

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022150Orig1s000**

**SUMMARY REVIEW**

## SUMMARY REVIEW OF REGULATORY ACTION

Date: August 24, 2011

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

Subject: Division Director Summary Review

NDA Number: 22-150

Applicant Name: Shire Orphan Therapies (Jerini Inc. a subsidiary of Shire Human Genetic Therapies, Inc.)

Date of Submission: February 25, 2011

PDUFA Goal Date: August 25, 2011

Proprietary Name: Firazyr

Established Name: Icatibant

Dosage form: Injection

Strength: 30 mg

Proposed Indications: Treatment of acute attacks of hereditary angioedema (HAE)

Action: Approval

### 1. Introduction

Jerini Inc. submitted this complete response on February 25, 2011, to the previous approvable action on this 505(b)(1) new drug application (NDA) 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, 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. The original NDA was submitted in October 2007, and a Not Approval action was taken in April 2008, because substantial evidence of efficacy was not demonstrated in two pivotal studies. The original NDA included one placebo-controlled study that did not show efficacy, and another tranexamic acid (TA) active-controlled study that showed efficacy. Demonstration of efficacy in the TA active-controlled study was not considered adequate for approval because TA is not approved for the treatment of acute attacks of HAE. Jerini has adequately addressed the efficacy deficiency with data submitted from a new placebo controlled study that shows efficacy. The NDA is being recommended for approval in this review cycle. This summary review will provide an overview of the original NDA and this complete response, with expanded discussion on the clinical efficacy and safety studies.

### 2. Background

HAE is a rare autosomal dominant inherited disease characterized by intermittent and unpredictable attacks of angioedema involving various organs, particularly the skin, intestine, and upper airway. HAE is estimated to affect 1 in 10,000 to 50,000 individuals worldwide and is categorized as an orphan disease in the US. There are two major types of HAE, called type I and type II, and a minor type called type III. Type I (80-85% of all

HAE patients) is caused by decreased production of C1-INH, and type II (most of the remaining cases) is caused by functional deficiency of C1-INH. Type III is a very rare form that seems to be X-linked.

HAE attacks are potentially life-threatening, particularly in 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 attacks<sup>1</sup>. Until recently, androgenic steroids were 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<sup>1,2</sup>. Stanazol and oxymetholone are also approved with a similar indication, but are no longer marketed in the US. Within the last 3 years three drugs were approved for HAE in the US. In 2008, Cinryze, a human plasma-derived C1 inhibitor was approved for routine prophylaxis of HAE attacks. In 2009, Berinert, human plasma-derived C1 esterase inhibitor was approved for the treatment of acute abdominal or facial attacks of HAE in adults and adolescent patients. Also in 2009, Kalbitor (ecallantide), an inhibitor of human plasma kallikrein, was approved for the treatment of acute attacks of HAE. 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 thought to be effective in acute attacks<sup>1,2</sup>. 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 kininogens<sup>1</sup>.

At present Berinert and Kalbitor are approved in the US and elsewhere in the world for treatment of acute attacks of HAE. Both of these products require administration by a healthcare professional and carry a risk of anaphylaxis. Icatibant is a new molecular entity proposed for the treatment of acute attacks HAE. 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

---

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

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

submitted with the original NDA. 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. Jerini 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 for the original NDA submission, the Division communicated to Jerini 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 attacks in the other phase 3 study.

Subsequent to the Not Approval action to the original NDA, Jerini met with the Division on December 15, 2008, to clarify the clinical deficiencies outlined. Jerini agreed to conduct a third, controlled study in patients with HAE to assess efficacy. Subsequently, Jerini submitted a request on February 12, 2009, for a Special Protocol Assessment for the third study. Although no agreement was reached, the Division informed Jerini that a trial that was generally similar in design to the two previous studies would be acceptable for addressing the clinical deficiencies.

### 3. Chemistry, Manufacturing, and Controls

Firazyr is supplied as a sterile solution in a pre-filled (b) (4) syringe which delivers 30 mg of icatibant in 3 mL of isotonic acetate buffer solution (10 mg icatibant base/mL), and one (b) (4) 25 G Luer lock needle. 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) 1.32 mg acetic acid (b) (4) and (b) (4) sodium hydroxide (b) (4) and water for injection, adjusted to pH of  $5.5 \pm$  (b) (4). The solution contains no preservatives. The proposed expiry period of 18 months for drug product when stored at 2-25°C is supported by the submitted stability data.

The drug substance is manufactured by (b) (4).  
 Analytical testing of the drug substance is performed by (b) (4).  
 (b) (4)  
 (b) (4) The (b) (4) Syringe and (b) (4)  
 (b) (4) Needle are produced by (b) (4). The  
 drug product manufacturing and assembly are performed by (b) (4).  
 (b) (4) Analytical testing of the drug product is performed by (b) (4).  
 (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).  
 (b) (4) All manufacturing and testing sites related to this product have  
 acceptable inspection status.

### CDRH Consult on prefilled syringe

During the review of this complete response, ONDQA of CDER consulted CDRH for human factors, performance and ruggedness assessment of the device component of Firazyr. The device components of Firazyr are (b) (4) syringe and (b) (4) Luer lock 25 G needle. Two consults reviews from General Hospital Device Branch, DAGID, ODE, CDRH, dated June 15, 2011, and August 8, 2011, were received that recommended against approval of this NDA because of concerns regarding syringe-needle compatibility and the lack of human factor study and suggested a potential switch to a different syringe prior to approval. ONDQA of CDER does not agree with these recommendations from CDRH and recommends approval of the current configuration of Firazyr. This Division concurs with ONDQA's recommendation of approval. CDRH's recommendations are discussed in the following section, along with ONDQA and this Division's reasoning for not following those recommendations.

Regarding syringe-needle compatibility, CDRH consult raises two concerns: first, (b) (4) syringe does not conform to ISO standards (b) (4) and, second, post-marketing reports of device failure with the (b) (4) Syringe. These concerns are not of a magnitude to preclude approval.

The ISO standards are intended to assure compatibility of syringes and needles across different manufacturers, which is not an issue for Firazyr because the (b) (4) syringe prefilled with formulation will be dispensed packaged with (b) (4) needle in a carton and the patient will attach the two before using. ISO standards are well intended, but these are not required for an NDA. Nevertheless, on the Division's request the Applicant performed bench performance testing per ISC (b) (4)

(b) (4) with success and demonstrated compatibility between the (b) (4) Syringe and the (b) (4) needle used in Firazyr. A summary of the study report was submitted to the Agency on July 29, 2011. CDRH maintains (August 8, 2011, consult review) that the demonstrated compatibility is not sufficient because the number of syringe-needle pairs tested was less than 30 devices ("statistically significant sample size") as originally recommended by CDRH. ONDQA maintains that additional testing of the syringe needle compatibility that is statistically relevant may be pursued post approval with the applicant since there are no safety or device performance issues identified so far.

The post-marketing failures noted by CDRH (consult dated June 15, 2011) as concerns are with Risperdal Consta® (risperidone), and generic adenosine. Both of these products use the (b) (4) syringe. The CDRH review cited examples of device failure and adverse events with these products, such as needlestick injuries, missed doses due to separation of the syringe from the needle or needleless IV access ports prior to completion of the injection. These examples and concerns are not relevant to Firazyr. Risperdal Consta® (risperidone), uses the (b) (4) syringe, but with needles from a different manufacturer, (b) (4)

(b) (4) Risperdal is a viscous solution and the drug is administered by deep intramuscular injection to deltoid or gluteal muscles in settings where patients may not be fully cooperative with the injection route. Generic adenosine is supplied in the (b) (4) (b) (4) syringe but does not use a needle and is administered through a needleless IV access port with a range of medical equipment. Firazyr uses a (b) (4) syringe and (b) (4) (b) (4) needle that are compatible with each other as mentioned above. The formulation is not viscous and the product will be administered subcutaneously by HAE patients who will be selected by health care providers as suitable candidates for self-administration.

CDRH recommends a human factor study before approval (consults dated June 15, 2011, and August 8, 2011) because Firazyr can be administered by patients in home settings and not always by a health care provider. CDRH asks that the human factor study be done in about 15 subjects, following general guidelines for such a study.<sup>3</sup> CDRH's stated purpose of the human factor study "is to demonstrate that Firazyr can be used by representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to device users." The Division's position is that the purpose of the human factor study has already been achieved through the conducted pivotal clinical studies (discussed in sections 7 and 8 of this review) and worldwide post-marketing experience with Firazyr, 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. 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.

While the concerns raised by CDRH highlight a general need for critical assessment of device compatibility, ONDQA and this Division conclude that such testing has been done and that the existing data support the proposed syringe-needle configuration for icatibant and, therefore, do not recommend further human factors testing. Furthermore, there appears to be no need to switch icatibant to a different syringe or needle device to conform to 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.

#### **4. Nonclinical Pharmacology and Toxicology**

Jerini submitted results of nonclinical toxicology studies lasting 6 months in rats and 9 months in dogs with this complete response. The primary toxicities were injection site irritation, testicular and uterine atrophy, and delay in sexual maturation. Injection site irritation was not of concern because it can be monitored in humans. The reproductive toxicities observed in animals would not preclude approval given the severity of HAE

---

<sup>3</sup> CDRH Guidance: Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management, issued on July 18, 2000; and ISO (International Organization for Standardization) IEC 6236:2007, Medical Devices – Application of usability engineering to medical devices.

disease and the fact that animals were dosed daily, whereas humans will receive icatibant intermittently. To address this finding further, a human clinical study to evaluate icatibant effects on reproductive hormones is currently ongoing. A complete genetic toxicology program was conducted, which was negative. 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.

Jerini has initiated carcinogenicity studies in rats and mice, which will be completed as post-marketing required (PMR) studies. Jerini will also complete a post-marketing commitment study (PMC) to qualify impurities occurring at concentrations higher than defined thresholds. Jerini has agreed to these PMR and PMC studies.

## **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 primarily 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 showed approximately 2-fold increase in AUC and about 12% to 15% increase in C<sub>max</sub> compared to younger subjects (18 to 45 years). Clearance of icatibant is significantly correlated with bodyweight with lower clearance values noted for lower bodyweights. Hence, females with typically lower bodyweights compared to males, exhibit lower clearance values resulting in approximately 2-fold higher systemic exposure (both AUC and C<sub>max</sub>) compared to males. These differences did not seem to impact clinical efficacy. However, the subject numbers in these subgroups are too small to make a firm conclusion.

A thorough QT/QTc study was submitted with the complete response. Review of the study results concluded that there was no QTc effect.

## **6. Clinical Microbiology**

The drug product is [REDACTED] (b) (4). Controls around these processes are adequate.

## 7. Clinical and Statistical – Efficacy

### a. Overview of the clinical program

Some characteristics of the relevant clinical studies that form the basis of review and regulatory decision for this application are shown in Table 1. The pivotal efficacy and safety clinical studies submitted with the original NDA consisted of two relatively small sized studies called FAST-2 and FAST-1. The complete response included a third relatively small sized study called FAST-3 and another study to assess self-administration called EASSI. The scope of the clinical program and the size of the studies are reasonable for this orphan indication. 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. HAE clinical studies**

ID Year*	Study type	Study duration	Patient Age, yr	Treatment groups <sup>†</sup>	N (ITT)	Primary endpoint	Countries
Submitted with original NDA							
2101 [2004]	Efficacy and safety Phase 2, open-label	Single dose	18 - 65	1 0.4 mg/kg, 2h 1 0.4 mg/kg, 30 min 1 0.8 mg/kg, 30 min 1 30 mg IV 1 45 mg IV	4 3 4 3 1	PK Symptom score	Germany
2102 FAST-2 [2006]	Efficacy and safety Phase 3	Single dose	19 - 68	1 30 mg SC TA 3 x 1, 2 days	36 38	Time to onset of symptom relief (single symptom VAS)	EU
2103 FAST-1 [2006]	Efficacy and safety Phase 3	Single dose	18 - 58	1 30 mg SC Placebo	27 29	Time to onset of symptom relief (single symptom VAS)	USA, Canada, Argentina, Australia,
4102 [2007]	Observational PRO outcome validation study			No intervention	57	Correlation of VDS to VAS	USA, Canada, EU, Argentina, others
Submitted with complete response							
054 FAST-3 [2010]	Efficacy and safety Phase 3	Single dose	18 -83	1 30 mg SC Placebo	43 45	Time to onset of symptom relief (3 symptom comp VAS)	USA, Canada, Mexico, Europe, others
3101 EASSI [2010]	Open-label self administration (ongoing)	Single dose	18 -83	1 30 mg SC	95 (as of 4/11)	Safety	
* Year study subject enrollment ended							
<sup>†</sup> I = Icatibant, TA = Tranexamic acid; Studies 2102 and 2103 had open-label extension							

### b. Design and conduct of the studies

As discussed above, the pivotal clinical studies efficacy and safety studies consisted of two relatively small sized studies called FAST-2 and FAST-1 submitted with the original NDA, and FAST-3 submitted with the complete response.

The general design of the pivotal efficacy and safety studies (FAST-1, FAST-2, and FAST-3) was similar. All 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; FAST-2 study used TA as the active control; FAST-1 and FAST-3 studies were 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 in FAST-1 and FAST-2 were not randomized but received icatibant 30 mg SC; patients with mild to moderate laryngeal attacks in FAST-3 were randomized with appropriate rescue treatment in place. Another difference among the trials was the prespecified primary efficacy endpoint. In all three trials, the primary efficacy endpoint was the median time from study treatment to the onset of symptom relief, but FAST-3 used a different definition of symptom relief from FAST-1 and FAST-2. The different definitions are described in further detail below. Secondary efficacy endpoints included response rate at 4 hours, time to relief of each symptom 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), investigator global assessment, and rescue medication use. 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.

Some issues of note for the icatibant clinical development program are discussed below. Of the various issues, the choice of active control was considered a major problem that led to the Not Approval action during the original review of this NDA.

#### Primary efficacy variable

The unpredictable, fluctuating nature of HAE attacks complicates the conduct of clinical trials for HAE, and there is limited regulatory precedent in terms of drug development programs for HAE. In the absence of an accepted standard endpoint, Jerini developed a new patient-reported outcome (PRO) instrument for use as primary efficacy variable in the pivotal studies.

The primary efficacy variable in FAST-1 and FAST-2 studies was time to onset of symptom relief assessed by a VAS for the single most severe presenting symptom (cutaneous swelling, cutaneous pain, or abdominal pain) before treatment. The VAS is a 100 mm horizontal line with 0 mm as no symptom and 100 mm as worst possible symptom. Onset of relief was defined by a response to the right and below the following line function:  $Y = 6/7X - 16$  with  $X \geq 30$  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. 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.

To support the use of the VAS in the original NDA, Jerini conducted study 4102, an observational non-intervention study to define the Minimum Clinically Significant Difference (MCSD) of the VAS. During HAE attacks, patients completed the VAS, and a patient rated Verbal Descriptor 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 the VAS to the VDS, a 9 mm change in the VAS was identified as the MCSD for symptom relief. Changes in the VAS corresponded to changes in the VDS ( $r=0.76$ ;  $p<0.0001$ ). The problem with this validation is that the VDS is another patient reported outcome that

itself does not seem to be validated. Nevertheless, the VDS seems to be more intuitive and closer 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 Agency asked for additional validation of the VAS in the Not Approval action letter of the original NDA.

Jerini conducted patient cognitive debriefing interviews, literature review, and sought additional expert input to support the PRO instrument. As a result of these additional efforts, Jerini proposed a modified, composite symptom VAS endpoint in the third confirmatory FAST-3 study. 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 time-points. For cutaneous and abdominal attacks, the 3 components of the composite VAS (VAS-3) were abdominal pain, skin pain, and skin swelling. Based on a receiver operating characteristics (ROC) curve analysis, Jerini proposed a MCSD value of 5 to 6 mm in patients with a baseline VAS-3 score of  $\geq 30$  mm for at least one symptom. While the validation data appear reasonable, changes in the single-symptom VAS or the 3-symptom 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.

#### 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 seem 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 the start of an acute attack and 3 patients received continuous treatment. One of the 2 patients receiving acute treatment is reported to have benefited.<sup>4</sup> 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 acute attacks by TA treatment.<sup>5</sup> 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.<sup>6</sup> 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)

<sup>4</sup> Blohme G. Treatment of hereditary angioneurotic edema with tranexamic acid: a random double-blind cross-over study. *Acta Med Scand* 1972; 192:293-298.

<sup>5</sup> Ohela K. Treatment of hereditary angioneurotic edema with tranexamic acid and cinnarazine. *Acta Dermatovener* 1976; 56:61-67.

<sup>6</sup> Agostoni A, Cicardi M. Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. *Medicine* 1992; 71:206-215.

(b) (4)

stating that TA is not worse than placebo. The results of FAST-1 and FAST-2 studies do not support this assertion. TA performed appreciably worse in one study compared to placebo in the other study (data shown in the subsequent section). While the validity of cross study comparison is uncertain, 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 affected (either increased or decreased) in patients with HAE presenting with abdominal symptoms with presumed intestinal wall edema.

### Blinding

All three pivotal 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 reactions, 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 was an issue with the original NDA review because of conflicting results of FAST-1 and FAST-2. Although the confounding influence of possible lack of blinding cannot be completely ruled out, the additional FAST-3 study showing efficacy in a placebo-controlled study is reassuring of efficacy.

### 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 dose ranging with clinical endpoints given the limited number of subjects available for study, and the subjective nature of efficacy measures. The PK-PD modeling data suggest that doses higher than 30 mg are unlikely to increase efficacy substantially. Given these considerations it was accepted that no further dose ranging would be necessary provided efficacy was shown with 30 mg dose.

#### c. Efficacy findings and conclusions

Findings from FAST-1, FAST-2, and FAST-3 studies support efficacy of icatibant at a dose 30 mg SC for treatment of acute attacks of HAE.

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 (Table 2 and Table 3). These results are shown with the caveat that the VAS-3 results for FAST-1 and FAST-2 reflect post hoc analyses.

Based on the prespecified primary efficacy endpoint of median time to onset of symptom relief as measured by single-symptom VAS, icatibant was statistically superior to TA in FAST-2 study, but not to placebo in FAST-1 study (Table 2). Results of FAST-1 showed numerical trend for icatibant over placebo, but the difference was not statistically significant. In the absence of a conclusive trial submitted with the original NDA, the Agency asked that Jerini conduct one additional controlled study. The additional study, FAST-3, which used a placebo control, showed that icatibant was statistically superior to placebo on the prespecified efficacy endpoint of 3-symptom composite VAS (Table 3). Since the primary efficacy endpoint used in FAST-3 was different from the preceding trials, a key secondary endpoint in FAST-3 was the median time to onset of symptom relief measured by the single-symptom VAS, which is the same endpoint designated as the primary endpoint in FAST-1 and FAST-2. On this key secondary endpoint, FAST-3 showed that icatibant was statistically superior to placebo (Table 2). On post-hoc analysis of FAST-1, a statistically significant difference between icatibant and placebo was demonstrated for the time to onset of symptom relief as defined by the 3-symptom composite VAS, the same endpoint designated as the primary endpoint in FAST-3 (Table 2). Secondary endpoints of the three studies were also generally supportive of icatibant's efficacy.

Laryngeal attacks are an important component of acute HAE attacks. Efficacy data to support laryngeal attacks were limited in FAST-1 and FAST-2 studies, and the VAS was not assessed for laryngeal attacks in these two trials. Instead, another patient-reported outcome, time to regression of symptoms/initial symptom improvement, was used. There were 3 patients in FAST-2 with laryngeal symptoms, 2 of whom reported regression of symptoms by 0.3 hour and 1 hour post-treatment and 1 patient who was intubated and unable to complete symptom scoring. In FAST-1, there were 8 patients with laryngeal attacks and the median time to regression was 0.6 hours. 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 as assessed by the VAS 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 studies. Patients' self-reported time to initial symptom improvement was consistent across the 3 studies, 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. 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. Furthermore, the pathophysiology and mechanisms of laryngeal attacks and attacks in other locations of the body are similar, therefore, the benefit across various locations of the body are expected to be similar. Existing data support this expectation.

Efficacy with repeated doses of icatibant was assessed in controlled phase of the studies where patients required more than one dose and also in open-label extension phase of the studies. In the controlled and open-label extension phase of the three studies a total of 225 patients were treated for a total of 987 attacks with 1076 doses of icatibant. Similar changes in primary and secondary efficacy endpoint measures were reported for subsequent multiple attacks, suggesting that icatibant remains effective with intermittent repeated use.

**Table 2. Median time to onset of symptom relief in hours based on the primary single-symptom VAS**

	Icatibant	Tranexamic acid (TA)	Placebo	p vs TA	p vs Pbo
FAST-2	n = 36	n = 38			
All attacks (primary endpoint) *	2.0	12.0		<0.001	
Cutaneous attacks	2.5	18.2		<0.001	
Abdominal attacks	1.6	3.5		0.026	
FAST-1	n = 27		n = 29		
All attacks (primary endpoint) *	2.5		4.6		0.142
Cutaneous attacks	3.4		10.0		0.221
Abdominal attacks	2.0		3.0		0.159
FAST-3	n = 43		n = 45		
All attacks (not primary endpoint) *	1.5		18.5		<0.001
Cutaneous attacks	2.0		22.5		<0.001
Abdominal attacks	1.0		3.6		0.002
* Median time to onset of relief in hours as measured by 0-100 mm visual analog scale on either cutaneous swelling, cutaneous pain, abdominal pain, or nausea. Sample size is for all attacks.					

**Table 3. Median time to onset of symptom relief in hours based on 3-symptom VAS**

	Icatibant	Tranexamic acid (TA)	Placebo	p vs TA	p vs Pbo
FAST-2	n = 33	n = 34			
All attacks (not primary endpoint) *	2.0	12.0		<0.001	
Cutaneous attacks	3.5	22.3		<0.001	
Abdominal attacks	1.6	2.3		0.216	
FAST-1	n = 26		n = 27		
All attacks (not primary endpoint) *	2.3		7.9		0.014
Cutaneous attacks	5.1		23.0		0.047
Abdominal attacks	2.0		6.0		0.103
FAST-3	n = 43		n = 42		
All attacks (primary endpoint) *	2.0		19.8		<0.001
Cutaneous attacks	2.0		23.9		<0.001
Abdominal attacks	1.5		4.0		0.002
* 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 abdominal pain. Sample size is for all attacks.					

## 8. Safety

### a. Safety database

The safety database for icatibant 30 mg is based primarily on data from the studies listed in Table 1. The safety database includes a total of 236 unique PHAE patients who received at least one dose of 30 mg icatibant, which includes 225 patients who participated in the three pivotal studies (FAST-1, FAST-2, and FAST-3) and their open-label extension phase. A total of 225 patients were treated for a total of 987 attacks with 1076 doses of icatibant. The safety database is small, but adequate for this orphan disease and the limited scope of treatment of acute attacks of HAE. In addition, post-marketing experience data exist from 37 countries outside the US where icatibant is marketed.

### b. Safety findings and conclusion

The safety review did not identify any major concerns. There were no deaths in the clinical studies associated with icatibant use. The most common adverse reactions were local injection site reactions. These reactions occurred in nearly all patients who received icatibant by subcutaneous injection, and were characterized by erythema and local swelling. These appeared self-limiting and resolved within a few hours of treatment. These reactions were not associated with hypersensitivity or anaphylaxis. These reactions appeared to be irritant in nature rather than mediated by specific immune response. Immunogenicity was not an issue with icatibant. Across the clinical studies, 4 patients tested positive for anti-icatibant antibodies, who subsequently tested negative.

Self-administration of icatibant was assessed in an open-label study in acute HAE attacks in patients 18 years of age and older (the EASSI trial). As of June 24, 2011, a total of 95 patients have enrolled. Of these 95 patients, 71 patients had received icatibant previously and 24 patients were naïve to icatibant at the time of enrollment. Eighty-eight of these 95 patients are reported in the self-injection safety database; the remaining 7 had received a physician-administered injection of icatibant but had not yet self-administered the drug. There were no findings of safety concerns or device problems or failures in this study.

Post-marketing data are from 37 countries outside the US where icatibant is marketed. Icatibant was first approved in the EU in July 2008, and self-administration was approved in the EU in February 2011. As of June 30, 2011, a total of (b) (4) icatibant doses (syringe and needle) have been sold in these countries. The most common adverse event reported has been injection site reactions, as observed in controlled clinical studies. Jerini has an ongoing voluntary registry that has been monitoring safety of icatibant, specifically for effects on sexual maturation (because of the animal findings), hypersensitivity reactions (because the product is a peptide), cardiac ischemic events in patients with cardiac risk factors (because of the potential effect of bradykinin inhibition on myocardial perfusion). So far no new safety signals have been identified from post-marketing experience. There was no post-marketing adverse event associated with device failure or inability of patients to comprehend instructions for use.

### c. REMS/RiskMAP

No post-marketing risk evaluation and mitigation strategies are recommended.

## **9. Advisory Committee Meeting**

A Pulmonary and Allergy Drugs Advisory Committee (PADAC) meeting was not held during review of the original NDA because the submitted studies at that time did not provide evidence of efficacy. During review of this complete response, a PADAC meeting was held on June 23, 2011. The discussion and questions were on the efficacy and safety of icatibant, and support of self-administration. The panel concluded that icatibant was efficacious, 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). The majority of panel members voted that safety data were adequate (11 Yes, 1 No, 1 Abstain). Several members suggested a post-marketing 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 benefit for the product, both in terms of patient convenience and 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).

## **10. Pediatric**

The Pediatric Research Equity Act is not triggered because of the orphan status of the application. The pivotal clinical studies enrolled patients 18 years of age and older. HAE occurs in pediatric patients younger than 18 years and it is expected that younger patients will be evaluated. Although HAE is an autosomal dominant disease, for reasons unknown, the disease often does not manifest until late childhood or adolescence. At the pre-NDA meeting for the original NDA, Jerini 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 during review of the original NDA. 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 outcomes. 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, DMEPA, DRISK, or from other groups in CDER.

## **12. Labeling**

a. Proprietary Name

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

b. Physician Labeling

Jerini submitted a label in the Physician's Labeling Rule format that contained information generally supported by the submitted data. The label was reviewed by various disciplines of this Division, DRISK, DMEPA, and by DDMAC. Various changes to different sections of the label were done to reflect the data accurately and better communicate the findings to healthcare providers. The senior Pharmacology and Toxicology staff designated icatibant as a bradykinin B2 receptor antagonist, which constitutes a new established pharmacological class. The clinical trials section (section 14) of the label primarily described the FAST-3 results, with results of FAST-1 and FAST-2 described as supportive evidence of efficacy. Adverse reactions section (Section 6) summarizes data from all pivotal studies and other sources. The Division and Jerini have agreed on the final labeling language.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division, and DMEPA, and found to be acceptable. The proposed carton labels contained a graphic symbol that has been removed because graphics decreased the prominence of the proprietary name and established name.

d. Patient Labeling and Medication Guide

There is a Patient Counseling Information (Instruction for Use and Patient Package Insert) that has been reviewed by the Division and other groups within the Center and found to be acceptable. There will no Medication Guide for this product.

## **13. Action and Risk Benefit Assessment**

a. Regulatory Action

Jerini has submitted adequate data to support approved of icatibant 30 mg subcutaneous injection for acute treatment of HAE. The recommended action on this application is Approval.

#### b. Risk Benefit Assessment

The overall risk and benefit assessment of icatibant for the treatment of acute attacks of HAE supports its approval. In terms of safety, local injection site reactions were the most common adverse event observed in clinical studies. Post-marketing safety data from 37 countries has not shown any new safety signals. Statistically significant evidence of efficacy was demonstrated in one placebo-controlled study (FAST-3) and one active-controlled study (FAST-1). Acute attacks of HAE are serious, debilitating, and potentially life-threatening. At present, Berinert, a human plasma derived C1 esterase inhibitor, and Kalbitor (ecallantide), an inhibitor of human plasma kallikrein, are approved in the US for acute attacks of HAE. Unlike icatibant, Berinert is administered intravenously, and like icatibant, Kalbitor is for subcutaneous injection. However, both Berinert and Kalbitor require administration by a healthcare professional and carry a risk of anaphylaxis. Unlike these two products, icatibant does not carry a risk of anaphylaxis and can be administered by patients at home. While CDRH has raised concerns regarding syringe-needle compatibility and recommended additional human factor testing and a potential change to a different syringe, the Division concludes that the available data are adequate to support approval of the product in the current syringe-needle configuration for reasons explained in section 3 of this review above.

#### c. Post-marketing Risk Management Activities

No post-marketing risk evaluation and management strategies are recommended.

#### d. Post-marketing Study Commitments

There will be two PMR studies and one PMC study as discussed in section 4 above.

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

/s/  
-----

BADRUL A CHOWDHURY  
08/24/2011