

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022150Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	August 8, 2011
From	Susan Limb, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 22-150 (Complete Response)
Applicant	Jerini US., Inc. (a subsidiary of Shire Human Genetic Therapies)
Date of Submission	February 25, 2011
PDUFA Goal Date	August 25, 2011
Proprietary Name / Established (USAN) names	Firazyr®/icatibant
Dosage forms / Strength	30 mg subcutaneous injection
Proposed Indication(s)	1. Treatment of acute attacks of hereditary angioedema in patients 18 years and older
Recommended:	Approval pending inspection

1. Introduction

Jerini US, Inc. submitted a Complete Response for NDA 22-150 on February 25, 2011, for icatibant acetate for injection (30 mg) for the treatment of hereditary angioedema (HAE) in patients 18 years and older. Icatibant is a new molecular entity, a novel decapeptide antagonist directed against the bradykinin type-2 receptor. The proposed dose is 30 mg of icatibant administered subcutaneously, with the option of two additional 30-mg doses administered at intervals of no less than 6 hours for cases of insufficient relief or relapse. A total of 3 doses in a 24-hour period may be administered. Icatibant is supplied as a pre-filled syringe containing 30 mg icatibant acetate in 3 mL solution. The proposed trade name is Firazyr®. Outside the US, icatibant was first approved for the treatment of HAE attacks in the European Union on July 11, 2008, and is currently marketed in 37 other countries.

HAE is a rare disease characterized by intermittent, unpredictable attacks of angioedema in various parts of the body, including the airway, face, intestinal wall, and extremities.^{1 2 3} The acute attacks of are potentially life-threatening, particularly in cases of airway compromise. Bradykinin is thought to be the major downstream mediator that increases vascular permeability and inflammation, leading to the swelling and pain characteristic of HAE.⁴

The Applicant originally submitted the application to the Agency on October 22, 2007, for the same dose and indication. A Not Approvable action was taken on April 23, 2008, due to

¹ Zuraw B. Hereditary angioedema. N Engl J Med 2008; 359:1027-1036

² Frank MM. Hereditary angioedema. J Allergy Clin Immunol. 2008 Feb;121(2 Suppl):S398-401

³ Bowen T et al. 2010 International consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema. Allergy Asthma Clin Immunol. 2010; 6(1):24

⁴ Frank MM. Complement disorders and hereditary angioedema. J Allergy Clin Immunol. 2010 Feb;125(2 Suppl 2):S262-71

clinical deficiencies. The Not Approvable letter cited a lack of substantial evidence of efficacy to support the proposed indication. The original submission included the results of two Phase 3 clinical trials in patients with HAE. One clinical trial had a placebo control while the second clinical trial used an active comparator, tranexamic acid. The placebo-controlled trial did not show a statistically significant difference between icatibant and placebo for the primary efficacy endpoint, time to onset of symptom relief. The second trial did demonstrate a statistically significant difference between icatibant and tranexamic acid. However, tranexamic acid is not approved for the treatment of HAE in the US, and there is limited data to support the efficacy of tranexamic acid for the treatment of acute HAE attacks. The uncertain efficacy of this active comparator complicated the interpretation of the results from the second trial. As a result, the Applicant was asked to conduct an additional controlled trial to confirm the efficacy of icatibant for the proposed indication. The Agency also requested that Jerini provide data to support the potential self-administration of icatibant by patients as had been proposed. To address these deficiencies, the Applicant submitted a Complete Response on February 25, 2011, which includes the results from another placebo-controlled trial and an open-label self-administration trial.

Since the application is for a new molecular entity (NME) and is a Priority Review, a Pulmonary Allergy Drugs Advisory Committee (PADAC) meeting was held on June 23, 2011, during the Complete Response review period. A PADAC meeting had been scheduled during the original review cycle but had been subsequently cancelled once it became clear that the application did not provide substantial evidence of efficacy of icatibant for the proposed indication. At the June 23, 2011, PADAC meeting, information from both the original application and the Complete Response was discussed.

This memorandum provides an overview of the original submission and the subsequent Complete Response, focusing on the data that address the deficiencies identified in the original application and that support the approval of icatibant for the proposed indication. In addition, this memorandum discusses concerns that were raised by CDRH during the Complete Response review period regarding the syringe device component of the product. These specific concerns are addressed in the CMC section and in the context of the overall risk-benefit assessment for the proposed product.

2. Background

HAE is a rare, inherited condition characterized by intermittent, unpredictable attacks of angioedema in various parts of the body, including the airway, face, intestinal wall, and extremities.^{5 6 7} The condition is associated with a defect in the C1-esterase inhibitor protein, resulting in low or absent functional protein. HAE is estimated to affect 1 in 10,000 to 50,000 individuals worldwide and is categorized as an orphan disease. HAE attacks are potentially life-threatening, particularly in cases of airway compromise. Attacks at other anatomic sites can cause disabling pain and significant morbidity. These attacks are highly variable in frequency and location among individuals and even within a given individual. Currently, there

⁵ Zuraw B. Hereditary angioedema. *N Engl J Med* 2008; 359:1027-1036

⁶ Frank MM. Hereditary angioedema. [J Allergy Clin Immunol](#). 2008 Feb;121(2 Suppl):S398-401

⁷ Bowen T et al. 2010 International consensus algorithm for the diagnosis, therapy, and management of hereditary angioedema. *Allergy Asthma Clin Immunol*. 2010; 6(1):24

are two products approved for the treatment of acute attacks of HAE in the US. The first product is a plasma-derived C1 inhibitor replacement product (Berinert®)⁸ that is administered intravenously. The other product is ecallantide (Kalbitor®),⁹ a kallikrein inhibitor delivered via subcutaneous injection. Both products require administration by a healthcare professional and carry a risk of hypersensitivity reactions, including anaphylaxis. Attenuated androgens and another plasma-derived C1 inhibitor replacement product (Cinryze®) are available for prophylaxis, but acute HAE attacks can still occur.

Icatibant was granted orphan drug status on November 25, 2003. Because of the potential life-threatening nature of HAE attacks and no approved effective therapies, fast track designation was granted on June 15, 2004. The opening IND (April 8, 2004) was initially reviewed in the Division of Gastrointestinal and Coagulation Drug Products (DGCDP) prior to reassignment to the Division of Pulmonary and Allergy Products (DPAP) in September 2005. The following timeline highlights pertinent aspects of the regulatory history:

- February 6, 2004 – Pre-IND meeting with DGCDP. Following requirements discussed:
 - Replicate, well-controlled trials
 - Validation of symptom-based endpoints
- June 11, 2004 - Request for a Special Protocol Assessment (SPA)
 - Study 2103, a randomized, double-blind, placebo-controlled efficacy trial
 - Proposed protocol, endpoints, and sample size acceptable with caveat that treatment difference should be clinically meaningful (Written communication, July 29, 2004)
- March 1, 2005 – Pre-NDA meeting with DGCDP
 - Proposed QT prolongation study (Study 1103) deemed acceptable
 - Dose selection questioned
- April 16, 2005 – IND transferred to DPAP
- September 8, 2005 and February 9, 2006– Jerini requested feedback regarding the patient reported-outcome (PRO) instrument validation protocol.
 - Written responses to Jerini (January 26, 2006, and August 24, 2006) raising concerns about the PRO.
- January 24, 2007 – Pre-NDA meeting with DPAP
 - Concern regarding the lack of replicate efficacy findings
 - The need for validation of the patient-reported outcomes instrument, the Visual Analogue Scale (VAS) used in the Phase 3 program
 - The need for additional data to support self-administration
 - The requirement for chronic repeat dose toxicity studies of 6- and 9-month duration and carcinogenicity studies to support chronic, intermittent use of icatibant
- October 22, 2007 – NDA submission
- April 23, 2008 – Not Approvable action letter issued.

In addition to various CMC and nonclinical deficiencies, the Not Approvable letter cited the following deficiencies:

⁸ US Professional drug label for Berinert (human C1 esterase inhibitor)

⁹ US Professional drug label for Kalbitor (ecallantide)

- 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. The completion of nonclinical, chronic, repeat-dose toxicity studies (6-month rat and 9-month dog) via the subcutaneous route of administration is required to support chronic intermittent clinical dosing. The icatibant labeling will reflect a clinical dosing regimen that is supported by the nonclinical toxicology studies in both dose and duration. At this time, you have nonclinical support for subcutaneous clinical dosing for up to 13-weeks duration. We acknowledge your submission stating that chronic toxicity studies have been initiated as of June 2007 (dog study) and July 2007 (rat study) and that the carcinogenicity studies will be initiated April 8, 2008, and July 7, 2008, for mice and rats, respectively.*
- 3. 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.*
- 4. Data from study JE049-1103 indicate that both age and gender have effects on icatibant pharmacokinetics. Address the scientific basis for these large differences in systemic exposure and possible role of proteolytic enzymes. Also provide justification for proposing the same dose regardless of age and gender.*
- 5. Dose selection should be further defined in sufficient patients based on the clinical endpoint or other biomarkers that are validated to be related to the clinical endpoint.*

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

Subsequently, the Applicant submitted a Complete Response on February 25, 2011, with results from another placebo-controlled trial and an open-label self-administration trial to address these deficiencies. The Complete Response also includes the results of a thorough QT

trial to evaluate the effects of icatibant on various ECG parameters as well as additional pharmacokinetic data to support dose selection.

6. CMC/Device

The recommended action from the CMC perspective is Approval, pending an overall Acceptable recommendation from the Office of Compliance on the manufacturing and testing facilities. Concern regarding syringe/needle compatibility was raised during a consultative review of the Complete Response provided by CDRH. The device-specific concerns are discussed in further detail below. The CMC review team in conjunction with the Nonclinical Pharmacology/Toxicology review has recommended a post-marketing commitment regarding structural identification of impurities. No other CMC issues remain outstanding.

- **General product quality considerations**

The drug substance, icatibant acetate, is a synthetic decapeptide based on the structure of bradykinin. It is a bradykinin B2 receptor antagonist. The drug product is provided as a sterile, isotonic, buffered solution of icatibant acetate in a single-use, prefilled glass syringe for subcutaneous administration. The solution is clear and colorless and also contains sodium chloride, glacial acetic acid, sodium hydroxide, and water for injection with a pH of approximately 5.5. Each syringe delivers 3 mL of solution equivalent to 30 mg icatibant dose. The container closure system consists of a glass syringe with a plunger stopper and a (b) (4) luer-lock adaptor. The drug product is supplied in a single pack and a multi-pack. The single pack size includes one prefilled, (b) (4) glass syringe and one (b) (4) (b) (4) needle (25 G, (b) (4)). The multi-pack includes three prefilled syringes and three needles. The prefilled syringe is intended to be used exclusively with the co-packaged needle and is not intended for use with other commercially available needles or for direct intravenous injection.

All the related substances in the drug substance specification have a limit of (b) (4), as specified in the April 23, 2008, Not Approvable letter. The total impurities limit of (b) (4) is deemed acceptable. Two degradation products, (b) (4) in the drug product have a specification limit of (b) (4), which is deemed qualified. Manufacturing processes that relate to product quality microbiology have been deemed acceptable. Both 24-month and 6-month stability studies scheduled at long-term and accelerated storage conditions, respectively, were submitted for the drug product. Stability and release data support an expiry period of 18 months stored between 2-25°C (36-77°F).

The CMC review team in conjunction with the Nonclinical Pharmacology/Toxicology review has recommended a post-marketing commitment regarding structural identification of impurities. No other product quality issues have been identified.

- **Facilities review/inspection**

The drug substance is manufactured by solid-phase peptide synthesis (b) (4). Analytical testing of the drug substance is performed by (b) (4).

(b) (4)

drug product manufacturing and assembly are performed by (b) (4). Analytical testing of the drug product is performed by (b) (4). Packaging, labeling, storage, and distribution of filled syringes is performed by (b) (4) and storage and distribution of unlabelled filled syringes is performed by (b) (4). The EER Report shows that all of the above facilities are acceptable as of July 21, 2011, with the exception of the (b) (4) site, for which a recommendation from the Office of Compliance remains pending.

- **Other notable issues (resolved or outstanding)**

During the original review cycle, the proposed prefilled syringe was deemed acceptable, provided monitoring of leachables. No additional deficiencies were noted regarding the proposed syringe-needle configuration. However, during the review of the Complete Response, the CMC review team requested a CDRH consult for the (b) (4) syringe regarding device performance and ruggedness. The CDRH review dated June 15, 2011, raised concerns regarding the (b) (4) syringe due to post-marketing reports of device failure. The (b) (4) syringe does not conform to ISO standards (b) (4).

which are not a requirement for an NDA. As a result, the syringe may be incompatible with other commercially marketed medical equipment, including needles and IV tubing. The CDRH review cited examples of device failure and adverse events in other products, such as needlestick injuries and missed doses due to separation of the syringe from the needle or needleless IV access ports prior to completion of the injection. Specifically, the review cited adverse events with Risperdal Consta® (risperidone), which uses the (b) (4) syringe with needles from a different manufacturer, a (b) (4) needle. The review recommended that the Applicant be required to conduct bench performance testing to demonstrate needle-syringe compatibility and conduct a human-factors study in a minimum of 15 subjects to validate use of the device.

Additional discussions between CDER and CDRH were held to clarify CDRH's recommendations. In addition to the Risperdal example, CDRH cited reports of device failure for generic adenosine, which is supplied in the (b) (4) syringe without a needle and administered through a needleless IV access port. CDRH recommended that the Applicant be required to switch to a new syringe that has been cleared through the 510(k) process and that meets ISO standards with additional supportive data from human-factors studies.

While acknowledging the general issues identified in the CDRH review, CDER noted several major differences between the proposed icatibant product and the examples of device failure cited by CDRH. Risperdal is a viscous solution and uses needles supplied by a manufacturer (b) (4) different from the syringe manufacturer (b) (4). Also, Risperdal may be administered in settings where patients are not fully cooperative with injection. Adenosine is supplied as a syringe alone, which is then used with a range of medical equipment which may

or may not be compatible. In contrast, icatibant is a non-viscous solution, supplied in a prefilled syringe with a needle from the same manufacturer, and is intended for use by a fairly select population of trained patients or healthcare providers.

In addition, CDER noted the extensive clinical experience with the proposed product, which was approved in Europe three years ago and is now marketed in 37 countries overseas. As of June 30, 2011, a total of 2,044 injections have been administered during clinical trials and (b) (4) syringe/needle units have been sold, including for patient self-administration. These numbers far exceed the sample size of a typical human factors study. To date, there have been no reports of device failure in the clinical trials, including a designated self-administration trial in 95 patients, and no post-marketing adverse events associated with device failure. There have been two device-related complaints: 1) One complaint of leakage from the connection of the syringe barrel to the luer lock tip cap. When attached to the co-packaged needle, the syringe was emptied as in normal use without leakage; and 2) one complaint from a distribution center of a leaking syringe in packaging due to a luer lock broken off during transport. Overall, the clinical experience to date has not indicated any major device-related safety issues.

To further validate the compatibility of the (b) (4) syringe and (b) (4) needle, CDER requested that the Applicant conduct bench performance testing as outlined in the ISO (b) (4) document for the following parameters: (b) (4)

(b) (4) A study report was submitted on July 29, 2011. The results of the additional bench performance testing as per ISO (b) (4) which is not a requirement for an NDA, support the compatibility of the proposed syringe and needle.

The extensive clinical experience and satisfactory bench performance testing, combined with a select patient population and lack of alternative therapies for self-administration, support the product as proposed. While the concerns raised by CDRH highlight a general need for critical assessment of device compatibility, CDER has concluded that the data support the proposed syringe-needle configuration for icatibant and does not recommend further human factors testing. Furthermore, there appears to be no need to switch icatibant to a device that conforms with ISO standards. Introduction of a new device for icatibant that has not been tested in clinical trials and that differs from the product marketed overseas may raise unforeseen safety issues, and such a risk does not appear warranted based on the available information.

7. Nonclinical Pharmacology/Toxicology

The application is recommended for Approval from a nonclinical pharmacology and toxicology perspective.

In consultation with the Study Endpoints and Labeling Development (SEALD) Review Team and senior pharmacology/toxicology staff, icatibant was designated as a bradykinin B2 receptor antagonist, which constitutes a new established pharmacological class.

The original application included a standard battery of required nonclinical toxicology studies with the exception of chronic toxicity studies and carcinogenicity studies. The Complete Response included a 6-month rat study and a 9-month dog study. In both studies injection site reactions and dose-schedule-dependent effects on male and female reproductive organs were observed with chronic daily dosing of icatibant. Testicular and uterine atrophy were observed in rats and dogs, and a reversible delay in sexual maturation was observed in sexually immature dogs. No teratogenicity was observed, but icatibant appears to affect the uterine implantation process, and embryotoxicity, increased spontaneous abortions, and increased pup deaths were observed in the reproductive toxicity battery for icatibant. As a result, the nonclinical review recommends classification of icatibant as Pregnancy Category C.

While the reproductive toxicities raise concerns, the findings in animals should be considered in the context of the disease being treated as well as the fact that the animals were dosed daily, while patients will receive icatibant intermittently. A clinical trial to evaluate icatibant effects on reproductive hormones is currently ongoing. Limited experience with human exposure to icatibant during pregnancy does not indicate any specific adverse effects.

The Applicant has initiated two 104-week carcinogenicity studies in mice and rats, respectively, with the concurrence of the Executive Carcinogenicity Committee. As these are considered safety assessments under the 2007 Food and Drug Administration Amendments Act (FDAAA), the Applicant has agreed to conduct the carcinogenicity studies as post-marketing requirements (PMR).

In addition, the Applicant has agreed to a post-marketing commitment (PMC) to identify the chemical structures of drug product impurities occurring at levels equal to or greater than (b) (4) and to more fully define the “minimal characterization” proposed for impurities occurring at levels greater than or equal to (b) (4) but less than (b) (4). There are no other outstanding nonclinical pharmacology/toxicology review issues.

8. Clinical Pharmacology/Biopharmaceutics

The application is recommended for Approval from a Clinical Pharmacology perspective, and there are no outstanding clinical pharmacology issues. The application included results from a comprehensive clinical pharmacology program, which included studies to assess protein binding and metabolism in vitro, single- and multiple-dose pharmacokinetics, effect of hepatic impairment, the effect of renal impairment in hepatorenal syndrome, QTc effect, and effect on CYP540 isoenzymes.

Icatibant has an absolute bioavailability of approximately 97% and displays linear pharmacokinetics, with a dose-proportional increase in mean C_{max} and mean AUC_{0-∞}. 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. Icatibant is extensively metabolized by proteolytic enzymes to inactive metabolites that are primarily excreted in the urine, with less than 10% of

the dose excreted in the urine as parent drug. Multiple dose administration does not lead to accumulation of icatibant.

During the review of the original submission, the Agency noted a difference in systemic exposure by gender and age, with women and patients >65 years of age achieving higher plasma levels of drug. The Agency requested that the Applicant justify why dose adjustments for gender and age were not necessary. In the Complete Response, the Applicant provided a post-hoc analysis of demographic variables on two newly conducted PK trials with rich sampling and a population PK analysis based on pooled data from seven different clinical trials to address the issue. Clearance and apparent volume of distribution were found to correlate significantly with body weight, accounting for the apparent differences in systemic exposure by gender. Similarly, icatibant clearance exhibited a decreasing trend with increasing age, resulting in higher systemic exposures in older patients. While systemic exposure does appear to vary with age and body weight, the pharmacokinetic differences do not appear to be clinically significant based on the results of pivotal Phase 3 trials. As a result, no dose adjustment is recommended.

The pharmacokinetics of icatibant in patients with HAE are 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 has postulated a theoretical pharmacodynamic interaction between icatibant and ACE inhibitors, suggesting that icatibant may compromise the antihypertensive effects of ACE inhibitors via bradykinin antagonism. Clinical trials excluded subjects taking ACE inhibitors. 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.

A possible QTc effect was noted in an earlier trial conducted in healthy volunteers who received 5 doses of icatibant 30 mg SC on 3 separate days. The Complete Response included a dedicated thorough QTc trial in 72 healthy subjects studying doses up to 90 mg SC with an active control, moxifloxacin. A review conducted by the Interdisciplinary Review Team for QT Studies (IRT-QT) has concluded that there is no QTc effect.

9. Clinical Microbiology

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

10. Clinical/Statistical- Efficacy

The recommended action from a clinical/statistical perspective is Approval.

The Applicant completed three Phase 3 efficacy and safety trials (FAST-1, FAST-2, and FAST-3) to support the use of icatibant in the treatment of acute attacks of HAE in patients 18 years of age and older. FAST-1 and FAST-2 were included in the original application; FAST-3 was included in the Complete Response. FAST-1 was a randomized, double-blind, placebo-controlled trial in 64 patients; FAST-2 (n=77) was similar in design to FAST-1 but included tranexamic acid as an active control instead of placebo. The third confirmatory trial, FAST-3 (n=98), was a placebo-controlled trial similar to FAST-1. A total of 223 patients were randomized in the controlled phase of these trials. All of these trials included an open-label extension phase where patients could continue to receive treatment as needed for subsequent acute HAE attacks. In addition to these efficacy and safety trials, the Applicant conducted a Phase 2 proof-of-concept/dose-ranging trial, a Phase 3 self-administration trial, and an observational study to evaluate the patient-reported instrument used to score symptoms, the VAS. Table 1 summarizes the key icatibant trials conducted in HAE patients.

Table 1 Clinical trials conducted in HAE patients for icatibant					
Study [year]^a	Study type	N^b N^c (n)^d	Dose	Endpoint	Study sites
Phase 2 trial					
2101 [2004]	Proof-of-concept, dose-ranging	15 ^e	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> PK Symptom score 	<ul style="list-style-type: none"> Germany
Pivotal Phase 3 efficacy and safety trials					
2102 (FAST-2) [2006]	Efficacy and safety	74 3 (39)	<ul style="list-style-type: none"> 30 mg SC icatibant Tranexamic acid (3 x 1g for 2 days) 	<ul style="list-style-type: none"> time to onset of symptom relief (single symptom VAS) 	<ul style="list-style-type: none"> W. and E. Europe Israel
	Open-label extension	54 ^f			
2103 (FAST-1) [2006]	Efficacy and safety	56 8 (36)	<ul style="list-style-type: none"> 30 mg SC icatibant Placebo 	<ul style="list-style-type: none"> time to onset of symptom relief (single symptom VAS) 	<ul style="list-style-type: none"> N. America Australia Argentina
	Open-label extension	72 ^f			
054* (FAST-3) [2010]	Efficacy and safety	93 5 (53)	<ul style="list-style-type: none"> 30 mg SC icat bant Placebo 	<ul style="list-style-type: none"> Time to onset of symptoms relief (3-symptom composite VAS) 	<ul style="list-style-type: none"> N. America Australia E. Europe Mexico S. Africa Turkey Israel
	Open-label extension (ongoing)	84 ^f as of Jun 2011			
Additional studies					
4102 [2007]	Observational patient-reported outcome validation study	60	<ul style="list-style-type: none"> No intervention 	<ul style="list-style-type: none"> Correlation of VDS to VAS to calculate MCS D 	<ul style="list-style-type: none"> W. and E. Europe N. America Argentina
3101* (EASSI) [2010]	Open-label self-administration trial (ongoing)	95 as of Jun 2011	<ul style="list-style-type: none"> 30 mg SC icatibant 	<ul style="list-style-type: none"> Safety 	<ul style="list-style-type: none"> W. Europe Israel

^a Year enrollment completed

^b Number of patients randomized (FAST-1 and FAST-2: abdominal and cutaneous attacks; FAST-3: abdominal, cutaneous, and mild to moderate laryngeal attacks)

^c Number treated with open-label icatibant for laryngeal attacks

^d Number of patients treated with at least 1 dose of icatibant during controlled portion of trial, including patients treated with open-label icat bant for laryngeal attacks or for rescue

^e A total of 15 patients enrolled.

^f Number of patients enrolled in open-label extension phase, including patients who rolled over from the preceding controlled phase of the trial.

* Submitted in the February 25, 2011, Complete Response
Source: Individual study reports, Jerini

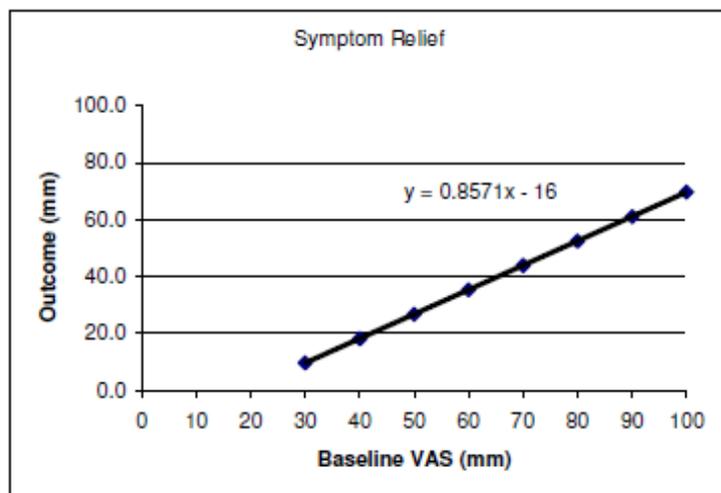
Efficacy variables

The unpredictable, fluctuating nature of HAE attacks complicates the conduct of clinical trials for HAE, and there is limited regulatory precedent in terms of drug development programs for HAE. In the absence of an accepted standard endpoint, the Applicant developed a new patient-reported outcome (PRO) instrument for use in the efficacy trials. A description of the PRO is provided here, followed by a discussion of the trial design and major efficacy results.

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

The Applicant used a PRO instrument called the Visual Analog Scale (VAS) to measure symptoms as the primary efficacy variable. The use of a VAS in HAE is novel. The VAS is a 100 mm horizontal line with 0 mm = no symptoms and 100 mm = worst possible symptom. Patients mark on the line to rate the intensity of each symptom at baseline and at pre-determined time points throughout the treatment period. The symptoms rated include the following: cutaneous swelling, cutaneous pain, abdominal pain and nausea. For cutaneous attacks, the time to onset of symptom relief was defined by a single symptom of “swelling” or “pain,” whichever was the most severe presenting symptom. If both were equally severe, “pain” was used as the primary endpoint. For abdominal attack patients, abdominal pain was used as the primary symptom to assess onset of symptom relief. In FAST-1 and FAST-2, the primary efficacy endpoint was the median time to onset of relief for the primary symptom as defined by the following (Figure 1):

- A response to the right and below a line $Y = 6/7 X - 16$ with $X \geq 30$ 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: Definition of onset of symptom relief by VAS in FAST-1 and FAST-2

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

To support the use of the VAS in the original application, the Applicant conducted Study 4102, an observational, non-interventional study in 80 adult HAE patients presenting with an acute abdominal and/or cutaneous HAE attack of at least moderate severity. The objective of the study was to identify the minimum clinically important difference (MCID) for the VAS instrument. Patients were asked to complete patient diaries, the VAS, and a five-category Verbal Descriptor Scale (VDS), where patients categorized changes in skin swelling, skin pain, and abdominal pain from baseline (“much more,” “a little more,” “about the same,” “a little less,” and “much less”). Based on comparison to the VDS, a 9 mm change in VAS was proposed as the MCID for “onset of symptom relief” and a cut-off of a change of ≥ 20 mm was defined as a responder. Changes in the VAS corresponded to changes in the VDS ($r=0.7576$; $p<0.0001$), as well as to patient diary data and physician assessments. Despite the results of 4102, the Agency noted some discrepancies between the VAS-based endpoint and other patient diary data collected in the clinical trials. The Agency requested additional validation of the instrument in the Not Approvable letter. To address these concerns, the Applicant conducted patient cognitive debriefing interviews, literature review, and sought additional expert input to support the instrument.

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

While the validation data appear supportive, changes in the single-symptom VAS or the composite VAS are not entirely intuitive. Given the lack of regulatory experience with the primary efficacy variable, the Agency also recommended the assessment of secondary efficacy variables that were independent of the VAS as additional measures of efficacy.

- ***Secondary efficacy variables***

Secondary endpoints in the pivotal trials included the time to relief of each symptom present in pre-dose VAS other than the primary symptom, time to almost complete symptom relief (0-10 mm on VAS), and individual symptom severity scoring on a 5-point scale of none to very severe. Patient self-reported regression of symptoms (start of improvement) was also assessed, although not as a prespecified endpoint in FAST-1 and FAST-2. Investigators scored specific symptoms and performed global assessments of patient improvement or worsening. Laryngeal attacks were analyzed separately from abdominal and cutaneous attacks. Patients and investigators scored symptoms on a similar 5-point severity scale, rating dysphagia and voice change. Investigators made additional assessments of breathing difficulties, stridor, and asphyxia. Rescue medication use was not assessed formally as a secondary endpoint, but information was provided as an additional indicator of efficacy.

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

Proof-of-concept and dose selection

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

Table 2 Study 2101: Median time to symptom relief by patient report and Visual Analogue Scale (VAS)					
Treatment Group	Onset of symptoms to treatment (h:min)	Change in VAS (cm) at 4 h	Onset of relief as reported by patient (h:min)	Onset of relief by VAS (h:min)	Time to complete relief by VAS
0.4mg/kg IV (2 hours)	8:22	5.31	1:30	2:00	50:00
0.4 mg/kg IV (30 min)	9:05	1.92	1:25	3:30	34:30
0.8 mg/kg IV (30 min)	9:50	5.61	1:08	3:30	20:30
30mg SC	7:20	3.15	0:35	3:00	34:00
45mg SC	6:07	4.31	0:27	5:00	60:00

Overall, quicker times to patient-reported onset of relief were reported for SC icatibant compared to IV icatibant. Quicker onset times might have been expected with the IV route, but the IV infusion times and the varying time intervals from onset of symptoms to treatment may explain this result. Alternatively, the result may be an artifact of the efficacy variable itself. The patient-reported times for onset of relief did not correspond with the VAS, underscoring some of the clinical uncertainty regarding subjective measures of symptom improvement. In the absence of a clinical dose separation, the Applicant relied on PK/PD data to guide dose selection. Reduction of bradykinin levels from baseline was observed for both the 30 mg (63 to 38 pmol/L) and 45 mg SC doses (82 to 71 pmol/L). PK/PD modeling suggested that higher doses were unlikely to have increased efficacy. Furthermore, higher doses administered subcutaneously were more likely to elicit stronger injection site reactions. Based on these results, the 30 mg SC dose was selected for evaluation in the Phase 3 trials.

Aside from Study 2101, no formal clinical dose-ranging trial in HAE patients was performed. Given the unpredictable nature of the attacks and the subjectivity of the efficacy measurements, establishing a true dose-response curve for icatibant may not be feasible. Instead, the primary support for the 30 mg dose resides in the Phase 3 efficacy data.

Efficacy

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

Original NDA : FAST-1 and FAST-2

The general trial design was similar for FAST-1 and FAST-2. Both trials were randomized, double-blind, and multi-center. The key difference was the comparator arms. FAST-1 used a placebo control, while FAST-2 used an active control, oral tranexamic acid. The efficacy of tranexamic acid, a synthetic antifibrinolytic, for the 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 limited.

In both trials, patients 18 years 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. Patients presenting with a laryngeal attack were not randomized but were eligible to receive a single dose of icatibant 30 mg SC. All patients were then eligible to participate in an open-label extension (OLE). For the OLE, any attack severe enough to warrant treatment qualified for treatment with icatibant 30 mg SC. If the attack worsened within 48 hours of initial treatment, additional injections were permitted (maximum of 3 injections per attack at least 6 hours apart). The OLE was later further modified to enroll patients who met original study criteria but who had not participated in the double-blind phase or who did not have an attack sufficiently severe to qualify during the double-blind phase.

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

Table 3 Median time to onset of symptom relief (hours) based on the primary single symptom VAS							
	Icatibant 30mg SC		Tranexamic acid		Placebo		P value
	N†	Time (h)	N†	Time (h)	N†	Time (h)	
Study 2102 (FAST-2)							
All attacks	36	2.0	38	12.0			<0.001
<i>Cutaneous</i>	24	2.5	23	18.2			<0.001
<i>Abdominal</i>	12	1.6	15	3.5			0.026
Study 2103 (FAST-1)							
All attacks	27	2.5			29	4.6	0.142
<i>Cutaneous</i>	14	3.4			13	10.0	0.221
<i>Abdominal</i>	13	2.0			16	3.0	0.159
FAST-3*							
All attacks	43	1.5			45	18.5	<0.001
<i>Cutaneous</i>	26	2.0			26	22.5	<0.001
<i>Abdominal</i>	17	1.0			19	3.6	0.002

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

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

Source: Individual study reports, NDA 22-150

Although numerically supportive, FAST-1 did not show a statistically significant benefit for icatibant over placebo (2.5 vs. 4.6 hours; p=0.142). The Applicant has suggested that the failure to show a statistically significant difference may be attributed to the number of patients in FAST-1 compared to FAST-2 who presented with abdominal pain. The Applicant states that abdominal pain symptoms are more likely to respond to placebo treatments; hence a robust placebo effect in this study minimized the treatment difference. Review of cutaneous pain VAS scores do not show a placebo effect of the same magnitude, but the assertion of a more robust placebo effect for abdominal symptoms is somewhat difficult to verify. At the

very least, this explanation indicates a potential shortcoming of the primary endpoint based on a single symptom.

Secondary endpoints in FAST-1 showed variable support for efficacy. Of particular concern was the durability of response, defined as the onset of symptom relief for the primary symptom within 8 hours after treatment that lasted for at least 24 hours. There were no differences between icatibant and placebo. In the icatibant group, 52% reported a durable response, same as the 50% in the placebo group ($p=1.0$). When examining attacks by anatomic sites, the results for abdominal attacks were unfavorable. For abdominal attacks, 46% of icatibant patients reported a durable response compared to 60% of placebo patients ($p=0.705$). For cutaneous attacks, 57% of icatibant patients compared to 39% of placebo patients reported a durable response ($p=0.449$). Other secondary endpoints were generally more supportive. For example, icatibant patients reported a time to start of improvement of 0.8 hours, compared to 16.9 hours for placebo patients ($p<0.001$; based on patients' self-reported, non-VAS, diary data). The median time to almost complete symptom relief ($VAS\leq 10$ mm) was 8.5 hours versus 23.3 hours ($p=0.07$). In terms of rescue medications, 22% of patients in the icatibant group ($n=6$) received rescue medication on the day of study drug administration compared to 52% ($n=15$) of placebo patients.

In contrast, FAST-2 met the prespecified primary efficacy endpoint. Patients in the icatibant arm reported a median time of 2.5 hours compared to 12.0 hours for the patients assigned to tranexamic acid ($p<0.001$). Although the treatment difference was smaller for the subset of patients with abdominal attacks, statistically significant differences were observed for both cutaneous and abdominal attacks. Secondary endpoints were also supportive of icatibant compared to tranexamic acid. Icatibant patients reported a median time to start of improvement of 1.7 hours, compared to 8.0 hours for tranexamic acid patients ($p<0.001$; based on patients' self-reported, non-VAS, diary data). In the icatibant group, 69% ($n=24$) reported a durable response, compared to 39% ($n=14$) in the tranexamic acid group ($p=0.017$), although minimal difference was observed for the subset of patients with abdominal pain attacks (75% vs. 69%, respectively; $p=1.0$). The median time to almost complete symptom relief ($VAS\leq 10$ mm) was 10.0 versus 51.0 hours, respectively ($p\leq 0.001$). In terms of rescue medication use, no patients in the icatibant group required rescue treatment during the first 12 hours after administration of study drug, compared to 5 patients in the tranexamic acid group.

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

In the absence of a conclusive trial in the original clinical program, the Agency requested that the Applicant conduct at least one additional well-controlled trial to confirm efficacy findings. In response, the Applicant initially provided a post-hoc analysis of FAST-1 and FAST-2 data

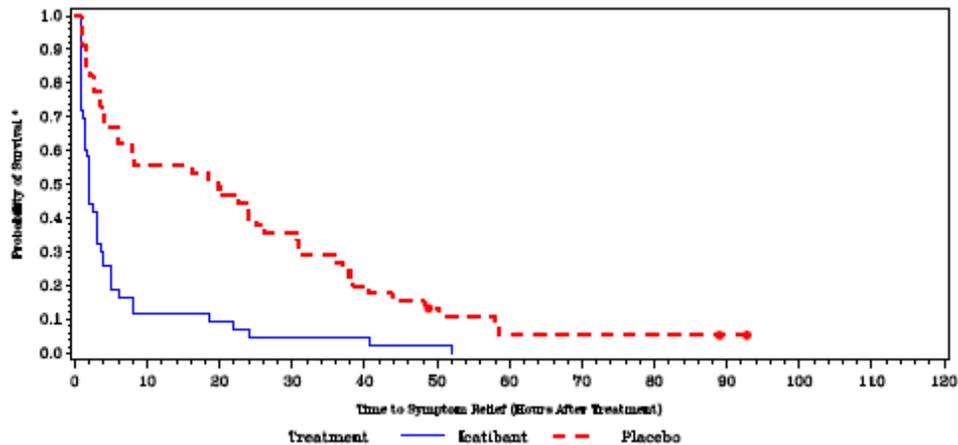
using the modified composite VAS (VAS-3) endpoint, which shows statistically significant findings for both FAST-1 and FAST-2 (Table 4). While these data provided some support for efficacy, the Agency declined to accept the post-hoc analysis as the basis for approval. The Agency advised the Applicant to conduct another placebo-controlled study with a comparable sample size to confirm efficacy findings. Also, given that icatibant was administered by healthcare professionals in both FAST-1 and FAST-2, the Agency requested that the Applicant provide data to support the proposed self-administration of icatibant by patients.

Complete Response: FAST-3

FAST-3 (n=98) was the third confirmatory trial conducted in response to the clinical deficiency identified in the original submission. Like FAST-1, FAST-3 utilized a placebo control. However, in contrast to the preceding trials, FAST-3 assessed a new primary endpoint based on a 3-symptom composite VAS (VAS-3) that is described in the preceding section. The primary endpoint was the time to onset of symptom relief for the first cutaneous and/or abdominal attack as defined by a 50% reduction in the VAS-3. The key secondary endpoint was the time to onset of symptom relief based on the single-symptom VAS score as assessed in FAST-1 and FAST-2. After the first attack, patients were eligible to continue to receive open-label icatibant for subsequent attacks.

As shown in Figure 2 and Table 4, a statistically significant difference was shown between the icatibant and placebo groups for the median time to onset of symptom relief based on the new VAS-3 in FAST-3: 2.0 hours [95% CI 1.5, 3.0] versus 19.8 hours [95% CI 6.1, 26.3].

Figure 2 FAST-3: Time to onset of symptom relief based on the 3-symptom composite VAS (VAS-3)



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As in FAST-2, the treatment difference for abdominal attacks was smaller compared to cutaneous attacks, but statistically significant results were observed for both anatomic sites. Similar results were observed in the key secondary endpoint analysis based on the single-symptom VAS shown in Table 3 (1.5 versus 18.5 hours; p<0.001). The single-symptom VAS was the basis for the prespecified primary endpoint in FAST-1 and FAST-2.

Table 4 Median time to onset of symptom relief (hours) based on 3-symptom composite VAS (VAS-3)							
	Icatibant 30mg SC		Tranexamic acid		Placebo		P value
	N†	Time (h)	N†	Time (h)	N†	Time (h)	
Study 2102 (FAST-2)*							
All attacks	33	2.0	34	12.0			<0.001
<i>Cutaneous</i>	22	3.5	20	22.3			<0.001
<i>Abdominal</i>	11	1.6	14	2.3			0.216
Study 2103 (FAST-1)*							
All attacks	26	2.3			27	7.9	0.014
<i>Cutaneous</i>	13	5.1			12	23.0	0.047
<i>Abdominal</i>	13	2.0			15	6.0	0.103
FAST-3							
All attacks	43	2.0			42	19.8	<0.001
<i>Cutaneous</i>	26	2.0			23	23.9	0.001
<i>Abdominal</i>	17	1.5			19	4.0	0.003

† Patients who did not achieve symptom relief within the observation period were censored at the last observation time.
 * Post-hoc analyses shown for comparison. The FAST-1 and FAST-2 primary endpoint was the median time to onset of symptom relief based on the single symptom VAS as shown in Table 2. Patient numbers vary slightly from the original pre-specified primary endpoint results shown in Table 3 due to reassignment of a patient from each trial as a laryngeal attack patient.

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

Secondary endpoints in FAST-3 were also generally supportive of icatibant’s efficacy. Based on non-VAS assessments, patient self-reported time of initial improvement was 0.8 hours versus 3.5 hours in the icatibant and placebo groups, respectively ($p < 0.001$). The majority of patients in the icatibant group (35 of 43, 81%) also reported a durable response compared to 36% (16 of 45) in placebo. Durability of response was demonstrated for both cutaneous (77%) and abdominal (88%) attacks treated with icatibant. These data help to counter the inconsistent responses observed in FAST-1 and confirm the durability of response findings of FAST-2. The median time to almost complete symptom relief (all VAS < 10 mm) was 8.0 hours versus 36.0 hours ($p = 0.012$). In terms of rescue medication use, three of 43 (7%) patients in the icatibant group used rescue medication (up to 120 hours post-treatment) compared to 18 of

45 (40%) patients in the placebo group. Sensitivity analysis which censored all patients who required rescue medications showed similar results as the primary analysis for the median time to onset of symptom relief.

Laryngeal attacks

In both FAST-1 and FAST-2, the data to support icatibant's efficacy in laryngeal attacks was limited by the small number of subjects and the open-label nature of the assessments (all laryngeal attack patients received icatibant). In FAST-1, 8 patients were treated with open-label icatibant during the controlled phase, and the median time to regression of symptoms as reported by the patients was 0.6 hours. In FAST-2, 3 patients presented with laryngeal attacks during the controlled phase of the study. In this study, 2 of the 3 patients self-reported a regression of symptoms by 0.3 and 1 hour post-icatibant. The third patient was intubated and unable to complete symptom scoring during the acute attack, but was successfully extubated 8 hours later and reported regression of symptoms 24 hours after icatibant administration. Time to onset of symptom relief as assessed by the VAS was not reported in either trial.

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

Overall, a total of 60 patients experienced a laryngeal attack during the conduct of FAST-1, FAST-2, and FAST-3 and the corresponding open-label extension trials. Patients' self-reported time to initial symptom improvement was consistent across the 3 trials, ranging from 0.6 to 0.8 hours. Additional assessments based on the VAS collected in FAST-3 showed that efficacy for laryngeal and non-laryngeal attacks was similar. In summary, despite the small sample size and the lack of a placebo control for comparison, the results generally support the efficacy of icatibant for the treatment of laryngeal HAE attacks.

Efficacy with repeat use

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

Efficacy findings for population subgroups

As mentioned previously, systemic exposure varied by age and gender, raising concern that the differential exposure may impact efficacy. In terms of gender, males tended to have a

numerically slower onset to symptom relief compared to females. However, the slowed response was most prominent for males allocated to placebo or tranexamic acid, while male patients who received icatibant had similar results as their female counterparts (2.5 and 2.0 hours, respectively, in the pooled Phase 3 analysis). There was no apparent correlation between gender and the baseline severity of attack, and the anatomic sites of attack were fairly equally distributed among males and females. The cause for the observed gender differences in the comparator arms is uncertain, but the pattern of results suggests that icatibant was efficacious in both males and females. Likewise, pooled analysis of patients treated with icatibant across different age brackets did not show any clear correlation with age. Furthermore, nearly 90% of all HAE attacks in the Phase 3 program were treated with a single 30 mg injection and did not require an additional icatibant injection as was permitted by the study protocols. Of the minority of patients who received a second and/or third icatibant injection, there was no predominant gender or age bracket. While the small size of the clinical trials limits such subgroup analyses, the results are reassuring and provide support for the proposed 30 mg dose without adjustment for gender, age, or body weight.

11. Safety

Safety data for icatibant include the clinical trial experience and postmarketing experience in 37 countries outside the US.

Clinical trial experience

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

Safety was assessed in the clinical trials with reports of adverse events, laboratory values, vital signs, and physical exams. No deaths were reported in patients treated with icatibant. A total of 27 icatibant-treated patients were reported to have a serious adverse event (SAE).¹⁰ The SAEs covered a range of conditions, and causality cannot be refuted or confirmed. A total of 4 icatibant-treated patients discontinued due to an AE. The AEs cited for discontinuation included pregnancy (n=2), vomiting (n=1), and coronary artery disease (n=1).

The safety data show that the most common adverse reactions were local injection site reactions. Local injection site reactions occurred in nearly all patients who received icatibant by subcutaneous injection, characterized predominantly by erythema and local swelling.

¹⁰ Serious Adverse Drug Experience is defined in 21 CFR 312.32 as any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience (defined in the same regulation as any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

These reactions appeared self-limited and generally resolved within a few hours of treatment. Signs of systemic hypersensitivity were not associated with these reactions. These reactions appear to be irritant in nature rather than mediated by a specific immune response. The second most common AE was HAE attack (worsening of HAE symptoms). HAE was to be reported as an AE only in the event of a new attack during treatment or significant worsening of an attack during treatment; however, these distinctions are difficult to make clinically during an acute attack. The reporting of HAE attacks as an AE is difficult to interpret, but is more likely a reflection of the fluctuating course of the underlying condition rather than a treatment-related exacerbation of symptoms.

Nonclinical studies in dogs and rabbits have raised concerns of reproductive toxicities. While the clinical safety database has not confirmed these toxicities in humans, the limitations of a small database based on intermittent use make it impossible to exclude this as a risk of the drug. Of six medically confirmed cases of icatibant exposure during pregnancy to date, three resulted in full-term healthy infants, and one was electively aborted. No follow-up information is available for the remaining two cases. Other reproductive adverse events were not reported in the HAE program. As mentioned previously in the summary of nonclinical information, a clinical trial to evaluate icatibant's effects on reproductive hormones is currently ongoing, which may provide additional insight into this potential risk. While the potential for reproductive toxicities is concerning, the findings in animals should be considered in the context of the disease being treated as well as the fact that the animals were dosed daily, while patients will receive icatibant intermittently.

An earlier clinical pharmacology trial showed several examples of transient ST/T wave changes and/or QT prolongation in healthy patients receiving 5 doses of icatibant 30 mg SC on 3 separate days. However, a subsequent formal QT prolongation trial with moxifloxacin as a positive control did not show evidence of clinically relevant prolongation of the QT interval at icatibant doses up to 90 mg SC. The Interdisciplinary Review Team for QT Studies has concluded that there is no QTc effect.

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

Self-administration

JE049-3101B (EASSI) is an ongoing open-label, multicenter trial to evaluate the efficacy and safety of patient self-administration of icatibant in acute HAE attacks in patients 18 years of age and older. As of June 24, 2011, a total of 95 patients have enrolled. All patients were trained in the method of self-administration at enrollment. Patients who had previously received icatibant (n=71) were given 1 pre-filled syringe for self-treatment. Icatibant-naïve patients (n=24) were to present to a clinical site for the treatment of the first attack before a single dose of icatibant for self-treatment was dispensed. The main objective was to evaluate the clinical safety of self-treatment, assessed through the reporting of adverse events (AEs) and grading of local injection site reactions. While the self-administration trial was not designed to assess device performance specifically, there were no reports of device failures in the trial. In

addition, patients recorded VAS scores for skin swelling, skin pain, and abdominal pain pre-dose and at interval times up to 48 hours post-dose. Other assessments included a physician Global Assessment at 48 hours after self-treatment and a patient questionnaire to evaluate satisfaction with self-administration.

Overall, the results of EASSI support the self-administration of icatibant. The majority of patients reported ease and a preference for self-administration, and the adverse events do not indicate any issues with device reliability or performance. The frequency and nature of the reported adverse events, including local injection site reactions, were similar to those observed for the injections administered by a healthcare professional. In terms of efficacy, the median time to onset of symptom relief based on the VAS-3 was 2.6 hours; for the single-symptom VAS, the median time was 2.0 hours. These times are consistent with the times observed in the pivotal efficacy trials and do not indicate any diminished efficacy with self-administration.

Postmarketing experience

Postmarketing experience overseas has not raised any new concerns regarding efficacy, safety, or device performance. Icatibant was first approved for the treatment of acute HAE attacks in the European Union on July 11, 2011, and currently has marketing approval in 37 countries outside the US. Self-administration was approved in the EU on February 28, 2011. The most commonly reported adverse event has been injection site reactions, as observed in the clinical trials. Jerini has an ongoing voluntary registry, the Icatibant Outcome Survey (IOS), which has been monitoring the safety of icatibant during long-term treatment. Adverse events of specific interest include effects on sexual maturation in pubertal adolescents, potential hypersensitivity reactions, and the frequency of cardiac ischemic events in patients with cardiac risk factors, given theoretical concerns regarding the effects of bradykinin inhibition on myocardial perfusion. No new safety signals have been identified from post-marketing experience. Device-specific experience from the post-marketing period is discussed in Section 3 CMC.

12. Advisory Committee Meeting

Since the application is for a new molecular entity (NME) and is a Priority Review, discussion at a Pulmonary Allergy Drugs Advisory Committee (PADAC) meeting was warranted. A PADAC meeting had been scheduled during the original review cycle but was subsequently cancelled once it became clear that the original application did not provide substantial evidence of efficacy of icatibant for the proposed indication. During the review cycle for the Complete Response, a PADAC meeting was held on June 23, 2011, to discuss information from both the original application and the Complete Response with a panel of 13 outside experts in a public forum. The discussion addressed the robustness of the efficacy findings, safety considerations, and the support for self-administration.

The panel concluded that icatibant appeared effective, although there was some concern expressed regarding the adequacy of blinding and the use of a median time point to summarize efficacy results with such a limited sample size. Overall, the voting favored that the efficacy data for icatibant were sufficient to support the proposed indication (12 Yes, 1 No). Likewise, the majority of panel members voted that safety data were adequate (11 Yes, 1 No, 1 Abstain).

Several members suggested a postmarketing registry to obtain additional safety information on long-term use. Consistent with these views on efficacy and safety, the panel members voted in favor of approval (12 Yes, 1 No). Self-administration was viewed as an important potential benefit for the product, both in terms of patient convenience but also in potentially shortening the time period between onset of symptoms and symptom relief. Although the issue of self-administration was originally intended for discussion only, the panel members requested an additional voting question to express their near unanimous support for patient self-administration of icatibant for acute attacks of HAE (11 Yes, 1 No, 1 Abstain).

13. Pediatrics

The application does not trigger the Pediatric Research Equity Act (PREA) due to its orphan status. The clinical trial data included in the application were limited to patients 18 years of age and older, and the application did not include a proposal for a pediatric program. However, the Applicant has indicated separately that pediatric studies will be conducted, the details of which have yet to be discussed. Pediatric studies will be of interest, since HAE is an autosomal dominant disease. For reasons that are uncertain, the disease often does not manifest until late childhood or adolescence, so the stage of human development may influence the vasoactive mediator cascades which are responsible for HAE symptoms. Whether this may impact efficacy or safety of icatibant in children has yet to be determined.

14. Other Relevant Regulatory Issues

DSI audit

Because icatibant is a new molecular entity, a DSI audit of the two largest study sites was requested during the original review cycle. Results from these two sites appeared to drive the results of the pivotal trials and due to their international locations, there was some uncertainty about the comparability of the local standard of care. Given these concerns, site visits and inspections were conducted. While some deficiencies in study oversight and monitoring were noted, the DSI audit determined that these issues did not significantly impact study execution and data quality. In the Complete Response, the majority of study sites were domestic in contrast to the original application. The statistical review did not identify any center-treatment interactions, and there were no financial disclosures of interest. As a result, a second DSI audit was not requested for the Complete Response.

15. Labeling

Final labeling is pending at the time of this memorandum. Draft labeling is comprised of the package insert in PLR format, patient package insert, and instructions for use. The proposed tradename is Firazyr®, which has been deemed acceptable following a review by the Division of Medication Error Prevention and Analysis (DMEPA). As noted in Section 7, Nonclinical Pharmacology/Toxicology, icatibant was designated as a bradykinin B2 receptor antagonist, which constitutes a new established pharmacological class. Comments from the Division of Risk Management (DRISK) and the Division of Drug Marketing, Advertising, and Communications (DDMAC) have been incorporated.

Section 6, Adverse Reactions, and Section 14, Clinical Studies, of the label primarily describe the results of FAST-3 with additional support from the two other pivotal trials. Efficacy is

described in terms of the pre-specified primary endpoint, the median time to onset of symptom relief, defined as a 50% reduction in the VAS-3 from the pretreatment composite score, sustained over 3 consecutive timepoints. In addition to description of the primary efficacy results, the Applicant proposed inclusion of a secondary endpoint, patient-reported time of initial improvement, as an additional onset of action claim. This endpoint was based on the time that patients recorded the start of symptom improvement in patient diaries. It is unclear whether the information was recorded prospectively or retrospectively, and the durability of improvement was not documented. Furthermore, this endpoint was not prespecified in FAST-1 and FAST-2. While results for this endpoint were considered supportive for the purposes of the review, the results are not sufficient to support an onset of action claim in the label.

16. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

The recommended regulatory action is Approval, pending an Acceptable recommendation from the Office of Compliance. The Applicant has provided substantial evidence of efficacy and safety for icatibant 30 mg SC for the treatment of acute attacks of hereditary angioedema.

- **Risk Benefit Assessment**

The risk-benefit assessment for icatibant supports its approval for the treatment of acute attacks of HAE in patients 18 years and older. Statistically significant evidence of efficacy was demonstrated in one active-controlled trial (FAST-2) and one placebo-controlled trial (FAST-3) for icatibant in the treatment of acute HAE attacks. Results from an additional placebo-controlled trial (FAST-1) were not statistically significant but were numerically supportive and consistent in terms of the effect of icatibant as measured by the primary endpoint. Across the three pivotal trials, it appeared that icatibant performed similarly, with a median onset of symptom relief of approximately 2 hours, with greater variability observed in the different comparator groups. In terms of safety, local injection site reactions were the most common adverse event attributable to icatibant. Patient self-administration of icatibant does not appear to pose any additional safety concerns. The efficacy and safety data combined support the proposed dose of 30 mg SC icatibant.

While CDRH has raised concerns regarding syringe-needle compatibility and recommended additional human factors testing and a potential switch to a different syringe that conforms with ISO standards, CDER has concluded that the available information is adequate to support approval. The clinical trial data and extensive post-marketing experience, in conjunction with satisfactory bench performance testing based on the ISO standards, provide reasonable assurance of device reliability. Introduction of a new device for icatibant that has not been tested in clinical trials and that differs from the product marketed overseas may raise unforeseen safety issues, and such a risk does not appear warranted based on the available information. These factors, combined with a select patient population and the lack of alternative therapies for self-administration, support the use of the proposed syringe-needle configuration for icatibant without need for further testing or other changes.

Aside from the pending inspection, there are no other outstanding issues from a CMC, nonclinical, clinical pharmacology, or clinical perspective.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

No postmarketing risk evaluation and management strategies are recommended.

- **Recommendation for other Postmarketing Requirements and Commitments**

During the review of the original application, comments were conveyed in the Not Approval letter to the Applicant regarding a future requirement for animal carcinogenicity studies. The Applicant has initiated studies in mouse and rat, and completion of these studies will be required as post-marketing requirements. A post-marketing commitment regarding structural identification of impurities will also be requested. Since icatibant is an orphan drug, the application does not trigger post-marketing requirements under PREA. The following post-marketing requirements and commitment are recommended:

FDAAA post-marketing requirements

- *Submit the results of your ongoing 104-week mouse carcinogenicity study of icatibant.*
 - Study Completion: March 2014
 - Final Report Submission: December 2014
- *Submit the results of your ongoing 104-week rat carcinogenicity study of icatibant.*
 - Study Completion: August 2011
 - Final Report Submission: March 2012

Post-marketing Commitments

- *Provide the following information to identify and characterize impurities in your drug product: the structures for all the unspecified impurities observed at (b) (4) in your drug product stability studies, the structures or at least “minimal structural information” for all the unspecified impurities observed at (b) (4) in the drug product stability studies and include suitable criteria for what constitutes “minimal structural information.”*
 - Study Completion: August 2012
 - Final Report Submission: September 2012

- Recommended Comments to Applicant

There are no comments.

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/s/

SUSAN L LIMB
08/08/2011