
| Bilirubin (% present) | 2 (4.3) | 1 (2.2) | 2 (4.3) | 1 (2.2) |
| Blood (% present) | 10 (21.7) | 4 (8.7) | 8 (17.4) | 5 (10.9) |
| Urobilinogen (% present) | 3 (6.5) | 2 (4.3) | 1 (2.2) | 1 (2.2) |
| Leukocytes (% present) | 17 (37.0) | 14 (30.4) | 12 (26.1) | 14 (30.4) |
| Nitrites (% present) | 2 (4.3) | 0 | 0 | 0 |

**Data presented in median pH units; all other results presented as number and percent of subjects with abnormal (positive) results*
*Source: FAST-3 Clinical Study Report, Table 8-15*

Immunogenicity

Immunogenicity samples were uniformly negative for all subjects tested in FAST-3, regardless of randomized or open-label treatment assignment during both the blinded treatment phase and open-label extension phase.

Physical Examination, Vital Sign, and 12-lead ECG Assessments

A review of physical examination findings by treatment group at baseline, Day 2, and Day 14 post-treatment, which were categorized by the Applicant as either abnormal or normal, revealed no concerning differences between groups, although 4 (8.7%) icatibant-recipients were noted to have abnormal findings in the Spine and Extremities versus only 1 (2.2%) placebo-recipient at Day 14. Similarly, no consistent patterns were noted in ECG findings between the icatibant and placebo groups during the blinded treatment phase, with abnormalities noted in 11 (23.9%) icatibant-recipients and 12 (26.1%) placebo-recipients, although none of these findings were considered AEs. Moreover, no ECG abnormalities were noted in any of the five subjects who received open-label icatibant treatment.

Table 49 summarizes the vital sign data for the blinded treatment phase of FAST-3, showing mean baseline and change from baseline values for the Day 2 and Day 14 follow-up time points. No clinically relevant changes were noted that were specific to icatibant treatment.

**Table 49: Mean baseline and follow-up (Day 2, Day 14) values for vital sign assessments by treatment group in FAST-3**

| Treatment Group | Icatibant 30 mg N = 46 | | | Placebo N = 46 | | |
|---|---|---|---|---|---|---|
| **Laboratory Parameter** | **Baseline** | **Day 2** | **Day 14** | **Baseline** | **Day 2** | **Day 14** |
| **Temperature** ($^{o}$C) | 36.6 | 0.1 | 0 | 36.7 | -0.1 | -0.1 |
| **Heart Rate** (beats/min) | 79.5 | -4.3 | -5.4 | 79.7 | -2.9 | -5.0 |
| **Systolic BP** (mmHg) | 122.1 | -0.2 | -0.1 | 122.3 | -1.0 | 0.6 |
| **Diastolic BP** (mmHg) | 77.9 | -0.4 | -0.5 | 76.3 | -3.8 | 0.1 |
| **Respiratory Rate** (breaths/min) | 17.8 | -0.3 | -0.6 | 17.2 | -0.6 | -0.7 |

*BP = blood pressure*
*Source: FAST-3 Clinical Study Report, Table 8-20, Table 8-21, Table 8-22, Table 10.3.19.1*

# III. Statistical Briefing Document

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

| | |
|---|---|
| **NDA/BLA Serial Number:** | NDA 22150 |
| **Drug Name:** | Firazyr (Icatibant) |
| **Indication(s):** | Hereditary angioedema |
| **Applicant:** | Shire Human Genetic Therapies, Inc. |
| **Date(s):** | Received: 02-25-2011; AC: 06-23-2011; PDUFA: 08-25-2011 |
| **Review Priority:** | P |
| **Documents Reviewed:** | primary reviews by Qian Li, PhD and David Hoberman, PhD |
| **Biometrics Division:** | Division of Biometrics 2 |
| **Statistical Reviewer:** | Joan Buenconsejo, PhD |
| **Concurring Reviewers:** | Thomas Permutt, PhD |
| **Medical Division:** | Division of Pulmonary, Allergy and Rheumatology Products |
| **Clinical Team:** | Brian Porter, MD<br>Susan Limb, MD |
| **Project Manager:** | Eunice Chung-Davis |

**Keywords:**

NDA review, clinical studies

# 1. CONCLUSIONS

Statistically significant treatment effects were observed in one active-controlled trial (FAST-2) and one placebo-controlled trial (FAST-3) for icatibant in the treatment of acute HAE attacks. However, based on the pre-specified primary endpoint in FAST-1, the treatment difference between icatibant and placebo did not reach statistical significance. There is a sharp contrast in placebo response between FAST-1 and FAST-3. Nonetheless, there is consistent evidence that median time to onset of symptom relief is about 2 hours when treated with icatibant regardless of how the primary endpoint is defined. All trends were in favor of the icatibant group for each of the three primary symptoms: abdominal pain, skin pain, and skin swelling; but at the end of the second day, median abdominal pain and skin pain scores were similar in both treatment groups.

Except for the concern about blinding, there are no other statistical issues identified that may impact the overall conclusions. The issue of blinding (i.e. injection site reaction caused by icatibant) and how it affects patient's assessment of a patient reported outcome, i.e. VAS score, is unclear and will remain unresolved given the lack of information or data to assess its impact. Almost all patients treated with icatibant experienced injection site reactions compared to less than 40% of placebo patients.

# 2. INTRODUCTION

This is a secondary statistical review considering and integrating the findings of the primary statistical reviewers, Dr. Qian Li and Dr. David Hoberman. Dr. Qian Li was the primary statistical reviewer in the original submission and Dr. Hoberman reviewed the complete response. I concur with their principal conclusions. Their conclusions are summarized in Sections 3.1 and 3.2.

The original NDA was submitted in October of 2007 by Jerini AG. In the original submission, the efficacy evaluation of icatibant 30 mg was based on two randomized, double-blind, and multicenter phase 3 studies; Study 2102 with an active-control (FAST-2) and Study 2103 (FAST-1) with a placebo-control.

A few deficiencies were identified in the first review cycle and a Not Approvable action letter was issued on April 28, 2008 due to lack of replicate evidence of efficacy.

The purpose of this current submission is to provide a Complete Response to the deficiencies outlined in the Not Approvable action letter. In response to the Division's comment that data from the clinical program did not provide substantial evidence that icatibant is sufficiently safe and effective for the proposed indication of the treatment of acute attacks of hereditary angioedema (HAE), Jerini US, Inc conducted a third Phase 3 clinical trial, HGT-FIR-054 (FAST-3). This study is a randomized, double-blind, placebo-controlled study and is similar to FAST-1. Unlike the previous Phase 3 studies (FAST-1 and FAST-2) which were based on one primary symptom, the primary efficacy endpoint for this study is the time from treatment

administration to the onset of symptom relief using the composite measure VAS-3 (mean of skin swelling, skin pain, and abdominal pain).

# 3. STATISTICAL EVALUATION

## 3.1 Review of the Statistical Issues and Conclusion in the Original Application

In the original application, two statistical issues were identified by Dr. Li. One issue is the concern of unblinding due to irritating reactions in the injection sites in the icatibant treatment group and the other issue is the definition of the primary endpoint.

Based on her analyses, compared to less than 10% in the control arm, close to 90% of the patients in the icatibant treatment group in both studies (FAST-1 and FAST-2) showed at least two reaction symptoms out of six symptoms assessed. These symptoms included erythema, irritation, pain pruritus, swelling and warmth. As stated in her review,

> As the efficacy assessment was based on the patient measurements using VAS, it was possible that bias was introduced in the assessment when the treatments could be unblinded easily. If the reaction at the injection site is unavoidable, covering the injection site during the period of symptom assessments might help to reduce the potential bias.

In the FAST-3 study, investigators were asked explicitly to report information concerning injection site reactions. According to the applicant, all patients (46 of 46 patients) randomized to icatibant experienced some form of injection site reaction, whereas injection site reactions were present in 41% (19 of 46 patients) placebo patients. The most common form of injection site reaction in patients treated with icatibant was erythema. Only one patient in the safety population who received blinded treatment with icatibant experienced an injection site reaction (injection site erythema) that was reported as a mild, definitely related adverse event. In addition, one patient treated with open-label icatibant for a fourth attack experienced an injection site reaction that was reported as a mild, possibly-related adverse event. Like in the original application, the applicant discussed this concern but was unable to find a solution to the problem.

The second issue that was raised by Dr. Li is on the definition of the primary endpoint. In the original application, the primary endpoint was defined as the time from the treatment to the onset of symptom relief in one primary symptom. The symptom relief was defined as a minimum reduction of 14 percent of the baseline score plus a further reduction of 16 mm in the primary symptom which was at least 30 mm at baseline.

Dr. Li questioned the adequacy of the definition given that a patient who experienced a reduction from 100 mm to 70 mm in VAS is considered to achieve symptom relief, even though the patient is still suffering from severe symptom. She also pointed out that as an attack could manifest several symptoms including abdominal pain, skin swelling, skin pain, and nausea, the information was wasted if the primary endpoint only focused on one primary symptom.

In the FAST-3 study, the applicant modified their primary endpoint to a composite symptom VAS endpoint. The time to symptom relief was defined as the first documented time point when the patient experiences a 50% reduction in the 3-symptom composite VAS from the pretreatment composite score. For cutaneous and abdominal attacks, the 3 components of the composite VAS (VAS-3) were abdominal pain, skin pain, and skin swelling. (For laryngeal attacks, the composite VAS (VAS-5) included these three symptom components plus the symptoms of difficulty swallowing and voice change. Laryngeal attack VAS scores were collected but were not included in the calculation of the primary efficacy endpoint.) While this new endpoint addresses Dr. Li's concerns, as stated in Dr. Limb's memo, given the lack of regulatory experience with the proposed primary efficacy endpoint, assessment of a range of secondary endpoints is crucial in determining the efficacy of icatibant for the treatment of acute attacks of HAE.

Dr. Li summarized the results from the original application as follows:

> The icatibant showed statistically significantly faster relief of symptoms (using predefined primary endpoint) in comparison to tranexamic acid in FAST-2. However, the treatment difference between icatibant and placebo did not reach statistical significance in FAST-1. (Table 1)

Table 1: Median time to onset of symptom relief (hours) based on the primary single symptom VAS

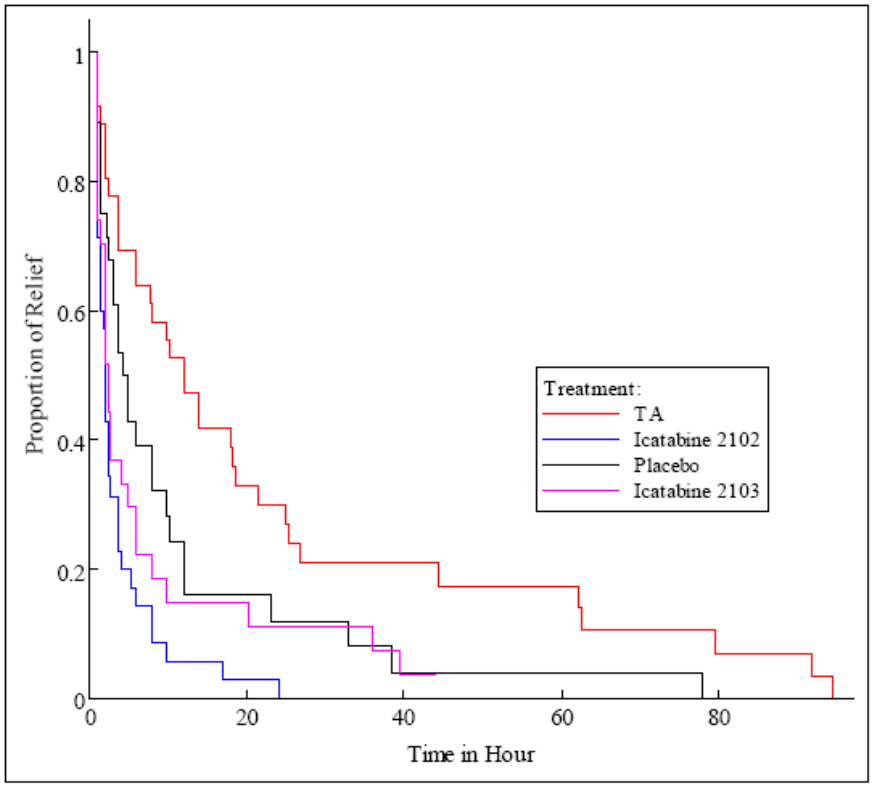
| | Icatibant 30mg SC | | Tranexamic acid | | Placebo | | P |
|---|---|---|---|---|---|---|---|
| | N† | Time (h) | N† | Time (h) | N† | Time (h) | value§ |
| **Study 2102 (FAST-2)** | | | | | | | |
| All attacks | 36 | 2.0 | 38 | 12.0 | | | <0.001 |
| *Cutaneous* | 24 | 2.5 | 23 | 18.2 | | | <0.001 |
| *Abdominal* | 12 | 1.6 | 15 | 3.5 | | | 0.026 |
| **Study 2103 (FAST-1)** | | | | | | | |
| All attacks | 27 | 2.5 | | | 29 | 4.6 | 0.142 |
| *Cutaneous* | 14 | 3.4 | | | 13 | 10.0 | 0.221 |
| *Abdominal* | 13 | 2.0 | | | 16 | 6.0 | 0.159 |

† Patients who did not achieve symptom relief within the observation period were censored at the last observation time. Also, patients who did not have baseline VAS ≥ 30 mm were removed from the analysis.

§ p-value was calculated based on Wilcoxon test.

She noted a difference in response time in symptom relief between tranexamic acid and placebo when she conducted cross-study comparison. The response of the symptom relief over time for the four treatments from the two studies is presented in Figure 1. To interpret this figure, at time 0 hour, all patients have no symptom relief. At time 4 hours, about 67% (FAST-1) and 80% (FAST-2) patients in the icatibant group have symptom relief, while only 46% in the placebo group and 31% in the transexamic acid group have symptom relief. At time 20 hours, greater than 90% of patients in the icatibant group (FAST-1 and FAST-2) and about 85% of patients in the placebo group have symptom relief, while only about 65% of patients in the transexamic acid group have symptom relief. This suggests that more time is needed to achieve the defined symptom relief in the tranexamic acid group compared to the placebo group. Slightly more time in the placebo group is needed to achieve the symptom relief compared to the two icatibant groups. The treatment difference between tranexamic acid and placebo was greater than the differences between placebo and either of the two icatibant treatment groups.

Figure 1 Response time of Symptom Relief (using pre-defined primary endpoint)




Source: Dr. Qian Li's statistical review

Dr. Li reached the following conclusions in her review of the original application:

- If it was a valid statement that tranexamic acid was no worse than placebo, given the observations that the difference between tranexamic acid and placebo was greater than the difference between placebo and icatibant, it was fair to conclude that placebo was no worse than icatibant. Therefore, icatibant was no better than placebo.
- If tranexamic acid was in fact worse than placebo, Study 2102 would no longer be a valid study to support the efficacy evaluation of icatibant. With only one placebo-controlled study which did not show significant treatment difference at the level of 0.05 for the two-sided p-value, there was no convincing evidence to support that icatibant was efficacious in treating patients with HAE attacks.

Her conclusions were consistent with the clinical review team.

### 3.2 Review of the Findings in the Complete Response

The general trial design for FAST-1, FAST-2, and FAST-3 is described in Dr. Susan Limb and Dr. Brian Porter's review. The statistical analysis plan for FAST-3 is briefly summarized in Dr. Hoberman's review.

As noted, the applicant modified their primary endpoint to a composite symptom VAS endpoint. The time to symptom relief was defined as the first documented time point when the patient

experiences a 50% reduction in the 3-symptom composite VAS from the pretreatment composite score. For cutaneous and abdominal attacks, the 3 components of the composite VAS (VAS-3) were abdominal pain, skin pain, and skin swelling. The result for FAST-3 is presented in Table 2. Of note, post-hoc analyses applying this modified definition were conducted on FAST-1 and FAST-2, and the results are also presented for comparison. FAST-3 demonstrated statistically significant treatment difference in time to onset of symptom relief based on 3-symptom composite VAS. Dr. Hoberman noted that despite the very low p-value generated by comparing the two groups in FAST-3, the placebo and the icatibant responses are noteworthy. Compared to FAST-1, the median time to onset of symptom relief for the placebo group is longer in FAST-3, while the median time to onset of symptom relief is essentially the same for the icatibant group (about 2 hours).

Table 2 Median time to onset of symptom relief (hours) based on 3-symptom composite VAS (VAS-3)

| | Icatibant 30mg SC | | Tranexamic acid | | Placebo | | P value § |
|---|---|---|---|---|---|---|---|
| | N† | Time (h) | N† | Time (h) | N† | Time (h) | |
| **FAST-3** | | | | | | | |
| All attacks | 43 | 2.0 | | | 45 | 19.8 | <0.001 |
| *Cutaneous* | 26 | 2.0 | | | 26 | 23.9 | <0.001 |
| *Abdominal* | 17 | 1.5 | | | 19 | 4.0 | 0.003 |
| **Study 2103 (FAST-1)*** | | | | | | | |
| All attacks | 26 | 2.3 | | | 27 | 7.9 | 0.014 |
| *Cutaneous* | 13 | 5.1 | | | 12 | 23.0 | 0.047 |
| *Abdominal* | 13 | 2.0 | | | 15 | 6.0 | 0.103 |
| **Study 2102 (FAST-2)*** | | | | | | | |
| All attacks | 35 | 2.0 | 38 | 12.0 | | | <0.001 |
| *Cutaneous* | 22 | 3.5 | 20 | 22.3 | | | <0.001 |
| *Abdominal* | 11 | 1.6 | 14 | 2.3 | | | 0.216 |

† Patients who did not achieve symptom relief within the observation period were censored at the last observation time. Also, patients who did not have baseline VAS ≥ 30 mm were removed from the analysis.

* Post-hoc analyses shown for comparison. The FAST-1 and FAST-2 primary endpoint was the median time to onset of symptom relief based on the single symptom VAS as shown in Table 2. Patient numbers vary slightly from the original pre-specified primary endpoint results shown in Table 3 due to reassignment of a patient from each trial as a laryngeal attack patient.

§ p-value was calculated based on Wilcoxon test for FAST-1 and FAST-2, and based on Peto-Peto Wilcoxon test for FAST-3.

The applicant also evaluated FAST-3 by applying the pre-specified definition of the primary endpoint from FAST-1 and FAST-2, and the results are presented in Table 3. Dr. Hoberman noted the following:

> In FAST-3, approximately 40% of the placebo patients achieved at least 50% relief in the first 8 hours, especially those with abdominal pain or skin pain. In contrast, the major reason that the FAST-1 (see table below) trial did not achieve statistical significance (although using the primary symptom score instead of an average and a different cutoff than FAST-3's for patient "symptom relief") was the almost 70% of placebo patients who achieved at least 50% relief in the first 8 hours, leading to a median time to relief of 4.6 hours while the median time to relief for icatibant was essentially the same as that in FAST-3.

Table 3 Median time to onset of symptom relief (hours) based on the primary single symptom VAS

| | Icatibant 30mg SC | | Tranexamic acid | | Placebo | | P value |
|---|---|---|---|---|---|---|---|
| | N† | Time (h) | N† | Time (h) | N† | Time (h) | |
| **FAST-3*** | | | | | | | |
| All attacks | 43 | 1.5 | | | 45 | 18.5 | <0.001 |
| *Cutaneous* | 26 | 2.0 | | | 26 | 22.5 | <0.001 |
| *Abdominal* | 17 | 1.0 | | | 19 | 3.6 | 0.002 |
| **Study 2103 (FAST-1)** | | | | | | | |
| All attacks | 27 | 2.5 | | | 29 | 4.6 | 0.142 |
| *Cutaneous* | 14 | 3.4 | | | 13 | 10.0 | 0.221 |
| *Abdominal* | 13 | 2.0 | | | 16 | 6.0 | 0.159 |
| **Study 2102 (FAST-2)** | | | | | | | |
| All attacks | 36 | 2.0 | 38 | 12.0 | | | <0.001 |
| *Cutaneous* | 24 | 2.5 | 23 | 18.2 | | | <0.001 |
| *Abdominal* | 12 | 1.6 | 15 | 3.5 | | | 0.026 |

† Patients who did not achieve symptom relief within the observation period were censored at the last observation time. Also, patients who did not have baseline VAS ≥ 30 mm were removed from the analysis.

* Designated as key secondary endpoint in FAST-3 and shown for comparison. The FAST-3 primary endpoint was the median time to onset of symptom relief based on the 3-symptom VAS.

§ p-value was calculated based on Peto-Peto Wilcoxon test for FAST-3 and Wilcoxon test for FAST-1 and FAST-2.

By applying the modified definition of the primary endpoint, larger treatment differences were seen in all three studies compared to the original definition of symptom relief. The difference can be due to more stringent criteria in defining symptom relief (i.e. 50% reduction in the average of the three symptoms, compared to the original definition), Table 4. As noted by Dr. Li, if you have a baseline VAS score of 100 mm, you need to experience 70 mm in one primary symptom to be considered to have symptom relief. In contrast, for the modified definition, you need to experience an average of 50 mm to be considered to have symptom relief. Only when your baseline VAS score is low (on average less than 40 mm) will the original definition can be more stringent. Nonetheless, there is consistent evidence that median time to onset of symptom relief is about 2 hours when treated with icatibant regardless of how the primary endpoint is defined. There is disparity in the median time to onset of symptom relief in the control groups, but in general, there is evidence that it takes longer for placebo group to achieve symptom relief. Therefore, I concur with Dr. Hoberman's conclusion that there was no benefit to the sponsor's shifting from the primary endpoint use in FAST-1 and FAST-2 to the average score in FAST-3.

Table 4 Change from baseline in VAS score to achieve Symptom Relief

| | Change from baseline VAS score (in mm) | |
|---|---|---|
| Baseline VAS (in mm) | Original Reduction of 14% baseline + 16 mm for the primary symptom | Modified 50% reduction in the average of 3 symptoms |
| 100 | 30 | 50 |
| 90 | 29 | 45 |
| 80 | 27 | 40 |
| 70 | 26 | 35 |
| 60 | 25 | 30 |
| 50 | 23 | 25 |
| 40 | 22 | 20 |
| 30 | 20 | 15 |

Dr. Hoberman conducted additional analyses to evaluate each of the components of the composite VAS (i.e. abdominal pain, skin pain and skin swelling). He concluded that although there is a clear treatment difference over time for each of the components, evaluating the difference at the end of the second day suggests the medians of the Abdominal Pain scores (when 'Abdominal' was the primary symptom), as well as the Skin Pain scores, were essentially the same in both treatment groups. However, there was more variability of scores in the placebo group. This is likely due to the greater number of 'zero' scores in the icatibant group. Skin Swelling shows the greatest separation of the groups at the end of the second day.

Dr. Hoberman reached the following conclusion in his review of the complete response:

> FAST-3 demonstrated statistically significant treatment differences for primary and secondary endpoints. This result contrasts sharply from FAST-I whose placebo response was notably larger than in FAST-3. All trends were in favor of the icatibant group for each of the three primary symptoms: abdominal pain, skin pain, and skin swelling. At the end of the second day, abdominal pain scores were similar in both treatment groups. Lastly, there was no benefit to the sponsor's shifting from the primary endpoint use in FAST-1 and FAST-2 to the average score in FAST-3.

## 4. STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

Except for the concern on blinding, there are no other statistical issues identified that may impact the overall conclusions. The issue of blinding (i.e. injection site reaction caused by icatibant) and how it affects patient's assessment of a patient reported outcome is unclear and will remain unresolved given the lack of information or data to assess its impact. Almost all patients treated with icatibant experienced injection site reactions compared to less than 40% of placebo patients.

Although statistically significant treatment effects were observed in one active-controlled trial (FAST-2) and one placebo-controlled trial (FAST-3) for icatibant in the treatment of acute HAE attacks, the impact of blinding is unclear. In addition, as noted by Dr. Hoberman, there is a sharp contrast in placebo response between FAST-1 and FAST-3. Nonetheless, there is consistent evidence that median time to onset of symptom relief is about 2 hours when treated with icatibant regardless of how the primary endpoint is defined. All trends were in favor of the icatibant group for each of the three primary symptoms: abdominal pain, skin pain, and skin swelling; but at the end of the second day, median abdominal pain and skin pain scores were similar in both treatment groups.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

| | |
|---|---|
| **NDA/BLA Serial Number:** | NDA 22150 |
| **Drug Name:** | Firazyr (Icatibant) |
| **Indication(s):** | Hereditary angioedema |
| **Applicant:** | Shire Human Genetic Therapies, Inc. |
| **Date(s):** | Received: 02-25-2011; AC: 06-23-2011; PDUFA: 08-25-2011 |
| **Review Priority:** | P |
| **Biometrics Division:** | Division of Biometrics 2 |
| **Statistical Reviewer:** | David Hoberman, PhD |
| **Concurring Reviewers:** | Joan Buenconsejo, PhD |
| | Thomas Permutt, PhD |
| **Medical Division:** | Division of Pulmonary, Allergy and Rheumatology Products |
| **Clinical Team:** | Brian Porter, MD |
| | Susan Limb, MD |
| **Project Manager:** | Eunice Chung-Davis |

**Keywords:**

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# 1. EXECUTIVE SUMMARY

Trial HGT-FIR-054 (FAST-3) compared icatibant to placebo for the treatment of hereditary angioedema using time to 50% reduction in the average of three symptom scores as the primary endpoint (skin pain, skin swelling and abdominal pain). Statistically significant results were found overall and also accounting for rescue medication. Results were consistent for males and females and also for the USA and the rest of the world. The success of this trial, as opposed to the previous trial (Study 2103, FAST-1) is due largely to the weaker placebo response in this trial.

# 2. INTRODUCTION

## 2.1 Overview

Shire HGT submitted icatibant 30 mg solution for injection for the treatment of hereditary angioedema (HAE) attack. The treatment is a single-dose administrated subcutaneously (s.c.). The proposed trade name is Firazyr. HAE is a rare genetic disease characterized by intermittent attacks of swelling of extremities, face, trunk, abdominal viscera, and upper airway. The attacks can be serious and life threatening. Icatibant is not currently marketed for any indication in the US or other countries. The original NDA was submitted in October of 2007 by Jerini AG. In the original submission, the efficacy evaluation of icatibant 30 mg was based on two randomized, double-blind, and multicenter phase 3 studies; Study 2102 with an active-control (FAST-2) and Study 2103 (FAST-1) with a placebo-control. The statistical review for the original application was conducted by Dr. Qian Li and the clinical review was conducted by Dr. Susan Limb.

A few deficiencies were identified in the first review cycle and a Not Approvable action letter was issued on April 23, 2008. A couple of the deficiencies are quoted as follows:

1. The submitted data from your clinical program do not provide substantial evidence that icatibant is sufficiently safe and effective for the proposed indication of the treatment of acute attacks of hereditary angioedema (HAE). The uncertain efficacy of the comparator drug, tranexamic acid, in the treatment of acute attacks of HAE complicates interpretation of the results of Study JE049-2102. Study JE049-2103 failed to demonstrate a statistically significant treatment difference between placebo and icatibant. In addition, there are concerns regarding the validity of the primary endpoint used in both studies (time to onset of symptom relief using the Visual Analog Scale). Without substantial evidence of the efficacy of the proposed dose of icatibant, we cannot evaluate if there is appropriate safety. Before icatibant may be approved, you must submit sufficient evidence of the efficacy of icatibant for the treatment of patients with acute attacks of HAE. This evidence must be generated by using a reliable instrument to assess efficacy and an appropriate control arm. You will need to demonstrate appropriate safety for the dose shown to be efficacious.

2. Dose selection should be further defined in sufficient patients based on the clinical endpoint or other biomarkers that are validated to be related to the clinical endpoint.

The purpose of this current submission is to provide a Complete Response to the deficiencies outlined in the Not Approvable action letter. In response to the Division's comment that data from the clinical program did not provide substantial evidence that icatibant is sufficiently safe and effective for the proposed indication of the treatment of acute attacks of hereditary angioedema (HAE), Jerini US, Inc conducted a third Phase 3 clinical trial, HGT-FIR-054 (FAST-3). This study is a randomized, double-blind, placebo-controlled study. Unlike the previous Phase 3 studies (FAST-1 and FAST-2) which was based on one primary symptom, the primary efficacy endpoint for this study is the time from treatment administration to the onset of symptom relief using the composite measure VAS-3 (mean of skin swelling, skin pain, and abdominal pain).

An advisory committee meeting is scheduled on June 23, 2011 to discuss the approvability of this application.

### 2.2 Data Sources

Documents reviewed were accessed from the CDER document room at:

\ \CDSESUB1\EVSPROD\NDA022150\022535.ENX

# 3. STATISTICAL EVALUATION

### Study Design and Endpoints

Trial HGT-FIR-054 was designed to evaluate the effect of icatibant (30 mg) versus placebo for the treatment of hereditary angioedema. A total of 98 subjects (88 with non-laryngeal (NL) symptoms and 10 with laryngeal (L) symptoms were enrolled among eleven (11) countries.

| Country | Number of Screened Subjects | Number of Enrolled Subjects |
|---|---|---|
| Australia | 13 | 5 |
| Canada | 14 | 1 |
| Hungary | 19 | 4 |
| Israel | 27 | 10 |
| Mexico | 1 | 0 |
| Romania | 13 | 5 |
| Russia | 22 | 3 |
| S. Africa | 20 | 4 |
| Turkey | 12 | 0 |
| Ukraine | 9 | 1 |
| United States | 219 | 65 |
| Total | 369 | 98 |

As stated in the applicant's report,

> Patients with at least moderate cutaneous and/or abdominal symptoms and patients with mild to moderate laryngeal symptoms were randomized to treatment with icatibant or placebo, using a stochastic minimization technique. Patients who had severe laryngeal symptoms (whether in combination with cutaneous and/or abdominal symptoms or not) were not randomized, but received open-label icatibant. Prior to protocol amendment 1, patients with mild to moderate laryngeal symptoms also were not randomized and, instead, were assigned to open-label icatibant. Stratification factors used in the randomization were symptom type (cutaneous, abdominal, or mild/moderate laryngeal) and previous use of C1-INH (yes or no). Patients with both cutaneous and abdominal symptoms were allocated to the abdominal group if at least one abdominal symptom (abdominal pain, vomiting, diarrhea) was moderate to very severe irrespective of the severity of cutaneous symptoms. The patient was allocated to the cutaneous group if the abdominal symptom(s) was mild, and at least one cutaneous symptom was moderate to very severe. Patients with any laryngeal symptom were allocated to the laryngeal group. The minimization technique identified the treatment assignment that minimizes the extent of imbalance between the treatment groups based on these stratification variables. The patient is randomly allocated to that treatment arm with 80% probability or to the other arm with 20% probability. The randomization was performed using a validated centralized procedure (internet web-based) that automated the random assignment of treatment groups to randomization numbers.

For NL subjects, the **primary endpoint** is the time to 50% reduction in the average of three (3) visual analogue scale scores indicating abdominal pain, skin swelling and skin pain at three consecutive time points. The earliest time point was used at the "time to 50% pain relief." For L subjects, the average also included scores for difficulty swallowing and voice change. For the first day after the injection for the attack, measurements were made at pretreatment and at hours 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, and 8. For the next two days, measurements were taken 3 times/day and then once on the $4^{th}$ day.

The key secondary endpoint involved only the primary symptom. For subjects with cutaneous symptoms only, the primary symptom was based on skin swelling or skin pain, whichever was most severe. For subjects with abdominal symptoms (with or without cutaneous symptoms) the primary symptom was based on abdominal pain.

As for a determination of sample size, the applicant states:

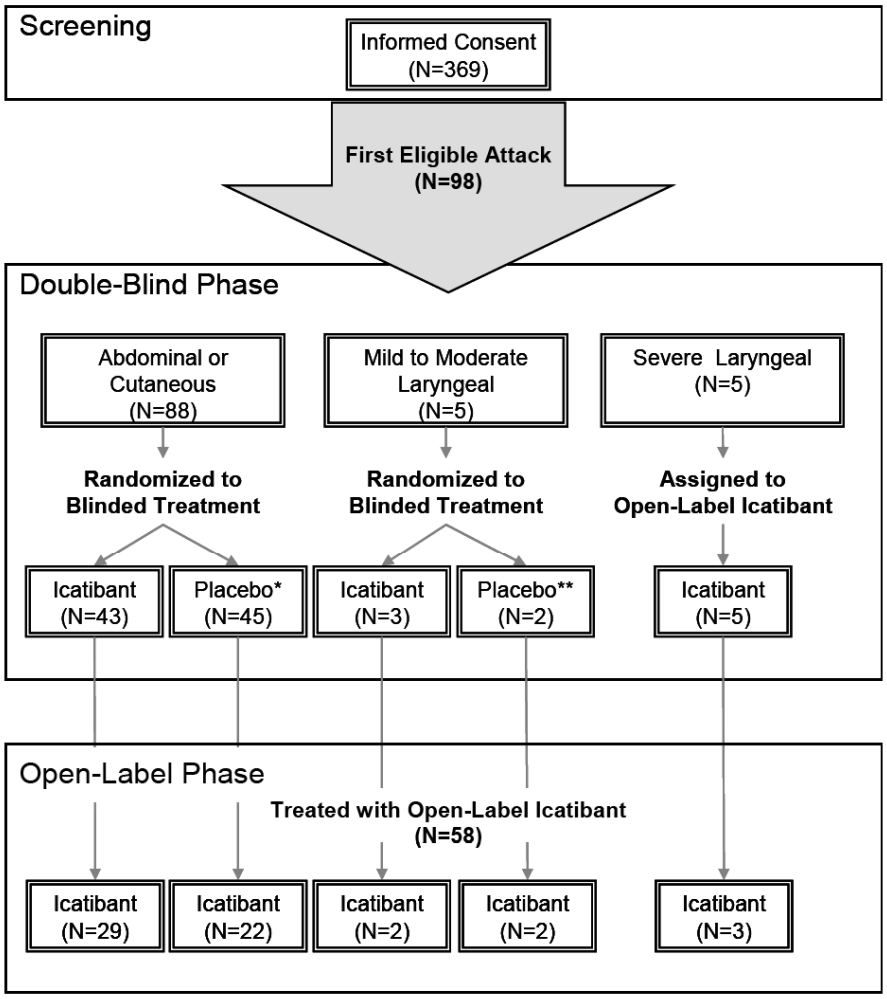
> Using the log-rank test for equality of survival curve and assuming a 0.05 2-sided significant level, a power of 80%, and 40 evaluable subjects per treatment, a total of 80 evaluable subjects would be required in the randomized controlled phase of the study.

However, there is no mention of a treatment effect which leads to the calculation of 80% power. Later, it sates that

> A sample size calculation was performed using Query Advisor software based on the percent of subjects who did not achieve symptom relief at 1, 2, 4, 6, 12, and 24 hours in Study JE049-2103. In this study, the median time to onset of symptom relief was 2.5 hours for icatibant and 4.6 hours for placebo.

**This review deals with only NL subjects because of the small sample of laryngeal subjects.**

Figure 1: Trial HGT-FIR-054 Design




* Subject 054-311-001 received treatment with placebo, but was treated with icatibant as a rescue medication due to increasing severity of symptoms.
** Subject 054-320-011 received treatment with placebo, but was treated with icatibant as a rescue medication due to increasing severity of symptoms. Subject 054-356-004 never received placebo, but was treated with open-label icatibant due to development of severe laryngeal symptoms.

## Statistical Methodologies

The following described the analytical approach used by the applicant:

A subject was considered evaluable if they had moderate to very severe cutaneous and/or abdominal angioedema (as judged by the investigator in the Global Assessment at pretreatment), VAS $\geq$ 30mm for any symptom pretreatment and completes the 8 hour assessment post dose or reaches the symptom relief as determine by 50% reduction in the composite VAS. A subject was also considered evaluable if they had mild to moderate laryngeal attacks (as judged by the investigator in the Global Assessment at pretreatment), and completed the 8 hour assessment post dose or reached the primary endpoint. Subjects with laryngeal symptoms were exempt from the requirement of at least 1 symptom that had a pretreatment VAS score of >30mm to be considered evaluable.

A Peto-Peto Wilcoxon test with a global 2-sided significance level of 5% was used to test the null hypothesis for the non-laryngeal ITT, non-laryngeal per-protocol, ITT, and laryngeal populations. The Peto-Peto Wilcoxon test was selected for this analysis as it gives more weight to earlier achievement of symptom relief. To control for study design factors, time to symptom relief was analyzed using a Cox proportional hazards model which included covariates for treatment and stratification factors, edema location and previous use of C1-INH. The hazard ratio (icatibant - control), corresponding 95% confidence interval, and p-value assessing differences among treatment groups were presented for the non-laryngeal ITT population. In addition, the p-value from the stratified Peto-Peto Wilcoxon test was presented as a parallel to primary analysis.

To evaluate the use of rescue medications, time to symptom relief was analyzed censoring subjects who took rescue medications before the onset of symptom relief. This analysis was conducted using the non-laryngeal ITT population. Subjects were censored at the time of administration of rescue medication, if symptom relief had not already occurred. Kaplan-Meier methods were used to estimate the median time to symptom relief and corresponding sign-test based 2-sided 95% confidence interval. The number (%) censored and achieving symptom relief was summarized. A Peto-Peto Wilcoxon test with a global 2-sided significance level of 5% was used to test for treatment differences.

**Results and Conclusions**

The following Kaplan-Meier plot and table illustrate the time to pain relief for the 50% decrease criterion using the compositve VAS score. There is significant difference in the time from treatment administration to the onset of symptom relief using the composite VAS score measure. The median time to pain relief for the icatibant group is about 2 hours (95%CI: 1.5 to 3 hours) compared to about 20 hours in the placebo group (95% CI: 6 to 26 hours).

Figure 2: Time to 50% Reduction in VAS (Composite Symptom Score: all subjects) - Primary Endpoint

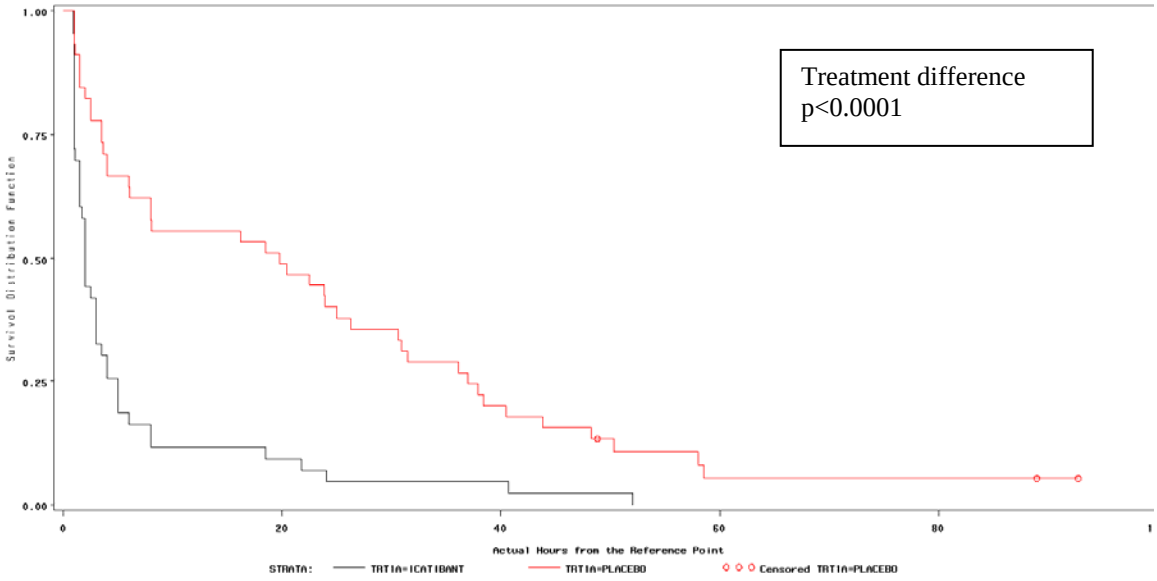



Table 1 Composite Symptom Score – All Subjects

| | Icatibant (N = 43) | Placebo (N = 45) | Peto-Peto Wilcoxon p-value |
|---|---|---|---|
| Number (%) of subjects with symptom relief | 43 (100.0) | 42 (93.3) | |
| Number of censored subjects[a] | 0 | 3 | |
| Kaplan-Meier Estimates | | | |
| Median time to onset of symptom relief (hours) | 2.0 | 19.8 | <0.001 |
| 95% Confidence Interval for the Median Time (hours) | 1.5, 3.0 | 6.1, 26.3 | |
| Q1 for time to onset of symptom relief (hours) | 1.0 | 3.5 | |
| Q3 for time to onset of symptom relief (hours) | 5.0 | 37.0 | |

Symptom relief was defined as a 50% reduction from pretreatment in the 3-symptom composite VAS score. The time to onset of symptom relief was defined retrospectively as the first of 3 consecutive visits at which symptom relief was observed. Subjects with all scores missing or zero at pretreatment or all post-treatment scores missing were excluded from the analysis.

[a] Subjects who did not achieve symptom relief within the observation period were censored at the last

## Secondary Endpoint

The following Kaplan-Meier plot and table illustrate the time to pain relief using the primary symptom score (see definition at bottom of table 2 below). There is significant difference in the time from treatment administration to the onset of symptom relief using the primary symptom VAS measure. The median time to pain relief for the icatibant group is about 2 hours (95%CI: 1.5 to 2 hours) compared to about 19 hours in the placebo group (95% CI: 4 to 24 hours).

Figure 3: Time to Secondary VAS Endpoint: all subjects

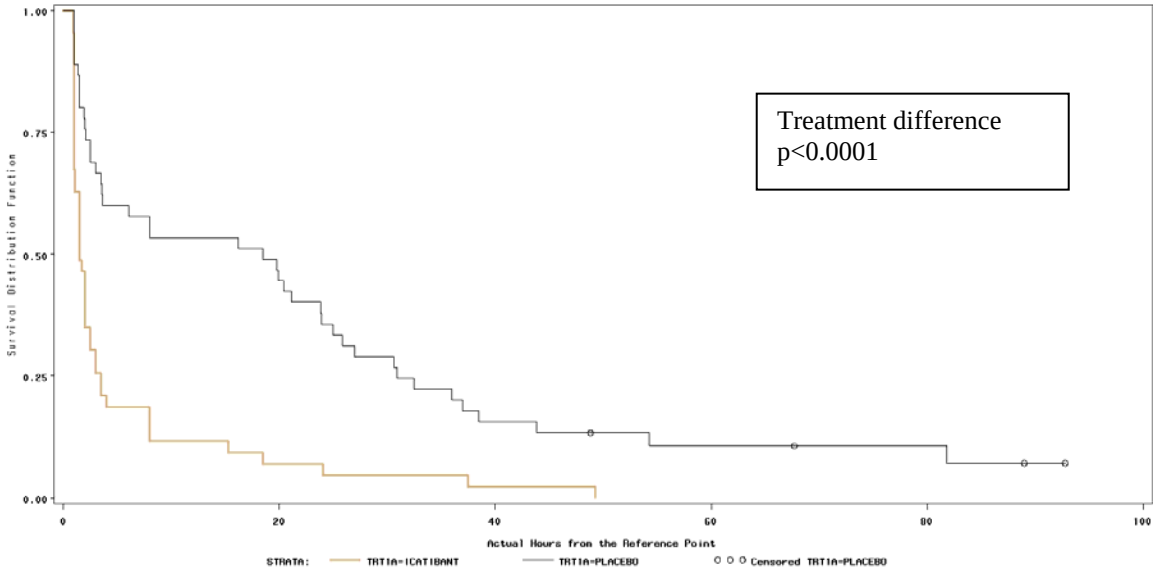



Table 2 Secondary VAS Endpoint – All Subjects

| | **Icatibant (N = 43)** | **Placebo (N = 45)** | **Peto-Peto Wilcoxon p-value** |
|---|---|---|---|
| Number (%) of subjects with symptom relief | 43 (100.0) | 41 (91.1) | |
| Number of censored subjects[a] | 0 | 4 | |
| Kaplan-Meier Estimates | | | |
| Median time to onset of symptom relief (hours) | 1.5 | 18.5 | <0.001 |
| 95% Confidence Interval for the Median Time (hours) | 1.0, 2.0 | 3.6, 23.9 | |
| Q1 for time to onset of symptom relief (hours) | 1.0 | 2.0 | |
| Q3 for time to onset of symptom relief (hours) | 3.5 | 30.9 | |

Primary symptom relief was defined as a reduction from pretreatment in the score for a single primary VAS symptom. Symptom relief was classified as any reduction below (6/7)*pretreatment value – 16 for pretreatment VAS ≥30mm. This criterion corresponds to a reduction by 31 mm at a pretreatment VAS of 100 mm and by 21 mm at a pretreatment VAS of 30mm. For subjects with a pretreatment VAS <30mm,

Sensitivity analyses were conducted to assess the effect of rescue medication to the primary and secondary endpoints. Subjects who required rescue medication were censored in the analyses and the results are presented in Figure 4 and Figure 5. The results were consistent with the primary analyses.

Figure 4: Time to 50% Reduction in VAS (Composite Symptom Score: all subjects) including censoring for Rescue Medication

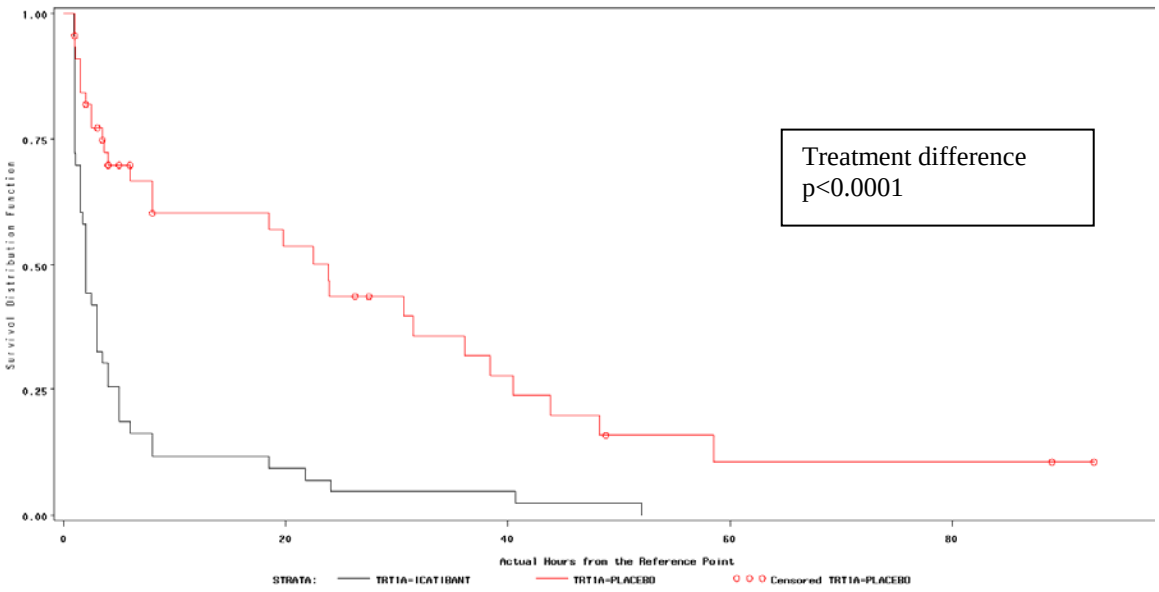
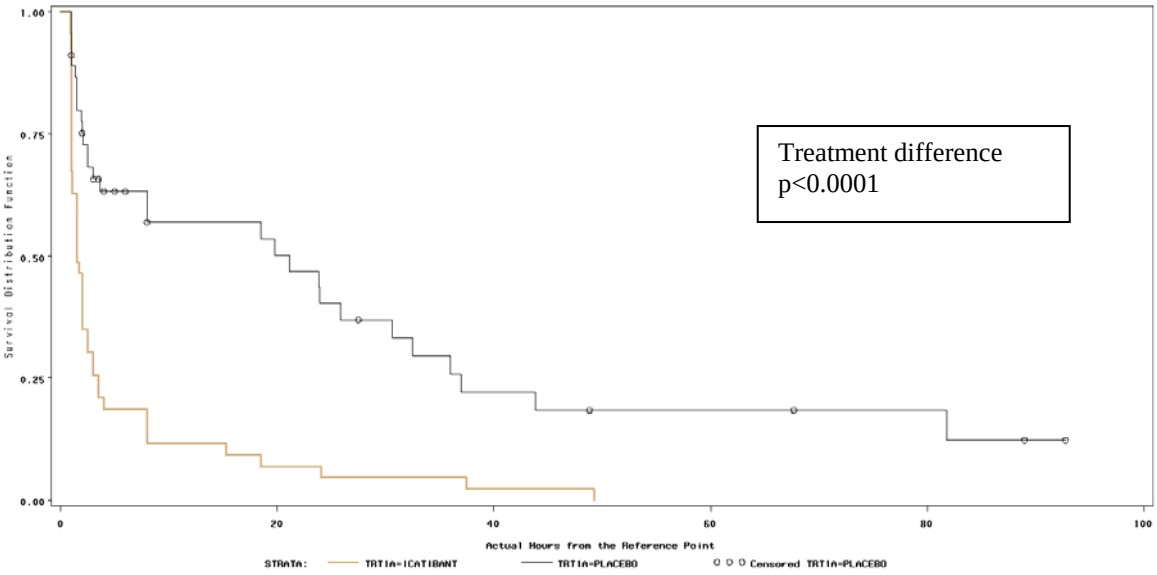



Figure 5: Time to 50% Reduction in VAS (Primary Symptom Score: all subjects) including censoring for Rescue Medication



Additional analyses were conducted to assess the treatment effect based on each cutaneous and abdominal symptoms (i.e. skin pain, skin swelling and abdominal pain). The results are presented in Figure 6 to Figure 9. Although clear separation was evident in all symptom groups, Skin Swelling shows the greatest separation of the groups.

Figure 6: Time to 50% Reduction in VAS (Primary Symptom – All Subjects)

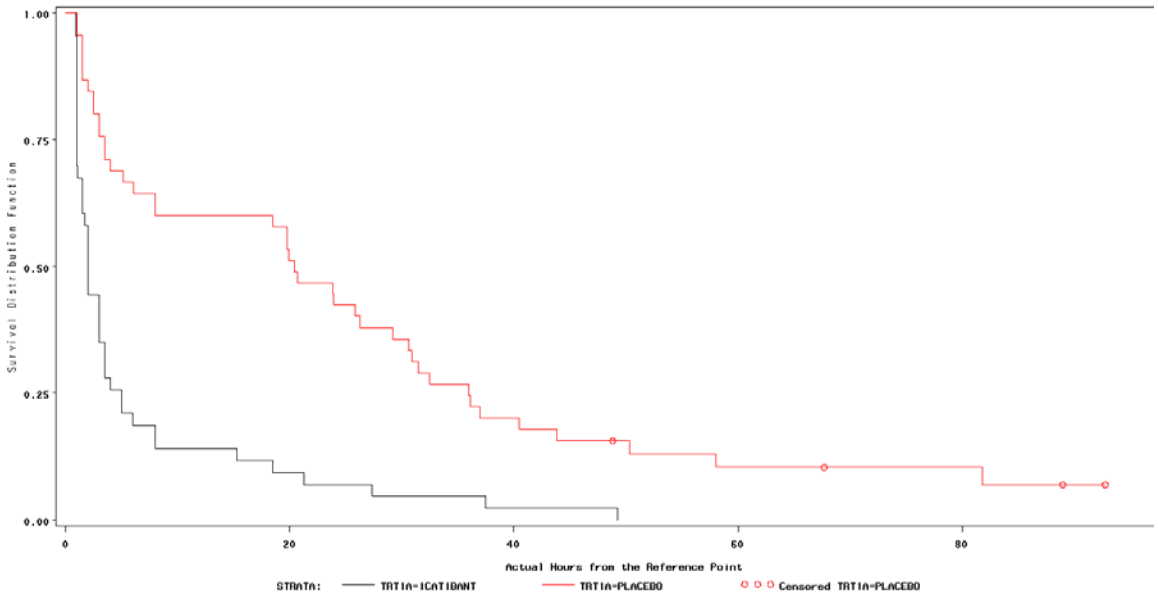



Figure 7: Time to 50% Reduction in VAS (Primary Symptom = Abdominal pain)

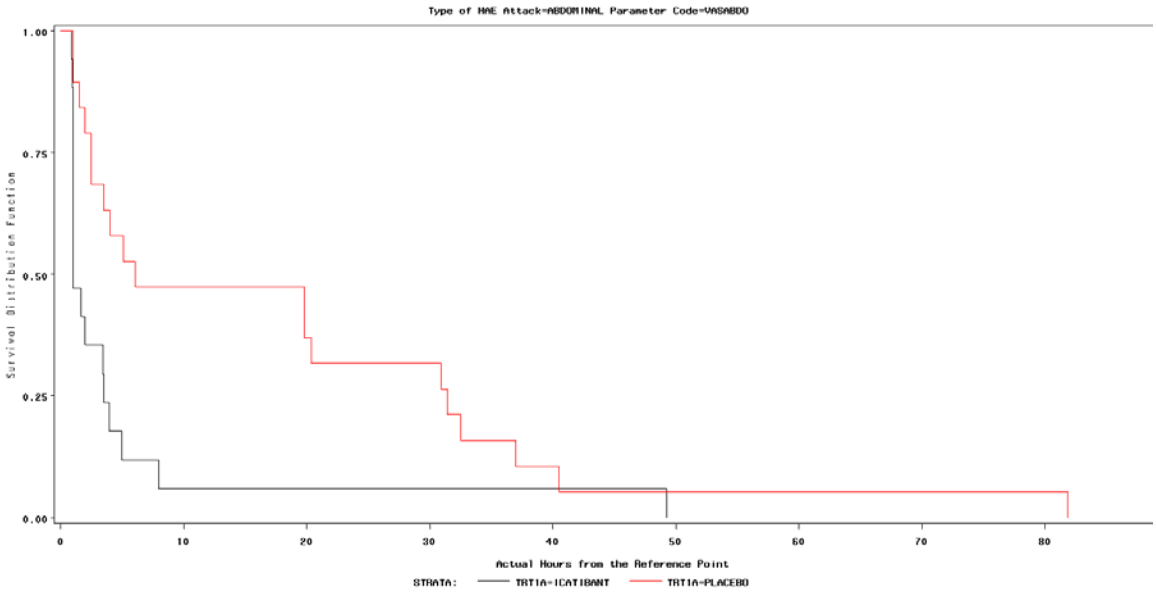


Figure 8: Time to 50% Reduction in VAS (Primary Symptom = Skin Pain)

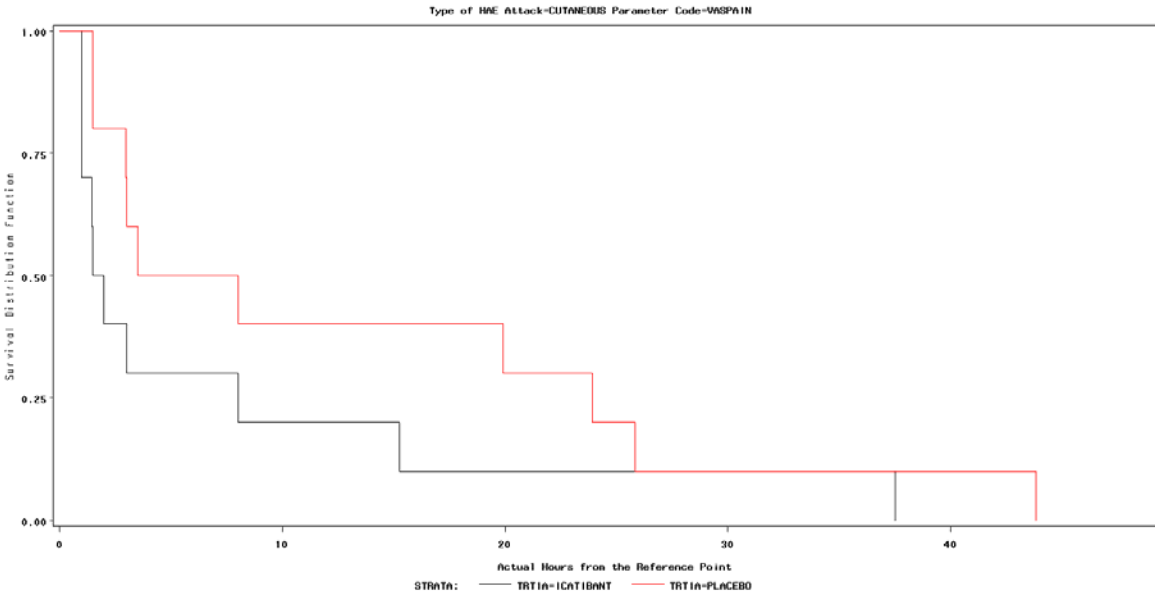
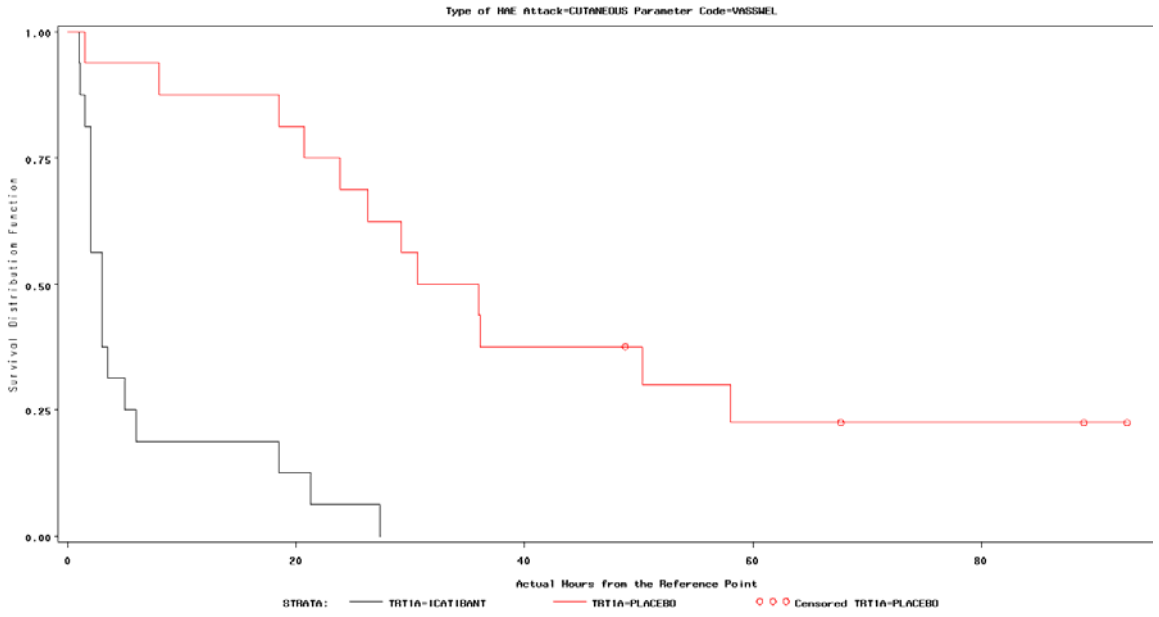



Figure 9: Time to 50% Reduction in VAS (Primary Symptom = Skin Swelling)



The box plots below (Figure 10 to Figure 12) depict the distributions of the average pain scores for each symptoms at three times for the two treatment groups: Baseline, 8 Hours and at the end of the second day. The box plots indicate that, at the end of the second day, the medians of the Abdominal Pain scores (when 'Abdominal' was the primary symptom) were essentially the same in both groups. However, there was more variability of scores in the placebo group. This is likely due to the greater number of 'zero' scores in the icatibant group. The same is true of Skin Pain. Skin Swelling shows the greatest separation of the groups at the end of the second day. The plots show the same pattern when rescued subjects are deleted.

Figure 10: VAS Scores at Pretreatment, 8 Hours, and Day 2 Evening – Abdominal Pain

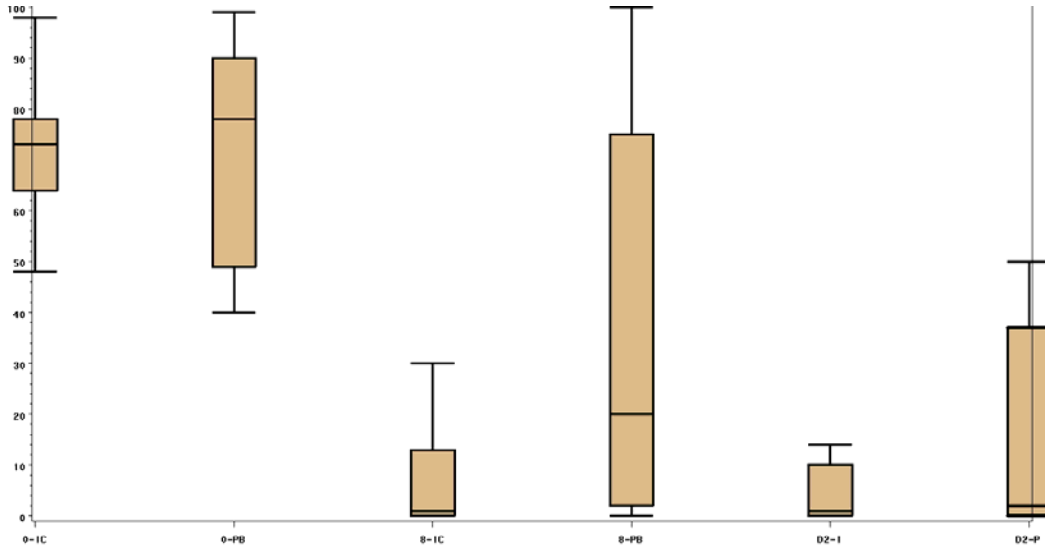



Figure 11: VAS Scores at Pretreatment, 8 Hours, and Day 2 Evening – Skin Pain

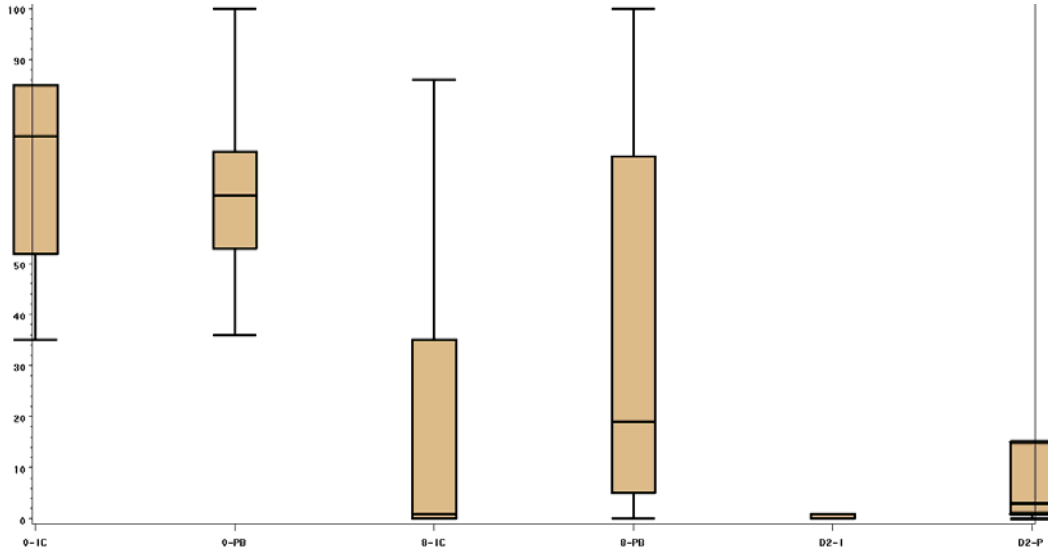
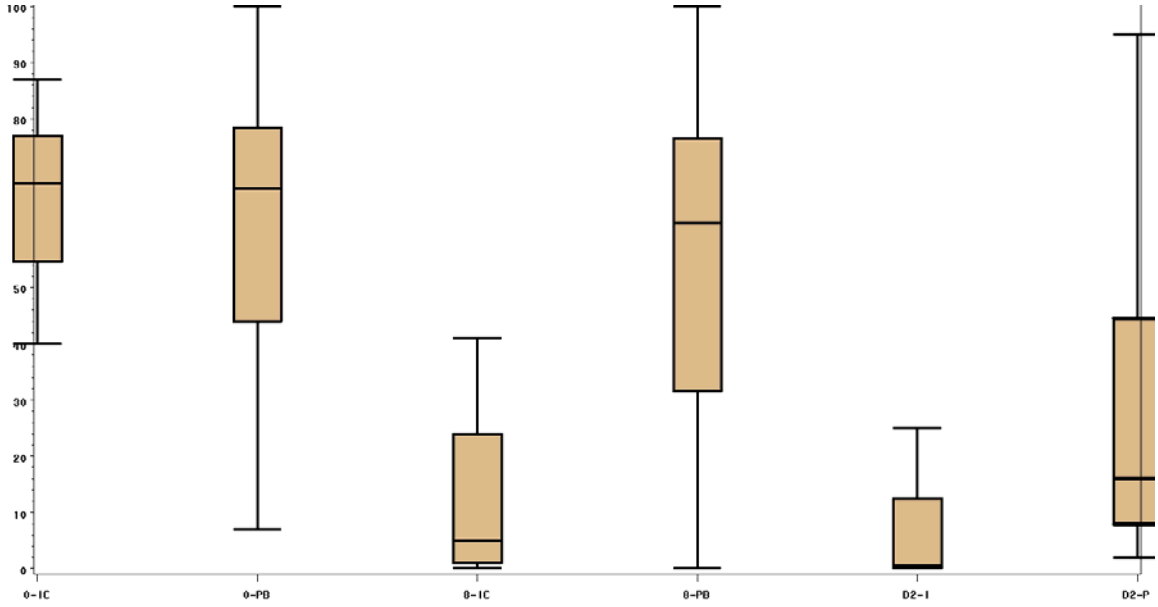


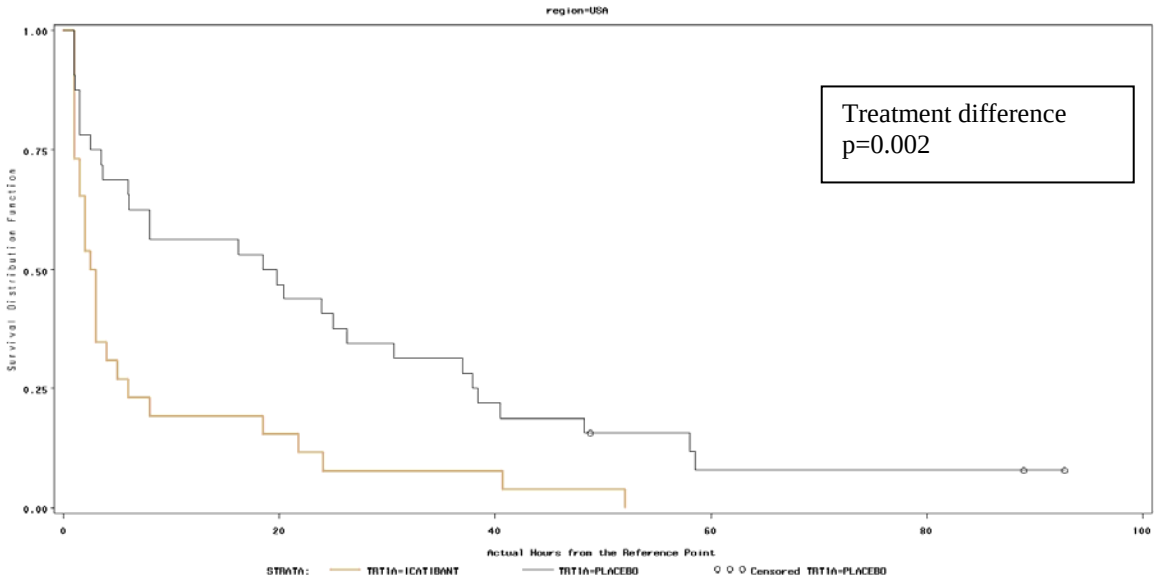

Figure 12: VAS Scores at Pretreatment, 8 Hours, and Day 2 Evening – Skin Swelling



# 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The following figures display Kaplan-Meier plots illustrating the times to pain relief for the 50% decease criterion using the primary endpoint (composite symptom score) by subgroup based on geographic region and gender. There is no significant treatment by subgroup interaction.

Figure 13: Time to 50% Reduction in VAS (Composite Symptom Score: all subjects) - USA




USA

Figure 14: Time to 50% Reduction in VAS (Composite Symptom Score: all subjects) - ROW

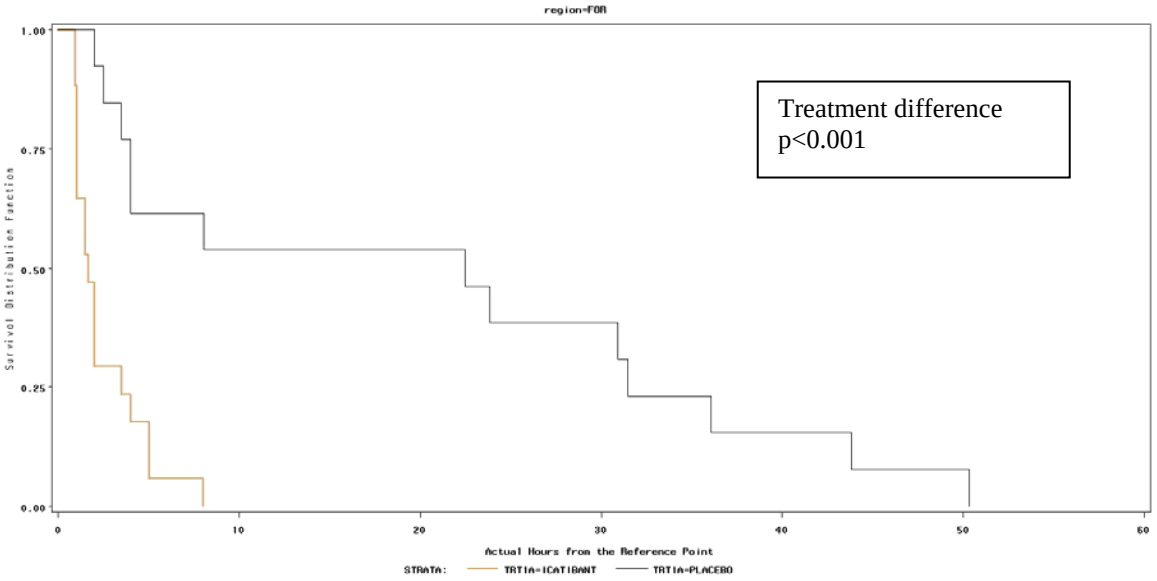


Figure 15: Time to 50% Reduction in VAS (Composite Symptom Score: all subjects) - FEMALE

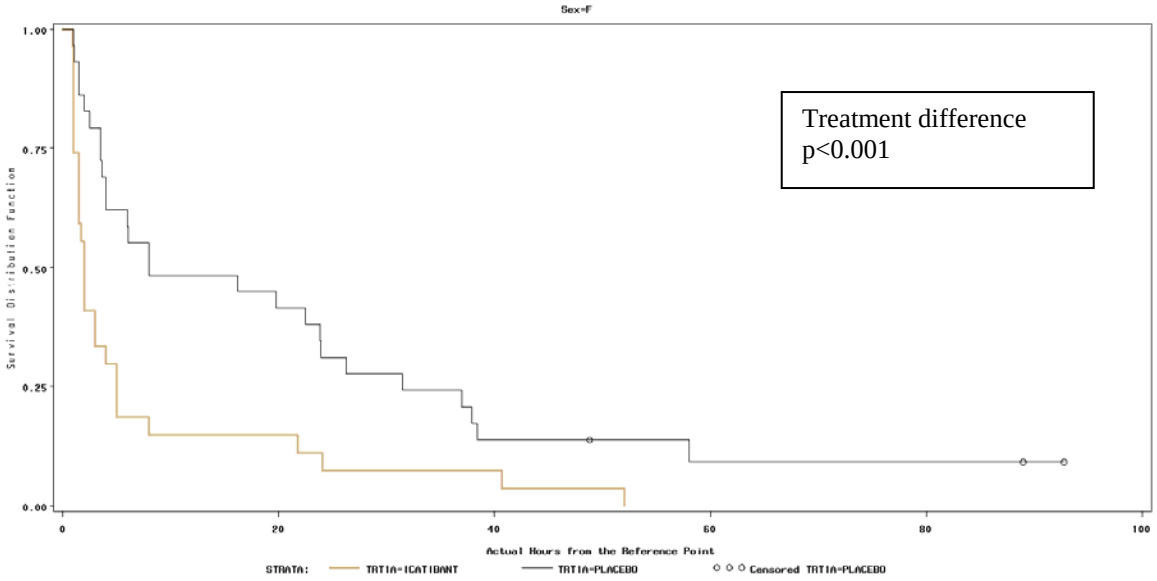
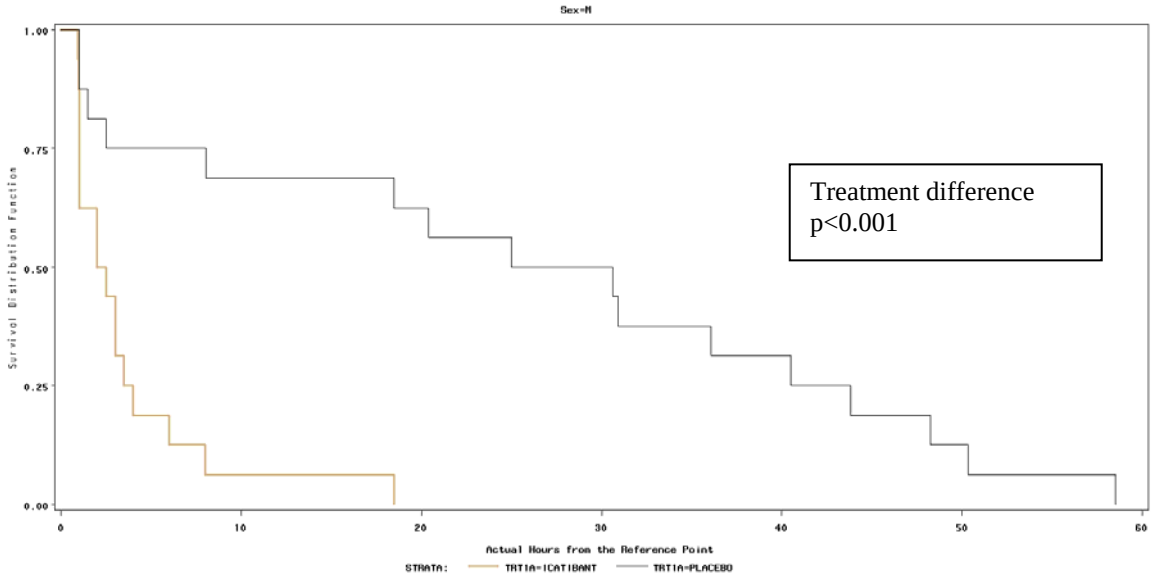



Figure 16: Time to 50% Reduction in VAS (Composite Symptom Score: all subjects) - MALE



# 5. SUMMARY AND CONCLUSIONS

## 5.1 Statistical Issues and Collective Evidence

1. Despite the very low p-value generated by comparing the two groups, the placebo response is noteworthy. In FAST-3, approximately 40% of the placebo subjects achieved at least 50% relief in the first 8 hours, especially those with abdominal pain or skin pain. In contrast, the major reason that the FAST-1 (see table below) trial did not achieve statistical significance (although using the primary symptom score instead of an average and a different cutoff than FAST-3's for patient "symptom relief") was the almost 70% of placebo subjects who achieved at least 50% relief in the first 8 hours, leading to a median time to relief of 4.6 hours while the median time to relief for Icatibant was essentially the same as that in FAST-3.

| | Icatibant | Placebo | Total | Log-rank test |
|---|---|---|---|---|
| Number of patients in ITT Population | 27 | 29 | 56 | |
| Number of patients with pre-treatment VAS ≥ 30 mm | 27 | 28 | 55 | |
| Number of censored* patients | 1 | 1 | 2 | |
| Percentage of patients with symptom relief | 96.3 | 96.4 | 96.4 | |
| Median time to onset of symptom relief (hours) | 2.5 | 4.6 | 3.0 | 0.142 |
| Q1 for time to onset of symptom relief (hours) | 1.1 | 1.8 | 1.5 | |
| Q3 for time to onset of symptom relief (hours) | 6.0 | 10.2 | 10.0 | |

Note: The median time to onset was calculated using Kaplan-Meier methodology.
The Wilcoxon version of the log-rank test of SAS was used

ITT = Intent to Treat, VAS = visual analogue scale, SAS = statistical analysis system

* = Patients were censored when the events (symptom relief) did not occur within the observation period.

2. The box plots indicate that, at the end of the second day, the medians of the Abdominal Pain scores (when 'Abdominal' was the primary symptom) were essentially the same in both groups. However, there was more variability of scores in the placebo group. This is likely due to the greater number of 'zero' scores in the icatibant group. The same is true of Skin Pain. Skin Swelling shows the greatest separation of the groups at the end of the second day. The plots show the same pattern when rescued subjects are deleted.

3. The sponsor may have decided to use the composite (average of 3 symptoms) in FAST-3 due to the failure of FAST-1. However, validation study failed to show that the average tracked the severity of abdominal pain scores as well as cutaneous scores when using "Global Assessment" as the 'gold standard'. See bar graphs below.

**Figure 5. Clinical validity of the VAS-3 according to the global assessment of cutaneous symptoms**

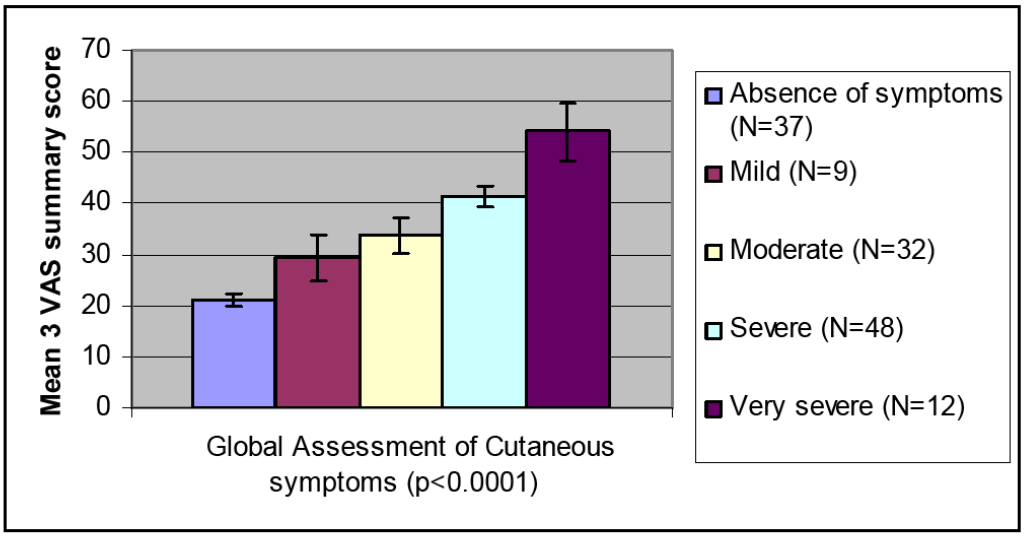
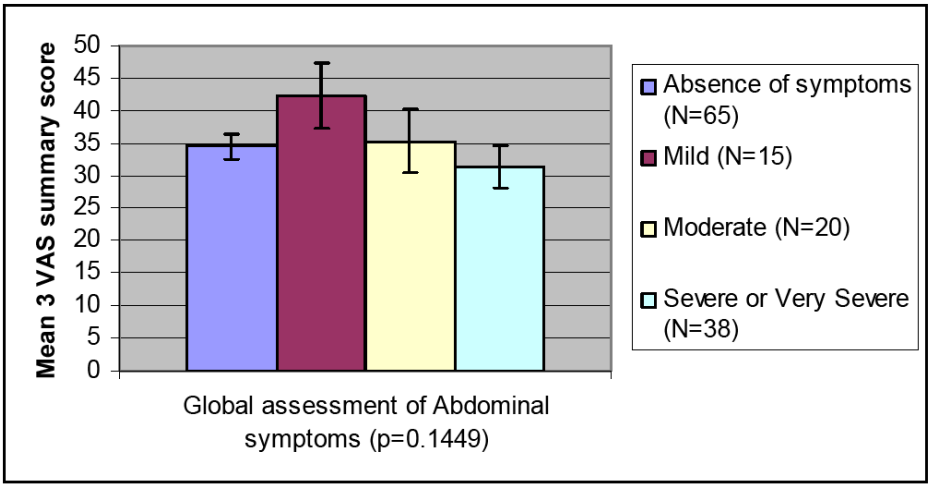



**Figure 6. Clinical validity of the VAS-3 according to the global assessment of abdominal symptoms**




## 5.2 Conclusions and Recommendations

FAST-3 demonstrated statistically significant treatment differences for primary and secondary endpoints. This result contrasts sharply from FAST-1 whose placebo response was notably larger than in FAST-3. All trends were in favor of the Icatibant group for each of the three primary symptoms: abdominal pain, skin pain, and skin swelling. At the end of the second day, abdominal pain scores were similar in both treatment groups. Lastly, there was no benefit to the sponsor's shifting from the primary endpoint use in FAST-1 and FAST-2 to the average score in FAST-3.

# IV. Clinical Pharmacology Summary

## Summary of Clinical Pharmacology

### Pharmacokinetics

Icatibant is rapidly absorbed after single 30 mg subcutaneous (SC) administration with peak plasma concentration achieving within 30 minutes of dosing. Absorption (i.e. bioavailability) is nearly complete (~97%) following SC injection. Icatibant displays linear pharmacokinetics with regards to both dose and time. Following IV infusion of Icatibant 0.4 mg/kg over 30 minutes, the mean volume of distribution is 0.25 L/kg in young healthy males. The binding of icatibant to human serum proteins is low (~44%). Icatibant is rapidly eliminated from the body with mean $T_{1/2}$ values ranging from 0.6 to 1.5 hours. Consistent with half-life estimates, no drug accumulation was observed following SC administration of 30 mg Icatibant every 6 hours for 3 doses in healthy subjects. Clearance of icatibant is predominantly non-renal with about 5-6% being excreted in the urine as parent drug, with less than 5% being excreted unchanged in the urine. Icatibant is extensively metabolized to two principal inactive metabolites, M1 and M2. While the exact pathway is undetermined, in vitro studies suggest that the metabolism of icatibant is primarily via NADPH-independent proteolytic (non-CYP450) enzymes such as peptidases.

### Pharmacokinetics in Specific Populations:

***Age and Gender:***
Following single-dose administration of 30 mg Icatibant, elderly subjects (>65 years) showed an approximately 66% to 116% higher AUC values than young subjects aged between 18-45 years. However, only minor differences (~12-14%) between Cmax of gender–matched elderly and young subjects were observed. The apparent clearance was decreased in elderly compared to younger subjects for both males (~60%) and females (~40%). The half-life ($T_{1/2}$) estimates were prolonged from approximately 30 minutes in young males and females to 1.5 hr in elderly males and 1.1 hr in elderly females

Following single-dose administration of 30 mg Icatibant, young female subjects showed approximately 2.3-fold increase in both Cmax and AUC values than young males. Elderly females exhibited a similar increase in Cmax (~2.3-fold) while AUC was increased by about 1.8-fold compared to elderly males. Since both apparent clearance and volume of distribution are decreased to similar extent in females compared to males, the half-life values are found to be nearly similar. The combined age and gender effects on Icatibant PK resulted, on average, in about 4-fold greater AUC and 2.5-fold higher Cmax in elderly females compared to younger males.

Clearance (CL/F) of Icatibant was found to be significantly correlated with bodyweight (BW) indicating that clearance increases as body weight increases (Figure 1). Since females generally have lower BWs compared to males, therefore females, on average, are expected to exhibit lower clearance values resulting in greater systemic exposure compared to males. Correction for body weight results in more comparable ranges of CL/F values for males and females (Figure 2).

**Figure 1.** Relationship between Icatibant CL/F and bodyweight after administration of a single 30 mg SC dose of Icatibant

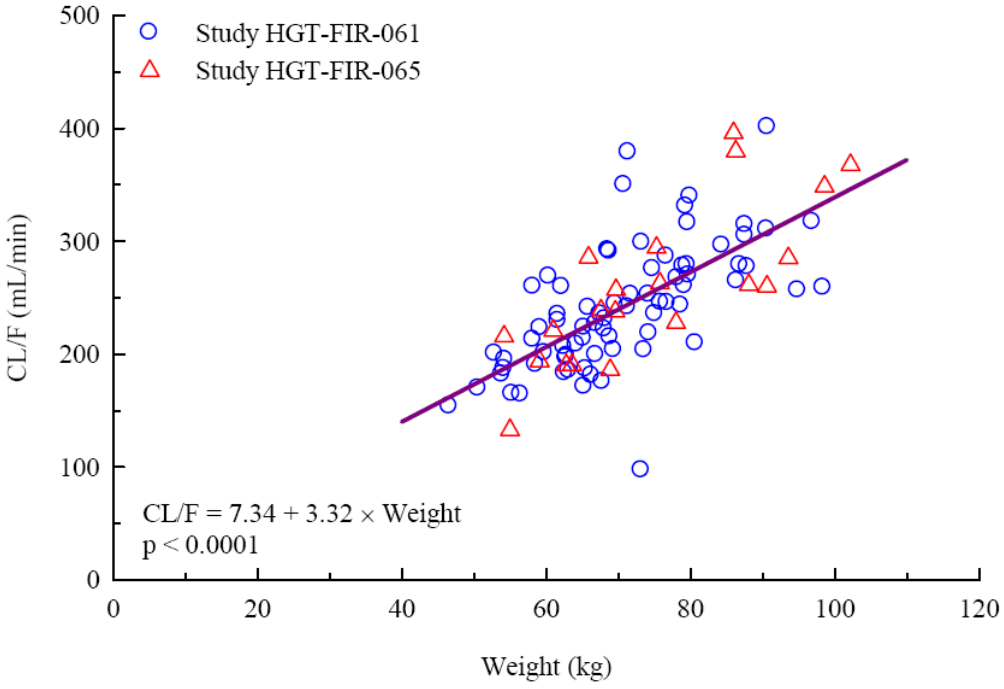
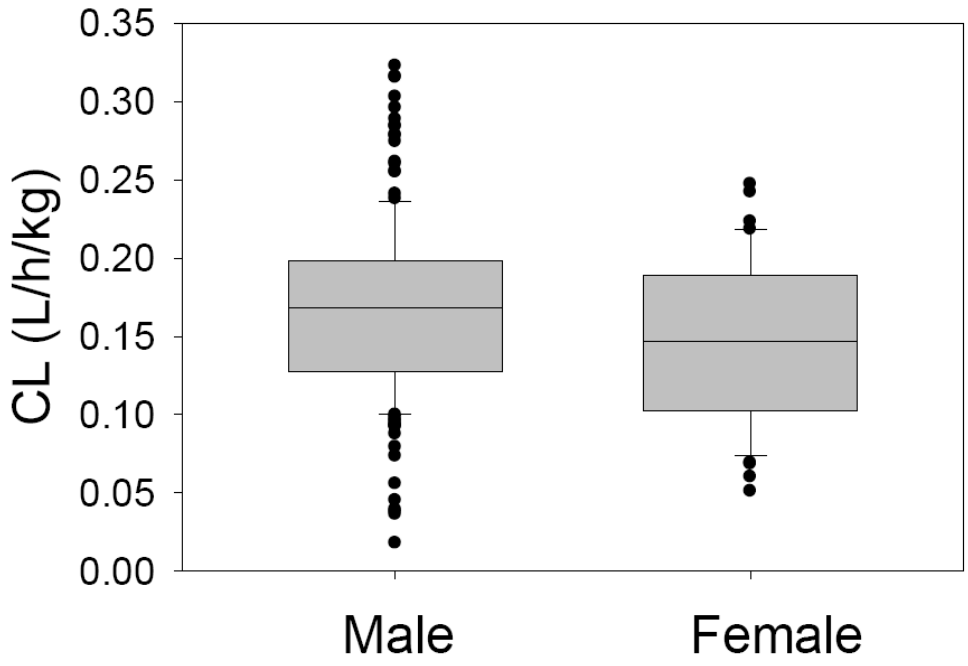



**Figure 2.** Overall comparison of bodyweight-corrected total body clearance in males (n=168) and females (n=42)



The question is whether these differences in exposure translate into clinically meaningful differences across different age groups and between male and female patients. Refer to Medical Officer's Clinical Review for demographic subgroup analysis of clinical data.

***Hepatic and Renal Impairment:***
The pharmacokinetics of icatibant and the M1 and M2 metabolites do not appear to be altered in patients with hepatic impairment nor are they altered in patients with liver cirrhosis and moderate renal function impairment secondary to hepatorenal syndrome. Therefore, no adjustment to the proposed 30 mg dose is recommended for patients with mild to moderate impairment of renal or hepatic function.

***HAE patients:***
The pharmacokinetics of icatibant in patients with HAE is similar to those in healthy subjects.

**Drug-Drug Interaction:**

In vitro studies suggest that icatibant does not inhibit any relevant drug metabolizing CYP450s (CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4) or induce CYP450 enzymes such as CYP1A2 and CYP3A4, implying that there is a low potential for metabolic drug-drug interactions with Icatibant. Formal drug-drug interaction studies were not performed for icatibant due to absence of any significant inhibition or induction of drug metabolizing CYP450 enzymes. The Applicant has postulated a theoretical pharmacodynamic interaction between icatibant and ACE inhibitors, suggesting that icatibant may compromise the antihypertensive effects of ACE inhibitors via bradykinin antagonism. Clinical trials excluded subjects taking ACE inhibitors. The possibility that short term administration of Icatibant will alter significantly the chronic antihypertensive effect of an ACE inhibitor is presently unknown.

In vitro studies also suggest that Icatibant does not inhibit any relevant drug metabolizing CYP450s or induce CYP450 enzymes (CYP1A2 and CYP3A4), implying that there is a low potential for metabolic drug-drug interactions with Icatibant.

**Dose Selection**

Icatibant is a competitive antagonist of the bradykinin type 2 (B2) receptor. It is hypothesized that inhibition of endogenous bradykinin (BK) is required to control key symptoms elicited by overproduction of BK during an acute angioedema attack. Therefore, an exogenous IV BK challenge was used as a pharmacological tool in healthy subjects to investigate the dose range and regimen for later trials. It was hypothesized that near complete BK antagonism would be required to establish the optimal dose, dose regimen, and time window for a clinically relevant inhibition. IV route was chosen for this initial exploration as it would provide the least uncertainty of the exposure-time profile of the drug. The phase 3 dose was selected based on expected systemic bradykinin concentration anticipated during an HAE attack and levels of Icatibant needed to completely antagonize the bradykinin effects.

Therefore, Icatibant dose selection was based on a biomarker (bradykinin challenge) rather than a clinical endpoint and/or clinical surrogate. No formal dose-ranging study based on clinical efficacy measure was performed.

# V. Other Product Labels

## HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use Berinert safely and effectively. See full prescribing information for Berinert.**

**Berinert [C1 Esterase Inhibitor (Human)]**
**For intravenous use. Freeze-Dried Powder for Reconstitution.**
**Initial U.S. Approval: 2009**

### ----------INDICATIONS AND USAGE----------

Berinert is a plasma-derived C1 Esterase Inhibitor (Human) indicated for the treatment of acute abdominal or facial attacks of hereditary angioedema (HAE) in adult and adolescent patients (1).
The safety and efficacy of Berinert for prophylactic therapy have not been established (1).

### ----------DOSAGE AND ADMINISTRATION----------

**For intravenous use only.**

- Store the vial in the original carton in order to protect from light. Store at 2-25°C (36-77°F). Do not freeze (2).
- Administer 20 units per kg body weight (2).
- Reconstitute Berinert prior to use using the diluent (sterile water) provided (2.1).
- Administer at room temperature within 8 hours of reconstitution (2.1).
- Inject at a rate of approximately 4 mL per minute (2.2).
- Do not mix Berinert with other medicinal products or solutions (2.2).

### ----------DOSAGE FORMS AND STRENGTHS----------

500 units lyophilized concentrate in a single-use vial for reconstitution with 10 mL of diluent (sterile water) (3).

### ----------CONTRAINDICATIONS ----------

- Do not use in patients with a history of life-threatening immediate hypersensitivity reactions, including anaphylaxis, to C1 esterase inhibitor preparations (4).

### ----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity reactions may occur. Epinephrine should be immediately available to treat any acute severe hypersensitivity reactions following discontinuation of administration (5.1).
- Thrombotic events have occurred in patients receiving off-label high doses of Berinert. Monitor patients with known risk factors for thrombotic events (5.2).
- Berinert is made from human plasma and may contain infectious agents, eg, viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent (5.3).

### ----------ADVERSE REACTIONS----------

- The most serious adverse reaction reported in subjects who received Berinert was an increase in the severity of pain associated with HAE (6.1).
- The most common adverse reactions observed by ≥4% of subjects after Berinert treatment were subsequent HAE attack, headache, abdominal pain, nausea, muscle spasm, pain, diarrhea and vomiting (6.1).

**To report SUSPECTED ADVERSE REACTIONS, contact the CSL Behring Pharmacovigilance Department at 1-866-915-6958 or to the FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.**

### ----------DRUG INTERACTIONS----------

No drug interaction studies have been conducted (7).

### ----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: No animal data. Limited human data. Use only if clearly needed (8.1).
- Children: Safety and effectiveness in children ages 0 through 12 have not been established. Berinert was evaluated in 5 children (ages 3 through 12) and in 8 adolescent subjects (ages 13 through 16) [8.4].
- Compared to adults, the half-life of Berinert was shorter and clearance was faster in children. The clinical implication of this difference is not known (12.3).

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**

**Revised: November 2009**

## FULL PRESCRIBING INFORMATION: CONTENTS*



*Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

**Berinert® [C1 Esterase Inhibitor (Human)]**
**Freeze-dried powder**

## 1 INDICATIONS AND USAGE

Berinert is a plasma-derived concentrate of C1 Esterase Inhibitor (Human) indicated for the treatment of acute abdominal or facial attacks of hereditary angioedema (HAE) in adult and adolescent patients.

The safety and efficacy of Berinert for prophylactic therapy have not been established.

## 2 DOSAGE AND ADMINISTRATION

**For Intravenous Use Only.**

Administer Berinert at a dose of 20 units per kg body weight by intravenous injection.

Berinert is provided as a freeze-dried powder for reconstitution with the diluent (sterile water) provided. Store the vial in the original carton in order to protect from light. Do not freeze.

### 2.1 Preparation and Handling

- Check the expiration date on the product vial label. Do not use beyond the expiration date.
- Use aseptic technique when preparing and administering Berinert *(see Reconstitution and Administration [2.2])*.
- After reconstitution and prior to administration, inspect Berinert visually for particulate matter and discoloration. The reconstituted solution should be colorless, clear, and free from visible particles. Do not use if the solution is cloudy, discolored, or contains particulates.
- The Berinert vial is for single use only. Berinert contains no preservative. Any product that has been reconstituted should be used promptly. The reconstituted solution must be used within 8 hours. Discard partially used vials.
- Do not freeze the reconstituted solution.

## 2.2 Reconstitution and Administration

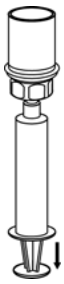
Each Berinert kit consists of one carton containing one single-use vial of Berinert, one 10 mL vial of diluent (sterile water), one Mix2Vial™ transfer set, and one alcohol swab.

Use either the Mix2Vial transfer set provided with Berinert (*see How Supplied [16.1]*) or a commercially available double-ended needle and vented filter spike.

Reconstitution

The procedures below are provided as general guidelines for the reconstitution and administration of Berinert.

| | |
|---|---|
| 1. Ensure that the Berinert vial and diluent vial are at room temperature. Use aseptic technique during the reconstitution procedure. | |
| 2. Place the Berinert vial, diluent vial and Mix2Vial transfer set on a flat surface. | |
| 3. Remove the flip caps from the Berinert and diluent vials. Treat the vial stoppers with the alcohol swab provided and allow to dry prior to opening the Mix2Vial transfer set package. | |
| 4. Open the Mix2Vial transfer set package by peeling away the lid (Fig. 1). Leave the Mix2Vial transfer set in the clear package. |  Fig. 1 |
| 5. Place the diluent vial on a flat surface and hold the vial tightly. Grip the Mix2Vial transfer set together with the clear package and snap the blue end of the Mix2Vial transfer set onto the diluent vial stopper at a 90° angle (Fig. 2). |  Fig. 2 |
| 6. Carefully remove the clear package from the Mix2Vial transfer set. Make sure that you pull up only the clear package, and not the Mix2Vial transfer set (Fig. 3). |  Fig. 3 |
| 7. With the Berinert vial placed firmly on a flat surface, invert the diluent vial with the Mix2Vial transfer set attached and snap the transparent adapter onto the Berinert vial stopper at a 90° angle (Fig. 4). The diluent will automatically transfer into the Berinert vial. |  Fig. 4 |
| 8. With the diluent and Berinert vial still attached to the Mix2Vial transfer set, gently swirl the Berinert vial to ensure that the Berinert is fully dissolved (Fig. 5). Do not shake the vial. |  Fig. 5 |

| | |
|---|---|
| 9. With one hand, grasp the Berinert-side of the Mix2Vial transfer set and with the other hand grasp the blue diluent-side of the Mix2Vial transfer set and unscrew the set into two pieces. (Fig. 6). |  Fig. 6 |
| 10. Draw air into an empty, sterile syringe. While the Berinert vial is upright, screw the syringe to the Mix2Vial transfer set. Inject air into the Berinert vial. While keeping the syringe plunger pressed, invert the system upside down and draw the concentrate into the syringe by pulling the plunger back slowly. (Fig. 7). |  Fig. 7 |
| 11. Now that the concentrate has been transferred into the syringe, firmly grasp the barrel of the syringe (keeping the plunger facing down) and unscrew the syringe from the Mix2Vial transfer set (Fig. 8). Attach the syringe to a suitable intravenous (IV) administration set. |  Fig. 8 |
| 12. If the same patient is to receive more than one vial, the contents of multiple vials may be pooled in a single administration device (eg, syringe). A new unused Mix2Vial transfer set should be used for each Berinert vial. | |
| 13. Do not refrigerate after reconstitution. When reconstitution is carried out using aseptic technique, administration may begin within 8 hours, provided the solution has been stored at up to 25ºC (77ºF). Do not refrigerate or freeze the reconstituted solution. | |

Administration

Do not mix Berinert with other medicinal products and administer by a separate infusion line.

Use aseptic technique when administering Berinert.

Administer Berinert by slow intravenous injection at a rate of approximately 4 mL per minute.

## 3 DOSAGE FORMS AND STRENGTHS

- Berinert is available in a single-use vial that contains 500 units of C1 esterase inhibitor as a lyophilized concentrate.
- Each vial must be reconstituted with 10 mL of diluent (sterile water) provided.

## 4 CONTRAINDICATIONS

Berinert is contraindicated in individuals who have experienced life-threatening hypersensitivity reactions, including anaphylaxis, to C1 esterase inhibitor preparations.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hypersensitivity

Severe hypersensitivity reactions may occur. Epinephrine should be immediately available for treatment of acute severe hypersensitivity reaction *(see Patient Counseling Information [17])*. The signs and symptoms of hypersensitivity reactions may include hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and/or anaphylaxis during or after injection of Berinert.

Because hypersensitivity reactions may have symptoms similar to HAE attacks, treatment methods should be carefully considered. In case of suspected hypersensitivity, immediately discontinue administration of Berinert and institute appropriate treatment.

### 5.2 Thrombotic Events

Thrombotic events have been reported in association with Berinert when used off-label and at higher than labeled doses.[1] Animal studies have confirmed the risk of thrombosis from intravenous administration of C1 esterase inhibitor products[2] (*see Overdosage [10] and Animal Toxicology and/or Pharmacology [13.2]*).

### 5.3 Transmission of Infectious Agents

Because Berinert is made from human blood, it may contain infectious agents (eg, viruses and, theoretically, the Creutzfeldt-Jakob disease [CJD] agent) that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by processes demonstrated to inactivate and/or remove certain viruses during manufacturing (*see Description [11] and Patient Counseling Information [17]*).

Despite these measures, such products may still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products.

Since 1979, a few suspected cases of viral transmission have been reported with the use of Berinert outside the US, including cases of acute hepatitis C. From the incomplete information available from these cases, it was not possible to determine with certainty if the infections were or were not related to prior administration of Berinert.

The physician should discuss the risks and benefits of this product with the patient before prescribing or administering it to the patient. *(See Patient Counseling Information [17.1]).*

All infections thought by a physician possibly to have been transmitted by Berinert should be reported by lot number, by the physician, or other healthcare provider to the CSL Behring Pharmacovigilance Department at 1-866-915-6958.

## 6 ADVERSE REACTIONS

The most serious adverse reaction reported in subjects enrolled in clinical studies who received Berinert was an increase in the severity of pain associated with HAE.

The most common adverse reactions that have been reported in greater than 4% of the subjects who received Berinert in clinical studies were subsequent HAE attack, headache, abdominal pain, nausea, muscle spasm, pain, diarrhea and vomiting.

### 6.1 Clinical Trials Experience

*Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.*

Placebo-controlled Clinical Study

In the placebo-controlled clinical study, referred to as the randomized clinical trial (RCT) (*see Clinical Studies [14]*), 124 subjects experiencing an acute moderate to severe abdominal or facial HAE attack were treated with Berinert (either a 10 unit per kg body weight or a 20 unit per kg body weight dose), or placebo (physiological saline solution).

The treatment-emergent serious adverse reactions/events that occurred in 5 subjects in the RCT were laryngeal edema, facial attack with laryngeal edema, swelling (shoulder and chest), exacerbation of hereditary angioedema, and laryngospasm.

**Table 1: Adverse Reactions* Occurring up to 4 hours After Initial Infusion in More Than 4% of Subjects, *Irrespective of Causality*†**

| Adverse Reactions | Number (%) of Subjects Reporting Adverse Reactions Berinert 20 units/kg (n = 43) | Number (%) of Subjects Reporting Adverse Reactions Placebo Group (n = 42) |
|---|---|---|
| Nausea† | 3 (7%) | 5 (11.9%) |
| Dysgeusia | 2 (4.7%) | 0 (0) |
| Abdominal Pain† | 2 (4.7%) | 3 (7.1%) |
| Vomiting† | 1 (2.3%) | 3 (7.1%) |
| Diarrhea† | 0 (0) | 4 (9.5%) |
| Headache | 0 (0) | 2 (4.8%) |

* The study protocol specified that adverse events that began within 72 hours of blinded study medication administration were to be classified as at least possibly related to study medication (ie, adverse reactions).

† The following abdominal symptoms were identified in the protocol as associated with HAE abdominal attacks: abdominal pain, bloating, cramps, nausea, vomiting, and diarrhea.

**Table 2: Adverse Reactions* Occurring in More Than 4% of Subjects up to 72 hours After Infusion of Initial or Rescue Medication† by Intent-to-Treat, *Irrespective of Causality***

| Adverse Reactions | Number (%) of Subjects Reporting Adverse Reactions†‡ Berinert 20 units/kg (n = 43) | Number (%) of Subjects Reporting Adverse Reactions†‡ Placebo Group (n = 42) |
|---|---|---|
| Nausea | 3 (7%) | 11 (26.2%) |
| Headache | 3 (7%) | 5 (11.9%) |
| Abdominal Pain | 3 (7%) | 5 (11.9%) |
| Dysgeusia | 2 (4.7%) | 1 (2.4%) |
| Vomiting | 1 (2.3%) | 7 (16.7%) |
| Pain | 1 (2.3%) | 4 (9.5%) |
| Muscle spasms | 1 (2.3%) | 4 (9.5%) |
| Diarrhea | 0 (0) | 8 (19%) |
| Back pain | 0 (0) | 2 (4.8%) |
| Facial pain | 0 (0) | 2 (4.8%) |

* The study protocol specified that adverse events that began within 72 hours of blinded study medication administration were to be classified as at least possibly related to study medication (ie, adverse reactions).

† If a subject experienced no relief or insufficient relief of symptoms within 4 hours after infusion, investigators had the option to administer a blinded second infusion ("rescue" treatment) of Berinert (20 units/kg for the placebo group or 10 units/kg for the 10 units/kg group), or placebo (for the 20 units/kg group).

‡ Adverse reactions following either initial treatment and/or blinded "rescue" treatment. Because more subjects in the placebo randomization group than in the Berinert randomization group received rescue treatment, the median observation period in this analysis for subjects randomized to placebo was slightly longer than for subjects randomized to receive Berinert.

Table 3 lists the adverse events that occurred in more than 4% of the subjects 7 to 9 days after the end of a Berinert infusion, *irrespective of causality.*

**Table 3: Adverse Events Occurring in More Than 4% of Subjects* Receiving Berinert at Either 10 Units/kg or 20 units/kg 7 to 9 Days after Infusion, *Irrespective of Causality***

| Adverse Events | Number (%) of Subjects Reporting Adverse Events (n=108) |
|---|---|
| Hereditary angioedema | 12 (11.1%) |
| Headache | 12 (11.1%) |
| Abdominal pain† | 7 (6.5%) |
| Nausea† | 7 (6.5%) |
| Muscle spasms | 6 (5.6%) |
| Pain | 6 (5.6%) |
| Diarrhea† | 5 (4.6%) |
| Vomiting† | 5 (4.6%) |

* Includes subjects in the placebo group who received Berinert 20 units/kg as rescue study medication.

† These symptoms were identified in the protocol as related to the underlying disease. Any increase in intensity or new occurrence of these symptoms after study medication administration was considered to be an adverse event.

Subjects were tested at baseline and after 3 months for possible exposure to Parvovirus B19, hepatitis B, hepatitis C, and HIV-1 and HIV-2. No subject who underwent testing evidenced seroconversion or treatment-emergent positive polymerase chain reaction testing for these pathogens.

Extension Study

In an interim safety analysis, of the ongoing open-label extension study, 56 subjects with 559 acute moderate to severe abdominal, facial, peripheral, and/or laryngeal attacks received a 20 unit/kg body weight dose of Berinert (*see Clinical Studies [14]*). This study provides additional safety data in subjects who received multiple infusions of the product for sequential HAE attacks (one infusion per attack).

Table 4 lists the adverse events that occurred in this interim safety analysis of the ongoing open-label extension study in more than 4% of subjects up to 72 hours or 9 days after the end of a Berinert infusion, *irrespective of causality.*

**Table 4: Incidence of Adverse Events by Descending Frequency Occurring in More Than 4% of Subjects Receiving Berinert up to 72 Hours or 9 Days After Infusion, *Irrespective of Causality***

| Adverse Events | Number (%) of Subjects Reporting Adverse Events up to 72 hours (n=56) | Number (%) of Subjects Reporting Adverse Events up to 9 Days (n=56) |
|---|---|---|
| Headache | 3 (5.4%) | 4 (7.1%) |
| Abdominal pain | 3 (5.4%) | 3 (5.4%) |
| Hereditary angioedema | 2 (3.6%) | 4 (7.1%) |
| Nasopharyngitis | 2 (3.6%) | 3 (5.4%) |

### 6.2 Postmarketing Experience

*Because postmarketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.*

Adverse reactions reported in Europe since 1979 in patients receiving Berinert for treatment of HAE include hypersensitivity/anaphylactic reactions, a few suspected cases of viral transmission, including cases of acute hepatitis C, injection-site pain, injection-site redness, chills, and fever.

The following adverse reactions, identified by system organ class, have been attributed to Berinert during post-approval use outside the US.

- *Immune System Disorder: Hypersensitivity/anaphylactic reactions, and shock*
- *General/Body as a Whole: Pain on injection, redness at injection site, chills, and fever*

## 7 DRUG INTERACTIONS

No drug interaction studies have been conducted.

# 8 USE IN SPECIFIC POPULATIONS

## 8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Berinert. It is not known whether Berinert can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Berinert should be given to a pregnant woman only if clearly needed. In a retrospective case collection study, 20 pregnant women ranging in age from 20 to 35 years received Berinert with repeated doses up to 3,500 units per attack; these women reported no complications during delivery and no harmful effects on their 34 neonates.

## 8.2 Labor and Delivery

The safety and effectiveness of Berinert administration prior to or during labor and delivery have not been established. Use only if clearly needed.

## 8.3 Nursing Mothers

It is not known whether Berinert is excreted in human milk. Because many drugs are excreted in human milk, use only if clearly needed when treating a nursing woman.

## 8.4 Pediatric Use

Safety and efficacy of Berinert in children (ages 0 through 12) have not been established. The clinical studies included an insufficient number of subjects in this age group to determine whether they respond differently from older subjects. The safety and efficacy of Berinert were evaluated in 5 children (ages 3 through 12) and in 8 adolescent subjects (ages 13 through 16) (*see Pharmacokinetics [12.3]*).

## 8.5 Geriatric Use

Safety and efficacy of Berinert in the geriatric population have not been established. Clinical studies with Berinert included four subjects older than 65 years. The clinical studies included an insufficient number of subjects in this age group to determine whether they respond differently from younger subjects.

# 10 OVERDOSAGE

The development of thrombosis has been reported after doses exceeding 20 units/kg body weight of Berinert when used off-label[1] in newborns and young children with congenital heart anomalies during or after cardiac surgery under extracorporeal circulation.

The maximum dose administered in clinical studies in hereditary angioedema was 20 units/kg body weight. Overdosage did not occur in connection with treatment of HAE.

## 11 DESCRIPTION

Berinert is a human plasma-derived, purified, pasteurized, lyophilized concentrate of C1 esterase inhibitor to be reconstituted for intravenous administration. Berinert is prepared from large pools of human plasma from US donors. One standard unit of C1 esterase inhibitor concentrate is equal to the amount of C1 esterase inhibitor in 1 mL of fresh citrated human plasma, which is equivalent to 270 mg/L or 2.5 μM/L. No international laboratory standard for quantifying C1 esterase inhibitor. An in-house standard is used to assure lot-to-lot consistency in product potency.

C1 esterase inhibitor is a soluble, single-chain glycoprotein containing 478 amino acid residues organized into three beta-sheets and eight or nine alpha-helices.[3] The heavily glycosylated molecule has an apparent molecular weight of 105 kD, of which the carbohydrate chains comprise 26% to 35%.[4]

Each vial of Berinert contains 500 units C1 esterase inhibitor, 50 to 80 mg total protein, 85 to 115 mg glycine, 70 to 100 mg sodium chloride, and 25 to 35 mg sodium citrate.

All plasma used in the manufacture of Berinert is obtained from US donors and is tested using serological assays for hepatitis B surface antigen and antibodies to HIV-1/2 and HCV. Additionally, the plasma is tested with Nucleic Acid Testing (NAT) for HCV and HIV-1 and found to be non-reactive (negative). In addition, the plasma is tested by NAT for HAV and Human Parvovirus B19. Only plasma that has passed virus screening is used for production, and the limit for Parvovirus B19 in the fractionation pool is set not to exceed $10^4$ IU of Parvovirus B19 DNA per mL.

The manufacturing process for Berinert includes multiple steps that reduce the risk of virus transmission. The virus inactivation/reduction capacity of three steps (pasteurization in aqueous solution at 60°C for 10 hours, hydrophobic interaction chromatography, and the combination of ion exchange chromatographies and ammonium sulphate precipitation) was evaluated in a series of *in vitro* spiking experiments. The total mean cumulative virus inactivation/reduction is shown in Table 5.

**Table 5: Mean Virus Inactivation/Reductions in Berinert**

| Virus Studied | Pasteurization [$log_{10}$] | Hydrophobic Interaction Chromatography [$log_{10}$] | DEAE-Sephadex A50 Chromatography QAE-Sephadex Chromatography and Ammonium Sulphate Precipitation [log10] | Total Cumulative [$log_{10}$] |
|---|---|---|---|---|
| **Enveloped Viruses** | | | | |
| HIV-1 | ≥6.6 | ≥4.5 | 4.3 | ≥15.4 |
| BVDV | ≥9.2 | ≥4.6 | NA | ≥13.8 |
| PRV | 6.3 | ≥6.5 | ≥7.7 | ≥20.5 |
| WNV | ≥7.0 | ND | NA | NA |
| **Non-Enveloped Viruses** | | | | |
| HAV | ≥6.4 | 4.5 | NA | ≥10.9 |
| CPV | 1.4 | 6.1 | NA | 7.5 |
| B19V | 3.9 | ND | NA | NA |

HIV-1, Human immunodeficiency virus type 1, a model for HIV-1 and HIV-2
BVDV, Bovine viral diarrhea virus, a model for HCV
PRV, Pseudorabies virus, a model for large enveloped DNA viruses (eg, herpes virus)
WNV, West Nile virus
HAV, Hepatitis A virus
CPV, Canine parvovirus
B19V, Human Parvovirus B19
ND, Not determined
NA, Not applicable

# 12 CLINICAL PHARMACOLOGY

## 12.1 Mechanism of Action

C1 esterase inhibitor is a normal constituent of human plasma and belongs to the group of serine protease inhibitors (serpins) that includes antithrombin III, alpha$_1$-protease inhibitor, alpha$_2$-antiplasmin, and heparin cofactor II. As with the other inhibitors in this group, C1 esterase inhibitor has an important inhibiting potential on several of the major cascade systems of the human body, including the complement system, the intrinsic coagulation (contact) system, the fibrinolytic system, and the coagulation cascade. Regulation of these systems is performed through the formation of complexes between the proteinase and the inhibitor, resulting in inactivation of both and consumption of the C1 esterase inhibitor.

C1 esterase inhibitor, which is usually activated during the inflammatory process, inactivates its substrate by covalently binding to the reactive site. C1 esterase inhibitor is the only known inhibitor for the subcomponent of the complement component 1 (C1r), C1s, coagulation factor XIIa, and kallikrein. Additionally, C1 esterase inhibitor is the main inhibitor for coagulation factor XIa of the intrinsic coagulation cascade.

HAE patients have low levels of endogenous or functional C1 esterase inhibitor. Although the events that induce attacks of angioedema in HAE patients are not well defined, it has been postulated that increased vascular permeability and the clinical manifestation of HAE attacks may be primarily mediated through contact system activation. Suppression of contact system activation by C1 esterase inhibitor through the inactivation of plasma kallikrein and factor XIIa is thought to modulate this vascular permeability by preventing the generation of bradykinin.[5]

Administration of Berinert to patients with C1 esterase inhibitor deficiency replaces the missing or malfunctioning protein in patients. The plasma concentration of C1 esterase inhibitor in healthy volunteers is approximately 270 mg/L.[6]

### 12.3 Pharmacokinetics

The pharmacokinetics of Berinert were evaluated in an open-label, uncontrolled, single-center study in 40 subjects (35 adults and 5 children under 16 years of age) with either mild or severe HAE. All subjects received a single intravenous injection of Berinert ranging from 500 units to 1500 units. Blood samples were taken during an attack-free period at baseline and for up to 72 hours after drug administration. Pharmacokinetic parameters were estimated using non-compartmental analysis (with or without baseline adjustment). Table 6 summarizes the pharmacokinetic parameters in 35 adult subjects with HAE.

**Table 6: Pharmacokinetic Parameters of Berinert in Adult Subjects with HAE by Non-compartmental Analysis (n=35)**

| Parameters | Unadjusted for baseline | Adjusted for baseline |
|---|---|---|
| $AUC_{(0-t)}$ (hr x IU/mL)* | 27.5 ± 8.5 (15.7-44.7) | 12.8 ± 6.7 (3.9-34.7) |
| CL (mL/hr/kg) | 0.60 ± 0.17 (0.34-0.96) | 1.44 ± 0.67 (0.43-3.85) |
| $V_{ss}$ (mL/kg) | 18.6 ± 4.9 (11.1-27.6) | 35.4 ± 10.5 (14.1-56.1) |
| Half-life (hrs) | 21.9 ± 1.7 (16.5-24.4) | 18.4 ± 3.5 (7.4-22.8) |
| MRT (hrs) | 31.5 ± 2.4 (23.7-35.2) | 26.4 ± 5.0 (10.7-33.0) |

AUC: Area under the curve
CL: Clearance
$V_{ss:}$ Volume steady state
MRT: Mean residence time
*Based on a 15 unit/kg dose. Numbers in parenthesis are the range.

Table 7 summarizes the pharmacokinetic parameters in 5 pediatric subjects (ages 6 through 13) with HAE. Based on adjusted baseline, compared to adults, the half-life of Berinert was shorter and clearance was faster in this limited cohort of children. However, the clinical implication of this difference is not known.

**Table 7: Pharmacokinetic Parameters of Berinert in Pediatric Subjects with HAE by Non-compartmental Analysis (n=5)**

| Parameters | Unadjusted for baseline | Adjusted for baseline |
|---|---|---|
| $AUC_{(0-t)}$ (hr x IU/mL)* | 25.45 ± 5.8 (16.8-31.7) | 9.78 ± 4.37 (4.1-15.2) |
| CL (mL/hr/kg) | 0.62 ± 0.17 (0.47-0.89) | 1.9 ± 1.1 (0.98-3.69) |
| $V_{ss}$ (mL/kg) | 19.8 ± 4.0 (16.7-26.1) | 38.8 ± 8.9 (31.9-54.0) |
| Half-life (hrs) | 22.4 ± 1.6 (20.3-24.4) | 16.7 ± 5.8 (7.4-22.5) |
| MRT (hrs) | 32.3 ± 2.3 (29.3-35.2) | 24.0 ± 8.3 (10.7-32.4) |

AUC: Area under the curve
CL: Clearance
$V_{ss:}$ Volume steady state
MRT: Mean residence time
*Based on a 15 unit/kg dose. Numbers in parenthesis are the range.

Studies have not been conducted to evaluate the pharmacokinetics of Berinert in special patient populations identified by gender, race, geriatric age, or the presence of renal or hepatic impairment.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies have been completed to evaluate the effects of Berinert on carcinogenesis, mutagenesis, and impairment of fertility.

### 13.2 Animal Toxicology and/or Pharmacology

Acute intravenous toxicity of Berinert was performed in mice at 1500, 3000, and 6000 units/kg and in rats at 1000, 2000, and 3000 units/kg. Berinert was well tolerated and no signs of toxicity were observed up to the highest dose administered.

Repeat intravenous dose toxicity was studied in a 14-day repeat dose study in rats at doses of 20, 60, and 200 units/kg/day. Berinert was well tolerated and no toxicity was observed up to the highest dose administered. No antibody response against C1 esterase inhibitor could be demonstrated in this study after multiple dosing with Berinert.

In a safety pharmacology study, Berinert was administered to beagle dogs intravenously at a cumulative dose of 3500 units/kg. No adverse effects were seen on the cardiovascular and respiratory system. There was a drop in body temperature, reduced coagulation time, and a decrease in thrombocyte aggregation.

Local intravenous tolerance of Berinert was evaluated in rabbits at 1500 units. No pathological changes were noted at the time of injection or during the following 24 hours. No pathological signs were noted during necropsy.

Thrombotic events have been reported in association with C1 esterase inhibitor products when used off-label and at higher than labeled doses[1] (*see Overdosage [10]*). Animal studies have confirmed the risk of thrombosis from intravenous administration of C1 esterase inhibitor products.[2]

## 14 CLINICAL STUDIES

The safety and efficacy of Berinert in the treatment of acute abdominal or facial attacks in subjects with hereditary angioedema were demonstrated in a placebo-controlled, double-blind, prospective, multinational, randomized, parallel-group, dose-finding, three-arm, clinical study, referred to as the randomized clinical trial (RCT). The RCT assessed the efficacy and safety of Berinert in 124 adult and pediatric subjects with C1 esterase inhibitor deficiency who were experiencing an acute moderate to severe attack of

abdominal or facial HAE. Subjects ranged in age from six to 72 years of age; 67.7% were female and 32.3% were male; and approximately 90% were Caucasian.

The study objectives were to evaluate whether Berinert shortens the time to onset of relief of symptoms of an abdominal or facial attack compared to placebo and to compare the efficacy of two different doses of Berinert. The time to onset of relief of symptoms was determined by the subject's response to a standard question posed at appropriate time intervals for as long as 24 hours after start of treatment, taking into account all single HAE symptoms. In addition the severity of the single HAE symptoms was assessed over time.

Subjects were randomized to receive a single 10 unit/kg body weight dose of Berinert (39 subjects), a single 20 unit/kg dose of Berinert (43 subjects), or a single dose of placebo (42 subjects) by slow intravenous infusion (recommended to be given at a rate of approximately 4 mL per minute) within 5 hours of an HAE attack. At least 70% of the subjects in each treatment group were required to be experiencing an abdominal attack.

If a subject experienced no relief or insufficient relief of symptoms by 4 hours after infusion, investigators had the option to administer a second infusion of Berinert (20 units/kg for the placebo group, 10 units/kg for the 10 units/kg group), or placebo (for the 20 units/kg group). This masked (blinded) "rescue study medication" was administered to subjects and they were then followed until complete resolution of symptoms was achieved. Adverse events were collected for up to 7 to 9 days following the initial administration of Berinert or placebo.

In the rare case that a subject developed life-threatening laryngeal edema after inclusion into the study, immediate start of open-label treatment with a 20 unit/kg body weight dose of Berinert was allowed.

All subjects who received confounding medication (rescue medication) before symptom relief were regarded as "non-responders." Therefore, time to onset of symptom relief was set at 24 hours if a subject received any rescue medication (ie, rescue study medication, narcotic analgesics, non-narcotic analgesics, anti-emetics, open-label C1 inhibitor, androgens at increased dose, or fresh frozen plasma) between 5 hours before administration of blinded study medication until time to onset of relief.

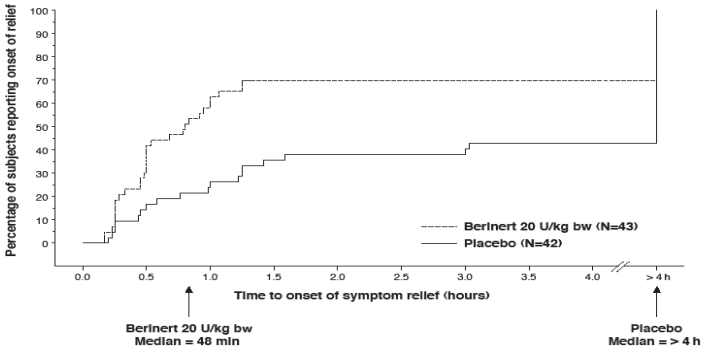
For the trial to be considered successful, the study protocol specified the following criteria for the differences between the Berinert 20 units/kg and the placebo group:

- The time to onset of relief of symptoms of the HAE attack had to achieve a one-sided p-value of less than 0.0249 for the final analysis, and at least one of the following criteria had to demonstrate a trend in favor of Berinert with a one-sided p-value of less than 0.1:
  - The proportion of subjects with increased intensity of clinical HAE symptoms between 2 and 4 hours after start of treatment with study medication compared to baseline, or
  - The number of vomiting episodes within 4 hours after start of study treatment.

Subjects treated with 20 units/kg body weight of Berinert experienced a significant reduction (p=0.0016; "Wilcoxon Rank Sum test") in time to onset of relief from symptoms of an HAE attack as compared to placebo (median of 48 minutes for Berinert 20 units/kg body weight, as compared to a median of >4 hours for placebo). The time to onset of relief from symptoms of an HAE attack for subjects in the 10 unit/kg dose of Berinert was not statistically significantly different from that of subjects in the placebo group.

Figure 9 is a Kaplan-Meier curve showing the percentage of subjects reporting onset of relief of HAE attack symptoms as a function of time. Individual time points beyond 4 hours are not presented on the graph, because the protocol permitted blinded rescue medication, analgesics, and/or anti-emetics to be administered starting 4 hours after randomized blinded study medication had been administered.

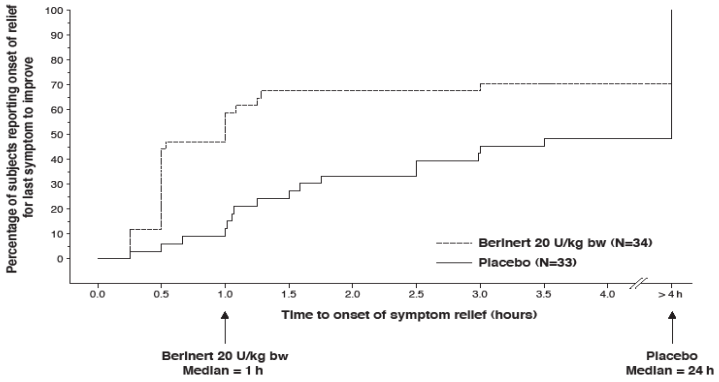
**Figure 9: Time to Onset of Symptom Relief With Imputation to >4 Hours for Subjects Who Received any Rescue Medication* or Non-narcotic Analgesics Before Start of Relief**




* Included rescue study medication (as blinded C1 inhibitor or placebo given as rescue medication), open-label C1 inhibitor, narcotic and non-narcotic analgesics, anti-emetics, androgens at increased dose or fresh frozen plasma.

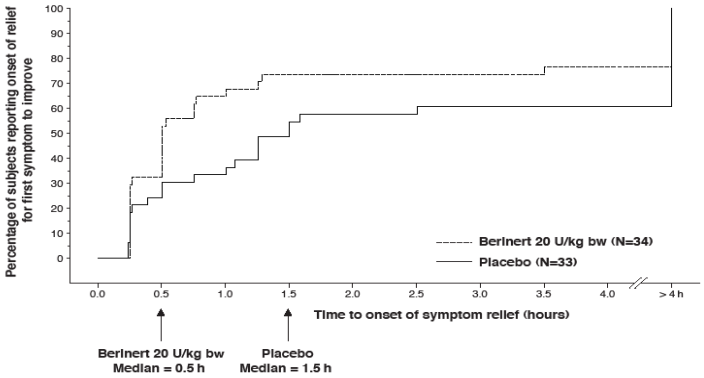
In addition, the efficacy of Berinert 20 units/kg body weight could be confirmed by observing a reduction in the intensity of single HAE symptoms at an earlier time compared to placebo. For abdominal attacks Figure 10a shows the time to start of relief of the *last* symptom to improve that was already present at baseline. Pre-defined abdominal HAE symptoms included pain, nausea, vomiting, cramps and diarrhea. Figure 10b shows the respective time to start of relief of the *first* symptom to improve that was already present at baseline.

**Figure 10a: Time to Start of Relief of the *Last* Symptom to Improve (Abdominal Attacks) with Imputation to >4 Hours for Subjects Who Received any Rescue Medication* Before Start of Relief**




* Included rescue study medication (as blinded C1 inhibitor or placebo given as rescue medication), open-label C1 inhibitor, narcotic and non-narcotic analgesics, anti-emetics, androgens at increased dose or fresh frozen plasma.

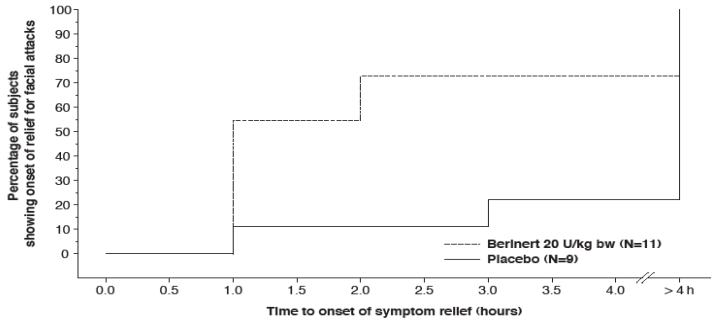
**Figure 10b: Time to Start of Relief of the *First* Symptom to Improve (Abdominal Attacks) With Imputation to >4 Hours for Subjects Who Received Any Rescue Medication* Before Start of Relief**




* Included rescue study medication (as blinded C1 inhibitor or placebo given as rescue medication), open-label C1 inhibitor, narcotic and non-narcotic analgesics, anti-emetics, androgens at increased dose or fresh frozen plasma.

For facial attacks, single HAE symptoms were recorded. In addition, photos were taken at pre-determined time points and assessed by the members of an independent Data Safety Monitoring Board (DSMB), who were blinded as to treatment, center and other outcome measures. The change in the severity of the edema when compared to baseline was assessed on a scale with outcomes "no change", "better", "worse" and "resolved". Figure 11 shows the time to start of relief from serial facial photographs by DSMB assessment.

**Figure 11: Time to Start of Relief From Serial Facial Photographs***




* Includes facial attacks in subjects with concomitant abdominal attacks.

Table 8 compares additional endpoints, including changes in HAE symptoms and use of rescue medication in subjects receiving Berinert at 20 units/kg body weight and placebo.

**Table 8: Changes in HAE Symptoms and Use of Rescue Medication in Subjects Receiving Berinert 20 units/kg Body Weight vs. Placebo**

| Additional Endpoints | Number (%) of Subjects Berinert 20 units/kg Body Weight Group (n=43) | Number (%) of Subjects Placebo Group (n=42) |
|---|---|---|
| Onset of symptom relief within 60 minutes after administration of study medication *(post-hoc)* | 27 (62.8%) | 11 (26.2%) |
| Onset of symptom relief within 4 hours after administration of study medication | 30 (69.8%) | 18 (42.9%) |
| Number of vomiting episodes within 4 hours after start of study treatment* | 6 episodes | 35 episodes |
| Worsened intensity of clinical HAE symptoms between 2 and 4 hours after administration of study medication compared to baseline† | 0 (0%) | 12 (28.6%) |
| Number (percent) of combined abdominal and facial attack subjects receiving rescue study medication, analgesics, or anti-emetics at any time prior to initial relief of symptoms | 13 (30.2%) | 23 (54.8%) |
| At least one new HAE symptom not present at baseline and starting within 4 hours after administration of study medication | 2 (4.6%) | 6 (14.3%) |

* p-value = 0.033
† p-value = 0.00008

Both the proportion of subjects with increased intensity of clinical HAE symptoms between 2 and 4 hours after start of treatment compared to baseline, and the number of vomiting episodes within 4 hours after start of study treatment demonstrated trends in favor of Berinert in comparison to placebo (p-values <0.1). Tables 9 through 12 present additional information regarding responses to treatment.

**Table 9: Proportion of Subjects Experiencing Start of Self-Reported Relief of Symptoms by 4 Hours by Attack Type**

| Attack Type | Berinert 20 units/kg Body Weight (Abdominal Subjects =34) (Facial Subjects = 9) (Other subjects = 0) | Placebo Group (Abdominal Subjects = 33) (Facial Subjects = 8) (Other subjects = 1)* |
|---|---|---|
| Abdominal | 24 (70.6%) | 15 (45.5%) |
| Facial | 6 (66.7%) | 3 (37.5%) |

* Laryngeal edema initially classified as facial edema.

**Table 10: Proportion of Subjects Experiencing Reduction in Severity of at Least One Individual HAE Attack Symptom by 4 Hours**

| Attack Type | Berinert 20 units/kg Body Weight (Abdominal Subjects = 34) (Facial Subjects = 9) | Placebo Group (Abdominal Subjects = 33) (Facial Subjects = 8) |
|---|---|---|
| Abdominal | 33 (97.1%) | 29 (87.9%) |
| Facial | 6 (66.7%) | 4 (50%) |

**Table 11: Proportion of Subjects with Facial Attacks Demonstrating Improvement in Serial Facial Photographs by 4 hours***

| Attack Type | Berinert 20 units/kg Body Weight (Subjects = 9) | Placebo Group (Subjects = 8) |
|---|---|---|
| Facial | 7 (77.8%) | 2 (25%) |

* Based on masked (blinded) evaluation by data safety monitoring board.

**Table 12: Proportion of Subjects with Abdominal and Facial Attacks Receiving Rescue Study Medication at any Time Prior to *Complete Relief of Symptoms***

| Attack Type | Berinert 20 U/kg Body Weight (Abdominal Subjects = 34) (Facial Subjects = 9) | Placebo Group (Abdominal Subjects = 33) (Facial Subjects = 8) |
|---|---|---|
| Abdominal | 7 (20.6%) | 17 (51.5%) |
| Facial | 1 (11.1%) | 6 (75%) |

No subjects treated with Berinert at 20 units/kg body weight reported worsening of symptoms at 4 hours after administration of study medication compared to baseline.

The study demonstrated that the Berinert 20 unit/kg body weight dose was significantly more efficacious than the Berinert 10 unit/kg body weight dose or placebo.

Open-Label Extension Study

Berinert was evaluated in a prospective, open-label, uncontrolled, multicenter extension study conducted at 10 centers in the US and Canada in subjects who had participated in the RCT study for the treatment of acute abdominal or facial attacks in subjects with hereditary angioedema.

The purpose of this ongoing extension study is to provide Berinert to subjects who had participated in the RCT study and who experienced any type of subsequent HAE attack (ie, abdominal, facial, peripheral, or laryngeal).

In a non-pre-specified interim safety analysis of the ongoing open-label extension study, a total of 56 subjects (19 males and 37 females, age range: 10 to 53 years) with 559 HAE attacks treated with 20 unit/kg body weight dose of Berinert per attack, were observed at the study site until onset of relief of HAE symptoms, and were followed up for adverse events for 7 to 9 days following treatment of each HAE attack (see *Adverse Reactions, Clinical Trials Experience [6.1]*). There were 49 subjects with abdominal attacks, 11 subjects with facial attacks, 28 subjects with peripheral attacks, and 12 subjects with laryngeal attacks.

## 15 REFERENCES


1. German Medical Profession's Drugs Committee. Severe thrombus formation of Berinert® HS. *Deutsches Ärzteblatt*. 2000;97:B-864.
2. Horstick, G *et al*. Application of C1-Esterase Inhibitor During Reperfusion of Ischemic Myocardium: Dose-Related Beneficial Versus Detrimental Effects. *Circulation.* 2002;104:3125-3131.
3. Carrell RW, Boswell DR. Serpins: the superfamily of plasma serine proteinase inhibitors. In: Barrett A, Salvesen G, eds. *Proteinase Inhibitors*. Amsterdam: Elsevier. 1986;12:403-420.
4. Harrison RA. Human C1 inhibitor: Improved isolation and preliminary structural characterization. *Biochemistry* 1983;22:5001-5007.
5. Davis AE, The pathophysiology of hereditary angioedema. *Clin Immunol.* 2005; 114:3-9.
6. Nuijens JH, Eerenberg-Belmer AJM, Huijbregts CCM, et al. Proteolytic inactivation of plasma C1 inhibitor in sepsis. *J Clin Invest*. 1989;84:443-450.


## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

Berinert is supplied in a single-use vial. Each carton contains a 500 unit vial of Berinert for reconstitution with 10 mL of diluent containing sterile water (meets USP chemistry requirements except for pH; pH 4.5-8.5). The components used in the packaging for Berinert are latex-free.

Each product package consists of the following:

| NDC Number | Component |
|---|---|
| 63833-825-02 | Carton (kit) containing one 500 unit vial of Berinert [NDC 63833-835-01], one 10 mL vial of diluent (sterile water) [NDC 63833-765-15], one Mix2Vial filter transfer set, and one alcohol swab. |

### 16.2 Storage and Handling

When stored at temperatures of 2-25°C (36-77°F), Berinert is stable for the period indicated by the expiration date on the carton and vial label (up to 30 months). Keep Berinert in its original carton until ready to use. Do not freeze. Protect from light.

## 17 PATIENT COUNSELING INFORMATION

**Inform patients to immediately report the following to their physician:**

- Signs and symptoms of allergic hypersensitivity reactions, such as hives, urticaria, tightness of the chest, wheezing, hypotension and/or anaphylaxis experienced during or after injection of Berinert *(see WARNINGS AND PRECAUTIONS/Hypersensitivity [5.1])*
- Signs and symptoms of thrombosis, such as new onset swelling and pain in the limbs or abdomen, new onset chest pain, shortness of breath, loss of sensation or motor power, or altered consciousness, vision, or speech *(see WARNINGS AND PRECAUTIONS/Thrombotic Events [5.2])*

Advise female patients to notify their physician if they become pregnant or intend to become pregnant during the treatment of acute abdominal or facial attacks of HAE with Berinert.

Advise patients to notify their physician if they are breastfeeding or plan to breastfeed.

Advise patients to consult with their healthcare professional prior to travel.

Advise patients that, because Berinert is made from human blood, it may carry a risk of transmitting infectious agents, eg, viruses, and, theoretically, the Creutzfeldt-Jakob (CJD) agent *(see WARNINGS AND PRECAUTIONS/Transmission of Infectious Agents [5.3] and Description [11])*. Inform patients of the risks and benefits of Berinert before prescribing or administering it to the patient.

### 17.1 FDA-Approved Patient Labeling – Patient Product Information (PPI)

**Berinert (BEAR-ĭ-nert)**
**C1 Esterase Inhibitor (Human)**
**Freeze-Dried Powder for Reconstitution**

This leaflet summarizes important information about BERINERT. Please read it carefully before using Berinert and each time you get a refill. There may be new information provided. This information does not take the place of talking with your healthcare provider, and it does not include all of the important information about BERINERT. If you have any questions after reading this, ask your healthcare provider.

**What is BERINERT?**

BERINERT is an injectable medicine used to treat swelling and/or painful attacks in adults and adolescents with hereditary angioedema (HAE). HAE is caused by the poor functioning or lack of a protein called C1 that is present in your blood and helps control inflammation (swelling) and parts of the immune system. Berinert contains C1 esterase inhibitor, a protein that helps control C1.

**Who should not use BERINERT?**

You should not use BERINERT if you have experienced life-threatening immediate hypersensitivity reactions, including anaphylaxis to the product.

**What should I tell my healthcare provider before BERINERT is given?**

Tell your healthcare provider about all of your medical conditions, including if you:

- Are pregnant or planning to become pregnant. It is not known if BERINERT can harm your unborn baby.
- Are breastfeeding or plan to breastfeed. It is not known if BERINERT passes into your milk and if it can harm your baby.
- Have a history of blood clotting problems. Blood clots (thrombosis) have occurred in patients receiving large amounts of Berinert. Very high doses of C1 esterase inhibitor could increase the risk of blood clots.

Tell your healthcare provider and pharmacist about all of the medicines you take, including all prescription and non-prescription medicines such as over-the-counter medicines, supplements, or herbal remedies.

**How is BERINERT given?**

Your healthcare provider will infuse BERINERT into your vein (intravenous injection). Before infusing, he or she must dissolve the BERINERT powder using the sterile water provided. Your healthcare provider will prescribe the dose that you should be given.

**What are the possible side effects of BERINERT?**

**Allergic reactions may occur with BERINERT. Call your healthcare provider or the emergency department right away if you have any of the following symptoms after using BERINERT:**

- **wheezing**
- **difficulty breathing**
- **chest tightness**
- **turning blue (look at lips and gums)**
- **fast heartbeat**
- **swelling of the face**
- **faintness**
- **rash**
- **hives**

Signs of a blood clot include:

- new onset of swelling and pain in the limbs or abdomen
- new onset of chest pain
- shortness of breath
- loss of sensation or control of muscles/muscle weakness on one side of the body
- altered consciousness, vision, or speech.

In clinical studies, the most severe side effect reported in subjects who received BERINERT was an increase in the severity of pain associated with HAE.

Other side effects patients experienced during clinical research studies include:

- subsequent HAE attack
- headache
- abdominal pain
- nausea
- muscle spasms
- pain
- diarrhea
- vomiting

Because BERINERT is made from human blood, it may carry a risk of transmitting infectious agents, eg, viruses, and, theoretically, the Creutzfeldt-Jakob (CJD) agent.

These are not all the possible side effects of BERINERT.

Tell your healthcare provider about any side effect that bothers you or that does not go away. You can also report side effects to the FDA at 1-800-FDA-1088.

**What else should I know about BERINERT?**

Medicines are sometimes prescribed for purposes other than those listed here. Do not use BERINERT for a condition for which it is not prescribed. Do not share BERINERT with other people, even if they have the same symptoms that you have.

This leaflet summarizes the most important information about BERINERT. If you would like more information, talk to your healthcare provider. You can ask your healthcare provider or pharmacist for information about BERINERT that was written for healthcare professionals.

Talk to your healthcare provider before traveling.

**This Patient Package Insert has been approved by the US Food and Drug Administration.**

Manufactured by:
**CSL Behring GmbH**
35041 Marburg, Germany
US License No. 1765

Distributed by:
**CSL Behring LLC**
Kankakee, IL 60901 USA

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use KALBITOR® safely and effectively. See full prescribing information for KALBITOR.**

**KALBITOR (ecallantide)**
**injection, for subcutaneous use**
**Initial U.S. Approval: 2009**

**WARNING: ANAPHYLAXIS**
***See full prescribing information for complete boxed warning***

**Anaphylaxis has been reported after administration of KALBITOR®. Because of the risk of anaphylaxis, KALBITOR should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema. Healthcare professionals should be aware of the similarity of symptoms between hypersensitivity reactions and hereditary angioedema and patients should be monitored closely. Do not administer KALBITOR to patients with known clinical hypersensitivity to KALBITOR [see *Contraindications (4), Warnings and Precautions (5.1), and Adverse Reactions (6)*].**

**----------INDICATIONS AND USAGE----------**
- KALBITOR is a plasma kallikrein inhibitor indicated for treatment of acute attacks of hereditary angioedema (HAE) in patients 16 years of age and older. (1)

**----------DOSAGE AND ADMINISTRATION----------**
- 30 mg (3 mL), administered subcutaneously in three 10 mg (1 mL) injections. If an attack persists, an additional dose of 30 mg may be administered within a 24 hour period. (2.1)
  - KALBITOR should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema. (2.2).

**----------DOSAGE FORMS AND STRENGTHS----------**
- Single use glass vial containing 10 mg/mL of ecallantide as a solution for injection. (3)

**----------CONTRAINDICATIONS----------**
- Do not administer KALBITOR to a patient who has known clinical hypersensitivity to KALBITOR. (4)

**----------WARNINGS AND PRECAUTIONS----------**
- Hypersensitivity Reactions Including Anaphylaxis: Anaphylaxis has occurred in 3.9% of treated patients. Administer KALBITOR in a setting equipped to manage anaphylaxis and hereditary angioedema. Given the similarity in hypersensitivity symptoms and acute HAE symptoms, monitor patients closely for hypersensitivity reactions (5).

**----------ADVERSE REACTIONS----------**
- The most common adverse reactions occurring in ≥3% of KALBITOR-treated patients and greater than placebo are headache, nausea, diarrhea, pyrexia, injection site reactions, and nasopharyngitis. (6)

**To report SUSPECTED ADVERSE REACTIONS, contact Dyax Corp. at 1-888-452-5248 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch***

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

**Revised: 12/2009**

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**FULL PRESCRIBING INFORMATION: CONTENTS***



*Sections or subsections omitted from the full prescribing information are not listed.

# FULL PRESCRIBING INFORMATION

**WARNING: ANAPHYLAXIS**

**Anaphylaxis has been reported after administration of KALBITOR. Because of the risk of anaphylaxis, KALBITOR should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema. Healthcare professionals should be aware of the similarity of symptoms between hypersensitivity reactions and hereditary angioedema and patients should be monitored closely. Do not administer KALBITOR to patients with known clinical hypersensitivity to KALBITOR. [see *Contraindications (4), Warnings and Precautions (5.1), and Adverse Reactions (6)*]**

## 1 INDICATIONS AND USAGE

KALBITOR® (ecallantide) is indicated for treatment of acute attacks of hereditary angioedema (HAE) in patients 16 years of age and older.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Dosing

The recommended dose of KALBITOR is 30 mg (3 mL), administered subcutaneously in three 10 mg (1 mL) injections. If the attack persists, an additional dose of 30 mg may be administered within a 24 hour period.

### 2.2 Administration Instructions

KALBITOR should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema.

KALBITOR should be refrigerated and protected from the light. KALBITOR is a clear, colorless liquid; visually inspect each vial for particulate matter and discoloration prior to administration. If there is particulate matter or discoloration, the vial should not be used.

Using aseptic technique, withdraw 1 mL (10 mg) of KALBITOR from the vial using a large bore needle. Change the needle on the syringe to a needle suitable for subcutaneous injection. The recommended needle size is 27 gauge. Inject KALBITOR into the skin of the abdomen, thigh, or upper arm. Repeat the procedure for each of the 3 vials comprising the KALBITOR dose. The injection site for each of the injections may be in the same or in different anatomic locations (abdomen, thigh, upper arm). There is no need for site rotation. Injection sites should be separated by at least 2 inches (5 cm) and away from the anatomical site of attack.

The same instructions apply to an additional dose administered within 24 hours. Different injection sites or the same anatomical location (as used for the first administration) may be used.

# 3 DOSAGE FORMS AND STRENGTHS

KALBITOR is a clear, colorless liquid free of preservatives. Each vial of KALBITOR contains ecallantide at a concentration of 10 mg/mL.

# 4 CONTRAINDICATIONS

Do not administer KALBITOR to a patient who has known clinical hypersensitivity to KALBITOR. [*see Warnings and Precautions (5.1)*].

# 5 WARNINGS AND PRECAUTIONS

## 5.1 Hypersensitivity Reactions, Including Anaphylaxis

Potentially serious hypersensitivity reactions, including anaphylaxis, have occurred in patients treated with KALBITOR. In 255 HAE patients treated with intravenous or subcutaneous KALBITOR in clinical studies, 10 patients (3.9%) experienced anaphylaxis. For the subgroup of 187 patients treated with subcutaneous KALBITOR, 5 patients (2.7%) experienced anaphylaxis. Symptoms associated with these reactions have included chest discomfort, flushing, pharyngeal edema, pruritus, rhinorrhea, sneezing, nasal congestion, throat irritation, urticaria, wheezing, and hypotension. These reactions occurred within the first hour after dosing.

Other adverse reactions indicative of hypersensitivity reactions included the following: pruritus (5.1%), rash (3.1%), and urticaria (2.0%).

Patients should be observed for an appropriate period of time after administration of KALBITOR, taking into account the time to onset of anaphylaxis seen in clinical trials. Given the similarity in hypersensitivity symptoms and acute HAE symptoms, patients should be monitored closely in the event of a hypersensitivity reaction.

KALBITOR should not be administered to any patients with known clinical hypersensitivity to KALBITOR [see *Contraindications (4)*].

# 6 ADVERSE REACTIONS

Hypersensitivity reactions, including anaphylaxis, have occurred in patients treated with KALBITOR [see *Contraindications (4) and Warnings and Precautions (5.1)*].

## 6.1 Clinical Trials Experience

Because clinical trials are conducted under varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflect exposure to KALBITOR in 255 patients with HAE treated with either intravenous or subcutaneous KALBITOR. Of the 255 patients,

66% of patients were female and 86% were Caucasian. Patients treated with KALBITOR were between the ages of 10 and 78 years.

Overall, the most common adverse reactions in 255 patients with HAE were headache (16.1%), nausea (12.9%), fatigue (11.8%), diarrhea (10.6%), upper respiratory tract infection (8.2%), injection site reactions (7.4%), nasopharyngitis (5.9%), vomiting (5.5%), pruritus (5.1%), upper abdominal pain (5.1%), and pyrexia (4.7%). Anaphylaxis was reported in 3.9% of patients with HAE. Injection site reactions were characterized by local pruritus, erythema, pain, irritation, urticaria, and/or bruising.

The incidence of adverse reactions below is based upon 2 placebo-controlled, clinical trials (EDEMA3® and EDEMA4®) in a total of 143 unique patients with HAE. Patients were treated with KALBITOR 30 mg subcutaneous or placebo. Patients were permitted to participate sequentially in both placebo-controlled trials; safety data collected during exposure to KALBITOR was attributed to treatment with KALBITOR, and safety data collected during exposure to placebo was attributed to treatment with placebo. Table 1 shows adverse reactions occurring in ≥3% of KALBITOR-treated patients that also occurred at a higher rate than in the placebo-treated patients in the two controlled trials (EDEMA3 and EDEMA4) of the 30 mg subcutaneous dose.

**Table 1: Adverse Reactions Occurring at ≥3% and Higher than Placebo in 2 Placebo Controlled Clinical Trials in Patients with HAE Treated with KALBITOR**

| | KALBITOR N=100 | Placebo N=81 |
|---|---|---|
| **Adverse Reactions** | n (%) [a] | n (%)[a] |
| Headache | 8 (8%) | 6 (7%) |
| Nausea | 5 (5%) | 1 (1%) |
| Diarrhea | 4 (4%) | 3 (4%) |
| Pyrexia | 4 (4%) | 0 |
| Injection site reactions | 3 (3%) | 1 (1%) |
| Nasopharyngitis | 3 (3%) | 0 |

[a] Patients experiencing more than 1 event with the same preferred term are counted only once for that preferred term.

Some patients in EDEMA3 and EDEMA4 received a second, open-label 30 mg subcutaneous dose of KALBITOR within 24 hours following the initial dose. Adverse reactions reported by these patients who received the additional 30 mg subcutaneous dose of KALBITOR were consistent with those reported in the patients receiving a single dose.

## 6.2 Immunogenicity

In the KALBITOR HAE program, patients developed antibodies to KALBITOR. Rates of seroconversion increased with exposure to KALBITOR over time. Overall, 7.4% of patients seroconverted to anti-ecallantide antibodies. Neutralizing antibodies to ecallantide were determined *in vitro* to be present in 4.7% of patients.

Anti-ecallantide and anti-*P. pastoris* IgE antibodies were also detected. Patients who seroconvert may be at a higher risk of a hypersensitivity reaction. The long-term effects of antibodies to KALBITOR are not known.

The test results for the ecallantide program were determined using one of two assay formats: ELISA and bridging electrochemiluminescence (ECL). As with all therapeutic proteins, there is a potential for immunogenicity with the use of KALBITOR. The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to KALBITOR with the incidence of antibodies to other products may be misleading.

# 7 DRUG INTERACTIONS

No formal drug interactions studies were performed. No *in vitro* metabolism studies were performed.

# 8 USE IN SPECIFIC POPULATIONS

## 8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled trials of KALBITOR in pregnant women. KALBITOR has been shown to cause developmental toxicity in rats, but not rabbits. Because animal reproductive studies are not always predictive of human response, KALBITOR should be used during pregnancy only if clearly needed.

In rats, intravenous KALBITOR at an intravenous dose approximately 13 times the maximum recommended human dose (MRHD) on a mg/kg basis caused increased numbers of early resorptions and percentages of resorbed conceptuses per litter in the presence of mild maternal toxicity. No development toxicity was observed in rats that received an intravenous dose approximately 8 times the MRHD on a mg/kg basis. There were no adverse effects of KALBITOR on embryofetal development in rats that received subcutaneous doses up to approximately 2.4 times the MRHD on an AUC basis, and in rabbits that received intravenous doses up to approximately 6 times the MRHD on an AUC basis.

## 8.2 Labor and Delivery

No information is available on the effects of KALBITOR during labor and delivery.

## 8.3 Nursing Mothers

It is not known whether ecallantide is excreted in human milk. Caution should be exercised when ecallantide is administered to a nursing woman.

### 8.4 Pediatric Use

Safety and effectiveness of KALBITOR in patients below 16 years of age have not been established.

### 8.5 Geriatric Use

Clinical trials of KALBITOR did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

## 10 OVERDOSAGE

There have been no reports of overdose with KALBITOR. HAE patients have received single doses up to 90 mg intravenously without evidence of dose-related toxicity. No deaths occurred in monkeys that received intravenous or subcutaneous doses up to 25 mg/kg (approximately 22 times the MRHD on an AUC basis).

## 11 DESCRIPTION

KALBITOR (ecallantide) is a human plasma kallikrein inhibitor for injection for subcutaneous use.

KALBITOR is a clear and colorless, sterile, and nonpyrogenic solution. Each vial contains 10 mg ecallantide as the active ingredient, and the following inactive ingredients: 0.76 mg disodium hydrogen orthophosphate (dihydrate), 0.2 mg monopotassium phosphate, 0.2 mg potassium chloride, and 8 mg sodium chloride in water for injection, USP. KALBITOR is preservative free, with a pH of approximately 7.0. A 30 mg dose is supplied as 3 vials each containing 1 mL of 10 mg/mL KALBITOR. Each vial contains a slight overfill. Vials are intended for single use. Ecallantide is a 60-amino-acid protein produced in *Pichia pastoris* yeast cells by recombinant DNA technology.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Hereditary angioedema (HAE) is a rare genetic disorder caused by mutations to C1-esterase-inhibitor (C1-INH) located on Chromosome 11q and inherited as an autosomal dominant trait. HAE is characterized by low levels of C1-INH activity and low levels of C4. C1-INH functions to regulate the activation of the complement and intrinsic coagulation (contact system pathway) and is a major endogenous inhibitor of plasma kallikrein. The kallikrein-kinin system is a complex proteolytic cascade involved in the initiation of both inflammatory and coagulation pathways. One critical aspect of this pathway is the conversion of High Molecular Weight (HMW) kininogen to bradykinin by the protease plasma kallikrein. In HAE, normal regulation of plasma kallikrein activity and the classical complement cascade is therefore not present. During

attacks, unregulated activity of plasma kallikrein results in excessive bradykinin generation. Bradykinin is a vasodilator which is thought by some to be responsible for the characteristic HAE symptoms of localized swelling, inflammation, and pain.

KALBITOR is a potent (Ki = 25 pM), selective, reversible inhibitor of plasma kallikrein. KALBITOR binds to plasma kallikrein and blocks its binding site, inhibiting the conversion of HMW kininogen to bradykinin. By directly inhibiting plasma kallikrein, KALBITOR reduces the conversion of HMW kininogen to bradykinin and thereby treats symptoms of the disease during acute episodic attacks of HAE.

## 12.2 Pharmacodynamics

No exposure-response relationships for KALBITOR to components of the complement or kallikrein-kinin pathways have been established.

The effect of KALBITOR on activated partial thromboplastin time (aPTT) was measured because of potential effect on the intrinsic coagulation pathway. Prolongation of aPTT has been observed following intravenous dosing of KALBITOR at doses ≥20 mg/m$^2$. At 80 mg administered intravenously in healthy subjects, aPTT values were prolonged approximately two-fold over baseline values and returned to normal by 4 hours post-dose.

For patients taking KALBITOR, no significant QT prolongation has been seen. In a randomized, placebo-controlled trial (EDEMA4) studying the 30 mg subcutaneous dose versus placebo, 12-lead ECGs were obtained at baseline, 2 hours and 4 hours post-dose (covering the time of expected $C_{max}$), and at follow-up (day 7). ECGs were evaluated for PR interval, QRS complex, and QTc interval. KALBITOR had no significant effect on the QTc interval, heart rate, or any other components of the ECG.

## 12.3 Pharmacokinetics

Following the administration of a single 30 mg subcutaneous dose of KALBITOR to healthy subjects, a mean (± standard deviation) maximum plasma concentration of 586 ± 106 ng/mL was observed approximately 2 to 3 hours post-dose. The mean area under the concentration-time curve was 3017 ± 402 ng*hr/mL. Following administration, plasma concentration declined with a mean elimination half-life of 2.0 ± 0.5 hours. Plasma clearance was 153 ± 20 mL/min and the volume of distribution was 26.4 ± 7.8 L. Based on a population pharmacokinetic analysis, body weight, age, and gender were not found to affect KALBITOR exposure significantly. Ecallantide is a small protein (7054 Da) and renal elimination in the urine of treated subjects has been demonstrated.

No pharmacokinetic data are available in patients or subjects with hepatic or renal impairment.

# 13 NONCLINICAL TOXICOLOGY

## 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no animal or human studies to assess the carcinogenic or mutagenic potential of KALBITOR (ecallantide).

KALBITOR had no effects on fertility and reproductive performance in rats at subcutaneous doses up to 25 mg/kg/day (approximately 21 times the MRHD on a mg/kg basis).

## 13.2 Animal Toxicology

Reproductive Toxicology Studies

KALBITOR has been shown to cause developmental toxicity in rats, but not rabbits. Treatment of rats with an intravenous dose of 15 mg/kg/day (approximately 13 times the MRHD on a mg/kg basis) caused increased numbers of early resorptions and percentages of resorbed conceptuses per litter in the presence of mild maternal toxicity. However, no development toxicity was observed in rats that received an intravenous dose of 10 mg/kg/day (approximately 8 times the MRHD on a mg/kg basis). KALBITOR was not teratogenic in rats at subcutaneous doses up to 20 mg/kg/day (approximately 2.4 times the MRHD on an AUC basis) and rabbits that received intravenous doses up to 5 mg/kg/day (approximately 6 times the MRHD on an AUC basis).

# 14 CLINICAL STUDIES

The safety and efficacy of KALBITOR was evaluated in 2 randomized, double-blind, placebo-controlled trials (EDEMA4 and EDEMA3) in 168 patients with HAE. Patients having an attack of hereditary angioedema, at any anatomic location, with at least 1 moderate or severe symptom, were treated with 30 mg subcutaneous KALBITOR or placebo. Because patients could participate in both trials, a total of 143 unique patients participated. Of the 143 patients, 94 were female, 123 were Caucasian, and the mean age was 36 years. There were 64 patients with abdominal attacks, 55 with peripheral attacks, and 24 with laryngeal attacks.

In both trials, the effects of KALBITOR were evaluated using the Mean Symptom Complex Severity (MSCS) score and the Treatment Outcome Score (TOS). These measures evaluated the severity of attack symptoms at all anatomical locations (MSCS score) and response to therapy (TOS).

MSCS score is a point-in-time measure of symptom severity. At baseline, 4 hours, and 24 hours, patients rated the severity on a categorical scale (0 = normal, 1 = mild, 2 = moderate, 3 = severe) for symptoms at each affected anatomical location. Ratings were averaged to obtain the MSCS score. A decrease in MSCS score reflected an improvement in symptoms.

TOS is a measure of symptom response to treatment. At 4 hours and 24 hours, patient assessment of response characterized by their change from baseline in symptom severity and collected by anatomic site of attack involvement, was recorded on a categorical scale (significant improvement [100], improvement [50], same [0], worsening [-50], significant worsening [-100]). The response at each anatomic site was weighted by baseline severity and then the weighted scores across all involved sites were averaged to calculate the TOS. A TOS value >0 reflected an improvement in symptoms from baseline.

**EDEMA4**

EDEMA4 was a randomized, double-blind, placebo-controlled trial in which 96 patients were randomized 1:1 to receive KALBITOR 30 mg subcutaneous or placebo for acute attacks of HAE. The primary endpoint was the change from baseline in MSCS score at 4 hours, and the TOS at 4 hours was a key secondary endpoint. Patients treated with KALBITOR demonstrated a greater decrease from baseline in the MSCS than placebo and a greater TOS than patients with placebo and the results were statistically significant (Table 2). At 24 hours, patients treated with KALBITOR also demonstrated a greater decrease from baseline in the MSCS than placebo (-1.5 vs. -1.1; p = 0.04) and a greater TOS (89 vs. 55, p = 0.03).

**Table 2: Change in MSCS Score and TOS at 4 Hours**

| | EDEMA4 | | EDEMA3 | |
|---|---|---|---|---|
| | KALBITOR (N=48) | Placebo (N=48) | KALBITOR (N=36) | Placebo (N=36) |
| **Change in MSCS Score at 4 Hours** | | | | |
| n | 47 | 42 | 34 | 35 |
| Mean | -0.8 | -0.4 | -1.1 | -0.6 |
| 95% CI | -1.0, -0.6 | -0.6, -0.1 | -1.4, -0.8, | -0.8, -0.4 |
| P-value | 0.010 | | 0.041 | |
| **TOS at 4 Hours** | | | | |
| n | 47 | 42 | 34 | 35 |
| Mean | 53 | 8 | 63 | 36 |
| 95% CI | 39, 68 | -12, 28 | 49, 76 | 17, 54 |
| P-value | 0.003 | | 0.045 | |

MSCS: Mean Symptom Complex Severity
TOS: Treatment Outcome Score
CI: confidence interval

More patients in the placebo group (24/48, 50%) required medical intervention to treat unresolved symptoms within 24 hours compared to the KALBITOR-treated group (16/48, 33%).

Some patients reported improvement following a second 30 mg subcutaneous dose of KALBITOR, administered within 24 hours following the initial dose for symptom persistence or relapse, but efficacy was not systematically assessed for the second dose.

**EDEMA3**

EDEMA3 was a randomized, double-blind, placebo-controlled trial in which 72 patients were randomized 1:1 to receive KALBITOR or placebo for acute attacks of HAE. EDEMA3 was similar in design to EDEMA4 with the exception of the order of the prespecified efficacy endpoints. In EDEMA3, the primary endpoint was the TOS at 4 hours, and the key secondary efficacy endpoint was the change from baseline in MSCS at 4 hours. As in EDEMA4, patients treated with KALBITOR demonstrated a greater decrease from baseline in the MSCS than placebo and a greater TOS than patients treated with placebo and the results were statistically significant (Table 2).

In addition, more patients in the placebo group (13/36, 36%) required medical intervention to treat unresolved symptoms within 24 hours compared to the KALBITOR-treated group (5/36, 14%).

## 16 HOW SUPPLIED/STORAGE AND HANDLING

KALBITOR (ecallantide) is supplied as three 10 mg/mL single-use vials packaged in a carton. Each vial contains 10 mg of ecallantide. Each vial contains a slight overfill.

- NDC (47783-101-01): 3 single-use vials in 1 carton

KALBITOR should be kept refrigerated (2ºC to 8ºC/36ºF to 46ºF). Vials removed from refrigeration should be stored below 86ºF/30ºC and used within 14 days or returned to refrigeration until use.

Protect vials from light until use.

Do not use beyond the expiration date.

## 17 PATIENT COUNSELING INFORMATION

*See Medication Guide*

- Patients should be advised that KALBITOR may cause anaphylaxis and other hypersensitivity reactions. Patients should be advised that KALBITOR should be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema. Patients who have known clinical hypersensitivity to KALBITOR should be instructed not to receive additional doses of KALBITOR. [see *Boxed Warning*, *Contraindications (4), and Warnings and Precautions (5.1)*]

- Patients should be advised to consult the Medication Guide for additional information regarding the risk of anaphylaxis and other hypersensitivity reactions.

# Medication Guide

# KALBITOR® (KAL-bi-tor)

# (ecallantide)

Read this Medication Guide before you start receiving KALBITOR and before each treatment. There may be new information. This Medication Guide does not take the place of talking to your doctor about your medical condition or your treatment.

**What is the most important information that I should know about KALBITOR?**

Serious allergic reactions may happen in some people who receive KALBITOR. These allergic reactions can be life-threatening and usually happen within 1 hour after receiving KALBITOR.

- KALBITOR should be given to you by a doctor or nurse in a healthcare setting where serious allergic reactions and hereditary angioedema (HAE) can be treated.
- Symptoms of a serious allergic reaction to KALBITOR can be similar to the symptoms of HAE, the condition that you are being treated for. Your doctor or nurse should watch you for any signs of a serious allergic reaction after treatment with KALBITOR.
- **Tell your doctor or nurse right away if you have any of these symptoms of a serious allergic reaction during or after treatment with KALBITOR:**
    - wheezing, shortness of breath, cough, chest tightness, or trouble breathing
    - dizziness, fainting, fast or weak heartbeat, or feeling nervous
    - reddening of the face, itching, hives, or feeling warm
    - swelling of the throat or tongue, throat tightness, hoarse voice, or trouble swallowing
    - runny nose or sneezing

**What is KALBITOR?**

KALBITOR is a prescription medicine used to treat sudden attacks of hereditary angioedema (HAE).
KALBITOR is not a cure for HAE.
It is not known if KALBITOR is safe and effective in children under 16 years of age.

**Who should not receive KALBITOR?**

Do not receive KALBITOR if you are allergic to KALBITOR.

**What should I tell my doctor before I receive KALBITOR?**

Before receiving KALBITOR, tell your doctor if you:

- have ever had an allergic reaction to KALBITOR. See "Who should not take KALBITOR?"
- are pregnant or plan to become pregnant. It is not known if KALBITOR will harm your unborn baby.
- are breast-feeding or plan to breast-feed. It is not known if KALBITOR passes into your breast milk.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.
Know the medicines you take. Keep a list of them to show to your doctor and pharmacist when you get a new medicine.

**How will I receive KALBITOR?**

For each dose, you will receive 3 injections just under the skin (subcutaneous or SC injections) of your abdomen, thigh, or upper arm.

**What are the possible side effects?**

**KALBITOR can cause serious allergic reactions.** See "What is the most important information I should know about KALBITOR?").

Common side effects of KALBITOR include:

- headache
- nausea
- diarrhea
- fever
- injection site reactions, such as redness, rash, swelling, itching, or bruising
- stuffy nose

Call your doctor for advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**General information about KALBITOR**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This Medication Guide gives you the most important information about KALBITOR. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about KALBITOR that is written for health professionals.

**What are the ingredients of KALBITOR?**

Active Ingredient: ecallantide

Inactive ingredients: disodium hydrogen orthophosphate (dihydrate), monopotassium phosphate, potassium chloride, sodium chloride in water for injection.

Manufactured for: Dyax Corp.

300 Technology Square, Cambridge, MA 02139

Issued December 2009

This Medication Guide has been approved by the U.S. Food and Drug Administration.

U.S. License No. 1789

# VI. References

# Bibliography

Frank MM. Hereditary angioedema, J Allergy Clin Immunol 2008; 121(2): S398-S401

Frank MM. Complement disorders and hereditary angioedema, J Allergy Clin Immunol 2010;125:S262-71

Zuraw BL. Clinical Practice: Hereditary Angioedema, N Engl J Med 2008; 359:1027-36

Bowen et al. 2010. International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. Allergy, Asthma & Clinical Immunology 2010; 6(1):24