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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW ADDENDUM

Application Type	NDA
Application Number(s)	22-150
Priority or Standard	Standard-Resubmission
Submit Date(s)	February 25, 2011
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Division/Office	Division of Pulmonary, Allergy, and Rheumatology Products
Reviewer Name(s)	Brian Oscar Porter, M.D. Ph.D., M.P.H.
Addendum Date	August 16, 2011
Established Name	Icatibant
(Proposed) Trade Name	Firazyr
Therapeutic Class	Bradykinin type 2 receptor antagonist
Applicant	Shire (for Jerini, U.S.)
Formulation(s)	Injectable solution in pre-filled syringe
Dosing Regimen	30 mg SC; may be given up to every 6 hours (no more than 3 injections within 24 hr)
Indication(s)	Treatment of acute attacks of hereditary angioedema

This Clinical Review Addendum clarifies the data presentation in the original NDA Primary Clinical Review by Dr. Brian Porter (submitted July 25, 2011) with regard to efficacy outcomes for laryngeal HAE attacks observed in the Phase 3 icatibant development program. In Section 6.1.5 Analysis of Secondary Endpoint(s) of the original NDA Clinical Review, the data discussed under the heading Detailed Analysis of Laryngeal HAE Attacks (pages 72-76) reflect the intent-to-treat (ITT) analysis for both the active treatment (icatibant) and placebo groups for FAST-3. Therefore, while the ITT analyses presented in this section (including Tables 19 and 20) are accurate, this Addendum clarifies that these subjects do not represent a true placebo comparator group.

Only two subjects were originally randomized to placebo in FAST-3 for the purposes of the ITT analysis. However, of these, one subject (054-320-011) received icatibant as rescue medication 3.4 hours after receiving placebo, due to worsening laryngeal symptoms. The second subject (054-356-004) never received blinded placebo as originally assigned, due to worsening laryngeal symptoms that led the Investigator to administer open-label icatibant to this patient, rather than blinded study treatment. This was considered a protocol violation, as discussed in the original Clinical Review under Section 3.2 Compliance with Good Clinical Practices. Thus, although both of these subjects are classified as placebo-recipients for the purposes of the ITT analysis, the laryngeal attack population lacks a true placebo comparator group. Therefore, as shown in Table 19 under the heading Patient-based Symptom Severity Scores (pages 72-73), although there was a greater decrease in self-reported symptoms at Hour 4 for subjects originally randomized to placebo versus icatibant in FAST-3, both these placebo subjects had actually received icatibant by Hour 4 post-dosing. In turn, the utility of this randomized ITT comparison is questionable. Moreover, with regard to rescue medication use, as discussed in the original Clinical Review under the heading Use of Rescue Medications (page 76), these data are difficult to interpret without a randomized placebo comparator group, although it is noteworthy that both subjects originally randomized to placebo in FAST-3 received icatibant either as a rescue medication or as open-label treatment, due to worsening laryngeal symptoms.

This Addendum is provided only for clarification of the data presentation in Section 6.1.5, as no conclusions discussed in the original Primary Clinical Review are affected.

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/s/

BRIAN PORTER

08/16/2011

Addendum to NDA Primary Clinical Review

SUSAN L LIMB

08/23/2011

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-150
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Submit Date(s)	February 25, 2011
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Division/Office	Division of Pulmonary, Allergy, and Rheumatology Products
Reviewer Name(s)	Brian Oscar Porter, M.D. Ph.D., M.P.H.
Review Completion Date	July 27, 2011
Established Name	Icatibant
(Proposed) Trade Name	Firazyr
Therapeutic Class	Bradykinin type 2 receptor antagonist
Applicant	Shire (for Jerini, U.S.)
Formulation(s)	Injectable solution in pre-filled syringe
Dosing Regimen	30 mg SC; may be given up to every 6 hours (no more than 3 injections within 24 hr)
Indication(s)	Treatment of acute attacks of hereditary angioedema
Intended Population(s)	Adults $\geq$ 18 years with HAE

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List of Abbreviations

<i>HAE</i>	hereditary angioedema
<i>C1-INH</i>	complement 1 esterase inhibitor
<i>VAS</i>	Visual Analog Scale
<i>FFP</i>	fresh frozen plasma
<i>PI</i>	Prescribing Information
<i>SPA</i>	Special Protocol Assessment
<i>VDS</i>	Verbal Descriptor Scale
<i>AE</i>	adverse event
<i>DSI</i>	Division of Scientific Investigations
<i>CDRH</i>	Center for Devices and Radiologic Health
<i>QT-IRT</i>	QT-Interdisciplinary Review Team
<i>ACE</i>	angiotensin converting enzyme
<i>ITT</i>	intent-to-treat
<i>TEAE</i>	treatment-emergent adverse event
<i>CTCAE</i>	Common Terminology Criteria for Adverse Events
<i>ULN</i>	upper limit of normal
<i>NML</i>	normal range
<i>ECG</i>	electrocardiogram
<i>TSQM</i>	Treatment Satisfaction Questionnaire for Medication
<i>SGSS</i>	Shire Global Safety Systems
<i>ADR</i>	adverse drug reaction
<i>PADAC</i>	Pulmonary-Allergy Drugs Advisory Committee

1 Recommendations/Risk-Benefit Assessment

1.1 Recommendation on Regulatory Action

According to a review of the clinical data, the recommended action for this Complete Response is Approval. In brief, Jerini US, Inc. originally submitted NDA 22-150 via the 505(b)(1) pathway on October 22, 2007, to seek approval for icatibant for the treatment of HAE, which was later revised to the treatment of acute attacks of HAE. The Agency issued a Not Approvable action letter for the original NDA on April 23, 2008, which cited multiple CMC deficiencies, a lack of long-term nonclinical toxicity studies, incomplete characterization of age and gender effects on pharmacokinetics, and several clinical deficiencies in the icatibant development program: 1) the failure to demonstrate the efficacy and safety of icatibant for the proposed indication, based on the results of the original pivotal Phase 3 program (e.g., lack of a statistically significant treatment effect versus placebo, the choice of a questionable active control comparator agent, the lack of established validity of the primary patient reported outcomes measure); 2) the lack of data demonstrating the safe use of Firazyr in non-healthcare settings, such as with self-injection by patients; 3) the need to further define dose selection in a sufficient number of patients based on the clinical endpoint or other validated and related biomarkers. In turn, on February 25, 2011, Shire HGT for Jerini US, Inc. submitted a Complete Response to this Not Approvable action letter, with additional information submitted to address the nonclinical and CMC deficiencies, as well as each of the clinical deficiencies, as discussed in this Clinical Review.

This review concludes that the Complete Response for NDA 22-150 supports the approval of icatibant (Firazyr) injectable solution in a pre-filled syringe for the treatment of acute attacks of hereditary angioedema (HAE) in adults 18 years of age and older. The Applicant has conducted an additional Phase 3 placebo-controlled efficacy trial (FAST-3) to establish the efficacy of icatibant for the proposed indication and has submitted a Complete Study Report for this trial, as well as an Integrated Summary of Efficacy in the context of results of two prior pivotal Phase 3 trials submitted with the original NDA (FAST-1 and FAST-2). In addition, another Phase 3 trial (FAST-4) was conducted to establish the safety and efficacy of self-administered icatibant by non-healthcare workers in non-healthcare settings for the treatment of acute HAE attacks. When considered in conjunction with pooled safety data from the icatibant Phase 3 development program, the efficacy data presented in this Complete Response supports approval of icatibant for the treatment of acute HAE attacks in adults.

1.2 Risk-Benefit Assessment

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. While two products are currently approved and available in the U.S. for the prophylaxis of HAE attacks (Cinryze, a highly purified human plasma-derived C1-INH replacement product, and danazol, a synthetic androgenic steroid), only two products are currently approved in the U.S. to treat acute HAE attacks: Berinert (a human plasma-derived 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 of bradykinin type 2 receptor antagonists. 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-bradykinin receptor pathway, as a novel treatment for acute HAE attacks in adults. 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) in adults with Type I or Type II HAE, as well as an additional Phase 3 trial, FAST-4, which evaluated the safety and efficacy of self-administered icatibant by non-healthcare workers for acute HAE attacks. FAST-1 and FAST-3 were both randomized, placebo-controlled, parallel group trials, whereas FAST-2 was similarly designed, but utilized tranexamic acid, an agent unapproved for the treatment of acute HAE attacks in the U.S., as a control treatment. In contrast, FAST-4 was an open-label, uncontrolled trial, focused primarily on evaluating the safety of the proposed mode of delivery (i.e., self-injection using a pre-filled syringe). Both FAST-3 and FAST-4 were conducted in response to clinical deficiencies cited in a Not Approvable action letter that was issued following review of the original icatibant NDA submission, which included FAST-1 and FAST-2. In turn, FAST-3 and FAST-4 are reviewed in detail in this Complete Response review, within the context of the original icatibant Phase 3 clinical program (FAST-1 and FAST-2) that was reviewed in the initial NDA submission.

The original Phase 3 icatibant program did not establish the safety and effectiveness of icatibant for the proposed indication. Using time to onset of primary symptom relief based on VAS assessments as the primary efficacy endpoint, FAST-1 failed to demonstrate a statistical difference between treatment groups, although a non-significant numerical trend was noted in favor of the icatibant group. While the results of

FAST-2 demonstrated a statistically significant decrease in time to symptom relief onset in the icatibant group versus control subjects, the use of tranexamic acid as a control treatment was questioned by the Division, as this agent is unapproved for this indication in the U.S., and its effects on HAE symptomatology have not been fully characterized. Thus, the use of tranexamic acid as a comparator could potentially inflate a positive treatment effect attributed to icatibant, if tranexamic acid were to have a negative treatment effect on HAE symptoms. In turn, the results of an additional randomized, placebo-controlled trial, FAST-3, were key to characterizing the risk-benefit profile of icatibant for the proposed indication. These Phase 3 trials all utilized a PRO measure, the Visual Analog Scale (VAS), to quantify self-reported (patient-assessed) symptomatology. Validation studies of this outcome measure were reviewed with the original NDA submission and ultimately found to be consistent with the Agency's guidance on PRO development. However, given the novelty of VAS-based outcome measures in HAE development programs and the Division's lack of regulatory experience with such efficacy endpoints, the Division concluded during the original NDA review that the validity of the VAS as used in the icatibant development program had not been fully established.

The additional Phase 3 trials submitted in the icatibant Complete Response (FAST-3 and FAST-4) addressed the clinical deficiencies of the original development program. As recommended by the Division, FAST-3 was similar in design and scope to FAST-1 and FAST-2 and was noted to have an increased proportion of subjects enrolled from domestic (U.S.) study sites. Although the primary efficacy endpoint was designated as a composite VAS-based symptom score encompassing both cutaneous and abdominal HAE symptoms (VAS-3: abdominal pain, skin pain, skin swelling), 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. The results of FAST-3 demonstrated a highly significant statistical difference in time to onset of symptom relief based on both primary VAS symptom rating and composite VAS-3 score, in favor of the icatibant group over placebo. This significant difference favoring icatibant was maintained when efficacy data were examined separately for cutaneous versus abdominal attacks. In addition, a *post hoc* analysis of time to symptom onset based on the composite VAS-3 score also demonstrated statistically significant group differences in FAST-1 and FAST-2, which favored icatibant-recipients. Secondary efficacy endpoint analyses, subgroup analyses, and sensitivity analyses generally support the results of the primary analysis for FAST-3. Thus, if the questionable efficacy results of FAST-1 and FAST-2 are taken as supportive data, the definitive efficacy results of FAST-3 support the approval of icatibant for the proposed indication of the treatment of acute HAE attacks in adults. Efficacy data generated from the icatibant self-administration trial (FAST-4) demonstrated a consistent treatment effect of icatibant, with regard to time to onset of symptom relief, confirming the effectiveness of icatibant when self-injected by non-healthcare workers in non-healthcare settings.

The safety profile of icatibant as determined from an individual review of each of the Phase 3 efficacy trials, as well as a pooled safety analysis of all subjects receiving blinded treatment for an initial HAE attack during the randomized treatment phase of these trials, demonstrates adequate safety and tolerability, thereby supporting the approval of this agent for this rare but potentially life-threatening indication. Although the safety database is relative small, given the rarity of HAE, which is a designated orphan disease, the feasibility of conducting larger controlled trials is questionable, particularly with regard to laryngeal HAE attacks, which are rarer than cutaneous and abdominal HAE attacks. Despite its limited scope, however, the icatibant safety database did not reveal any significant safety signals, which are uniquely attributable to icatibant, other than the development of local injection site reactions in nearly all icatibant recipients that far exceeded rates seen with placebo treatment. These included injection site erythema, swelling, pruritus, burning sensation, and warmth. However, these reactions were rarely severe and generally improved without medical intervention within several hours of icatibant injection. Given the potentially life-threatening effects of HAE, these adverse events are considered acceptable as a consequence of effective treatment. Icatibant use was also shown to minimize rescue medication use (i.e., C1-INH replacement therapy, opioids, anti-emetics, NSAIDs, corticosteroids) during acute HAE attacks.

Moreover, in contrast to adverse drug reactions that have been reported for both Berinert (C1-INH replacement) and Kalbitor (ecallantide), no hypersensitivity reactions were observed following icatibant treatment in the Phase 3 clinical program. In addition, studies across all three pivotal efficacy trials revealed no significant risk of immunogenicity, which was not unexpected for this decapeptide drug. Postmarketing data from the European Union submitted in this Complete Response, which the Applicant estimates encompasses 5,379 patient exposures to Firazyr since the time of E.U. approval on July 11, 2008, through July 11, 2010, have also not revealed any safety signals related to drug hypersensitivity. Thus, this decreased risk of drug-specific antibody formation may represent a significant benefit of icatibant over currently approved treatments for acute HAE attacks.

A review of safety data from FAST-4 suggests that icatibant pre-filled syringes are a safe and effective mode of drug delivery outside of a clinical setting by patients who are non-healthcare workers. In contrast, ecallantide, which is also delivered subcutaneously, is labeled for delivery exclusively by qualified healthcare workers only in clinical settings equipped to diagnose and treat anaphylaxis. Similarly, C1-INH replacement therapies must be administered intravenously by trained persons (whether in clinical or nonclinical settings) and, thus, carry the risks and challenges associated with all intravenous formulations, including the need for adequate vascular access. Thus, self-administration of subcutaneous icatibant may be a significant improvement over currently available treatments, from both a logistical and safety perspective.

Of note, the potential role of icatibant as a prophylactic treatment for HAE was not evaluated in this development program, and it is not clear whether icatibant treatment will lead to fewer HAE attacks over time. During the open-label extension phases of the three pivotal Phase 3 efficacy trials, patients received repeated long-term intermittent icatibant dosing (e.g., up to 142 total doses of icatibant delivered over several years in one patient). 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 dosing for multiple attacks over time. Nonetheless, the available safety data are adequate to support a regulatory decision for drug approval.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarketing risk evaluation and mitigation strategies are recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

No clinical trial postmarketing requirements or commitments are recommended.

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 glass syringe (b) (4) which contains 30 mg of icatibant acetate in a 3 mL solution. The Applicant proposes to co-package the pre-filled syringe with a single (b) (4) 25G needle (b) (4) packed separately in the same carton.

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 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 highly purified plasma-derived C1 esterase inhibitor replacement product, and danazol, a synthetic androgenic steroid). Not listed in this table are stanozolol and oxymetholone, two synthetic androgenic steroids that were approved for HAE prophylaxis but are no longer marketed in the U.S. for this indication (stanozolol is no longer manufactured in the U.S., although oxymetholone is still marketed for other non-HAE-related indications). 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 for HAE attacks, although its efficacy is controversial.

Table 1: 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 Human C1 esterase inhibitor	Cinryze	Highly purified plasma-derived 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: Initiate at 200 mg 2-3 times/day, then decrease by $\leq 50\%$ 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 in the European Union on July 11, 2008, for the symptomatic treatment of acute attacks of HAE in adults. According to the Summary of Product Characteristics labeling, "Firazyr may be self-administered or administered by a caregiver only after training in subcutaneous injection technique by a healthcare professional," as "Firazyr is intended for use under the guidance of a healthcare professional."

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 via the 505(b)(1) pathway 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 2, 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 2 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 2: 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) Icatibant 0.4 mg/kg IV (0.5 hr infusion) Icatibant 8 mg/kg IV (1 hr infusion) Placebo	Single dose on three occasions	Safety, tolerability, PK

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JE049-1102	I	<u>Part I:</u> Healthy (16) <u>Part II:</u> Healthy (24)	<u>Part I:</u> DB, PC, AD <u>Part II:</u> R, OL, XO	<u>Part I:</u> Icatibant 0.05 mg/kg SC (40 mg/mL) Icatibant 0.2 mg/kg SC (40 mg/mL) Icatibant 0.2 and 0.4 mg/kg SC (20 mg/mL) <u>Part II:</u> Icatibant 0.4 mg/kg SC (10 or 20 mg/mL) Icatibant 0.4 mg/kg IV	<u>Part I:</u> Single ascending dose <u>Part II:</u> Single dose	Bioavailability of SC versus IV delivery
JE049-1103	I	Healthy (32)	DB, PC	Icatibant 30 mg SC (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, 18 to ≤65 yrs (15)	OL, POC, RD	Icatibant 0.4 mg/kg IV (0.5 hr infusion) Icatibant 0.4 mg/kg IV (2 hr infusion) Icatibant 8 mg/kg IV (0.5 hr infusion) Icatibant 30 mg SC Icatibant 45 mg SC	Sequential dosing over 5 days	Efficacy, safety and tolerability, PK, PD
JE049-4102	---	Adults with HAE (80)	Observational	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 <i>Tranexamic acid 1000 mg PO every 6-8hr for 2 days (up to 6 doses)</i>	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 ^^Ongoing OL EXT (96)	Icatibant 30 mg SC Placebo	Single dose, with 14-day observation period	Efficacy versus placebo on time to onset of symptom relief (composite symptom VAS rating)

*JE049-3101 (FAST-4 or EASSI)	III	Adults with HAE (151; 56 completed)	OL ^^Ongoing (95)	Icatibant 30 mg SC	Single self-administered dose	Safety of self-administration of SC drug

**Not included in the original NDA submission (submitted in the Complete Response)*

^Patients listed as open-label recipients in the Subjects column are those who received open-label icatibant during the primary treatment phase of the trial, rather than blinded treatment, due to qualifying laryngeal HAE symptoms

^^Numbers in parentheses indicate the number of subjects enrolled in the open-label extension phases or other ongoing data collection period in each trial

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, AC = active-controlled

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 NDA Review), 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

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, similar in scope to 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 and 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 symptom rating (VAS-3), comprised of skin pain, skin swelling, and abdominal pain symptom components. Given the Division's recommendation at 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. A Special Protocol Assessment (SPA) for this trial was submitted by the Applicant on February 13, 2009.

In reviewing the SPA, one of the Division's major considerations was the validity of the VAS rating scale used to define the main efficacy endpoints in the pivotal Phase 3 trials, as previously noted in the Not Approvable action letter issued for the original NDA. 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 this continuum, with reference to the two extremes. While the VAS has been widely used as a pain assessment tool in clinical research, its proposed use in the icatibant development program to assess individual symptom domains in acute HAE attacks was novel. In the original NDA submission, the Applicant had addressed the validity of the VAS through a series of PRO validation studies evaluating the face, content, and clinical validity of the VAS, including *post hoc* comparative analyses from the Phase 3 database of patient symptom diary data and physician-based clinical assessments during acute HAE attacks. In addition, the Applicant conducted Study JE049-4102 to characterize the minimum clinically significant difference in the VAS by correlating self-assessed VAS ratings with ratings on the Verbal Descriptor Scale (VDS), a 5-point scale that the Applicant considered to be a comparative gold standard for evaluating self-reported symptom change over time. By determining the relationship between incremental changes in the VAS and clinically relevant changes in the VDS, the Applicant proposed that the minimum clinically significant difference in VAS rating was 9 mm on the 100 mm scale.

While collectively, these validation studies were consistent with Agency guidance on PRO development programs (*Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims -- December 2009*), the Division was cognizant of the lack of prior regulatory experience with VAS-based efficacy endpoints in HAE clinical programs, as well as the novel nature of the VAS when used in this manner. In turn, the Division was unable to make a final determination as to the validity of the VAS in assessing HAE symptomatology, during review of the original NDA submission. Likewise, in response to the proposed SPA, although the Division was generally supportive of the overall trial design of FAST-3, given the novelty of the proposed primary endpoint and the lack of regulatory experience with VAS-based outcome measures in HAE clinical programs, the Agency issued a No Agreement SPA letter on April 2, 2009, indicating that the design and planned analysis of FAST-3 did not adequately address the objectives required to support a marketing submission. Ultimately, the Applicant conducted FAST-3 as originally proposed, enrolling the first subject in July of 2009.

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 intravenous and subcutaneous dose-ranging (JE049-2101), data generated from a human intravenous 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 E.U. approval) and July 11, 2010. Safety data from this postmarketing exposure is discussed in Section 8 Postmarket 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 Chemistry Manufacturing and Controls

With regard to the drug substance, all related substance impurities have limits (b) (4) and the total impurities are (b) (4). A total of 17 impurity peaks were not identified, with a specification limit of (b) (4) each, but this was deemed acceptable for NDA approval, following discussion with the Pharmacology/Toxicology Review Team. Specifically, the CMC Review Team has recommended approval of this drug product, with a post-approval commitment to provide chemical structures for impurity peaks (b) (4) that were not fully identified with structures and impurity peaks (b) (4) that were not identified. With regard to the drug product, the degradation product (b) (4) in the injection has a specification limit of (b) (4) at batch release and (b) (4) during stability testing, which was deemed acceptable for NDA approval, following consultation with the Pharmacology/Toxicology Review Team. The specification limits for heavy metals (b) (4) were determined to be (b) (4) based on USP standards. Batch analysis of 17 batches indicated the following heavy metal levels: (b) (4). In turn, the Applicant committed to set alert and action limits for manufacturing to complement these specifications and to reevaluate these limits upon obtaining a sufficient number of production batches (b) (4). This approach was deemed acceptable by the CMC

Review Team, following consultation with the Pharmacology/Toxicology Review Team. In addition, structural alerts were identified for three leachables: (b) (4). Although these leachables are not detected in the drug product, given that their detection limits range from (b) (4).

However, upon consultation with the Pharmacology/Toxicology Review Team, none of these leachables were considered genotoxic, based on AMES testing or quantitative structure-activity relationships. Thus, overall, the CMC Review Team recommends approval of the drug product.

Given that icatibant is supplied in pre-filled syringes, a Quality Microbiology Review to assess the adequacy of the sterilization and (b) (4) manufacturing processes for the drug-device product was completed (see Quality Microbiology Review by Dr. Vinayak Pawar, dated June 3, 2011). This review indicated that these procedures were acceptable and recommended approval of the drug product. In addition, the Office of Compliance determined that all the pertinent facilities in the Establishment Evaluation System are acceptable, although a final determination regarding the drug product manufacturing facility is pending at the time of this Clinical Review.

A consultation from the Center for Devices and Radiologic Health (CDRH) raised a concern with the proposed pre-filled syringe device, regarding the potential for inappropriate disconnection of the (b) (4) needle hub from the (b) (4) pre-filled syringe after or during assembly by the user, due to potential incompatibility between the needle hub and syringe tip. This potential problem was identified in several postmarketing reports of device failures with the same (b) (4) syringe used for the delivery of other drugs (adenosine, risperidone) via both needle-containing and needleless (IV connector) delivery systems that utilized luer lock devices. In turn, CDRH has recommended that the Applicant address any potential design flaws by conducting device performance testing (per ISO (b) (4)) prior to NDA approval, as well as completing a formal simulated use/human factors study to assess the functionality and usability of the proposed Firazyr syringe-needle configuration. Of note, limit syringe/needle leak test data were submitted with the NDA, which will be reviewed for ISO (b) (4) compliance. The CMC Review Team has indicated with it is acceptable to provide ISO (b) (4) testing as a post-approval commitment, given that the Clinical Review Team did not identify immediate concerns regarding syringe-needle device failures from the available clinical trial and postmarketing data.

In turn, in response to a request for information from the Division dated July 8, 2011, the Applicant communicated to the Division on July 13, 2011, that no premarketing or postmarketing adverse event reports of device failures had been submitted for icatibant. The Applicant estimated that inclusive of clinical trials and postmarket use, the number

of syringe-needle units used to date was 1,189 in the U.S. and 14,788 outside of the U.S. These totals included both icatibant injections in clinical trials and commercial use, as well as placebo injections delivered in clinical trials, which utilized the same syringe-needle devices and were delivered in identical fashion as icatibant, either by healthcare providers or through self-injection by patients. There have been two postmarketing reports associated with syringe complaints: one report of icatibant leakage from the capped syringe when pressure was applied to the pre-filled syringe and a second report of syringe leakage in its original packaging, which the investigator felt was due to the luer lock breaking off from the syringe during transport. Neither of these syringe complaints related to detachment of the needle hub from the syringe tip during or after assembly by the user. With regard specifically to self-administration, the Applicant reported 92 self-injections in the single clinical trial that evaluated icatibant self-administration (FAST-4), along with 96 placebo self-injections with the same syringe-needle configuration, which were done for training purposes in this same trial. Although there were five AE reports in a total of four icatibant-recipients that were categorized under the MedDRA System Organ Class of "General disorders and administration site conditions," these AEs all related to local injection site reactions and were not associated with device failures. The Applicant cannot quantify the precise number of icatibant self-injections in the postmarketing setting from the E.U., but an ongoing Icatibant Outcome Survey involving eight E.U. countries indicated that as of April 21, 2011, out of 378 icatibant-treated attacks, 47.6% were reported as treated with self-injected icatibant. Thus, overall, from the safety data reported (and in the absence of formal human factor studies), syringe-needle device failures do not appear to be a significant safety issue for the icatibant device configuration.

4.2 Clinical Microbiology

Icatibant is not an antimicrobial agent and is not intended to impact microbial growth. Thus, a Clinical Microbiology Review will not be completed.

4.3 Preclinical Pharmacology/Toxicology

The Pharmacology/Toxicology Review Team has completed review of the pivotal 39-week toxicology study in dogs and an impurity qualification study that directly responded to nonclinical requirements listed in the Not Approvable action letter for the original NDA submission. A 26-week pivotal rat study that was submitted to IND 68,214 was reviewed prior to this Complete Response submission, for which a NOAEL was not identified due to reproductive tract toxicities. In the pivotal 39-week dog study, end-organ toxicity was noted in the reproductive tract of male and female animals, including testicular, ovarian, prostatic, and uterine atrophy and decreased sperm counts. Systemic injection reactions were noted in high-dose animals, and decreases in heart rate were noted following icatibant treatment. The histopathologic effects of icatibant on

both the reproductive tract and heart appear related to the drug's primary mechanism of action of bradykinin type 2 receptor inhibition. In the 26-week pivotal rat study, end-organ toxicity was noted in the reproductive tract of male and female animals, including testicular, ovarian, prostatic, and uterine atrophy (as in the 39-week dog study), delayed parturition leading to fetal death, as well as additional toxicities, including skin ulceration, focal fibrosis at injection sites, macrovesicular vacuolation of brown fat (in the aorta and connective tissue), adrenal gland hypertrophy, decreased hematopoiesis in the bone marrow, lymphocyte depletion in the thymus, and agonal congestion in the lungs. Of note, reproductive toxicities were observed with daily administration of icatibant, which does not reflect the intended clinical dosing of icatibant for human use. In the pivotal dog toxicology study, adverse histopathologic findings were not observed in dogs that were dosed with icatibant biweekly for nine months.

The Pharmacology/Toxicology Review Team also evaluated the proposed impurity specifications, which the Applicant plans to control at the level of the drug substance, rather than the drug product, in order to ensure that these are process impurities, rather than drug degradants. Proposed limit specifications for metals (b) (4) were also evaluated. In addition, the Review Team requested from the Applicant additional historical control data and histopathology results for low and mid-dose rats in the (b) (4) impurity qualification study, given findings of myocarditis and kidney sclerosis seen in high-dose rats; a signed final report of these data had not yet been received from the Applicant at the time of this Clinical Review. Discussions between the Pharmacology/Toxicology Review Team and the CMC Review Team regarding impurities, degradants, leachables, and heavy metal content are all discussed in Section 4.1 Chemistry Manufacturing and Controls. Overall, given the relatively low dosing frequency expected with icatibant in the clinical setting and its dose-dependent nonclinical toxicity profile, as well as the favorable benefit-risk ratio demonstrated in the icatibant clinical program, the Pharmacology/Toxicology Review Team has recommended approval of the drug product with a nonclinical postmarketing requirement for the submission of long-term carcinogenicity studies in rat and mouse.

4.4 Clinical Pharmacology

Icatibant is rapidly absorbed after subcutaneous injection, with peak plasma concentrations noted at 30 minutes post-dosing and rapid elimination ($t_{1/2}$ = 0.6 – 1.5 hours) that is predominantly non-renal. Icatibant exhibits low serum protein binding (~44%) and is extensively metabolized into two main inactive metabolites, M1 and M2. In this Complete Response submission, the Applicant has submitted two new Phase 1 clinical pharmacology trials (HGT-FIR-061, a thorough QT prolongation study that was 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 with respect to rates of icatibant clearance in clinical pharmacology trials of healthy subjects. While elderly subjects (> 65 years) had similar C_{max} values as younger adults (18-45 years), AUC values were increased by approximately 66-116%. This resulted predominantly from reductions in icatibant clearance by 40-60% in elderly subjects compared to younger adults, which correlated to a longer half-lives in elderly subjects ($t_{1/2}$ in males = 1.5 hours; $t_{1/2}$ in females = 1.1 hours). Decreased rates of icatibant clearance were also noted in females compared to males, with 2.3-fold increases in both C_{max} and AUC noted for young females. In elderly females, C_{max} was similarly increased 2.3-fold compared to elderly males, whereas AUC was increased 1.8-fold. Thus, this interaction between age and gender effects resulted in a 2.5-fold greater C_{max} value and a 4-fold greater AUC value in elderly females compared to younger males. 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. Whether these subgroup effects on icatibant clearance had any demonstrable impact on clinical efficacy is discussed in Section 6.1.7 Subpopulations, while potential effects on safety are discussed in Section 7.5.3 Drug-Demographic Interactions.

Overall, the Clinical Pharmacology Review Team has recommended approval of this drug product, as the Applicant has provided adequate explanation of the age and gender-related differences in icatibant pharmacokinetics, as well as justification for proposing the same dose of icatibant, regardless of age and gender. This determination was based on *post hoc* PK analyses from the two newly conducted PK trials (HGT-FIR-061 and HGT-FIR-065) and a population PK analysis of all available PK data focusing on the effects of age and gender. In addition, the Clinical Pharmacology Review Team feels that although a formal dose-ranging trial was not completed, dose selection was adequately characterized by the Applicant, based on several clinical pharmacology trials, pharmacokinetic/pharmacodynamic modeling data, a human intravenous bradykinin challenge model, and the Phase 3 clinical evaluation of the selected 30 mg SC dose of icatibant.

4.4.1 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.

4.4.2 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 intravenous 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 with improvement in bradykinin-mediated symptoms of acute HAE attacks. Thus, the dose of icatibant selected for exploration in Phase 3 trials was largely determined mechanistically, based on the plasma levels of bradykinin expected to occur in acute HAE attacks and the plasma levels of icatibant needed to completely antagonize these bradykinin effects, as assessed in the human bradykinin challenge model.

A Phase 2 proof-of-concept trial (JE049-2101), which was reviewed with the original NDA submission (see the Clinical Review by Dr. Susan Limb, dated February 29, 2008, and the Clinical Pharmacology Review by Dr. Partha Roy, dated March 21, 2008), suggested the comparability of the pharmacokinetic and pharmacodynamic profile of icatibant in HAE patients versus healthy volunteers at equivalent doses (assessed in separate clinical pharmacology trials). In addition, this trial generated limited dose-ranging information based on clinical efficacy and safety data for single doses of icatibant at a limited number of intravenous and subcutaneous dose levels, as acute treatment for moderate to severe cutaneous or abdominal HAE attacks, including the 30 mg subcutaneous dose, which was the dose ultimately studied in Phase 3 clinical trials. Based on the results of this trial, the time to self-reported symptom relief appeared relatively rapid with subcutaneous dosing of icatibant--approximately 30 minutes to the onset of symptom relief. In addition, efficacy results were similar for the 30 mg subcutaneous dose and the highest intravenous dose tested of 0.8 mg/kg, while the

higher 45 mg subcutaneous dose did not appear to offer any added benefit over the 30 mg dose. In turn, the 30 mg subcutaneous dose was carried forward into Phase 3 clinical trials.

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 NDA Review. 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 trial was conducted voluntarily by the Applicant, after 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. A review of the 12-lead ECG and Holter monitoring data from this trial by the Agency's QT-Interdisciplinary Review Team identified several instances of ST/T wave changes and QT prolongation (report submitted to IND 68,214 and dated January 30, 2007). Given this evidence of QT prolongation by icatibant, the Agency concluded that although a thorough QT study was not warranted, these findings would have to be addressed in the product labeling. However, the Applicant chose to evaluate this effect further in this thorough QT prolongation study, which 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 subcutaneous 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 QTcI 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 QTcI, 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 QTcI 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 QTcI 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 QTcI 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 also 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). A review of this trial by the Agency's QT-Interdisciplinary Review Team (QT-IRT) concluded that the effects of icatibant on the length of the QT interval were below the threshold level of regulatory concern (see QT-IRT Consult Review by Moh-Jee Ng, dated May 26, 2011). A description of the trial's findings was recommended for inclusion in the proposed icatibant product label. 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.

4.4.3 Pharmacokinetics

A review of data establishing the pharmacokinetic profile of icatibant is discussed in the Clinical Pharmacology NDA Review. These data were generated from Phase 1 clinical pharmacology trials and a Phase 2 proof-of-concept trial with intravenous and subcutaneous 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 NDA Review.

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

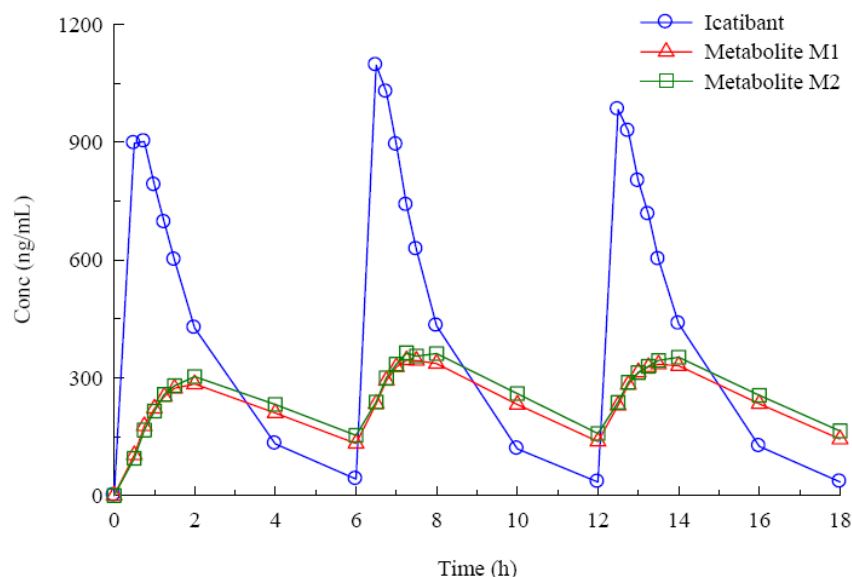
Enrollment Completion Date: May 16, 2010

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/m² 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 C_{max}, t_{max}, t_{1/2}, AUC_{last}, AUC_∞) 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 C_{max} and AUC_{0-6hr} 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 subcutaneous 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 non-healthcare settings by non-healthcare workers, as shown in Table 3 (the first two pivotal Phase 3 efficacy trials included in the original NDA submission are listed in italics).

Table 3: Phase III clinical development program for icatibant

Trial	Phase	Subjects [^]	Design	Treatment Arms	Duration	Relevance
<i>*JE049-2103 (FAST-1)</i>	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)
<i>*JE049-2102 (FAST-2)</i>	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)
<i>**HGT-FIR-054 (FAST-3)</i>	III	Adults with HAE (98, including 88 randomized abdominal & cutaneous, 5 randomized laryngeal, & 5 open-label)	R, DB, PC ^{^^} Ongoing OL EXT (96)	Icatibant 30 mg SC Placebo	Single dose, with 14-day observation period	Efficacy versus placebo on time to onset of symptom relief (composite symptom VAS rating)
<i>**JE049-3101 (FAST-4)</i>	III	Adults with HAE (151; 56 completed)	OL ^{^^} Ongoing (95)	Icatibant 30 mg SC	Single self-administered dose	Safety of self-administration of SC drug

**Included in the original NDA submission; **Included in the Complete Response submission;*

[^]Patients listed as open-label recipients in the Subjects column are those who received open-label icatibant during the primary treatment phase of the trial, rather than blinded treatment, due to qualifying laryngeal HAE symptoms

^{^^}Numbers in parentheses indicate the number of subjects enrolled in the open-label extension phases or other ongoing data collection period in each trial

R = randomized, DB = double-blind, PC = placebo-controlled, OL =open-label, EXT = extension, SC = subcutaneous, VAS = visual analog scale, DD = double-dummy, AC = active-controlled

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 of FAST-3 is presented in Section 5.3 Discussion of Individual Studies/Clinical Trials. 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). In addition, the individual safety results from FAST-3 are also presented separately at the end of each pertinent subsection of Section 7 Review of Safety. Of note, 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 non-healthcare 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 during the review of the original NDA submission, a final determination was not made regarding the validity of the VAS as an acceptable PRO measure. 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.

As the pivotal Phase 3 efficacy and safety trial submitted in this Complete Response, a detailed review of the methodology of FAST-3 is discussed here. Efficacy data from 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 data for FAST-3 are pooled with the safety results for FAST-1 and FAST-2 and are discussed throughout Section 7 Review of Safety. However, as FAST-3 was the pivotal Phase 3 safety and efficacy trial submitted with this Complete Response, individual safety results from this trial are also discussed separately at the end of each pertinent subsection in Section 7 Review of Safety.

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 was 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 ($\pm$ 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 4: 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 Impression		X									X			X	X		
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																	

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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 5: 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	

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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 89th subject in the trial (last on-study follow-up visit: October 1, 2010). 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.

6 Review of Efficacy

Efficacy Summary

The Applicant has presented results from three pivotal Phase 3 efficacy trials (FAST-1, FAST-2, and FAST-3) to support the proposed indication of icatibant for the treatment of acute HAE attacks in adults. Each of these trials was a randomized, controlled, double-blinded, 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 in FAST-1 and FAST-3 or tranexamic acid (1000 mg of an oral tablet formulation every 6-8 hours over two days, for a total of six doses) 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 at the same dose. Each of these pivotal efficacy trials also had open-label extension phases, 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 with icatibant 30 mg SC for persistent HAE symptoms, with each dose separated by at least six hours, for a total of no more than three 30 mg injections within a 24-hour period. The Applicant has also submitted data from an additional Phase 3 trial, FAST-4, which specifically evaluated the efficacy (and safety) of icatibant self-administration by 56 non-healthcare workers in non-healthcare settings for urgent, on-site treatment of acute HAE attacks by self-injection of icatibant, as the drug has been developed for distribution in pre-filled syringes containing a single 30 mg dose that is co-packaged with a 25G needle for subcutaneous injection.

The main efficacy analyses in these trials were based on the median time to onset of symptom relief, as determined by subject-assessed symptom ratings on a Visual Analog Scale (VAS). A series of validation studies establishing the utility of the VAS as a PRO were reviewed previously by the Division and were determined to be consistent with the Agency's guidance on PRO development. As used in these trials, 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 use to rate the intensity of each HAE symptom at baseline and at predetermined time points post-dosing. Onset of primary symptom relief based on VAS ratings of individual symptom domains was defined graphically, as a response to the right and below a line defined 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. VAS scores for individual symptom domains were also averaged to create composite symptom indices for abdominal and cutaneous HAE attacks (VAS-3: abdominal pain, skin pain, skin swelling), as well as laryngeal HAE attacks (VAS-5: abdominal pain, skin pain, skin swelling, difficulty swallowing, voice change—calculated for FAST-3 only). Time to onset of symptom relief based on these composite VAS endpoints was defined as a reduction of at least 50% from baseline VAS-3 or VAS-5 values.

Collectively, the findings from the Phase 3 clinical program support the efficacy of icatibant for the proposed indication. 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 (either abdominal pain, skin pain, or skin swelling), despite a numerical trend that favored active treatment (icatibant = 2.5 hrs; placebo = 4.6 hrs; non-significant). In addition, 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 that was observed in this trial between icatibant-recipients versus control subjects was unclear (icatibant = 2.0 hrs; tranexamic acid = 12.0 hrs; $p < 0.001$). Given that 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 potentially negative therapeutic effects of tranexamic acid on HAE symptomatology. In turn, upon review of the original

NDA submission, data from FAST-1 and FAST-2 were deemed insufficient to establish the efficacy of icatibant. However, with the submission of data from FAST-3 in this Complete Response, the Applicant demonstrated a statistically significant decrease in time to primary symptom relief onset (designated as the key secondary efficacy endpoint in FAST-3) in icatibant versus placebo-recipients in this third trial (icatibant = 1.5 hrs; placebo = 18.5 hrs; $p < 0.001$). In addition, time to onset of symptom relief based on composite VAS-3 symptom score (the primary efficacy endpoint for FAST-3) was also found in FAST-3 to be statistically decreased in icatibant versus placebo-recipients (icatibant = 2.0 hrs; placebo = 19.8 hrs; $p < 0.001$). *Post hoc* efficacy analyses of time to symptom relief onset based on VAS-3 from FAST-1 (icatibant = 2.3 hrs; placebo = 7.9 hrs; $p = 0.14$) and FAST-2 (icatibant = 2.0 hrs; tranexamic acid = 12.0 hrs; $p < 0.001$) were also found to be statistically significant and in favor of icatibant treatment.

Given the recurrent nature of HAE attacks, 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 at any point in the three pivotal efficacy trials ($N = 225$), i.e., during the blinded treatment or open-label extension phases. 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.

Support for the efficacy of icatibant in the treatment of HAE attacks with distinct edema locations was established by stratified efficacy analyses of time to primary symptom relief onset, based on cutaneous, abdominal, or laryngeal manifestations. The strongest treatment effect of icatibant appeared to be in cutaneous HAE attacks across the three trials (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 positive treatment effect favoring icatibant in abdominal HAE attacks was also observed in FAST-2 and FAST-3 (FAST-1: icatibant = 2.0 hrs, placebo = 3.0 hrs, $p = 0.159$; FAST-2: icatibant = 1.6 hrs, tranexamic acid = 3.5 hrs, $p = 0.026$; FAST-3: icatibant = 1.0 hrs, placebo = 3.6 hrs, $p = 0.002$). The efficacy assessment of icatibant in laryngeal HAE attacks was complicated by the lack of control subjects treated with placebo for laryngeal HAE attacks, by virtue of the trial designs for FAST-1 and FAST-2. Moreover, although FAST-3 randomized patients with mild to moderate laryngeal attacks to blinded treatment, this constituted only a limited number of exposures. Thus, efficacy data were also compiled for all subjects treated at any time with icatibant for their first laryngeal HAE attack in blinded or open-label fashion. Efficacy analyses for these initial laryngeal

3HAE attacks demonstrated similar times to symptom relief onset based on primary symptom VAS (2.2 hrs) and VAS-5 (2.2 hrs), as well as progressive reductions in laryngeal symptomatology, which suggests a clinically significant treatment effect of icatibant in potentially life-threatening laryngeal HAE attacks.

While subgroup analyses revealed increased times to symptom relief onset in male versus female subjects, these times were consistently lower in icatibant-recipients versus control subjects in each gender, confirming the efficacy of icatibant in both men and women. In addition, this same pattern was also seen in placebo-recipients, suggesting that the relatively longer times to symptom relief onset seen in males versus females were not a function of icatibant but were reflected in data from the overall study population. Other secondary efficacy analyses based on patient and investigator-reported symptom ratings, rescue medication use, durability of response, and global indices of improvement generally support the efficacy of icatibant for the proposed indication. However, as several of these secondary efficacy measures are based on unvalidated assessment tools, their clinical significance is questionable.

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.

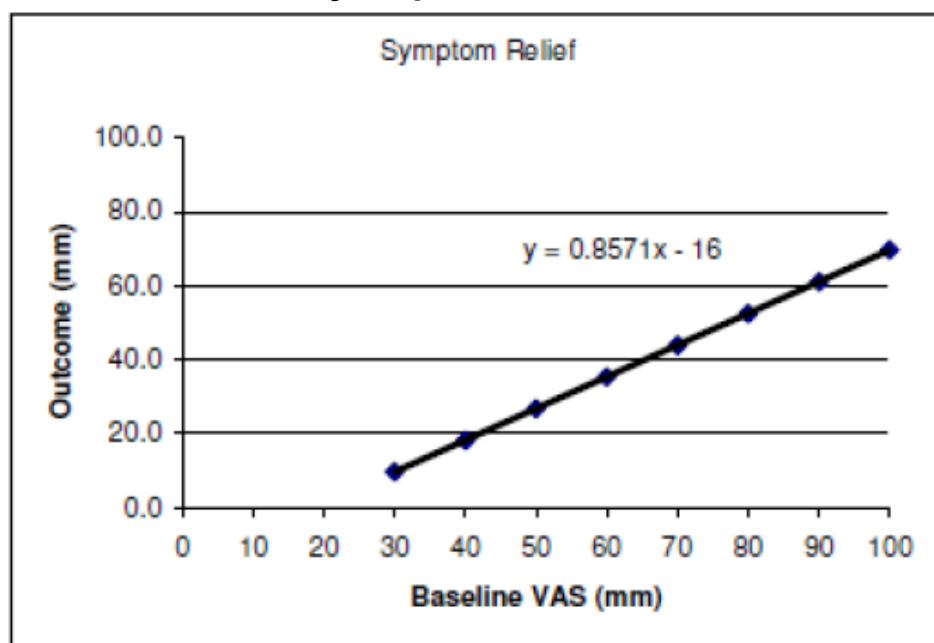
Primary Efficacy Endpoints

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 conducted by the Applicant to establish the utility of the VAS as a PRO measure to assess acute HAE symptoms 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. Additional studies included assessments of the face, content, and clinical validity of the VAS, as well as *post hoc* comparative analyses of patient symptom diary data and physician-based clinical assessments during acute HAE attacks, drawn from the Phase 3 database.

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 1) abdominal symptoms were no worse than mild and 2) cutaneous symptoms were at least moderate to severe; otherwise, these combined 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 $X \geq 30$ 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



BEST AVAILABLE
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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 $\geq 50\%$ 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 ≤ 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 6 summarizes patient demographics for the three Phase 3 efficacy trials. Female subjects predominated in each trial, despite there being no gender predominance in this autosomal dominant disorder. 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.

Table 6: 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, %)						
<i>Caucasian</i>	25 (92.6)	25 (86.2)	36 (100)	38 (100)	38 (88.4)	40 (88.9)
<i>Black</i>	0	0	0	0	3 (7.0)	0
<i>Asian</i>	0	1 (3.4)	0	0	0	0
<i>Multiracial</i>	0	1 (3.4)	0	0	0	0
<i>Other</i>	2 (7.4)	2 (6.9)	0	0	2 (4.7)	5 (11.1)
Age (years)						
<i>Mean</i>	34.8	34.9	40.4	41.9	36.1	36.6
<i>Median</i>	35.0	34.0	38.0	42.0	36.0	36.0
<i>Range</i>	20-54	18-58	20-68	19-66	19-83	18-66
Mean number of HAE attacks over previous 6 mon						
<i>Cutaneous</i>	8.6	9.9	7.4	7.9	6.7	7.3
<i>Abdominal</i>	5.1	6.8	4.2	8.7	4.2	3.8
<i>Cutaneous/Abdominal</i>	7.3	4.9	6.5	2.4	3.6	3.8
<i>Laryngeal</i>	1.7	2.8	2.4	1.0	1.0	0.7
On-study HAE attacks (n,%)						
<i>Cutaneous</i>	14 (51.9)	13 (44.8)	24 (66.7)	23 (60.5)	26 (60.5)	26 (57.8)
<i>Abdominal</i>	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 7, 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 7: 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 8 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 8: 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 9, 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 9: 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 (the pivotal Phase 3 trial submitted in this Complete Response) was time to onset of symptom relief based on the mean composite endpoint VAS-3. 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-recipient 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 12 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

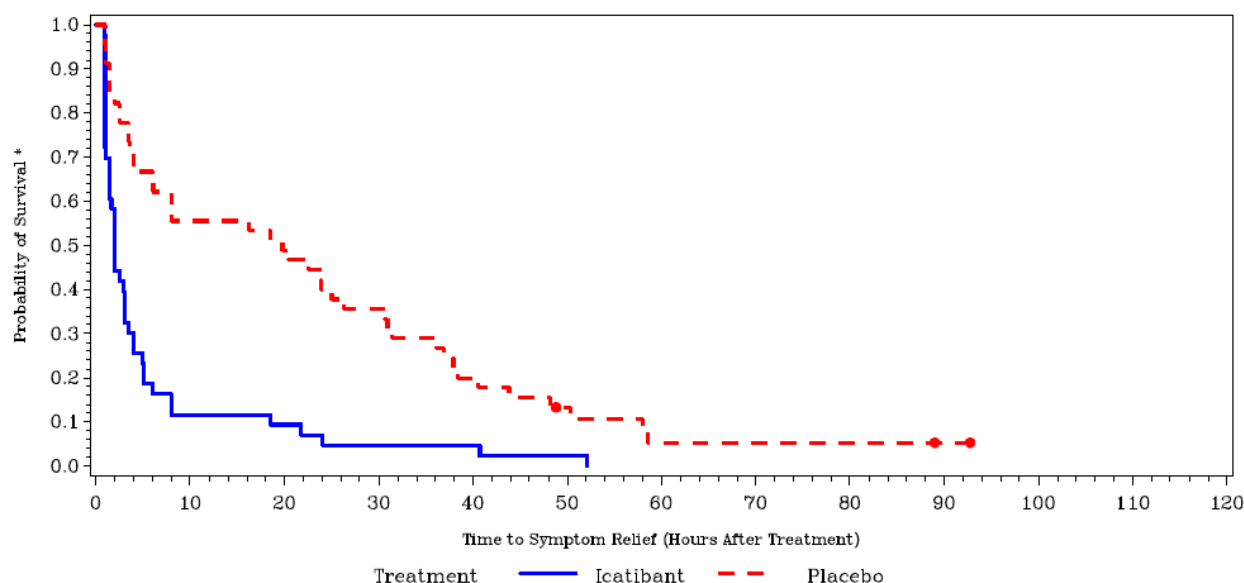
[^]Post hoc analyses for FAST-1 and FAST-2

Versus control group: * $0.01 < p \leq 0.05$, ** $p \leq 0.001$

Source: Summary of Clinical Efficacy, Table 2.7.3-20

As FAST-3 was the only pivotal Phase 3 efficacy trial to include VAS-3 as a prespecified primary endpoint, Figure 3 shows the Kaplan-Meier survival curve estimates for time to onset of symptom relief (based on composite VAS-3 symptom score) of icatibant versus placebo recipients, where survival is defined as failure to achieve symptom relief.

Figure 3: Kaplan-Meier curve estimates of time to onset of symptom relief based on composite VAS-3 score by treatment group in FAST-3



Source: Clinical Study Report for FAST-3, Figure 7-1

For the purposes of comparison across clinical trials, Table 11 summarizes the time to onset of primary symptom relief for all three pivotal efficacy trials, which was the key secondary efficacy endpoint for FAST-3. 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 11: 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
Time from attack onset to study treatment (hrs) ^{^^}	7.6	10.0	10.5	6.9	6.5	5.5
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

[^]Key secondary efficacy endpoint for FAST-3

^{^^}Presented as post-hoc analyses for FAST-1 and FAST-2, excluding two icatibant-recipients reclassified into laryngeal HAE attack population and excluded from this analysis

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 3-16, 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 *post hoc* 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.

Given the consistent median time to primary symptom relief onset noted in FAST-1 (2.5 hours) and FAST-3 (1.5 hours), the conflicting efficacy results of these two placebo-controlled trials is largely due to the disparate placebo effect observed in each trial, with control subjects in FAST-1 having a time to symptom relief onset of 4.6 hours versus 18.5 hours in FAST-3. Given that the symptoms of acute HAE attacks may spontaneously resolve over time in the absence of treatment, it is noteworthy that the time to study treatment from the onset of HAE attack for placebo-recipients was nearly twice as long in FAST-1 (10.0 hours), as it was in FAST-3 (5.5 hours), as summarized in Table 3-16 of the Integrated Summary of Efficacy. This could potentially suggest that placebo-recipients in FAST-1 were further along in the course of their HAE attacks than placebo-recipients in FAST-3, potentially accounting for their shorter time to symptom relief onset. However, the overall severity of HAE attacks in each treatment arm would also be expected to influence spontaneous recovery time (i.e., with severe HAE attacks potentially taking longer to recover than moderate HAE attacks). As the placebo group

in FAST-1 had a greater proportion of severe attacks (58.6%) than the placebo group in FAST-3 (37.8%), this distribution of attack severity would not support the shorter recovery time seen in FAST-1 versus FAST-3 placebo-recipients. Thus, it remains unclear what factors led to the relatively shorter time to symptom relief onset observed in placebo-recipients in FAST-1, which may have contributed to the failure of this trial to demonstrate a statistically significant treatment effect of icatibant.

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 12 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 as 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 attacks.

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 establish 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 $\geq$ 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 12.

Table 12: 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: * $p = 0.01 < p \leq 0.05$, ** $p \leq 0.001$, *** $p = 0.001 < p \leq 0.01$

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 13. Similar to other secondary efficacy endpoint findings, however, the results of FAST-1 reflected a numerical trend favoring icatibant.

Table 13: 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: * $p \leq 0.001$, ** $p = 0.012$

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 14, 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 14: 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 for 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 15 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 was observed at statistically greater rates in icatibant-recipients versus control subjects for cutaneous and overall HAE attacks, but not for abdominal HAE attacks.

Table 15: 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 15.

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 16. 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 16: 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*

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 17, 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 17: 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 18. 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 18: 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: * $p \leq 0.01$, ** $0.01 < p < 0.05$

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. In FAST-2 and FAST-3, the overall distribution of cutaneous symptom severity ratings at 4 hours post-dose differed statistically between icatibant-recipients and control subjects. In both these trials, a greater proportion of ratings at the lower end of this ordinal rating scale were noted in the icatibant group, reflecting milder symptoms compared to control subjects. However, this finding was not observed in FAST-1. Differences in global assessments of abdominal symptoms were more similar between icatibant and control groups. However, symptom improvement based on clinical global assessments occurred more rapidly in icatibant-recipients versus control subjects in FAST-2 and FAST-3. Moreover, in FAST-1, these rating distributions also favored the icatibant group at Hour 24 post-dosing. However, despite these statistically significant differences, interpretation of the global assessment endpoint is complicated by an imbalance noted at baseline in which icatibant-recipients in all three trials had a greater proportion (albeit not statistically different) of severe cutaneous symptoms at pretreatment, 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 19. 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 19: 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 20.

Table 20: 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 21. 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 21: 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 $X \geq 30$ 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 22, 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 22: 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 23 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 longer response times in male versus female icatibant-recipients. 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, times to symptom relief onset were lower in both male and female icatibant-recipients compared to gender-matched controls, thus establishing the efficacy of icatibant in both genders. In addition, the same pattern of delayed symptom

relief in male versus female subjects was also seen in the placebo and tranexamic acid control groups, suggesting that the relatively longer time to symptom relief onset seen in males versus females in the active treatment groups was not a function of icatibant but rather was reflected in data from the overall study population. Interestingly, longer times to symptom onset relief were also evident for increasing weight groups in icatibant-recipients in FAST-2, although 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 23: 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, dose-selection was determined mechanistically, based primarily 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 intravenous 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 intravenous or subcutaneous icatibant for an acute cutaneous or abdominal HAE attack. Likewise, efficacy and safety data in support of dose-selection were also generated in this trial for three intravenous 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 subcutaneous 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 limited dose-selection program by further defining dose-selection in a sufficient number of patients, based on an appropriate clinical endpoint or other validated related biomarker. The Applicant has not submitted additional dose-ranging data in this Complete Response based on clinical endpoints or validated biomarkers. However, as discussed in Section 4.4 Clinical Pharmacology, the Clinical Pharmacology Review Team agrees that the Applicant has adequately characterized dose selection, based on the several Phase 1 and 2 clinical pharmacology trials, pharmacokinetic/pharmacodynamic modeling data (including data from the human intravenous bradykinin challenge model), population PK analyses (including pooled analyses from the newly submitted trials, HGT-FIR-061 and HGT-FIR-065, which specifically characterized the pharmacokinetic impacts of age and gender), and the Phase 3 clinical evaluation of the 30 mg SC dose of icatibant.

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. In turn, 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, as previously described. In addition, the capacity of the 30 mg SC dose to confer a significant treatment benefit over 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. Therefore, the Applicant has adequately addressed the clinical deficiency noted in the Not Approvable action letter pertaining to further definition of icatibant dose-selection.

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 24. Thus, the development of tolerance to icatibant does not appear to be a concern.

Table 24: 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

6.1.10 Additional Efficacy Issues/Analyses

Efficacy findings were inconsistent across the three pivotal Phase 3 efficacy trials, although the results of FAST-3 provide convincing evidence of the efficacy and safety of icatibant for the proposed indication, in contrast to the original Phase 3 development program, consisting of FAST-1 and FAST-2. As discussed previously in Section 2.5 Summary of Presubmission Regulatory Activity Related to Submission, although an efficacy trend favoring icatibant treatment was evident in FAST-1, statistical significance of this treatment effect in the main efficacy endpoint of time to onset of primary symptom relief was not established. Moreover, although a statistically significant treatment effect in favor of icatibant was evident in FAST-2, the Division noted the inappropriateness of selecting tranexamic acid as an active control treatment, given that it is an unapproved treatment in the U.S. for acute HAE attacks. Thus, confirmation of a statistically significant treatment effect of icatibant versus placebo rests largely on the results of FAST-3.

7 Review of Safety

Safety Summary

The Applicant reports total icatibant exposure across the entire HAE clinical program to include 236 HAE patients who have been treated with icatibant 30 mg SC administered by healthcare workers for a total of 999 HAE attacks as of October 20, 2010 (the date of the original FAST-4 database lock; database lock for FAST-3 was October 1, 2010). Another 56 doses of icatibant 30 mg SC have been self-administered in 56 HAE patients (one dose each), with one of these subjects receiving an additional icatibant 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. For this integrated review of safety, analyses were reviewed from a pooled safety database consisting of all subjects administered blinded study treatment during the randomized treatment phases of the three pivotal Phase 3 efficacy trials: FAST-1, FAST-2, and FAST-3. Thus, for the purposes of safety assessment comparisons (e.g., AEs, clinical laboratory tests, vital signs, 12-lead ECG) between icatibant-recipients and control subjects, data were pooled for a total 113 subjects who received icatibant, 38 subjects who received tranexamic acid, and 75 subjects who received placebo for their first qualifying on-study HAE attack that was treated with blinded study drug.

In addition, major safety findings (e.g., deaths, SAEs, AE-related discontinuations) were also reviewed for subjects treated with icatibant during the open-label extension phases of each trial. This includes 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 (for whom data were not yet fully reported in the Complete Response submission). Summary data for all three pivotal Phase 3 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. However, 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. 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 local injection site reactions (erythema, swelling, pruritus, burning sensation, warm sensation) and HAE. While HAE was reported as an AE at similar rates in control subjects, local injection site reactions were far more common with icatibant and appeared in some form in almost all icatibant-recipients soon after injection. In general, however, these reactions were self-limited and resolved without sequelae within 24 hours, e.g., most cases of erythema (the most common type of localized injection site reaction) were mild in intensity by two hours post-dosing, with 85% resolving completely within 8 hours of icatibant-dosing. With regard to other treatment-emergent AEs, no clear patterns emerged that would be attributable to icatibant, as most of the AEs seen disproportionately in icatibant-recipients were noted in only 1-2 subjects (versus 0 or 1 control subjects). Of note, rare Grade 3 elevations in hepatic transaminases (without accompanying increases in bilirubin) and Grade 4 elevations in creatine kinase and uric acid were noted, but the clinical significance of these laboratory abnormalities is unclear, as accompanying physical signs and symptoms were not reported.

No hypersensitivity reactions were observed following icatibant-treatment in the Phase 3 clinical program, and immunogenicity studies across all three pivotal efficacy trials identified only one incidence of post-treatment icatibant-specific antibodies in the Phase

3 safety population. This subject also had anti-drug antibodies at baseline (prior to any icatibant exposure) of similar titer, with all subsequent immunogenicity samples over the following five months confirmed as negative. Given that a second subject also had drug-specific antibodies at baseline, but not after icatibant dosing, collectively these results were considered by the Applicant to be non-specific background findings of the detection assay, which appears to be a reasonable hypothesis. Thus, drug hypersensitivity and immunogenicity do not appear to be significant risks with icatibant.

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 self-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.

Overall, the safety profile of icatibant is sufficient to allow for its approval in adults, although in general, the safety assessment is limited by the size of the database. However, given the rarity of HAE, which is a designated orphan disease, and the questionable feasibility of completing larger controlled trials (particularly those evaluating laryngeal HAE attacks), the safety database is nonetheless sufficient on which to base a regulatory decision regarding drug approval.

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. Data from ongoing clinical trials

(FAST-3 and FAST-4) reported in the 120-day Safety Update are discussed in Section 7.7 Additional Submissions/Safety Issues. Postmarketing data reported in the 120-day Safety Update are discussed in Section 8 Postmarket Experience.

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 25, summarizing the total number of HAE attacks treated and subcutaneous 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 ≤ 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 25: 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			Number of Subjects		
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 (97.0)	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 6 in Section 6.1.2 Demographics. However, Table 26 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 26: 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/cm²)			
<i>Mean</i>	27.9	25.3	27.9
<i>Median</i>	26.3	24.05	26.6
<i>Range</i>	15.8-49.7	17.7-35.1	18.0-44.7
Geographic Region (n, %)			
<i>North America</i>	51 (45.1)	0	51 (68.0)
<i>(United States)</i>	48 (42.5)	0	47 (62.7)
<i>Western Europe</i>	27 (23.9)	27 (71.1)	0
<i>Eastern Europe</i>	14 (12.4)	7 (18.4)	4 (5.3)
<i>Other</i>	21 (18.6)	4 (10.5)	20 (26.7)
Initial HAE attack (n, %)			
<i>Cutaneous</i>	64 (56.6)	23 (60.5)	39 (52.0)
<i>Abdominal</i>	42 (47.2)	15 (39.5)	35 (46.7)
<i>Laryngeal</i>	7 (6.2)	0	1 (1.3)

Source: Integrated Summary of Safety, Table 4-5

Specific Results for FAST-3

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 27 summarizes the characteristics of the initial HAE attack treated with blinded or open-label study treatment in FAST-3, which appear well-balanced between treatment groups.

Table 27: 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, %)			
<i>Cutaneous</i>	26 (56.5)	26 (55.3)	0
<i>Abdominal</i>	17 (37.0)	19 (41.3)	0
<i>Laryngeal</i>	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 of FAST-3, 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.

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 25, 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.

Specific Results for FAST-3

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.

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 10 days after fourth icatibant-treated HAE attack

- Subject 359-002: Cholecystitis and pneumonia (recorded as separate SAEs) that developed 4 days and 8 days, respectively, 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.

Other Specific Results for FAST-3

Although no SAEs were noted in any icatibant-recipients during the blinded treatment phase of FAST-3, 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. No pregnancies were reported for any subject in FAST-3.

7.3.3 Dropouts and/or Discontinuations

To compare relative dropout and discontinuation rates between treatment groups, subject disposition data are summarized in Table 28 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 among treatment groups during the randomized treatment phases of each trial did not reveal a safety signal associated with icatibant exposure.

Table 28: 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	No discontinuations reported	
Other	3 (11.1)	2 (6.9)	1 (2.8)	0		
Withdrawn consent	0	3 (10.3)	0	0		
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 in total (one in the aforementioned icatibant-recipient and one in a placebo-recipient). In addition, overall rates of headaches of any severity were lower 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 31, 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. Local injection site reactions were reported separately from other AEs and were graded in terms of severity using a different set of criteria than that used for other AEs. Thus, severe local injection site reactions are discussed separately in Section 7.3.5 Submission Specific Primary Safety Concerns. No other significant AEs were reported for the Phase 3 clinical program that would be consistent with the ICH E3 Guidance for Industry: Structure and Content of Clinical Study Reports (July 1996).

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 based on extent and/or intensity using different grading criteria than for other AEs and were summarized separately from the general reporting of AEs. Investigators were not required to report local injection site reactions as AEs unless they met criteria for SAEs, which accounts for the differences in reported rates of local injection site reaction AEs versus the protocol-specified focused assessment of injection sites.

Multiple types of local injection site reactions and/or complications were documented following subcutaneous 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 29 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 29: 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

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. In addition, no hypersensitivity reactions were reported following icatibant administration.

Results Specific for FAST-3

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-dosing, 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 subcutaneous 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.

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 (from Day 1 through Day 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 30 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 30: 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 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

**Injection site reactions were systematically assessed in all subjects separately from other AEs and were only required to be reported as AEs if meeting SAE criteria (see Section 7.3.5 Submission Specific Primary Safety Concerns)*

Source: Integrated Summary of Safety, Table 17.1

Table 31 summarizes all AEs occurring during the observation period (from Day 1 through Day 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 31: Adverse events during post-dosing observation period (from Day 1 through Day 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 noted across the entire 14-day observation period were 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.

Results Specific for FAST-3

Summary AE data were presented for all AEs recorded in FAST-3 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 32 summarizes all AEs observed in FAST-3 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 32: 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 Preferred Term (n, %)	Icatibant 30 mg N = 46	Placebo 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

Adverse Events in FAST-3 with Repeated Icatibant treatment

Treatment-emergent AEs reported in 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 of FAST-3, 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%]).

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 33 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 33: Median baseline and end-of-observation (Day 14) values for hematologic laboratory parameters by treatment group in pooled Phase 3 safety population

Treatment Laboratory Parameter	Icatibant 30 mg N = 113		Tranexamic Acid N = 38		Placebo N = 75	
	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 34 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 34: 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	
	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 (≤ 2.5 times ULN). The Applicant reports one subject (Subject 321-005) who developed clinically relevant elevations in AST (without pretreatment elevations) to ≥ 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 latter 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 35 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 than the rates seen in control subjects.

Table 35: 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	
	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 36 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 36: 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 37 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 34, cases of transaminemia were not accompanied by other laboratory abnormalities reflective of functional hepatic damage.

Table 37: 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-H		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.

Results Specific for FAST-3

Serum chemistry, hematology, and urinalysis parameters were assessed during the blinded treatment phase of FAST-3 at Day 2 and Day 14 post-dosing. Few laboratory abnormalities qualified as AEs. Treatment-emergent AEs related to clinical laboratory evaluations were reported in only three subjects in FAST-3 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 4.45×10^{12} cells/L (NML: $4.5\text{-}6.5 \times 10^{12}$ 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)

Only minor changes from baseline were observed in laboratory parameters during the blinded treatment phase of FAST-3, as noted in Table 38, with similar findings in the open-label extension phase. Thus, no safety signals related to laboratory findings were noted in FAST-3.

Table 38: 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)	
	Baseline	Day 14	Baseline	Day 14
Hgb (g/L)	143.0	-3.0	148.4	-8.7
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

As median changes in post-dosing laboratory values during the blinded treatment phase of FAST-3 did not reveal any potential safety signals, laboratory safety data were also examined for potentially significant outliers. Only one subject (Subject 427-002, noted

above) 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 this patient. 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.

Laboratory abnormalities were also rarely reported as AEs during the extension phase of FAST-3:

- 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 4.45×10^{12} cells/L (NML: $4.5-6.5 \times 10^{12}$ 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 WBC count to 18.5×10^9 cells/L (NML: $4-11 \times 10^9$ 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
- 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

Another subject was also noted to have a clinically relevant, persistently elevated creatine phosphokinase level 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.

Of note, the elevations noted in hepatic transaminases during both the blinded and open-label treatment phases of FAST-3 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 unclear.

Summary urinalysis results are presented in Table 39, 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 39: 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	
	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

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°C) were done at baseline and at 0.5 hr, 12 hr, 2 days, and 14 days post-dosing. Table 40 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 40: 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		
	Baseline	Day 2	Day 14	Baseline	Day 2	Day 14	Baseline	Day 2	Day 14
Laboratory Parameter									
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 41 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 41: 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 29.

Results Specific for FAST-3

Table 42 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 42: 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		
	Baseline	Day 2	Day 14	Baseline	Day 2	Day 14
Laboratory Parameter						
Temperature (°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

Physical Examination Findings for FAST-3

A Review of physical examination findings from FAST-3 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.

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 QT-Interdisciplinary Review Team identified several instances of ST/T wave changes and QT prolongation (report submitted to IND 68,214 and dated January 30, 2007). 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) that has been reviewed by the Agency's QT- Interdisciplinary Review Team, which concluded that the effects of icatibant on the length of the QT interval were below the threshold level of regulatory

concern. 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 43, 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.

Table 43: 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

Results Specific for FAST-3

No consistent patterns were noted in ECG findings between the icatibant and placebo groups during the blinded treatment phase of FAST-3, 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 in FAST-3.

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 or EASSI): 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 subcutaneous injections of icatibant

Key Secondary Objective: To determine local tolerability, convenience, and clinical efficacy of self-treatment of HAE attacks with subcutaneous 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: At the time of database lock for this Complete Response submission, results from 56 subjects with either Type I or Type II HAE were evaluated and reported. Eight of these 56 subjects were icatibant-naïve at baseline, while 48 had been previously treated with icatibant for a prior HAE attack. A total of 151 subjects were enrolled in this trial, which the Applicant states is ongoing, with the 95 subjects who have not yet self-treated remaining in the trial until either they self-treat or the trial is closed.

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 44: Timetable of assessments and procedures for FAST-4

Visit	Screen	HCW-Tx for Naïve	Additional Doses for Naïve	48-hr F-U for Naïve	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-naïve	X								
Symptom Diary to naïve		X		X					
TSQM to naïve				X					
Icatibant to Non-naïve	X								
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	

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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 44, 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 $X \geq 30$ 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, which will include data generated from any of the 95 remaining enrollees in the trial, who had not yet self-treated at the time of the database lock for this Complete Response submission and are still being followed, provided they self-treat for an acute HAE attack prior to closure of the trial.

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 8 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 45. 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 45: 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 device-related AEs or syringe-needle device malfunctions were noted. Clinical laboratory assessments were not 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 46 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 46: 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 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 47: 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

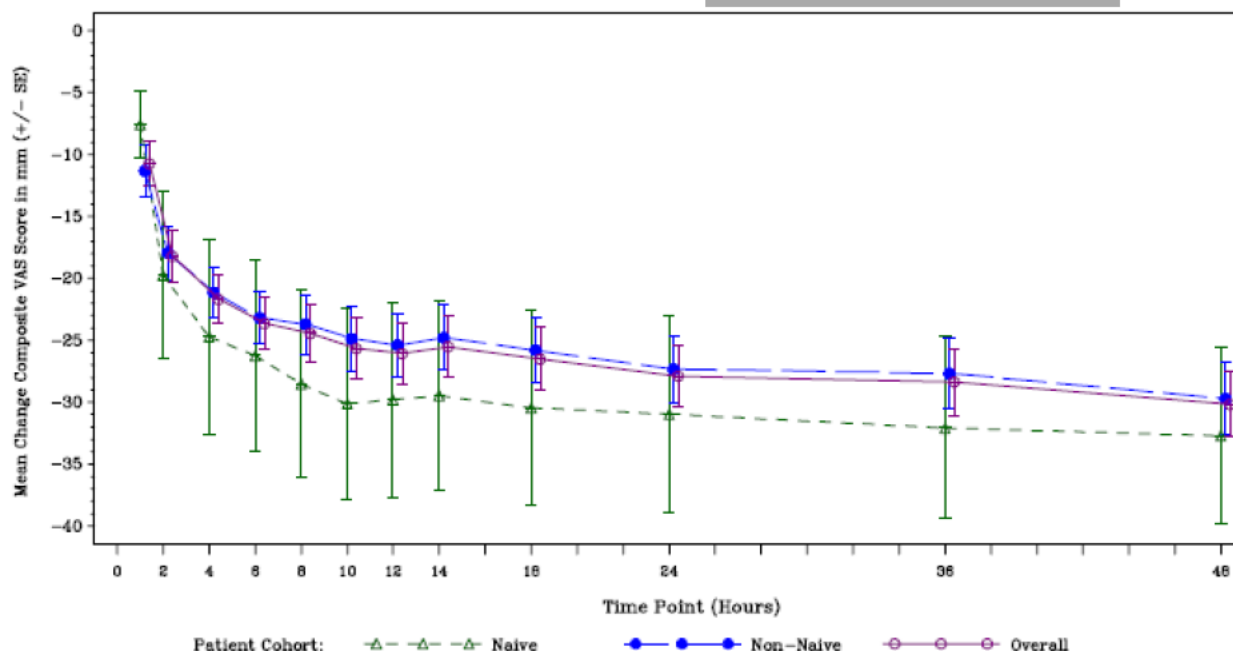
The efficacy of self-administered icatibant was evaluated as a secondary study endpoint in FAST-4. Efficacy analyses from this trial were based primarily on the self-administration phase involving all 56 subjects in the trial. Data from the subset of eight icatibant-naïve patients in this trial who participated 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 4.

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

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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, FAST-2, and FAST-3 were analyzed by both screening and confirmatory ELISA for icatibant-specific IgG. In addition, samples from FAST-3 were additionally tested for icatibant-specific IgE. Samples drawn both pretreatment and post-treatment (at Day 14 post-doing for the initial HAE attack) were tested and considered positive 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. In addition, the Applicant states that the icatibant treatment response was maintained in this patient during subsequent HAE attacks that occurred after the detection of icatibant-specific antibodies. Thus, the Applicant suggests these positive findings were related to nonspecific background noise for both subjects, which appears to be a reasonable hypothesis.

During the open-label extension phases of the three trials, two additional subjects from FAST-2 had two sporadic antibody (icatibant-specific IgG)-positive post-treatment samples. However, in both cases, these titers were transient, with documentation of multiple negative follow-up samples, and did not exceed the minimum required dilution of the assay. The Applicant also indicated that icatibant treatment-responses were maintained in both of these patients with subsequent HAE attacks that occurred following the detection of icatibant-specific antibodies.

Of note, no anaphylactic or otherwise significant hypersensitivity reactions were noted for any subject during the controlled or open-label extension phases of the three pivotal Phase 3 trials. Therefore, icatibant appears to have a low likelihood of immunogenicity.

Results Specific for FAST-3

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.

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 48.

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 48: 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 rat and mouse are currently ongoing (mouse carcinogenicity studies were originally halted by the Applicant due to severe injection reactions and were then re-started at lower icatibant doses).

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.

Collectively, nonclinical studies of icatibant in rats and dogs demonstrated delayed maturation of reproductive organs, impaired uterine implantation, delayed parturition leading to fetal death, atrophy/degeneration in the uterus, ovary, testis, and prostate, and decreased levels of testosterone (but no clinically significant changes in luteinizing hormone). Studies in rabbits further demonstrated premature births and abortions associated with icatibant exposure. The Pharmacology/Toxicology Review Team noted that these toxicities were associated with daily dosing of test animals, which is much higher than the expected dosing for humans in clinical practice. Of note, adverse histopathological findings were not observed in dogs treated biweekly for nine months in the pivotal dog toxicity study. In addition, 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.

7.7 Additional Submissions / Safety Issues

On June 30, 2011, the Sponsor submitted a 120-day Safety Update, which included safety data from the ongoing open-label extension phase of FAST-3 and the ongoing icatibant self-administration trial FAST-4. With a data cut-off date of April 18, 2011, this 120-day Safety Update encompasses data from 84 subjects from the ongoing FAST-3 extension phase and 95 subjects enrolled in FAST-4. In addition, newly reported postmarketing AE data are included, which are discussed in Section 8 Postmarket Experience. Overall, the data in this 120-day Safety Update are consistent with the safety profile observed in the original Complete Response submission, and no new safety signals emerged during this reporting period.

FAST-3 Extension Phase Safety Update

Data were summarized for those subjects in the FAST-3 extension phase who had received treatment for up to five HAE attacks from the time of the original database lock (October 1, 2010) through April 18, 2011. This included 11 subjects treated for a first attack, 18 subjects for a second attack, 20 subjects for a third attack, 18 subjects for a fourth attack, and 13 subjects for a fifth attack. Narratives for all SAEs were provided. The demographic and baseline characteristics of the FAST-3 Safety Update population were similar to those of the safety population reported in the original submission (e.g., female predominance, nearly all White). In addition, similar to what was reported in the original FAST-3 extension phase safety analysis, 92.5% (74 subjects) of subjects treated during this 120-day reporting period received a single injection of icatibant for any given HAE attack, with only one subject receiving three injections for a single, prolonged HAE attack. AEs were again categorized according to whether they occurred during the acute observation period (within 24 hours of icatibant dosing) or during the overall 14-day observation period.

During the acute post-treatment period, three SAEs were reported in this population (one each after a first, second, and fourth HAE attack). Severe AEs were similarly rare with only two events reported, one after a second HAE attack and one after a third HAE attack. No deaths were reported during the acute observation period, although two subjects were hospitalized for either a prolonged HAE attack or further clinical observation, and one subject discontinued during this reporting period due to an arrhythmia that was considered related to treatment of a fourth HAE attack. The overall AE patterns over the full 14-day observation period were similar: four SAEs (two worsening HAE episodes, one arrhythmia, and one non-cardiac chest pain), three severe AEs (two episodes of worsening HAE and one episode of non-cardiac chest pain), no deaths, three hospitalizations (due to a prolonged HAE attack, further clinical observation, and non-cardiac chest pain that was considered treatment-related), and one discontinuation due to an arrhythmia. Consistent with safety data from the original submission, worsening or recurrent HAE was the most commonly listed AE, while local

injection site reactions that resolved spontaneously were observed almost universally with icatibant dosing across all five sequential HAE attacks (89-100%), as expected. In addition, a single episode of transient transaminemia was observed, as well as one episode of elevated creatine kinase levels. In addition, one subject developed a weak IgG antibody response to icatibant during the 120-day reporting period at approximately 5 months after a second icatibant-treated HAE attack; no follow-up immunogenicity testing results were available for this patient. Of note, no clinically relevant changes in vital signs or physical examination findings were reported. However, one episode of generalized pruritus and cutaneous burning sensation occurred after icatibant treatment for an eighth HAE attack, although there were no associated rashes, respiratory symptoms, or vital sign abnormalities reported in this subject. Moreover, this patient reported no other signs or symptoms related to hypersensitivity during seven prior and two subsequent icatibant-treated HAE attacks. Thus, this episode does not appear to represent an event of anaphylaxis.

FAST-4 Ongoing Treatment Phase Update

In this 120-day Safety Update, cumulative safety data are reported for FAST-4 from the initiation of this trial (September 2009) through April 18, 2011. Thus, in addition to the original 56 subjects reported in the original Complete Response submission, this Safety Update adds 39 new subjects, for a total of 95 subjects. With regard to icatibant self-administration, 88 of these 95 subjects are reported in the self-injection safety database, as 32 additional subjects had self-administered icatibant (per protocol) during the 120-day reporting period. The remaining seven subjects had received an initial physician-administered icatibant dose but had not yet self-administered icatibant at the time of the original FAST-4 database lock (October 20, 2010). The demographics and baseline characteristics of this expanded population was comparable to that reported for the initial 56 subjects in the original submission. Eighty (90%) of the 88 self-treated subjects received only a single icatibant injection for their HAE attack, while seven subjects required a second dose administered in the clinic, and one subject required two additional doses. The AE profile for this updated safety population was similar to that reported in the original submission, with worsening or recurrent HAE being the most commonly reported AE in 25% of subjects, with no new or unexpected AEs reported, in comparison to the prior safety database. One or more local injection site reactions were observed in all subjects, with most severe reactions becoming mild to moderate within 8 hours. There were no AE-related trial discontinuations, no SAEs, and no deaths reported. Two subjects were reported as having had severe AEs during the 120-day reporting period (compared to four severe AEs in the original submission), both of which were cases of severe HAE.

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 E.U. 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.

Postmarketing 120-day Safety Update

One serious, unexpected spontaneous event was reported in the 120-day postmarketing period. This case was a 39 year-old woman with HAE who developed arthralgia, hand paresthesia, localized pain, and extremity edema 15 minutes after treatment with a single dose of icatibant 30 mg SC. Following hospitalization, these symptoms resolved by the next morning without sequelae. This AE was considered an HAE event and was classified as serious due to the hospitalization. The reporter considered this event to be probably related to icatibant. In contrast, the Applicant considered this event unrelated to icatibant and attributable to the underlying disorder of HAE.

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.

These five publications identified by the Applicant described the following adverse drug reactions in humans related to icatibant (*in vitro* and nonclinical effects are not described in this Clinical Review): 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 Labeling Recommendations

A formal review of the proposed trade name Firazyr by DMEPA concluded that this name is acceptable. Proposed package labeling has been included in this Complete Response submission. The Applicant seeks an indication for the “treatment of acute attacks of HAE in adults” at a dose of 30 mg of subcutaneously injected icatibant, with two additional doses of icatibant permitted for persistent or recurrent symptoms, with all doses administered at least 6 hours apart, with the total number of injections in a 24-hour period not to exceed three. The proposed dosing is consistent with the results of the icatibant dose-selection program, as discussed in Section 4.4 Clinical Pharmacology and Section 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations. The proposed indication for icatibant self-administration is supported by the results of FAST-4.

At the time of this review, labeling discussions are pending. Key elements of the Prescribing Information, with proposed revisions by the Division, are described below:

- Highlights of Prescribing Information
 - Indications and Usage indicates that the pharmacologic drug class of icatibant will be listed as a bradykinin B2 receptor antagonist. The SEALD Review Team deferred this determination to the Office of Clinical Pharmacology, which agreed with this designation of a new pharmacologic class. In addition, the proposed indication for the treatment of acute attacks of HAE in adults has been clarified to indicate the treatment of patients 18 years of age and older.
 - The proposed Dosage and Administration specifications are acceptable and supported by the results of the icatibant dose-selection program (limited dose-ranging information from Phase 2 trials and pharmacokinetic/pharmacodynamic modeling using data generated by a human intravenous bradykinin challenge model) and FAST-4 (icatibant self-administration). In addition, safety and efficacy data from the icatibant Phase 3 program (namely, the results of FAST-3, with supportive results from FAST-1 and FAST-2) confirm the appropriateness of the proposed 30 mg subcutaneous dose of icatibant. Further dose exploration is not expected, as the proposed dosage is acceptable.

- Warnings and Precautions have been updated to instruct patients to seek immediate medical care for laryngeal attacks, following use of Firazyr, while the warnings regarding cautious use in patients with ischemic heart disease and stroke have been revised to remove the phrase (b) (4) from this section. Section 5 has been similarly revised.
- Adverse Reactions have been revised to include common AEs occurring in (b) (4) patients, consistent with the presentation of clinical trial AE data.

- (b) (4)
- Section 6, Adverse Reactions: Section 6.1, Clinical Trials Experience has been revised to focus only on subjects from the three Phase 3 controlled trials, with a request for the Applicant to describe the demographics of this specific safety population. Table 1, based on pooled AE data from FAST-1 and FAST-3, has been revised to include only those AEs occurring in $\geq 1\%$ of patients and at a higher rate with icatibant versus placebo. Safety results from FAST-2 are described in the text with a summary statement. Similarly, safety data from the open label extension phases of these trials, as well as from FAST-4, are also described in the text.
 - Section 7, Drug Interactions: This section has been expanded to include a subsection on potential interactions with ACE inhibitors.
 - Section 8, Use in Specific Populations: This section has been revised by the Pharmacology/Toxicology Review Team to better organize teratogenicity and reproductive findings from animal studies, which have resulted in a Pregnancy Category C classification for icatibant. In addition, a section has been added regarding the use of icatibant during labor and delivery. Potentially promotional language regarding the likelihood of icatibant to be passed in breast milk has been removed from Section 8.3, Nursing Mothers. Finally, the section on hepatorenal impairment has been divided into separate sections for each of these special patient populations, describing clinical trial data from patients with hepatic and renal insufficiency.
 - Section 11, Description: The wording of this section has been altered slightly to indicate that the trade name Firazyr collectively refers to the injection formulation of icatibant supplied in a single-use prefilled syringe.
 - Section 12, Clinical Pharmacology: Section 12.1, Mechanism of Action and Section 12.2, Pharmacodynamics have been re-written to increase clarity. The Agency's QT-Interdisciplinary Review Team has also provided draft labeling

language describing the results of a thorough QT study submitted with this Complete Response. In addition, a sentence has been added to Section 12.2 to indicate that the clinical significance of the pharmacodynamic findings described in the proposed label is unknown at this time. Several sections describing pharmacokinetic data in special patient populations and demographic subgroups (e.g., based on age and gender) were added by the Clinical Pharmacology Review Team.

- Section 13, Nonclinical Toxicology: This section has been revised by the Pharmacology/Toxicology Review Team to improve clarity and organization.
- Section 14, Clinical Studies: This section summarizes the clinical efficacy results from the three pivotal controlled Phase 3 trials, focusing primarily on the results of FAST-3, for which the Applicant has been asked to provide a demographic description for this section of the label. (b) (4)



- Section 16, How Supplied/Storage and Handling: The Applicant has been requested to specify the acceptable temperature range for storage.
- Section 17, Patient Counseling Information: The Instructions for Use section has been extensively revised by DRISK Reviewers and the Clinical Review Team to improve ease of understanding by potential users of the product. In addition, the

Sponsor has been asked to describe in the label how training in the use of Firazyr under the guidance of a healthcare professional will be operationalized in the real-world setting, as a trainer device for Firazyr has not been proposed by the Applicant.

9.3 Advisory Committee Meeting

A Pulmonary-Allergy Drugs Advisory Committee (PADAC) Meeting was held on June 23, 2011, for this Complete Response submission, as icatibant is a new molecular entity that is unapproved in the U.S. for any indication. Icatibant was not reviewed by the PADAC during the initial review cycle for the original NDA, and the goal of this meeting was to discuss the icatibant program's efficacy and safety results with a panel of 13 external experts in a public forum. In addition to formal presentations by the Applicant, the DPARP's Primary Clinical Reviewer, and the Division of Biometric's Statistical Team Leader, the meeting included personal testimonies from HAE patients and patient advocates that highlighted the need for a convenient, self-administered treatment for this life-threatening and often debilitating condition.

The six questions posed to the Committee and a tabulation of votes are shown in Table 49. Of note, Question #6 was created during the PADAC Meeting itself upon agreement by the PADAC Chair, the Agency, and a favorable consensus among committee members, at the behest of several physician committee members who sought to make their opinions on icatibant self-administration known through an official vote.

Table 49: Questions and voting results for June 23, 2011, Pulmonary-Allergy Drugs Advisory Committee Meeting on icatibant

Questions	Votes		
	Yes	No	Abstain
1. Discuss the efficacy and safety data for icatibant. (Discussion Question)	Non-voting		
2. Do the data provide substantial and convincing evidence of a clinically meaningful benefit for icatibant in the treatment of acute attacks of hereditary angioedema? <i>(If not, what further data should be obtained?)</i>	12	1	0
3. Has the safety of icatibant been adequately assessed for the treatment of acute attacks of hereditary angioedema? <i>(If not, what further data should be obtained?)</i>	11	1	1

4. 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? <i>(If not, what further data should be obtained?)</i>	12	1	0
5. Discuss the potential impact of self-administration on the safety and efficacy of icatibant, if any. (Discussion Question)	Non-voting		
6. Do the data support the self-administration of icatibant? <i>(If not, what further data should be obtained?)</i>	11	1	1

In response to the non-voting discussion questions, the PADAC noted the following points:

- Safety and efficacy data have been generated from a relatively small and homogeneous clinical trial population, particularly with regard to ethnic distribution. However, given the orphan nature of the disease and the difficulty in conducting large clinical trials, the majority of the committee members considered these data generally acceptable, as a basis for drug approval.
- A limited number of committee members noted that the clinical development program did not include an adequate number of patients with comorbidities that could pose a particular risk with icatibant treatment (e.g., ischemic heart disease).
- Phase 3 clinical trial participants and investigators were likely unblinded as to treatment assignment, given the nearly universal development of local injection site reactions in icatibant-recipients, versus far lower rates in control subjects.
- Comparisons of time to onset of symptom relief are inherently affected by protocol-specified assessment schedules, in which symptom assessments were minimal between Hours 12 and 48 post-dosing. Thus, in the present database, the onset of symptom relief within a limited post-dosing time frame (suggested by one committee member as 8 hours) provides a more robust efficacy outcome measure versus calculations over a longer duration, which are complicated by large gaps in assessment time points.
- The validation program submitted by the Applicant for the VAS appears adequate to establish VAS-based outcome measures as appropriate efficacy endpoints, although single symptom scores may introduce less bias than composite symptom scores, such as the VAS-3.

- The treatment effect of icatibant (i.e., time to onset of symptom relief) appeared consistent across the Phase 3 clinical trials, as well as with open-label and self-administered icatibant treatment.
- Large differences in placebo effects appeared to account for the conflicting efficacy results of FAST-1 and FAST-3, with potential bias introduced by differences in the time from attack onset to study administration in the placebo groups, which was nearly twice as long in FAST-1 (~10 hours) compared to FAST-3 (~5 hours).

With regard to icatibant self-administration, overall the PADAC expressed strong support for this proposed use, noting that most emergency departments do not have adequate staff training or the most recently approved treatments for acute HAE attacks. Supported by comments from several HAE patients and patient advocates during the Open Public Hearing portion of the meeting, the committee members overwhelmingly felt that HAE patients were capable of self-diagnosing acute HAE attacks. Of note, the need for patient education in proper administration techniques was stressed, and the possibility of a potential delay in seeking medical care due to self-dosing at home was discussed. However, several committee members noted that self-administered icatibant posed less of a safety risk than self-administered epinephrine, which has been approved for many years for the treatment of acute anaphylaxis.

Thus, the PADAC recommended approval of icatibant on the basis of the available efficacy and safety data, with favorable voting results. In addition, while it was recognized that the single icatibant self-administration trial, FAST-4, was ongoing, the committee members nonetheless indicated that the available data support self-administration of icatibant, given the caveat that the Division will review additional data from the ongoing FAST-4 trial at a later date and respond appropriately. In turn, the Applicant indicated that the final data analysis from FAST-4 is projected to be available by September 2011.

Of note, concerns were consistently raised by the Consumer Representative committee member that the available data may not be generalizable to the larger HAE patient population who would ultimately use the drug, given the relatively small size of the icatibant clinical program. Given the demographics of the Phase 3 participants, this concern was cited with particular regard to certain patient subgroups, including ethnic minorities, obese patients, pregnant women, and those with ischemic heart disease and other comorbidities. This resulted in consistent “No” votes by the Consumer Representative on all voting questions. The Patient Representative committee member also expressed these same concerns, and as a result, abstained from voting for Question #3, stating that insufficient data had been presented to support the safety of icatibant in these patient subgroups. In response to these concerns, several committee members supported the development of a postmarketing patient registry for icatibant.

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/s/

BRIAN PORTER
07/25/2011

SUSAN L LIMB
07/25/2011

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Products (HFD-570)

APPLICATION:	NDA 22-150	TRADE NAME:	Firazyr (proposed)
APPLICANT/SPONSOR:	Shire/Jerini	USAN NAME:	Icatibant
MEDICAL OFFICER:	Susan Limb, MD		
TEAM LEADER:	Sally Seymour, MD	CATEGORY:	Bradykinin inhibitor
DUE DATE:	June 17, 2008	ROUTE:	SC injection

SUBMISSIONS REVIEWED IN THIS DOCUMENT

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
November 20, 2008			End-of-review meeting package

RELATED APPLICATIONS

<u>Document Date</u>	<u>Application Type</u>	<u>Comments</u>
October 22, 2007	NDA 22-150, N000	NDA
February 18, 2008	NDA 22-150, N004	Interim update and post-hoc analyses

REVIEW SUMMARY:

This is a medical officer review of materials submitted in anticipation of an End-of-review (EOR) meeting for NDA-22-150, Icatibant. The NDA was submitted October 22, 2007, and reviewed under Priority Review. A decision of Not Approvable was made, and an action letter was issued on April 23, 2008, citing multiple clinical and CMC deficiencies. The clinical deficiencies cited included the following:

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 HAE. The uncertain efficacy of the comparator drug, TAE, 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 VAS). 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 safety for the dose shown to be efficacious.

The Applicant has requested an EOR meeting for further clarification of the items listed in the Not Approvable letter. Responses to these questions are provided. Details of the NDA review can be found in the individual reviews from each discipline.

OUTSTANDING ISSUES: None

Questions

- 1. The sponsor believes that the validation studies conducted to establish the validity of the PRO diary in measuring HAE systems are consistent with the requirements of the draft PRO guidance. Does the Agency agree?**

Division response: The validation studies outlined in Table 1 appear to be consistent with the requirements of the draft guidance, but whether the results of these studies confirm the validity of the PRO instrument is a review issue. As noted, some of the study reports were not submitted in the NDA for review and, therefore, we cannot comment on their content. Based on the information provided in the original NDA, we concluded that the VAS has its limitations which may have contributed to the non-significant results of FAST-1.

Should you elect to conduct another Phase 3 efficacy and safety study, you could use the VAS as a primary efficacy variable; however, you should include additional supportive efficacy variables, such as a composite symptom score like the VDS to support the efficacy of icatibant and the validity of the VAS. Alternatively, you could consider a different primary endpoint, such as a composite symptom score and include the VAS as a key secondary endpoint to facilitate cross-study comparisons. In either case, all data to support the chosen instrument should be included at the time of submission.

- 2. Based on the additional re-analyses conducted by the sponsor, the FAST-1 study demonstrated a statistically significant and clinically relevant treatment difference between placebo and icatibant which confirms the efficacy of Firazyr. Does the Agency agree that the results from FAST-1 and FAST-2 are adequate to support the approval of Firazyr?**

Division response: No, we do not agree. While the additional efficacy analyses are supportive, post hoc analyses do not replace or outweigh the results generated from a pre-specified statistical analysis plan. An additional confirmatory study will be required to support approval of Firazyr.

- 3. The sponsor believes the additional evidence presented based on pathophysiological rationale for use of anti-fibrinolytic agents and the comparison of FAST-2 study with literature data on natural time course of HAE attacks adequately ameliorates any concern of possible adverse effects of tranexamic acid in the treatment of acute HAE attacks. Does the Agency agree that the FAST-2 study data can be used as evidence of efficacy and safety for Firazyr?**

Division response: We agree that FAST-2 generally supports the efficacy and safety of icatibant; however, based upon the totality of the information provided in the NDA, a confirmatory placebo-controlled study is required. Replicate findings of efficacy from at least two studies are required to support approval. Your application contained only one study with statistically significant results, and this issue remains the primary deficiency of the application.

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/s/

Susan L Limb
12/22/2008 02:30:16 PM
MEDICAL OFFICER

Sally Seymour
12/22/2008 02:46:21 PM
MEDICAL OFFICER
I concur.

SUMMARY REVIEW OF REGULATORY ACTION

Date: April 23, 2008

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy Products,
CDER, FDA

Subject: Division Director Summary Review

NDA Number: 22-150

Applicant Name: Jerini AG

Date of Submission: October 26, 2007

PDUFA Goal Date: April 26, 2008

Proprietary Name: Firazyr

Established Name: Icatibant

Dosage form: Injection

Strength: 30 mg

Proposed Indications: Hereditary angioedema (HAE)

Action: Not Approval

1. Introduction

Jerini submitted this 505(b)(1) application for use of icatibant for the treatment of acute attacks hereditary angioedema (HAE) in patients 18 years of age and older. The proposed dose is 30 mg by subcutaneous injection. The application is based on clinical efficacy and safety studies. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies.

2. Background

HAE is a rare inherited disease characterized by intermittent and unpredictable attacks of angioedema involving various organs, particularly the skin, intestine, and upper airway. HAE attacks are potentially life-threatening, particularly cases that involve the upper airway. The treatment options for HAE are usually divided into three categories – chronic long-term therapy, short-term prophylaxis to prevent attacks, and treatment of acute attacks¹. Androgenic steroids are the only drug class approved for use in patients with HAE in the United States (US). Danazol is approved and marketed in the US with the label indication “prevention of attacks of angioedema.” The drug is also used for chronic long-term therapy^{1,2}. Stanazol and oxymetholone are also approved with similar indication, but are no longer marketed in the US. Elsewhere in the world epsilon aminocaproic acid (EACA) and tranexamic acid (TA) are approved for use in HAE patients. EACA and TA are used as chronic long-term therapy in HAE, but these are not

¹ MM Frank. Hereditary angioedema: The clinical syndrome and its management in the United States. *Immunol Allergy Clin N Am* 2006; 26:653-668.

² MM Frank, Jiang H. New therapies for hereditary angioedema: Disease outlook changes dramatically. *J Allergy Clin Immunol* 2008; 121:272-280.

thought to be effective in acute attacks^{1,2}. Fresh frozen plasma is often used for short-term prophylaxis to prevent acute attacks and for treatment of acute attacks, but the use of fresh frozen plasma in HAE is controversial as it can worsen an attack by providing more substrate that can be acted on to release additional mediators such as high molecular weight kininogens¹.

At present there are no drugs approved in the US or elsewhere for treatment of acute attacks of HAE. Icatibant is a new molecular entity proposed for the treatment of HAE. The applicant initially proposed a broad HAE indication, but during the review period modified the indication to limit to acute attacks of HAE. The modified indication is consistent with the clinical program that studied efficacy during acute attacks only. The putative mechanism of action of icatibant is inhibition of the bradykinin pathway by blocking the bradykinin type 2 receptor. The bradykinin pathway is not directly responsible etiologically for HAE, but is thought to play an important role in causing the symptoms of HAE when the complement pathway is activated due to deficiency of C1 inhibitor (C1-INH) in these patients.

The Agency and the applicant had various interactions dating back to 2003 when the applicant first came to the Agency seeking an orphan drug designation for icatibant, which was granted. This product was initially assigned to the Division of Gastrointestinal and Coagulation Drug products, and in 2005 the product was assigned to this Division. There were many issues discussed at various meetings, the major issue was the validity of the primary efficacy endpoint of time to onset of symptom relief assessed by a Visual Analogue Scale (VAS) that was used in the two phase 3 studies. In response to a Special Protocol Assessment (SPA) for one of two phase 3 studies (the placebo-controlled study), it was stipulated that the primary endpoint was acceptable, provided adequate validation of the VAS was provided in the NDA. The applicant conducted an observational study in HAE patients to define the Minimum Clinically Significant Difference (MCSD) and submitted that study with the NDA. During the pre-NDA meeting the Division communicated to the applicant concerns that the phase 3 efficacy data were not convincing with the placebo-controlled study failing to show statistically significant efficacy. In addition, the Division questioned the appropriateness of using TA as an active control for acute attack in the other phase 3 study. The same comments were also communicated in the filing letter.

3. Chemistry, Manufacturing, and Controls

Firazyr is supplied as a sterile solution in pre-filled syringe containing 30 mg of icatibant in 3 mL of isotonic acetate buffer solution (10 mcg icatibant base/mL). The drug substance icatibant acetate is a synthetic decapeptide with a structure similar to the nonapeptide hormone bradykinin. In addition to the drug substance, each mL of the drug product contains (b) (4) sodium chloride (b) (4) acetic acid (b) (4), and (b) (4) sodium hydroxide (b) (4), and water for injection, adjusted to pH of 5.5± (b) (4). The solution contains no preservatives. The proposed expiry period is 18 months for drug product stored (b) (4) (do not freeze). The proposed expiry period and the storage conditions are not supported by the submitted data due to

temperature dependent peptide hydrolysis, with one of the degradants testing positive in the genotoxicity study. In addition, the proposed specifications for the drug substance and drug product and the stability testing protocols are not adequate and have to be re-submitted with supporting data. Main issues include drug substance and drug product impurities, stability imbalance between the assay and total impurities, control of biological activity and tertiary structure of the peptide and deficient stability protocols. The applicant will need to revise specifications to address the issues pertaining to impurities or provide results from supporting qualification studies.

Establishment evaluation requests (EER) were made for the two sites manufacturing the drug substance (b) (4) and the drug product (b) (4) for five sites associated with testing of the drug substance, and two sites associated with testing of the drug product. The drug substance and drug product manufacturing sites in (b) (4) respectively, have their inspections completed. Drug product manufacturing site and its associated two testing sites have acceptable inspection status, but the drug substance inspection report is still pending. Two analytical establishments in (b) (4) are assigned for inspection but have not been inspected. These pending inspections will not preclude taking action on this NDA because it is likely to take the applicant more than one year to respond to the clinical deficiencies.

4. Nonclinical Pharmacology and Toxicology

The applicant submitted results of nonclinical toxicology studies lasting 13 weeks in duration. The primary toxicities were injection site irritation, and immature male and female reproductive organs. Injection site irritation was not of concern because it can be monitored in humans. For the reproductive organ toxicities, a NOAEL was identified in rats that provided an adequate margin of safety, while no NOAEL was identified in dog studies. The dog study did, however, achieve systemic exposures that covered the potential clinical exposures. A complete genetic toxicology program was conducted, which was negative. Carcinogenicity studies have not been conducted but are currently underway. A complete battery of reproductive toxicology studies was conducted and the results support a Pregnancy Category C designation. Although there were no observed teratogenic effects, there were signs of embryotoxicity, and dose-related decreases in post-implantations and total number of live fetuses. Additionally, icatibant prolonged gestation, resulting in spontaneous abortions and litter deaths. The Division accepted the limited toxicology program for submission of the application because there are no effective therapies for acute attacks of HAE. The Division also informed the applicant that treatment of acute attacks of HAE is considered chronic intermittent use, therefore, to avoid labeling restrictions, the applicant was asked to conduct chronic repeat dose toxicity studies of 6 month in duration in rats and 9 months in duration in dogs, and standard carcinogenicity studies. These were communicated to the applicant at the Pre-NDA meeting, in the filing letter, and also will be included in the NDA action letter.

5. Clinical Pharmacology and Biopharmaceutics

The applicant submitted results of an adequate clinical pharmacology program with the application. There are no outstanding clinical pharmacology issues.

Icatibant is absorbed within 30 minutes after injection and eliminated with a half-life of 0.6 to 1.5 hours. The clearance is primary non-renal with only 5-6% of parent drug excreted in the urine. The metabolic pathway is not certain, but in vitro studies suggest that the metabolism is CYP450 independent. Icatibant does not inhibit or induce the major CYP450 enzymes, implying low potential for drug-drug interaction. There is a theoretical pharmacodynamic interaction possibility of icatibant with ACE inhibitors. But this possible interaction is of little concern because of the general avoidance of ACE inhibitors in HAE patients due to their potential for angioedema.

Icatibant exposure seems to be dependent on age and gender. Subjects over 65 years of age had 66% to 116% increase in AUC and 12% to 15% increase in Cmax compared to younger subjects. Young female subjects had approximately 2.3-fold increase in both AUC and Cmax compared to young males. The reasons for these differences are not known. These differences did not seem to impact clinical efficacy. But the subject numbers in these subgroups are too small to make a firm conclusion.

A thorough QT/QTc study was not conducted. Given the nature of the disease and proposed indication and possible use of the drug, a thorough QT/QTc study was not deemed necessary. The applicant assessed serial ECGs from other studies. Analyses of these ECGs suggest possible QT prolongation and ST/T wave changes with icatibant. One subject had 120 msec QTcF prolongation with ST/T wave change after dosing and another subject had 38 msec QTcF prolongation after dosing.

6. Clinical Microbiology

The drug product is (b) (4) Controls around these processes are adequate. The applicant has not provided container closure integrity study and sterility assurance information on the needle to be included in the final packaging of the product. These deficiencies will be communicated in the action letter.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

The clinical program submitted with this application consists of two relatively small sized phase 3 studies. The scope of the clinical program and the size of the studies are reasonable for this orphan indication. Some characteristics of the pivotal studies are shown in Table 1. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

Table 1. Pivotal clinical studies

ID	Study type	Study duration	Patient Age, yr	Treatment groups*	N (ITT)	Study Year#	Countries
2101	Efficacy and safety Phase 2, open label	Single dose	18 - 65	I 0.4 mg/kg, 2h I 0.4 mg/kg, 30 min I 0.8 mg/kg, 30 min I 30 mg IV I 45 mg IV	4 3 4 3 1	2004	Germany
2102	Efficacy and safety Phase 3	Single dose	19 - 68	I 30 mg SC TA 3 x 1, 2 days	36 38	2006	EU
2103	Efficacy and safety Phase 3	Single dose	18 - 58	I 30 mg SC Placebo	27 29	2006	USA, Canada, Argentina, Australia,
4102	Observational PRO assessment study			No intervention	57	2007	EU, USA, Canada, Argentina, etc
* I = Icatibant, TA = Tranexamic acid; Studies 2102 and 2103 had open label extension							
# Year study subject enrollment ended							

b. Design and conduct of the studies

The pivotal clinical studies included a small open-label proof-of-concept dose-ranging study (study 2101), and 2 phase 3 studies (study 2102 for FAST 2, and study 2103 for FAST 1). Study 2101 was small and of limited value and is not discussed further in this document.

The general design of the phase 3 studies (study 2101 and study 2103) was similar. Both were randomized, double-blind, double-dummy, and multi-center in design conducted in HAE patients in a physician supervised setting during acute attacks. A key difference was the use of controls; study 2102 used TA as the active control; study 2103 was placebo controlled. Patients were dosed within 6 hours of onset of symptoms and were observed for up to 48 hours for symptom assessments. Patients with laryngeal attacks were not randomized but received icatibant 30 mg SC. The primary efficacy endpoint was the time from the beginning of receiving treatment to the onset of symptom relief as measured by a visual analogue scale (described further below). Secondary efficacy endpoints included response rate at 4 hours, time to relief of each symptoms present at pre-dose, time to almost complete symptom relief, assessment of each symptom on a 0-5 scale (none, mild, moderate, severe, very severe), and investigator global assessment. No composite symptom scoring was performed by patients. Safety assessment included recording of adverse events, vital signs, clinical laboratory measures, ECG, and physical examination. Patients treated in the double-blind phase were then continued into open-label extension phase.

There are major concerns with the design and conduct of the phase 3 studies noted below:

Primary efficacy variable

The primary efficacy variable in the phase 3 studies was time to onset of symptom relief assessed by a VAS for the single most severe presenting symptoms before treatment. The VAS is a 100 mm horizontal line with 0 mm as no symptom and 100 mm as worst possible symptom. The symptoms rated included cutaneous swelling, cutaneous pain, abdominal pain, and nausea. Time to onset of symptom relief was defined as the time between injection and the time of symptom relief (defined as an absolute reduction from pretreatment VAS of ≥ 20 mm if pre-treatment VAS was ≥ 30 and ≤ 50 , or of ≥ 30 mm if pre-treatment VAS was > 50 mm). This rather complicated definition of symptom relief is not intuitive. It is quite removed from actual patient report of symptom scores. Also it is based on identification of one predominant symptom, which may not capture the extent of a whole HAE attack.

Study 4102 was an observational non intervention study to define the Minimum Clinically Significant Difference (MCSD) of the VAS. During HAE attacks, patients completed VAS, and a patient rated Verbal Description Scale (VDS) that rated symptom change from baseline as “much less,” “a little less,” “the same,” “a little more,” or “much more.” The applicant designated the VDS as the “gold standard.” Based on comparison of VAS to VDS, a 9 mm change in VAS was identified as the MCSD for symptom relief. Changes in the VAS corresponded to changes in VDS ($r=0.76$; $p<0.0001$). The problem with this validation is that VDS is another patient reported outcome that itself does not seem to be validated. Nevertheless, VDS seems to be more intuitive and close to patient report of symptoms. If VDS is indeed the “gold standard,” it begs the question as to why VDS was not itself used as the primary endpoint, or even a secondary endpoint in the phase 3 studies.

The applicant attempted to provide further validation of the VAS by pooling data from the two phase 3 studies and comparing VAS to physician assessment to assess the test-retest reliability and clinical validity. These analyses did not provide reliable results and VAS appeared to have limited test-test validity.

Choice of active control

The selection of TA as an active control is questionable. The efficacy of antifibrinolytic agents such as TA or EACA for the treatment of acute attack of HAE is not established. TA is approved in some EU countries and South Africa for HAE. The package insert and existing literature seems to support its use for chronic long term therapy, but not for acute attacks. Extensive literature search shows 3 studies that used TA for acute attacks. In one double-blind study involving 5 patients treated with TA or placebo for 2-4 months, 2 patients received acute intermittent treatment at start of acute attack and 3 patients received continuous treatment. One of the 2 patients receiving acute treatment is reported to have benefited.³ In an open label study involving 7 patients, 4 patients received TA during acute attacks, and 3 patients received TA during an acute attack and also received continuous TA treatment. Six of these 7 patients are reported to have improved during

³ Blohme G. Treatment of hereditary angioneurotic edema with tranexamic acid: a random double-blind cross-over study. Acta Med Scand 1972; 192:293-298.

acute attacks by TA treatment.⁴ In another open label longitudinal study, 27 patients are reported to have less severe attacks with a high dose of TA (1 g every 3 to 4 hours) given during acute attacks.⁵ There are no published studies reporting benefit with EACA in acute attacks of HAE.

The existing data do not support use of TA as a valid active control. With no data supporting its use, an important question is whether TA could perform worse than placebo. The applicant submitted expert opinion (b) (4)

stating that TA is not worse than placebo. The results of the phase 3 studies do not support this assertion. TA performed appreciably worse in one phase 3 study compared to placebo in the other phase 3 study (data shown in the subsequent section). While the validity of cross study comparison is limited, the comparison nevertheless does not support the expert opinion assertion.

Another problem of using TA is the fact that TA is dosed orally. It is not known to what extent absorption of TA can be effected (either increased or decreased) in patients with HAE presenting with abdominal symptoms with presumed intestinal wall edema.

Blinding

Both phase 3 studies were designed to be blinded, but there is no assurance that the blinding succeeded. Icatibant is associated with a high rate of injection site reaction, and TA is associated with a high frequency of nausea, vomiting, and diarrhea, as well as color vision disturbance. It is not possible to predict whether a compromise of blinding would favor icatibant or the comparator group. Nevertheless, possible incomplete blinding somewhat undermines the strength of the efficacy findings.

Selection of dose

Dose selection was based on PK-PD modeling using bradykinin challenge in healthy subjects. Doses ranging from 0.005 mg/kg to 3.2 mg/kg IV icatibant were used to establish a dose response to bradykinin, based on measurement of blood pressure, heart rate, and cutaneous blood flow. The phase 3 dose was selected based on expected systemic bradykinin concentration anticipated during an HAE attack. With that assumption no formal dose-ranging study was performed, and it may be difficult to do given the limited number of subjects available for study, and the subjective nature of efficacy measure. Although PK-PD modeling data suggest that a higher dose is unlikely to increase efficacy substantially, it is unclear how representative the modeling is in HAE patients. It may be prudent for the applicant to explore higher doses if the 30 mcg dose ultimately fails to show substantial efficacy.

⁴ Ohela K. Treatment of hereditary angioneurotic edema with tranexamic acid and cinnarazine. *Acta Dermatovener* 1976; 56:61-67.

⁵ Agostoni A, Cicardi M. Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. *Medicine* 1992; 71:206-215.

c. Efficacy findings and conclusions

Findings of studies 2102 and 2103 do not support efficacy of icatibant at a dose 30 mg SC for treatment of acute attacks of HAE.

Findings of the primary efficacy endpoint for the primary endpoint and for the two major organ systems are shown in Table 2. Icatibant was statistically superior to TA, but not to placebo. Subgroup analysis for study 2102 suggested a differential response according to gender. The time to onset of symptom relief was 3.5 hours in male patients compared to 1.6 hours in female patients. No difference was observed by stratifying patients on body weight or by race in this study. Subgroup analysis in study 2103 did not show any difference according to gender. Secondary efficacy endpoint analyses were generally consistent with the primary endpoint analysis. Efficacy data to support laryngeal attacks were limited. There were 3 patients in study 2102 with laryngeal symptom, 2 of whom reported regression of symptoms by 0.3 hour and 1 hour post treatment and 1 patient was intubated and unable to complete symptom scoring. In study 2103, there were 8 patients with laryngeal attacks and the median time to regression was 0.6 hours.

The two controlled studies are suggestive of icatibant's efficacy for treating acute attacks of HAE, but the data provided from these two studies are not convincing or adequate to support approval. The placebo controlled study (study 2103) showed numerical trends in favor of icatibant, but did not reach statistical significance of superiority over placebo. The active controlled study showed statistically significant difference in favor of icatibant, but the conclusion is questionable and not sufficient to support approval because of issues with choice of the active control as discussed above. Both studies have issues with the primary efficacy endpoint, and blinding as discussed above. To support approval, the applicant will need to conduct a clinical program to show superiority of icatibant over placebo. A reasonable active control that can be used in a clinical program possibly does not exist. The clinical program should use a patient centric efficacy measure, such as the VDS scale, and also use the VAS to link back to the clinical studies already conducted.

Table 2. Median time to onset of symptom relief in hours

	Icatibant	Tranexamic acid (TA)	Placebo	p vs TA	p vs Pbo
Study 2102	n = 36	n = 38			
Median time (Primary endpoint) *	2.0	12.0		<0.001	
Cutaneous attacks	2.5	18.2		<0.001	
Abdominal attacks	1.6	3.5		0.026	
Study 2103	n = 27		n = 29		
Primary endpoint *	2.5		4.6		0.142
Cutaneous attacks	3.4		10.0		0.221
Abdominal attacks	2.0		6.3		0.159
* Median time to onset of relief in hours as measured by 0-100 mm visual analog scale on cutaneous swelling, cutaneous pain, abdominal pain, and nausea					

8. Safety

a. Safety database

The safety database for icatibant 30 mg is based primarily on data from two phase 3 studies (Table 1). The safety database includes 63 patients treated in the controlled portions of the studies. Additional safety data is obtained from the open-label portions of these studies that included patients rolled over from the controlled portions and other patients enrolled after completion of double-blind portions. The database is limited, but adequate for this orphan disease and the limited scope of treatment of acute attacks of HAE.

b. Safety findings and conclusion

The safety data were generally supportive, but the major limitation is that efficacy has not been established. Safety will ultimately be assessed in the context of an efficacious dose and a successful program. Nevertheless, in the clinical program no significant finding of concern was seen. There were some serious adverse events, but the temporal relationship to dose did not suggest causality, and some serious adverse events were difficult to interpret in the presence of acute HAE attacks. The most common adverse event was injection site irritation, which was expected with the preclinical toxicology study showing the same finding.

c. REMS/RiskMAP

REMS and RiskMAP will likely not be necessary for this drug. A final decision will be made later prior to approval.

9. Advisory Committee Meeting

A Pulmonary and Allergy Drug Advisory Committee (PADAC) meeting was scheduled for February 20, 2008. The meeting was scheduled as soon as the NDA was received and before any review of the data because this was a priority review. It was thought that a meeting would be necessary because icatibant is a new molecular entity and first-in-the class, the indication is unique with no other drugs approved to treat acute attacks of HAE, and the disease is rare with an orphan status. As the review proceeded it became evident that the submitted studies do not provide adequate evidence of efficacy of icatibant. Thus the PADAC meeting was cancelled and the applicant notified of the reason for the cancellation in a teleconference on January 11, 2008.

10. Pediatric

The Pediatric Research Equity Act is not triggered because of the orphan status of the application. The phase 3 clinical studies enrolled patients 18 years of age and older. HAE occurs in pediatric patients and it is expected that younger patients will be evaluated once efficacy and safety in adults is shown. At the pre-NDA meeting the applicant stated that it plans to study pediatric patients later. This plan is reasonable and acceptable.

11. Other Relevant Regulatory Issues

a. DSI Audits

DSI audited two sites recommended by the clinical review team. These two sites enrolled the largest number of patients in the pivotal phase 3 studies. Audit of these sites showed some compliance violations and inadequate clinical monitoring of study sites; however, the observations did not appear to significantly alter the overall study outcome. Review of the application did not identify any irregularities that would raise concerns regarding data integrity. No ethical issues were present. All studies were conducted in accordance with accepted ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. The applicant certified that no investigator entered into any financial arrangements that could affect the outcome of the study.

c. Others

There are no outstanding issues with consults received from DDMAC, DMETS, or from other groups in CDER.

12. Labeling

a. Proprietary Name

The proposed proprietary name Firazyr was reviewed by DMETS and found to be acceptable. The name was also found to be acceptable to DDMAC from a promotional perspective.

b. Physician Labeling

The labeling was not reviewed in detail during review of this application because the application cannot be approved based on the submitted data. The applicant will need to conduct at least one more phase 3 study to support approval, and based on that study or other studies the label will be substantially different than the present version. It will be more useful to do a comprehensive label review and discuss with the applicant with a label that is expected to be final or close to final.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division, and DMETS, and found to be generally acceptable. The drug product name needs to be changed from (b) (4) to "Firazyr (icatibant) Injection, 30* mg" (b) (4)

Also the carton labels contain a graphic symbol that should be removed as it decreases the prominence of the proprietary name and established name.

d. Patient Labeling and Medication Guide

There is not patient labeling for this product as it is proposed to be administered by a health care provider.

13. Action and Risk Benefit Assessment

a. Regulatory Action

The submitted clinical data has failed to demonstrate substantial evidence of efficacy for icatibant 30 mg subcutaneous injection for acute treatment of HAE. The action on this application will be Not Approval.

The demonstrated efficacy of icatibant over TA in one study is not adequate because efficacy of TA in acute attacks in HAE is not known. The placebo control study failed to demonstrate statistically significant difference between icatibant and placebo. In addition, there are concerns regarding validity of the use of VAS as the primary efficacy variable. Without substantial evidence of efficacy of the proposed dose of icatibant, safety cannot be assumed. To support approval of this product the applicant will need to conduct a clinical program showing efficacy of icatibant over placebo in acute attacks of HAE. The study should use reliable measures of efficacy, such as the VDS described by the applicant as the “gold standard” and also include the VAS as frame of reference to the phase 3 studies already conducted.

Icatibant is likely to be used in setting outside the usual healthcare delivery setting, such as use by patients at home. The applicant will need to provide data to show that icatibant can be safely used at such setting.

Data from the clinical program indicate that both age and gender have effects on icatibant exposure. The applicant will need to explore the scientific basis of these differences in exposure, and also justify the same dose regardless of age and gender.

There are also substantial comments from other disciplines, notably Chemistry, Manufacturing, and Controls, and Nonclinical Pharmacology and Toxicology, which will be included in the action letter.

b. Risk Benefit Assessment

The overall risk and benefit assessment of icatibant does not support its approval as discussed above in section 13 a.

c. Post-marketing Risk Management Activities

Not relevant because the application will not be approved.

d. Post-marketing Study Commitments

Not relevant because the application will not be approved.

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/s/

Badrul Chowdhury
4/23/2008 01:22:12 PM
MEDICAL OFFICER

Summary Basis for Regulatory Action

Date	April 22, 2008
From	Curtis J Rosebraugh, MD, MPH Acting Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	22-150
Proprietary / Established (USAN) Names	Firazyr Icatibant
Dosage Forms / Strength	Injection 30 mg
Proposed Indication(s)	Hereditary angioedema (HAE)
Action:	<i>Not Approval</i>

1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action on icatibant and I refer the reader to the reviews in the action package for a more detailed discussion. Jerini US Inc. is seeking licensing approval under the orphan drugs provisions (CFR 316) for icatibant, which is a synthetic decapeptide competitive antagonist of the bradykinin type 2 (B2) receptor, for use in the treatment of acute attacks of hereditary angioedema (HAE) in patients 18 years of age and older. Currently domestically approved treatments for HAE include the androgenic steroid Danazol, but it is only approved for the prevention of attacks of angioedema. There are no approved products for use in acute attacks of HAE although effective therapies for acute attacks of HAE are sorely needed. In other countries (European Union and South Africa), epsilon aminocaproic acid (EACA) and tranexamic acid (TA) are approved for use in HAE, although foreign package inserts do not specify whether the indication is for chronic or acute treatment. The review team performed a literature search to evaluate the possible efficacy of TA in acute attacks, as this is an important issue regarding the sponsor's use of TA as a comparison group, but were unable to find literature that demonstrate adequate trials for the efficacy of TA for acute HAE. Literature reviewed by Dr. Chowdhury would indicate that TA may not be effective in acute attacks (the reader is referred to Dr. Chowdhury's review for further details).

HAE is caused by deregulation of the complement cascade. The activity of the first component of complement, C1, is controlled by a serine protease inhibitor known as C1 inhibitor (C1INH). Inherited deficiency (autosomal dominant) of C1INH results in excessive activation of C2 and C4 which ultimately results in the symptoms of HAE which are episodic, localized, and recurrent edema of skin, gastrointestinal tract and upper airway. It is believed by the sponsors, and others, that a consequence of the uncontrolled activated complement cascade is the uncontrolled release of the vasoactive peptide bradykinin which is thought to be partially or wholly responsible for the symptoms. Therefore, icatibant, while not affecting the

disease or the cascade pathway itself, was designed to block the product of the cascade pathway (bradykinin) and its biologic effects by competitively blocking the B2 receptor.

The main reason for a 'not approval action' is because the sponsor has not adequately demonstrated efficacy. I will discuss that below, but would like to note that there were other deficiencies or noted safety issues, none of which insurmountable or a cause for a 'not approval' action (although some of the CMC issues may have resulted in an 'approvable' action):

Regarding CMC, there are some issues regarding qualification of impurities in the drug substance and product, tightening of acceptance criteria, stability protocol data requests and data requests to support the 18 month expiry which is not presently supported by the submitted stability data.

Regarding Pharm/Tox, the sponsor has not completed chronic, repeat-dose toxicity studies. Although they have completed non-clinical studies supporting acute use of their product, they will need to have animal data to support the chronic intermittent clinical dosing which will clearly occur should this product ever receive approval.

Regarding Pharmacology and biopharmaceutics, icatibant has not been evaluated in a thorough QT study. This is because in clinical study, icatibant has demonstrated a prolongation of QT. As such, a thorough study is moot and the label should indicate the QT and EKG findings that were demonstrated in the clinical trials.

A clinical development program for HAE at present relies on patient reported outcomes (PRO) as there are no objective measures available for evaluation in this situation that are predictive of disease activity. Due to the limited population and limited interest by others in HAE, there has not been a great deal of work done in this area, so there is not a well-established development program that the sponsors could follow. The clinical program itself had very limited exposure of drug to patients, but that is also to be expected in a program seeking an orphan indication. The demonstration of efficacy for HAE rests on two small trials. These trials are discussed in the excellent reviews of Drs. Limb, Seymour and Chowdhury and I would refer the reader to those for a detailed description.

The two trials were of similar design, except one trial compared icatibant to placebo and the other trial compared icatibant to TA. Both of these trials would have probably had some blinding issues as the injection of icatibant is irritating due to the drug and not the vehicle. This will probably always be an issue, even with future trials. Both trials also relied on a patient symptoms measure developed by the sponsor that was a Visual Analog Scale (VAS) based on a 100mm horizontal line, which was itself based on a patient rated Verbal Description Scale (VDS) which has been used in the past in clinical research. The sponsor was using the VAS to measure the highest rated single symptom (vs. a complex) to the patient (i.e. cutaneous swelling or pain, abdominal pain or nausea). The primary endpoint was time to onset of symptom relief based on a derived clinically important change in the VAS. The minimal clinically significant difference in VAS scores is discussed in detail in the other

reviews but I would comment that the formula the sponsor has arrived at is not intuitive or easily understandable.

Results from these two studies are summarized below in the table from Dr. Seymour's excellent review:

Primary Endpoint - Median Time to Onset of Symptom Relief (hours)				
	Icatibant 30mg SC	Tranexamic Acid	Placebo	p value
Study 2102	N=36	N=38		
All attacks	2.0	12.0		<0.001
Cutaneous attacks	2.5 (n=24)	18.2 (n=23)		<0.001
Abdominal attacks	1.6 (n=12)	3.5 (n=15)		0.026
Study 2103	N=27		N=29	
All attacks	2.5		4.6	0.142
Cutaneous attacks	3.4 (n=14)		10.0 (n=13)	0.221
Abdominal attacks	2.0 (n=13)		6.0 (n=16)	0.159

In study 2103, the sponsor failed to demonstrate overall statistical significance. The difference in time to onset of their definition of clinical important relief was 2.1 hours. This is in contrast to study 2102 where the sponsor did demonstrate overall statistical significance when compared to TA. It has been noted that across studies, the time to relief for TA was much longer than that of placebo (12 hours compared to 4.6 hours). This could lead one to wonder if TA, while having little evidence in the literature of its efficacy in acute HAE, is actually detrimental in treating HAE. Although it is tempting to make cross study comparisons, this should only been done as a hypothesis generation exercise and with great caution, particularly in small studies where one cannot rely on large numbers in the randomization to avoid any potential biases. It could be that there were imbalances in the numbers of persons with cutaneous attacks vs abdominal attacks or gender differences (women seem to respond sooner to treatment) such that tranexamic seems to have worse effects when in reality it is a matter of confounding due to assignment (more men with cutaneous attacks in the tranexamic acid arm) and limited trial size. However, the results for study 2102 must be kept in mind, as well as the limitations, and do not convincingly demonstrate that icatibant has clinical efficacy, or that TA is detrimental. Most of the secondary endpoints revealed the same type of results as discussed above. Safety is thoroughly discussed in all the reviews and no safety signals that would preclude marketing were noted, but it was a limited data base.

2. Conclusions and Recommendations

HAE is a rare disorder that is in need of effective therapies for when patients have acute attacks. The sponsor has submitted a database that does not demonstrate efficacy to the extent that would allow marketing. As such, the sponsor will need to provide further evidence that icatibant has the purported effect.

This may be accomplished with one trial instead of two, but it would have to be robust as the two existing would only be minimally supportive and we have questions regarding the evaluation instrument. Further development will also have to include a PRO that we feel can adequately monitor for clinically important efficacy for the disease complex. This application is a Not Approval as further trials will be needed.

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/s/

Curtis Rosebraugh
4/23/2008 01:52:42 PM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW**Division of Pulmonary, Allergy, and Rheumatology Products**

Application #: NDA 22-150	Application Type: NDA Complete Response
Applicant: Shire	Proprietary Name: Firazyr
Clinical Reviewer: Brian Oscar Porter, M.D., Ph.D., M.P.H.	USAN Name: Icatibant
Team Leader: Susan Limb, M.D.	Category: Bradykinin B2 Receptor Antagonist
Review Date: April 13, 2011	Route: Subcutaneous Injection

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	Submission Type	Comments
February 25, 2011	NDA 22-150 SD-21	Electronic submission

REVIEW SUMMARY: This is a Complete Response Planning Review of a Complete Response to a Not Approvable letter issued for NDA 22-150 on April 23, 2008, for the decapeptide bradykinin receptor antagonist icatibant with a proposed indication of the treatment of acute attacks of hereditary angioedema, delivered as a subcutaneous injection. Icatibant is not approved in the U.S. for any other indication, although it is currently approved in the European Union for this indication. The Complete Response submission includes data to support this proposed indication from a new placebo-controlled Phase 3 clinical trial (HGT-FIR-054) that was not included in the original NDA submission.

The clinical review concludes that the Complete Response is adequate for review.

OUTSTANDING ISSUES: None

RECOMMENDED REGULATORY ACTION: None

I. General Information and Background

Jerini, U.S. originally submitted NDA 22-150 via the 505(b)(1) pathway on October 22, 2007, to seek approval for the synthetic decapeptide bradykinin B2 receptor antagonist icatibant (Firazyr) for the treatment of hereditary angioedema (HAE), later revising this indication to the treatment of acute attacks of HAE. The Division subsequently issued a Not Approvable action letter on April 23, 2008, which cited multiple CMC deficiencies (discussed in the CMC Planning Review by Dr. Eugenia Nashed), the lack of long-term nonclinical toxicity studies (discussed in the Pharmacology/Toxicology Planning Review by Dr. Timothy Robison), age and gender effects on icatibant pharmacokinetics (discussed in the Clinical Pharmacology Planning Review by Dr. Partha Roy), as well as the following deficiencies in the icatibant clinical 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. 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. 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 (on behalf of Jerini) submitted a Complete Response to this Not Approvable letter, which addressed the concerns above as follows:

Demonstration of Clinical Efficacy

With regard to establishing the clinical efficacy of icatibant, the original NDA submission included two Phase 3 clinical trials of patients presenting with acute HAE attacks who were treated with either icatibant 30 mg SC (up to 3 injections per attack, given at least 6 hours apart), placebo, or tranexamic acid (1000 mg administered orally up to 3 times over 2 days, given at least 6 hours apart), depending on the particular trial. JE049-2103 (FAST-1) was a placebo-controlled trial of icatibant in 64 patients (56 with cutaneous or abdominal edema, who were randomized to icatibant versus placebo and 8 patients with laryngeal edema, who were treated with open-label icatibant). JE049-2102 (FAST-2) was an active-controlled trial of icatibant versus tranexamic acid in 77 patients (74 with cutaneous or abdominal edema, who were randomized to icatibant versus tranexamic acid and 3 patients with laryngeal edema,

who were treated with open-label icatibant). A total of 72 subjects were treated with icatibant during the extension phase of FAST-1, while 54 subjects were treated during the extension phase of FAST-2.

In brief, although a numerical trend in favor of icatibant efficacy was observed in FAST-1, statistically significant differences were not observed in the primary efficacy endpoint of time to onset of symptom relief, as determined by self-reported Visual Analogue Scale (VAS) ratings of the primary symptom manifestation based on the predominant location of the HAE attack (e.g., skin, abdomen). In contrast, FAST-2 demonstrated a statistically significant decrease in the time to onset of symptom relief in the icatibant arm versus the active-control tranexamic acid arm. However, upon initial review of this NDA, the Division indicated that tranexamic acid was an inappropriate comparator for the study of HAE, given that it is not an approved treatment for acute HAE attacks in the U.S., and it was unclear whether this agent could potentially lengthen the time to symptom relief in the control arm, thereby inflating any positive 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 that the Applicant conduct an additional placebo-controlled trial of icatibant of similar scope as FAST-1 and FAST-2, using the same efficacy endpoint (time to symptom onset based on the VAS primary symptom rating) in order to establish replicate efficacy results in support of the proposed claim. The Applicant responded by completing trial HGT-FIR-054 (FAST-3), which was a placebo-controlled trial conducted in 93 subjects and similar in design to FAST-1, with the main difference being the selection of the primary efficacy endpoint. Despite recommendations by the Division during the post-NDA follow-up meeting dated December 15, 2008, to use the same primary endpoint in FAST-3 as was used in FAST-1 and FAST-2, the Applicant designated a new primary efficacy endpoint of time to onset of symptom relief based on a composite VAS rating (denoted as VAS-3), which encompassed skin pain, skin swelling, and abdominal pain, as the collective symptom components. However, time to onset of symptom relief based on the primary symptom complex VAS rating (as in FAST-1 and FAST-2) was still examined and reported as a secondary endpoint. A complete Clinical Study Report has been submitted for FAST-3 with this Complete Response, which appears to adequately address this deficiency for the purposes of initiating review. The major findings of FAST-3 are discussed in Section V of this review.

Of note, concerns were also raised by the Division in the Not Approvable action letter regarding the validity of the VAS rating scale used to operationalize the primary efficacy endpoints for FAST-1 and FAST-2. The Applicant responded to these concerns by completing a series of PRO validation studies that were communicated to the Division in a request for Special Protocol Assessment for the FAST-3 protocol, dated February 13, 2009. In a No Agreement SPA letter dated April 2, 2009, the Division indicated that these validation studies were consistent with the draft Agency guidance on PRO development.

Safety of 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) in 56 subjects to assess the safety, tolerability, and patient 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 previously treated with icatibant) were trained in the self-administration of icatibant using a placebo-filled syringe. Non-naïve subjects were given a single icatibant syringe for

self-administration and a symptom diary and were given permission to self-administer this dose at the outset of their next HAE attack. 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 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 self-treatment, and 95 additional subjects were enrolled in the trial, trained in the use of icatibant, but never experienced an HAE attack and therefore did not self-administer icatibant. The Applicant suggests that the nature and severity of adverse events documented in this trial following self-administration of open-label icatibant were similar to what was observed in prior clinical trials of icatibant administered in medical settings by healthcare professionals and identified no new safety signals. A full Clinical Study Report was submitted for JE049-3101 as part of this Complete Response, which appears to adequately address this deficiency for the purposes of initiating a review.

Dose Selection based on Clinical Endpoint or Biomarkers

The Applicant states that icatibant dose selection was originally based on several clinical pharmacology studies, pharmacokinetic/pharmacodynamic modeling, and data generated from a human bradykinin challenge model. An integrated analysis of these data are presented in this Complete Response, in which the Applicant argues that the 30 mg SC dose of icatibant carried forward into three pivotal Phase 3 clinical trials is safe and effective for the proposed indication and no further dose definition is unnecessary. The Applicant also describes findings from two additional clinical pharmacology studies (HGT-FIR-061, a QT prolongation study, and HGT-FIR-065, a pharmacokinetic study in healthy adults) that were conducted since the original NDA was denied approval, which are said to further support the designated dose selection. Complete study reports for both of these new studies are included in this Complete Response submission and the information submitted appears adequate to initiate review.

II. Icatibant Clinical Development Program

The Phase 1 clinical program for icatibant consisted of five Phase 1 trials (four placebo-controlled and one open-label) of icatibant in healthy subjects: two single dose trials and three repeat dose trials. As noted in Table 1, this program assessed the effects of icatibant on QT prolongation, reproductive hormone effects, pharmacokinetics, and bioavailability. The Phase 2 program consisted of a single open-label proof-of-concept trial in patients with HAE that assessed the efficacy, safety, pharmacokinetics, and pharmacodynamic properties of icatibant as acute treatment for HAE attacks. All of these Phase 1 trials were submitted and reviewed with the original NDA submission, except for HGT-FIR-061 (QT prolongation study), which along with the Phase 2 trial HGT-FIR-065 (pharmacokinetic study in healthy adults), was completed after issuance of the Not Approvable action letter and submitted with this Complete Response.

The Phase 3 clinical program for icatibant in the acute treatment of HAE attacks in adults 18 years of age and older was based on four trials. The first two of these trials (FAST-1 and FAST-2) were submitted and reviewed in the original application for NDA 22-150, whereas a complete study report for FAST-3 is included in the current Complete Response submission. In addition, a fourth Phase 3 trial

(JE049-3101) was conducted in response to the clinical deficiency noted in the Not Approvable letter indicating that additional data were needed to establish the safety of SC icatibant for self-administration.

Table 1. Clinical development program for icatibant in the treatment of acute attacks of HAE

Trial	Phase	Subjects	Design	Treatment Arms	Duration	Relevance
HGT-FIR-061	I	Healthy subjects, 18-50 yrs (82)	R, PC, AC, 4-period XO	Icatibant 30 mg SC Icatibant 90 mg SC Placebo Moxifloxacin 400 mg	Single dose (4 cycles)	QT prolongation study
HGT-FIR-062	I	Healthy subjects, 18-35 yrs (39)	R, PC, DB	Icatibant SC Placebo	Up to 3 doses every 6 hours on Days 1, 4, 7	Effect on reproductive hormone levels
HGT-FIR-065	I	Healthy subjects, >45 yrs (21)	OL, MD	Icatibant 30 mg SC	Up to 3 doses every 6 hours for 22 days	PK of icatibant and M1/M2 metabolites
JE049-1102	I	<u>Part I:</u> Healthy (16) <u>Part II:</u> Healthy (24)	<u>Part I:</u> DB, PC, AD <u>Part II:</u> R, OL, XO	<u>Part I:</u> Icatibant 0.05 mg/kg SC (40 mg/mL) Icatibant 0.2 mg/kg SC (40 mg/mL) Icatibant 0.2 and 0.4 mg/kg SC (20 mg/mL) <u>Part II:</u> Icatibant 0.4 mg/kg SC (10 or 20 mg/mL) Icatibant 0.4 mg/kg IV	<u>Part I:</u> Single ascending dose <u>Part II:</u> Single dose	Bioavailability of SC versus IV delivery
JE049-1103	I	Healthy (32)	DB, PC	Icatibant 30 mg SC (3 doses every 6 hours on Day 1 and single dose on Days 8 and 15)	5 doses over 15 days	PK, safety (including QT) in young and elderly subjects
JE049-2101	II	Adults with HAE, 18-≤65 yrs (35)	OL, POC, RD	Icatibant 0.4 mg/kg IV (0.5 hr infusion) Icatibant 0.4 mg/kg IV (2 hr infusion) Icatibant 8 mg/kg IV (0.5 hr infusion) Icatibant 30 mg SC Icatibant 45 mg SC	Sequential dosing over 5 days	Efficacy, safety and tolerability, PK, PD
JE049-2102	III	Adults with HAE (74)	R, DB, AC *24-wk OL Ext	Icatibant 30 mg SC Tranexamic acid 1 gm PO	Single dose for 14 days	Efficacy versus tranexamic acid on time to onset of symptom relief (primary symptom VAS rating)
JE049-2103	III	Adults with HAE (64)	R, DB, PC *24-wk OL Ext	Icatibant 30 mg SC Placebo	Single dose for 14 days	Efficacy versus placebo on time to onset of symptom relief (primary symptom VAS rating)

HGT-FIR-054	III	Adults with HAE (98)	R, DB, PC *OL Ext	Icatibant 30 mg SC Placebo	Single dose for 14 days (EXT ongoing)	Efficacy versus placebo on time to onset of symptom relief (composite symptom VAS rating)
JE049-3101	III	Adults with HAE (150; 56 complete)	OL	Icatibant 30 mg SC	Single dose (2 days non-naïve and 2 days naïve)	Safety of self-administration of SC drug

III. Foreign Marketing and Regulatory History

Icatibant was approved for use in the European Union on July 11, 2008, and is currently approved in 36 countries worldwide for the treatment of HAE attacks. A brief timeline of key regulatory events and Division guidance regarding NDA 22-150 is presented below:

- **November 25, 2003:** Orphan Drug Designation granted
- **June 15, 2004:** Fast Track Designation granted
- **September, 2005:** Re-assignment of IND from Division of Gastrointestinal and Coagulation Drug Products to DPARP
- **October 22, 2007:** NDA 22-150 submitted by Jerini, U.S. for acute treatment of HAE attacks
- **April 23, 2008:** Division issues Not Approvable letter (see Section I for description of clinical deficiencies)
- **December 15, 2008:** End-of-Review Meeting to discuss approach to VAS PRO endpoint validation and requirements to establish icatibant efficacy for proposed indication (i.e., the need for an additional placebo-controlled trial)
- **February 13, 2009:** Request for Special Protocol Assessment submitted for an additional pivotal Phase 3 trial, FAST-3; submission also included PRO validation studies for the VAS.
- **April 2, 2009:** No Agreement Letter issued by Division in response to request for Special Protocol Assessment for FAST-3, citing lack of agreement with proposed primary and secondary efficacy endpoints and trial participation criteria; however, PRO validation studies for VAS noted by Division to be consistent with draft Agency guidance on PRO development.
- **April 13, 2009:** Comments sent from the Division regarding Clinical Protocol JE049-3101 (safety assessment of self-administered icatibant), indicating reasonableness of approach, while suggesting that similar efficacy endpoints be assessed as for FAST-1 and FAST-2, as well as the Visual Descriptor Scale (VDS) for validation purposes.
- **June 2, 2009:** Teleconference held in which Division recommended that FAST-3 keep the same primary endpoint as used in FAST-1 and FAST-2, with a similar sample size, include the VDS as an assessment tool, and incorporate the blinded evaluation of icatibant for the treatment of acute laryngeal HAE attacks, which was not included in the designs of FAST-1 and FAST-2.
- **February 25, 2011:** Complete Response submitted by Shire on behalf of Jerini

IV. Items Required for Review Planning (21 CFR 314.50)

The following items pertinent to the NDA Complete Response were included in this submission:

- Form FDA 356h [Vol 1.1.2]
- Debarment certification [Not required for Complete Response; see original NDA submission]
- Financial disclosure statement [Vol 1.3.4]
- Statement of Good Clinical Practice [Vol 2.5, Clinical Overview Section 2.5.1.4.3]
- Summary of Efficacy and Safety [Vol 2.5; Vol 2.7.3; Vol 2.7.4]
- Integrated Summary of Effectiveness (ISE) [Vol 5.3.5.3.27]
- Integrated Summary of Safety (ISS) [Vol 5.3.5.3.28]
- Complete study report for HGT-FIR-054 (FAST-3) [Vol 5.3.5.1.3]
- Literature review for safety [Vol 2.7.4; Summary of Clinical Safety Section 2.7.4.6.3]
- Proposed labeling and annotated labeling [Vol 1.14.1]
- Integrated summary of benefits and risks [Vol 2.5, Clinical Overview Section 2.5.6]
- Overdose information provided in labeling [Vol 1.14.1.2, Full Prescribing Information Section 10], but no information on abuse potential is submitted

Reviewer's Comment: Icatibant has postmarketing safety data from Europe since its approval in July of 2008, with no apparent addiction safety signals. Given its intended infrequent episodic use for acute HAE attacks, its abuse potential appears limited.

- Environmental assessment [Not required for Complete Response; see original NDA submission]
- Summary data tabulations for primary and secondary outcome measures [Vol 5.3.5.1.3, Study Report HGT-FIR-054 (FAST-3); multiple locations throughout report]
- Individual subject level data listings [Vol 5.3.5.1.21 - 5.3.5.1.23]
- Case report forms for HGT-FIR-054 (FAST-3) [Vol 5.3.5.1.24]
- Electronic data sets for HGT-FIR-054 (FAST-3) [Vol 5.3.5.1.25.3]

V. Newly Submitted Pivotal Clinical Trial

A. 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

B. Responsible Medical Officer

Bradley J. Bloom, M.D.

C. Primary Objective

To compare efficacy of icatibant versus placebo on 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

D. Trial Design

Randomized, placebo-controlled, double-blind, multicenter, parallel group, Phase 3 efficacy and safety trial

E. Dosing Schedule/Materials

- Single dose of icatibant 30 mg SC versus placebo following first moderate to severe abdominal/cutaneous HAE attack
- Single dose of icatibant 30 mg SC versus placebo following first mild to moderate laryngeal HAE attack
- Single dose of icatibant 30 mg SC following first severe laryngeal HAE attack
- Up to 3 doses of icatibant 30 mg SC (separated by at least 6 hours) following any subsequent HAE attack

F. Trial Summary

1. Overview/Conduct

FAST-3 was a randomized, placebo-controlled, double-blind, multicenter, parallel group, Phase 3 efficacy and safety trial of icatibant for the acute treatment of abdominal, cutaneous, and laryngeal HAE attacks. Adult patients with a documented diagnosis of Type I or II HAE were screened and upon presentation of their first post-screening moderate to severe abdominal or cutaneous HAE attack or first mild to moderate laryngeal attack were randomized to receive a single dose of either icatibant 30 mg SC or placebo. Patients presenting with an initial severe laryngeal attack were treated with a single dose of open-label icatibant 30 mg SC. Subjects then continued into an open-label extension phase in which all HAE attacks were treated with up to three doses of icatibant 30 mg, each given up to every 6 hours. Efficacy was assessed as time to onset of symptom relief based on a patient-reported composite VAS rating comprised of skin swelling, skin pain, and abdominal pain.

2. Population

Adults with diagnosed HAE who experience moderate to severe abdominal or cutaneous attacks or mild to severe laryngeal attacks.

3. Treatment groups

Upon the first moderate to severe abdominal or cutaneous or mild to moderate laryngeal HAE attack, subjects were randomized to receive a single dose of either icatibant 30 mg SC or placebo. Initial severe laryngeal attacks were treated with a single dose of open-label icatibant 30 mg SC. All subsequent attacks of any area were treated with open-label icatibant 30 mg SC at up to three injections per attack every 6 hours.

4. Inclusion/Exclusion

Pertinent Inclusion Criteria

- Males or females ≥ 18 years
- Diagnosis of Type I/II HAE confirmed by decreased C4 levels and/or immunogenic/functional C1-INH deficiency or by medical history
- Current HAE attack in cutaneous, abdominal, or laryngeal areas
- Cutaneous or abdominal HAE attacks must have been moderate to very severe by investigator global assessment
- At least 1 VAS score ≥ 30 mm
- Commenced treatment within 6 hours of attack becoming at least mild (laryngeal) or moderate (abdominal and/or cutaneous) in severity, but not > 12 hours after onset
- Women of childbearing potential must have negative urine pregnancy test and use appropriate pregnancy prevention methods during study
- Voluntary informed consent

Pertinent Exclusion Criteria

- Diagnosis of angioedema other than HAE
- Prior icatibant treatment
- Previous participation in clinical trial and received another investigational product within past 30 days
- Treatment with pain medication since onset of current angioedema attack
- Treatment with ACE inhibitor
- Evidence of CAD (unstable angina, severe coronary heart disease, Class 3-4 CHF) based on history at screening
- Serious concomitant illness/condition that investigator feels would be contraindication to participation in trial
- Pregnancy or breastfeeding
- Unable to understand nature, scope, and consequences of protocol or unlikely to comply with protocol assessments and follow-up

5. Concomitant Medications

Attenuated androgens for prophylactic treatment of HAE were allowed at a stable or decreased dose, but doses could not be increased after screening. Prior replacement therapy (fresh frozen plasma or C1-INH) was allowed if given > 5 days prior to onset of current HAE attack. Other HAE rescue medications were permitted, but were avoided for as long as possible (ideally for 8-9 hours) following the initial injection of icatibant. Morphine sulfate 0.05 mg/kg or equivalent low-dose narcotic was permitted for analgesia. Anti-emetics, FFP, epinephrine, C1-INH, and NSAIDs were all permitted. Antihistamines and glucocorticoids were also permitted as concomitant, rather than rescue medications.

6. Outcome measures (Safety/Efficacy/PK)

Efficacy parameters

- **Primary:** Time to onset of symptom relief (50% reduction from baseline) based on symptom rating with composite patient-reported VAS in the non-laryngeal intention to treat population, based on three symptoms (skin swelling, skin pain, abdominal pain)
- **Secondary:** Efficacy in the non-laryngeal and laryngeal study populations was also assessed using patient- and investigator-assessed symptom scores for 10 symptoms, investigator global assessment of abdominal, cutaneous, and laryngeal symptoms, patient- and investigator-assessed clinical global impression and improvement, and patient- and investigator-assessed time to initial primary symptom improvement.

Safety parameters

- Local tolerability based on injection site reactions (e.g., erythema, swelling, burning, itching, warmth, pain)
- Adverse events (including worsened HAE symptoms within 48 hours of onset of attack)
- Immunogenicity
- Clinical laboratory results (chemistry, hematology, urinalysis)
- Physical examination and vital signs
- ECG

7. Statistical Considerations

A sample of 80 subjects (40 per treatment arm) was calculated to provide 80% power using the log-rank test for equality of survival curve at a 2-sided significance level of 0.05. The primary efficacy endpoint of time to symptom relief was analyzed via the Kaplan-Meier method. Median time to onset of symptom relief and corresponding sign-test based 2-sided 95% confidence intervals were summarized by treatment group for the intention to treat and per protocol populations for subjects experiencing either non-laryngeal or laryngeal attacks. Time to onset of symptom relief based on primary VAS symptom rating was similarly analyzed, which mirrored the primary endpoints of the earlier FAST-1 and FAST-2 pivotal trials. Adverse event data and other safety outcomes were summarized via descriptive statistics. The primary safety adverse event analysis consisted of events that occurred within 16 days of treatment with study drug.

8. Results

8.1. Demographics and patient disposition

A total of 369 subjects were screened, of which 42 failed to meet entry criteria and 229 did not experience a qualifying HAE attack during the trial period. Of the 98 subjects who experienced an initial eligible attack, 93 were randomized to double-blind treatment for moderate to severe abdominal or cutaneous attacks and mild to moderate laryngeal attacks, while five subjects were treated to open-label icatibant for severe laryngeal attacks. Three subjects randomized to placebo subsequently received open-label icatibant for progressive HAE symptoms. In addition, one placebo recipient died, while one recipient of open-label icatibant for a severe laryngeal attack was lost to follow-up. A total of 58

subjects were treated for subsequent HAE attacks with open-label icatibant during the extension phase. Protocol violations were noted in two open-label icatibant-recipients and two placebo-recipients.

Table 2. FAST-3: Baseline demographic traits of randomized study population

Non-Laryngeal Intent To Treat Population (n = 88)		
Demographic Trait	Icatibant (n = 43)	Placebo (n = 45)
Sex (n, %)		
Female	27 (62.8)	29 (64.4)
Male	16 (37.2)	16 (35.6)
Race (n, %)		
White	38 (88.4)	40 (88.9)
Black or African-American	3 (7.0)	0
Other	2 (4.7)	5 (11.1)
Age (years)		
Mean (SD)	36.1 (13.7)	36.6 (11.2)
Median	36.0	36.0
Range	19-83	18-66
Age (n, %)		
≤ 65 yrs	42 (97.7)	44 (97.8)
> 65 yrs	1 (2.3)	1 (2.2)
Weight (kg)		
Mean (SD)	81.7 (25.1)	80.7 (20.9)
Range	41.7-157.1	41.5-130.0
Previous C1-INH use (n, %)		
Yes	1 (2.3)	1 (2.2)
No	40 (93.0)	41 (91.1)
Laryngeal Intent to Treat Population (n = 5)		
Demographic Trait	Icatibant (n = 3)	Placebo (n = 2)
Sex (n, %)		
Female	2 (66.7)	1 (50.0)
Male	1 (33.3)	1 (50.0)
Race (n, %)		
White	3 (100.0)	2 (100.0)
Age (years)		
Mean (SD)	40.3 (6.7)	50.0 (22.6)
Median	37.0	50.0
Range	36-48	34-66
Age (n, %)		
≤ 65 yrs	3 (100.0)	1 (50.0)
> 65 yrs	0	1 (50.0)
Weight (kg)		
Mean (SD)	86.6 (33.4)	70.3 (5.0)
Range	55.0-121.5	66.8-73.8

Previous C1-INH use (n, %)		
Yes	1 (33.3)	0
No	2 (66.7)	2 (100.0)

Source: Clinical Study Report for HGT-FIR-054, Table 10.1.4.1, Table 10.1.4.4

8.2. Treatment Adherence and Exposure

As randomized treatment was administered by health care providers in an observed clinical setting, subject compliance was not an issue, and all subjects received randomized treatment as intended. During the double-blind treatment phase, four subjects were treated outside of the intended treatment window (i.e., within six hours of symptoms becoming moderate and within 12 hours of the onset of the attack) at 6.5, 6.7, 12.4, and 14 hours. In addition, four placebo-recipients subsequently received a single dose of icatibant as rescue medication. During the open-label extension phase of the trial, all subjects received a single dose of icatibant, except for one subject who received a total of 2 injections.

8.3. Efficacy Results

Nearly all subjects in the non-laryngeal intent to treat population experienced symptom relief (43 of 43 icatibant-recipients and 42 of 45 placebo-recipients), with a median time to onset of symptom relief (50% reduction in composite VAS symptom rating) of 2.0 hours in the icatibant group and 19.8 hours in the placebo group ($p < 0.001$). Similarly, 43 of 43 icatibant-recipients and 41 of 45 placebo-recipients experienced primary symptom relief, with a median time to onset of 1.5 hours for the icatibant group and 18.5 hours for the placebo group ($p < 0.001$).

In contrast to the primary efficacy analysis of FAST-1 (time to onset of primary symptom relief based on VAS), the results of FAST-3 demonstrated a significant decrease from placebo. The following table represents the summary findings of all three pivotal Phase 3 trials (FAST-1, FAST-2, and FAST-3), including time to onset of symptom relief based on both composite 3-symptom VAS score and primary symptom VAS score. As shown, the icatibant groups in all three trials demonstrated significant decreases in the former endpoint versus either placebo- or tranexamic acid-treated controls, whereas only FAST-3 demonstrated a statistically significant decrease in time to onset of primary symptom relief in the icatibant group.

Reviewer's Comment: The Applicant presents summary efficacy data from each Phase III trial for median time to onset of symptom relief as defined by both the VAS-3 composite score and the VAS primary symptom score. Symptom relief in FAST-3 was defined as a 50% reduction from baseline in VAS score, i.e., VAS-3 and possibly primary symptom VAS score, although there is discrepant information in the FAST-3 final study report to this effect. This methodology was also used to analyze time to onset of symptom relief based on composite VAS scores (VAS-3 and VAS-5) in the Integrated Summary of Efficacy presented by the Applicant. However, in FAST-1 and FAST-2, symptom relief based on primary symptom VAS score was defined as a reduction in VAS score to any value to the right and below the line defined as $Y = 6/7 X - 16$ with $X \geq 30$ mm, where X = pre-treatment (baseline) VAS in mm and Y = post-treatment VAS in mm. This corresponded to a reduction by 31 mm at a baseline VAS of 100 mm and by 21 mm at a baseline VAS of 30 mm. The Sponsor also states that this methodology was used to analyze this efficacy endpoint in the Integrated Summary of Efficacy. However, the median times to onset of primary symptom relief presented in summary Table 3 below (taken directly from the ISE) are inconsistent with those presented in the primary study reports for FAST-1 and FAST-2.

Table 3. Summary of VAS-based efficacy endpoints in non-laryngeal intent to treat population within the Phase 3 icatibant HAE development program

	----FAST-2----- Tranexamic		----FAST-1-----		----FAST-3-----	
	Icatibant (N=35)	Acid (N=38)	Icatibant (N=26)	Placebo (N=29)	Icatibant (N=43)	Placebo (N=45)
Primary Endpoint:						
Time to Onset of Symptom Relief (VAS-3)						
Median time to onset of symptom relief (h)	2.0 ^{***}	12.0 ^{***}	2.3 [*]	7.9 [*]	2.0 ^{***}	19.8 ^{***}
Key Secondary Endpoint:						
Time to Onset of Primary Symptom Relief						
Median time to onset of primary symptom relief (h)	2.0 ^{***}	10.1 ^{***}	2.3	5.0	1.5 ^{***}	18.5 ^{***}
Other VAS-Based Endpoints:						
Median time to onset of symptom relief for the individual VAS score of:						
Skin swelling (h)	3.7 ^{***}	21.3 ^{***}	4.3	7.9	3.0 ^{***}	22.3 ^{***}
Skin pain (h)	1.5 ^{**}	18.1 ^{**}	4.0	6.0	2.0 [*]	8.0 [*]
Abdominal pain (h)	1.8	3.5	2.0	4.9	1.8 ^{**}	3.5 ^{**}

Source: Integrated Summary of Efficacy Table 6.1.1, Table 8.1.1, Table 12.1

8.4. Safety Results

Adverse Events

The safety population used for the primary safety analysis of FAST-3 consisted of 98 subjects: 46 randomized to icatibant, 46 randomized to placebo, and 6 treated with open-label icatibant. The total icatibant-treated population consisted of 75 icatibant-treated subjects: 46 randomized to icatibant for first attacks and 29 treated with open-label icatibant for their first icatibant-treated attack. The following table summarizes the overall adverse event experience for the safety population, as well as the most common treatment-emergent adverse events reported within 16 days of blinded treatment in 2 or more subjects within a given treatment group and at a greater frequency in icatibant-treated patients than in placebo-treated patients.

Table 4. FAST-3: Common adverse events by system organ class, preferred term, and treatment group

	Icatibant (n = 46)	Placebo (n = 46)
Overview of Adverse Events (n, %)		
Subjects with ≥ 1 AE	19 (41.3)	24 (52.2)
Subjects with ≥ 1 drug-related AE	5 (10.9)	3 (6.5)

Subjects with ≥ 1 SAE	0	3 (6.5)
Subjects with ≥ 1 drug-related SAE	0	0
Subjects who died due to an AE	0	1 (2.2)
Subjects who died due to a drug-related AE	0	0
Subjects with ≥ 1 severe AE	2 (4.3)	10 (21.7)
Subjects with ≥ 1 drug-related severe AE	2 (4.3)	0
System Organ Class (n, %) Preferred Term (n, %)		
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
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
General Disorders and Administration Site Conditions	4 (8.7)	1 (2.2)
Pyrexia	2 (4.3)	0

Source: Clinical Study Report for HGT-FIR-054, Table 10.3.1.1.1, Table 10.3.2.1

As noted above, one death occurred in a placebo recipient who experienced a fatal myocardial infarction 10 days after receiving blinded placebo treatment, which was reported as unrelated to study drug. A complete narrative is provided. No SAEs occurred in the icatibant group during the blinded treatment phase, while the rate of severe AEs was lower in the icatibant group (4.3%) compared to the placebo group (21.7%). However, both severe AEs in the icatibant group were considered to be drug-related (although neither was considered to be an SAE). Of note, one subject who received open-label icatibant for a third HAE attack experienced severe cholecystitis 4 days post-treatment and severe pneumonia 8 days post-treatment. A second subject treated with open-label icatibant developed a pulmonary embolus of moderate severity 10 days post-treatment. None of these events were considered by the Applicant to be related to study-drug.

VI. Brief Review of Proposed Labeling

Revised product labeling has been submitted by the Applicant, which incorporates findings from FAST-3 in support of the proposed indication for the treatment of acute HAE attacks in adults. While a more

extensive review of the proposed label will be conducted during the review process, a preliminary review identified the following potential issues:

- **Highlights, Dosage and Administration:** Findings from JE049-3101 have been submitted in this Complete Response in support of the assertion that icatibant is suitable for self-administration. Section 6.2 Adverse Reactions in Other Studies indicates that the safety profile of self-administered icatibant is similar to that administered by healthcare professionals, and Section 14 Clinical Studies cites efficacy data from this trial.

(b) (4)

Reviewer's Comment: During the Response Planning Meeting, it was discussed that rat and dog reproductive toxicity data will be required in the product labeling. In addition, a nonclinical carcinogenicity study will likely be cited as a postmarketing requirement by the Pharmacology/Toxicology Review Team.

VII. DSI Review/Audit

Initial review of the application did not raise any data integrity concerns. Data for 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 vast 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 0-5 subjects were enrolled from each of the other countries. No investigators associated with FAST-3 were listed as having any financial conflicts of interest. (One financial disclosure is made for a German-based investigator involved in one of the prior trials of icatibant that was reviewed in the original NDA submission.) As icatibant is a new NME, a DSI audit was already conducted for the original NDA. In contrast to the original application, however, the large majority of study sites for FAST-3 were domestic. A preliminary statistical review of the raw efficacy data from FAST-3 by the Biometrics Review Team did not detect any outliers in performance by individual study site. No additional DSI audit is recommended by the Clinical Team at this time.

VIII. Pediatrics

The Applicant states that pediatric subjects were not included in the icatibant Phase 3 development program, as the reproductive effects of icatibant remain under investigation. The Complete Response

does not include any other trials conducted in pediatric subjects. Given the orphan drug status of icatibant for the proposed indication, PREA requirements do not apply. However, during previous discussions with the Agency (Pre-NDA meeting with the Division of Gastrointestinal and Coagulation Drug Products on March 1, 2005; Pre-NDA meeting with DPARP on January 24, 2007), the Applicant stated an intent to evaluate its pediatric use during the postmarketing stage, pending the approval of icatibant for use in adults, which the Division stated was a reasonable approach.

IX. Consults Needed

The following consults will be requested:

- CDRH: Evaluate patient use of prefilled syringes with regard to self-administration outside of clinical settings (e.g., user errors, device malfunctions, extractables).
- QT-Interdisciplinary Review Team: Evaluate new Thorough QTc Trial (HGT-FIR-061) that was conducted since the time of issuance of the Complete Response to the original NDA.
- Microbiology Review

X. Advisory Committee

As icatibant is a NME and is under review for a novel indication, a Pulmonary and Allergy Drugs Advisory Committee Meeting has been scheduled for June 23, 2011, which will focus on the requirements for demonstrating efficacy and safety for the proposed indication.

XI. Conclusions

The study report for HGT-FIR-054 appears complete, and the information is appropriately indexed for review. No review planning issues are identified.

XII. Comments for the Applicant

The Clinical Review Team has no comments for the Applicant at this time, although the Statistical Review Team will seek clarification as to how the Applicant defined time to onset of symptom relief for the primary and secondary efficacy endpoints in the Integrated Summary of Efficacy and the final study reports for the individual Phase III trials, as the final study report for FAST-3 contains discrepancies in this regard. In addition, the Clinical Pharmacology Review Team will also request that electronic datasets be submitted for all population PK data, as well as individual study data from the two additional PK trials that were conducted since the time of issuance of the Complete Response to the original NDA (i.e., HGT-FIR-061 and HGT-FIR-065).

XIII. Review Timeline

February 25, 2011	Complete Response receipt date
March 30, 2011	Response planning meeting
May 23, 2011	Mid-cycle meeting
May 26, 2011	AC briefing package due
June 23, 2011	AC meeting
June 29, 2011	Internal labeling meeting
July 15, 2011	Wrap-up meeting
July 25, 2011	Labeling teleconference
July 27, 2011	Primary reviews due
August 25, 2011	PDUFA goal date

XIV. Clinical Filing Checklist**NDA/BLA Number: 22-150 Applicant: Shire****Stamp Date: 2/25/11****Drug Name: Icatibant NDA/BLA Type: NDA Standard Resubmission
(Firazyr)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			

	Content Parameter	Yes	No	NA	Comment
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			Complete Response to 505(b)(1) NDA
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (<i>i.e.</i>, appropriately designed dose-ranging studies)? Study Number: JE049-1102 Study Title: Tolerability and absolute bioavailability of a single subcutaneous dose of icatibant compared to a single intravenous infusion of icatibant in healthy subjects Sample Size: Part I=16; Part II=24 Arms: <u>Part I:</u> Icatibant 0.05 mg/kg SC (40 mg/mL) Icatibant 0.2 mg/kg SC (40 mg/mL) Icatibant 0.2 and 0.4 mg/kg SC (20 mg/mL) <u>Part II:</u> Icatibant 0.4 mg/kg SC (10 or 20 mg/mL) Icatibant 0.4 mg/kg IV Location in submission: Original NDA dated 10/22/07, Section 5.3.1.1 Study Number: JE049-2101 Study Title: Proof-of-concept study to investigate in patients with hereditary angioedema the efficacy and safety of icatibant administered intravenously at various infusion rates and subcutaneously at different doses Sample Size: 35 Arms: Icatibant 0.4 mg/kg IV (0.5 hr infusion) Icatibant 0.4 mg/kg IV (2 hr infusion) Icatibant 8 mg/kg IV (0.5 hr infusion) Icatibant 30 mg SC Icatibant 45 mg SC Location in submission: Original NDA dated 10/22/07, Section 5.3.5.2.3	X			Single SC dose was evaluated in Phase III trials based on PK/PD data in healthy adults at HAE patients; Applicant provided additional rationale for dose selection based on clinical endpoint and related validated biomarkers in this Complete Response.
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 JE049-2102 Indication: Treatment of acute HAE attacks Pivotal Study #2 JE049-2103 Indication: Treatment of acute HAE attacks Pivotal Study #3 HGT-FIR-054 Indication: Treatment of acute HAE attacks	X			

15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			No SPA reached for HGT-FIR-054; the primary endpoint recommended by the Division designated as a key secondary endpoint by Applicant.
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (<i>e.g.</i> , QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			MedDRA v. 8.1
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

PEDIATRIC USE				
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X		
ABUSE LIABILITY				
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?		X	
FOREIGN STUDIES				
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X		
DATASETS				
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X		
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X		
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X		
34.	Are all datasets to support the critical safety analyses available and complete?	X		
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X		
CASE REPORT FORMS				
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X		
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X		
FINANCIAL DISCLOSURE				
38.	Has the applicant submitted the required Financial Disclosure information?	X		
GOOD CLINICAL PRACTICE				
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X		

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___Yes___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter:

The Clinical Review Team has no comments for the Applicant at this time, although the Statistical Review Team will seek clarification as to how the Applicant defined time to onset of symptom relief for the primary and secondary efficacy endpoints in the Integrated Summary of Efficacy and the final study reports for the individual Phase III trials, as the final study report for FAST-3 contains discrepancies in this regard. In addition, the Clinical Pharmacology Review Team will also request that electronic datasets be submitted for all population PK data, as well as individual study data from the two additional PK trials that were conducted since the time of issuance of the Complete Response to the original NDA (i.e., HGT-FIR-061 and HGT-FIR-065).

Brian Oscar Porter, M.D. Ph.D., M.P.H.

4/13/11

Reviewing Medical Officer

Date

Susan Limb, M.D.

Clinical Team Leader

Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BRIAN PORTER
04/13/2011

SUSAN L LIMB
04/14/2011

Cross-Discipline Team Leader Review

Date	March 20, 2008
From	Sally Seymour, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #, Supplement#	22-150
Applicant	Jerini AG
Date of Submission	October 22, 2007
PDUFA Goal Date	April 28, 2008
Proprietary Name / Established (USAN) names	Firazyr (b) (4) /icatibant
Dosage forms / Strength	Solution for injection / 30mg
Proposed Indication(s)	Treatment of acute attacks of hereditary angioedema
Recommended:	Not Approvable

1. Introduction

Jerini AG submitted a new drug application (NDA# 22-150) on October 22, 2007, for icatibant acetate for injection (30mg) for the treatment of hereditary angioedema (HAE) in patients 18 years of age and older. Icatibant is a bradykinin type 2 (B2) receptor antagonist proposed for administration by subcutaneous (SC) injection. 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. Although Jerini originally requested an indication for the treatment of HAE, the clinical program was designed to assess the efficacy of icatibant for the treatment of acute HAE attacks. The Division raised this issue in the January 8, 2008, filing letter. In a submission dated January 28, 2008, Jerini agreed to revise the indication to reflect the treatment of acute attacks of HAE, rather than the treatment of HAE. Currently there are no approved treatments for acute HAE attacks in the US. The Applicant requested a Priority Review and since there are no safe and effective treatments for acute HAE attacks, a Priority Review was granted.

The primary review issue for this application is the lack of substantial evidence of efficacy. To support the proposed indication, this application includes the results of two phase 3 clinical trials in patients with HAE. One clinical trial was placebo-controlled and the second clinical trial was active-controlled with tranexamic acid (TA). The placebo-controlled trial did not show a statistically significant difference between icatibant and placebo for the primary endpoint, time to onset of symptom relief. The active control used in the second trial is not approved for the treatment of HAE in the US and there is limited data supporting the efficacy of TA for the treatment of acute HAE attacks. The lack of substantial evidence of efficacy is discussed in detail in Section 6. Concern regarding the adequacy of the clinical program to support the proposed indication was raised during the January 24, 2007, Pre-NDA meeting with the Applicant and again in the January 8, 2008, NDA filing letter.

Since the application is for a new molecular entity (NME) and is a Priority Review, a Pulmonary Allergy Drugs Advisory Committee (PADAC) meeting was planned as soon as the NDA was submitted. The PADAC meeting was organized and scheduled for February 20, 2008. However, as the review proceeded, it became clear that the application did not provide substantial evidence of the efficacy of icatibant for the proposed indication. Thus, the PADAC meeting was cancelled. The Applicant was notified of the reason for the cancellation in a teleconference on January 11, 2008. Of note, the Applicant requested a 90-day meeting to discuss the NDA, which was held on March 5, 2008.

This memo will provide an overview of the NDA, with a focus on the review issues that warrant discussion, primarily the lack of substantial evidence of efficacy. There are no significant disagreements between the primary and secondary reviewers to expand upon.

2. Background

Icatibant is a bradykinin type 2 (B2) receptor antagonist and is not currently marketed for any indication in the US or other countries. Currently there are no approved treatments for the treatment of acute HAE attacks in the US. Danazol is approved in the US for the prevention of HAE attacks and oxandrolone is used off-label in the US as an alternative to danazol. Jerini conducted one Phase 3 study with an active comparator, tranexamic acid (TA). TA is an antifibrinolytic related to epsilon-aminocaproic acid that inhibits the activation of plasminogen to plasmin and is approved in the US for the prophylaxis and treatment of hemorrhage in patients with hemophilia. TA is not approved in the US for treatment of acute HAE attacks, but is approved in a few countries (e.g. EU) for treatment of HAE. However, the product label does not specify whether the indication is for chronic or acute treatment of HAE and does not include information from clinical studies in HAE patients. In addition, the published literature does not provide support for the use of TA for treatment of acute HAE attacks.

The IND for icatibant was initially opened (April 8, 2004) in the Division of Gastrointestinal and Coagulation Drug Products (DGCDP), but was later reassigned to the Division of Pulmonary and Allergy Drug Products (DPAP). Because of the potential life-threatening nature of HAE attacks and no approved effective therapies, icatibant was granted fast track designation on June 15, 2004, and orphan drug status on November 25, 2003. The following are pertinent aspects of the regulatory history:

- June 11, 2004 - Jerini requested a Special Protocol Assessment for Study 2103 (Placebo-Controlled, Phase 3 study)
 - In a letter dated July 29, 2004, DGCDP responded to Jerini's SPA questions in which the design, endpoints, sample size, and monitoring were deemed acceptable, with the caveat that onset of symptom relief should be clinically meaningful. No significant concerns with the protocol were raised.
- March 1, 2005 – PreNDA meeting held with DGCDP
 - Proposed QT prolongation study (Study 1103) deemed acceptable
 - Dose selection (30mg) questioned
- August 16, 2005 – IND transferred to DPAP
- September 8, 2005 and February 9, 2006– Jerini requested feedback regarding the VAS validation protocol. DPAP and the SEALD group reviewed the protocol and provided

responses. In facsimiles dated January 26, 2006, and August 24, 2006, the Agency raised concerns regarding the VDS.

- January 24, 2007 – PreNDA meeting held with DPAP
 - Jerini informed that DPAP considers treatment of acute attacks of HAE chronic intermittent use; therefore, chronic repeat dose toxicity studies of 6 and 9-month duration, and carcinogenicity studies are required.
 - DPAP raised concern that Jerini did not have two confirmatory studies that won on primary endpoint and one phase 3 study conducted with active comparator that is not approved in the US.
- January 30, 2007 – QT IRT group consult
 - Study 1103 not a thorough QT study
 - Because evidence of QT prolongation was noted in clinical studies, a thorough QT study is not required. This was conveyed to the Sponsor. Evidence of QT prolongation included a subject who had a 120msec increase in QT_{CF} 59 minutes post-dose of icatibant and another who had a 38msec increase in QT_{CF} 55 minutes post dose of icatibant.

3. CMC/Device

General product quality considerations

Icatibant acetate for injection contains the active drug substance, icatibant, as well as the following inactive ingredients: glacial acetic acid, sodium hydroxide, sodium chloride, and water for injection. The drug product is a pre-filled single dose syringe, containing 3 mL of a 10mg/mL sterile solution for SC use manufactured by (b) (4). The drug substance is a synthetic decapeptide with a structure similar to bradykinin. (b) (4)

The proposed expiry is 18 months stored at/below 25°C. However, according to the CMC reviewer, Dr. Eugenia Nashed, the proposed storage and expiry period are not supported by the submitted data. (b) (4) one of the degradants (b) (4) tested positive for genotoxicity; therefore the CMC reviewer recommends storage in the refrigerator.

In addition to the storage issue, the CMC reviewer identified several additional deficiencies, including the following: inadequate controls for drug substance, including inadequate specifications for impurities (see below); inadequate controls for drug product, including biological activity, impurity profile, and leachable testing; stability protocols; and inadequate microbiological controls for the product as described below.

A pharmacology/toxicology consult was obtained regarding impurities and leachables identified in the drug product. (b) (4)

According to the pharmacology/toxicology review team, the specifications for most of the impurities in the drug substance and all of the impurities in the drug product exceed the acceptable qualification threshold of (b) (4) for peptides (recommendations from the 2005 TIDES Conference). The pharmacology/toxicology review team recommends that the Applicant conduct an adequate qualification study or the Applicant should modify the proposed acceptance criterion to less than (b) (4).

A microbiology consult was obtained because sterility and endotoxin content of the drug product were identified as critical issues. Dr. Anastasia Lolas identified multiple product quality microbiology deficiencies in her review dated March 11, 2008. The deficiencies included the following: container-closure integrity, sterility assurance of needle, (b) (4), discrepancy of validation of bacterial endotoxin method reports, and lack of description of microbiological monitoring program. These comments will be conveyed to the Applicant.

The CMC and Microbiology deficiency comments will be conveyed to the Applicant.

Facilities review/inspection

Establishment evaluation requests (EER) were made. Two analytical establishments (b) (4) were assigned for inspection and inspections are currently pending at the drug product (b) (4) and drug substance (b) (4) manufacturing sites. The inspections are pending at finalization of this review.

4. Nonclinical Pharmacology/Toxicology

The Applicant submitted the standard battery of required nonclinical toxicology studies with the exception of chronic toxicity studies and carcinogenicity studies. In the January 24, 2007, Pre-NDA meeting, DPAP informed Jerini that the treatment of acute attacks of HAE is considered chronic intermittent use; therefore, chronic repeat dose toxicity studies of 6 and 9-month duration, and carcinogenicity studies would be required. Because this determination had not been previously conveyed and the lack of effective therapies for the treatment of acute HAE attacks, DPAP allowed Jerini to submit the NDA prior to completion of these studies.

Although the pharmacology/toxicology review is pending at the time of finalization of this memo, the nonclinical program for icatibant is considered complete with the exception of the chronic toxicity studies and carcinogenicity studies. The focus of this discussion is on the most relevant findings from the toxicology program. Jerini submitted nonclinical studies that included 13 week repeat dose toxicology studies in Sprague-Dawley rats and dogs. In these studies icatibant was administered SC once daily for 13 weeks. The majority of the toxicology findings were observed in the dog studies, which indicate the following targets of toxicity:

- skin - local injection site irritation
- reproductive tract – immature sexual organs and decreased weights (testes, prostate, epididymides, mammary gland, ovaries, uterus, vagina)
 - testes - arrest of maturation, oligospermia, necrosis
 - epididymus – oligospermia
 - decreased testosterone, HL and FSH in males

The local reactions are considered monitorable and were noted in the clinical program. The reproductive tract findings were noted primarily in studies conducted with sexually immature animals and were dose schedule dependent. The reproductive 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 administer icatibant intermittently with a limit in the number of doses recommended (b) (4). Chronic toxicology

studies are pending and may provide additional information regarding these reproductive findings.

The genetic toxicology studies were negative. The reproductive toxicology studies show that icatibant is not teratogenic, but icatibant affects the uterine implantation process and uterine stability in early pregnancy as well as delayed parturition in late pregnancy.

Outstanding issues include the chronic toxicity studies and carcinogenicity studies. The Applicant indicates that the chronic toxicity studies will be available in September 2008 and the carcinogenicity study in 2011.

5. Clinical Pharmacology/Biopharmaceutics

The Applicant submitted multiple clinical pharmacology studies that were reviewed in detail by the Clinical Pharmacology reviewer, Dr. Partha Roy. The pertinent findings from the clinical pharmacology program are described here, but detailed discussion can be found in Dr. Roy's clinical pharmacology review.

Following SC administration, icatibant is absorbed within 30 minutes and displays linear pharmacokinetics. Protein binding is approximately 44%. Icatibant has an elimination half life of approximately 0.6 to 1.5 hours. The clearance of icatibant is primarily non-renal as only 5-6% of the parent drug is excreted in the urine. No accumulation was noted following SC administration of 30mg icatibant every 6 hours for 3 doses. Icatibant is extensively metabolized into two inactive metabolites, M1 and M2. M1 (b) (4) and M2 is (b) (4). The metabolism pathway is not certain, but in vitro studies suggest that the metabolism of icatibant is P450-independent.

There are some differences in icatibant exposure based upon age and gender. Clearance was decreased and half-life was prolonged in elderly subjects compared to younger subjects. Elderly subjects (>65 years) showed an increase in AUC (66% to 116%) compared to younger subjects, but the effect on Cmax was less (12-14% increase). Young female subjects showed approximately 2.3-fold increase in both Cmax and AUC values compared to young males. Elderly females exhibited similar increase in Cmax (~2.3-fold) while AUC was increased by about 1.8-fold compared to elderly males. The reason for the difference in exposure in males and females is not clear.

The pharmacokinetics of icatibant in patients with HAE is similar to those in healthy subjects. The pharmacokinetics of icatibant do not appear to be significantly affected by renal or hepatic impairment. *In vitro* studies suggest that icatibant does not inhibit any relevant drug metabolizing CYP450s 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. The Applicant 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. Dr. Limb addressed this issue in her clinical review as follows. Given the intermittent use of icatibant, the life-threatening potential of HAE attacks, and the general avoidance of ACE inhibitors in HAE

patients due to their potential for angioedema, the risk of this particular drug-drug interaction does not seem significant. I concur with this conclusion.

The Applicant assessed the effects of icatibant on ECGs with serial ECGs. The results of a clinical pharmacology study (Study 1103) were reviewed by the Interdisciplinary Review Team for QT Studies (IRT-QT). The IRT-QT determined that there were some ECG effects (ST/T wave changes and QT prolongation) associated with icatibant and a thorough QT study was not necessary. According to the IRT-QT review dated January 30, 2007, following icatibant 30mg SC one subject was noted to have a 120msec increase in QTcF at 59 minutes post-dosing and another subject was noted to have an increase in QTcF from 376 to 414 msec at 55 minutes post-dosing. Both subjects had ST-T wave changes. Since there is no thorough QT study to evaluate effect of icatibant on the QT interval, these findings should be described in the product label.

6. Clinical Microbiology

Clinical microbiology is not applicable for this NDA.

7. Clinical/Statistical- Efficacy

Jerini proposes the use of icatibant for the indication of the treatment of HAE. The proposed dosing regimen is 30 mg icatibant administered subcutaneously, repeated at intervals of not less than 6 hours and not to exceed 3 injections in 24 hours. To support this indication, this application includes the results of 3 clinical trials in patients with HAE (Studies 2101, 2102, 2103), one study to evaluate the effect of icatibant on the QT interval (Study 1103), two phase 1 studies in healthy volunteers, and one observational PRO validation study (Study 4102). The table below displays the clinical studies pertinent to this program, which will be addressed in this review. For detailed review of the clinical program, refer to Dr. Susan Limb's Clinical Review.

Table 1 Icatibant Clinical Development Program				
Study	Design	Duration	Population	Treatment Groups
2101	R, OL, MC Proof of Concept Germany	Single Dose July 2003 – August 2004	HAE patients Age ≥ 18 years N=15	0.4mg/kg IV icatibant over 2 hours 0.4mg/kg IV icatibant over 30 min 0.8mg/kg IV icatibant over 30 min 30 mg SC icatibant 45 mg SC icatibant
2102	R, DB, MC, AC with OLE Efficacy/Safety MC – International	Single Dose with OLE March 2005-July 2006	HAE patients Age ≥ 18 years N=72	30 mg SC icatibant Tranexamic acid 3 x 1 g for 2 days
2103	R, DB, MC, PC with OLE Efficacy/Safety MC–International (US)	Single Dose with OLE Dec 2004 - July 2006	HAE patients Age ≥ 18 years N=56	30 SC mg icatibant Placebo
1103	R, DB, PC QTc PK – age, gender Germany	5 doses on D1 SD on D8, D15 June 2005-Nov 2006	Healthy subjects Ages 18-40 & >65 yrs N=32	30 mg SC icatibant 5 doses on Day 1 SD on Day 8 and 15 Placebo
4102	Observational VAS MCSD MC	No treatment June 2006-March 2007	HAE patients Age ≥ 18 years N=80	No intervention

The pertinent regulatory interactions were outlined in Section 2. Concern regarding the adequacy of the clinical program to support the proposed indication was raised during the January 24, 2007, Pre-NDA meeting with the Applicant and in the January 8, 2008, NDA filing letter.

Primary Efficacy Variable – Visual Analog Scale

The clinical development program for a medication for the treatment of acute HAE attacks is not well-established. The Applicant chose to use a patient reported outcome instrument called the Visual Analog Scale (VAS) to measure patient symptoms during an attack as the primary efficacy variable. The VAS has a 100mm horizontal line where 0 mm = no symptoms and 100mm = worst possible symptoms. Patients rate the intensity of symptoms by marking a line on the horizontal linear scale. The Applicant conducted Study 4102 to determine the minimal clinically significant difference (MCSD) in the VAS score.

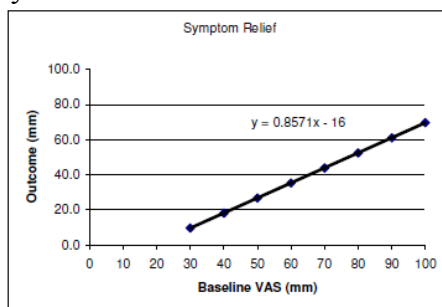
Study 4102 was an observational, non-interventional study in 80 adult HAE patients presenting with an acute abdominal and/or cutaneous HAE attack. Patients received the standard of care and were asked to complete patient diaries until complete resolution of their symptoms or 48 hours from baseline, whichever occurred first. In addition to patient symptom scores, patients were asked to complete the VAS and a Verbal Descriptor Scale (VDS). Based on comparison to the VDS, a 9 mm change in VAS was identified as the MCSD for “onset of symptom relief.”

There are several issues worth noting about the VAS and the determination of the MCSD. The content validity of the VAS has not been established, which is an important step in the development/use of a PRO as described in the February 2006, Draft Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. The development program for icatibant predated the draft guidance, so

adherence to the draft guidance is not necessarily expected. That being said, to establish the efficacy of icatibant using the VAS, it is important that the VAS is an accurate measure of patient symptoms.

Study 4102 raised some concerns with the use of the VAS. First, as Dr. Limb noted, the Applicant indicated that the VDS was the gold standard, by which to determine the MCSD, but did not include the VDS in the pivotal studies. In addition, data from some of the patients were not included in the analyses because there was discordance between the VAS and VDS, which raises the question of the validity of the VAS or VDS. In addition, the results of Study 4102 identified 9mm as the MCSD on the VAS; however, one could question the relevance of moving only 9mm on the VAS (e.g. going from 90mm to 81mm).

For the clinical program, the Applicant chose the primary endpoint of the time to onset of symptom relief of the first moderate to very severe cutaneous (swelling, skin pain) or abdominal (abdominal pain, nausea) edema attack by patient assessed VAS. A response to the right and below a line $Y = 6/7 X - 16$ with $X \geq 30$ mm, where X is the pre-treatment VAS in mm and Y is the post-treatment VAS in mm. This corresponds to a reduction by 30 mm at a baseline VAS = 100 mm and by 21 mm at a baseline VAS = 30 mm.



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In addition to concerns regarding the validity of the VAS, use of the time to onset of symptom relief with a complex definition is problematic as it adds an additional layer of complexity. Despite concerns with the VAS and VDS, if the Applicant performs an additional study, inclusion of the VAS and VDS as efficacy variables is recommended to provide additional information about these endpoints and correlate with Studies 2102 and 2103.

Proof of Concept (Study 2101)

The Applicant conducted one proof of concept/dose ranging study, Study 2101, to identify a dose and route of administration to further evaluate in Phase 3 studies. Study 2101 was a multicenter, randomized, open-label single dose study in 15 patients 18 years and older with HAE. Fifteen patients with 20 unique abdominal (GI) or cutaneous HAE attacks were randomized to one of the following 5 treatment groups: 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. Efficacy was evaluated using a variety of measures of patient symptoms. The VAS was used as the primary efficacy variable. 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. Patients also rated onset of symptom relief. Pertinent results are shown in the following table.

Table 2 Study 2101: Median Time to Symptom Relief by Patient Report and 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
I – 0.4mg/kg IV (2 hours)	8:22	5.31	1:30	2:00	50:00
II – 0.4 mg/kg IV (30 min)	9:05	1.92	1:25	3:30	34:30
III- 0.8 mg/kg IV (30 min)	9:50	5.61	1:08	3:30	20:30
IV – 30mg SC	7:20	3.15	0:35	3:00	34:00
V – 45mg SC	6:07	4.31	0:27	5:00	60:00

There was no placebo control group, which limits interpretation of the results and 5 patients were treated twice for separate HAE attacks. In general, the patients in the IV treatment group had a longer median time from onset of symptoms to treatment. Using patient reports, median onset of relief occurred in less than 1.5 hours and appeared to be earlier in the SC groups. Using the VAS, there does not appear to be a dose related treatment effect. The VAS and the onset of symptom relief as reported by the patient do not correlate well, which calls into question the validity of the VAS. Because of these issues, it is difficult to distinguish between the doses. Based upon this study and PK/PD modeling, the Applicant has chosen to pursue icatibant 30mcg SC.

Phase 3 Clinical Trials

The Applicant conducted two Phase 3 clinical trials for this application: Study 2102 and 2103. Both clinical trials are multicenter, randomized, double-blind, controlled, single-dose clinical trials with an open label extension in patients with HAE 18 years of age and older. The icatibant treatment group in both trials was 30mg SC. The main difference between the two clinical trials was the control groups. Study 2102 was active controlled with tranexamic acid (TA) as the control group and Study 2103 was placebo controlled. Issues with use of TA have been discussed in Section 2. In Study 2102, TA 1000mg was administered every 6 to 8 hours for a total of 4 doses. In Study 2103, the placebo group used a vehicle control solution matched to study drug.

Patients 18 years of age and older with Type I or Type II HAE (history and/or function C1INH < 50% normal) were enrolled. As Dr. Limb noted C1q levels were not measured so there is a potential that patients with acquired HAE could have been enrolled. Patients with moderate to very severe acute abdominal or cutaneous HAE attacks who presented within 6 hours of onset of attack were randomized 1:1 to icatibant or control group. Patients who presented with laryngeal HAE attacks received open-label icatibant. Icatibant and placebo were administered SC in the abdomen. Following 14 days after the initial attack, patients were rolled over into the one year OLE, in which patients could receive open-label icatibant 30mg SC for acute HAE attacks. Patients could receive a repeat dose within 48 hours with a maximum of 3 injections per attack at least 6 hours apart.

The primary efficacy endpoint was the time to onset of symptom relief of the first moderate to very severe cutaneous (swelling, skin pain) or abdominal (abdominal pain, nausea) edema

attack by patient assessed Visual Analogue Scale. Secondary efficacy variables included investigator scores, response rate at 4 hours, time to relief of each symptom present, investigator global assessment, and symptom scores by investigator and patient. Laryngeal edema was scored separately with a symptom score (0-4, none to very severe) and was not included in the primary analysis.

Primary Endpoint - Median Time to Onset of Symptom Relief (hours)				
	Icatibant 30mg SC	Tranexamic Acid	Placebo	p value
Study 2102	N=36	N=38		
All attacks	2.0	12.0		<0.001
Cutaneous attacks	2.5 (n=24)	18.2 (n=23)		<0.001
Abdominal attacks	1.6 (n=12)	3.5 (n=15)		0.026
Study 2103	N=27		N=29	
All attacks	2.5		4.6	0.142
Cutaneous attacks	3.4 (n=14)		10.0 (n=13)	0.221
Abdominal attacks	2.0 (n=13)		6.0 (n=16)	0.159

In Study 2102, icatibant was statistically significant compared to TA for the primary endpoint; however, the efficacy of TA for the treatment of acute HAE attacks is not established.

Although approved in other countries for the treatment of HAE, the data supporting this indication and the published literature do not provide convincing evidence that TA is effective for the treatment of acute HAE attacks. The Applicant argues that use of TA is acceptable even if the benefit of TA is uncertain. Cross study comparison shows that icatibant performed similarly (median time to onset of symptom relief of 2-2.5 hours), but the comparator groups performed quite differently with TA having 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 how the comparators performed calls into question whether TA is worse than placebo. Secondary endpoints were generally statistically significant for icatibant compared to TA in Study 2102. Adequacy of the blinding in Study 2102 is worth noting as icatibant causes local injection site reactions and TA is associated with nausea. Adequate blinding is imperative with a primary efficacy variable that is subjective like the VAS. Overall, there are limitations with Study 2102; however, the results of the study suggest that icatibant may be of some benefit for the treatment of acute HAE attacks.

In Study 2103, icatibant was not statistically significant compared to placebo for the primary endpoint although the results were numerically favorable for icatibant. Similarly, secondary endpoints were numerically favorable for icatibant compared to placebo, but did not consistently reach statistical significance. Although some of the secondary endpoints reached statistical significance, the results of Study 2103 are not robust. The Applicant asserts that the treatment difference was less in patients with abdominal versus cutaneous attacks and there were more patients having abdominal attacks in Study 2103 than in Study 2102 and this may have contributed to the loss of statistical significance. This post hoc theory to explain the findings in Study 2103 is purely speculative. If the assessment of the abdominal symptoms versus the cutaneous symptoms is problematic using the VAS, this calls into question the validity of the VAS instrument. Study 2103 suggests there may be a treatment benefit with icatibant; however, the results are not robust.

Patients with laryngeal HAE attacks were treated in an open-label fashion, were assessed differently, and there is limited efficacy data available for these types of attacks.

The clinical pharmacology data showed that females have a higher exposure of icatibant compared to males. While in Study 2102 and 2103, females treated with icatibant had a shorter time to onset of symptom relief (1.6-2.0 hours) compared to males (2.7-3.5 hours), there was a greater discrepancy in time to onset of symptom relief in the placebo group (females 3.3 hours compared to males 23 hours). Because of the small size of the two phase 3 studies, no definitive conclusions can be made about any differences in response to icatibant in males versus females.

In summary, the Applicant submitted two phase 3 clinical trials that suggest that icatibant has some benefit for the treatment of acute HAE attacks; however, the clinical program has limitations including the questionable validity of the VAS and appropriateness of TA as an active comparator. The submitted clinical trials do not provide substantial evidence of efficacy necessary to support the approval of icatibant. Dr. Limb has concluded that the data submitted in this application are not substantial evidence of the efficacy of icatibant for the treatment of acute HAE attacks and that additional efficacy data is necessary. Another placebo controlled clinical trial is recommended. I concur with Dr. Limb's determination.

8. Safety

The safety database for icatibant 30mg is based primarily on data from the two phase 3 trials (Study 2102 and Study 2103), including both the controlled and uncontrolled portions of the trials. The safety database includes 63 patients who received 30 mg icatibant in the controlled portion of the trials. Additional safety data is obtained from the open-label portions of the Phase 3 trials that included patients rolled over from the controlled portion and other patients enrolled after completion of the double-blind portion. The open label experience provided data with repeat dosing of icatibant for acute HAE attacks. During the controlled and open-label portions of the phase 3 trials, over 600 HAE attacks were treated with icatibant. Although the protocol allowed for up to 3 doses of icatibant for treatment of a single attack, the majority of attacks were treated with a single dose of icatibant. While the safety database is somewhat small, due to the limited HAE population, the safety database for 30mcg icatibant is acceptable. However, the size of the safety database is not adequate to assess for uncommon adverse events. In addition, there is limited safety data for treatment with more than one dose of icatibant for a single HAE attack.

Safety assessments included adverse events, laboratories, vital signs, and ECG assessments. No deaths were reported in any patients who received icatibant. A few SAEs were noted, however, the temporal relationship with icatibant does not suggest causality. In addition, ongoing HAE attacks confounded interpretation of some of the SAEs (e.g. pancreatitis with abdominal HAE attack). There were no discontinuations from the controlled portions of the phase 3 trials due to adverse events. The safety data shows that the most common adverse reactions were local injection site reactions and HAE attacks (worsening of HAE symptoms). The reporting of HAE attacks as adverse events is difficult to interpret, but is more likely a reflection of limited efficacy. Other safety assessments included laboratory, ECGs, and vital

signs, the results of which do not suggest a safety signal with icatibant 30mg. Based on a clinical pharmacology study, icatibant has an effect on the QT interval, which should be described in the product label. Refer to Section 5 for more detailed discussion.

The primary clinical reviewer, Dr. Susan Limb, has concluded that the safety of icatibant 30mg for the treatment of acute HAE attacks is generally supported by the safety data submitted in this application, but acknowledges the limitations of the size of the safety database. I concur with Dr. Limb's determination.

9. Advisory Committee Meeting

Since this application is for a new molecular entity (NME) and is a Priority Review, a Pulmonary Allergy Drugs Advisory Committee (PADAC) meeting was planned as soon as the NDA was submitted. The PADAC meeting was organized and scheduled for February 20, 2008. However, as the review proceeded, it became clear that the application did not provide substantial evidence of the efficacy of icatibant for the proposed indication (*see Section 7*). Thus, the PADAC meeting was cancelled. The Applicant was notified of the reason for the cancellation in a teleconference on January 11, 2008.

10. Pediatrics

Icatibant for the treatment of attacks of HAE was given orphan drug status on November 25, 2003. The Pediatric Research Equity Act is not applicable for an indication with orphan drug designation. No pediatric studies or pediatric plan were submitted with this application. The phase 3 clinical trials enrolled patients 18 years of age and older. However, HAE occurs in pediatric patients and the safety and efficacy of icatibant in patients less than 18 years of age should be evaluated. In the Pre-NDA meeting on February 22, 2007, Jerini agreed to address pediatric studies after approval.

11. Other Relevant Regulatory Issues

DSI Audit

Because icatibant is a new molecular entity, a DSI audit was requested. During the preparation for the DSI audit, it was noted that Jerini did not have a US base of operations. The Applicant's address provided in the application for Morristown, New Jersey did not exist when inspectors went to visit. The Applicant was notified and during the review period has set up the appropriate base of operations in the US.

The information submitted by the Applicant did not indicate a financial conflict of interest with any clinical investigators. Preliminary review of the efficacy data by the statistician did not indicate a treatment by center interaction. Therefore, the sites for the DSI audit were chosen based upon the clinical investigators who enrolled the most patients in the pivotal studies: Study 2102, Site #070 (Dr. Werner Abere) in Austria enrolled 7 patients; Study 2103, Site #040 (Dr. Alejandro Malbran) in Argentina enrolled 14 patients. At the time of finalization of this review, the results of the DSI audit are pending.

12. Labeling

The proposed proprietary name is Firazyr. The Applicant submitted the proposed trade name on October 13, 2006. A consult to the Division of Medication Errors and Technical Support (DMETS) was submitted regarding the proposed trade name and at that time DMETS had no objection to the proposed trade name.

The Applicant submitted labeling in the Physician Labeling Rule (PLR) format. DDMAC and DMETS consults were requested upon submission of the NDA. In a consult dated November 20, 2007, DDMAC reviewer Michelle Safarik provided comments about the product labeling. In a consult dated March 10, 2008, DMETS reviewer Richard Abate noted that DMETS continued to have no objection with the trade name, Firazyr. DMETS recommended consistent expression of the trade name, established name and strength throughout the labeling and also provided detailed comments about the syringe, blister, and carton labeling.

The carton label submitted by Jerini (partially shown below) contains a graphic which should be removed as it decreases the prominence of the trade name and established name. A comment regarding this issue was conveyed in the January 8, 2008, Filing letter to the Applicant.



During the review period, the review team determined that this application contained insufficient evidence of the efficacy of icatibant. Since additional clinical trial information is required, the review team decided that detailed strike out of the label was not warranted as the label may change significantly with additional clinical data. However, the labeling was reviewed and the following are some general issues with the proposed label:

- Indication of treatment of HAE is not acceptable as the clinical program evaluated the treatment of acute HAE attacks. This comment was also conveyed in the January 8, 2008, Filing letter and in the March 5, 2008, 90-Day meeting package, the Applicant agreed to revise the indication.
- The label should specify that injections should be administered by a health care professional as this is how icatibant was administered in the clinical trials.



- Adverse reactions table should not include Phase 2 data as originally proposed by the Applicant.



13. Recommendations/Risk Benefit Assessment

- Recommended regulatory action

The Applicant submitted two phase 3 clinical trials that suggest that icatibant is effective for the treatment of acute HAE attacks; however, the clinical program has limitations as described in Section 6 and the trials do not provide substantial evidence of efficacy necessary to support the approval of icatibant. The safety of icatibant 30mg for the treatment of acute HAE attacks is generally supported by the safety data submitted in this application. However, safety cannot be established without assurance of efficacy at the proposed dose. Because of the lack of substantial evidence of efficacy, the recommended regulatory action is **Not Approvable** under 21 CFR 314.125(b)(5).

- Risk Benefit Assessment

Because the efficacy of icatibant has not been established, the risk benefit profile for icatibant is not established. However, if the efficacy of icatibant 30mg is established, the safety data for icatibant 30mg suggests a favorable risk benefit profile.

- Recommendation for Postmarketing Risk Management Activities

Because the recommendation for this application is Not Approvable, there are no recommendations regarding risk management activities at this time.

- Recommendation for other Postmarketing Study Commitments

Because the recommendation for this application is Not Approvable, there are no recommendations regarding post-marketing studies. PREA is not triggered by this application because icatibant for the treatment of acute HAE attacks was granted Orphan Drug Status.

- Recommended Comments to Applicant

The following clinical deficiency should be conveyed to the Applicant:

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 hereditary angioedema (HAE) attacks. The uncertain efficacy of tranexamic acid in the treatment of acute attacks of HAE complicates interpretation of the results of Study JE049-2102. Study JE049-2103 used a placebo control, but 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, safety cannot be assured. To support the approval of icatibant for the treatment of acute attacks of HAE, you will need to conduct at least one placebo-controlled clinical study in HAE patients using a reliable measure to assess efficacy.

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this page is the manifestation of the electronic signature.**

/s/

Sally Seymour
3/20/2008 08:59:11 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type NDA
Submission Number NDA 22-150
Submission Code N000

Letter Date October 22, 2007
Stamp Date October 26, 2007
PDUFA Goal Date April 26, 2008

Reviewer Name Susan Limb, MD
Review Completion Date February 29, 2008

Established Name Icatibant
(Proposed) Trade Name Firazyr (b) (4)
Therapeutic Class Bradykinin antagonist
Applicant Jerini AG

Priority Designation P

Formulation Solution for injection
Dosing Regimen 30 mg single dose
Indication Hereditary angioedema (HAE)
Intended Population Patients ≥ 18 years with acute HAE attacks

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The clinical recommendation for this application is Not Approvable. The application requires additional evidence of efficacy to support the proposed indication, “treatment of hereditary angioedema in adults ages 18 years of age and older.”

This is a 505(b)(1) application for Icatibant (b) (4) for the treatment of hereditary angioedema (HAE) in patients 18 years of age and older. HAE is a rare, inherited condition characterized by intermittent, unpredictable attacks of angioedema. HAE attacks are potentially life-threatening, particularly in cases of airway compromise. Currently, there are no drug products approved for the treatment of acute attacks of HAE. Several drug products are available for prophylaxis, although their effectiveness in preventing acute attacks is limited.

Icatibant is a new molecular entity. The clinical development program included two small Phase 3 studies, one active-controlled and one placebo-controlled study. Although numerically favorable, the placebo-controlled study failed to show a statistically significant difference for icatibant over placebo for the primary efficacy endpoint, time to onset of symptom relief for an acute cutaneous or abdominal HAE attack as assessed by a Visual Analogue Scale (VAS). The active-controlled study did demonstrate a statistically significant benefit for icatibant, but used an active comparator, tranexamic acid, whose efficacy is not established. Tranexamic acid is not approved for use in HAE in the US, and literature to support the efficacy of tranexamic acid for acute attacks of HAE is limited. As a result, the benefit of icatibant in this trial is more difficult to assess. An additional study, preferably placebo-controlled, is needed to confirm the efficacy of icatibant for the treatment of acute HAE attacks.

The safety of icatibant at the proposed dose of 30 mg is supported by the submitted clinical study data. Safety data showed that icatibant is most commonly associated with transient, local injection site reactions. The size of the safety database is small due to the rarity of HAE and the difficulty of conducting controlled trials to evaluate unpredictable, acute HAE attacks. As a result, the safety assessment is limited. However, given the potential severity of HAE and the lack of effective treatment alternatives, the safety profile for the proposed dose is acceptable.

Therefore, although the Applicant has provided some evidence of the efficacy and safety of icatibant for the treatment of acute attacks of HAE, the efficacy data remains insufficient. An additional well-controlled efficacy and safety trial is needed to confirm efficacy findings. As a result, the recommendation of the clinical review is Not Approvable.

1.2 Recommendation on Postmarketing Actions

The recommendation of the clinical review is Not Approvable, so no recommendations on post-marketing actions are made at this time.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Icatibant is a synthetic decapeptide, competitive antagonist of the bradykinin type 2 (B2) receptor. The structure is similar to bradykinin, but contains 5 non-proteinogenic amino acids. The proposed dose and route of administration is icatibant 30 mg by subcutaneous injection. The proposed indication is treatment of HAE in patients 18 years of age and older.

The Applicant's clinical development program relies on two pivotal Phase 3 studies, one performed in Europe (Study JE049-2102; FAST-2; N=72) and one multinational study with sites in the US (Study JE049-2103; FAST-3; N=56). Only Study 2103 was placebo-controlled; Study 2102 used tranexamic acid as an active-control. Both studies used the same efficacy endpoint, time to onset of symptom relief as measured by a Visual Analogue Scale (VAS). These studies are presented in further detail below. In addition to these Phase 3 studies, the Applicant has submitted study reports for pharmacokinetic studies in healthy volunteers (Studies 1101, 1102, and 1103), an open-label proof-of-concept study in HAE patients (Study 2101; N=8), and a non-interventional study to establish the Minimum Clinically Significant Difference (MCSD) for the patient-reported outcome instrument, the VAS (Study 4102; N=60).

The safety database includes 63 patients who received one 30 mg SC injection of icatibant for acute abdominal or cutaneous HAE attack during the two Phase 3 studies and 11 patients who received open-label icatibant for laryngeal attacks. The Applicant has also provided safety data up to September 2007 from 118 subjects who were treated for a total of 602 attacks from ongoing open-label extension studies conducted after each of the Phase 3 studies. During the OLE studies, patients have been permitted to receive up to 3 x 30-mg icatibant injections per attack, separated by an interval of 6 hours or more in a 24-hour period.

1.3.2 Efficacy

The Applicant submitted reports for two Phase 3 efficacy and safety studies for icatibant: Study 2102 and Study 2103. HAE is a rare condition characterized by intermittent, unpredictable attacks of angioedema that are potentially life-threatening, and there are no drug products currently approved for the treatment of acute attacks of HAE. Studies 2102 and 2103 are suggestive of icatibant's efficacy for this novel indication, but the data provided from these two studies are not convincing or adequate to support approval. A brief overview of each study and the major review issues are summarized below.

Study 2102

Study 2102 was a randomized, multi-center, double-blind, double-dummy, active-controlled trial of icatibant 30 mg QD single dose versus tranexamic acid 1000 mg every 6-8 hours for a total of 6 doses administered within 6 hours of onset of an acute cutaneous or abdominal HAE attack of at least moderate severity. Patients presenting with laryngeal symptoms were not randomized but received open-label 30 mg icatibant. Tranexamic acid, the active comparator, is not

approved for HAE in the US and there is scant literature to support its efficacy in the treatment of acute HAE attacks.

The primary efficacy endpoint was the time to onset of symptom relief as assessed by the VAS. A primary symptom was determined and assessed by the patient using the VAS. Onset of symptom relief was defined by graphical formula as a response to the right and below a line $Y = 6/7 X - 16$ with $X \geq 30$ mm, where X = pre-treatment VAS in mm and Y = post-treatment VAS in mm. Important secondary endpoints included response rate at 4 hours, time to relief of each symptom present in pre-dose VAS other than the primary symptom, time to almost complete symptom relief, and patient symptom severity scores. Descriptive narratives and symptom scores were provided for laryngeal attack patients.

Study 2102 demonstrated a statistically significant difference between icatibant and tranexamic treatment arms (2.0 vs. 12.0 hours in time to onset of symptom relief; $P < 0.0001$). Secondary endpoints were generally supportive as well, if not statistically significant. However, as the efficacy of the active comparator, tranexamic acid, is not established, the study results are not conclusive. Theoretically, the treatment benefit observed for icatibant may be due to tranexamic acid exacerbating the HAE attack. While an effect worse than placebo seems unlikely, the uncertain efficacy of tranexamic acid makes the results more difficult to interpret. Furthermore, both primary and secondary efficacy endpoints rely on patient-reported outcomes with limited validation. This issue is compounded by the fact that icatibant is associated with ubiquitous local injection site reactions, compromising blinding. Support for the efficacy of icatibant in laryngeal attacks is even more limited, as only 3 laryngeal attack patients were treated in the original study, with 4 additional patients in the OLE phase. In terms of laryngeal attacks, the study results are favorable, but the selection of unvalidated subjective endpoints combined with the small sample size make efficacy for this particular type of HAE attack difficult to assess. Given these considerations, Study 2102 provides substantial but not conclusive evidence for icatibant's efficacy and the proposed indication.

Study 2103

Study 2103 was a randomized, multi-center, double-blind, placebo-controlled trial of icatibant 30 mg QD single subcutaneous dose versus placebo in the treatment of acute cutaneous or abdominal HAE attacks. As in Study 2102, patients presenting with laryngeal symptoms were not randomized but received open-label 30 mg icatibant subcutaneously. The primary and secondary efficacy endpoints were the same endpoints defined in Study 2102. Laryngeal attack patients scored symptom severity separately and descriptive narratives were provided.

Although numerically supportive, Study 2103 did not show a statistically significant benefit for icatibant over placebo (2.5 vs. 4.6 hours, respectively; $p = 0.142$). The Applicant reasons that a greater proportion of patients in Study 2103 compared to Study 2102 presented with abdominal pain as the primary symptom assessed by the VAS. The Applicant states that pain symptoms in general are more likely to respond to placebo treatments, hence a robust placebo effect in this study that minimized the treatment difference from placebo. Whether this assertion explains the lack of benefit is difficult to verify; review of cutaneous pain VAS scores do not show a placebo effect of the same magnitude. At the very least, this explanation indicates a potential

shortcoming in the VAS. If the “sensitivity/specificity” of the instrument varies significantly with the specific symptom assessed, the VAS may not be an appropriate instrument for evaluating multiple types of acute HAE attack symptoms. Secondary endpoints were generally supportive but not robust. Of particular concern was the durability of response, which appeared to be limited for both abdominal and cutaneous HAE attacks. Additional study of dose or dosing interval may address this issue, although based on the pharmacodynamic information available, the utility of a higher dose appears limited.

In summary, Study 2103 does not provide adequate support for the efficacy of icatibant in the treatment of acute attacks of HAE. Although the data are suggestive of efficacy, at least one more placebo-controlled trial is needed to confirm the findings. If the VAS is used as the primary endpoint for another trial, additional validation is recommended. Alternatively, other symptom scoring scales could be used potentially with the VAS included as a key secondary endpoint to facilitate comparison with Studies 2102 and 2103.

1.3.3 Safety

The safety database includes 63 patients who received 30 mg icatibant in the randomized phase of the Phase 3 studies and 11 additional patients treated with open-label icatibant during the controlled phase of the study for laryngeal attacks at baseline. A total of 118 patients with 602 attacks collectively were included in the open-label portions of the Phase 3 studies. The OLE studies include patients who had been treated during the controlled phase of the Phase 3 studies who were automatically enrolled in the OLE and other patients who enrolled after completion of the double-blind phase. From the total safety database, 47 patients have been treated with icatibant for 1 attack to date, 68 patients for 2 to 5 attacks, 14 patients for 6 to 10 attacks, and 12 patients have experienced more than 10 attacks for which they have received icatibant. The majority of attacks have been treated with a single dose of icatibant (611 out of 665 attacks total). Fifty-six attacks in 27 patients have been treated with 2 x 30-mg icatibant doses, and 4 attacks in 4 patients have been treated with 3 x 30-mg doses. The Applicant has also provided information from 15 HAE patients treated in an open-label, proof-of-concept Phase 2 study (Study 2101) for additional support of safety.

The safety of 30 mg icatibant for the treatment of acute HAE attacks is generally supported by safety data from the Phase 2 and Phase 3 clinical development program. Aside from self-limited local injection site reactions, the frequency of other adverse events was low and the relationship to treatment was indeterminate. HAE was reported as the second most common adverse event, but the overall frequency was comparable to the frequency observed in the comparator arms and most likely reflects limited efficacy rather than a worsening of the underlying disease. Overall, the safety assessment was limited by the small sample size, particularly for repeat and chronic dosing. The conduct of an additional placebo-controlled trial may facilitate more reliable analysis of infrequent adverse events as well as provide confirmatory data for the use of icatibant in repeat and chronic dosing. However, the reviewer acknowledges that larger studies may not be feasible due to the rare nature of HAE. Because of the life-threatening potential of HAE attacks and the lack of other efficacious drugs currently available for this indication, if the

efficacy of icatibant is established, the safety data suggests a favorable risk:benefit profile for icatibant at the 30 mg dose. If doses higher than 30 mg or alternative dosing regimens are shown to be efficacious, additional safety data to support higher dosing will be required.

1.3.4 Dosing Regimen and Administration

The proposed dosing regimen is 30 mg icatibant administered subcutaneously, repeated at intervals of not less than 6 hours and not to exceed 3 injections in 24 hours.

In general, the efficacy of icatibant at this dose is not convincingly established, and an additional placebo-controlled study will be needed to confirm efficacy for the treatment of acute attacks. In addition, the proposed dosing regimen should reflect the limitations of the clinical studies. For example, there is little data to support repeat and chronic dosing in the current NDA submission.

(b) (4)

As data to support long-term, repeat use is limited at this time, dosage recommendations should reflect these limitations. The regimen also does not specify the circumstances for appropriate use, (b) (4) as was done in the supporting clinical trials. Formal recommendations on dosage and administration from the clinical review may be altered should the Applicant elect to perform another Phase 3 study and submit additional data.

1.3.5 Drug-Drug Interactions

No formal drug interaction studies were conducted with icatibant. Review of adverse event reports does not reveal any apparent interactions between icatibant and other drug products often used in the treatment of HAE patients, including opioids for pain relief, antiemetics, gonadotropins, C1 INH replacement therapy, and corticosteroids. The Applicant cites a theoretical interaction between icatibant and ACE inhibitors, whereby icatibant may attenuate the antihypertensive effect of ACE inhibitors by blockade of bradykinin receptors. Patients taking ACE inhibitors were excluded from the icatibant studies. The proposed labeling does not contain any restrictions, however, on the concomitant use of ACE inhibitors. However, given the expected, limited manner of use of icatibant, the life-threatening potential of HAE attacks, and the general avoidance of ACE inhibitors in HAE patients due to their potential for angioedema, the risk of this particular drug-drug interaction does not seem significant.

1.3.6 Special Populations

No formal studies in special populations have been conducted with icatibant. Review of data from the Phase 3 studies, particularly Study 2102, suggests a potential difference in efficacy between male and female patients, with females experiencing a slightly quicker time to onset of symptom relief. The small sample size limits the utility of subgroup analysis, but there is no clear explanation for the differences seen in male versus female patients. Pharmacokinetic assessments show higher plasma levels in females, but primarily elderly females, who comprised only a minor fraction of the population enrolled. In terms of types of attacks, a similar

proportion of patients were male versus female in the icatibant cutaneous and abdominal attack subgroups in Study 2102 (see Table 26). No differences were noted in terms of ethnicity, although the diversity of the patient population was restricted given the small sample size and study site locations. As mentioned, pharmacokinetic assessments suggest higher plasma levels in the elderly but no dose adjustments are recommended. Icatibant clearance does not appear to be affected by hepatic or renal impairment.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The established name of the subject product of this application is icatibant and the proposed trade name is Firazyr® (b) (4). The established name will be used in this review to refer to the product. Icatibant is supplied as a pre-filled syringe containing 30 mg icatibant acetate in 3 mL solution. In addition to the active ingredient, the sterile, acetate buffer solution contains (b) (4) sodium chloride, (b) (4) acetic acid, and (b) (4) sodium hydroxide/mL and water for injection adjusted to pH 5.5 (b) (4). The solution contains no preservatives.

The active ingredient is a new molecular entity, a novel decapeptide antagonist directed against the bradykinin type-2 receptor.

The proposed indication for icatibant is the treatment of HAE of patients 18 years of age and older. The proposed dosing regimen is 30 mg icatibant injected subcutaneously for the treatment of an HAE attack. In cases of insufficient relief or recurrence of symptoms, up to two additional 30-mg injections may be administered at intervals of no less than 6 hours. No more than 3 injections within a 24-hour period are recommended.

2.2 Currently Available Treatment for Indications

Currently, there are no drug products approved for the treatment of acute attacks of HAE in the US. Several drug products are available for prophylaxis, although their effectiveness in preventing acute attacks is limited. Danazol (NDA 74-582) is approved for the prevention of attacks of hereditary angioedema of all types (cutaneous, abdominal, and laryngeal). Oxymetholone (b) (4) and stanazolol (NDA 12-885) had similar indications but are no longer marketed in the US. Another androgen, oxandrolone, is used off-label in the US as an alternative to danazol.

2.3 Availability of Proposed Active Ingredient in the United States

Icatibant is not currently marketed in the US.

2.4 Important Issues With Pharmacologically Related Products

No other members of the pharmacologic class are currently marketed.

2.5 Presubmission Regulatory Activity

The opening IND (April 8, 2004) was initially reviewed in the Division of Gastrointestinal and Coagulation Drug Products prior to reassignment to the Division of Pulmonary and Allergy Products in September 2005. A timeline of pertinent regulatory proceedings is included below:

July 31, 2003	Request for Orphan Drug Designation
November 25, 2003	Orphan Drug Designation #03-1762 granted
February 6, 2004	Pre-IND meeting: Discussion focused on selection and validation of symptom-based endpoints, including justification of the minimum important difference. The Applicant was also reminded that two adequate, well-controlled studies were the usual requirement for a new indication. The ongoing, open-label, proof-of-concept study, #2101, being conducted at that time in Europe was unlikely to meet this requirement. Other issues discussed included eligibility for Fast Track Designation and Priority Review.
April 8, 2004	Opening IND: The proposed study was a multi-center, double-blind, placebo-controlled trial in 56 adult subjects with moderate to severe cutaneous or abdominal symptoms of HAE. The primary efficacy endpoint was time to onset of symptom relief assessed by a Visual Analogue Scale (VAS) completed by patients; symptom score and global assessment score were secondary efficacy outcomes. Patients with laryngeal symptoms were enrolled in an open-label arm of the study and their outcomes were to be reported descriptively. Comments communicated to the Applicant following review were to include adequate dose-ranging studies in the clinical development program, as well as validating the VAS instrument and justifying a time to onset of symptom relief that is clinically meaningful.
June 11, 2004	Request for SPA (SN 004); Protocol JE049 #2103 (SN 005): The Applicant amended the opening IND protocol and requested a SPA. The main changes were addition of an open-label extension phase, assessment of laryngeal symptoms using a 5-point symptom score, and new pharmacoeconomic and safety secondary endpoints. In a response dated July 29, 2004, the Division confirmed that the proposed endpoints and sample size were acceptable, with the caveat that onset of symptom relief should be clinically meaningful. The Division also advised that safety data should be recorded in detail from the extension phase of the study.
June 15, 2004	Fast Track Designation granted
July 1, 2004	EOP2 CMC meeting
March 1, 2005	Pre-NDA meeting with Div. of GI and Coagulation Drug Products Major clinical issues raised: • QTc data should be collected in the proposed PK study JE049 #1103 with additional time points at or near C_{max}

	• Data obtained from the open-label, Phase 2 study JE049 #2101 did not fully support the 30 mg SC dose used in the Phase 3 pivotal trials • Pediatric use to be assessed in post-marketing phase
September 2005	Reassignment of IND to Division of Pulmonary and Allergy
September 8, 2005	Protocol JE049 #4102 (PRO endpoint validation) submitted (SN 0013) The study was intended to estimate the Minimum Clinically Significant Difference (MCSD) in VAS scores. Patients were asked to score their symptom response using the Verbal Descriptor Scale (VDS), classifying their symptom as “much more,” “a little more,” “about the same,” “a little less,” or “much less” compared to baseline. The MCSD was defined as the VAS change most predictive of the VDS categories of “a little less” and “a little more” for each symptom. The MO review dated January 26, 2006, and SEALD consult cited several concerns with the protocol: • The VDS required more rigorous definition. Incorporation of a temporal element in the VDS makes this measure less reliable. • The patient population in the validation study was not representative of the patients participating in the phase 3 study. • Patient diaries used in Phase 3 studies should be included in the validation protocol. • Potential labeling limitations for claims supported solely by the VAS
February 9, 2006	Response to Division/SEALD review regarding validation study (SN 015). Reference to other clinical studies that have used a Verbal Descriptor Scale to determine the MCSD in VAS scores.
June 1, 2006	SEALD review of February 9, 2006 response. Patient diaries and planned subject enrollment deemed acceptable. Concern raised that the VAS is not a comprehensive measure of HAE symptoms and does not correlate clearly with the proposed indication.
June 20, 2006	SAP for Study #2103 (FAST-1) submitted via email The Statistical review team asked the Applicant to provide the assumed MCSD used to calculate the sample size of N=56. The review team recommended that the Applicant prespecify alternative analyses to be used if the proportional hazards assumption was not supported by the observed data.
October 10, 2006	Revised SAP submitted (SN 0026)
October 13, 2006	Proposed trade name application submitted (SN 0027)
January 24, 2007	Pre-NDA meeting. The discussion included several key topics: • Nonclinical study requirements, including chronic repeat dose toxicity studies of 6 and 9-month duration, and carcinogenicity studies • Separation of Phase 1 and 2 data in the Integrated Summary of Safety • Validation of the VAS used in the Phase 3 studies • Preliminary assessment of Phase 3 efficacy data in suggested that the Applicant did not have replicate findings of the efficacy of icatibant • Limitations of self-administration usage data

2.6 Other Relevant Background Information

Icatibant has not yet been approved for marketing for any indication [2.5.5.13]

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The CMC reviewer's recommended action on this application at the time of this review is pending. Based on preliminary review, the CMC reviewer has noted that the Applicant has limited manufacturing experience with icatibant, and current specifications for impurities do not meet the TIDES Oligonucleotide and Peptide Technology Product and Development Conference 2005 guidelines. Also, recent changes have been made in the drug sterilization process that may affect the microbiology standards. GMP inspection of the manufacturing sites is pending and is expected to be completed by the end of March 2008.

3.2 Animal Pharmacology/Toxicology

The Pharmacology/Toxicology reviewer's recommended action on this application at the time of this review is pending. Based on preliminary review, the Pharmacology/Toxicology reviewer has identified several major issues. The Applicant has provided preclinical data to support human dosing only up to 13 weeks. Updates regarding chronic dosing studies (6-month in rat and 9-month in dog via the subcutaneous route) as well as carcinogenicity toxicology studies have been requested from the Applicant. The Applicant has also been asked to qualify impurities and/or degradants exceeding the qualification threshold of (b) (4) for peptides.

No apparent issues are identified upon preliminary review of the genotoxicology battery. The safety battery is complete and preliminary review is notable for dose-schedule-dependent effects on male and female reproductive organs in sexually immature rats and dogs. In SC dosing studies, these effects included arrest in the maturation of reproductive organs in both males and females. After the recovery period, the females had recovered but half of the male dogs still had immature prostate and testes. Also, decreases in testosterone, LH, and FSH were observed in male animals. Based on reproductive organ findings, no NOAEL was established.

Specific reproductive toxicology studies are currently under review, but preliminary review indicates that icatibant increases the frequency of spontaneous abortions and fetal resorptions.

Reviewer's Comment: The clinical relevance of the reproductive findings is unclear, given the fact that most patients would use a single dose of icatibant on intermittent occasion. Additional chronic toxicology studies are pending and may provide additional information regarding these reproductive findings. The Applicant did assess FSH and LH levels in the pharmacokinetic study, Study 1103, and did not observe any clinically relevant changes.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary source of clinical data for this review was the studies conducted by Jerini AG, presented in the clinical study reports. Data from literature reports referenced by the Applicant, expert opinions solicited and compiled by the Applicant, and literature reports collated from a PubMed literature search performed by the reviewer were also used. Prior communications with the Applicant were used as regulatory references.

4.2 Tables of Clinical Studies

Table 1 shows the main clinical studies presented by the Applicant in support of this application. Studies 2102 and 2103 are the major efficacy (“pivotal”) studies in this application. Each of these studies was followed by open-label extensions (OLE) to obtain additional safety and efficacy data on repeat administration. In addition to these Phase 3 studies, the Applicant has submitted study reports for pharmacokinetic studies in healthy volunteers (Studies 1101, 1103, and 1103), an open-label proof-of-concept study in HAE patients (Study 2101), and a non-intervention study to define the Minimum Clinically Significant Difference (MCSD) as measured by the VAS instrument (Study 4102).

Table 1 Summary of key clinical studies for Icatibant				
Study	Design	N	Dose	Endpoint
Phase 1 studies				
1101	SD, safety and tolerability	Healthy subjects	• IV	•
1102	SD, safety and tolerability	16 healthy subjects	• 0, 0.5, 0.2, 0.4 mg/kg SC vs IV	• PK
Efficacy studies				
2101	Open-label, Phase 2 study	15 adult HAE patients	• 0.4mg/kg IV over 30 min • 0.8mg/kg IV over 30 min • 0.4mg/kg IV over hours • 30 mg SC icat bant • 45 mg SC icat bant	• PK • Symptom score
2102 (FAST-2)	MC, R, DB, active-control trial with OLE	72 adult HAE patients with cutaneous or abdominal HAE sx Additional subjects with laryngeal sx	• 30 mg SC icatibant • Tranexamic acid (3 x 1 g for 2 days)	• time to onset of symptom relief (VAS)
2103 (FAST-1)	MC, R, DB, PC with OLE	56 adult patients with cutaneous or abdominal HAE sx Additional subjects with laryngeal sx	• 30 SC mg icatibant • Placebo	• time to onset of symptom relief (VAS)
Additional clinical studies				
1103	R, DB, PC, QTc study	32 healthy subjects (18-40 and >65 yrs)	• 30 mg SC icatibant (5 doses on Day 1, QD on Day 8 and 15) • Placebo	• Age subgroup PK • QTc interval
4102	Observational PRO validation study	60 adult HAE subjects	• No intervention	• Correlation of VDS to VAS to calculate MCSD

4.3 Review Strategy

The two Phase 3 studies, the open-label proof-of-concept study, and the PRO validation study presented in Table 1 were reviewed, with greater emphasis placed on the two Phase 3 efficacy and safety studies, 2102 and 2103. Data from the OLE phases of both pivotal studies was included in the review. The proof-of-concept study was briefly reviewed to assess the extent of dose-ranging performed in the clinical development program and for additional safety and efficacy information, given the small number of patients exposed in the overall clinical development program. Study 4102 was reviewed to assess the validity of the VAS instrument, the basis of the primary efficacy endpoint used in both Phase 3 studies.

Reviews of the studies are based primarily on the Jerini AG study reports, original protocols, and statistical analysis plans. The Applicant's summary data tables were reviewed in details. Appendix tables were also reviewed in varying amounts of detail, depending upon the endpoint and review issue. Case report forms (CRFs) were also reviewed.

The Applicant provided bibliographies within the study reports and expert opinion reports in the application. These references in addition to the results of a literature search conducted by the reviewer were reviewed to the extent of their relevance to the review.

4.4 Data Quality and Integrity

The Applicant states that no debarred investigators participated in the study, and all investigators certified to having no financial conflicts of interest.

The Division requested an audit by the Division of Scientific Investigations (DSI) for this NDA since icatibant is a new molecular entity and the majority of the supporting efficacy data had been obtained from international study sites. A DSI audit was requested for the study sites which enrolled the most patients in Studies 2102 and 2103, Sites 070 and 014, respectively. Study 2102, Site 070 (Dr. Werner Abere) in Austria enrolled 7 patients; Study 2103, Site 040 (Dr. Alejandro Malbran) in Argentina enrolled 14 patients.

In Study 2103, the Applicant identified Study Site 070 (n=10; 5 assigned to icatibant) as an outlier. At this study site, patients receiving icatibant were noted to have a poorer response to icatibant (time to onset of symptom relief ≥ 10 hours) compared to other study sites. *Post hoc* analysis performed excluding this site resulted in a statistically significant treatment difference between icatibant and placebo (2 vs 6 hours; $p=0.026$). According to the Applicant's own audit of data, one patient from this site (007-008) was wrongly assigned skin pain as the primary symptom instead of skin swelling. A second patient who received icatibant for an abdominal attack was later revealed to have narcotic drug addiction, violating inclusion/exclusion criteria.

Reviewer's comment: While the protocol violations at Study Site 070 in Study 2103 are noteworthy, there does not appear to be evidence of systematic bias at this study site to merit full exclusion of these site results. Further discussion of the post hoc analyses are included in Section 7 of this review.

4.5 Compliance with Good Clinical Practices

The Applicant states that all Phase 1, 2, and 3 clinical trials performed by Jerini were conducted in accordance with applicable standards and ICH-GCP [2.5.1.4]. However, the individual study reports note several GCP violations. In Study 2102, Study Site 020 (n=6) was found to have some data entered retrospectively by the investigator for one patient. Study Site 050 (n=2) had lost source documents and both patients enrolled at this site signed informed consents after the screening visit. In Study 2103, Study Site 090 was noted to have missing source data for the two patients enrolled at this site.

4.6 Financial Disclosures

Based upon the information provided by Jerini AG, no disclosable financial arrangements occurred for Studies 2101, 2102, and 2103.

5 CLINICAL PHARMACOLOGY

The Applicant has submitted clinical pharmacology data generated from 4 studies in healthy subjects conducted by Jerini (1001, 1101, 1102, and 1103), and one study in patients with HAE (2101). Pharmacokinetics in patients with hepatic and/or renal impairment were assessed in Studies 2001 and 2002 as part of the development programs for other indications. The application also includes summaries of 3 preliminary studies using continuous IV infusions conducted by Hoechst in the early 1990's in anticipation of development for other indications (Studies 9101, 9103, and 9106). This review briefly focuses on the studies based on the subcutaneous formulation (Studies 1102, 1103, and 2101) to provide an overview of the formulation and dose exploration performed for icatibant and the proposed HAE indication.

5.1 Pharmacokinetics

Icatibant has linear pharmacokinetics, with a dose-proportional increase in mean C_{max} and mean AUC_{0-∞}. The elimination profile is triphasic, with the majority of the drug eliminated with a half-life of ~1 hour. There appears to be a difference in gender that is not readily explained by body weight differences, with women achieving higher plasma levels of drug. The principal findings of the main clinical pharmacology studies are summarized below.

Study 1102

Study 1102, a randomized, controlled, open crossover study in 24 subjects, assessed the bioavailability of a single SC dose of icatibant compared to IV infusion in healthy subjects. Results of the study are summarized in Table 2. The study report concludes that mean icatibant C_{max} values after IV infusion are approximately 2-fold higher than after SC injection with no relevant differences found in the extent of exposure between the different administration routes or concentrations. C_{max} was reached in approximately 0.5 h. Elimination half-lives were similar for both routes of administration. The pharmacokinetics of the M2 metabolite, the major metabolite (inactive), were similar between routes as well.

Table 2 Pharmacokinetic parameters for single-dose SC icatibant (Study 1102)*

Dose	Substance	Tmax (h)	Cmax (ng/ml)	AUC _{0-t} (h*ng/ml)	AUC _{0-∞} obs (h*ng/ml)	T1/2λz (h)
0.4 mg/kg SC (20mg/ml) N=12	Icat bant	0.561	1132.772	2492.375	2549.985	1.223
	M2 metabolite	2.235	354.101	2056.975	2201.240	2.604
0.4 mg/kg SC (10mg/ml) N=12	Icat bant	0.595	1386.895	2984.018	3057.004	1.191
	M2 metabolite	2.182	373.174	1973.530	2117.390	2.759
0.4 mg.kg IV over 30 min (1mg/ml) N=24	Icat bant	0.500	2875.572	3033.558	3118.507	1.366
	M2 metabolite	1.517	462.674	2079.084	2191.209	2.590

* values provided as geometric means

Source: je049-1102-report-body.pdf, Section 10.2.1, Table 7

Study 2101

Similar values were obtained in Study 2101, an open-label, proof-of-concept study conducted in HAE patients that evaluated single doses of 30 mg and 45 mg SC icatibant. The mean Cmax for the 30 mg dose was 1278.3 ng/ml, compared to 2229.8 n/ml with the 45 mg dose. The mean AUC_{0-t} for the 30 mg dose was 2555.1 ng*h/ml compared to 4886.1 ng*h/ml for the 45 mg dose. C_{max} was reached in approximately 0.5 h.

Study 1103

Study 1103 was a randomized, double-blind study in 32 healthy subjects intended to evaluate the pharmacokinetics of icatibant after SC injection by gender and age. Eight males and 8 females ages 19 to 40 years and 8 males and 8 females >65 years were enrolled. Patients received 5 doses of 30 mg icatibant on Day 1, and single injections of 30 mg icatibant on Days 8 and 15. No gender-specific difference in plasma exposure was observed. Females had a 1.6 to 2.4-fold higher AUC_{0-t} (3818.6 vs. 1853.4 ng*h/ml) and 1.6 to 2.2-fold higher Cmax (1814 vs. 805.39 ng/ml) compared to males. No gender differences were noted for tmax or t_{1/2}, but t_{1/2} was longer in elderly patients (>1.1h) compared to younger subjects (0.5h). Multiple dose administration did not lead to accumulation of icatibant.

As part of the safety evaluation, plasma LH and FSH levels were assessed at pre-dose, 0.5, 2, 4, 6, 12, 12.5, and 14h post-dose on Day 1 and at pre-dose, 0.5, and 2h post-dose on Day 15. No consistent effect on these hormonal levels was reported.

Study 1103 included 12-lead standard ECG and Holter ECG measurements. Standard ECGs were recorded at Screening, pre-dose, 0.5, 1, and 4h after the first dose, pre-dose and 2h after each following dose on Day1, before and 0.5, 1, and 4h post-dose on Days 8 and 15, and at the first follow-up visit (within 36 hours). Holter ECGs were recorded for 24 h on Days -1 and 1 and for 12 h on Days 8 and 15. ECGs were analyzed by a central reader. The Applicant concluded that no consistent relationship between icatibant and QT interval prolongation was observed. However, this study was reviewed by the Interdisciplinary Review Team for QT Studies who cited several examples of ST/T wave changes and/or QT prolongation in healthy patients receiving 5 doses of icatibant 30 mg SC on 3 separate days. Details of the IRT's review can be found in the review dated January 30, 2007 under IND 68,214.

Reviewer's comment: This study was reviewed by the Interdisciplinary Review Team for QT Studies, who concluded that icatibant showed evidence of QT prolongation and thus a thorough QT study was not warranted. At the pre-NDA meeting, these comments were communicated to the Applicant, and the Applicant was informed that QT prolongation would be included in product labeling unless the Applicant chose to refute these findings. The Applicant has not provided any additional data to refute these findings.

Other studies

The Applicant reports that in vitro studies have demonstrated that icatibant does not inhibit or significantly induce CYP450 isoenzymes [summary-clin-pharm.pdf, Section 2.7.2.3.1].

The pharmacokinetics of icatibant do not appear to be altered in patients with hepatic impairment or impaired renal function secondary to hepatorenal syndrome (Studies 2001 and 2002). More detailed discussion of these studies may be found in the Clinical Pharmacology reviewer's analysis.

Reviewer's comment: The gender difference in plasma exposure may be partly responsible to for the gender difference in efficacy noted between male and female patients in the Phase 3 studies, particularly Study 2102.

5.2 Pharmacodynamics

Study 2101 evaluated several pharmacodynamic parameters at baseline, 0, 4, and 20 hours post-dose: C1 inhibitor, C4, C1q, and bradykinin. 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 63.25 to 37.93 pmol/L. In the 45 mg dose group, bradykinin decreased from 82.00 to 70.67 pmol/L. The normal range for bradykinin ranges from 2.2 to 7.1 pmol/L, according to the assay used in the analysis. Presumably, the elevated bradykinin levels are due to the underlying HAE attack. Based on the time-course, icatibant does not appear to have increased bradykinin levels.

5.3 Exposure-Response Relationships

Dose selection was based on pharmacokinetic/pharmacodynamic modeling using bradykinin challenge. Doses ranging from 0.005 mg/kg to 3.2 mg/kg IV icatibant in earlier studies were used to establish a dose response curve to bradykinin, based on measurements of blood pressure, heart rate, and cutaneous blood flow. The 0.4 mg/kg IV dose was selected as being sufficiently high to counteract the elevated systemic bradykinin concentrations anticipated during an HAE attack for up to 6 to 12 hours. The PK/PD modeling suggested that repeat administration was more likely to prolong the duration of effect rather than higher doses. In addition, higher doses administered subcutaneously were more likely to elicit stronger injection site reactions.

Aside from the assessments of the 30 and 45 mg SC doses performed in Study 2101, no formal dose-ranging study in HAE patients was performed. Pharmacodynamic data suggest that higher

dosing is unlikely to increase efficacy substantially and no safety issues are identified with the proposed 30 mg dose. Furthermore, establishing a true dose-response curve for icatibant may not be feasible, given the highly subjective nature of the efficacy measurements. However, it is unclear how representative the pharmacodynamic modeling is of HAE attacks. Thus, clinical dose ranging data is necessary. Alternative dosing regimens may improve the durability of response and are recommended as a consideration for future clinical trials.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication for icatibant is “the treatment of hereditary angioedema” in patients 18 years of age and older.

Reviewer’s comment: The proposed indication is not supported by the Phase 3 studies, which were designed to assess the efficacy of icatibant in acute attacks of HAE only, not prophylaxis or chronic treatment.

6.1.1 Methods

The efficacy review is based on the two, Phase 3 studies conducted by Jerini, Study 2102 and Study 2103. Study 2102 was a randomized, double-blind, active-controlled trial in the treatment of patients presenting with acute cutaneous and abdominal HAE attacks with icatibant 30 mg SC versus oral tranexamic acid as an active comparator. Study 2103 had a similar study design to Study 2102 but used a placebo control. Both studies provided open-label treatment to patients presenting with laryngeal attacks and both studies were followed by open-label extension phases which permitted repeat dosing with icatibant. Detailed reviews of the individual studies are provided in the Appendix. Study 2101, a Phase 2 proof-of-concept study in HAE patients, and Study 4102, a non-interventional validation study of the patient-reported outcome instrument used in the efficacy studies, are briefly reviewed as well. The other pharmacokinetic studies discussed in Section 5 are not included in the efficacy review.

6.1.2 General Discussion of Endpoints

The primary and secondary endpoints evaluated in Studies 2102 and 2103 were based on patient-reported (PRO) and investigator-reported outcomes. Given the variable nature of HAE attacks, more objective endpoints have not been established and PRO-based efficacy variables are considered acceptable by this reviewer if accompanied by appropriate validation and consistency between different measures is observed.

The endpoints used in the Phase 3 studies were previously discussed with the Division of Gastrointestinal and Coagulation Drug Products as part of a Special Protocol Assessment for Study 2103 and predate the publication of the *Guidance for Industry: Patient-reported Outcomes Measures: Use in Medical Product Development to Support Labeling Claim*. The primary

efficacy endpoint, time to onset of symptom relief, is based on a Visual Analogue Scale (VAS). At the time of the SPA, the review division stipulated that this endpoint was acceptable if adequate validation of the VAS instrument was provided in the NDA application. To meet this requirement, the Applicant has submitted results of Study 4102, a non-interventional, observational study in HAE patients intended to define the Minimum Clinically Significant Difference as measured by the VAS. The application also includes a third-party analysis (Mapi Values) of VAS and patient symptom scores collected during the Phase 3 trials (Report No. JE049-5110) and a briefing document that discusses the conceptual framework for the endpoints selected (Report No. JE049-5105). A brief review of these results and additional study reports is presented below. Study 4102 is discussed in further detail in the Appendix as well.

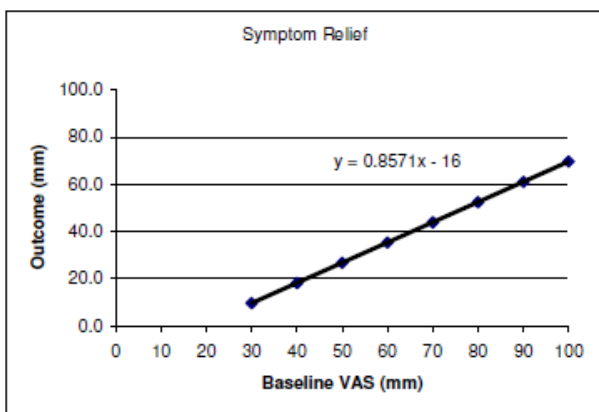
The primary efficacy endpoint was the **time to onset of symptom relief as measured by the Visual Analogue Scale (VAS)** for the single most severe, presenting symptom. The VAS is a 100 mm horizontal line with 0mm = no symptoms and 100mm = worst possible symptom. Patients mark on the line to rate the 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 “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 to assess onset of symptom relief. Time to onset of symptom relief is defined as the time between injection and time of first documented onset of symptom relief, as defined below, at 3 consecutive measurements. Subjects with no documented onset of symptom relief were to be censored at the time of their last symptom assessment.

Onset of symptom relief was originally defined as follows: Absolute reduction from pre-treatment VAS of ≥ 20 mm if pre-dose VAS ≥ 30 and ≤ 50 , or of ≥ 30 mm if VAS > 50 mm.

A modified definition of onset of relief was presented in the SAP dated August 24, 2006 for both Studies 2102 and 2103 as follows (Figure 1):

- A response to the right and below a line $Y = 6/7 X - 16$ with $X \geq 30$ mm.
 - 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 Study 2102: Definition of onset of symptom relief by VAS as presented in the statistical analysis plan dated August 24, 2006



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

Secondary endpoints included 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 also scored individual symptoms, as well as making Global Assessments, Clinical Global Impression, observable regression of symptoms, and overall patient improvement. Laryngeal attacks were treated on an open-label basis. 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.

Reviewer's comment: While the use of a PRO for measuring symptoms is reasonable for HAE attacks, the Applicant's definition of symptom relief is quite complicated and not entirely intuitive. Time to onset of symptom relief is farther removed from the measured symptom scores and is not easily described. Also, the primary endpoint is based on identification of a predominant symptom, which may not capture the extent of an HAE attack or may not be possible for different patient presentations. No formal composite symptom scoring by patients was assessed, which would be a useful indicator of the patient's overall response to treatment.

Study 4102

Study 4102 was 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 MCSD for the VAS instrument. Patients received the standard of care as determined by the physician and were asked to complete patient diaries until complete resolution of their symptoms or 48 hours from baseline, whichever occurred first. In addition to patient symptom scores, patients were asked to complete the VAS and a Verbal Descriptor Scale (VDS), which the Applicant designated as the "gold standard". Based on comparison to the VDS, a 9 mm change in VAS was identified as the MCSD for "onset of symptom relief." This cut-point provided 88.24% specificity and 82.61% sensitivity at 6 hours post baseline. Changes in the VAS corresponded to changes in the VDS ($r=0.7576$; $p<0.0001$). A more complete discussion of Study 4102 is located in the Appendix.

Reviewer’s comment: Although the study demonstrated statistically significant correlation between the VAS and VDS, the value of this correlation is uncertain. The Applicant proposes the VDS as the “gold standard,” which begs the question as to why the VDS was not used as a primary endpoint or even a key secondary endpoint. Furthermore, the study did not include any patient interviews to substantiate the terms used in the VAS or VDS, nor did it provide illustrative examples for patients filling out patient diaries. For example, the concept of “a little less” symptom may vary widely among individuals with HAE. In addition, the Applicant has not reconciled the discordance in VAS and VDS observed in several study participants’ diaries (n=7 out of 80 patients who completed the study). Whether the discordance reflects a lack of comprehension on the part of the patient or error in data collection is uncertain. In either circumstance, the observed discordance with the proposed gold standard is problematic and raises concerns regarding the validity of the VAS instrument for HAE attacks.

Post-hoc analyses of patient diary data from pivotal studies (Study Report 5110) and PRO validation briefing document (Study Report 5105)

The application includes a study report, “Validation of PRO endpoints using pooled clinical trial data from the FAST hereditary angioedema studies,” Report No. JE049-5110. Post-hoc analyses patient diary entries from Studies 2102 and 2103 were compared to physician assessments to assess the test-retest reliability and clinical validity. The VAS appeared to have limited test-retest validity compared to patient individual symptom scores, although the retest validity was not formally assessed. The VAS and patient symptom scores performed comparably in terms of clinical validity and responsiveness when compared against various physician assessments.

In addition, the application includes a briefing document that provides an overview of the conceptual framework for the endpoints selected. The study report cites market research in HAE patients that identifies the key symptoms and attack locations relevant to acute HAE attacks as represented in the VAS PRO. Third-party translation and back-translation was used for most countries, except for Argentina (Spanish), Canada (Canadian French), Austria, and Israel (Israel) where back translation was not performed. No patient testing of the translations was conducted.

Reviewer’s comment: In general, the VAS is difficult to interpret. Although the time to onset of symptom relief statistically correlates with patient-reported start of improvement, the actual times reported vary. As a result, it is unclear whether the VAS measurement or the patient symptom score reflects the true onset of symptom relief. The time to onset of symptom relief as assessed by the VAS is not entirely intuitive or easily described. Validation of this PRO instrument is limited by the lack of cognitive debriefing interviews and patient-based test-retest evaluations.

6.1.3 Study Design

6.1.3.1 General study design of Phase 3 studies

The general study design was similar for both Phase 3 studies. Studies 2102 and 2103 were randomized, double-blind, multicenter safety and efficacy studies. The key difference between

the studies was the controls used; Study 2102 used an active control, oral tranexamic acid, while Study 2103 used a placebo control. The appropriateness of tranexamic acid as an active control is discussed in Section 6.1.3.2.

In both studies, 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 OLE studies are ongoing and presently there is no limitation to the total number of attacks for which a patient may receive icatibant.

Reviewer's comment: The general study design is acceptable for demonstrating the efficacy of icatibant for the treatment of acute HAE attacks. However, the proposed indication, treatment of HAE, is broad and not supported by the design of the Phase 3 studies. A general treatment indication would be expected to include studies addressing chronic and short-term prophylaxis of attacks, in addition to treatment of acute attacks. Dose-ranging data to support the 30 mg SC icatibant dose is limited, as discussed in Section 5.

6.1.3.2 Selection of control groups

Only one of the two pivotal studies used a placebo-control design. Study 2102 used a double-dummy design with oral tranexamic acid (1g by mouth every 6 to 8 hours for 2 days) as an active comparator. 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. A PubMed literature search using the terms “tranexamic acid,” “hereditary angioedema,” and “hereditary angioneurotic (o)edema” yields few references with clinical trial data. The three studies referenced by this reviewer includes a single blinded trial conducted by Blohme et al, which demonstrated that 1 out of 2 patients treated benefited from treatment of tranexamic acid during an acute HAE attack. Ohela et al. observed that 6 out of 7 patients who received open-label tranexamic acid during a period that

ranged from 3 to 22 months appeared to have acute attacks of lessened severity. Finally, in a longitudinal study of HAE patients, Agostoni et al. reported that 27 patients appeared to have less severe attacks when given tranexamic acid for acute attacks.

Reviewer's comment: The treatment difference between tranexamic acid and icatibant is difficult to interpret, since the efficacy of tranexamic acid in acute HAE attacks is not established. Also, oral bioavailability may be compromised or unpredictable in cases of mucosal edema resulting in altered gut absorption, in addition to vomiting and diarrhea. Theoretically, a statistically significant treatment difference between tranexamic acid and icatibant could be attributed to tranexamic acid worsening an HAE attack. The Applicant has provided an expert opinion summarizing that at the very least, tranexamic acid is not worse than placebo. Most likely, this statement is correct but the data to support this assertion is limited. For example, tranexamic acid in Study 2102 appears to perform appreciably worse than the placebo arm in Study 2103. While the validity of such a cross-study comparison may be limited, the comparison certainly does not support the Applicant's assertion.

6.1.3.3 Patient selection criteria

Both studies included adult patients with a documented diagnosis of either Type I or Type II HAE. The diagnosis could be confirmed either by functional and immunogenic C1-INH results from the central laboratory or by medical history. Inclusion on medical history alone was permitted if a clear diagnosis had been made on all of the following criteria:

- Family history
- Characteristic attack manifestations, recurrent attacks
- Historical functional C1-INH <50%
- Exclusion of other forms of angioedema

Patients with C1-INH >50% could be included if an acceptable rationale for the higher level was provided.

Reviewer's comment: These inclusion/exclusion criteria could be more stringent for confirming the diagnosis of HAE as opposed to acquired angioedema (AAE). Although both functional C1-INH and C4 levels were collected, the inclusion criteria were based only on the C1-INH level. C1q levels, which are ordinarily depressed in AAE but normal in HAE, were not obtained for the study and were not routinely documented. Although a diagnosis of acquired angioedema (AAE) is an exclusion criterion, it is possible that patients with AAE who have previously been presumed to have HAE may have been enrolled in this study.

6.1.3.4 Blinding

Although both studies were blinded, the adequacy of the blinding may have been compromised by the near ubiquity of local injection site reactions associated with icatibant in contrast to placebo injections. Furthermore, tranexamic acid is associated with GI disturbances (nausea, vomiting, and diarrhea), as well as a distinctive adverse effect of color vision disturbances, which may have further compromised blinding.

Reviewer's comment: As the primary and secondary endpoints are based on subjective symptom assessments, incomplete blinding further undermines the strength of the efficacy findings.

6.1.4 Efficacy Findings

6.1.4.1 Patient population and disposition

Table 3 shows the enrollment and patient disposition in each of the two efficacy studies. A total of 63 patients received icatibant 30 mg SC, 38 patients received tranexamic acid, and 29 patients received placebo in the two Phase 3 studies. An additional 3 patients in Study 2102 and 8 patients in Study 2103 received open-label icatibant for an initial HAE attack with laryngeal symptoms.

Table 3 Patient disposition in Phase 3 studies for icatibant				
	Study 2102		Study 2103	
	Icatibant	Tranexamic acid	Icatibant	Placebo
Total N	36 (100%)	38 (100%)	27 (100%)	29 (100%)
Discontinuations	1 (2.8%)	3 (7.9%)	1 (3.7%)	1 (1.8%)
Other	1 (2.8%)	1 (2.6%)	1 (3.7%)	1 (1.8%)
Withdrawal of consent	0	0	0	0
Adverse events	0	0	0	0
Lost to follow-up	0	1 (2.6%)	0	0
Death	0	1 (2.6%)	0	0

Source: je049-2102-report-body.pdf, Section 16, Table 3.3.1, P354-7 and je049-2103-report-body.pdf, Section 16, Table 6.21.1.3, P 1994

6.1.4.2 Baseline characteristics

Table 4 summarizes the demographics and baseline HAE characteristics of the patients enrolled in both studies. The patient populations for the two studies differed slightly. The patients enrolled in Study 2102 were slightly older (mean age 41.1 years) compared to patients in Study 2103 (mean age 34.9 years). Study 2102 was racially homogenous, whereas Study 2103 enrolled several non-Caucasian patients. The two studies were comparable in overall gender distribution. In addition, Study 2103 had a balanced number of abdominal versus cutaneous attacks, whereas Study 2102 had a proportionally greater number of cutaneous attacks. The Applicant states that this disparity in attack site may explain the lack of statistically significant findings in Study 2103, which is discussed in more detail in Section 6.1.4.3. Baseline attack frequency, as assessed by attack history over the prior 6 months, appeared comparable between the two studies and suggested that most patients had fairly active disease with regular attacks.

Table 4 Phase 3 studies: Demographics and baseline characteristics

	Study 2102		Study 2103	
	Icatibant	Tranexamic acid	Icatibant	Placebo
ITT population	36	38	27	29
Male	12 (33.3%)	15 (39.5%)	11 (40.7%)	8 (27.6%)
Race				
Caucasian	36 (100.0%)	38 (100.0%)	25 (92.6%)	25 (86.2%)
Black	0	0	0	0
Asian	0	0	0	1
Multiracial	0	0	0	1 (3.4%)
Other	0	0	2 (7.4%)	2 (6.9%)
Cutaneous attack	24 (100.0%)	23 (100.0%)	14 (100.0%)	13 (100.0%)
Male	8 (33.3%)	12 (52.8%)	8 (57.1%)	5 (38.5%)
Female	16 (66.7%)	11 (47.8%)	6 (42.9%)	8 (61.5%)
Abdominal attack	12 (100.0%)	15 (100.0%)	13 (100.0%)	16 (100.0%)
Male	4 (33.3%)	3 (20.0%)	3 (23.1%)	3 (18.8%)
Female	8 (66.7%)	12 (80.0%)	10 (76.9%)	13 (81.3%)
Age (years)				
Mean	40.4	41.9	34.8	34.9
Median	38.0	42.0	35.0	34.0
Range	20-68	19-66	20-54	18-58
Mean number of attacks during the last 6 months				
Cutaneous	7.4	7.9	8.6	9.9
Abdominal	4.2	8.7	5.1	6.8
Cutaneous and abdominal	6.5	2.4	7.3	4.9
Laryngeal	2.4	1.0	1.7	2.8

Source: je049-2102-report-body.pdf, Section 10.5, Tables 10, 11, 12 and Section 10.8, Table 17 and je049-2103-report-body.pdf, Section 10.5

6.1.4.3 Primary efficacy findings

6.1.4.3.1 Primary efficacy findings: Study 2102

Onset of symptom relief for the ITT population is shown in Table 5. For all attacks, the treatment difference between icatibant and tranexamic groups was 10.0 hours ($p < 0.001$). Also shown in the table are the median times to onset of symptom relief for the subpopulation of patients with cutaneous versus abdominal HAE attacks.

Table 5 Study 2102: Median time to onset of symptom relief as assessed by the VAS

	Icatibant	Tranexamic acid	Total	P
All attacks, N	36	38	74	
# patients with pre-treatment VAS ≥30 mm	35	36	71	
# censored patients*	0	2	2	
Median time to onset of symptom relief (hours)	2.0	12.0	3.5	<0.001
Cutaneous attacks, N	24	23	47	
# patients with pre-treatment VAS ≥30 mm	23	23	46	
# censored patients*	0	2	2	
Median time to onset of symptom relief (hours)	2.5	18.2	7.0	<0.001
Abdominal attacks, N	12	15	27	
# patients with pre-treatment VAS ≥30 mm	12	13	25	
# censored patients*	0	0	0	
Median time to onset of symptom relief (hours)	1.6	3.5	2.0	0.026

* Patients censored when symptom relief did not occur within the observation period. No data imputation.

Reviewer's comment : The icatibant group had a statistically significant faster onset of symptom relief compared to the tranexamic acid group overall, although the treatment difference between icatibant and tranexamic acid is much less in the abdominal attack subgroup compared to the cutaneous group (1.9 hours versus 15.7 hours, respectively). According to the Applicant, pain symptoms in general are more likely to respond to treatment, including placebo. Since abdominal pain was the abdominal symptom used for VAS scoring, the Applicant states that abdominal attacks were more likely to show improvement after any treatment. Whether this explanation is true is uncertain. When looking at time to onset of symptom relief for individual symptoms aside from the primary symptom, skin pain does not appear to have the same "placebo response." The literature does not indicate that abdominal attacks differ from cutaneous attacks in terms of bradykinin pathophysiology.

Subgroup analysis suggested a differential response according to gender. The time to onset of symptom relief was greater in male patients (3.5 hours) compared to female (1.6 hours) patients treated with icatibant. The small sample size limits the utility of subgroup analysis, but there is no clear explanation for the differences seen in male versus female patients. In terms of types of attacks, a similar proportion of patients were male versus female in the icatibant cutaneous and abdominal attack subgroups (see Table 4). Pharmacokinetic assessments show higher plasma levels in females, but pharmacodynamic data from clinical pharmacology studies suggest that a 30 mg dose should be sufficient for maximal bradykinin inhibition in both sexes. No differences were observed between patients weighing 50-75 kg and 75-100kg. As the entire study population was reported as Caucasian, no subgroup analysis by race was provided.

Reviewer's comment: As shown in Section 6.1.4.3.2, it appears that male patients appear to have slower resolution of HAE attacks based on data from the placebo group. Review of the literature does not indicate any gender-based differences in terms of HAE attack severity, frequency, or course, so the reason for the observed discrepancy remains unknown.

6.1.4.3.2 Primary efficacy findings: Study 2103

Onset of symptom relief for the ITT population is shown in Table 6. For all attacks, the treatment difference between icatibant and placebo groups was 2.1 hours ($p=0.142$). Also shown in the table are the median times to onset of symptom relief for the subpopulation of patients with cutaneous versus abdominal HAE attacks.

Table 6 Study 2103: Median time to onset of symptom relief as assessed by the VAS				
	Icatibant	Placebo	Total	P
All attacks, N	27	29	56	
# patients with pre-treatment VAS ≥ 30 mm	27	28	55	
# censored patients*	1	1	2	
Median time to onset of symptom relief (hours)	2.5	4.6	3.0	0.142
Cutaneous attacks, N	14	13	27	
# patients with pre-treatment VAS ≥ 30 mm	14	13	27	
# censored patients*	0	1	1	
Median time to onset of symptom relief (hours)	3.4	10.0	6.0	0.221
Abdominal attacks, N	13	16	29	
# patients with pre-treatment VAS ≥ 30 mm	13	15	28	
# censored patients*	1	3.0	1	
Median time to onset of symptom relief (hours)	2.0	6.0	2.3	0.159

* Patients censored when symptom relief did not occur within the observation period

Source: je049-2103-report-body.pdf, Section 11.4.1, Tables 22, 23, 24

Reviewer's comment: Although the VAS results were numerically favorable to icatibant, icatibant failed to demonstrate a statistically significant quicker onset of symptom relief compared to placebo. The clinical relevance of the 2.1 hour treatment difference is difficult to assess, as HAE attacks may be quite variable and the natural course for most attacks is spontaneous resolution. There did not appear to be any clear differences in icatibant efficacy in cutaneous versus abdominal HAE attacks.

The Applicant states that an exaggerated placebo response was observed in Study 2103 due to the higher number of patients with abdominal versus cutaneous attacks enrolled compared to Study 2102. According to the Applicant, pain symptoms in general are more likely to be responsive to placebo. Since abdominal pain was the base symptom scored on the VAS, patients presenting with abdominal attacks were more likely to show improvement, regardless of allocation to treatment group. Whether this explanation is true is uncertain.

Unlike Study 2102, subgroup analysis did not show any statistically significant differences between male and female patients. When divided by weight, patients weighting between 75 to 100kg treated with icatibant were observed to have a faster onset of symptom relief compared to their placebo counterparts (3.9 v. 23.0 hours; $p=0.030$). No statistically significant differences were noted in patients weighing 50 to 100 kg ($n=3$) or patients >100 kg ($n=9$). These differences do not appear clinically relevant and more likely are a reflection of the small sample size in the study.

6.1.4.4 Secondary efficacy findings

6.1.4.4.1 Secondary efficacy findings of Study 2102

The Applicant performed analysis on multiple secondary endpoints, including response rate at 4 hours, time to relief on non-primary symptoms, time to almost complete symptom relief (VAS 0-10mm), assessment of each symptom by severity, durability of response, start of improvement, and rescue medication use. Several of these endpoints were not pre-specified and no adjustment was made for multiplicity. No composite symptom scoring was performed by the patients. In general, the secondary endpoints supported the efficacy of icatibant over tranexamic acid. This portion of the review provides an overview of the patient-derived endpoints that were deemed most clinically relevant and provided added perspective on the primary efficacy variable. Additional patient-reported endpoints and physician assessments are presented in detail in the Appendix.

Responder analysis

As a form of responder analysis, the study report presents response rate at 4 hours after start of treatment, using the same definition of response as used in the primary efficacy endpoint. At 4 hours after start of treatment, the response rate based on the primary symptom was 80.0% (n=28) for icatibant versus 30.6% (n=11) for tranexamic acid ($p<0.001$). In the cutaneous attack subgroup, the response rate at 4 hours was 73.9% (n=17) versus 17.4% (n=4), respectively ($p<0.001$). In the abdominal attack subgroup, the response rate was 91.7% (n=11) versus 53.8% (n=7), respectively ($p=0.073$).

Reviewer's comment: One issue with this definition of responder is that patients who may have persistent moderate-to-severe symptoms would be considered responders, e.g. if a patient has a baseline VAS of 100mm that decreases to 70mm, that patient would be classified as a responder. Also, since the VAS is based on a single primary symptom, a "responder" may have other symptoms that worsen or develop from baseline which would not be captured by this assessment.

Durability of response

A durable response was defined as onset of symptom relief for the primary symptom within 8 hours after treatment that lasted for at least 24 hours. In the icatibant group, 68.6% (n=24) reported a durable response, compared to 38.9% (n=14) in the tranexamic acid group ($p=0.017$). For cutaneous attacks, 65.2% (n=15) of icatibant patients compared to 21.7% (n=5) of tranexamic acid patients reported a durable response ($p=0.007$). For abdominal attacks, 75.0% (n=9) of icatibant patients reported a durable response compared to 69.2% (n=9) of tranexamic acid patients ($p=1.0$).

Reviewer's comment: Icatibant performed favorably in terms of durability of response compared to tranexamic acid for all attacks and the subset of cutaneous attacks. No differences were seen, however, in the abdominal attack group. Overall, less than $\frac{3}{4}$ of patients reported a durable response. Whether a more durable response could be achieved with repeat dosing is unclear. Of note, the definition does not take into account rescue medication use, although in general, the tranexamic acid group received more rescue medications.

Assessment of each symptom by severity

In general, statistically significant differences were observed for individual cutaneous symptoms scored by patients at the various time points between icatibant and tranexamic acid treatment groups. For abdominal symptoms, abdominal pain was scored more favorably by icatibant patients starting at 1 h post-dose and sustained through the Visit 3 timepoint ($p=0.001$ to 0.045). No statistically significant differences were reported for nausea, vomiting, or diarrhea. This analysis only includes patients who reported the symptom as at least of mild severity at baseline.

Regression of symptoms (start of improvement) according to the patient

Icatibant patients reported a median time to start of improvement of 0.8 hours, compared to 7.9 hours for tranexamic acid patients ($p<0.001$).

Reviewer's comment: The start of improvement by this symptom index differs from the onset of symptom relief as estimated by the VAS. The Applicant has not conducted any separate studies to validate this patient-reported endpoint. In addition, this particular endpoint is not described in the protocol and the study report does not describe how the information was collected (retrospectively versus prospectively). However, it is worth noting the disparity in this measurement and the time to onset of symptom relief as assessed by the VAS.

Rescue medication use

Although not evaluated as a formal secondary efficacy endpoint, the data is reviewed here as a reflection of icatibant's efficacy. Seven patients in the icatibant group and 12 patients in the tranexamic acid group received rescue medication for the initial HAE attack. The most commonly administered rescue medication was C1-INH ($n=5$ in the icatibant group; $n=8$ in the tranexamic acid group). Other medications administered included opioids for pain relief and glucocorticoids. Rates of rescue medication usage were similar between cutaneous and abdominal attack groups. The study report states that 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.

Reviewer's comment: Rescue medication usage data is supportive of icatibant's efficacy.

6.1.4.4.2 Secondary efficacy findings of Study 2103

The secondary efficacy endpoints evaluated in Study 2103 are the same as those endpoints evaluated for Study 2102. In general, the secondary endpoints were numerically favorable but did not show a statistically significant benefit for icatibant over placebo. The data are suggestive of icatibant's efficacy for acute HAE attacks but are not robust findings.

Durability of response

A durable response was defined as onset of symptom relief for the primary symptom within 8 hours after treatment that lasted for at least 24 hours. In the icatibant group, 51.9% reported a durable response, similar to the 50.0% in the placebo group ($p=1.0$). For cutaneous attacks, 57.1% of icatibant patients compared to 38.5% of placebo patients reported a durable response

($p=0.449$). For abdominal attacks, 46.2% of icatibant patients reported a durable response compared to 60.0% of placebo patients ($p=0.705$).

Reviewer's comment: Icatibant and placebo groups performed similarly in terms of durability of response. Results were numerically unfavorable for icatibant for patients with abdominal attacks. These results suggest that icatibant's impact on the overall resolution of an acute attack may be limited.

Response rate at 4 hours after start of treatment

At 4 hours after start of treatment, the response rate based on the primary symptom was 66.7% for icatibant versus 46.4% for placebo (0.176). When classified by cutaneous versus abdominal attacks, no statistically significant differences were noted as well ($p=0.252$ and 0.435 , respectively).

Assessment of each symptom by severity

No consistent, statistically significant differences were observed for individual cutaneous symptoms scored by patients at the various time points between icatibant and placebo treatment groups. For abdominal symptoms, both abdominal pain and nausea were scored more favorably by icatibant patients starting at 1 h post-dose and sustained through the 12-h timepoint ($p=0.001$ to 0.033).

Regression of symptoms (start of improvement) according to the patient

Icatibant patients reported a median time to start of improvement of 0.8 hours, compared to 16.9 hours for placebo patients ($p<0.001$).

Reviewer's comment: As noted for the results of Study 2102, the disparity between this measure and the VAS time to onset of symptom relief for individual patients is noteworthy. To some extent, the "start of improvement" according to the patient is more easily understood and provides a composite score of the patient's overall attack status.

Rescue medication use

Although not presented as a formal secondary endpoint, rescue medication use is included here as a reflection of icatibant's efficacy in relieving symptoms of an acute HAE attack. Twenty patients total received rescue medication: 6 patients in the icatibant group and 14 in the placebo group. The most commonly administered rescue medication were opioids for pain relief. One patient (015-006) in the placebo group subsequently developed laryngeal symptoms and was treated with open-label icatibant as a rescue medication.

Reviewer's comment: On this basis, icatibant compares favorably to placebo. The Applicant has also provided additional subgroup analysis of the primary efficacy endpoint in terms of patients who were using attenuated androgens as a concomitant medication versus those who were not. Icatibant appears to be more efficacious in patients without androgen ($p=0.019$); plausibly, the concomitant use of androgens may blunt the treatment difference observed for icatibant. However, the numbers are small, making subgroups analysis difficult.

6.1.4.5 Laryngeal attack efficacy results

Overall, the data to support icatibant's efficacy in laryngeal attacks was limited by the small number of subjects. In Study 2102, 3 patients presented with laryngeal attacks during the controlled phase of the study. In this study, 2 of the 3 patients 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 Study 2103, 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. Symptom scoring by both patients and investigators at 0, 2, and 4 hours after study drug administration is presented below. Patients were asked to score only 2 attributes of a laryngeal attack, voice changes and difficulties in swallowing. Although laryngeal attacks are typically considered the most severe manifestation of HAE, the cases in Study 2103 appeared to be mostly mild in severity.

Table 7 Study 2103: Laryngeal attack symptom scores as reported by patients (N=8 attacks in 8 patients)						
Severity	Voice change			Difficulties in swallowing		
	0h	2h	4h	0h	2h	4h
Very severe	1	-	-	1	-	-
Severe	-	-	-	-	-	-
Moderate	1	-	-	2	-	-
Mild	3	2	1	5	3	1
Absence	3	6	7	-	5	7
Not scored	-	-	-	-	-	-

Source: je049-2103-report-body.pdf, Section 11.4.3, Table 43, Page 128

During the OLE phase of Study 2102 and 2103, an additional 8 attacks in 4 patients and 11 attacks in 6 patients, respectively, were treated with open-label icatibant. A median time to regression of symptoms or onset of symptom relief was not reported for Study 2102's OLE, but symptom scores reported at 0, 2, and 4 hours suggested that most patients experienced symptom improvement within 4 hours of treatment. For Study 2103's OLE, the time to regression of symptoms ranged from 0.3 to 1.4 hours, consistent with prior observations. The overall severity of laryngeal attacks in the OLE phase appears to have been more severe than that reported during the controlled phase of Study 2103.

Reviewer's comment: The small sample size and lack of placebo control limits the interpretation of these results. Whether the improvements observed over time were attributable to icatibant or reflected the gradual resolution of the attack is difficult to discern, especially in cases where the presenting symptoms were mild at baseline. In one report in the literature (Bork and Barnstedt), patients with untreated laryngeal attacks averaged 100.8h (324 attack episodes) from onset of symptoms to time of symptom resolution. However, the baseline severity of these cases is not well-documented, thus limiting the utility of these cases as a historical control. Furthermore, laryngeal efficacy data in the icatibant Phase 3 program were presented descriptively and time

to onset of symptom relief or median time to regression were not consistently reported, complicating the comparison of individual cases.

6.1.4.6 Open-label extension efficacy data

In general, the open-label extension data from both Phase 3 studies were consistent with results obtained from the respective controlled-phases of each study and were supportive of icatibant's efficacy, in the absence of formal statistical comparisons. The onset of symptom relief was evaluated in the open-label extension phase by the number of attacks treated with icatibant.

In Study 2102, the greatest number of attacks for any one patient treated in this portion of the study was 38. (More detailed information regarding total drug exposure is discussed in the Appendix, Section 10.2.2, Drug exposure.) The onset of symptom relief ranged from 1.5 to 12.0 hours for all attacks and 1.6 to 2.5 hours for patients where data was available for 10 or more patients (2nd and 3rd attacks).

In Study 2103, the greatest number of attacks treated for any one patient in this portion of the study was 12. More detailed information regarding total drug exposure is discussed in the Appendix, Section 10.3.2.5, Safety analysis. The onset of symptom relief ranged from 1.0 to 4.0 hours for all reported attacks and 1.5 to 1.8 hours for patients who experienced 2 to 4 attacks during the OLE (n=59).

6.1.4.7 Post hoc efficacy analyses

In Study 2103, the Applicant identified Study Site 070 (n=10; 5 assigned to icatibant) as an outlier. At this study site, patients receiving icatibant were noted to have a poorer response to icatibant (time to onset of symptom relief ≥ 10 hours) compared to other study sites. *Post hoc* analysis performed excluding this site resulted in a statistically significant treatment difference between icatibant and placebo (2.0 vs 6.0 hours; p=0.026). According to the Applicant's own audit of data, one patient from this site (007-008) was wrongly assigned skin pain as the primary symptom instead of skin swelling. A second patient who received icatibant for an abdominal attack was later revealed during the audit to have narcotic drug addiction, violating inclusion/exclusion criteria. A third patient (015-007) at Study Site 015 was found to have a history of pancreatitis, which may have confounded the reporting of abdominal pain symptoms. *Post hoc* analysis performed excluding Patients 007-014 and 015-007 and reassignment of Patient 007-008 for the primary symptom resulted in a statistically significant treatment difference between icatibant and placebo (2.0 vs 5.0 hours; p=0.049). *Post hoc* analysis performed excluding Patients 007-014 and 015-007 results in a treatment difference 2.0 vs. 4.6 hours (p=0.069).

Reviewer's comment: While the protocol violations at Study Site 070 are noteworthy, there does not appear to be evidence of systematic bias at this study site to merit full exclusion of these site results. Given the small total sample size, post hoc exclusion of 10 patients from the efficacy database, including 3 patients with laryngeal edema attacks, is far from trivial. Also, as the unfavorable direction of the results prompted the data audit for this particular study site, the

possibility of bias in this type of post hoc analysis remains an issue. From the perspective of the clinical review, these post hoc analyses are considered supportive of efficacy but are not considered as a substitute for the pre-specified analyses based on the ITT population.

Additional *post hoc* analysis stratifying the results of Study 2103 by US versus non-US locations indicates that efficacy results were fairly comparable, without any clear geographic differences. Further details regarding *post-hoc* analysis can be found in the statistical team's review. According to the statistical reviewer, the median time to onset of symptom relief for icatibant recipients at US and non-US locations was 2.25 and 2.5 hours respectively. In the placebo arm, the times were 7.0 and 3.6 hours, respectively.

6.1.5 Clinical Microbiology

Icatibant is not an antimicrobial drug product, and the application does not contain any clinical microbiology data.

6.1.6 Efficacy Conclusions

The Applicant has provided reports for two Phase 3 efficacy and safety studies, Study 2102 and Study 2103, as well as uncontrolled efficacy data on laryngeal attack treatment and treatment of abdominal and cutaneous HAE attacks during the open-label portions of each study. Only Study 2103 was placebo-controlled. While the results were numerically favorable, this study failed to show a statistically significant benefit for icatibant over placebo in the treatment of acute HAE attacks. Study 2102 did show a statistically significant benefit for icatibant over the active comparator, but the efficacy of the active comparator in the treatment of acute HAE attacks is not established, making the comparison more difficult to interpret. Notably, the time to onset of symptom relief for the tranexamic treatment arm is considerably longer than the median time observed for the placebo arm in Study 2103. While the reliability of such a cross-study comparison may be questionable, the assertion that tranexamic acid should perform no worse than placebo is not reinforced by the information presented in the application. As a result, the application does not provide sufficient data to support the proposed indication, treatment of hereditary angioedema.

In the absence of a conclusive study in the current clinical program, at least one additional placebo-controlled study with a comparable sample size is required. Ideally, the additional study would use a primary efficacy endpoint that has confirmed test-retest validity and transparency. A composite symptom endpoint, such as the Verbal Descriptor Scale used as the "gold standard" in Study 4102, is a candidate endpoint if supported by validation methods as described in the *Guidance for Industry: Patient-reported Outcomes Measures: Use in Medical Product Development to Support Labeling Claims*. The VAS could be included as a key secondary endpoint to facilitate comparison with the data obtained from Studies 2102 and 2103. Alternatively, the same primary efficacy endpoint used in Studies 2102 and 2103 may be used in another placebo-controlled study if the Applicant provides additional information to support the validity of the VAS PRO instrument. Of note, such a study would support an indication for treatment of acute HAE attacks. Should the Applicant seek a broader indication such as the one

proposed in this application, treatment of HAE, the clinical development program will require additional studies that assess the use of icatibant in short-term and chronic prophylaxis as well.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Safety was assessed in the clinical studies with reports of adverse events, laboratory values, vital signs, and physical exams. A total of 63 patients treated with a single injection of icatibant 30 mg SC in the controlled phase of the two Phase 3 studies is the focus of this Integrated Review of Safety. Additional safety information obtained from 118 patients treated for a total of 602 HAE attacks with open-label icatibant during the Phase 3 studies is also reviewed and discussed. Additional discussion is found in the individual study reports (Appendix, Sections 10.2 and 10.3). A few patients treated during the open-label phase received up to 30-mg doses for a single attack, but the majority of patients were treated with 1 injection per attack. Exposure data are summarized in Table 8, Table 20, Table 25, Table 35, and Table 36. Table 8 shows the number of patients by the number of attacks treated and doses administered, as well as the number of patients who received 1, 2, or 3 sequential 30-mg icatibant injections for a single attack. Additional safety information from a Phase 2 study in HAE patients was reviewed as well, but given the small number of patients and consistency with the data obtained from the Phase 3 studies, these results are not discussed in detail here but may be found in the Appendix.

The overall safety profile of icatibant 30 mg was acceptable without any concerning safety signals. The most relevant safety issues for this review were local injection site reactions and recurrent or progressive hereditary angioedema attacks.

Table 8 Summary of all attacks treated with icatibant in Phase 3 studies			
	N	# attacks treated in the study	# doses administered
Duration of exposure			
1 attack	47	47	48
2-5 attacks	68	202	218
6-10 attacks	14	115	128
>10 attacks	12	308	341
Dose of exposure			
30 mg	140	611	611
60 mg (2 x 30 mg)	27	56	112
90 (3 x 30 mg)	4	4	12

Source: je049-5113-a-iss-pdf. Appendix, Table 3.3

7.1.1 Deaths

No deaths were reported in any patients who received icatibant. One death was reported in Study 2102 for a 53-year-old male randomized to the tranexamic acid treatment arm. Forty-one days after drug administration, the patient collapsed and died. An autopsy showed coronary artery disease and aortic stenosis.

7.1.2 Other Serious Adverse Events

Controlled phase

In addition to the patient death described above in Study 2102, 5 SAEs were reported in 4 patients who received icatibant.

- Patient 75-013 experienced a severe laryngeal HAE attack requiring tracheostomy 5 months after the last receipt of icatibant.
- Patient 90-004 experienced an abdominal HAE attack 2 weeks after initial treatment with icatibant, notably accompanied by hypotension, pyuria, and microhematuria. She was deemed fully recovered by 5 days after treatment with C1 INH concentrate, volume resuscitation, and antibiotic therapy. Additional icatibant was not administered.
- Patient 16-005 was hospitalized for viral gastroenteritis and hypertensive crisis 3 months after receipt of icatibant.
- Patient 075-014 experienced a laryngeal HAE attack, the same attack that qualified him for treatment with open-label icatibant in the study.

No SAEs were reported during the controlled phase for Study 2103.

OLE phase

In Study 2102's OLE, 5 patients experienced 9 SAEs, including HAE and renal failure requiring hospitalization (4 months after last treatment with icatibant), elective tooth extraction requiring hospitalization for precautionary monitoring, rotavirus-associated diarrhea with increased pancreatic enzymes requiring hospitalization (3 months post-icatibant), and a motor vehicle accident with minor head injury and hospitalization (2 days post-icatibant). The motor vehicle accident occurred in the setting of road flooding and hazardous driving conditions.

In Study 2103's OLE, 4 SAEs were reported for 4 patients, including 2 events of pancreatitis associated with an abdominal HAE attack in one patient (10 and 14 days post-icatibant; prior history of pancreatitis), worsened abdominal HAE attack despite 3 sequential doses of icatibant, and chest pain accompanied by abdominal and cutaneous HAE symptoms (7 days post-icatibant).

Phase 2 (Study 2101)

Two SAEs were reported for Study 2101. One patient with a longstanding history of schizoaffective disorder and 8 prior psychiatric hospitalizations experienced an acute manic episode 7 days after infusion of 0.4 mg/kg IV over 2 hours. CK levels were reported as elevated (level not reported), as had been noted in past psychiatric hospitalizations for the patient. A second patient reported recurrence and worsening of HAE symptoms 20 hours after treatment with 30 mg SC icatibant and was hospitalized for an additional 12 hours prior to resolution of his symptoms.

Reviewer's comment: The timing of the SAEs makes a causal relationship with icatibant appear less likely. In the case of the CK abnormalities observed in the Phase 2 study, CK elevations during psychotic episodes have been previously reported in the literature and seem unlikely to have been caused by a single dose exposure to icatibant.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Of patients treated with icatibant, 1 patient discontinued prematurely from Study 2102 due to a desire to become pregnant. One patient discontinued early from Study 2102's OLE due to unavailability for follow-up. In Study 2103, one patient discontinued early after completion of Visit 6. According to the study report, the patient is reported as discontinuing for "other" reasons but according to the CRF narrative, the patient withdrew consent. During the OLE phase, 4 patients were lost to follow-up, 1 patient completed Visit 6 but was unable to attend the 6-month follow-up visit due to a motor vehicle accident and scheduling problems, 1 patient withdrew citing lack of efficacy, and 4 patients withdrew consent after Visit 4 for reasons not specified.

No patients from the controlled phase of either study discontinued due to adverse events. No premature discontinuations were reported for the Phase 2 study, Study 2101.

7.1.3.2 Adverse events associated with dropouts

No dropouts associated with adverse events were reported.

7.1.3.3 Other significant adverse events

No other significant adverse events are reported by the Applicant or noted in the safety database.

7.1.4 Other Search Strategies

Icatibant and pharmacologically related products are not currently marketed for any indication, so no post-marketing data or additional clinical reports of safety in the literature are available.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

In both Studies 2102 and 2103, an adverse event was defined as any untoward medical occurrence in a patient administered a pharmaceutical product, and which did not necessarily have a causal relationship with this treatment. All pre-existing medical conditions were to be documented at the Screening Visit, and all AEs occurring from Visit 1 to the study assessment were recorded in the CRF, whether the AE was deemed treatment-related or not. During the controlled phase of the studies, HAE was to be documented as an AE only if there was worsening of symptoms during a treated attack. New HAE attacks that were not treated with icatibant were to be recorded in the CRF as "Occurrence of HAE attack," and were not considered AEs, although the Applicant notes that some investigators may have reported new

attacks as AEs, leading to an over-reporting of HAE attack as an AE. HAE attacks with laryngeal symptoms that occurred during the OLE phase were considered AEs. AEs were elicited from patients at all study visits, including at the 24-hour follow-up, Weeks 2, 5, 12, 24 and the final follow-up telephone call. Formal checklists were not employed. Investigators were instructed to follow-up all AEs until they had stabilized or resolved, or until the end of the protocol-defined study period, whichever came first.

Reviewer's comment: The categorization of HAE as an AE is problematic. Worsening of symptoms during a treated attack may be difficult to discern clinically and may merely be a reflection of the natural course of an attack. Also, it appears that there was some variability among investigators in how HAE attacks were reported. It is unclear why the Applicant made the distinction that only HAE attacks with laryngeal symptoms would be considered an AE. While laryngeal attacks have more life-threatening potential, the pathophysiology of these attacks versus attacks at other sites is presumably the same and it is arguable whether a mild laryngeal attack should be considered an AE instead of a severe GI or cutaneous attack.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were coded by the Applicant using Version 9.1 of the MedDRA coding dictionary. Preferred terms and primary system organ class designation for each event were reviewed and spot-checked against case narratives, particularly for the SAEs. In general, the Applicant appears to have categorized AEs appropriately, although the categorization of HAE as an AE appears to have been handled somewhat inconsistently among the various study investigators as discussed in Section 7.1.5.1.

7.1.5.3 Incidence of common adverse events

The Applicant's report and display of AEs were consistent within each study report and in the Integrated Summary of Safety (Revised ISS; dated December 20, 2007). The Applicant tabulated all AEs, but classified local injection site reactions separately as these reactions occurred in almost all subjects who received icatibant.

In the ISS, the Applicant combined data from the two Phase 3 trials. Although the study design and dose regimens were comparable, the studies used different comparator arms, limiting the pooling of data. As a result, data from the studies were reviewed separately then compared for consistency. Open-label data from both studies was pooled. Safety data from the Phase 2 Study 2101 was presented separately and is reviewed in the Appendix. Phase 1 data was not reviewed in depth, as these data did not present any unique safety signals and the IV formulation was used in these early studies.

7.1.5.4 Common adverse event tables

Adverse events in the controlled phase of the Phase 3 studies, Study 2102 and Study 2103, occurring more commonly in the icatibant treatment group compared to tranexamic acid or placebo are shown in Table 9 and Table 10, respectively.

Table 9 Study 2102: Adverse events in the double-blind phase occurring more commonly in the icatibant treatment group compared to tranexamic acid

Adverse event	Icatibant (N=36)	Tranexamic acid (N=38)
Local injection site reaction	35 (97.2%)	10 (26.3%)
Hereditary angioedema	7 (19.4%)	6 (15.8%)
Abdominal pain	1 (2.8%)	0
Asthenia	1 (2.8%)	0
Blood urine present	1 (2.8%)	0
Borrelia infection	1 (2.8%)	0
Chest wall pain	1 (2.8%)	0
Cystitis	1 (2.8%)	0
Diabetes mellitus	1 (2.8%)	0
Diarrhea	1 (2.8%)	0
Fall	1 (2.8%)	0
Gastroenteritis	1 (2.8%)	0
Headache	1 (2.8%)	0
Hypertensive crisis	1 (2.8%)	0
Influenza	1 (2.8%)	0
Joint pain	1 (2.8%)	0
Nasopharyngitis	1 (2.8%)	0
Nausea	1 (2.8%)	0
Pyrexia	1 (2.8%)	0
Rash	1 (2.8%)	0
Sinusitis	1 (2.8%)	0
Skin laceration	1 (2.8%)	0
Vaginal candidiasis	1 (2.8%)	0
Viral infection	1 (2.8%)	0
White blood cells in urine	1 (2.8%)	0
Blood in urine	1 (2.8%)	0

Source: je049-2102-report-body.pdf, Section 12.2.2.1 and Section 16, Table 6.17.1.1, Page 2843

Table 10 Study 2103: Adverse events in the double-blind phase occurring more commonly in the icatibant treatment group compared to placebo

Adverse event	Icatibant (N=27)	Placebo (N=29)
Local injection site reaction	26 (96.3%)	8 (27.6%)
Nasal congestion	2 (7.4%)	0
Abdominal pain	1 (3.7%)	0
AST increased	1 (3.7%)	0
Bilirubin increased	1 (3.7%)	0
CPK increased	1 (3.7%)	0
Contusion	1 (3.7%)	0
Erythema	1 (3.7%)	0
Hand dermatitis	1 (3.7%)	0
Herpes simplex	1 (3.7%)	0
LFT abnormality	1 (3.7%)	0
Nasopharyngitis	1 (3.7%)	0
Pyrexia	1 (3.7%)	0
Rash	1 (3.7%)	0
Throat irritation	1 (3.7%)	0
Vocal cord disorder	1 (3.7%)	0

Source: je049-2103-report-body.pdf, Section 12.2.2.1 and Section 16, Table 6.17.1.1, Page 1970

Reviewer's comment: HAE was to be recorded only in the event of worsening of symptoms during a treated attack. In Study 2102, HAE was reported by 7 patients (19.4%) in the icatibant group as an AE and 6 patients (15.8%) in the tranexamic acid group. In Study 2103, HAE was reported by 3 patients (11.1%) in the icatibant group as an AE and 5 patients (17.2%) in the placebo group. The AE frequency reported for icatibant contradicts the efficacy results reported for icatibant over tranexamic acid but favors the efficacy of icatibant over placebo.

Laryngeal attack patients

Injection site reactions were reported by all 11 subjects who received open-label icatibant in both studies. The type of reaction and duration were similar to those reactions reported for abdominal and cutaneous attack patients. Other AEs reported in this group included HAE attacks (n=4), headache (n=2), viral infection (n=1), thermal burn (n=1), epistaxis (n=1), dermal cyst (n=1), and urticaria (n=1). The case of urticaria does not appear to be treatment-related as the patient developed the urticaria nearly 10 months after the initial administration of icatibant.

OLE phase of Study 2102 and Study 2103

Seventy-nine (66.9%) of patients in the OLE reported at least one AE during the study. Similar types of AEs were reported during the OLE phases, with local injection site reactions predominating. Hereditary angioedema was reported in 27 (22.9%) of patients, which could be interpreted to be mean that icatibant lacked efficacy, caused an exacerbation of symptoms, a late relapse occurred, or a secondary attack occurred. Other AEs occurring in $\geq 3\%$ of patients included the following: headache (n=13, 11%), nasopharyngitis (n=8, 6.8%), urinary tract infection (n=8, 6.8%), pharyngitis (n=6, 5.1%), chest pain (n=5, 4.2%), pyrexia (n=5, 4.2%), vomiting (n=4, 3.4%), and urticaria (n=4, 3.4%). Nine SAEs for 5 patients described above were also reported during the OLE phase.

7.1.5.5 Identifying common and drug-related adverse events

A wide range of adverse events were reported for the icatibant arms of both Phase 3 studies; however, the majority of these AEs were reported in a single patient. Comparison of incidence rates across the studies does not highlight specific adverse events which are likely treatment-related, with the exception of local injection site reactions which were nearly ubiquitous. The reporting of hereditary angioedema attacks as AEs is difficult to interpret, but most likely reflects limited efficacy of icatibant rather than HAEs attacks worsened or triggered by icatibant. This assumption is supported by data from Study 2103, the placebo-controlled trial.

Stratification of these events by attack site (cutaneous and abdominal), age, or gender, does not indicate any clinically relevant differences. Review of the laryngeal attack patients also does not suggest any clinically relevant differences. Subgroup analysis by ethnicity is limited by the small number of non-White study participants.

7.1.5.6 Additional analyses and explorations

Local injection site reactions were nearly ubiquitous across all the studies, occurring in patients of both sexes, all ethnicities, and age groups and comparable among cutaneous, abdominal, and

laryngeal attack patients. The reactions were self-limited and immediate, generally resolving within a few hours after dose administration. The main characteristics were local erythema, swelling, burning, itching, warmth, and cutaneous pain. Based on the few patients who received additional doses for separate attacks during the OLE, there did not appear to be any intensification or diminishment of local injection site symptoms upon repeat dosing. During the Phase 2 study, Study 2101, both the 30-mg and 45-mg SC treatment groups (N=5 in each dose group) reported injection site reactions without a clear dose dependency for severity or duration of the reaction. No injection site reactions were reported for intravenous dosing groups.

7.1.6 Less Common Adverse Events

The size of the safety database for the two Phase 3 studies is unlikely to provide an adequate evaluation of less common adverse events. Aside from local injection site reactions, 31 (49.2%) patients in the icatibant group reported an AE, in comparison to 19 patients (65.5%) in the placebo group and 16 (42.1%) in the tranexamic acid group. With the exception of local injection site reactions and hereditary angioedema, all of the other adverse events were reported in 1 or 2 patients during the controlled phases of each study. Evaluation of these rare events and their relationship to drug treatment is difficult.

In the OLE phase, 79 (66.9%) of patients reported at least one AE. As in the controlled phase, the relationship of the less common AEs to treatment is difficult to ascertain. Of the AEs reported, 6 cases of urticaria in 5 patients are noted. In 4 of the patients, the urticaria was noted to occur 1, 4, 9, and 11 days after treatment with icatibant; in the 5th patient, the urticaria developed at 9 months after the last injection of icatibant. Patient 40-010 had urticaria 4 days after icatibant on 2 consecutive occasions. Allergic dermatitis was reported in 1 patient (Patient 004, Study 2102), but occurred approximately 6 months after receipt of icatibant. The long time interval between receipt of icatibant and the skin eruptions for some of these reactions makes a relationship to icatibant unlikely. However, for the episodes occurring within several days, including the patient who experienced urticaria twice after 2 consecutive treatments with icatibant, a causal relationship remains a possibility.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Routine laboratory testing was performed regularly during each study and as dictated by individual AEs. In the Phase 3 studies, blood sampling for safety monitoring was performed as Screening, Time 0h, Day 2, and 14 during the controlled phase. During the OLE, laboratory testing for safety was performed at Time 0 and Day 14. The range of normal values for hematology and chemistry parameters varied by study site; no uniform cutoff values were applied for identifying patients with high or low values or for categorization of extreme laboratory values as adverse events.

- Hematology: complete blood cell count with white cell count differential

- Coagulation parameters
- Hepatic chemistries: alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALK PHOS), and total bilirubin (TBILI)
- Renal: uric acid, blood urea nitrogen (BUN), creatinine
- Metabolic: glucose, creatinine phosphokinase (CPK)
- Urinalysis by dipstick (recorded as normal/abnormal)
- Urine pregnancy test in women of childbearing age at Screening, Day 2, and during the OLE

Reviewer's comment: The routine laboratory assessments were adequate.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The two Phase 3 studies were the focus for the review of drug-control comparisons of laboratory values, with particular attention paid to Study 2103, the placebo-controlled study. Data from the OLE of each Phase 3 study are reviewed also, although the duration of follow-up and degree of exposure varied among individuals. Longer-term data on icatibant is not available.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

7.1.7.3.1.1 Hematology

Mean hematology values were similar among the icatibant, placebo, and tranexamic acid treatment groups. A small reduction in mean hemoglobin, hematocrit, and WBC count at the 24-hour and Day 14 visits was observed in all groups, most likely reflecting acute changes in volume status during the onset and recovery from an acute HAE attack. Evaluation of other laboratory parameters such as bilirubin does not suggest acute hemolysis. Similar changes were observed in the OLE.

Table 11 Hematology parameters: Summary of Study 2102 and 2103 [Mean(SD)]

INDICES	Time	Icatibant (N=43 to 63)*	Placebo (N=23 to 26)	Tranexamic acid (N=28 to 37)
Hemoglobin (g/dl)	0 h	147.6 (16.2)	151.4 (16.1)	150.6 (13.9)
	24 h	139.9 (16.0)	137.5 (17.9)	143.3 (12.2)
	Day 14	138.7 (14.9)	140.4 (13.3)	142.1 (11.0)
Hematocrit (%)	0 h	0.432 (0.04)	0.445 (0.04)	0.441 (0.04)
	24 h	0.411 (0.04)	0.408 (0.05)	0.424 (0.04)
	Day 14	0.410 (0.04)	0.414 (0.04)	0.418 (0.03)
Platelets (x 10 ⁹ /L)	0 h	276.7 (82.5)	285.92 (56.9)	265.1 (63.8)
	24 h	267.6 (76.2)	265.64 (55.0)	256.8 (62.8)
	Day 14	283.8 (70.9)	286.40 (45.8)	252/4 (59.0)
WBC (x 10 ⁹ /L)	0 h	9.70 (3.96)	10.11 (3.53)	9.17 (3.52)
	24 h	8.13 (2.63)	6.98 (2.30)	7.42 (2.78)
	Day 14	7.55 (2.11)	6.68 (1.56)	6.27 (1.38)
Neutrophils (%)	0 h	6.87 (3.40)	7.43 (3.64)	6.56 (3.46)
	24 h	5.29 (2.24)	4.26 (1.75)	4.81 (2.49)
	Day 14	4.67 (1.60)	3.99 (1.12)	3.74 (1.23)
Lymphocytes (%)	0 h	1.96 (0.85)	2.99 (4.72)	1.92 (0.60)
	24 h	2.13 (0.81)	2.08 (0.65)	1.92 (0.62)
	Day 14	2.16 (0.77)	2.09 (0.55)	1.91 (0.58)
Monocytes (%)	0 h	0.51 (0.21)	0.76 (0.93)	0.50 (0.19)
	24 h	0.53 (0.21)	0.47 (0.19)	0.48 (0.28)
	Day 14	0.48 (0.16)	0.45 (0.16)	0.40 (0.19)
Eosinophils (%)	0 h	0.14 (0.08)	0.20 (0.22)	0.16 (0.10)
	24 h	0.15 (0.07)	0.16 (0.15)	0.20 (0.20)
	Day 14	0.16 (0.11)	0.14 (0.08)	0.17 (0.16)
Basophils (%)	0 h	0.03 (0.04)	0.06 (0.20)	0.04 (0.03)
	24 h	0.02 (0.03)	0.02 (0.03)	0.03 (0.04)
	Day 14	0.02 (0.02)	0.02 (0.03)	0.04 (0.03)

*Based on patients with baseline and follow-up laboratory values for comparison

Source: je049-5113-a-iss/pdf, Table 6.1.1.1-6.1.1.3

7.1.7.3.1.2 Chemistry

Mean chemistry values were similar among the icatibant, placebo, and tranexamic acid groups. Small reductions in glucose, uric acid, ALT, AST, and GGT at the 24-hour and Day 14 time points were observed in all three treatment groups. The magnitude of changes was limited and unlikely to be clinically relevant.

Table 12 Chemistry parameters: Summary for Studies 2102 and 2103 [mean(SD)]

INDICES	Time	Icatibant (N=45 to 62)*	Placebo (N=21 to 26)	Tranexamic acid (N=29 to 37)
Glucose (mmol/L)	0 h	5.23 (1.01)	5.14 (1.05)	5.76 (1.82)
	24 h	5.18 (1.04)	4.92 (1.32)	5.69 (1.65)
	Day 14	4.88 (0.78)	4.98 (1.11)	4.96 (0.72)
Uric acid (μmol/L)	0 h	306.0 (97.8)	288.8 (62.5)	295.93 (75.81)
	24 h	297.4 (99.0)	274.9 (84.8)	283.26 (74.36)
	Day 14	277.3 (80.1)	266.4 (60.4)	278.57 (71.15)
Total bilirubin (μmol/L)	0 h	9.83 (5.48)	9.12 (5.21)	9.89 (3.82)
	24 h	9.89 (6.11)	8.84 (4.79)	9.29 (3.38)
	Day 14	9.23 (5.17)	9.02 (4.46)	9.73 (2.72)
ALT (U/L)	0 h	35.05 (42.79)	38.77 (48.18)	25.80 (17.60)
	24 h	32.87 (41.53)	26.46 (15.78)	25.25 (18.61)
	Day 14	26.85 (15.40)	27.42 (17.33)	24.37 (14.39)
AST (U/L)	0 h	28.08 (15.56)	29.54 (20.02)	23.90 (8.01)
	24 h	25.48 (41.53)	23.62 (8.29)	22.90 (7.35)
	Day 14	24.05 (15.40)	25.23 (10.96)	23.51 (8.23)
GGT (U/L)	0 h	27.04 (19.28)	23.64 (15.72)	24.25 (17.52)
	24 h	26.02 (18.28)	22.00 (13.54)	23.60 (17.60)
	Day 14	25.62 (18.09)	23.56 (14.08)	21.52 (13.96)
CK (U/L)	0 h	107.50 (82.80)	96.52 (64.06)	99.99 (56.42)
	24 h	97.29 (56.42)	73.42 (39.97)	79.43 (51.62)
	Day 14	111.05 (59.30)	96.36 (44.20)	109.69 (72.07)
Creatinine (μmol/L)	0 h	78.37 (21.3)	76.27 (18.72)	78.91 (15.91)
	24 h	77.69 (21.44)	74.86 (20.22)	77.23 (16.69)
	Day 14	77.45 (18.84)	72.45 (13.20)	77.32 (18.76)
Urea (mmol/L)	0 h	7.39 (3.90)	6.79 (3.71)	7.62 (3.83)
	24 h	7.06 (3.73)	5.85 (4.79)	7.26 (3.39)
	Day 14	7.06 (3.58)	5.84 (4.46)	6.91 (3.84)

*Based on patients with baseline and follow-up laboratory values for comparison.

Source: je049-5113-a-iss/pdf, Table 6.2.1.1-6.2.1.3

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

The Applicant has not provided formal analyses of outliers or shifts from normal to abnormal. A glossary of normal laboratory ranges specific to each laboratory is provided. Upon review of individual patient data listings, the following shifts from normal to abnormal values were noted.

7.1.7.3.2.1 Hematology

No clinically significant changes from normal to abnormal were noted for the icatibant treatment group.

7.1.7.3.2.2 Chemistry

The following shifts from normal to abnormal values were noted in the metabolic evaluations from the Phase 3 studies.

Study 2102

- Patient 001-004 had an increase in total bilirubin from 15.2 to 22.9 μmol/L from pre-treatment to Day 14. The bilirubin returned to the normal range by 2 days later when the patient presented for a new HAE attack in the OLE.

Study 2103

- Patient 055-002 was noted to have an increase in CK from pre-treatment to the 24-hour follow-up (81 → 166 U/L). Upon subsequent treatment for 3 additional HAE attacks over the ensuing 7 months in the OLE, the CK fluctuated (112-215 U/L). No other follow-up for this abnormality is reported.
- Patient 071-002 had an elevated CK level (249 U/L) at the 14-day follow-up but no pre-treatment value is available for comparison. The level had returned to normal range by the time the patient returned for treatment of a second HAE attack in the OLE phase 3 months later.

Patients with marked laboratory abnormalities are discussed in Section 7.1.7.3.3.

Reviewer's comment: In the absence of formal analysis, review of the individual patient data listings for various laboratory parameters do not indicate any consistent laboratory abnormalities associated with icatibant treatment or any clear differences between the icatibant and respective comparator groups.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

No laboratory abnormalities led to subject discontinuation from the study. Several laboratory abnormalities were reported as adverse events, however. The criteria used for designating laboratory abnormalities as AEs are not described in the study protocols.

Study 2102

- Patient 016-005 was reported to have blood in the urine which resolved by the time of follow-up 40 days later. This patient had proteinuria noted at pre-treatment.
- During the OLE, Patient 070-004 presented with rotavirus gastroenteritis accompanied by a transaminitis 3 months after open-label treatment for her 3rd HAE attack. Three days following hospital discharge, she received icatibant 30 mg SC for an HAE attack. Five days later she was readmitted for persistent diarrhea, this time accompanied by an increase in pancreatic enzymes (amylase 110 U/L and lipase 63 U/L). The patient was discharged 1 week later and reported as recovered.

Study 2103

- Patient 017-002 was reported to have a mild elevation of ALT (77→164 U/L), AST (50→80 U/L), and GGT (60→77 U/L) from pre-treatment to Day 6 which spontaneously returned to baseline by 2-week follow-up.
- During the OLE, Patient 015-007 in Study 2103 developed severe pancreatitis requiring hospitalization that was reported as an AE. The episode occurred approximately 10 days after receipt of open-label icatibant. During the hospitalization, several laboratory derangements consistent with severe pancreatitis (elevated WBC count, increased cholesterol) were reported.
- Patient 040-003 was noted to have increases in CK (175→309 U/L), total bilirubin (8.55→82.08 mmol/L), and AST (52→136 U/L) from pre-treatment to Day 17. At 1 month follow-up, the total bilirubin and AST had returned to baseline but the CK remained elevated at 278 U/L.

- Patient 022-003 was noted to have an elevation in CK from baseline to 1-month follow-up (177→280 U/L). Additional follow-up was not provided.

Reviewer's comment: There is no clear association between the laboratory abnormalities reported as adverse events and ictaibant, although the two cases of elevated CK enzymes appear temporally related. CK enzyme elevation has been reported with use of anabolic androgens, including those agents used for prophylaxis in HAE. Based on the individual patient listings, Patients 040-003 and 022-003 do not have any androgens recorded as concomitant or rescue medications during the study period. A review of the literature does not suggest a relationship between CK elevations or pancreatitis in HAE. Conceivably, mucosal edema could lead to transient pancreatic obstruction and subsequent pancreatic enzyme leak, but such an explanation is speculative.

7.1.7.4 Additional analyses and explorations

No formal dose-ranging studies were performed for icatibant aside from the limited dose exploration performed in the Phase 2 study, Study 2101. Likewise, no drug-demographic, drug-disease, or drug-drug interaction studies were performed in the clinical development program for icatibant. Information on drug-drug interactions is extrapolated from in vitro data, showing no relevant inhibition or induction of CYP450 enzymes. The Applicant has postulated based on the mechanism of action that icatibant may attenuate the antihypertensive effect of ACE inhibitor drugs, but there is no clinical data regarding this issue.

Reviewer's comment: Given the expected, limited manner of use of icatibant, the life-threatening potential of HAE attacks, and the general avoidance of ACE inhibitors in HAE patients due to their potential for angioedema, the risk of this particular drug-drug interaction does not seem significant.

7.1.7.5 Special assessments

No special laboratory assessments for safety were reported.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs, including blood pressure, sitting pulse rate, respiratory rate, and body temperature were assessed as Screening, Time 0h, 0.5h, 24h, Week 2, and Week 24 during the controlled phased of the study. During the OLE, vital signs were assessed at Time 0h, 0.5, and Week 2. These results were not summarized by treatment group in the ISS provided by the Applicant. An information request was made on February 14, 2008 and additional summary statistics and tables were provided by the Applicant on February 26, 2008. According to the additional information, the following were considered normal ranges for vital signs: pulse (60-100 beats/min), systolic

blood pressure (90-140 mmHg), diastolic blood pressure (60-90 mmHg), and temperature (36.5-37.2°C).

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The two Phase 3 studies were the primary basis for the review of drug-control comparisons of vital signs, with particular attention paid to the placebo-controlled study, Study 2103.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Mean values for vital sign parameters were similar between the icatibant treatment groups in both Phase 3 studies, as well as for the placebo and tranexamic acid comparator groups. Results are summarized in Table 13.

Table 13 Mean vital sign parameters for Studies 2102 and 2103					
INDICES	Time	Study 2103		Study 2102	
		Icatibant (N=21 to 26)*	Placebo (N=26 to 29)	Icatibant (N=26 to 36)	Tranexamic acid (N=28 to 38)
Pulse (beats/min)	Screening	70.3	71.5	73.2	72.6
	0 h	78.4	80.4	76.9	80.6
	0.5 h	74.7	74.6	74.1	75.0
	24 h	74.4	77.9	77.1	76.3
	Day 14	70.9	76.4	79.0	72.8
Systolic blood pressure (mmHg)	Screening	122.5	119.4	126.5	123.6
	0 h	120.1	121.4	126.3	123.9
	0.5 h	119.6	117.7	123.7	118.1
	24 h	118.0	117.9	123.3	119.7
	Day 14	117.6	118.4	122.4	118.6
Diastolic blood pressure (mmHg)	Screening	76.1	76.2	77.7	78.0
	0 h	73.9	76.9	77.5	77.5
	0.5 h	74.9	76.8	77.8	75.5
	24 h	75.6	73.3	76.3	74.7
	Day 14	74.2	74.5	77.2	76.1
Temperature (°C)	Screening	36.5	36.5	36.8	36.6
	0 h	36.6	36.5	36.7	36.6
	0.5 h	36.6	36.6	36.8	36.5
	24 h	36.6	36.7	36.7	36.5
	Day 14	36.5	36.6	36.6	36.5

Source: je049-2103-study-report-1.pdf, Additional Table 19.1.1 and je049-2102-study-report-1.pdf, Additional Table 19.1.1

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Review of individual patient data listings did not reveal any clinically relevant outliers or shifts from normal to abnormal.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Review of individual patient data listings did not reveal any marked outliers. No patients discontinued prematurely from the studies due to vital sign abnormalities.

7.1.8.4 Additional analyses and explorations

No other additional analyses or data explorations were performed for vital signs results.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

In terms of ECG assessment, the Applicant did not conduct a formal thorough QT study. The clinical pharmacology study, Study 1103 (Section 5), showed several examples of ST/T wave changes and/or QT prolongation in healthy patients receiving 5 doses of icatibant 30 mg SC on 3 separate days. This study was reviewed by the Interdisciplinary Review Team for QT Studies (IRT-QT), who concluded that icatibant showed evidence of QT prolongation and a thorough QT study was not warranted. At the pre-NDA meeting, these comments were communicated to the Applicant, and the Applicant was informed that QT prolongation would be included in product labeling unless the Applicant chose to refute these findings. The Applicant has not provided any additional data to refute these findings.

In the Phase 3 program, a 12-lead ECG was performed on all patients enrolled in Studies 2102 and 2103 at Time 0h prior to study drug administration, 0.5h post-dose, 24h post-dose, and at Week 2 follow-up. ECG interpretation was performed by a central reader, Pierre Maison-Blanche, who prepared an ECG expert report for each individual study separate from the Applicants' ISS. The ECG variables – PQ, QRS, QT, and QTc (Bazett, Fridericia, and Framingham) intervals and changes from baseline – were summarized by treatment group. Categorical ECG results (normal and abnormal) were presented by frequencies and percentages. The results of the ECG analysis from the Phase 3 studies are discussed in more detail in this section of the review.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

The clinical development program does not include any clinical studies with a positive control for QT prolongation. The two Phase 3 studies were the primary basis for the review of drug-control comparisons of vital signs, with particular attention paid to the placebo-controlled study, Study 2103. The clinical pharmacology study, 1103, which indicates a QT prolongation effect was also reviewed, although this study was an open-label, uncontrolled study.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

The mean QTcF interval (msec) for each study is presented. In Study 2102, the mean change from baseline at 30 minutes and 24-48 hours post-icatibant was -5.7 msec and -3.1 msec, respectively, compared to 1.4 msec and -4.4 msec for the tranexamic acid treatment group. For

Study 2103, the mean changes from baseline for the icatibant group were 5.3 msec and -3.8 msec, respectively, compared to 1.9 msec and -2.2 msec for the placebo group.

Table 14 Mean QTcF intervals in Study 2102 and 2103					
Visit		Study 2102		Study 2103	
		Tranexamic acid	Icatibant	Placebo	Icatibant
Day 1 Time 0h	N	37	35	27	25
	Mean	388.7	391.9	388.8	393.3
	SD	22.12	28.95	26.41	24.06
Day 1 0.5 h	N	38	35	27	24
	Mean	389.9	386.2	390.2	399.1
	SD	26.45	27.39	25.67	28.97
Day 2 24-48h	N	33	33	29	26
	Mean	382.9	389.4	386.2	390.8
	SD	18.45	27.96	19.46	23.37

Source: je049-2103-statistical.pdf, Table 5 and je049-2102-statistical.pdf, Table 5

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

No persistent shifts from normal to abnormal were reported.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

No marked outliers or dropouts for ECG abnormalities were reported from the Phase 3 studies.

In Study 1103, several examples of icatibant-associated ST-T wave changes and QT prolongation were noted by the IRT-QT consult.

- Subject 203 was noted to have 120 msec increase in QTcF at 59 minutes post-dosing. The QTcF at this time point was 530 msec. Significant ST-T waves changes were also noted. These changes resolved by ~2 hours post dosing, with the QTcF interval measuring 412 msec.
- Subject 106 was noted to have ST-T wave changes and an increase in QTcF interval from 376 to 414 msec at 55 minutes post-dosing. These changes were resolved on subsequent ECGs and the QTcF interval returned to 385 msec.

7.1.9.4 Additional analyses and explorations

No additional analyses or explorations were performed on the ECG data.

7.1.10 Immunogenicity

The study report states that an assay for detection of icatibant antibodies remains under development at this time and data will be reported separately when available. There are no reports of anaphylaxis or allergic reactions to study drug administration. There are 5 reports of urticaria; the relationship to study drug administration remains uncertain.

Reviewer's comment: As a peptide drug product, albeit a small peptide, the formation of blocking antibodies may theoretically decrease efficacy of icatibant with repeat administration.

7.1.11 Human Carcinogenicity

Long-term human carcinogenicity data is not available for icatibant. During the Phase 2 and Phase 3 clinical development program up to September 30, 2007, no new cases of malignancy were reported during the clinical trials.

Reviewer's comment: Given the mechanism of action and the limited exposure expected with the use of the drug for intermittent HAE attacks, a tumorigenic effect seems unlikely.

7.1.12 Special Safety Studies

No special safety studies were conducted for icatibant.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No special studies regarding withdrawal phenomena and/or abuse potential have been conducted for icatibant, as these issues were not considered to pertain to this class of drugs.

7.1.14 Human Reproduction and Pregnancy Data

There is no drug exposure data in pregnancy for icatibant. No formal studies of icatibant in pregnancy have been conducted, and pregnancy was an exclusion criterion for the clinical studies. No pregnancies have been reported after receipt of icatibant.

Preclinical studies have demonstrated delayed maturation of reproductive organs in sexually immature rats and dogs, with decreased testosterone and FDS levels. In the clinical pharmacology study, Study 1103, no clinically relevant changes in FDS and LH were observed.

Reviewer's comment: Given the proposed intermittent use of icatibant, clinically relevant suppression of the gonadal pituitary axis is not expected.

7.1.15 Assessment of Effect on Growth

The clinical development program included adults ages 18 years and older, so no formal assessment of icatibant's effect on growth was made.

7.1.16 Overdose Experience

There is no overdose experience with icatibant. The clinical pharmacology study, Study JE049 1001, showed that a dose of 3.2 mg/kg administered by IV infusion over 1 hour caused symptoms of partial B2 receptor agonism, including erythema, flushing, hypotension, and generalized pruritus at the time of maximum plasma concentration. These effects were transient and self-limited. Similar effects might be expected in the event of an overdose with the SC formulation. As of now, icatibant is not intended for patient self-administration and the potential for overdose with SC formulation in the hands of a healthcare provider appears low.

7.1.17 Postmarketing Experience

Icatibant is currently not approved for marketing in the US or overseas. No postmarketing experience is available for report.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The primary source of clinical data for the safety review were the two Phase 3 studies conducted by Jerini, Study 2102 and Study 2103. This review focuses primarily on data collected during the controlled phase of each study with additional support from data collected during the OLE portion of each study. Phase 1 studies were briefly reviewed but their contribution to the safety database is limited given the type of patient enrolled (healthy volunteers). Safety data from the Phase 2 study, Study 2101, in HAE patients was evaluated in more detail (Appendix) and is discussed in terms of the consistency of findings with the Phase 3 data. Per patient data was available from individual patient data listings in the NDA, case narratives in the NDA, electronic data sets provided for statistical review, and patient CRFs. Literature reports referenced by the Applicant were reviewed briefly. In addition, the reviewer performed an electronic PubMed search [search term: icatibant; search restrictions; human] that yielded 184 literature reports. These reports were reviewed briefly and did not suggest additional safety concerns.

Table 1 summarizes the study design and subject enrollment of the key clinical studies relevant to this application. Additional detail of the individual studies can be found in the individual study reviews included in the Appendix.

7.2.1.2 Demographics

Demographic information for the Phase 1 studies (Studies 1101, 1102, and 1103) in the HAE development program are presented below. All Phase 1 participants were healthy volunteers.

Table 15 Demographic data for Phase 1 study participants						
	Placebo	Icatibant				All subjects on icatibant
		< marketing dose	= marketing dose	> marketing dose	≥ maximum tolerated dose	
N	71	64	75	8	4	133
Gender						
Male	65 (92%)	62 (97%)	63 (84%)	8 (100%)	4 (100%)	119 (89%)
Female	6 (8%)	2 (3%)	12 (16%)	0	0	14 (11%)
Race						
Caucasian	63 (89%)	59 (92%)	71 (92%)	6 (75%)	3 (75%)	125 (94%)
Black	3 (4%)	2 (3%)	2 (3%)	0	0	3 (2%)
Asian	3 (4%)	2 (3%)	2 (3%)	1 (13%)	0	2 (2%)
Multiracial	2 (3%)	0	1 (1%)	1 (13%)	1 (25%)	2 (2%)
Other	0	1 (2%)	0	0	0	1 (<1%)
Age						
Mean (range)	33.6 (18-72)	31.4 (19-49)	36.1 (19-82)	26.1 (21-38)	27.8 (21-38)	34.6 (19-82)

Source: je049-5113-iss.pdf, Table 1.38

In the Phase 2 study, Study 2101, 15 subjects with a total of 20 HAE attacks. The patients ranged in age from 20 to 61 years (median 42 years). Five patients were male, 10 were female. All patients were Caucasian.

Demographic data for the two Phase 3 studies is shown in Table 16. Only Study 2103 had non-White patients, and in general, the study participants were younger than the patients enrolled in Study 2102.

Table 16 Demographic data for Phase 3 study participants				
	Icatibant	Placebo	Tranexamic acid	Total
N	63	29	38	130
Gender				
Male	23 (36.5%)	8 (27.6%)	15 (39.5%)	46 (35.4%)
Female	40 (63.5%)	21 (72.4%)	23 (60.5%)	84 (64.6%)
Race				
Caucasian	61 (96.8%)	25 (86.2%)	38 (100.0%)	124 (95.4%)
Black	0	0	0	0
Asian	0	1 (3.4%)	0	1 (0.8%)
Multiracial	0	1 (3.4%)	0	1 (0.8%)
Other	2 (3.2%)	2 (6.9%)	0	4 (3.1%)
Missing	0	0	0	0
Age				
Mean (range)	38.0 (20-68)	34.9 (18-58)	41.9 (19-66)	38.4 (18-68)
≤65 years (%)	96.8	100.0	97.4	97.7
>65 years (%)	3.2	0	2.6	2.3

Source: je049-5113-a-iss.pdf, Tables 1.1 and 2.1

7.2.1.3 Extent of exposure (dose/duration)

The Phase 3 studies used the same dose of icatibant, a single 30 mg SC injection. During the OLE, patients were permitted up to 3 injections separated by a minimum of 6 hours in a 48 hour period per HAE attack. Based on the number of attacks and response to icatibant, patients therefore had a range of exposures during the OLE. The exposure is detailed in the individual study reports in the Appendix. From the total safety database, 47 patients have been treated with

icatibant for 1 attack to date, 68 patients for 2 to 5 attacks, 14 patients for 6 to 10 attacks, and 12 patients have experienced more than 10 attacks for which they have received icatibant. The majority of attacks have been treated with a single dose of icatibant (611 out of 665 attacks total). Fifty-six attacks in 27 patients have been treated with 2 x 30-mg icatibant doses, and 4 attacks in 4 patients have been treated with 3 x 30-mg doses.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No additional studies were reviewed for this application. Postmarketing experience for icatibant is not available. The referenced literature was reviewed primarily for background information on HAE and the rationale for icatibant as a treatment for HAE; no clinical safety data from the literature was available.

7.2.2.1 Other studies

No additional studies were reviewed for this application.

7.2.2.2 Postmarketing experience

Icatibant is not marketed for any indication at the time of this review.

7.2.2.3 Literature

The Applicant provided 279 literature references, and for certain reports, electronic copies of articles regarding hereditary angioedema, the role of bradykinin, and icatibant. In addition, the reviewer performed an electronic PubMed search [search term: icatibant; search restrictions: human] that yielded 184 literature reports, the majority of which overlapped with the references provided by the Applicant. These reports were reviewed briefly and did not suggest additional safety concerns.

7.2.3 Adequacy of Overall Clinical Experience

Due to the rarity of HAE, the overall number of patients evaluated in the clinical development program for icatibant was limited but appears comparable in scope to the clinical development programs currently underway for other drug products intended for a similar indication. In addition, there are presently no drug products approved for the treatment of acute HAE attacks, which are potentially life-threatening. Given these considerations, the total number of patients in the safety database is sufficient to support the safety of single-dose 30 mg icatibant for the intermittent treatment of acute cutaneous and abdominal HAE attacks. However, safety data to support repeat dosing within a 24-hour interval is limited (only 4 patients treated with 3 x 30 mg doses for an attack) and additional clinical information on icatibant used in this manner is desirable.

The number of patients treated for laryngeal HAE attacks is limited as well, although the safety of icatibant for laryngeal attacks can likely be extrapolated from the cutaneous and abdominal

attacks. Safety data on the subset of laryngeal patients in the clinical development program appears comparable to the data collected for the other patients. Data to support the efficacy of icatibant for laryngeal attacks is a separate issue and is discussed in Section 6 of this review.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

At the time of this review, the Division was awaiting updates from the Applicant on preclinical chronic dosing and carcinogenicity studies. The Applicant has provided preclinical data to support dosing for up to 13 weeks.

7.2.5 Adequacy of Routine Clinical Testing

The laboratory parameters and vital signs and the timing of these assessments were adequate.

In terms of ECG assessment, the Applicant did not conduct a formal thorough QT study. Limited ECG monitoring performed in the Phase 3 studies described in Section 7.1 did not show any QT prolongation effects. However, the clinical pharmacology study, Study 1103, showed several examples of ST/T wave changes and/or QT prolongation in healthy patients receiving 5 doses of icatibant 30 mg SC on 3 separate days. This study was reviewed by the Interdisciplinary Review Team for QT Studies, who concluded that icatibant showed evidence of QT prolongation and a thorough QT study was not warranted. At the pre-NDA meeting, these comments were communicated to the Applicant, and the Applicant was informed that QT prolongation would be included in product labeling unless the Applicant chose to refute these findings. The Applicant has not provided additional data to refute these findings.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The pharmacokinetic evaluation of icatibant is discussed in more detail in Section 5 and the Clinical Pharmacology review. Formal drug-drug interaction studies were not conducted and limited data has been collected on special populations; however, given the proposed indication and intended manner of use, the pharmacokinetic evaluation of icatibant is generally adequate.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

As discussed above in Section 7.2.5, clinical data indicate a QT prolongation effect for icatibant. The Applicant has not submitted additional data to refute these findings and product labeling in the future should reflect this potential toxicity unless other data is provided.

Otherwise, the safety profile for intermittent 30 mg single-dose use of icatibant is acceptable. Data for repeat dosing in a 24-hour period is limited, and additional clinical data to support such a dosing regimen is desirable. This data may be obtained in the ongoing OLE studies, or preferably, in an additional placebo-controlled study.

7.2.8 Assessment of Quality and Completeness of Data

The data and form of the data provided for the safety review are described in Section 7.2.1. Initially, the Applicant pooled Phase 2 and 3 data together in the ISS. The Applicant submitted a revised ISS on December 20, 2007, summarizing the Phase 2 and Phase 3 data separately. In general, the Applicant provided limited formal analysis of safety monitoring assessments (laboratory parameters, vital signs, and ECG findings) in the initial submission. Several clinical information requests were made, and the Applicant provided the requested information in amendments to the NDA (Letter dates: December 28, 2007, February 20, 2008, and February 26, 2008).

7.2.9 Additional Submissions, Including Safety Update

The initial NDA submission contained safety information up to July 26, 2006. In the revised ISS submitted December 28, 2007, the Applicant included updated safety data up to September 30, 2007. The clinical review is based on safety information up to the September 30, 2007 cutoff date. The clinical review team also made several information requests to clarify the presentation of the safety data. Responses to these requests were received on February 11, 2008, February 18, 2008, February 20, 2008, and February 26, 2008 and the information is incorporated into this review.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

7.3.1 Local injection site reactions

Local injection site reactions occurred in nearly all patients receiving icatibant by subcutaneous injection. These reactions appeared self-limited and generally resolved within a few hours of treatment. More serious adverse events were not associated with these reactions. No special monitoring is recommended for these reactions, but information regarding these reactions should be included in the icatibant product label.

7.3.2 Hereditary angioedema

Hereditary angioedema was the second most commonly reported adverse event, as discussed in Sections 7.1.5.4 and 7.1.5.5. 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. Given the overall limited support for efficacy and the mechanism of action of icatibant, the most likely conclusion is that HAE AEs reflect the underlying disease condition and limited efficacy of icatibant rather than a treatment-related exacerbation of the condition.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The Applicant pooled Phase 3 data for the ISS, providing safety assessments for the individual studies in the respective study reports. The two studies differed in terms of the comparator arms, so both pooled data and individual study data were examined for the purpose of this review. Incidence rates for local injection site reactions were comparable. HAE as an adverse event was reported more frequently in Study 2102 compared to Study 2103; the frequency reported for the icatibant arm in Study 2102 rivaled the tranexamic acid arm in that study and the rate reported for the placebo arm in Study 2103. As mentioned in Section 7.3.2, interpretation of HAE as an AE is unclear and a causal relationship is not established. Other adverse events were much less common in both studies, supporting the overall safety profile of icatibant. Overall, the pooling of data did not appear to hide any substantial informative differences. Phase 2 data consisted of data from a single study that did not indicate any additional safety signals. Phase 1 data from healthy volunteers also did not raise any additional safety concerns, although the utility of the data was somewhat limited by the use of an alternate drug formulation (IV versus SC).

7.4.1.2 Combining data

When data were combined, the numerators and denominators were simply combined.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Limited dose exploration was performed for icatibant. There is some evidence to suggest that local injection site reactions are dose-dependent. There does not appear to be any other consistent relationships with other reported adverse events.

7.4.2.2 Explorations for time dependency for adverse findings

Local injection site reactions appear to follow immediately after dosing. Data from the clinical studies do not suggest a clear time dependency for other adverse events.

7.4.2.3 Explorations for drug-demographic interactions

Pharmacokinetic evaluation suggests higher systemic exposure in female patients and older patients. Given the low incidence of individual adverse events (besides local injection site reactions) as well as the low number of non-white study participants and patients >65 years of

age, a stratification of adverse events by gender, age, or ethnicity was not possible. Local injection site reactions were ubiquitous and do not appear to be more severe in a particular demographic. In terms of HAE attacks, which were reported as AEs, icatibant appeared to be more efficacious in female patients, which may be related to the higher exposure observed in PK studies.

7.4.2.4 Explorations for drug-disease interactions

The population enrolled in both studies was adult HAE patients with acute cutaneous, abdominal, or laryngeal attacks. Data from the clinical studies do not suggest an attack-site dependency for adverse events.

7.4.2.5 Explorations for drug-drug interactions

Formal drug-drug interaction studies were not performed for icatibant. In vitro study does not show any significant inhibition or induction of CYP450 enzymes. The Applicant has postulated a theoretical interaction between icatibant and ACE inhibitors, suggesting that icatibant may compromise the antihypertensive effects of ACE inhibitors via bradykinin antagonism. However, given the expected, limited manner of use of icatibant, the life-threatening potential of HAE attacks, and the general avoidance of ACE inhibitors in HAE patients due to their potential for angioedema, the risk of this particular drug-drug interaction does not seem significant.

7.4.3 Causality Determination

Of the adverse events described, local injection site reactions are clearly drug-related. HAE attacks, which were sometimes reported as AEs, are more difficult to interpret. Given the limited efficacy demonstrated in the Phase 3 trials, it appears that HAE as an AE is most likely a reflection of limited efficacy and the natural course of HAE attacks rather than a treatment-related exacerbation of underlying disease. Other adverse events were reported at such low frequency that their relationship to treatment is difficult to ascertain without further study.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed dose of icatibant is 30 mg SC, which may be repeated for an additional 2 doses at intervals of 6 hours or more in a 24-hour period. The application does not provide convincing evidence of efficacy for this dose for the treatment of acute HAE attacks. Lack of efficacy may be due in part to unequal bioavailability in male versus female patients. Alternatively, a different dosing regimen may provide more consistent inhibition of bradykinin effects. Pharmacodynamic data suggests that higher doses are unlikely to augment bradykinin inhibition, but repeat dosing, which has not been formally evaluated for efficacy against a control, may improve the efficacy profile. Should a higher dose or alternative dosing regimens prove more efficacious in future clinical studies, additional safety information will be needed to support their use.

8.2 Drug-Drug Interactions

Formal drug-drug interaction studies were not performed for icatibant. In vitro study does not show any significant inhibition or induction of CYP450 enzymes. The Applicant has postulated a theoretical interaction between icatibant and ACE inhibitors, suggesting that icatibant may compromise the antihypertensive effects of ACE inhibitors via bradykinin antagonism.

However, given the expected, limited manner of use of icatibant, the life-threatening potential of HAE attacks, and the general avoidance of ACE inhibitors in HAE patients due to their potential for angioedema, the risk of this particular drug-drug interaction does not seem significant and no dosing adjustment is recommended for this scenario.

8.3 Special Populations

Pharmacokinetic data suggests higher bioavailability in female and older patients. No clinically relevant pharmacokinetic differences were observed in patients with hepatic and renal impairment. On the basis of safety, no dosing adjustments are recommended for any patient subgroup; however, alternative doses and/or dosing schedules may be a consideration to improve efficacy, particularly in male patients. No information on icatibant in pregnancy or lactation is available.

8.4 Pediatrics

Icatibant was granted Orphan Drug status on November 25, 2003 and is subsequently exempt from the submission of pediatric studies. No pediatric data was included in the NDA submission. In a prior discussion with the Division of Gastrointestinal and Coagulation Drug Products (March 1, 2005 – February 22, 2007 Pre-NDA Meeting Minutes), the Applicant stated that any plans for pediatric studies would be discussed pending NDA approval. In a later pre-NDA meeting held with the Division of Pulmonary and Allergy Products (February 22, 2007 – January 24, 2007 Pre-NDA Meeting Minutes), the Applicant agreed to submit their pediatric plan prior to NDA submission. As of the time of this review, the Applicant has not submitted a pediatric plan for review.

8.5 Advisory Committee Meeting

An Advisory Committee meeting related to this application was originally planned but later cancelled as the ongoing review indicated insufficient evidence of efficacy.

8.6 Literature Review

The Applicant provided 279 literature references, and for certain reports, electronic copies of articles regarding hereditary angioedema, the role of bradykinin, and icatibant. In addition, the reviewer performed an electronic PubMed search [search term: icatibant; search restrictions: human] that yielded 184 literature reports, the majority of which overlapped with the references provided by the Applicant. These reports were reviewed briefly and did not suggest additional safety concerns.

8.7 Postmarketing Risk Management Plan

No post-marketing risk management plan was submitted with this application.

8.8 Other Relevant Materials

Consultations were requested for this application by the Division of Drug Marketing, Advertising, and Communication (DDMAC); the Division of Medication Errors and Technical Support (DMETS), Study Endpoints and Label Development group (SEALD), and the Division of Scientific Investigation (DSI). At the time of finalization of this review, the consults are pending.

9 OVERALL ASSESSMENT

9.1 Conclusions

This reviewer finds the data submitted by the Applicant inadequate to support the indication proposed by the Applicant: “the treatment of hereditary angioedema.” The application does not contain two adequate, well-controlled studies demonstrating substantial evidence of effectiveness. Study 2102 used an active comparator, tranexamic acid, whose efficacy in acute HAE attacks is not established. While results of Study 2102 supported the efficacy of icatibant over tranexamic acid, the validity of the comparative difference is unconfirmed. Study 2103 used a placebo control but failed to demonstrate a statistically significant benefit for icatibant over placebo. While results were numerically favorable, the results were not statistically robust. In addition, the VAS PRO instrument used for the primary efficacy variable in both studies would benefit from further validation. While a PRO-based endpoint is acceptable for studies in HAE, the primary endpoint based on the VAS is difficult to interpret. Other PRO-based endpoints, perhaps with the VAS as a supportive secondary endpoint, may be more appropriate for future clinical trials.

Given these issues, this review concludes that the Applicant has not sufficiently demonstrated icatibant’s efficacy for the treatment of acute HAE attacks. Another placebo-controlled trial with a valid primary endpoint and statistically robust results is recommended to support efficacy. Other concerns include the very small sample size to support repeat dosing for a single attack and to support chronic use in the absence of preclinical data to support chronic dosing beyond 13 weeks. The reviewer acknowledges that the size of the clinical database is inherently limited due to the rarity of HAE and agrees with the Applicant that single-dose administration may be extrapolated to a certain extent. However, clinical data on repeat and chronic dosing obtained from another placebo-controlled trial will permit a more thorough evaluation of non-single-dose regimens.

This reviewer agrees with the Applicant’s conclusion that the safety profile of 30 mg icatibant is acceptable for the proposed patient population and the treatment of acute HAE attacks. If higher

doses or alternative dosing regimens are shown to be efficacious, additional safety information will be required to support other doses.

9.2 Recommendation on Regulatory Action

From the clinical standpoint, the recommended action is Not Approvable.

The data submitted in this application provide suggestive but not conclusive evidence of efficacy for icatibant in the treatment of acute HAE attacks. Additional evidence from another placebo-controlled trial is required to support icatibant's efficacy. While no particular safety concerns were identified in the course of this review, additional evidence of safety from another clinical trial will bolster the safety findings of the current, limited clinical database.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No risk management activities are recommended.

9.3.2 Required Phase 4 Commitments

As the recommended action of this review is Not Approvable, no Phase 4 commitments are recommended at this time.

9.3.3 Other Phase 4 Requests

As the recommended action of this review is Not Approvable, no other Phase 4 requests are recommended at this time.

9.4 Labeling Review

As the recommended action of this review is Not Approvable, a broad overview of the major changes needed for the proposed labeling is presented here. A line-by-line review is not included in this review.

Proposed package labeling has been included in this submission [1.14]. The Applicant seeks an indication for the treatment of hereditary angioedema.

1. The efficacy and safety studies conducted in support of this application addressed the treatment of *acute attacks* of HAE specifically, not a general treatment indication.
2. The Dosage and Administration describes the subcutaneous use of icatibant, but does not specify that injections should be administered by a trained health professional in a monitored setting, i.e. not for home use or self-administration.
3. The Adverse Reactions section should be revised to present Phase 3 safety data only.

4. Under Clinical Studies, the proposed label [REDACTED] (b) (4)
5. Although numerically supportive, Study 2103, the single placebo-controlled study in the application, did not demonstrate a statistically significant benefit for icatibant over placebo. The Clinical Studies section presents the results [REDACTED] (b) (4)

9.5 Comments to Applicant

The clinical recommended action for this application is Not Approvable. The major deficiencies of the application to be communicated to the Applicant are outlined below:

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 hereditary angioedema (HAE). The clinical development program does not include at least two well-controlled, adequate studies that provide substantial evidence of icatibant's efficacy in the treatment of acute attacks of hereditary angioedema. Study JE049-2102 used an active comparator, tranexamic acid. As the efficacy of tranexamic acid in the treatment of acute attacks of HAE is not well established, the efficacy comparison between tranexamic acid and icatibant is more difficult to assess. Study JE049-2103 used a placebo control, but failed to demonstrate a statistically significant treatment difference between placebo and icatibant. Although the results were numerically favorable for icatibant, the results were not statistically robust. In addition, the primary endpoint used in both studies (time to onset of symptom relief using the Visual Analog Scale) was not adequately validated, further complicating interpretation of study results.

The above deficiencies may be addressed by the following:

- Provide data from at least one adequate and well-controlled (placebo) study to demonstrate the efficacy and safety of icatibant for the treatment of acute hereditary angioedema attacks. The additional study(ies) should include the following elements:
 - Stringent inclusion and exclusion criteria for hereditary angioedema. In addition to a consistent medical history, patients should have documented laboratory values to support the diagnosis, including a low functional C1 inhibitor level, depressed C4 levels, and normal C1q levels.
 - Stratification of patients by attack site, including patients with laryngeal edema in the randomization.
 - A primary endpoint with adequate validation. A patient-reported outcome, such as the VAS, may be acceptable but should have reasonable content validity, test-retest validity and the results should be supported by secondary endpoints in a clinically meaningful way (i.e. not just statistically significant correlation). Should you elect to use a different efficacy endpoint, we recommend inclusion of "the time to onset of symptom relief" as assessed by the VAS as a key secondary

endpoint to facilitate cross-study comparisons with the other Phase 3 studies in your development program.

- Revise the proposed indication to more accurately reflect your clinical program, e.g. the treatment of acute attacks of hereditary angioedema.

10 APPENDICES

10.1 Individual Study Report: Study 2101

10.1.1 Study protocol: Study 2101 – Proof of concept study to investigate in patients with HAE the efficacy and safety of icatibant administered intravenously at various infusion rates and subcutaneously at different doses

10.1.1.1 Study administrative information

- Study sites: Multicenter

(b) (4)

- Study initiation date: July 2003
- Study completion date: August 2004
- Study report date: April 18, 2007

10.1.1.2 Objectives/rationale

- Assess the efficacy and tolerability of icatibant when administered as an IV infusion at various rates or as a SC injection in subjects with acute HAE attacks involving cutaneous and gastrointestinal areas
- Assess and compare the onset and duration of action of icatibant to guide dose selection and investigate the kinetic profile in HAE patients

10.1.1.3 Design overview

Study 2101 was an open-label, multi-center, sequential, single dose study in HAE patients, divided into 5 sequential dose groups. Following initial screening, patients presenting with an acute cutaneous or gastrointestinal HAE attack received a single dose of icatibant in one of 5 possible dosing IV or SC dosing regimens (Section 10.1.1.5.1). The first 2 subjects at each study site were observed for 20 h following infusion/injection. Other subjects were observed for a minimum of 4 h. Patients completed symptom scores, visual analogue scales (VAS), and diaries. Investigators recorded global clinical impression (GCI). Other assessments performed included physical exams, vital signs, clinical laboratory tests, C1q/C4/C1 INH/bradykinin levels, and photographic documentation of swelling in some cases. Serum was also collected for pharmacokinetic analysis.

10.1.1.4 Study population

15 adult patients with documented HAE presenting with an acute cutaneous or GI HAE attack.

Inclusion criteria

- Ages 18-65 years

- Documented history of HAE
- HAE attack frequency of at least 1 every 3 months
- Presentation with moderate to severe HAE attack of any location, except laryngeal, within 10 hours of the start of the attack
- If of child-bearing potential, reliable contraception and negative urine pregnancy test at baseline

Exclusion criteria

- Laryngeal edema
- Concomitant diseases or medication which may interfere with the study, at the discretion of the investigator, including the following:
 - Medical condition capable of altering the metabolism or elimination of drugs
 - History of allergy or hypersensitivity to any medication

10.1.1.5 Study treatments

10.1.1.5.1 Dosing materials

- IV infusion: IV infusion of icatibant was prepared ex tempore under aseptic conditions and infused via an indwelling venous cannula in the forearm
- SC injection: 10 mg/ml icatibant solution

10.1.1.5.2 Treatment groups

- Group I: 0.4 mg/kg IV infused over 2 h
- Group II: 0.4 mg/kg IV infused over 30 min
- Group III: 0.8 mg/kg IV infused over 30 min
- Group IV: 30 mg SC injection
- Group V: 45 mg SC injection

10.1.1.5.3 Randomization

Allocation to treatment groups was done in chronological fashion upon presentation with an acute attack of HAE.

10.1.1.5.4 Blinding

Open-label study.

10.1.1.5.5 Administration

Within 10 hours of onset of an acute HAE attack, patients were administered icatibant per dosing group assignment in a monitored study center.

10.1.1.5.6 Treatment compliance

Treatment was administered by the investigator or sub-investigators.

10.1.1.6 Study procedures

10.1.1.6.1 Concomitant medications

Other concomitant medications were not permitted for the duration of the study with the exception of oral contraceptives. Subjects requiring treatment with another drug were to be withdrawn if the investigator and Sponsor deemed that the drug may affect the outcome of the study. All previous treatments within 2 weeks of the study treatment were to be documented in the CRF.

10.1.1.6.2 Assessments and evaluations

In addition to symptom scoring, VAS, physical exams, vital signs, injection/infusion site exams, and elective photographic documentation of swelling, patient underwent serum sampling for clinical laboratory evaluations (screening, baseline, discharge, and follow-up at 36-60h post infusion), pharmacodynamic measurements (baseline, end of infusion, 4 h post-infusion, and 20 h post-infusion), and PK profiling. Pharmacodynamic sampling included assays for levels of C1q, C4, C1 INH, and bradykinin.

10.1.1.7 Efficacy parameters

The study was intended as an exploratory, proof-of-concept study. Efficacy was evaluated in terms of onset of symptom relief, almost complete symptom relief, and complete symptom relief on the basis of the following parameters:

Skin swelling score

- Assessed as baseline and end of infusion (time 0) for Groups I, II, and III and for all groups at 2 and 4 h post-drug administration. For Groups IV and V, skin swelling scores were also assessed at 0.5 and 1 h post-dose.
- For patients observed for 20 h post-dose, additional scoring was performed at 6, 10, and 20 h post-dose.

Abdominal score

- Assessed as baseline and end of infusion (time 0) for Groups I, II, and III and for all groups at 2 and 4 h post-drug administration. For Groups IV and V, skin swelling scores were also assessed at 0.5 and 1 h post-dose.
- For patients observed for 20 h post-dose, additional scoring was performed at 8 and 20 h post-dose.

Visual analogue scale (VAS)

- A patient reported outcome (PRO) symptom scale. The VAS is a 100 mm horizontal line with 0mm = no symptoms and 100mm = 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.
- Performed at baseline and 2, 4, 8, 20, 48, 72, 96, and 120 h post-dose.
- For Groups IV and V, also performed at 0.5 and 1 h post-dose.
- Later time points completed only if clinically meaningful symptoms present.
- Symptom relief defined as 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 deemed not assessable by this evaluation

Photographic documentation of swelling

- Taken at baseline and 4 h post-dose for all groups and electively at 20 h post-dose.

Subject diary

- Used to record symptoms, concomitant medications, VAS, and AEs after patients discharged from the clinic and returned at the follow-up visit.

Global Clinical Impression (GCI)

- GCI was assessed by the physician at baseline and 4 h post-dose.
- Severity of attack scored from 0 to 4 (not relevant to severest intensity).
- Individual symptom scoring: facial edema (0-3), extremities edema (0-4), abdominal edema (0-4), and laryngeal edema (0-4).

10.1.1.8 Pharmacokinetic parameters

Plasma samples were collected before, during and after infusions/injections, with a total volume ranging from 20-52 ml. The following variables were analyzed: C_{max} , t_{max} , AUC_{0-t} , $AUC_{0-\infty}$, λ_z and $t_{1/2}$.

10.1.1.9 Safety parameters

10.1.1.9.1 Adverse events

Any adverse events were recorded from the time of admission to the unit until follow-up 60-120 hours after the end of the infusion/injection. AEs occurring outside of the clinic were recorded in patients diaries first prior to recording in the CRF.

10.1.1.9.2 Laboratory assessments

Laboratory assessments included the following: routine clinical blood chemistries and complete blood counts, coagulation panels, serology for HIV, HBsAg, and HCV, urinalysis, and urine pregnancy test for women of childbearing age.

10.1.1.9.3 Physical exams

Physical exams were performed at screening, 4 h post-dose, and at follow-up. Particular attention was placed on infusion/injection site reactions, which were scored at baseline, 2, and 4-hr post-dose.

10.1.1.9.4 Vital signs

Vital signs (blood pressure, pulse) were performed at screening, baseline, during infusion, and hourly for 8 hours after infusion, as well as 10, 20, and 36 hours post infusion.

10.1.1.9.5 ECGs

ECGs were assessed at baseline, 4 h post-dose and 20 h post-dose for those patients observed for 20 h. Detailed ECG evaluation for QTc effects was performed by a central ECG lab (Prof. Pierre Maison-Blanche at Hospital Lariboisiere in Paris, France).

10.1.1.10 Statistical plan

No formal inferential tests were performed. Efficacy, safety, and PK data were reported using standard descriptive statistics. No formal sample size calculation was used.

10.1.2 Results

10.1.2.1 Protocol amendments

Five amendments were made to the protocol, listed by date:

- July 7, 2003
 - Addition of study site
 - Typographical error correction
 - Elaboration of subject diary procedures
- August 11, 2003 – Addition of study site
- December 5, 2003 – Dose adjustment for Group III based on results of preceding Groups I and II. Original protocol proposed a dose range of 0.2 – 0.8 mg/kg; revised protocol allowed for 0.8 mg/kg over 30 min.
- March 17, 2004
 - Group IV route of administration changed from IV to SC
 - Four additional subjects added to constitute Group V
- May 5, 2004 – Addition of study site

10.1.2.2 Protocol deviations

No subjects were excluded from analysis due to protocol deviations. The following deviations were noted:

- The dose of 30 mg in Group IV was administered as 3 abdominal SC injections of 1 ml each (10 mg/ml) rather than as a single injection. The dose of 45 mg in Group V was administered as 2 abdominal SC injections of 2.25 ml each instead of a single injection.
- Subject 303 received study drug at 10 h 20 min after the onset of attack, rather than 10 h after onset of attack.
- Subjects 411 and 412 were enrolled although their HAE type was not documented at screening.

Reviewer's comment: The protocol deviations noted are unlikely to have had major impact on overall conclusions of efficacy and safety from this small, proof-of-concept study.

10.1.2.3 Treatment compliance

Treatment was administered in all cases by the investigator or sub-investigators.

10.1.2.4 Datasets analyzed

Analysis is based on 20 attacks in all 15 patients enrolled.

10.1.2.5 Study patients

Fifteen subjects with a total of 20 HAE attacks were treated in the study. The patients ranged in age from 20 to 61 years (median 42 years). Five patients were male, 10 were female. All patients were Caucasian. Ten subjects experienced one attack; 5 subjects experience two attacks and were treated in a higher dose group for the second attack. These subjects received separate subject ID numbers for each of the two treatments received. Of the 20 attacks, 10 were cutaneous, 7 were cutaneous and abdominal, and 3 were abdominal attacks. Of the 15 subjects, 12 were HAE Type I, 1 subject was HAE Type 2, and no information was provided for 2 subjects. An additional subject was initially classified as Type I then classified as Type 2 during a second attack.

Table 17 Study 2101: Disposition of subjects						
No. subjects	Group I 0.4 mg/kg IV over 2 h	Group II 0.4 mg/kg IV over 30 min	Group III 0.8 mg/kg IV over 30 min	Group IV 30 mg SC	Group V 45 mg SC	Total
Enrolled	4	3	4	3	1	15
Treated	4	4 (1 also enrolled in Group I)	4	4 (1 also enrolled in Group III)	4 (1 in Group I, 1 Group II, and 1 in Group III)	20
Completed	4	4	4	4	4	20

Source: JE049-2010-report-body.pdf, Section 9.1, P42

Reviewer's comment: Patients were eligible to re-enroll in the same study in a higher dose group and were assigned new subject ID numbers (103/201, 104/502, 203/501, 302/402, 304/503). Inclusion of the same patients in multiple stages of the study is a potential confounder of study results, given the possibility of "double-counting" adverse events or biasing enrollment in terms of drug responders.

10.1.2.6 Concomitant medications

Fifteen subjects in Groups I (n=3), II (n=4), III (n=3), IV (n=2), and V (n=3) took concomitant medication during the treatment period and follow-up, including medications intended for the treatment of HAE, 1 patient was taking danazol and 5 patients were reported to have received Berinert P, a plasma-derived C1 INH concentrate licensed in Germany, Austria, Switzerland, and Japan. At least 2 of these patients are documented to have received multiple infusions of Berinert P.

Reviewer's comment: The concomitant use of medications for HAE, particularly replacement C1 INH therapy, is problematic and obscures the efficacy findings. Although not currently approved in the US at the time of this review, it is reasonable to assume that replacement therapy could alter the natural course of an attack and potentially alter efficacy results.

10.1.2.7 Demographics and baseline characteristics

Demographic characteristics are summarized by treatment in the table below.

Table 18 Study 2101: Patient demographics and baseline demographics						
Characteristic	Group I	Group II	Group III	Group IV	Group V	Total

Mean (SD)	(n=4)	(n=4)	(n=4)	30 mg SC (n=4)	45 mg SC (n=4)	treatments (n=20) Subjects (n=15)
Age (yrs)	44.0 (12.9)	37.0 (15.0)	46.8 (6.7)	36.3 (10.5)	43.0 (9.5)	41.1 (11.8)
Caucasian	4	4	4	4	4	
Male	2	-	-	2	2	5

Source: je049-2101-report-body.pdf, Section 9.3, Table 10, P 43.

Reviewer's comment: The comparability of treatment groups is difficult to assess given the small number and the fact that 5 patients were treated twice as part of two different treatment groups.

10.1.2.8 Efficacy endpoint outcomes

10.1.2.8.1 Onset of symptom relief as reported by subject

Symptom relief as reported by the subject and according to the VAS is summarized in Table 19. For the IV treatment groups, the median onset of symptom relief as reported by the patient was between 1:08 and 1:30 h:min. For the SC treatment groups, the onset of symptom relief was between 27 and 35 minutes. As assessed by the VAS, median onset of symptom relief ranged from 2 to 5 hours for all treatment groups. Of note, the SC treatment groups had on average a shorter duration between onset of attack and treatment in comparison to the IV groups.

Table 19 Study 2101: Time to symptom relief by patient report and VAS

Group	Patient ID	HAE type	Attack site	Time from onset of sx to treatment (h:min)	Δ VAS (cm) at 4 h	Onset of relief as reported by patient (h:min)	Onset of relief by VAS	Time to almost complete relief by VAS	Time to complete relief by VAS
I	101	I	Arms	8:00	9.07	1:00	2:00	2:00	20:00
	102	I	L cheek arms, legs	8:45	8.25	2:00	2:00	22:00	50:00
	103	I	Abdomen	9:45	0.72	5:00	Not assessable	10:00	50:00
	104	I	Eyelids/periorbital	7:25	2.37	1:00	6:00	22:00	74:00
	Median			8:22	5.31	1:30	2:00	16:00	50:00
II	201	I	Abdomen	8:40	1.58	2:55	Not assessable	8:30	72:30
	202	I	Legs, abdomen	9:35	1.88	1:20	Not assessable	4:30	20:30
	203	II	Face, arms	5:15	4.02	0:45	4:30	20:30	48:30
	204	I	Legs	9:30	1.96	1:30	2:30	8:30	8:30
	Median			9:05	1.92	1:25	3:30	8:30	34:30
III	301	I	Abdomen	UNK	1.72	0:45	8:30	8:30	20:30
	302	I	Arms, abdomen	7:10	6.88	1:30	2:30	8:30	20:30
	303	I	L foot	10:20	5.86	1:30	2:30	8:30	20:30
	304	I	Legs, abdomen	9:50	5.36	0:35	4:30	8:30	8:30
	Median			9:50	5.61	1:08	3:30	8:30	20:30
IV	401	I	Legs, abdomen	8:30	4.11	1:40	2:00	4:00	48:00
	402	I	Arms, legs, gluteal	7:35	2.19	1:00	4:00	20:00	20:00
	411	UNK	Eyelids/periorbital, perioral, arms, legs, abdomen	7:05	7.29	0:10	0:30	4:00	8:00
	412	UNK	Arms	5:00	0.63	0:05	20:00	20:00	72:00
	Median			7:20	3.25	0:35	3:00	12:00	34:00
V	501	II	Perioral, arms, neck	7:30	6.18	0:10	2:00	20:00	48:00
	502	I	Lids, perioral	7:05	1.36	0:40	20:00	20:00	48:00
	503	I	Arms, legs, abdomen	5:10	6.77	0:45	2:00	4:00	72:00
	531	I	Legs, abdomen	3:49	2.43	0:14	8:00	8:00	84:00
	Median			6:07	4.31	0:27	5:00	14:00	60:00

Source: je049-2101-report-body.pdf, Table 12, P 49

Reviewer's comment: SC appears to be superior to IV administration, although on average the interval between onset of attack and treatment was shorted in the SC groups, which may account for this difference. In terms of individual patients who enrolled in more than one phase of the study (Patient ID 103/201, 104/502, 203/501, 302/402, 304/503), there does not appear to be a major difference in onset of relief as reported by the patient by administration route or by dose.

10.1.2.8.2 Symptom relief according to VAS

Symptom relief according to VAS, defined as an absolute reduction from the pre-treatment VAS of ≥ 20 mm if baseline VAS was ≥ 30 mm and ≤ 30 mm if baseline VAS was > 50 mm, is summarized in Table 19. Almost complete symptom relief was defined as duration from start time of injection to the first time point with a VAS score of 0-10 mm for at least 3 consecutive measurements for all 5 symptoms. Complete symptom relief was defined as the first time point with a VAS of 0 for all 5 symptoms assessed. The onset of symptoms relief according to VAS appeared comparable among treatment groups, although there appeared to be a large degree of individual variability, and ranged from 2:00 to 20:00 h. Similarly, the time to almost complete

relief ranged from 2:00 to 22:00 h. Time to complete relief ranged greatly, from 8:30 h to 84:00 h, without any clear differences among dose groups and routes of administration.

Reviewer's comment: Based on the VAS assessments, there do not appear to be any clear dose response or differences in efficacy in terms of routes of administration. Dose group III may also be a potential treatment, but the differences between the IV and SC formulation are not great and the SC is a more patient-friendly route of administration. For some individuals, the onset of symptom relief according to the VAS versus as reported by the patient did not match, which calls into question the underlying validity of the VAS instrument.

10.1.2.8.3 Symptom relief according to GCI

The GCI was assessed at 4 and 20 hours post infusion/injection. According to the study report, the GCI at 4 indicated a “considerable reduction” in symptoms at 4 hours that correlated with the VAS.

Reviewer's comment: According to the Applicants calculations, the VAS correlated more closely with the GCI rather than patient's symptom scoring. However, the GCI is presented as a composite severity score that is difficult to interpret. Information regarding the individual components of the score is not clearly provided and illustrative examples of the severity ranking are not provided. The intra- and inter-observer reliability of the scoring is uncertain.

10.1.2.8.4 Additional treatment with C1 INH

Five patients received C1 inhibitor replacement therapy within 28 hours of receiving icatibant treatment: Subjects 304/503, 411, and 531. All three subjects reportedly experienced onset of relief with icatibant prior to receiving replacement C1 INH for recurrence of symptoms. According to the study report, C1 INH was not administered as a rescue therapy for worsening symptoms.

10.1.2.8.5 Pharmacodynamic parameters

No changes were noted in C1-INH, C, or C1q levels following administration of icatibant. Bradykinin levels were reduced from baseline to 4 hours post-dose, without any differences among treatment groups.

Reviewer's comment: The role of bradykinin in acute HAE attacks has not been clearly delineated, although there is literature to support the notion that bradykinin may be responsible for many of the clinical manifestations of HAE.

10.1.2.9 Safety assessments

10.1.2.9.1 Extent of exposure

The extent of exposure for individual patients is summarized in Table 20.

Table 20 Study 2101: Extent of exposure

Group	Patient ID	Total dose (mg)
I 0.4 mg/kg IV	101	48
	102	42
	103	24
	104	30
II 0.4 mg/kg IV	201	24
	202	25
	203	34
	204	20
III 0.8 mg/kg IV	301	43
	302	52
	303	60
	304	56
30 mg SC	401	30
	402	30
	411	30
	412	30
45 mg SC	501	45
	502	45
	503	45
	531	45

10.1.2.9.2 Adverse events

10.1.2.9.2.1 Serious adverse events

No deaths were reported. Two SAEs were reported. One patient in Group I (Patient 101) was admitted to the hospital for an acute manic episode of a pre-existing schizoaffective psychoses seven days after icatibant infusion. The other patient in Group IV (Patient 411) was classified as having a prolonged hospitalization due to an infusion of C1 INH replacement therapy that was administered 21 hours after initial icatibant injection.

10.1.2.9.2.2 Discontinuations from the study due to adverse events

No patients were discontinued from the study due to adverse events.

10.1.2.9.2.3 Other adverse events

A total of 11 subjects reported 41 AEs during the course. The majority of AEs occurred in the SC injection groups (Group IV – 4 subjects reporting 17 AEs and Group V – 4 subjects reporting 19 AEs). Thirty-three of these 36 AEs were related to local injection site reactions, including feeling of warmth, pruritus, erythema, burning sensation, itching, swelling, and pain. All of these resolved spontaneously. No local reactions were reported after IV infusion. The other main AE was coded as HAE, which was meant only to include a separate recurrence of symptoms rather than a progression or exacerbation of initial presenting symptoms.

Reviewer's comment: The majority of AEs attributable to drug appear to be local injection site reactions. The two SAEs do not appear to be directly related to icatibant, although the recurrence of symptoms in Patient 411 may be related to poor efficacy. Likewise, the other main AE of HAE may reflect limited efficacy of the drug.

10.1.2.10 Vital signs

No changes in blood pressure or pulse from screening were noted.

10.1.2.11 Physical exams

Pertinent physical exam findings including local injection site reactions for all patients who received SC icatibant, as described in the section above. No other changes in physical exam findings are reported.

10.1.2.12 Laboratory parameters

No systematic changes from screening baseline were observed for any of the clinical chemistry or hematology parameters.

10.1.2.13 ECGs

The Applicant states that no significant differences were found between pre- and post-dose ECGs in any of the treatment groups. A statistical report on ECG parameters read by a central reader is not provided.

Reviewer's comment: Study 2101 does not show any obvious QT prolongation effects, but the study was not designed to assess this issue methodically.

10.1.3 Study summary and conclusions

As a proof-of-concept study, Study 2101 provides some support for the efficacy of icatibant. However, the small number of patients evaluated and the use of the same individuals in multiple phases of the study limit the generalizability of the results. As a dose-ranging study, the data to support the dose selected for pivotal trials is limited. The 30 mg SC dose appears to have had similar results as the 45 mg dose, and lower doses were not studied. Durability of response was not assessed in a systematic fashion.

In terms of safety data, no significant safety issues are identified. The most common AE, local injection site reactions for the patients treated subcutaneously, does not appear to have been severe or to have had any persistent effects on patients.

10.2 Individual Study Report: Study 2102

10.2.1 Study protocol: Study 2102

Title: A randomized, double-blind, controlled, parallel group multicenter study of a SC formulation of icatibant versus oral tranexamic acid for the treatment of HAE

10.2.1.1 Study administrative information

- Study sites: 31 active centers (1 Austria, 4 France, 8 Germany, 1 Hungary, 2 Switzerland, 1 Ireland, 3 Israel, 3 Italy, 1 Lithuania, 1 Poland, 4 UK, 2 Sweden)
- Study dates: March 1, 2005 to July 25, 2006
- Date of study report: May 10, 2007

10.2.1.2 Objectives/rationale

- Assess the efficacy of icatibant compared with tranexamic acid on the onset of symptom relief from moderate to very severe acute cutaneous and/or abdominal HAE attacks
- Assess the rate of response, time to almost complete relief, global outcome, severity of each symptom, and safety and tolerability of icatibant
- Assess the efficacy and safety of repeated administration of icatibant in an open-label extension phase (OLE)
- Assess the efficacy and safety of open-label icatibant in laryngeal HAE attacks
- Assess the relative pharmacoeconomic impact of icatibant

10.2.1.3 Design overview

Study 2102 was a multicenter, randomized, double-blind, double-dummy, active-controlled, Phase 3 study. The study also included open-label treatment for patients with laryngeal HAE attacks and an open-label extension phase for all patients who experienced a recurrent HAE attack and a modified open-label extension phase for patients who were not treated during the double-blind treatment phase of the study. Results of the modified open-label extension phase were provided separately.

Double-blind treatment phase

- Patient presentation with moderate-to-severe cutaneous and/or abdominal edema no later than 6 hours after the time the current attack became moderate in severity (Visual Analogue Scale ≥ 30 mm)
- Hospitalization for a minimum of 12 hours during acute attack, with follow-up on Day 2 and Day 14
- If no symptom relief by 12 hours post-dose, hospitalization extended for an additional 3 hours with additional symptom assessment at 14 hours after injection
- Rescue medications to be avoided if possible, otherwise documented in the CRF

Open label treatment with icatibant for laryngeal edema attack

- Similar study procedures as those summarized above for patients enrolled in the controlled portion of the study

Open-label extension phase (OLE)

- After completion of Visit 4 (Day 14) follow-up of initial attack, patients enrolled in OLE
- Any attack severe enough to warrant treatment can qualify for treatment with icatibant 30 mg SC
- Hospitalization for 5 hours, with follow-up on Day 2 and Day 14 and long term follow-up by telephone every 4 months and clinic visit every 6 months
- Repeated dosing
 - If attack worsens within 48 hours of initial treatment, additional injections permitted
 - Maximum of 3 injections per attack at least 6 hours apart
- Duration: 1 year after closure of double-blind phase

10.2.1.4 Study population

The study population included patients 18 years of age and older with a documented diagnosis of either Type I or II HAE, presenting with moderate to severe cutaneous or abdominal HAE attacks. Patients with laryngeal HAE attacks were treated separately with open-label icatibant.

Inclusion criteria

- Age 18 years of age and older
- Documented diagnosis of HAE Type I or II. The diagnosis could be confirmed either by functional and immunogenic C1-INH results from the central laboratory or by medical history. Inclusion on medical history alone were permitted if a clear diagnosis had been made on all of the following criteria:
 - Family history
 - Characteristic attack manifestations, recurrent attacks
 - Historical functional C1-INH <50%
 - Exclusion of other forms of angioedema
- Patients with C1-INH >50% could be included if an acceptable rationale for the higher level was provided
- Current moderate to severe HAE attack in the cutaneous, abdominal, and/or laryngeal area
- For patients with cutaneous and/or abdominal attacks, a VAS ≥ 30 mm at baseline
- Able to complete baseline assessments and commence treatment no later than 6 hours after the current attacks became moderate
- Negative urine pregnancy test for women of childbearing potential

Exclusion criteria

- Diagnosis of angioedema other than HAE
- Participation in a clinical trial of another investigational agent within the past month
- Treatment with any pain medication since onset of the current attack
- Treatment with replacement therapy, including C1-INH, within 3 days from the onset of the current edema attack
- Treatment with tranexamic acid within 7 days
- Any contraindications for tranexamic acid, including hypersensitivity, severe renal failure, active thromboembolic disease, massive bleeding in upper urinary tract, impaired color vision
- Treatment with ACE inhibitors
- Evidence of coronary artery disease based on medical history or screening examination
- Congestive heart failure (Class III or IV)
- Serum creatinine $\geq 250 \mu\text{mol/L}$
- Other serious concomitant illness or mental condition per investigator's discretion
- Pregnancy or breastfeeding

Reviewer's comment: Although both functional C1-INH and C4 levels were collected, the inclusion criteria were based only on the C1-INH level. C1q levels were not obtained for the study and were not routinely documented. Although a diagnosis of acquired angioedema (AAE)

is an exclusion criterion, it is possible that patients with AAE who have previously been presumed to have HAE may have been enrolled in this study.

10.2.1.5 Study treatments

10.2.1.5.1 Dosing materials

- Icatibant acetate 30 mg SC x 1 in the abdominal region (3 mL of 10 mg/mL sterile, isotonic, acetate-buffered solution for injection containing no preservative (pH 5.5; packaged in 5 mL glass ampules)
- Placebo injection matched to icatibant solution, 3 mL SC injection
- Tranexamic acid 500 mg over-encapsulated film tablet, 1000 mg every 6 to 8 hours apart for 2 days (total of 6 doses)
- Placebo capsule matched to tranexamic acid

10.2.1.5.2 Treatment groups

Double-blind treatment phase

- 30 mg icatibant acetate SC x 1 and placebo capsule every 6 to 8 hours for 2 days (6 doses)
- Tranexamic acid 1000mg every 6 to 8 hours for 2 days (6 doses) and placebo SC injection

Open-label treatment for laryngeal edema

- 30 mg icatibant SC x 1

Open-label extension phase

- 30 mg icatibant SC x 1. If attack worsened within 48 hours of the initial treatment, a maximum of 2 additional doses could be administered at least 6 hours apart.
- Worsening symptoms or new symptoms occurring more than 48 hours after initial treatment were considered new attacks.
- No more than 8 injections of icatibant could be given within any 4-week period

Reviewer's comment: The lack of a separate placebo arm is a significant review issue. Tranexamic acid is not approved for HAE in the US, and data to support its efficacy for this indication has not been formally evaluated. As a result, any observed benefit of icatibant over tranexamic acid may be due to tranexamic acid worsening the patient's condition, rather than improvement attributable to icatibant, i.e. tranexamic acid may be worse than placebo.

10.2.1.5.3 Randomization

Seventy-four patients were randomized 1:1 to receive treatment with icatibant or tranexamic acid and were stratified according to attack site, cutaneous versus abdominal. Random assignments were made through a centralized, automated system via allocation of a kit number of the study medication to be used for treatment based on a stochastic minimization procedure.

Patients with both cutaneous and abdominal symptoms were to be allocated to the abdominal group if at least one abdominal symptom (pain, vomiting, diarrhea, nausea) was moderate to very severe. An exception was made in the SAP dated August 24, 2006, stating that if patients have moderate diarrhea as the only abdominal symptom along with moderate-to-severe cutaneous patients, these patients were to be categorized as cutaneous attack patients.

Patients with laryngeal symptoms were allocated to the open-label treatment group regardless of coexistent cutaneous or abdominal symptoms.

10.2.1.5.4 Blinding

Ampoules of study drug were masked to blind both investigators and patients for the double-blind treatment phase of the study. Tranexamic acid tablets were over-encapsulated to conceal their identity.

Reviewer's comment: Blinding of study treatments was incomplete, as is acknowledged by the Applicant. Subcutaneous injection of icatibant is associated with a high rate of local injection site reactions. The Applicant states that for ethical reasons, a placebo injection with similar irritant properties could not be used. Furthermore, oral tranexamic acid is known to cause nausea, vomiting, and diarrhea, in addition to a distinctive adverse effect of color vision disturbances. Since the primary and secondary endpoints are subjective, self-reported outcomes, the blinding issue may have had a direct impact on the study results.

10.2.1.5.5 Treatment compliance

Study medications were administered under direct observation at the study sites for the first 12 hours. The 4th, 5th, and 6th doses of oral study medication were dispensed to patients at the time of discharge with instructions. Patients were to return blisters/unused medication at follow-up for drug accountability. Icatibant was not self-administered.

10.2.1.6 Study procedures

10.2.1.6.1 Concomitant and rescue medications

- Concomitant medications were defined as any medication other than rescue medications which were taken during the trial.
- Antipyretics, corticosteroids, and antihistamine use was discouraged but permitted at the discretion of the investigator.
- Narcotics and other pain medications were to be avoided if possible for the first 8-9 hours of study treatment. If required, the medication was recorded in the CRF as rescue medication. The narcotic of choice was morphine sulfate 0.05 mg/kg
- Use of androgens for regular prophylaxis was permitted at stable or decreased doses. Increases in doses were not permitted and those patients were excluded from the efficacy analysis of the double-blind portion of the study.
- Receipt of replacement C1-INH within 3 days from the onset of a new attack was an exclusion criterion.

10.2.1.6.2 Assessments and evaluations

Double-blind phase

Table 21 and Table 22 describe the schedule of assessments for the double-blind treatment phase of Study 2102 starting at Screening (Visit 0). Aside from open-label treatment with icatibant, laryngeal patients were expected to follow the same sequence of procedures and assessments.

Table 21 Study 2102: Schedule of assessments

	Visit 0	Visit 1	Visit 2												3	4 ³	5	X ⁴	Y ⁴	F ⁵
Procedure		0 h	0.5	1	1.5	2	2.5	3	3.5	4	5	6	8	10	12 ¹	24 ²	Wk 2	Wk 5	Wk 12	Wk 24
Pregnancy test		X															X			
Blood sample ⁶	X	X	X				X				X					X	X	X		X
Medical history	X	X																		
HAE history	X	X																		
Physical exam	X	X													X	X	X		X	
Vital signs	X	X	X													X	X		X	
ECG		X	X													X				
Urinalysis		X														X	X			
Randomization		X																		
SC study medication		X																		
Oral study medication		X										X			X	X ⁸				
Patient diary collection																X	X			
VAS ⁷		X		X	X	X	X	X	X	X	X	X	X	X	X	X				
Symptom score by patient ⁷		X		X	X	X	X	X	X	X	X	X	X	X	X	X				
Symptom score by investigator		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Global assessment		X								X					X	X	X			
GCI																				
Clinical global improvement																X	X			
Local tolerability			X	X		X				X			X		X	X	X			

¹ If no symptom relief by hour 12, observation could continue through hour 15 with additional assessments at hour 14.

² Visit 3 to take place 24 to 48 hours after study drug administration

³ If new attack occurred prior to Day 14, only the final assessment to be completed.

⁴ Telephone call every 12 weeks; visit at site every 6 months until study end

⁵ Final visit, could be by telephone

⁶ Blood sampling per protocol, see Table 32

⁷ Recorded 3 times a day until symptoms resolved or until day 5 post-treatment, whichever was earlier

⁸ 3 additional doses of oral study medication taken 6 to 8 hours apart

Source: je049-2102-report-body.pdf, Section 9.5.1, Table 1, P42

Table 22 Study 2102: Blood sampling schedule

		C1-INH, C4	Antibody assessment	Complement activation	Safety
Screening		X	X		X
Double blind phase					
Pre-treatment	Time 0		X	X	X
Post-treatment	Visit 2 (0.5h)			X	
	Visit 2 (2.5h)			X	
	Visit 2 (5.0h)			X	
	Visit 3 (Day 2)				X

	Visit 4 (Day 14) Visit 5 (Week 5)		X X		X
Follow-up	Week 24		X		
OLE					
Pre-treatment	Time 0		X	X	X
Post-treatment	Visit A2(0.5h) Visit A2 (2.5 h) Visit A2 (5.0 h) Visit A4 (Day 14) Week 24 (6 mo follow-up)		X X X X	X X X X	X X

Source: je049-2102-report-body.pdf, Section 9.5.3.3, Table 6, P60

Open-label extension phase

Table 23 describes the schedule of assessments for the open-label extension portion of the study.

Table 23 Study 2102a: Schedule of assessments for open-label portion of study																
	A1	A2													A3	A4
Procedure	0 h	0.5	1	1.5	2	2.5	3	3.5	4	5	6	8	10	12 ¹	24 ²	Wk 2
Pregnancy test	X															X
Blood sample	X	X				X				X						X
Physical exam	X													X		X
Vital signs	X	X														X
Urinalysis	X															X
Study medication administration	X															
Patient diary collection															X	X
VAS ⁷	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Symptom score by patient ⁷	X				X				X		X		X		X	
Global assessment	X								X						X	X
Local tolerability		X							X						X	X

Source: je049-2102-report-body.pdf, Section 9.5.4, Table 2, P44

10.2.1.7 Efficacy parameters

10.2.1.7.1 Primary efficacy variable

The primary efficacy endpoint was the **time to onset of symptom relief as measured by the Visual Analogue Scale (VAS)**. The VAS is a 100 mm horizontal line with 0mm = no symptoms and 100mm = 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 “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 to assess onset of symptom relief. Time to onset of symptom relief is defined as the time between injection and time of first documented onset of symptom relief, as defined below, at 3 consecutive measurements. Subjects with no documented onset of symptom relief were to be censored at the time of their last symptom assessment.

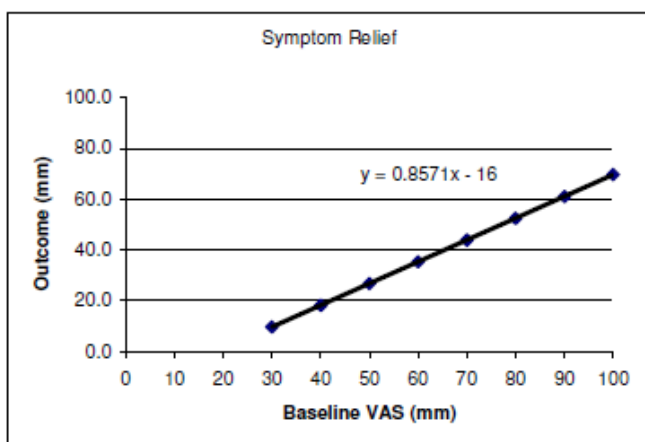
Onset of symptom relief was originally defined as follows:

- Absolute reduction from pre-treatment VAS of ≥ 20 mm if pre-dose VAS ≥ 30 and ≤ 50 , or of ≥ 30 mm if VAS > 50 mm

A modified definition of onset of relief was presented in the SAP dated August 24, 2006 as follows (Figure 1 Study 2102: Definition of onset of symptom relief by VAS as presented in the statistical analysis plan dated August 24, 2006):

- A response to the right and below a line $Y = 6/7 X - 16$ with $X \geq 30$ mm.
 - 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 2 Study 2102: Definition of onset of symptom relief by VAS as presented in the statistical analysis plan dated August 24, 2006



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

10.2.1.7.2 Secondary efficacy variables

- Response rate at 4 hours
 - Proportion of patients with onset of symptom relief for the primary symptom within 4 hours after treatment
- 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 for at least 3 consecutive measurements)
- Global Assessment
 - Investigators made a global assessment of all HAE symptoms, using the 5-point symptom scale described below.
- Assessment of each symptom by severity
 - 5-point symptom scale
 - 0 = none

- 1 = mild
- 2 = moderate (moderate interference with daily activities and no other interventions required)
- 3 = severe (severe interference with daily activities and intervention may or may not be required)
- 4 = very severe (very severe interference with daily activities and intervention required)
- Scored by patient: cutaneous swelling, cutaneous pain, abdominal pain, nausea, erythema, irritation, vomiting, and diarrhea
- Scored by investigator: cutaneous swelling, cutaneous pain, abdominal pain, nausea, erythema, abdominal tenderness, vomiting, and diarrhea
- Clinical global impression/improvement
 - Investigators made assessments of global impression on the patients acuity using a 7-point scale from “normal, not ill” to “among the most extremely ill patients.”
 - Investigators made assessments of improvement on a 7-point scale from “very much improved” to “very much worse.”
- Regression of symptoms (start of improvement) according to the patient (details not provided in the protocol)
- Observable regression of symptoms according to the physician
- Overall patient improvement according to the physician
- Patient satisfaction

10.2.1.7.3 Laryngeal efficacy parameters

Laryngeal attacks were treated on an open-label basis. 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. The protocol also states that aside from the open-label treatment, other study procedures were to be the same as those for patients enrolled for cutaneous and abdominal attacks.

10.2.1.8 Safety parameters

- Number and proportion of AEs
- Vital signs
- 12-lead ECGs at baseline, 0.5h, and 24 hours, read by a central reader (b) (4)
- Local injection site tolerability: erythema, swelling, burning sensation, itching/pruritus, warm sensation, pain, and other
- Laboratory assessments
 - Hematology parameters: hemoglobin, hematocrit, red blood cell count and differential, platelet count, mean corpuscular hemoglobin, and mean corpuscular volume
 - Clinical chemistry parameters: glucose, creatinine, uric acid, urea, total bilirubin, AST, ALT, GGT, and CPK
 - Urinalysis by dipstick
 - Urine pregnancy test for women of childbearing potential

- Physical exams and vital signs
- Antigenicity
- Complement C3a-desArg

10.2.1.9 Statistical plan (SAP dated August 24, 2006)

Efficacy analysis

The primary efficacy endpoint was calculated using the Wilcoxon version of the log-rank test, at a 2-sided significance level of 5%. Secondary endpoints described above were evaluated without adjustment for multiplicity. Outcomes for laryngeal attacks were evaluated using descriptive statistics. A sample size of 74 patients was calculated to provide 80% power to detect a difference of 4 hours between treatment groups and assuming a 10% dropout rate.

Safety analysis

Safety endpoints were analyzed using descriptive statistics. Statistical evaluation of ECG QT intervals was performed by Paraxel International GmbH.

10.2.1.10 Protocol amendments

Study 2101 was formally amended twice. In addition, the Applicant included other modifications of the original protocol in the Statistical Analysis Plan dated August 24, 2006.

- October 25, 2005 Amendment
 - Clarification of inclusion and exclusion criteria, including contraindications to tranexamic acid
 - Inclusion of patients with a medical history of HAE alone if patient also has a consistent family history, characteristic, recurrent attack manifestations, historical function C1-INH level <50% and exclusion of other forms of edema. Subsequent confirmation of diagnosis to be made by functional C1-INH measurement in central laboratory.
 - Specification of use of a medically acceptable form of contraception for the duration of the study in all women of childbearing age
 - Clarification that laryngeal edema patients would follow the same study procedures as patients on double-blind treatment
 - Omission of interim analysis
- June 2, 2006 amendment
 - Addition of Modified OLE to permit patients who were not otherwise eligible to receive icatibant in the double-blind phase of the study or the follow-up OLE
 - Addition of study results from Study JE049-2101
 - Modification of the primary endpoint to a more stringent definition (See Section 10.2.1)
- Statistical analysis plan dated August 24, 2006
 - Modified definition of the Onset of Symptom Relief definition to the following:
 - A response to the right and below a line $Y = 4/7 X - 50/7$ with $X=30\text{mm}$.

- X = pre-treatment VAS in mm
- Y = post-treatment VAS in mm
- Corresponds to a reduction by 50 mm at a baseline VAS = 100 mm and by 20 mm at a baseline VAS = 30 mm.
- Modification of stratification of patients. Patients with moderate diarrhea as the only abdominal symptom with moderate to severe cutaneous symptoms were to be classified in the cutaneous group.

10.2.2 Results

10.2.2.1 Protocol deviations

The Applicant reports a total of 16 protocol deviations for 14 patients (8 patients in the icatibant group, 6 patients in the tranexamic acid group). Eight major protocol deviations resulted in exclusion from the per-protocol population dataset. These deviations included failure to record a pre-dose VAS, mishandling of source data, mishandling of informed consent procedures, pre-dose VAS <30mm, failure to dispense oral study medication, and mishandling of patient diary.

10.2.2.2 Treatment compliance

The study report does not specifically describe treatment compliance, although it is noted that 4 patients did not receive oral study drug on the second day in violation of the protocol. In Section 11.3 of the study report, the Applicant states that drug accountability was assessed by used blister packs and unused medication at Visit 4 of the protocol.

10.2.2.3 Datasets analyzed

The Applicant has defined the following analysis populations:

- ITT population: intent-to-treat, all randomized patients who received double-blind trial medication
- Per protocol population: all patients from the ITT population without major deviations from the protocol. Patients with a pre-dose VAS of <30mm for the primary symptom were excluded.
- Safety population: all randomized patients who received trial medication and for whom a safety assessment was available
- Patients with laryngeal symptoms at Baseline: all patients who received icatibant open-label for laryngeal attack
- Patients treated in the controlled phase: all randomized patients and patients with laryngeal symptoms at baseline
- Patients treated in the OLE: all patients who received treatments for second or subsequent attacks, including patients with laryngeal symptoms as Baseline

10.2.2.4 Study patients

10.2.2.4.1 Patient disposition

A total of 74 patients were enrolled and treated in the double-blind portion of the study.

Patient disposition for the double-blind phase of Study 2102 is presented in Table 24. One patient (081-003) withdrew from the icatibant arm due to her desire to become pregnant. In the tranexamic acid arm, 1 patient discontinued due to pregnancy (082-005), patient 096-001 discontinued due to death, and Patient 096-004 was lost to follow-up. None of the 3 patients enrolled in the open-label treatment portion of Study 2102 for laryngeal symptoms discontinued prematurely.

Table 24 Study 2102: Patient disposition		
	Icatibant	Tranexamic acid
Total N	36 (100%)	38 (100%)
Discontinuations	1 (2.8%)	3 (7.9%)
<i>Other</i>	1 (2.8%)	1 (2.6%)
<i>Withdrawal of consent</i>	0	0
<i>Adverse events</i>	0	0
<i>Lost to follow-up</i>	0	1 (2.6%)
<i>Death</i>	0	1 (2.6%)

Source: je049-2102-report-body.pdf, Section 10.3, Table 9, P 79

The OLE phase of Study 2102 consisted of 35 patients (34 from the double-blind portion, 1 patient from the laryngeal symptoms at baseline portion). One patient (020-012) discontinued prematurely after one administration during the OLE due to unavailability for follow-up.

10.2.2.4.2 Patient study drug exposure

Thirty-six patients received 1 SC injection of icatibant during the controlled phase of the study; an additional 3 patients with laryngeal symptoms at baseline received 1 dose of open-label icatibant.

During the OLE, a total of 122 attacks in 35 patients were treated with 131 SC injections of icatibant (49 abdominal, 65 cutaneous, and 8 laryngeal). Six of 35 patients (10 attacks) enrolled in the OLE were treated with more than 1 dose of icatibant for a single attack. The majority of patients experienced (N=16) experienced 1 additional attack during the OLE and were treated with a single icatibant dose. At the other extreme, one patient received 41 injections of icatibant for 38 HAE attacks. Extent of exposure during the OLE is summarized in Table 25.

Table 25 Study 2102 OLE: Icatibant exposure			
Attack number	# patients by attack	# icatibant doses received	# patients
2 nd	34	1 2 3	31 3 0
3 rd	16	1 2 3	14 1 1
4 th	13	1 2 3	11 2 0
5 th	8	1 2 3	8 0 0
6 th	6	1 2 3	6 0 0
7 th	4	1 2 3	4 0 0
8 th	4	1 2 3	4 0 0
9 th	3	1 2 3	3 0 0
10 th	2	1 2 3	2 1 0
11 th	2	1 2 3	2 0 0
12 th	1	1 2 3	1 0 0
13 th	1	1 2 3	0 1 0
14 th	1	1 2 3	1 0 0
15 th	1	1 2 3	1 0 0
16 th	1	1 2 3	1 0 0
17 th	1	1 2 3	1 0 0
18 th	1	1 2 3	1 0 0
19 th	1	1 2 3	1 0 0
20 th	1	1 2 3	1 0 0
21 st	1	1 2 3	1 0 0
22 nd	1	1	1

		2	0
		3	0
23 rd	1	1	1
		2	0
		3	0
24 th	1	1	1
		2	0
		3	0
25 th	1	1	1
		2	0
		3	0
26 th	1	1	1
		2	0
		3	0
27 th	1	1	1
		2	0
		3	0
28 th	1	1	0
		2	1
		3	0
29 th	1	1	1
		2	0
		3	0
30 th	1	1	1
		2	0
		3	0
31 st	1	1	1
		2	0
		3	0
32 nd	1	1	1
		2	0
		3	0
33 rd	1	1	1
		2	0
		3	0
34 th	1	1	1
		2	0
		3	0
35 th	1	1	1
		2	0
		3	0
36 th	1	1	1
		2	0
		3	0
37 th	1	1	1
		2	0
		3	0

Source: je049-2102-report-body.pdf, Section 16, Table 3.3.1, P354-7

Reviewer's comment: The amount of data on repeated exposures in Study 2102 is limited to 6 patients. Only 1 patient received 3 doses for a single attack.

10.2.2.4.2 Demographics and baseline characteristics

A total of 74 patients ranging in age from 19 to 68 years were randomized in this study. The majority of patients had Type I HAE (n=67, 90.5%), and had positive family histories (n=62, 83.7%). The demographics and baseline characteristics of the ITT population for the controlled phase of Study 2102 are shown in Table 26.

Table 26 Study 2102: Demographics and baseline characteristics			
	Icatibant	Tranexamic acid	Total
ITT population	36	38	74
Male	12 (33.3%)	15 (39.5%)	27 (36.5%)
Race			
Caucasian	36 (100.0%)	38 (100.0%)	74 (100.0%)
Black	0	0	0
Asian	0	0	0
Multiracial	0	0	0
Other	0	0	0
Cutaneous attack	24 (100.0%)	23 (100.0%)	47 (100.0%)
Male	8 (33.3%)	12 (52.8%)	20 (42.6%)
Female	16 (66.7%)	11 (47.8%)	27 (57.4%)
Abdominal attack	12 (100.0%)	15 (100.0%)	27 (100.0%)
Male	4 (33.3%)	3 (20.0%)	7 (25.9%)
Female	8 (66.7%)	12 (80.0%)	20 (74.1%)
Age (years)			
Mean	40.4	41.9	41.1
Median	38.0	42.0	40.0
Range	20-68	19-66	19-68
Mean number of attacks during the last 6 months			
Cutaneous	7.4	7.9	
Abdominal	4.2	8.7	
Cutaneous and abdominal	6.5	2.4	
Laryngeal	2.4	1.0	

Source: je049-2102-report-body.pdf, Section 10.5, Tables 10, 11, 12 and Section 10.8, Table 17

Reviewer's comment: The demographic and baseline disease characteristics appear comparable between the treatment groups. One outlier patient in the tranexamic acid group reported a total of 72 abdominal HAE attacks in the previous 6 months, indicative of individual variability in attack frequency. The three laryngeal patients also had similar baseline characteristics and did not appear to have a more severe history or frequency of HAE attacks.

10.2.2.4.3 Concomitant medication use

At baseline, 9 patients in the icatibant group and 6 patients in the tranexamic acid group reported use of antgonadotropins and androstan derivatives for chronic HAE prophylaxis upon study entry. The most common concomitant medication was danazol. Ten patients in the icatibant group and 8 patients in the tranexamic acid group reported receiving C1 INH replacement therapy for prior attacks; during Study 2102, 4 patients in the icatibant group and 5 patients in the tranexamic acid received C1-INH upon entering the study.

For laryngeal attack patients, 1 patient was on danazol prior to treatment with icatibant.

Reviewer's comment: The study report distinguished between the use of C1-INH as a concomitant medication and as a rescue medication (discussed in Section 10.2.2.6.2). Details are not provided, although presumably C1-INH as a concomitant medication was used primarily for prophylactic purposes, e.g. prior to surgery.

10.2.2.5 Efficacy endpoint outcomes

10.2.2.5.1 Primary endpoint analysis

The primary endpoint was the time to onset of symptom relief resulting from moderate-to-severe cutaneous and abdominal HAE attacks. All analyses and discussion are based on the ITT population, unless otherwise indicated.

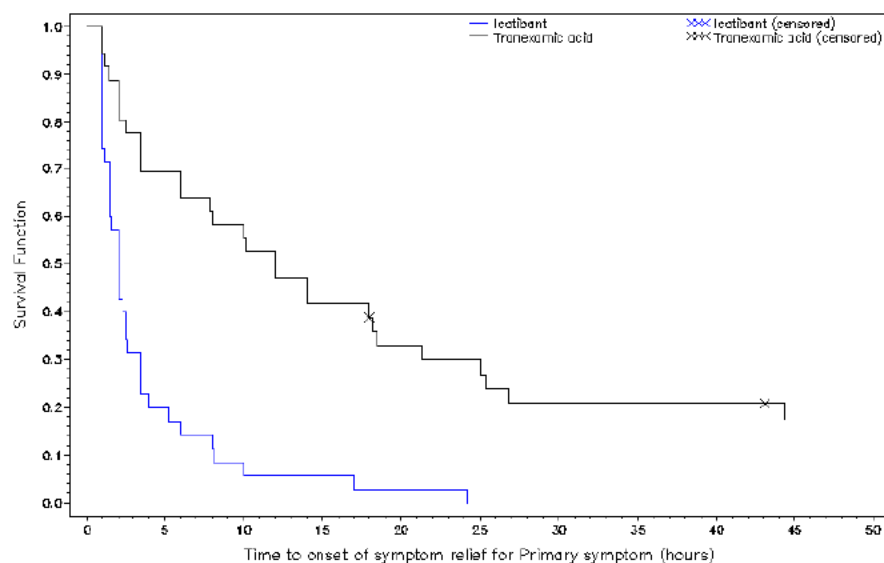
Onset of symptom relief for the ITT population is shown in Table 5 and Figure 3. For all attacks, the treatment difference between icatibant and tranexamic groups was 10.0 hours ($p < 0.001$). Also shown in the table are the median times to onset of symptom relief for the subpopulation of patients with cutaneous versus abdominal HAE attacks.

Table 27 Study 2102: Median time to onset of symptom relief as assessed by the VAS				
	Icatibant	Tranexamic acid	Total	P
All attacks, N	36	38	74	
# patients with pre-treatment VAS ≥ 30 mm	35	36	71	
# censored patients*	0	2	2	
Median time to onset of symptom relief (hours)	2.0	12.0	3.5	<0.001
Cutaneous attacks, N	24	23	47	
# patients with pre-treatment VAS ≥ 30 mm	23	23	46	
# censored patients*	0	2	2	
Median time to onset of symptom relief (hours)	2.5	18.2	7.0	<0.001
Abdominal attacks, N	12	15	27	
# patients with pre-treatment VAS ≥ 30 mm	12	13	25	
# censored patients*	0	0	0	
Median time to onset of symptom relief (hours)	1.6	3.5	2.0	0.026

* Patients censored when symptom relief did not occur within the observation period

Source: je049-2102-report-body.pdf, Section 11.4.1, Tables 22, 23, 24

Figure 3 Study 2102: Time of onset of symptom relief (hours)



Source: je049-report-body.pdf, Section 16, Figure 8.1a, P 3173

Reviewer's comment : The icatibant group had a statistically significant faster onset of symptom relief compared to the tranexamic acid group overall, although the treatment difference between icatibant and tranexamic acid is much less in the abdominal attack subgroup compared to the cutaneous group (1.9 hours versus 15.7 hours, respectively). According to the Applicant, pain symptoms in general are more likely to respond to treatment, including placebo. Since abdominal pain was the abdominal symptom used for VAS scoring, the Applicant states that abdominal attacks were more likely to show improvement after any treatment. Whether this explanation is true is uncertain. When looking at time to onset of symptom relief for individual symptoms aside from the primary symptom, skin pain does not appear to have the same "placebo response." The literature does not indicate that abdominal attacks differ from cutaneous attacks in terms of bradykinin pathophysiology.

Durability of response

A durable response was defined as onset of symptom relief for the primary symptom within 8 hours after treatment that lasted for at least 24 hours. In the icatibant group, 68.6% (n=24) reported a durable response, compared to 38.9% (n=14) in the tranexamic acid group (p=0.017). For cutaneous attacks, 65.2% (n=15) of icatibant patients compared to 21.7% (n=5) of tranexamic acid patients reported a durable response (p=0.007). For abdominal attacks, 75.0% (n=9) of icatibant patients reported a durable response compared to 69.2% (n=9) of tranexamic acid patients (p=1.0).

Reviewer's comment: Icatibant performed favorably in terms of durability of response compared to tranexamic acid for all attacks and the subset of cutaneous attacks. No differences were seen, however, in the abdominal attack group. Overall, less than ¾ of patients reported a durable response. Whether a more durable response could be achieved with repeat dosing or a different dose is unclear. Of note, the definition does not take into account rescue medication use, although in general, the tranexamic acid group received more rescue medications.

Time to onset of symptom relief – subgroup analysis

The time to onset of symptom relief was greater in male patients (3.5 hours) compared to female (1.6 hours) patients treated with icatibant. No differences were observed between patients weighing 50-75 kg and 75-100kg. As the entire study population was reported as Caucasian, no subgroup analysis by race was provided.

Reviewer's comment: The small sample size limits the utility of subgroup analysis, but there is no clear explanation for the differences seen in male versus female patients. In terms of types of attacks, a similar proportion of patients were male versus female in the icatibant cutaneous and abdominal attack subgroups (see Table 26).

Open-label extension phase

The onset of symptom relief was evaluated in the open-label extension phase by the number of attacks treated with icatibant. The greatest number of attacks treated for any one patient in this portion of the study was 38. More detailed information regarding total drug exposure is discussed in Section 10.2.2.4.2, Drug exposure. The onset of symptom relief ranged from 1.5 to

12.0 hours for all attacks and 1.6 to 2.5 hours for patients where data was available for 10 or more patients (2nd and 3rd attacks).

Reviewer's comment: The efficacy data from the OLE are generally consistent with results obtained from the double-blind portion of the study.

10.2.2.5.2 Secondary endpoints analyses

Time to onset of symptom relief using a modified definition of response

The study report presents time to onset of symptom relief using a more stringent definition of response as a secondary endpoint analysis. The modified definition is as follows:

- A response to the right and below a line $Y = 4/7 X - 50/7$ with $X=30\text{mm}$.
 - X = pre-treatment VAS in mm
 - Y = post-treatment VAS in mm
- Corresponds to a reduction by 50 mm at a baseline VAS = 100 mm and by 20 mm at a baseline VAS = 30 mm.

Based on the modified definition, the median time to onset of symptom relief for the icatibant group versus tranexamic acid is 2.5 versus 21.3 hours ($p<0.001$), with a treatment difference of 18.8 hours.

Reviewer's comment: A more stringent definition for onset of symptom relief increases the treatment difference seen between the two arms of the study.

Response rate at 4 hours after start of treatment

At 4 hours after start of treatment, the response rate based on the primary symptom was 80.0% ($n=28$) for icatibant versus 30.6% ($n=11$) for tranexamic acid ($p<0.001$). In the cutaneous attack subgroup, the response rate at 4 hours was 73.9% ($n=17$) versus 17.4% ($n=4$), respectively ($p<0.001$). In the abdominal attack subgroup, the response rate was 91.7% ($n=11$) versus 53.8% ($n=7$), respectively ($p=0.073$).

Time to relief of each symptom present in pre-dose VAS other than the primary symptom

Table 28 Study 2102: Time to relief of each symptom $\geq 30\text{mm}$ present in the VAS other than the primary symptom

	Icatibant	Tranexamic acid	Total	P
ITT population, N	36	38	74	
Skin swelling, N	8	6	14	
Median time to onset of symptom relief (hours)	2.0	7.5	3.0	0.220
Skin pain, N	12	13	25	
Median time to onset of symptom relief (hours)	1.5	12.0	10.0	0.018
Abdominal pain, N	0	0	0	-
Nausea, N	4	7	11	
Median time to onset of symptom relief (hours)	1.3	1.5	1.5	0.550

Source: je049-2102-report-body.pdf, Section 11.4.2.7, Table 40, P 121

Time to almost complete symptom relief

Almost complete symptom relief was defined as a VAS of 0-10 mm on at least 3 consecutive measurements.

Table 29 Study 2102: Time to almost complete symptom relief				
	Icatibant	Tranexamic acid	Total	P
ITT population, N	36	38	74	
# censored patients	3	9	12	
Median time to almost complete symptom relief (hours)	10.0	51.0	14.0	<0.001

Source: je049-2102-report-body.pdf, Section 11.4.2.9, Table 42, P 124

Global Assessment

Statistically significant differences in Global Assessment as scored by the investigator on a 5-point scale were observed between icatibant and tranexamic acid groups at 4, 12, 14, and 24 hours in favor of icatibant ($p < 0.001$ to 0.013).

Clinical global impression/improvement

As Baseline, the majority of patients in both treatment groups were scored as “moderately ill”: 16 patients (44.4%) in the icatibant group and 16 patients (42.1%) in the tranexamic acid group. At 4 hours, 18 patients (50.0%) in the icatibant were reported to be “very much improved,” 15 patients (41.7%) were “much improved,” and 3 (8.3%) were minimally improved. In the tranexamic acid group, 3 patients (7.9%) was “very much improved,” 7 (18.4%) were “much improved,” 11 (28.9%) were “minimally improved,” 10 (26.3%) had “no change,” 5 (13.1%) were “minimally worse,” 1 (2.6%) was “much worse,” and 1 (2.6%) was “very much worse).

Assessment of each symptom by severity

In general, statistically significant differences were observed for individual cutaneous symptoms scored by patients at the various time points between icatibant and tranexamic acid treatment groups. For abdominal symptoms, abdominal pain was scored more favorably by icatibant patients starting at 1 h post-dose and sustained through Visit 3 timepoint ($p = 0.001$ to 0.045). No statistically significant differences were reported for nausea, vomiting, or diarrhea.

Reviewer’s comment: This analysis only includes patients who reported the symptom as at least of mild severity at baseline.

Regression of symptoms (start of improvement) according to the patient

Icatibant patients reported a median time to start of improvement of 0.8 hours, compared to 7.9 hours for tranexamic acid patients ($p < 0.001$).

Reviewer’s comment: The start of improvement by this symptom index differs from the onset of symptom relief as estimated by the VAS. The Applicant has not conducted any separate studies to validate this patient-reported endpoint. In addition, this particular endpoint is not described in the protocol and the study report does not describe how the information was collected (retrospectively versus prospectively).

Observable regression of symptoms according to the physician

Investigators reported a median time to visible regression of symptoms of 1.7 hours for icatibant patients, compared to 8.0 hours for tranexamic acid patients ($p < 0.001$).

Overall patient improvement (time to regression/start of improvement) according to the physician

Investigators reported a median time to start of improvement of 1.5 hours for icatibant patients, compared to 6.9 hours for tranexamic acid patients ($p < 0.001$).

Rescue medication use

Seven patients in the icatibant group and 12 patients in the tranexamic acid group received rescue medication for the initial HAE attack. The most commonly administered rescue medication was C1-INH ($n=5$ in the icatibant group; $n=8$ in the tranexamic acid group). Other medications administered included opioids for pain relief and glucocorticoids. Rates of rescue medication usage were similar between cutaneous and abdominal attack groups. The study report states that 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.

Reviewer's comment: In terms of the primary endpoint, the data supports the efficacy of icatibant over tranexamic acid in the treatment of acute HAE attacks. However, in the absence of a placebo arm, assessment of efficacy remains difficult, especially since tranexamic acid is not approved for treatment of HAE in the US. The Applicant has provided multiple post-hoc secondary analyses to support the primary efficacy conclusions, but these additional analyses do not ameliorate this central study design issue. Furthermore, these other analyses rely primarily on unvalidated patient- and investigator-reported outcomes, further complicating the review.

10.2.2.5.3 Laryngeal attack efficacy analysis

Laryngeal attacks in 3 patients were treated with open-label icatibant in the controlled phase of the study. An additional 8 attacks in 4 patients were treated in the OLE phase of Study 2102.

Laryngeal attack symptom scores – double blind phase

Patient 075-001 presented with severe voice change and difficulty swallowing. Regression of symptoms was reported by the patient at 1-hour post-icatibant. No rescue medications or ventilatory assistance was required.

According to the patient narratives, Patient 075-014 was too ill to complete any symptom scoring and was intubated 5 minutes after icatibant administration. The patient was successfully extubated 8 hours later. Regression of symptoms was reported at 24 hours post-dose by Patient 075-014.

Patient 078-001 presented with severe voice change and difficulty swallowing. The patient reported regression of symptoms at 0.3 hours post-icatibant and absence of any symptoms by 4 hours post-dose.

Reviewer's comment: The small sample size limits any conclusions of efficacy. Also, whether the improvements observed over time are attributable to icatibant or reflect the gradual resolution of the attack cannot be ascertained in the absence of a placebo. The Applicant has not provided VAS scores for the laryngeal attack patients, although the protocol dated April 10, 2006, states that all study procedures described in Section 6.1 for the double-blind study participants would be followed.

Laryngeal attack symptom scores – OLE

A total of 4 patients were treated for 8 laryngeal attacks during the OLE.

Reviewer's comment: Based on symptom scores reported at 0, 2, and 4 hours, the data suggest that most patients experienced some improvement of symptoms within 4 hours of icatibant administration. Whether this improvement is attributable to icatibant is difficult to determine. Also, a median time to regression of symptoms or onset of symptom relief is not provided to facilitate comparison with cutaneous and abdominal attacks.

10.2.2.6 Safety assessments

10.2.2.6.1 Adverse events

Serious adverse events and death

One death (Patient 096-001) occurred in the tranexamic acid group. The cause of death is reported as sudden cardiac death due to aortic valve sclerosis. This patient died suddenly approximately 41 days after study drug administration. He was out walking and suddenly lost consciousness and died.

In addition to the patient death described above in Study 2102, 5 SAEs were reported in 4 patients who received icatibant.

- Patient 75-013 experienced a severe laryngeal HAE attack requiring tracheostomy 5 months after the last receipt of icatibant.
- Patient 90-004 experienced an abdominal HAE attack 2 weeks after initial treatment with icatibant, notably accompanied by hypotension, pyuria, and microhematuria. She was deemed fully recovered by 5 days after treatment with C1 INH concentrate, volume resuscitation, and antibiotic therapy.
- Patient 16-005 was hospitalized for viral gastroenteritis and hypertensive crisis 3 months after receipt of icatibant.
- Patient 075-014 experienced a laryngeal HAE attack, the same attack that qualified him for treatment with open-label icatibant in the study.

During the OLE, 5 patients experienced 9 SAEs, including HAE and renal failure requiring hospitalization (4 months after last treatment with icatibant), elective tooth extraction requiring hospitalization for precautionary monitoring, rotavirus-associated diarrhea with increased pancreatic enzymes requiring hospitalization (3 months post-icatibant), and a motor vehicle accident with minor head injury and hospitalization (2 days post-icatibant). The motor vehicle accident occurred in the setting of road flooding and hazardous driving conditions.

Reviewer's comment: The disparate nature of the SAEs and the timing of events in relation to study drug suggest that these events were not treatment-related.

Discontinuations from the study due to adverse events

No patients discontinued from the study due to adverse events, but one patient (082-005) in the tranexamic acid group was found to be pregnant on Day 14 of the treatment phase of the study and excluded.

Common adverse events

Injection site reactions were the most common adverse event and were assessed separately from other AEs in the Applicant's study report. HAE attacks were only to be reported as an AE if there was a worsening of symptoms during a treated attack. New HAE attacks were not to be reported as AEs, but the study report states that some investigators reported new attacks as AEs, leading to an over-reporting of HAE attack as an AE.

- *Double-blind phase*

The most common AE were local injection site reactions, reported by 35 patients (97.2%) in the icatibant treatment group compared to 10 patients (26.3%) who received placebo injection. These reactions were characterized most commonly by erythema (97.2%) and swelling (69.4%), followed by burning (69.4%), itching (30.6%), warmth (47.2%), and cutaneous pain (19.4%). Patients with primary cutaneous HAE attack symptoms reported swelling (83.3%) more commonly than abdominal attack patients (41.7%). The median duration of the reaction was 1.5 hours, with erythema as the principal persistent symptoms for that duration.

Eighteen patients (50.0%) in the icatibant group reported an adverse event besides a local injection site reaction, compared to 14 patients (36.8%) in the tranexamic acid group. The most common AE aside from local site reaction was HAE attack, reported by 7 patients (19.4%) in the icatibant group and 6 patients (15.8%) in the tranexamic acid group. A table of AEs occurring more commonly in the icatibant group than in the tranexamic acid group is presented below.

Table 30 Study 2102: Adverse events in the double-blind phase occurring more commonly in the icatibant treatment group compared to tranexamic acid

Adverse event	Icatibant (N=36)	Tranexamic acid (N=38)
Local injection site reaction	35 (97.2%)	10 (26.3%)
Hereditary angioedema	7 (19.4%)	6 (15.8%)
Abdominal pain	1 (2.8%)	0
Asthenia	1 (2.8%)	0
Blood urine present	1 (2.8%)	0
Borrelia infection	1 (2.8%)	0
Chest wall pain	1 (2.8%)	0
Cystitis	1 (2.8%)	0
Diabetes mellitus	1 (2.8%)	0
Diarrhea	1 (2.8%)	0
Fall	1 (2.8%)	0
Gastroenteritis	1 (2.8%)	0
Headache	1 (2.8%)	0
Hypertensive crisis	1 (2.8%)	0
Influenza	1 (2.8%)	0
Joint pain	1 (2.8%)	0
Nasopharyngitis	1 (2.8%)	0
Nausea	1 (2.8%)	0
Pyrexia	1 (2.8%)	0
Rash	1 (2.8%)	0
Sinusitis	1 (2.8%)	0
Skin laceration	1 (2.8%)	0
Vaginal candidiasis	1 (2.8%)	0
Viral infection	1 (2.8%)	0
White blood cells in urine	1 (2.8%)	0

Source: je049-2102-report-body.pdf, Section 12.2.2.1 and Section 16, Table 6.17.1.1, Page 2843

Reviewer's comment: Given the statistically significant benefit observed for icatibant over tranexamic acid in terms of the primary efficacy endpoint, the frequency of HAE reported as an AE seems incongruous.

- *Laryngeal attack patients*
Injection site reactions were reported by all 3 subjects who received open-label icatibant. The type of reaction and duration were similar to those reactions reported for abdominal and cutaneous attack patients. One patient also reported HAE attack, which was the same qualifying laryngeal attack for the study.
- *OLE phase*
Injection site reactions were reported in all 35 patients who received open-label icatibant during the OLE of Study 2102. Other common AEs occurring in $\geq 3\%$ of patients included the following: HAE attacks (n=5, 14.7%), urinary tract infection (n=4, 11.8%), nasopharyngitis (n=3, 8.8%), pharyngitis (n=3, 8.8%), chest pain (n=2, 5.9%), vomiting (n=2, 5.9%), and dehydration (n=2, 5.9%). Nine SAEs for 5 patients described above were also reported during the OLE phase.

Reviewer's comment: Adverse event findings are relatively consistent among the different phases of Study 2102. Local injection site reactions are nearly ubiquitous. Other common AEs are HAE attack and headache. Whether HAE attack is a true AE or a reflection of the underlying disease is unclear. In terms of attack site locations – cutaneous, abdominal, and laryngeal – there did not appear to be any differences in the nature or frequency of AEs among these patient subgroups.

10.2.2.6.2 Vital signs

No consistent changes in vital signs from baseline occurred during the study.

10.2.2.6.3 Physical exams

Aside from local injection site reactions and manifestations of the presenting HAE attack, no clinically significant physical exam findings are reported after administration of icatibant.

10.2.2.6.4 Laboratory parameters

Hematology

No consistent changes in hematology indices or coagulation parameters were observed in either the icatibant or tranexamic acid treatment groups.

Chemistry laboratory testing

Decreases in mean CK were observed for both icatibant (19.1 U/L) and tranexamic acid (19.7 U/L) groups at 24 hours after study drug administration. These decreases persisted through the follow-up visit on Day 14. Decreases were also observed for uric acid from baseline to Day 14 in both groups (10.6 mmol/L and 11.5 mmol/L, respectively).

During the OLE, one patient (070-004) with no prior history of pancreatitis had a pancreatic enzyme elevation (amylase 110 U/L) and mild hepatic enzyme elevations in the setting of rotavirus gastroenteritis which resolved in 30 days.

Urinalysis

One patient (016-005) was noted to have transient hematuria and proteinuria, which appeared to resolve by Day 40.

Antigenicity

The Applicant states that the antigenicity assay had not yet been developed at the time of the study report and that data will be reported separately when available.

Reviewer's comment: The Applicant reports being unable to induce antibodies to icatibant in animal models to develop antigenicity assays. Theoretically, development of blocking antibodies could diminish efficacy of icatibant over time.

10.2.2.6.5 ECGs

The study report states that there were no significant QT prolongation effects noted after icatibant administration. No patient has a difference from baseline above 60 msec or a QTcF value >500 msec. One patient was noted to have changes consistent with left and right

ventricular hypertrophy (096-001), who later suffered a sudden cardiac death, presumably secondary to aortic valve sclerosis.

Reviewer's comments: Overall, the safety profile of icatibant from Study 2102 and the OLE appear acceptable. The main toxicity appears to be self-limited injection site reactions. HAE attacks are the second most common adverse event, which may reflect the underlying disease condition rather than exacerbation caused by the study drug.

10.2.3 Study summary and conclusions

Study 2102 provides support for the efficacy of icatibant in the treatment of acute cutaneous and abdominal HAE attacks, with the caveat that the efficacy of the active comparator used in this trial, tranexamic acid, is not established. Tranexamic acid is not approved for the treatment of HAE in the US and evidence for tranexamic acid's efficacy in HAE in the literature is limited. Secondary efficacy endpoints are generally supportive, although many of these endpoints were assessed as post hoc analyses without any adjustment for multiplicity and based on subjective, unvalidated symptom score scales. Support for the efficacy of icatibant in laryngeal attacks is limited, given the low numbers treated in the trial (n=3 in the original study and 4 patients in the OLE phase).

The safety profile for 30 mg icatibant appears acceptable, although again this assessment is restricted by the small number of patients evaluated in the Phase 3 program. Aside from local injection site reactions, there do not appear to be any major safety issues. Data on repeated dosing, especially beyond 2 doses, is limited to a few patients; although no concerning safety issues are identified, the safety database in this regard is too limited to make an accurate assessment at this time. Of note, the Applicant has not provided any information on the antigenicity of icatibant in this study report.

10.3 Individual Study Report: Study 2103

10.3.1 Study protocol: Study 2103

Randomized, double blind, placebo-controlled multicenter study of a subcutaneous formulation of icatibant for the treatment of hereditary angioedema

10.3.1.1 Study administrative information

- Sites: 1 center in Argentina, 17 US centers, 5 Canada centers, 3 Australia centers
- Study dates: December 28, 2004 to July 17, 2006
- Date of study report: May 11, 2007

Reviewer's comment: The Argentinian study site enrolled the highest number of subjects (n=14). Thirty-one patients were enrolled in the US, 6 in Canada, and 6 in Australia. The US site with the highest enrollment was Site 070 (n=10).

10.3.1.2 Objectives/rationale

- Assess the efficacy of icatibant compared with placebo on the time of onset of symptom relief from moderate to very severe acute cutaneous or abdominal HAE attacks
- Assess the rate of response, time to almost complete symptom relief, global outcome, severity of each symptoms, safety and tolerability of icatibant compared to placebo
- Assess efficacy and safety of repeated treatments in the open-label extension phase
- Assess the efficacy and safety of icatibant in open-label use for laryngeal edema
- Assess the relative pharmacoeconomic impact of icatibant

10.3.1.3 Design overview

Study 2103 was a multicenter, randomized, double-blind, placebo-controlled, single-dose Phase 3 study. The study also included open-label treatment for patients with laryngeal HAE attacks and an open-label extension phase for all patients who experienced a recurrent HAE attack and a modified open-label extension phase for patients who were not treated during the double-blind treatment phase of the study. Results of the modified open-label extension phase were provided separately.

10.3.1.4 Study population

The study population included patients 18 years of age and older with a documented diagnosis of either Type I or II HAE, presenting with moderate to severe cutaneous or abdominal HAE attacks. Patients with laryngeal HAE attacks were treated separately with open-label icatibant.

Inclusion criteria

- Age 18 years of age and older
- Documented diagnosis of HAE Type I or II. The diagnosis could be confirmed either by functional and immunogenic C1-INH results from the central laboratory or by medical history. Inclusion on medical history alone were permitted if a clear diagnosis had been made on all of the following criteria:
 - Family history
 - Characteristic attack manifestations, recurrent attacks
 - Historical functional C1-INH <50%
 - Exclusion of other forms of angioedema
- Patients with C1-INH >50% could be included if an acceptable rationale for the higher level was provided
- Current moderate to severe HAE attack in the cutaneous, abdominal, and/or laryngeal area
- Able to complete baseline assessments and commence treatment no later than 6 hours after the current attacks became moderate
- Negative urine pregnancy test for women of childbearing potential

Exclusion criteria

- Diagnosis of angioedema other than HAE
- Participation in a clinical trial of another investigational agent within the past month
- Treatment with any pain medication since onset of the current attack

- Treatment with replacement therapy, including C1-INH, within 3 days from the onset of the current edema attack
- Treatment with ACE inhibitors
- Evidence of coronary artery disease based on medical history or screening examination
- Congestive heart failure (Class III or IV)
- Other serious concomitant illness or mental condition per investigator's discretion
- Pregnancy or breastfeeding

Reviewer's comment: Although both functional C1-INH and C4 levels were collected, the inclusion criteria were based only on the C1-INH level. C1q levels were not obtained for the study and were not routinely documented. Although a diagnosis of acquired angioedema (AAE) is an exclusion criterion, it is possible that patients with AAE who have previously been presumed to have HAE may have been enrolled in this study.

10.3.1.5 Study treatments

10.3.1.5.1 Dosing materials

- Icatibant acetate 30 mg SC in the abdominal region (3 mL of 10 mg/mL sterile, isotonic, acetate-buffered solution for injection containing no preservative (pH 5.5; packaged in 5 mL glass ampules)
- Placebo injection in the abdominal region (3 mL of sterile, isotonic, acetate-buffered solution for injection without preservative (pH 5.5))

10.3.1.5.2 Treatment groups

Double-blind treatment phase

- 30 mg icatibant acetate SC x 1
- Placebo SC (vehicle matched to study drug)

Open-label treatment for laryngeal edema

- 30 mg icatibant SC x 1

Open-label extension phase

- 30 mg icatibant SC x 1. If attack worsened within 48 hours of the initial treatment, a maximum of 2 additional doses could be administered at least 6 hours apart.
- Worsening symptoms or new symptoms occurring more than 48 hours after initial treatment were considered new attacks.
- No more than 8 injections of icatibant could be given within any 4-week period

10.3.1.5.3 Randomization

Fifty-six patients were randomized in a 1:1 ratio to receive icatibant or placebo. Random assignments were made through a centralized, automated system via allocation of a kit number of the study medication to be used for treatment. Patients with both cutaneous and abdominal symptoms were to be allocated to the abdominal group if at least one abdominal symptom (pain,

vomiting, diarrhea, nausea) was moderate to very severe. An exception was made in the SAP dated August 24, 2006, stated that if patients has moderate diarrhea as the only abdominal symptom along with moderate-to-severe cutaneous patients, these patients were to be categorized as cutaneous attack patients. Patients with laryngeal symptoms were allocated to the open-label treatment group regardless of coexistent cutaneous or abdominal symptoms.

10.3.1.5.4 Blinding

Ampoules of study drug were masked to blind both investigators and patients for the double-blind treatment phase of the study.

Reviewer's comment: Blinding of study treatments was incomplete due to the ubiquity of local injection site reactions associated with icatibant.

10.3.1.5.5 Treatment compliance

All study medications were administered under direct observation at the study sites. Icatibant was not self-administered.

10.3.1.6 Study procedures

10.3.1.6.1 Concomitant medications

- Concomitant medications were defined as any medication other than rescue medications which were taken during the trial.
- Antipyretics, corticosteroids, and antihistamine use was discouraged but permitted at the discretion of the investigator.
- Narcotics and other pain medications were to be avoided is possible for the first 8-9 hours of study treatment. If required, the medication was recorded in the CRF as rescue medication. The narcotic of choice was morphine sulfate 0.05 mg/kg/
- Use of androgens for regular prophylaxis was permitted at stable or decreased doses. Increases in doses were not permitted and those patients were excluded from the analysis of the double-blind portion of the study.
- Receipt of replacement C1-INH within 3 days from the onset of a new attack was an exclusion criterion.

10.3.1.6.2 Assessments and evaluations

Double-blind treatment phase

Table 31 describes the schedule of assessments for the double-blind treatment phase of Study 2103 starting at Screening (Visit 0). Aside from open-label treatment with icatibant, laryngeal patients were expected to follow the same sequence of procedures and assessments.

Table 31 Study 2103: Schedule of assessments

	Visit 0	Visit 1	Visit 2												3	4 ³	5	X ⁴	Y ⁴	F ⁵
Procedure		0 h	0.5	1	1.5	2	2.5	3	3.5	4	5	6	8	10	12 ¹	24 ²	Wk 2	Wk 5	Wk 12	Wk 24
Pregnancy test		X															X			
Blood sample ⁶	X	X	X				X				X					X	X	X		X
Medical history	X	X																		
HAE history	X	X																		
Physical exam	X	X													X	X	X			X
Vital signs	X	X	X													X	X			X
ECG		X	X													X	X			
Urinalysis		X														X	X			
Randomization		X																		
Study medication administration		X																		
Patient diary collection																X	X			
VAS ⁷		X		X	X	X	X	X	X	X	X	X	X	X	X	X				
Symptom score by patient ⁷		X		X	X	X	X	X	X	X	X	X	X	X	X	X				
Symptom score by investigator		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Global assessment		X								X					X	X	X			
GCI																				
Clinical global improvement																X	X			
Local tolerability			X	X		X				X			X		X	X	X			

¹ If no symptom relief by hour 12, observation could continue through hour 15 with additional assessments at hour 14.

² Visit 3 to take place 24 to 48 hours after study drug administration

³ If new attack occurred prior to Day 14, only the final assessment to be completed.

⁴ Telephone call every 12 weeks; visit at site every 6 months until study end

⁵ Final visit, could be by telephone

⁶ Blood sampling per protocol, see Table 32

⁷ Recorded 3 times a day until symptoms resolved or until day 5 post-treatment, whichever was earlier

Source: je049-2103-report-body.pdf. Table 1. P43

Table 32 Study 2103: Blood sampling schedule

		C1-INH, C4	Antibody assessment	Complement activation	Safety
Screening		X	X		X
Double blind phase					
Pre-treatment	Time 0		X	X	X
Post-treatment	Visit 2 (0.5h)			X	
	Visit 2 (2.5h)			X	
	Visit 2 (5.0h)			X	
	Visit 3 (Day 2)		X		X
	Visit 4 (Day 14)		X		X
	Visit 5 (Week 5)				
Follow-up	Week 24		X		
OLE					
Pre-treatment	Time 0		X	X	X
Post-treatment	Visit A2(0.5h)			X	
	Visit A2 (2.5 h)			X	
	Visit A2 (5.0 h)			X	
	Visit A4 (Day 14)		X		X
	Week 24 (6 mo follow-up)		X	X	X

Source: je049-2103-report-body.pdf. Table 6. P60

Open-label extension phase

Table 33 describes the schedule of assessments for the open-label extension portion of the study.

Table 33 Study 2103a: Schedule of assessments for open-label portion of study																
Procedure	A1 0 h	A2												A3 24 ^h	A4 Wk 2	
Pregnancy test	X															X
Blood sample	X	X				X				X						X
Physical exam	X												X			X
Vital signs	X	X														X
Urinalysis	X															X
Study medication administration	X															
Patient diary collection														X		X
VAS ⁷	X		X	X	X	X	X	X	X	X	X	X	X	X		
Symptom score by patient ⁷	X				X				X		X		X	X		
Global assessment	X								X					X		X
Local tolerability		X							X					X		X

Source: je049-2103-report-body.pdf. Table 2. P44

10.3.1.7 Efficacy parameters

10.3.1.7.1 Primary efficacy variable

The primary efficacy endpoint was the **time to onset of symptom relief as measured by the Visual Analogue Scale (VAS)**. The VAS is a 100 mm horizontal line with 0mm = no symptoms and 100mm = worst possible symptom. Patients mark on the line to rate the intensity of each symptoms 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 “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 to assess onset of symptom relief. Time to onset of symptom relief is defined as the time between injection and time of first documented onset of symptom relief, as defined below, at 3 consecutive measurements. Subjects with no documented onset of symptom relief were to be censored at the time of their last symptom assessment.

Onset of symptom relief was originally defined as follows:

- Absolute reduction from pre-treatment VAS of ≥ 20 mm if pre-dose VAS ≥ 30 and ≤ 50 , or of ≥ 30 mm if VAS > 50 mm

A modified definition of onset of relief was presented in the SAP dated August 24, 2006 as follows (see Figure 1):

- A response to the right and below a line $Y = 6/7 X - 16$ with $X \geq 30$ mm (see Figure 1).
 - 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.

Reviewer's comment: The modified definition using more stringent criteria is used in the primary endpoint analysis. For post-hoc analysis, the Applicant has provided results using even more stringent criteria.

10.3.1.7.2 Secondary efficacy variables

- Response rate at 4 hours
 - Proportion of patients with onset of symptom relief for the primary symptom within 4 hours after treatment
- 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 for at least 3 consecutive measurements)
- Global Assessment
 - Investigators made a global assessment of all HAE symptoms, using the 5-point symptom scale described below.
- Assessment of each symptom by severity
 - 5-point symptom scale
 - 0 = none
 - 1 = mild
 - 2 = moderate (moderate interference with daily activities and no other interventions required)
 - 3 = severe (severe interference with daily activities and intervention may or may not be required)
 - 4 = very severe (very severe interference with daily activities and intervention required)
 - Scored by patient: cutaneous swelling, cutaneous pain, abdominal pain, nausea, erythema, irritation, vomiting, and diarrhea
 - Scored by investigator: cutaneous swelling, cutaneous pain, abdominal pain, nausea, erythema, abdominal tenderness, vomiting, and diarrhea
- Clinical global impression/improvement
 - Investigators made assessments of global impression on the patients acuity using a 7-point scale from “normal, not ill” to “among the most extremely ill patients.”
 - Investigators made assessments of improvement on a 7-point scale from “very much improved” to “very much worse.”
- Regression of symptoms (start of improvement) according to the patient (details not provided in the protocol)
- Observable regression of symptoms according to the physician
- Overall patient improvement according to the physician
- Patient satisfaction

10.3.1.7.3 Laryngeal attack efficacy assessment

Laryngeal attacks were treated on an open-label basis. 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. The protocol also states that aside from the open-label treatment, other study procedures were to be the same as those for patients enrolled for cutaneous and abdominal attacks.

10.3.1.8 Safety parameters

Safety endpoints included the following:

- Number and proportion of AEs
- Vital signs
- 12-lead ECGs performed at baseline, 0.5h, and 24 hours post-dose
- Local injection site tolerability: erythema, swelling, burning sensation, itching/pruritus, warm sensation, pain, and other
- Laboratory assessments
 - Hematology parameters: hemoglobin, hematocrit, red blood cell, white blood cell count and differential, platelet count, mean corpuscular hemoglobin, and mean corpuscular volume
 - Clinical chemistry parameters: glucose, creatinine, uric acid, urea, total bilirubin, AST, ALT, GGT, and CPK
 - Urinalysis by dipstick
 - Urine pregnancy test for women of childbearing potential
- Physical exams and vital signs
- Antigenicity
- Complement C3a-desArg

10.3.1.9 Statistical plan (dated August 24, 2006)

Efficacy analysis

The primary efficacy endpoint was calculated using the Wilcoxon version of the log-rank test, at a 2-sided significance level of 5%. Secondary endpoints described above were evaluated without adjustment for multiplicity. Outcomes for laryngeal attacks were evaluated using descriptive statistics. A sample size of 56 patients was calculated to provide 80% power to detect a difference of 5.5 hours between treatment groups and assuming a 10% dropout rate.

Safety analysis

Safety endpoints were analyzed using descriptive statistics.

10.3.1.10 Protocol amendments

- Amendment dated September 7, 2004 (prior to screening of first patient). Major changes included the following:
 - Administration of the study medication from 3 to 1 SC injection
 - Criteria for treatment in the OLE changes from “moderate to severe” attacks to “any attack severe enough to warrant treatment”
 - VAS $\geq$ 30mm added to Inclusion Criteria

- Onset of symptom relief definition changed”
 - Original: absolute reduction by ≥ 20 mm observed at 3 consecutive measurements
 - Amended definition: absolute reduction from pre-treatment VAS of ≥ 20 mm if pre-dose VAS ≥ 30 and ≤ 50 , or of ≥ 30 mm if VAS > 50 mm
- Amendment dated April 10, 2006
 - Addition of Modified OLE to permit patients who were not otherwise eligible to receive icatibant in the double-blind phase of the study or the follow-up OLD
 - Modification of the inclusion criterion for diagnosis of HAE to allow inclusion of patients based on medical history alone with later confirmation by C1-INH levels.
 - Increase in the time following an attack (8-9 hours) before rescue medication permitted
 - Decision to omit planned interim analysis by DSMB
- Statistical analysis plan dated August 26, 2006
 - Modification of the Onset of Symptom Relief definition to the following:
 - A response to the right and below a line $Y = 6/7 X - 16$ with $X \geq 30$ mm.
 - 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 20 mm at a baseline VAS = 30 mm.
 - Modification of stratification of patients. Patients with moderate diarrhea as the only abdominal symptom with moderate to severe cutaneous symptoms were to be classified in the cutaneous group.

10.3.1.11 Datasets analyzed

The Applicant has defined the following analysis populations:

- ITT population: intent-to-treat, all randomized patients who received double-blind trial medication
- Per protocol population: all patients from the ITT population without major deviations from the protocol. Patients with a pre-dose VAS of < 30 mm for the primary symptom were excluded.
- Safety population: all randomized patients who received trial medication and for whom a safety assessment was available
- Patients with laryngeal symptoms at Baseline: all patients who received icatibant open-label for laryngeal attack
- Patients treated in the controlled phase: all randomized patients and patients with laryngeal symptoms at baseline
- Patients treated in the OLE: all patients who received treatments for second or subsequent attacks, including patients with laryngeal symptoms as Baseline

10.3.2 Results

10.3.2.1 Protocol deviations

Fifteen protocol violations were reported for 9 randomized patients. Of these, 5 violations for 5 patients were considered major violations, and these subjects were excluded from the per-protocol population. These violations included missing source data/lab results/ECGs, receipt of pain medication, pre-dose VAS <30mm, and missing documentation of the time of the attack and last receipt of replacement C1-INH therapy.

Nine patients were granted waivers to enter the study based on historical data and confirmed diagnoses of HAE, even though laboratory results were unavailable or C1-INH levels were higher than the inclusion criteria: 025-004, 001-002, 001-001, 002-003, 018-001, 018-002, 018-003, 057-001, and 056-003.

Patient 015-006 was entered into the study for a moderate cutaneous attack and received placebo. Six hours after study drug administration, he developed laryngeal edema and was given icatibant as a rescue medication.

Patient 02-003 was documented as having severe abdominal HAE attacks every 2-4 days for which she typically received C1-INH replacement. The patient was granted a waiver to enter the study despite receiving C1-INH more recently than 3 days prior to study drug administration, on the condition that a minimum 24-hour washout period for C1-INH was observed.

10.3.2.2 Study patients

10.3.2.2.1 Patient disposition

Patient disposition for the double-blind phase of Study 2103 is presented in Table 34. One patient categorized under “Other,” was found to be pregnant upon presentation for the first HAE attack and was never randomized. In addition, 1 of 8 patients enrolled in the open-label treatment portion of Study 2103 for laryngeal symptoms at baseline withdrew consent and discontinued from the study prematurely.

Table 34 Study 2103: Patient disposition		
	Icatibant	Placebo
Total N	27 (100%)	29 (100%)
Discontinuations	1 (3.7%)	0
Other	1 (3.7%)	0
Withdrawal of consent	0	0
Adverse events	0	0
Lost to follow-up	0	0
Death	0	0

Source: je049-2103-report-body.pdf, Section 16, Table 6.21.1.1, P 1782

In the OLE phase of Study 2103, 10 patients discontinued the study early, citing withdrawal of consent (n=6) and other (n=4) as the reasons. Further details were not provided.

10.3.2.2.2 Study drug exposure

Double-blind phase drug exposure

Exposure to study drug during the double-blind phase of Study 2103 is summarized below. Eight patients with laryngeal attacks each received 1 open-label dose of icatibant

subcutaneously. The remainder of patients with cutaneous and abdominal symptoms were randomized to icatibant and placebo and their exposure is summarized in **Table 35**.

Table 35 Study 2103: Double-blind study drug exposure			
	Icatibant (N=27)	Placebo (N=29)	Total
1 dose study drug	27	28	55
2 doses study drug	0	1*	1

* 1 patient in the placebo group (015-006) developed laryngeal symptoms 6 hours after receipt of a placebo injection and was given icatibant as a rescue medication. This patient is not included in the efficacy data for the icatibant group.

Source: je049-2103-report-body.pdf, Section 12.1, Table 45, Page 137

OLE phase drug exposure

Forty-two patients from the double-blind phase of Study 2103 (including patients treated with open-label icatibant for laryngeal attacks) participated in the OLE phase and received open-label icatibant. Patients were eligible to receive more than a single dose based on the frequency and severity of the attacks. A total number of 109 attacks were treated. Ninety-three attacks were treated with a single dose. The exposure during the OLE is described in Table 36.

Table 36 Study 2103 OLE: Icatibant exposure			
Attack number	# patients by attack	# icatibant doses received	# patients
2 nd	42	1	38
		2	3
		3	1
3 rd	23	1	20
		2	3
		3	0
4 th	14	1	14
		2	0
		3	0
5 th	7	1	4
		2	2
		3	1
6 th	4	1	2
		2	2
		3	0
7 th	4	1	3
		2	1
		3	0
8 th	3	1	2
		2	0
		3	1
9 th	3	1	3
		2	0
		3	0
10 th	3	1	2
		2	1
		3	0
11 th	3	1	2
		2	1
		3	0
12 th	2	1	2
		2	0
		3	0
13 th	1	1	1
		2	0
		3	0

Source: je049-2103-report-body.pdf, Section 16, Table 3.3.3, P327

10.3.2.2.3 Demographics and baseline characteristics

Demographic and baseline characteristics are summarized in Table 37.

Table 37 Study 2103: Demographics and baseline characteristics			
	Icatibant	Placebo	Total
ITT population	27	29	56
Male	11 (40.7%)	8 (27.6%)	19 (33.9%)
Race			
Caucasian	25 (92.6%)	25 (86.2%)	50 (89.3%)
Black	0	0	0
Asian	0	1	1 (1.8%)
Multiracial	0	1 (3.4%)	1 (1.8%)
Other	2 (7.4%)	2 (6.9%)	4 (7.1%)
Cutaneous attack	14 (100.0%)	13 (100.0%)	27 (100.0%)
Male	8 (57.1%)	5 (38.5%)	13 (48.1%)
Female	6 (42.9%)	8 (61.5%)	14 (51.9%)
Abdominal attack	13 (100.0%)	16 (100.0%)	29 (100.0%)
Male	3 (23.1%)	3 (18.8%)	6 (20.7%)
Female	10 (76.9%)	13 (81.3%)	23 (79.3%)
Age (years)			
Mean	34.8	34.9	34.9
Median	35.0	34.0	34.5
Range	20-54	18-58	18-58
Mean number of attacks during the last 6 months			
Cutaneous	8.6	9.9	
Abdominal	5.1	6.8	
Cutaneous and abdominal	7.3	4.9	
Laryngeal	1.7	2.8	

Source: je049-2103-report-body.pdf. Section 10.5

The study report notes that the severity of previous attacks by history varied slightly between treatment groups. More patients in the placebo group reported having had a severe cutaneous attack in the past 6 months compared to the icatibant group (12 v. 9 patients). More patients in the icatibant group reported having had a severe laryngeal attack (6 v. 5 patients).

Reviewer's comments: Demographics and baseline characteristics, including HAE attack history in the previous 6 months, appear comparable between the two treatment groups. Although differences exist, the small sample size is taken into account and the differences do not appear to be significant enough to have impacted the final efficacy results.

10.3.2.2.3 Concomitant medications

At baseline, 6 patients in the icatibant group and 13 patients in the placebo group reported use of antgonadotropins and androstan derivatives for chronic HAE prophylaxis. Two patients in the icatibant group and 3 patients in the placebo group reported receiving C1 INH replacement therapy for prior attacks.

For laryngeal attack patients, 1 patient was on regular antgonadotropins prior to treatment with icatibant.

10.3.2.3 Efficacy endpoint outcomes

10.3.2.3.1 Primary endpoint analysis: Onset of symptom relief

The primary endpoint was the time to onset of symptom relief resulting from moderate-to-severe cutaneous and abdominal HAE attacks, using the following definition: Absolute reduction from pre-treatment VAS of ≥ 20 mm if pre-dose VAS ≥ 30 and ≤ 50 , or of ≥ 30 mm if VAS > 50 mm. All analyses and discussion are based on the ITT population, unless otherwise indicated.

Onset of symptom relief for the ITT population is shown in Table 6. For all attacks, the treatment difference between icatibant and placebo groups was 2.1 hours ($p=0.142$). Also shown in the table are the median times to onset of symptom relief for the subpopulation of patients with cutaneous versus abdominal HAE attacks.

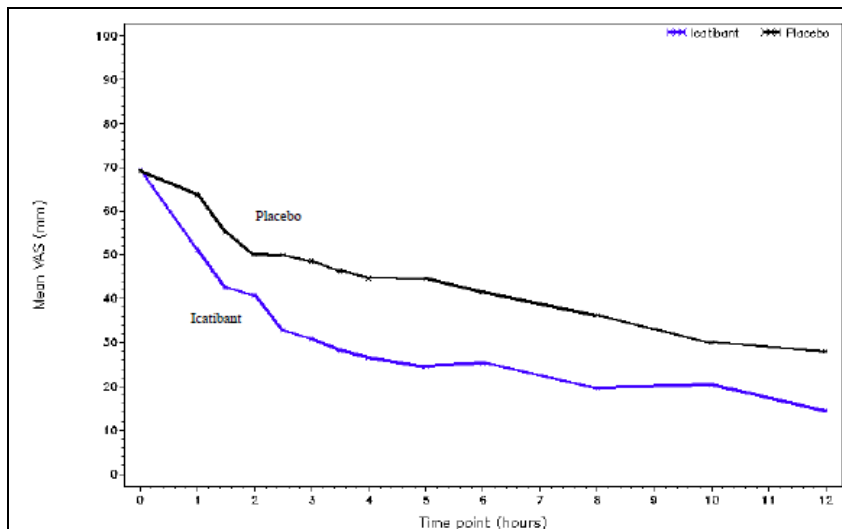
Table 38 Study 2103: Median time to onset of symptom relief as assessed by the VAS				
	Icatibant	Placebo	Total	P
All attacks, N	27	29	56	
# patients with pre-treatment VAS ≥ 30 mm	27	28	55	
# censored patients*	1	1	2	
Median time to onset of symptom relief (hours)	2.5	4.6	3.0	0.142
Cutaneous attacks, N	14	13	27	
# patients with pre-treatment VAS ≥ 30 mm	14	13	27	
# censored patients*	0	1	1	
Median time to onset of symptom relief (hours)	3.4	10.0	6.0	0.221
Abdominal attacks, N	13	16	29	
# patients with pre-treatment VAS ≥ 30 mm	13	15	28	
# censored patients*	1	0	1	
Median time to onset of symptom relief (hours)	2.0	6.0	2.3	0.159

* Patients censored when symptom relief did not occur within the observation period. These patients were excluded from the analysis.

Source: je049-2103-report-body.pdf, Section 11.4.1, Tables 22, 23, 24

Mean VAS values over time for the symptom used for the primary endpoint are shown in Figure 4.

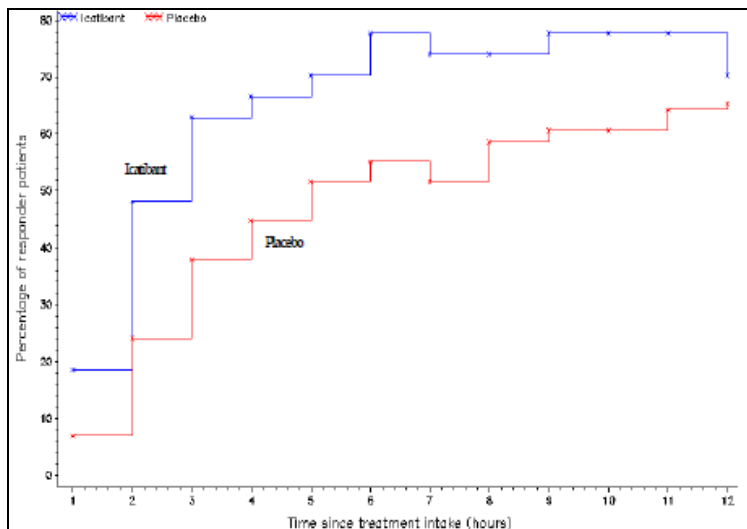
Figure 4 Study 2103: Mean VAS over time for the symptom used for the primary endpoint



Source: je049-2103-report-body.pdf, Section 11.4, Figure 5, P 97

The Applicant provided post-hoc responder analysis for onset of symptom relief as shown in the Kaplan-Meier curve in Figure 5.

Figure 5 Study 2103: Onset of symptom relief responders



Source: je049-2103-report-body.pdf, Section 11.4, Figure 4, P 96

Reviewer's comment: Although the VAS results were numerically favorable to icatibant and supported by post-hoc responder analysis, icatibant failed to demonstrate a statistically significant quicker onset of symptom relief compared to placebo. The clinical relevance of the 2.1 hour treatment difference is difficult to assess, as HAE attacks may be quite variable and the natural course for most attacks is spontaneous resolution. There did not appear to be any clear differences in icatibant efficacy in cutaneous versus abdominal HAE attacks.

The Applicant states that an exaggerated placebo response was observed in Study 2103 due to the higher number of patients with abdominal versus cutaneous attacks enrolled compared to Study 2102. According to the Applicant, pain symptoms in general are more likely to be responsive to placebo. Since abdominal pain was the base symptom scored on the VAS, patients presenting with abdominal attacks were more likely to show improvement, regardless of allocation to treatment group.

Durability of response

A durable response was defined as onset of symptom relief for the primary symptom within 8 hours after treatment that lasted for at least 24 hours. In the icatibant group, 51.9% reported a durable response, similar to the 50.0% in the placebo group ($p=1.0$). For cutaneous attacks, 57.1% of icatibant patients compared to 38.5% of placebo patients reported a durable response ($p=0.449$). For abdominal attacks, 46.2% of icatibant patients reported a durable response compared to 60.0% of placebo patients ($p=0.705$).

Reviewer's comment: Icatibant and placebo groups performed similarly in terms of durability of response. Results were numerically unfavorable for icatibant for patients with abdominal attacks. These results suggest that icatibant has limited impact on the overall resolution of an acute attack.

Time to onset of symptom relief – subgroup analysis

No statistically significant differences were reported between male and female patients. When divided by weight, patients weighting between 75 to 100kg treated with icatibant were observed to have a faster onset of symptom relief compared to their placebo counterparts (3.9 v. 23.0 hours; $p=0.030$). No statistically significant differences were noted in patients weighing 50 to 100 kg ($n=3$) or patients >100 kg ($n=9$).

Reviewer's comment: The small sample size limits the utility of subgroup analysis. No formal subgroup analysis was performed by age or ethnicity.

Open-label extension phase

The onset of symptom relief was evaluated in the open-label extension phase by the number of attacks treated with icatibant. The greatest number of attacks treated for any one patient in this portion of the study was 12. More detailed information regarding total drug exposure is discussed in Section 10.3.2.4.2, Safety analysis. The onset of symptom relief ranged from 1.0 to 4.0 hours for all reported attacks and 1.5 to 1.8 hours for patients who experienced 2 to 4 attacks during the OLE ($n=59$).

Reviewer's comment: The efficacy data from the OLE are consistent with results obtained from the double-blind portion of the study.

10.3.2.3.2 Secondary endpoints analyses

Time to onset of symptom relief using a modified definition of response

The study report presents time to onset of symptom relief using a more stringent definition of response as a secondary endpoint analysis. The modified definition is as follows:

- A response to the right and below a line $Y = 4/7 X - 50/7$ with $X=30$ mm.
 - X = pre-treatment VAS in mm
 - Y = post-treatment VAS in mm
- Corresponds to a reduction by 50 mm at a baseline VAS = 100 mm and by 20 mm at a baseline VAS = 30 mm.

Based on this more stringent definition, the median time to onset of symptom relief for the icatibant group versus placebo is 2.5 versus 8.1 hours ($p=0.058$), with a treatment difference of 5.6 hours.

Reviewer's comment: Although a more stringent definition for onset of symptom relief increases the treatment difference seen between the two arms of the study, the comparison still does not show a statistically significant difference.

Response rate at 4 hours after start of treatment

At 4 hours after start of treatment, the response rate based on the primary symptom was 66.7% for icatibant versus 46.4% for placebo (0.176). When divided by cutaneous versus abdominal attacks, no statistically significant differences were noted as well ($p=0.252$ and 0.435 , respectively).

Time to relief of each symptom present in pre-dose VAS other than the primary symptom

Table 39 Study 2103: Time to relief of each symptom present in the VAS other than the primary symptom				
	Icatibant	Placebo	Total	P
ITT population, N	27	29	56	
Skin swelling, N	5	11	16	
Median time to onset of symptom relief (hours)	3.5	10.0	9.0	0.053
Skin pain, N	8	7	15	
Median time to onset of symptom relief (hours)	1.6	23.9	3.0	0.018
Abdominal pain, N	2	3	5	
Median time to onset of symptom relief (hours)	2.1	10.0	3.5	0.046
Nausea, N	10	8	18	
Median time to onset of symptom relief (hours)	1.1	2.3	1.5	0.080

Source: je049-2103-report-body.pdf, Section 11.4.2.7, Table 31, P 109

Time to almost complete symptom relief

Almost complete symptom relief was defined as a VAS of 0-10 mm on at least 3 consecutive measurements.

Table 40 Study 2103: Time to almost complete symptom relief				
	Icatibant	Placebo	Total	P
ITT population, N	27	29	56	
# censored patients	3	8	11	
Median time to almost complete symptom relief (hours)	8.5	23.3	14.0	0.069

Global Assessment

No statistically significant differences in Global Assessment as scored by the investigator on a 5-point scale were observed between icatibant and placebo groups, with the exception of abdominal symptoms at the 24-hour mark alone ($p=0.041$).

Clinical global impression/improvement

As Baseline, 15 patients (55.6%) in the icatibant group were scored as “moderately ill,” compared to 19 patients (65.5%) in the placebo group. At 4 hours, 10 patients (37.0%) in the icatibant group were reported to be “very much improved,” 9 patients (33.3%) were “much improved, and 5 (18.5%) were minimally improved. In the placebo group, 1 patient (3.5%) was “very much improved,” 10 (34.5%) were “much improved,” 7 (24.1%) were “minimally improved,” 4 (13.9%) had “no change,” 5 (17.3%) were “minimally worse”, and 2 (7%) were “much worse.”

Assessment of each symptom by severity

No consistent, statistically significant differences were observed for individual cutaneous symptoms scored by patients at the various time points between icatibant and placebo treatment groups. For abdominal symptoms, both abdominal pain and nausea were scored more favorably by icatibant patients starting at 1 h post-dose and sustained through the 12-h timepoint ($p=0.001$ to 0.033).

Regression of symptoms (start of improvement) according to the patient

Icatibant patients reported a median time to start of improvement of 0.8 hours, compared to 16.9 hours for placebo patients ($p<0.001$).

Reviewer’s comment: The start of improvement does not correlate clearly with the onset of symptom relief as assessed by the VAS, calling into question the reliability and reproducibility of either measure. This particular endpoint is not described in the protocol and the study report does not describe how the information was collected (retrospectively versus prospectively).

Observable regression of symptoms according to the physician

Investigators reported a median time to visible regression of symptoms of 6.5 hours for icatibant patients, compared to 14.0 hours for placebo patients ($p<0.240$).

Overall patient improvement according to the physician

Investigators reported a median time to start of improvement of 1.0 hours for icatibant patients, compared to 5.7 hours for placebo patients ($p<0.001$).

Reviewer’s comment: The patient- and physician-reported times to start of improvement for placebo patients differs substantially (16.9 versus 5.7 hours, respectively) for unclear reasons. The reliability of a patient-reported outcome versus physician scoring is difficult to assess, although overall the patient-reported time to start of improvement appears to correlate better with the primary efficacy endpoint, onset of symptom relief as assessed by the VAS.

Rescue medication use

Twenty patients total received rescue medication: 6 patients in the icatibant group and 14 in the placebo group. The most commonly administered rescue medication were opioids for pain relief. One patient (015-006) in the placebo group subsequently developed laryngeal symptoms and was treated with open-label icatibant as a rescue medication.

Reviewer's comment: Although not presented as a formal secondary endpoint, rescue medication use is reviewed here as a reflection of icatibant's efficacy in relieving symptoms of an acute HAE attack. On this basis, icatibant compares favorably to placebo. The Applicant has also provided additional subgroup analysis of the primary efficacy endpoint in terms of patients who were using attenuated androgens as a concomitant medication versus those who were not. Icatibant appears to be more efficacious in patients without androgen ($p=0.019$); plausibly, the concomitant use of androgens may blunt the treatment difference observed for icatibant. However, the numbers are small in these subgroups making analysis difficult.

10.3.2.3.3 Laryngeal attack analysis

Laryngeal attacks in 8 patients were treated with open-label icatibant in the controlled phase of the study. An additional 6 attacks in 11 patients were treated in the OLE phase of Study 2103. One patient (024-002) was treated for a laryngeal attack in both phases of the study. These results are discussed separately.

Laryngeal attack symptom scores – double blind phase

The median time to regression of symptoms as reported by the patients was 0.6 hours. Symptom scoring by both patients and investigators at 0, 2, and 4 hours after study drug administration is presented below. Patients were asked to score only 2 attributes of a laryngeal attack, voice changes and difficulties in swallowing.

Table 41 Study 2103: Laryngeal attack symptom scores as reported by patients (N=8 attacks in 8 patients)						
Severity	Voice change			Difficulties in swallowing		
	0h	2h	4h	0h	2h	4h
Very severe	1	-	-	1	-	-
Severe	-	-	-	-	-	-
Moderate	1	-	-	2	-	-
Mild	3	2	1	5	3	1
Absence	3	6	7	-	5	7
Not scored	-	-	-	-	-	-

Source: je049-2103-report-body.pdf, Section 11.4.3, Table 43, Page 128

Table 42 Study 2103: Laryngeal attack symptom scores as reported by the investigator															
Severity	Voice change			Dysphagia			Breathing difficulties			Stridor			Asphyxia		
	0h	2h	4h	0h	2h	4h	0h	2h	4h	0h	2h	4h	0h	2h	4h
Very severe	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Severe	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-

Moderate	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Mild	3	3	1	5	1	1	3	-	-	-	-	-	-	-	-
Absence	3	5	7	2	7	7	5	8	8	8	8	8	8	7	7
Not scored	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1

Source: je049-2103-report-body.pdf, Section 11.4.3, Table 43, Page 128

Reviewer's comment: The symptoms scores by investigators and patients appear to correspond for voice change and difficulties in swallowing/dysphagia, suggesting improvement for both symptoms over time. For the most part, even at baseline, the symptoms appeared to have been limited in severity. Whether the improvements observed over time are attributable to icatibant or reflect the gradual resolution of the attack cannot be ascertained in the absence of a placebo. The Applicant has not provided VAS scores for the laryngeal attack patients, although the protocol dated April 10, 2006 states that all study procedures described in Section 6.1 for the double-blind study participants would be followed.

Laryngeal attack symptom scores – Open-label extension

The time to regression of symptoms as reported by the patients was ranged from 0.3 to 1.4 hours. Symptom scoring by patients and investigators at 0, 2, and 4 hours after study drug administration is presented below.

Table 43 Study 2103 OLE: Laryngeal attack symptom scores as reported by patients (N=11 attacks in 6 patients)						
Severity	Voice change			Difficulties in swallowing		
	0h	2h	4h	0h	2h	4h
Very severe	1	-	-	2	1	-
Severe	4	2	-	4	2	1
Moderate	2	2	2	3	3	2
Mild	4	3	5	2	-	3
Absence	-	4	4	-	5	5
Not scored	-	-	-	-	-	-

Source: je049-2103-report-body.pdf, Section 11.4.3, Table 44, Page 129

Reviewer's comment: The results from the OLE phase in laryngeal attack patients appear relatively comparable to those collected during the controlled phase of Study 2103. Again, whether improvement is related to an effect of icatibant versus natural resolution of these symptoms is unclear.

10.3.2.3.4 Post hoc analyses

In Study 2103, the Applicant identified Study Site 070 (n=10; 5 assigned to icatibant) as an outlier. At this study site, patients receiving icatibant were noted to have a poorer response to icatibant (time to onset of symptom relief ≥ 10 hours) compared to other study sites. *Post hoc* analysis performed excluding this site resulted in a statistically significant treatment difference between icatibant and placebo (2.0 vs 6.0 hours; $p=0.026$). According to the Applicant's own audit of data, one patient from this site (007-008) was wrongly assigned skin pain as the primary symptom instead of skin swelling. A second patient who received icatibant for an abdominal

attack was later revealed during the audit to have narcotic drug addiction, violating inclusion/exclusion criteria. A third patient (015-007) at Study Site 015 was found to have a history of pancreatitis, which may have confounded the reporting of abdominal pain symptoms. *Post hoc* analysis performed excluding Patients 007-014 and 015-007 and reassignment of Patient 007-008 for the primary symptom resulted in a statistically significant treatment difference between icatibant and placebo (2.0 vs 5.0 hours; $p=0.049$). *Post hoc* analysis performed excluding Patients 007-014 and 015-007 results in a treatment difference 2.0 vs. 4.6 hours ($p=0.069$).

Reviewer's comment: While the protocol violations at Study Site 070 are noteworthy, there does not appear to be evidence of systematic bias at this study site to merit full exclusion of these site results. Given the small total sample size, post hoc exclusion of 10 patients from the efficacy database, including 3 patients with laryngeal edema attacks, is far from trivial. Also, as the unfavorable direction of the results prompted the data audit for this particular study site, the possibility of bias in this type of post hoc analysis remains an issue. From the perspective of the clinical review, these post hoc analyses are considered supportive of efficacy but are not considered as a substitute for the pre-specified analyses based on the ITT population.

Additional *post hoc* analysis performed by the statistical reviewer stratifying the results of Study 2103 by US versus non-US locations indicates that efficacy results were fairly comparable, without any clear geographic differences. Further details regarding *post-hoc* analysis can be found in the statistical team's review. The median time to onset of symptom relief for icatibant recipients at US and non-US locations was 2.25 and 2.5 hours respectively. In the placebo arm, the times were 7.0 and 3.6 hours, respectively.

Table 44 Study 2103: Time to onset of symptom relief, US vs. non-US sites, post hoc analysis				
	US subgroup		Non-US subgroup	
	Icatibant (n=16)	Placebo (n=14)	Icatibant (n=11)	Placebo (n=15)
Responder	15	13	11	14
Censored	1	1	0	0
Median (hr)	2.25	7.0	2.5	3.6
Wilcoxon test, p-value	0.129		0.550	
Logrank test, p-value	0.331		0.774	

10.3.2.4 Safety assessments

10.3.2.4.1 Adverse events

Serious adverse events

No deaths were reported from Study 2103. No SAEs were reported during the controlled phase of the study. In the OLE, 4 SAEs for 3 patients (3 of 42 patients, 7.1%) were reported. Patient 015-007, who had a prior history of pancreatitis, experienced 2 episodes of severe pancreatitis at 11 and 14 days after the start of the OLE. Patient 007-008 had a worsening, severe HAE attack (the patient's 7th attack) despite 3 sequential 30 mg doses of icatibant. Patient 018-002 developed severe chest pain and abdominal and cutaneous HAE attack symptoms 7 days after

receipt of icatibant for a second HAE attack. The patient had a negative evaluation for cardiac causes of chest pain and was discharged later that evening.

Discontinuations from the study due to adverse events

No patients discontinued from the study due to adverse events.

Common adverse events

Injection site reactions were the most common adverse event and were assessed separately from other AEs in the Applicant's study report. HAE attacks were only to be reported as an AE if there was a worsening of symptoms during a treated attack. New HAE attacks were not to be reported as AEs, but the study report states that some investigators reported new attacks as AEs, leading to an over-reporting of HAE attack as an AE.

- *Double-blind phase*

The most common AE were local injection site reactions, reported by 26 patients (96.3%) in the icatibant treatment group and 8 patients (27.6%) in the placebo group. These reactions were characterized most commonly by erythema (96.3%) and swelling (85.2%), following by burning, itching, warmth, and cutaneous pain. The median duration of the reaction was 3.5 hours, with erythema as the principal persistent symptoms for that duration.

Eleven patients (40.7%) in the icatibant group reported an adverse event besides a local injection site reaction, compared to 18 (62.1%) in the placebo group. The most common AE aside from local site reaction was HAE attack, reported by 3 patients (11.1%) in the icatibant group and 5 patients (17.2%) in the placebo group. A table of AEs occurring more commonly in the icatibant group than placebo is presented below.

Table 45 Study 2103: Adverse events in the double-blind phase occurring more commonly in the icatibant treatment group compared to placebo

Adverse event	Icatibant (N=27)	Placebo (N=29)
Local injection site reaction	26 (96.3%)	8 (27.6%)
Nasal congestion	2 (7.4%)	0
Abdominal pain	1 (3.7%)	0
AST increased	1 (3.7%)	0
Bilirubin increased	1 (3.7%)	0
CPK increased	1 (3.7%)	0
Contusion	1 (3.7%)	0
Erythema	1 (3.7%)	0
Hand dermatitis	1 (3.7%)	0
Herpes simplex	1 (3.7%)	0
LFT abnormality	1 (3.7%)	0
Nasopharyngitis	1 (3.7%)	0
Pyrexia	1 (3.7%)	0
Rash	1 (3.7%)	0
Throat irritation	1 (3.7%)	0
Vocal cord disorder	1 (3.7%)	0

Source: je049-2103-report-body.pdf, Section 12.2.2.1 and Section 16, Table 6.17.1.1, Page 1970

- *Laryngeal attack patients*
Injection site reactions were reported by all 8 subjects who received open-label icatibant. The type of reaction and duration were similar to those reactions reported for abdominal and cutaneous attack patients. Other AEs reported in this group included HAE attacks (n=3), headache (n=2), viral infection (n=1), thermal burn (n=1), epistaxis (n=1), dermal cyst (n=1), and urticaria (n=1).
- *OLE phase*
One-hundred-four AEs other than injection site reactions were reported in 39 patients (out of 42 total) during the OLE phase of the study. Injection site reactions were reported in 41 of 42 (97.6%) patients who received open-label icatibant during the OLE of Study 2103. Other common AEs occurring in $\geq 3\%$ of patients included the following: HAE attacks (n=12, 28.6%), headache (n=11, 26.2%), upper respiratory tract infection (n=5, 11.9%), abdominal pain (n=2, 4.8%), chest pain (n=3, 7.1%), nasopharyngitis (n=4, 9.5%), and sinusitis (n=2, 4.8%). Four SAEs described above were also reported during the OLE phase.

Reviewer's comment: Adverse event findings are relatively consistent among the different phases of Study 2103. Local injection site reactions are nearly ubiquitous. Other common AEs are HAE attack and headache. Whether HAE attack is a true AE or a reflection of the underlying disease is unclear, although the frequency of this AE was higher in the placebo group than in the icatibant treatment group, suggesting the latter explanation. In terms of attack site locations – cutaneous, abdominal, and laryngeal – there did not appear to be any differences in the nature or frequency of AEs among these patient subgroups.

10.3.2.4.2 Vital signs

No consistent or lasting vital sign changes were noted over the course of visits in the double-blind portion of the study, laryngeal attack patients, or during the OLE phase.

10.3.2.4.3 Physical exams

Aside from local injection site reactions, physical exam findings were consistent the abdominal, cutaneous, and laryngeal manifestations of HAE attacks.

10.3.2.4.4 Laboratory parameters

Hematology

Drops in hematocrit and total white counts were observed in both icatibant and placebo patients from baseline to time of attack, which appeared to resolve by the 24 hour time-point.

Reviewer's comment: As the change in hematocrit and WBC count was observed in both treatment groups and rapidly resolved, the change most likely represent changes in fluid volume status during an acute HAE attack, rather than destruction or decreased production of blood cells.

Clinical chemistry

No persistent derangements in blood chemistry parameters were reported for the icatibant treatment group versus placebo. In terms of outliers, 1 patient (017-002) was noted to have an

elevation in LFTs (ALT 77 → 164 U/L, AST 50 → 80 U/L, and GGT 60 → 77 U/L) after study drug administration that resolved spontaneously by 30 days.

During the OLE phase, one patient (040-003) had a similar transient increase in AST from 52 → 136 U/L. This patient was also reported to have a transient increase in total bilirubin from 8.55 to 82.08 µmol/L, and a more persistent increase in serum CK levels (175 → 309 U/L). Two weeks after treatment, the CK level was 278 U/L and further follow-up is not provided.

Antigenicity

The study report states that an assay for detection of icatibant antibodies remains under development at the time of the study report and data will be reported separately when available.

ECGs

No consistent derangements in ECGs were noted for patients. Two patients in the icatibant group were noted to have abnormal ECGs at baseline, including a left bundle branch block and Wolff-Parkinson-White Type A abnormality. No QT prolongation was reported in any of the patients.

10.3.3 Study summary and conclusions

Study 2103 provides limited support for the efficacy of icatibant in the treatment of acute attacks of HAE. While numerically favorable, the study did not show a statistically significant difference between icatibant and placebo for the primary efficacy endpoint, time to onset of symptom relief as measured by the VAS. Similarly, the secondary efficacy results were generally numerically favorable for icatibant but were far from robust. Of particular concern was the durability of response, which appeared to be limited for both abdominal and cutaneous HAE attacks. Additional study of dose or dosing interval may address this issue.

In terms of laryngeal attacks, the study results are favorable, but the selection of unvalidated subjective endpoints combined with the small sample size make efficacy for this particular type of HAE attack difficult to assess. As these patients were treated with open-label icatibant, no placebo comparison is available.

In terms of safety, the safety profile for icatibant in limited repeat dosing appears acceptable based on the information provided. The most common adverse event that is clearly attributable to the drug is local injection site reaction, which appears to be relatively mild and self-limited in the majority of cases. Several cases of mild transient transaminitis raise hepatotoxicity as a possibility, but the small number of patients assessed in the study does not permit a more thorough evaluation. In consideration of the proposed indication and the intended manner of use, the nature of hepatic enzyme elevations observed to date is not particularly concerning. Of note, safety information on the antigenicity of the drug has not been provided.

10.4 Individual Study Report: Study 4102

10.4.1 Study protocol: Study 4102

Title: Study to estimate the minimum clinically significant difference (MCSD) in Visual Analogue Scale (VAS) scores for skin swelling, skin pain, and abdominal pain in subjects with hereditary angioedema (HAE)

10.4.1.1 Study administrative information

- Study dates: June 19, 2006 to March 24, 2007
- Study site: Multicenter (20 international study sites)
- Study report date: May 31, 2007

10.4.1.2 Objectives/rationale

- To estimate the MCSD in VAS scores as the basis for defining “onset of symptom relief” for cutaneous and abdominal HAE attacks of at least moderate severity.

Reviewer’s comment: The “time to onset of symptom relief” is the primary efficacy endpoint for the two pivotal Phase 3 trials, Studies 2101 and 2103.

10.4.1.3 Design overview

Non-interventional, observational study to validate the patient-reported outcome tool, the Visual Analogue Scale (VAS), used in the Phase 3 program for icatibant.

10.4.1.4 Study population

80 adult subjects with HAE, presenting with an acute abdominal and/or cutaneous HAE attack of at least moderate severity

Inclusion criteria

- Age of 18 years or older
- Documented diagnosis of HAE Type I or II (confirmed by medical history and C1-INH deficiency/<50% functional level). Subjects with higher C1-INH levels permitted to enroll if HAE clearly confirmed clinically and an acceptable rationale provided for the higher functional level of C1-INH.
- History of angioedema attacks involving the skin or abdominal areas

Exclusion criteria

- Other form of angioedema, such as acquired angioedema
- Participation in Studies 2102 or 2103 if the current attack is treated with an investigational drug product

10.4.1.5 Study treatments

No study treatments were administered. Standard of care (danazol, C1-INH, fresh frozen plasma, tranexamic acid, or other investigational medications except icatibant) was selected by the primary care physician and documented in the CRF.

10.4.1.6 Study procedures

Study 4102 was a non-interventional, observational study. Patients meeting screening criteria were instructed to come to the clinic or contact by telephones in the event of a cutaneous and/or abdominal HAE attack. Attacks involving only laryngeal edema were excluded. At least one symptom had to be rated as moderate severity in order to qualify for the study. Patients were instructed on the various assessments and asked to complete the following in the patient diaries until complete resolution of symptoms or 48 hours from baseline, whichever occurred first:

- Visual Analogue Scale (VAS) of skin swelling, skin pain, abdominal pain, and nausea
- Verbal Descriptor Scale (VDS) for skin swelling, skin pain, and abdominal pain
- Patient Symptom Score (PSS) for skin swelling, erythema, irritation, skin pain, abdominal pain, nausea, vomiting, diarrhea
- Physicians completed a Global Assessment, Clinical Global Impression, and Physician Symptom score.

Based on the severity of the attack, patients were managed in the clinic or were followed by telephone contact, completing the diaries at home. Diaries were filled out at Baseline (0 h), 1, 2, 4, 6, 8, 10, 12, 14, 18, 24, 36, and 48 hours post-baseline.

All concomitant medications were recorded in the CRF.

10.4.1.7 Efficacy parameters

10.4.1.7.1 Primary efficacy variables

- VAS of skin swelling, skin pain, and abdominal pain
 - The VAS is a 100 mm horizontal line with 0mm = no symptoms and 100mm = 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 MCSD was defined as a change in VAS corresponding to subject report of “a little less” symptom according to the VDS, used as the basis for defining the “onset of symptom relief” for skin swelling, skin pain, and/or abdominal pain
 - For cutaneous attack patients, the MCSD analysis was based on the most severe symptoms; if both equally severe, “pain” used.
- VDS for skin swelling, skin pain, and abdominal pain
 - Change from baseline rated as “much less,” “a little less,” “the same,” “a little more,” or “much more”

10.4.1.7.2 Secondary efficacy variables

- Severity of symptoms (scored by physician). Physician scores the following on a 5-point scale, with 0=absence of symptoms and 4=very severe: cutaneous swelling, erythema, cutaneous pain, abdominal pain, nausea, abdominal tenderness, vomiting, and diarrhea.
- Clinical Global Impression. Physician rates patient’s overall presentation relative to other HAE patients in the physician’s experience on an 8-point scale, with 0=not assessed, 1=normal, to 7=among the most extremely ill patients.

- Global Assessment (physician). Physician scores the following 3 symptom categories – “cutaneous,” “abdominal,” and “laryngeal” – on 5-point scale, with 0=absence of symptoms and 4=very severe.
- VAS for nausea (subject)
- PSS for skin swelling, erythema, irritation, skin pain, abdominal pain, nausea, vomiting, diarrhea. Each symptom scored on a scale from 0 to 4, with 0=absence of symptoms and 4=very severe. For vomiting and diarrhea, patients were instructed to assess symptoms over the last 2 hours.

10.4.1.8 Safety parameters

As a non-interventional, observational study, no formal safety evaluations were planned. Patients were treated according to standard of care at the discretion of the physician. Adverse events were recorded in the CRF.

10.4.1.9 Statistical plan

The intended purpose of the study was to identify the change in VAS score that corresponded most closely to a VDS measurement, taken as the “gold standard,” that indicates that a patient has had a clinically meaningful symptom improvement (“a little less”). Receiver Operating Characteristics Curve (ROC) analysis was used to identify an optimum cut-point for the VAS change from baseline that corresponded with the VDS. A sample size of 60 evaluable patients was calculated to provide 80% power to detect a correlation of 0.36 between the VDS (ordinal variable) and the change in VAS from baseline.

Reviewer’s comment: The Applicant does not explain why the VDS should be taken as the “gold standard.” From the description provided, the VDS is another PRO without any validation.

10.4.2 Results

10.4.2.1 Protocol amendments

No formal amendments were made to the original protocol. A change was made on the study population in the statistical analysis plan (March 27, 2007) that utilized a computer algorithm to identify patients with usable symptom data. Patients who did not report any improvement from baseline on the VDS and patients with obvious discordance between the trend in VAS, PSS, and VDS were excluded.

Reviewer’s comment: The issue of unusable data as defined by the Applicant illustrates potential pitfalls with the VAS as an efficacy endpoint. The Applicant does not explain how these weaknesses might limit interpretation of VAS data or how they might be addressed in practice to maximize the collection of usable data.

10.4.2.2 Protocol deviations

Patient 120-012 was identified as a protocol violation for failure to contact the investigator prior to diary completion.

10.4.2.3 Datasets analyzed

The outcome analyses are based on the evaluable patient population, defined by a diary review algorithm in the statistical analysis plan dated March 27, 2007 and briefly described in Section 10.4.2.1 of this review.

10.4.2.4 Study patients

10.4.2.4.1 Patient disposition

An initial 149 patients were enrolled. During the study period, 81 patients experienced a qualifying HAE attack and 80 patients completed the study. Of these 80 patients, 57 patients had diary data which was deemed usable based on the diary review algorithm described in Section 10.4.2.1 of this review.

Table 46 Study 4102: Patient disposition	
Screened and enrolled	149
Completed study	80
Evaluable patient population	57
Reasons for exclusion	
<i>No improvement in symptoms</i>	8
<i>Discordance between VDS and VAS (i.e. improvement on VDS but ≥ 20mm worse on VAS)</i>	7
<i>All VAS scores <10mm at baseline</i>	4
<i>Diaries returned after database lock</i>	2
<i>No VAS or VDS recorded for 6-hour timepoint</i>	2

Source: je049-4102-report-body.pdf, Section 4.1, Table 3, P 27

10.4.2.4.2 Demographics and baseline characteristics

Of 57 evaluable patients, 43 (75.44%) were female, 54 (94.74%) were White and 3 (5.26%) were Asian. The mean age was 41.61 years (range 18.63 to 75.68 years). Four patients were categorized as having Type II HAE; the remainder was categorized as Type I HAE. As a group, the study cohort averaged 10 HAE attacks within the past 6 months, ranging from 0 to 51 attacks.

10.4.2.4.3 Concomitant therapies

Patients received a variety of therapies during the course of the study for treatment of HAE. The most common therapies administered included danazol, C1-INH replacement, aminocaproic acid, and antiemetics.

10.4.2.5 Efficacy endpoint outcomes

10.4.2.5.1 Primary endpoint analysis

Based on ROC analysis, a 9 mm change in VAS was identified as the MCSd for “onset of symptom relief.” This cut-point provided 88.24% specificity and 82.61% sensitivity at 6 hours post baseline. Changes in the VAS corresponded to changes in the VDS ($r=0.7576$; $p<0.0001$).

10.4.2.5.2 Secondary endpoints analyses

The Applicant has not provided analyses for the other symptom scores collected in the study.

10.4.2.6 Safety assessments

No formal safety assessments were performed.

10.4.3 Study summary and conclusions

Study 4102 provides limited support for the use of the VAS to determine onset of symptom relief. Although the study demonstrates strong correlation between the VAS and VDS, the value of this correlation is uncertain as the VDS is another type of PRO which has not been validated, even though the Applicant proposes the VDS as the “gold standard.” Furthermore, the study did not include any patient interviews to substantiate the terms used in the VAS or VDS, nor did it provide illustrative examples for patients filling out patient diaries. For example, the concept of “a little less” symptom may vary widely among individuals with HAE. In addition, the Applicant has not reconciled the discordance in VAS and VDS observed in several study participants’ diaries (n=7 out of 80 patients who completed the study). Whether the discordance reflects a lack of comprehension on the part of the patient or error in data collection is uncertain. In either circumstance, the observed discordance with the proposed gold standard is problematic and reflects a potential flaw with the VAS instrument.

10.5 Line-by-Line Labeling Review

As the recommended action is Not Approvable, a detailed line-by-line labeling review was not performed. Major issues identified with the proposed labeling are discussed in Section 9.4, Labeling Review.

11 REFERENCES

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/s/

Susan L Limb
2/29/2008 04:43:58 PM
MEDICAL OFFICER

Sally Seymour
2/29/2008 07:04:33 PM
MEDICAL OFFICER
I concur. See my CDTL memo.

MEDICAL OFFICER REVIEW Division Of Pulmonary and Allergy Drug Products (HFD-570)			
APPLICATION:	NDA 22-150	TRADE NAME:	Firazyr
APPLICANT/APPLICANT:	Jerini AG	USAN NAME:	Icatibant
MEDICAL OFFICER:	Susan Limb, MD		
ACTING TEAM LEADER:	Sally Seymour, MD	CATEGORY:	Bradykinin receptor antagonist
DATE:	December 18, 2007	ROUTE:	Subcutaneous injection
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
July 30, 2006	July 31, 2006	NDA 22-150	NDA electronic submission
RELATED APPLICATIONS			
<u>Document Date</u>	<u>Application Type</u>	<u>Comments</u>	
<u>REVIEW SUMMARY:</u> This is a 45-day filing and planning review of an NDA for icatibant, a selective competitive antagonist at the bradykinin type 2 (B2) receptor. The Applicant, Jerini AG, has developed icatibant 30 mg subcutaneous injection for acute, intermittent use. The proposed indication is the treatment of hereditary angioedema (HAE). Two pivotal efficacy and safety studies are submitted in support of this application (JE049 2102 and 2103). The Applicant has provided additional data from several uncontrolled studies, including an open-label Phase 2 study of intravenously and subcutaneously administered icatibant in HAE patients (Study 2101) and pharmacokinetic studies in healthy volunteers (Studies 1101, 1102, and 1103). Safety information on repeated, long-term use is presented from the ongoing open-label extension studies for Studies 2102 and 2103 (2102-B and 2103-B, respectively). The Applicant has also provided results of a non-interventional study, 4102, to demonstrate the validity of the patient-completed Visual Analogue Scale (VAS), which was used as the primary efficacy parameter in the Phase 3 studies. These study reports are appropriately indexed and organized to allow review. The Applicant has provided an Integrated Summary of Efficacy, Integrated Summary of Safety, Integrated Summary of Benefits and Risks, copies of proposed labeling, and appropriate case report forms. The submission is adequate to allow clinical review. The submission is fileable. <u>OUTSTANDING ISSUES:</u> None.			
RECOMMENDED REGULATORY ACTION			
NDA/SUPPLEMENTS:	X FILEABLE	NOT FILEABLE	

1. GENERAL INFORMATION AND BACKGROUND

Icatibant is a bradykinin type-2 receptor antagonist under development for treatment of acute attacks of hereditary angioedema (HAE). It was previously developed by Aventis AG under IND (b) (4) for treatment of allergic rhinitis, asthma, and post-operative pain. IND (b) (4) was subsequently withdrawn on August 9, 1996 (not for safety reason per communication dated August 28, 1996). Jerini subsequently acquired the drug product and right of reference to IND (b) (4) opening IND 68,214 (April 8, 2004) for further evaluation of icatibant as a treatment for HAE. (b) (4)

The proposed dose for acute attacks of HAE is 30 mg icatibant administered subcutaneously.

The text from the proposed INDICATIONS AND USAGE section of the label follows: (b) (4)

The 505(b)(1) application is an electronic submission.

2. CLINICAL DEVELOPMENT PROGRAM

The Applicant's clinical development program relies on two pivotal Phase 3 studies, one performed in Europe (Study 2102; FAST-2) and one conducted in the US (Study 2103; FAST-3). Of note, only Study 2103 was placebo-controlled; Study 2101 used tranexamic acid as an active-control. Both studies used the same efficacy endpoint, time to onset of symptom relief. These studies are presented in further detail below. In addition to these Phase 3 studies, the Applicant has submitted study reports for pharmacokinetic studies in healthy volunteers, an open-label proof-of-concept study in HAE patients, and a PRO validation, non-intervention study.

The table below outlines key clinical pharmacology studies and the two Phase 3 trials in the clinical development program:

Summary of Clinical Development Program for Icatibant				
Study	Design	N	Dose	Endpoint
Phase 1 studies				
1101	SD, safety and tolerability	Healthy subjects	• IV	•
1102	SD, safety and tolerability	16 healthy subjects	• 0, 0.5, 0.2, 0.4 mg/kg SC vs IV	• PK
Efficacy studies				
2101	Open-label, Phase 2 study	8 adult HAE patients	• 30 mg SC icatibant • 45 mg SC icatibant	• PK • Symptom score
2102 (FAST-2)	MC, R, DB, active-control trial with OLE	72 adult HAE patients with cutaneous or abdominal HAE sx Additional subjects with laryngeal sx	• 30 mg SC icatibant • Tranexamic acid (3 x 1 g for 2 days)	• time to onset of symptom relief (VAS)
2103 (FAST-1)	MC, R, DB, PC with OLE	56 adult patients with cutaneous or abdominal HAE sx Additional subjects with laryngeal sx	• 30 SC mg icatibant • Placebo	• time to onset of symptom relief (VAS)
Additional clinical studies				
1103	R, DB, PC, QTc study	32 healthy subjects (18-40 and >65 yrs)	• 30 mg SC icatibant (5 doses on Day 1, QD on Day 8 and 15) • Placebo	• Age subgroup PK • QTc interval
4102	Observational PRO validation study	60 adult HAE subjects	• No intervention	• Correlation of VDS to VAS to calculate MCS

3. FOREIGN MARKETING AND REGULATORY HISTORY

Icatibant has not yet been approved for marketing for any indication [2.5.5.13].

The opening IND (April 8, 2004) was initially reviewed in the Division of Gastrointestinal and Coagulation Drug Products prior to reassignment to the Division of Pulmonary and Allergy Products in September 2005. A timeline of regulatory proceedings is included below:

July 31, 2003	Request for Orphan Drug Designation
November 25, 2003	Orphan Drug Designation #03-1762 granted
February 6, 2004	Pre-IND meeting: Discussion focused on selection and validation of symptom-based endpoints, including justification of the minimum important difference. The Applicant was also reminded that two adequate, well-controlled studies were the usual requirement for a new indication. The ongoing, open-label, proof-of-concept study, #2101, being conducted at that time in Europe was unlikely to meet this requirement. Other issues discussed included eligibility for Fast Track Designation and Priority Review.
April 8, 2004	Opening IND: The proposed study was a multi-center, double-blind, placebo-controlled trial in 56 adult subjects with moderate to severe cutaneous or abdominal symptoms of HAE. The primary efficacy endpoint was time to onset of symptom relief assessed by a Visual Analogue Scale (VAS) completed by patients; symptom score and global assessment score were secondary efficacy outcomes.

	Patients with laryngeal symptoms were enrolled in an open-label arm of the study and their outcomes were to be reported descriptively. Comments communicated to the Applicant following review were to include adequate dose-ranging studies in the clinical development program, as well as validating the VAS instrument and justifying a time to onset of symptom relief that is clinically meaningful.
June 11, 2004	Request for SPA (SN 004); Protocol JE049 #2103 (SN 005): The Applicant amended the opening IND protocol and requested a SPA. The main changes were addition of an open-label extension phase, assessment of laryngeal symptoms using a 5-point symptom score, and new pharmacoeconomic and safety secondary endpoints. In a response dated July 29, 2004, the Division confirmed that the proposed endpoints and sample size were acceptable, with the caveat that onset of symptom relief should be clinically meaningful. The Division also advised that safety data should be recorded in detail from the extension phase of the study.
June 15, 2004	Fast Track Designation granted
July 1, 2004	EOP2 CMC meeting
March 1, 2005	Pre-NDA meeting with Div. of GI and Coagulation Drug Products Major clinical issues raised: • QTc data should be collected in the proposed PK study JE049 #1103 with additional time points at or near C_{max} • Data obtained from the open-label, Phase 2 study JE049 #2101 did not fully support the 30 mg SC dose used in the Phase 3 pivotal trials • Pediatric use to be assessed in post-marketing phase
September 2005	Reassignment of IND to Division of Pulmonary and Allergy
September 8, 2005	Protocol JE049 #4102 (PRO endpoint validation protocol) submitted (SN 0013) The study was intended to estimate the Minimum Clinically Significant Difference (MCSD) in VAS scores. Patients were asked to score their symptom response using the Verbal Descriptor Scale (VDS), classifying their symptom as “much more,” “a little more,” “about the same,” “a little less,” or “much less” compared to baseline. The MCSD was defined as the VAS change most predictive of the VDS categories of “a little less” and “a little more” for each symptoms. The MO review dated January 26, 2006, and SEALD consult cited several concerns with the protocol: • The VDS required more rigorous definition. Incorporation of a temporal element in the VDS makes this measure less reliable. • The patient population in the validation study was not representative of the patients participating in the phase 3 study. • Patient diaries used in Phase 3 studies should be included in the validation protocol.

	• Potential labeling limitations for claims supported solely by the VAS
February 9, 2006	Response to Division/SEALD review regarding validation study (SN 015). Reference to other clinical studies that have used a Verbal Descriptor Scale to determine the MCSD in VAS scores.
June 1, 2006	SEALD review of February 9, 2006 response. Patient diaries and planned subject enrollment deemed acceptable. Concerns raised regarding that the VAS is not a comprehensive measure of HAE symptoms and does not correlate clearly with the proposed indication.
June 20, 2006	SAP for Study #2103 (FAST-1) submitted via email The Statistical review team asked the Applicant to provide the assumed MCSD used to calculate the sample size of N=56 with a 1:1 randomization to icatibant or placebo. The review team also recommended that the Applicant prespecify alternative analyses to be used if the proportional hazards assumption was not supported by the observed data.
October 10, 2006	Revised SAP submitted (SN 0026)
October 13, 2006	Proposed trade name application submitted (SN 0027)
January 24, 2007	Pre-NDA meeting. The discussion included several key topics: • Nonclinical study requirements, including chronic repeat dose toxicity studies of 6 and 9-month duration, and carcinogenicity studies • Separation of Phase 1 and 2 data in the Integrated Summary of Safety • Validation of the VAS used in the Phase 3 studies • Preliminary assessment of Phase 3 efficacy data in support of an NDA submission • Limitations of self-administration usage data

4. ITEMS REQUIRED FOR FILING AND REVIEWER COMMENTS (21 CFR 314.50)

The following items were included in this submission:

- Form FDA 356h [1.1.2]
- Debarment certification [1.3.3]
- Financial disclosure statement [1.3.4]
- Statements of Good Clinical Practice [2.5.1.4]
- Integrated Summary of Effectiveness (ISE) [2.7.3]
 - Overview of clinical studies [2.7.3.1]
 - Definition of ISE analysis populations [2.7.3.3.1]
 - Design of controlled clinical studies [2.5.4.2]
 - Statistical methodology [2.7.3.3.2]
 - Patient enrollment, Study 2102 and 2103 [Item 8.11, Vol 122, P 28]
 - Study results [2.7.3.3]
 - Evidence for an effective dosing regimen [2.7.3.4]
 - Conclusions [2.7.3.4]

- Integrated Summary of Safety (ISS) [2.7.4]:
 - Overview of clinical studies [2.7.4.1.1]
 - Definitions of ISS analysis populations [2.7.4.1.3]
 - Methodology for evaluation of safety [2.7.4.1.1, 5.3.5.3]
 - Phase 3 integrated safety analysis [Not included]
 - Phase I final formulations studies and phase I exploratory formulations [Not included]
 - Adverse events including laboratory abnormalities, from sources other than clinical studies [Not applicable]
 - Animal data [2.5.5.3]
 - Analysis of adverse effect dose-response information []
 - Drug-drug interactions [2.7.4.5.3]
 - Drug-demographic and drug-disease interactions [2.7.4.5.1]
 - Pharmacologic properties other than the property of interest []
 - Overdose [2.7.4.5.5]
 - Drug abuse [2.7.4.5.6]
 - Long-term adverse events [2.5.5.9]
 - Withdrawal effects [2.7.4.5.7]
 - Post-marketing data [2.7.4.5.6]
 - Review of the literature for safety information relevant to icatibant [Not included]
- Proposed labeling and annotated labeling [1.14].
- Integrated summary of benefits and risks [2.5.6]
- Case report tabulations [] and forms for patients with serious adverse events or discontinuing studies [5.3.5.1]
- Environmental assessment [1.12.14]
- Pediatric assessment/plan [1.2]
- Pharmacokinetic studies in special populations (geriatric, pediatric, gender, race, body size, renal impairment, hepatic impairment) [2.7.2.2.4]

Reviewer's comment: Despite previous discussion at the pre-NDA meeting (January 24, 2007, Pre-NDA Meeting Minutes), the Applicant has submitted an Integrated Summary of Safety based on data pooled from Phase 1, 2, and 3 studies, combining data from both healthy volunteers and HAE patients. An Information Request was sent to the Applicant on December 7, 2007.

5. CLINICAL STUDIES

The submission refers to seven clinical studies: two Phase 1 studies in healthy volunteers (1101 and 1102), one Phase 2 pharmacokinetic study to assess the effects of age and gender (1103), one Phase 2 open-label study in HAE patients (2101), two Phase 3 efficacy and safety studies in HAE patients (2102 and 2103), and a non-interventional validation study of the PRO instrument used in the Phase 3 studies (4102).

The clinical review of efficacy and safety of the proposed product will focus on the two Phase 3 trials and the open-label extensions of these studies. The Phase 2 open-label study in HAE patients and the validation study will be reviewed for additional efficacy

support. Data from healthy volunteers will also be reviewed, primarily for assessment of safety, with particular focus on Study 1103 which included serial ECG monitoring. The study reports and synopses are appropriately indexed to allow review. A brief overview of the two Phase 3 trials is provided below.

Reviewer's comment: In prior discussion (February 6, 2007, Teleconference Minutes), the Division informed the Applicant that Study 1103 did not meet the requirements of a thorough QT study. Preliminary review of the data at that time suggested that icatibant did prolong the QT interval. As a result, a thorough QT study was not warranted unless the Applicant chose to refute the Division's assessment.

Study 2102 (FAST-2)

- Dates: March 1, 2005 to July 25, 2006, multicenter European study
- Design
 - Double-blind, double-dummy, randomized, active controlled Phase 3 study in patients with acute attacks of HAE
 - Open label treatment with icatibant for patients presenting with laryngeal edema
 - Open-label extension phase for all patients
- Objective: Assess the efficacy of a single treatment of icatibant compared with oral tranexamic acid on the onset of relief of symptoms during moderate to very severe acute cutaneous and/or abdominal HAE attacks
- Treatments (double-dummy design; no placebo arm)
 - Icatibant 30 mg SC injection
 - Tranexamic acid 1000 mg (2 x 500 mg tablet) every 6- 8 hours for a total of 4 doses (blinded with over-encapsulating)
 - Placebo SC injection solution
 - Placebo oral tablet
- Patients
 - Documented Type I or Type II HAE (medical history and/or functional C1-INH <50% normal)
 - 18 years of age and older
 - N=74 (36 in icatibant treatment group; 38 in tranexamic acid group)

Reviewer's comment: Although both functional C1-INH and C4 levels were collected, the inclusion criteria were based only on the C1-INH level. C1q levels were not obtained. Although a diagnosis of acquired angioedema (AAE) is an exclusion criterion, it is possible that patients with AAE who have previously been presumed to have HAE may have been enrolled in this study.

- Study conduct
 - Initial screening for eligibility and randomization
 - Double-blind treatment phase
 - Patient presentation with moderate-to-severe cutaneous and/or abdominal edema no later than 6 hours after the time the

- current attack became moderate in severity (Visual Analogue Scale ≥ 30 mm)
 - Hospitalization for a minimum of 12 hours during acute attack, with follow-up on Day 2 and Day 14
 - VAS scoring Q30min for 1 to 4 hours after initial injection, then 5, 6, 8, 10, and 12 hours post-dose
 - If no symptom relief by 12 hours post-dose, hospitalization extended for an addition 3 hours with additional symptoma assessment at 14 hours after injection
 - Rescue medications to be avoided if possible, otherwise documented in the CRF
- Open label treatment with icatibant 30 mg SC for laryngeal edema attack
- Open-label extension phase (OLE)
 - After completion of Visit 4 (Day 14) follow-up of initial attack, patients enrolled in OLE
 - Any attack severe enough to warrant treatment can qualify for treatment with icatibant 30 mg SC
 - Hospitalization for 5 hours, with follow-up on Day 2 and Day 14 and long term follow-up by telephone every 4 months and clinic visit every 6 months
 - Repeated dosing
 - If attack worsens within 48 hours of initial treatment, additional injections permitted
 - Maximum of 3 injections per attack at least 6 hours apart
 - Duration: 1 year after closure of double-blind phase
- Efficacy variables
 - Primary: Time to onset of symptom relief (cutaneous swelling, skin pain, abdominal pain, and nausea) by patient assessed Visual Analogue Scale (VAS, 10 cm line)
 - If pre-dose VAS ≥ 30 mm, absolute reduction from pre-treatment VAS of ≥ 20 mm
 - If pre-dose VAS > 50 mm, absolute reduction from pre-treatment VAS of ≥ 30 mm
 - Laryngeal edema
 - Symptom score (0-4, none to very severe) of dysphagia, voice
 - Investigator to score abdominal tenderness, breathing difficulties, stridor, and asphyxia in addition
 - Secondary
 - Response rate at 4 hours
 - Time to relief of each symptom present in pre-dose VAS other than the primary symptoms
 - Time to almost complete symptom relief (0-10 mm on VAS)
 - Investigator Global Assessment

- Symptom Score by investigator and subject
- Results
 - Patient disposition
 - 74 patient randomized (n=36 icatibant; n=38 tranexamic acid) plus 3 patients with laryngeal edema treated with open-label icatibant
 - 47 patients treated for cutaneous attacks
 - 27 patients treated for abdominal attacks
 - 35 patients (122 attacks total) treated in OLE
 - Laryngeal attacks
 - 3 patients in initial open-label treatment
 - 4 patients (8 attacks) in OLE)
 - Efficacy results

Study 2102: Median time to onset of symptom relief (h)			
	Icatibant (n=36)	Tranexamic acid (N=38)	P
All attacks (n=74)	2.0	12.0	<0.001
Cutaneous (n=47)	2.5	18.2	<0.001
Abdominal (n=27)	1.6	3.5	0.026
Males, all attacks (n=27)	3.5	14.0	0.013
Females, all attacks (n=47)	1.6	10.0	<0.001

For laryngeal edema patients (n=3), the median time to regression of symptoms was 1.0 hours.

- Safety
 - N=35 (97.5%) had injection site reactions (erythema, swelling, warmth, burning, cutaneous pain, and itching) lasting ~ 3.5 hours
 - HAE attacks
 - Nasopharyngitis, upper and urinary tract infections also reported more commonly in the icatibant treatment group
 - 1 death reported (sudden cardiac death attributed to aortic valve sclerosis; 41 days after receipt of TA)

Reviewer's comment: Blinding of study treatments was incomplete, as is acknowledged by the Applicant. Subcutaneous injection of icatibant is associated with a high rate of local injection site reactions, presumably secondary to a pH buffer that is not included in the placebo injection. Oral tranexamic acid is known to cause nausea, vomiting, and diarrhea, in addition to a distinctive adverse effect of color vision disturbances. Since the primary and secondary endpoints are subjective, self-reported outcomes, the blinding issue is more prominent. Aside from the blinding issue, the lack of a separate placebo arm is another review issue. Tranexamic acid is not approved for HAE in the US, and data to support its efficacy for this indication has not been formally evaluated. As a result, any observed benefit of icatibant over tranexamic acid may be due to tranexamic acid worsening the patient's condition, rather than improvement attributable to icatibant, i.e. tranexamic acid may be worse than placebo.

Study 2103 (FAST-1)

- Dates: December 28, 2004 to July 17, 2007 (OLE ongoing)
- Design
 - Randomized, double-blind, placebo-controlled study
 - Open-label study for laryngeal edema attacks
 - Open-label extension
- Objective: Assess the efficacy of icatibant compared with placebo on the onset of relief of symptoms resulting from moderate to very severe acute cutaneous and abdominal edema HAE attacks
- Treatments
 - Icatibant 30 mg SC injection (divided into 3 1-cc injections)
 - Placebo SC injection
- Patients
 - 18 years of age and older
 - Documented diagnosis of HAE Type I or Type II (medical history and/or functional C1-INH <50% normal)

Reviewer's comment: Although both functional C1-INH and C4 levels were collected, the inclusion criteria were based only on the C1-INH level. C1q levels were not obtained for the study and were not routinely documented. Although a diagnosis of acquired angioedema (AAE) is an exclusion criterion, it is possible that patients with AAE who have previously been presumed to have HAE may have been enrolled in this study. Furthermore, the listing of protocol violations shows that 9 patients were granted study entry waivers on the basis of historical data and confirmed diagnosis of HAE, despite unavailable lab results or C1-INH levels higher than allowed. Of note, this protocol was previously reviewed under SPA in the Division of GI and Coagulation Drug Products (Medical Officer reviews – May 11, 2004 and July 28, 2004; SPA response letter – July 20, 2004) prior to transfer to DPAP in August 2005. Prior reviews and discussions did not address this aspect of the inclusion criteria.

- Conduct
 - Double-blind treatment phase
 - Initial screening visit for eligibility
 - Patient presentation with moderate-to-severe acute HAE attack no later than 6 hours after the time the current attack becomes moderately severe
 - Hospitalization for minimum of 12 hours with study drug administration and follow-up 24 hours post-dose, Day 14
 - Symptom scoring every 30 min for first 4 hours, then at Hours 3, 6, 8, 10, 12, 24
 - Rescue medications to be avoided if possible; if used, recorded in the CRF
 - Open-label treatment for laryngeal attacks
 - Open-label extension

- Open to all patients who have completed either double-blind treatment phase or open-label treatment for laryngeal attack
 - Also open to patients who did not have an attack sufficiently severe enough to qualify for the double-blind treatment phase or have their 1st attack after the 56th patient has completed the double-blind treatment phase (Modified OLE)
 - Repeat injections
 - If attack worsens within 48 hours of treatment, may have repeated doses
 - Maximum of 3 doses per attack at least 6 hours apart
 - No more than 8 doses within any 4-week period
 - Regular visits every 3 months in addition to unscheduled visits for acute attacks
 - Additional follow-up on Day 2 and 14 for each new attack treated with icatibant
- Efficacy
 - Primary endpoint: time to onset of symptom relief
 - Absolute reduction by ≥ 20 mm observed at 3 consecutive measurements
 - Secondary endpoints
 - Response rate at 4 hours
 - Time to relief of nausea, vomiting, diarrhea in the abdominal group and the symptom less severe in the cutaneous group
 - Time to almost complete symptom relief
 - Global Assessment
 - Assessment of each symptom by severity (0-5, not present to very severe)
- Results
 - Patient disposition
 - 56 patients randomized (27 to icatibant, 29 to placebo)
 - 27 patients with cutaneous attacks and 29 with abdominal attacks
 - 8 patients with laryngeal attacks in open-label treatment arm
 - 42 patients in OLE, including 6 patients (11 attacks total) with laryngeal edema
 - Efficacy

Study 2103: Median time to onset of symptom relief (h)			
	Icatibant (n=27)	Placebo (n=29)	P
All attacks (n=55)	2.5	4.6	0.142
Cutaneous (n=27)	3.4	10.0	0.221
Abdominal (n=28)	2.0	3.0	0.159
Males, all attacks (n=19)	2.7	23.0	0.160
Females, all attacks (n=36)	2.0	3.3	0.273

The Applicant reports that the median time to regression of symptoms as reported by the patient for laryngeal attacks (n=8) was 0.6 hours.

The Applicant has provided an alternate analysis excluding Study Site #7, citing inconsistencies in the classification of patient attack locations. Study Site #7 treated 10 patients in the double-blind treatment phase, as well as 1 laryngeal attack patient. The Applicant has also included another post-hoc analysis using a more stringent definition of onset of symptom relief (“any value to the right and below a line $Y=4/7X - 50/7$ with $X = 30$ mm”). Based on this analysis, the median time to onset of symptom relief is 2.5 versus 8.1 hours for icatibant and placebo, respectively ($p=0.058$).

Reviewer’s comment: While the additional analyses may be used as supportive sensitivity analyses, the primary review will focus on the ITT population. The study report does not provide the median time to onset of symptom relief for laryngeal patients. Combined with results of Study 2102, efficacy support for the use of icatibant in laryngeal HAE is based on a total of 11 patients, with additional supportive data from the open-label extension portions of each of the Phase 3 studies.

- Safety
 - The most common adverse events was injection site reaction ($n=26$, 96.3%) as noted in Study 2102. Other adverse events reported more commonly in the icatibant group was nasopharyngitis, upper respiratory and urinary tract infections. The other common adverse event was HAE attack.

Reviewer’s comment: The Applicant states that “HAE attack” may have been over-reported with patients and investigators mistakenly identifying new attacks as AEs. HAE was only to be reported as an AE in the study protocol if these were laryngeal attacks or if there was “relevant worsening of an attack treated with study drug.”

6. BRIEF REVIEW OF PROPOSED LABELING

Proposed package labeling has been included in this submission [1.14]. The Applicant seeks an indication for the treatment of hereditary angioedema.

1. The efficacy and safety studies conducted in support of this application addressed the treatment of *acute attacks* of HAE specifically, not a general treatment indication.
2. The Dosage and Administration describes the subcutaneous use of icatibant, but does not specify that injections should be administered by a trained health professional in a monitored setting, i.e. not for home use.
3. The Adverse Reactions section includes data pooled from Phase 2 and 3 studies.
4. Under Clinical Studies, the proposed label (b) (4)

5. Although numerically supportive, Study 2103, the single placebo-controlled study in the application, did not demonstrate a statistically significant benefit for icatibant over placebo.

6. The Clinical Studies section presents the result

(b) (4)

A more extensive review of the product label is to follow.

Reviewer's comments: The proposed label follows the new content and format requirements.

7. DSI REVIEW/AUDIT

The Applicant states that no debarred investigators participated in the study, and all investigators certified to having no financial conflicts of interest. Preliminary review of the data does not show any treatment-center effects. Since icatibant is a new molecular entity, a DSI audit is recommended. Because there are no financial conflicts with investigators or treatment-center effects, A DSI audit is recommended for the study sites which enrolled the most patients in Studies 2102 and 2103, respectively.

8. PEDIATRIC ASSESSMENT

As Orphan Drug designation has been granted for icatibant, the Pediatric Research Equity Act of 2003 does not apply. The submission does not include any studies in pediatric subjects. The Applicant states that pediatric studies will be addressed pending approval in the adult population, as discussed during prior pre-NDA meetings (Meeting Minutes – March 1, 2005 and Meeting Minutes – February 22, 2007).

9. ADVISORY COMMITTEE

As icatibant is a new molecular entity and is under evaluation for a novel indication, a Pulmonary and Allergy Drugs Advisory Committee Meeting has been tentatively scheduled for February 20, 2007. The discussion will focus on requirements for demonstrating efficacy and general safety.

10. SUMMARY

This is a 45-day filing and planning review of an NDA for icatibant, a selective competitive antagonist at the bradykinin type 2 (B2) receptor. The Applicant, Jerini AG, has developed icatibant 30 mg subcutaneous injection for acute, intermittent use. The proposed indication is the treatment of hereditary angioedema (HAE). Two pivotal efficacy and safety studies are submitted in support of this application (JE049 2102 and 2103). The Applicant has provided additional data from several uncontrolled studies, including an open-label Phase 2 study of intravenously and subcutaneously administered icatibant in HAE patients (Study 2101) and pharmacokinetic studies in healthy volunteers (Studies 1101, 1102, and 1103). Safety information on repeated, long-term use is presented from the ongoing open-label extension studies for Studies 2102 and 2103 (2102-B and 2103-B, respectively). The Applicant has also provided results of a non-interventional study, 4102, to demonstrate the validity of the patient-completed Visual

Analogue Scale (VAS), which was used as the primary efficacy parameter in the Phase 3 studies. These study reports are appropriately indexed and organized to allow review. The Applicant has provided an Integrated Summary of Efficacy, Integrated Summary of Safety, Integrated Summary of Benefits and Risks, copies of proposed labeling, and appropriate case report forms.

The submission is adequate to allow clinical review. The submission is fileable.

11. COMMENTS TO THE APPLICANT

The following comment will be conveyed to the Applicant in the 74-day filing letter regarding potential review issues:

1. As discussed in the January 24, 2007, Pre-NDA meeting, you do not have two confirmatory studies demonstrating the efficacy of icatibant for the proposed indication. Of the two Phase 3 studies included in your NDA submission, the first study, Study 2102, used an active comparator which is not approved for the treatment of HAE in the United States and, the second study, Study 2103, did not demonstrate a statistically significant benefit of icatibant over placebo for the primary efficacy endpoint, time to onset of symptom relief. The adequacy of your data to support the efficacy of icatibant for the proposed indication will be a review issue.
2. The proposed indication, treatment of hereditary angioedema, is broad and does not reflect your clinical development program. The efficacy and safety studies conducted in support of this application addressed the treatment of *acute attacks* of HAE specifically, not a general treatment indication.
3. On the carton and container labels, remove the graphic next to the proprietary name as it detracts from the proprietary name (21 CFR 201.15(a)(6)) and decreases the relative prominence of the established name (21 CFR 201.10(g)(2)).

The following information will be requested from the Applicant in the 74-day filing letter:

1. Define the following abbreviations used in the Patient Data Listings (Section 17.2) in the JE049 #2103 Clinical Study Report: NA, ND, NK, and UNK.
2. Provide the median time to onset of symptom relief for laryngeal attack patients in Studies 2102 and 2103.
3. Provide samples of the drug product for our review.

12. TIME LINE FOR REVIEW

The timeline for review and processing of the NDA application is as follows:

Proposed schedule for review of NDA 22-150

Milestone	Target Date for Completion
74-day Letter due date	January 8, 2008
Mid-cycle review meeting	January 23, 2008
Advisory Committee Meeting	February 20, 2008
Wrap-up meeting	March 11, 2008
Primary reviews due date	March 26, 2008
Internal labeling meeting	February 25, 2008

Milestone	Target Date for Completion
Labeling teleconference	March 12, 2008
PDUFA due date, 6 month Priority Review	April 26, 2008

Reviewed by:

Susan Limb, M.D.

Medical Officer, Division of Pulmonary and Allergy Drug Products

Sally Seymour, M.D.

Medical Team Leader, Division of Pulmonary and Allergy Drug Products

**This is a representation of an electronic record that was signed electronically and
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/s/

Susan L Limb
12/19/2007 09:25:35 AM
MEDICAL OFFICER

Sally Seymour
12/19/2007 11:32:21 AM
MEDICAL OFFICER
I concur.