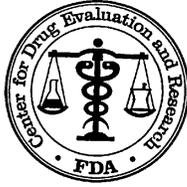


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022150Orig1s000

STATISTICAL REVIEW(S)



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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number: NDA 22150

Drug Name: Firazyr (Icatibant)

Indication(s): Hereditary angioedema

Applicant: Shire Human Genetic Therapies, Inc.

Date(s): Received: 02-25-2011; AC: 06-23-2011; PDUFA: 08-25-2011

Review Priority: P

Documents Reviewed: primary reviews by Qian Li, PhD and David Hoberman, PhD

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Keywords:

NDA review, clinical studies

1. CONCLUSIONS

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

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

2. INTRODUCTION

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

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

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

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

primary symptom, the primary efficacy endpoint for this study is the time from treatment administration to the onset of symptom relief using the composite measure VAS-3 (mean of skin swelling, skin pain, and abdominal pain).

3. STATISTICAL EVALUATION

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

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

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

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

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

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

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

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

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

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

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

	Icatibant 30mg SC		Tranexamic acid		Placebo		P value§
	N†	Time (h)	N†	Time (h)	N†	Time (h)	
Study 2102 (FAST-2)							
All attacks	36	2.0	38	12.0			<0.001
Cutaneous	24	2.5	23	18.2			<0.001
Abdominal	12	1.6	15	3.5			0.026
Study 2103 (FAST-1)							
All attacks	27	2.5			29	4.6	0.142
Cutaneous	14	3.4			13	10.0	0.221
Abdominal	13	2.0			16	3.0	0.159

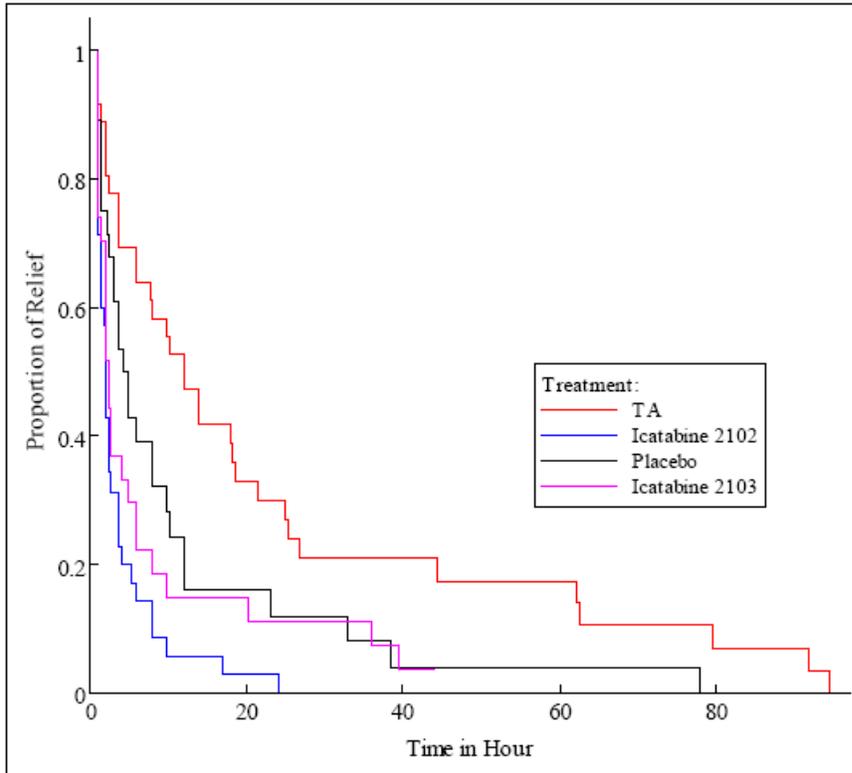
† Patients who did not achieve symptom relief within the observation period were censored at the last observation time.

Also, patients who did not have baseline VAS \geq 30 mm were removed from the analysis.

§ p-value was calculated based on Wilcoxon test.

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

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



Source: Dr. Qian Li's statistical review

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

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

Her conclusions were consistent with the clinical review team.

3.2 Review of the Findings in the Complete Response

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

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

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

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

	Icatibant 30mg SC		Tranexamic acid		Placebo		P value §
	N†	Time (h)	N†	Time (h)	N†	Time (h)	
FAST-3							
All attacks	43	2.0			45	19.8	<0.001
<i>Cutaneous</i>	26	2.0			26	23.9	<0.001
<i>Abdominal</i>	17	1.5			19	4.0	0.003
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
Study 2102 (FAST-2)*							
All attacks	35	2.0	38	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

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

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

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

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

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

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

	Icatibant 30mg SC		Tranexamic acid		Placebo		P value
	N†	Time (h)	N†	Time (h)	N†	Time (h)	
FAST-3*							
All attacks	43	1.5			45	18.5	<0.001
<i>Cutaneous</i>	26	2.0			26	22.5	<0.001
<i>Abdominal</i>	17	1.0			19	3.6	0.002
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
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

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

Also, patients who did not have baseline VAS ≥ 30 mm were removed from the analysis.

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

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

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

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

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

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

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

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

4. STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

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

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

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/s/

JOAN K BUENCONSEJO

06/29/2011

This is a secondary statistical review considering and integrating the findings of the primary statistical reviewers, Dr. Qian Li and Dr. David Hoberman. Refer to their reviews for more information about the original submission and the complete response.

THOMAS J PERMUTT

06/29/2011

concur



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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number: NDA 22150
Drug Name: Firazyr (Icatibant)
Indication(s): Hereditary angioedema
Applicant: Shire Human Genetic Therapies, Inc.
Date(s): Received: 02-25-2011; AC: 06-23-2011; PDUFA: 08-25-2011
Review Priority: P

Biometrics Division: Division of Biometrics 2
Statistical Reviewer: David Hoberman, PhD
Concurring Reviewers: Joan Buenconsejo, PhD
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Medical Division: Division of Pulmonary, Allergy and Rheumatology Products
Clinical Team: Brian Porter, MD
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Keywords:

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1. EXECUTIVE SUMMARY

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

2. INTRODUCTION

2.1 Overview

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

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

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

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

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

2.2 Data Sources

Documents reviewed were accessed from the CDER document room at:

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3. STATISTICAL EVALUATION

Study Design and Endpoints

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

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

As stated in the applicant's report,

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

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

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

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

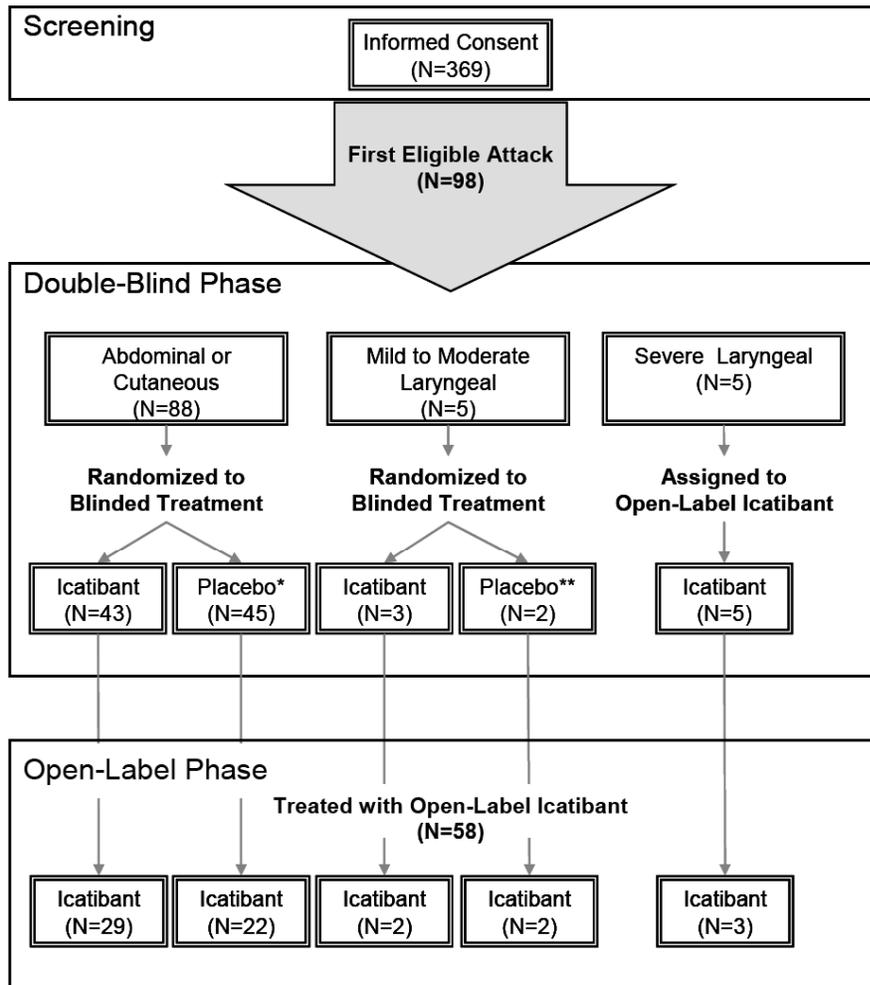
Using the log-rank test for equality of survival curve and assuming a 0.05 2-sided significant level, a power of 80%, and 40 evaluable subjects per treatment, a total of 80 evaluable subjects would be required in the randomized controlled phase of the study.

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

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

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

Figure 1: Trial HGT-FIR-054 Design



* Subject 054-311-001 received treatment with placebo, but was treated with icatibant as a rescue medication due to increasing severity of symptoms.

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

Statistical Methodologies

The following described the analytical approach used by the applicant:

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

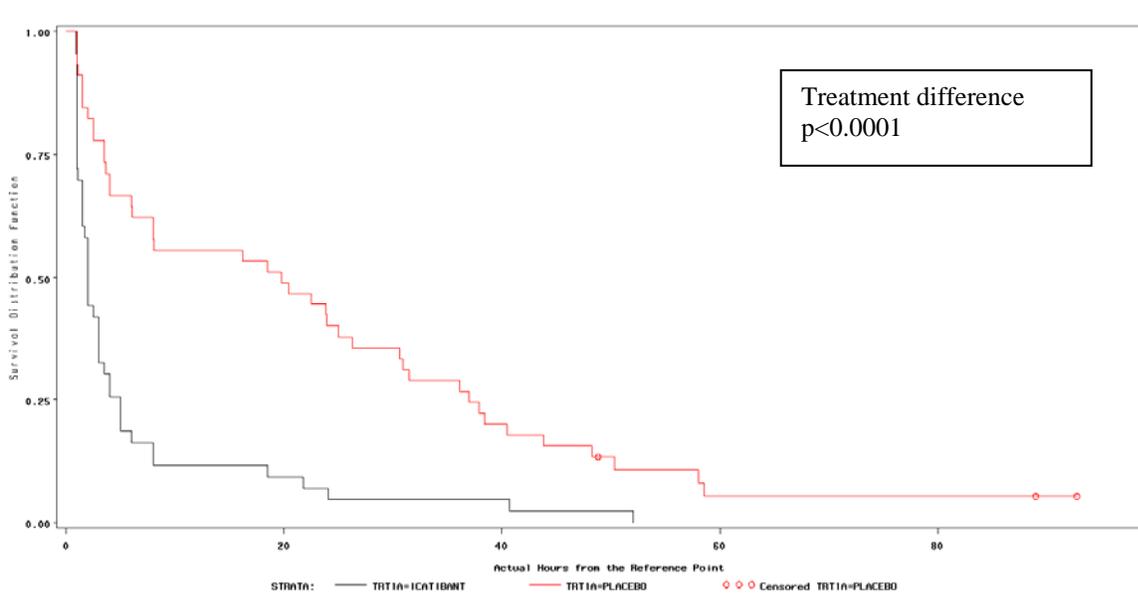
A Peto-Peto Wilcoxon test with a global 2-sided significance level of 5% was used to test the null hypothesis for the non-laryngeal ITT, non-laryngeal per-protocol, ITT, and laryngeal populations. The Peto-Peto Wilcoxon test was selected for this analysis as it gives more weight to earlier achievement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

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

Results and Conclusions

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

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



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Table 1 Composite Symptom Score – All Subjects

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

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

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

Secondary Endpoint

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

Figure 3: Time to Secondary VAS Endpoint: all subjects

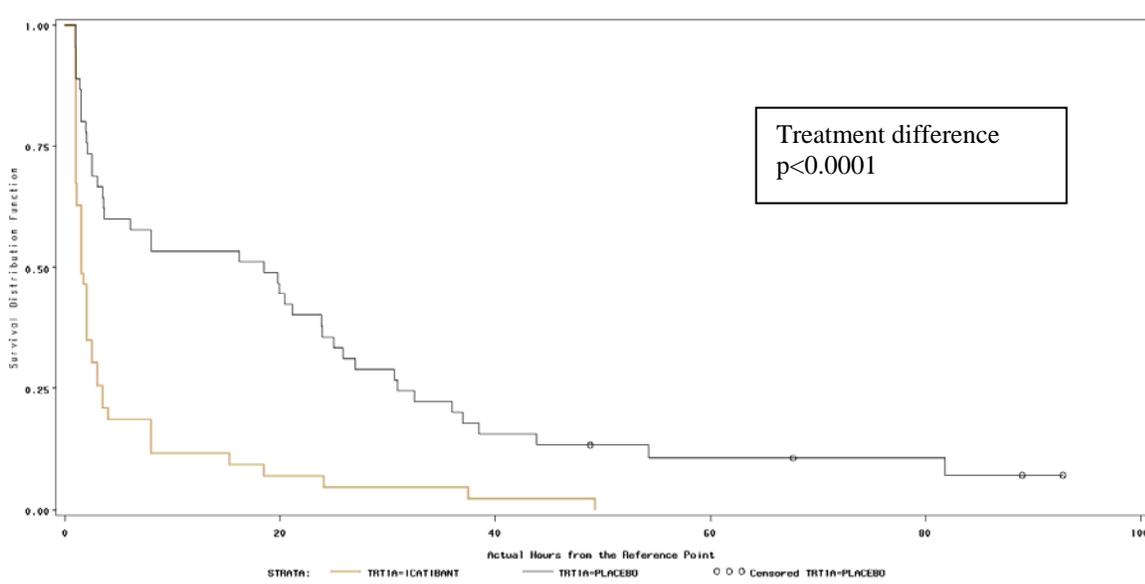


Table 2 Secondary VAS Endpoint – All Subjects

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

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

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

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

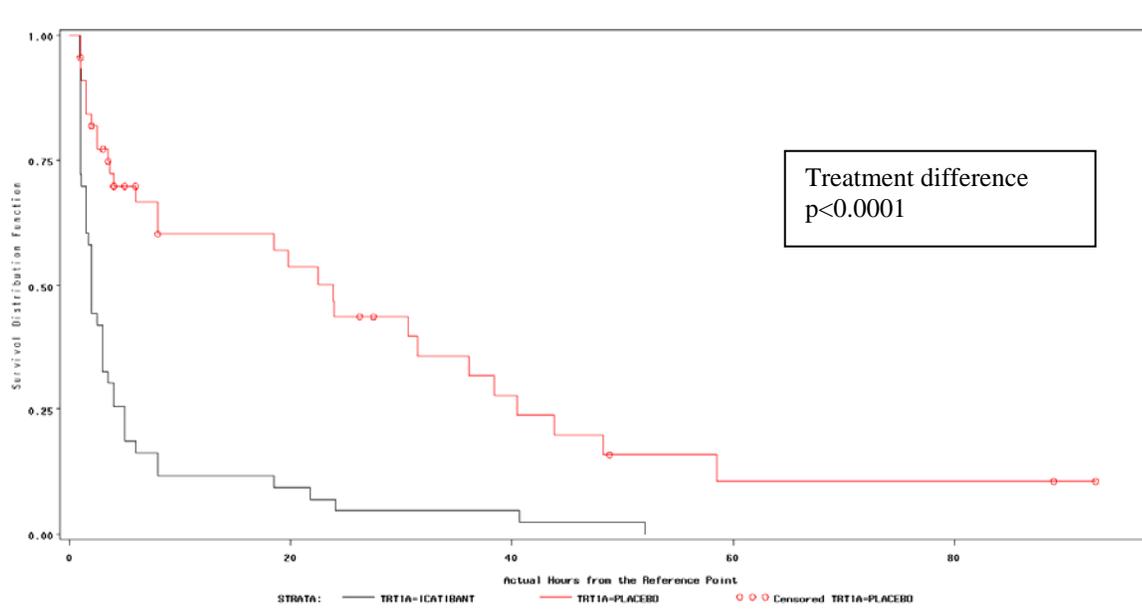
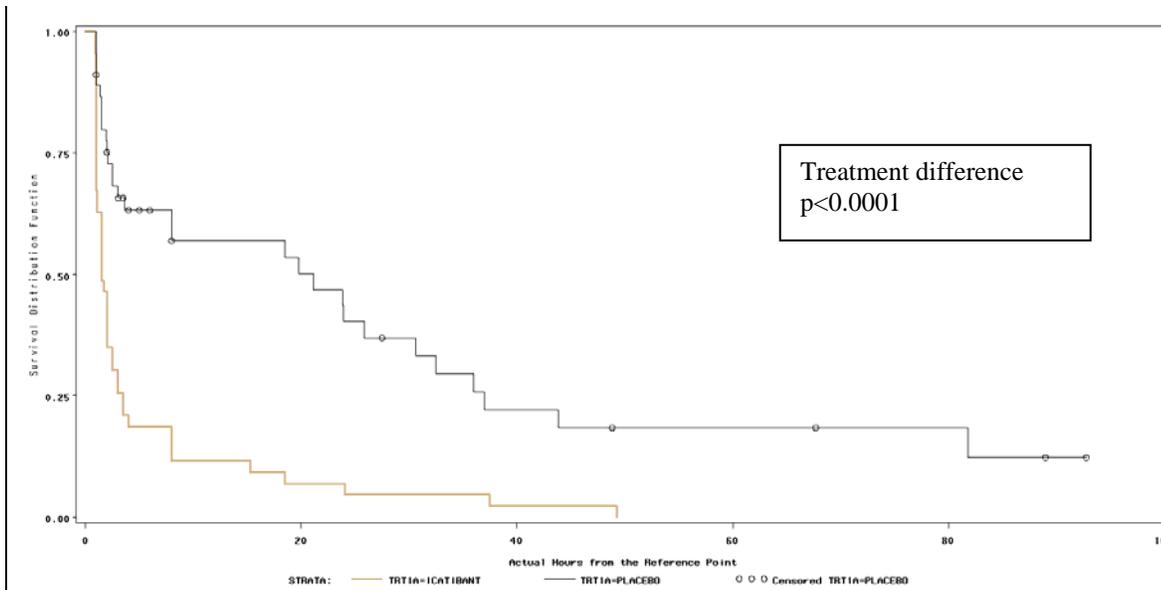


Figure 5: Time to 50% Reduction in VAS (Primary Symptom Score: all subjects) including censoring for Rescue Medication



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

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

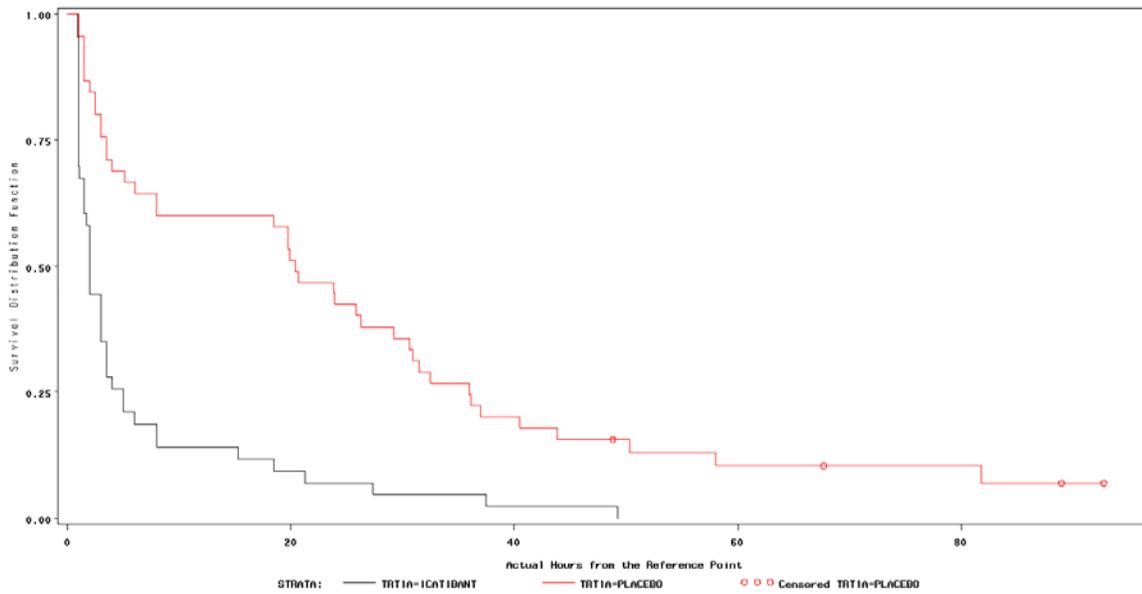


Figure 7: Time to 50% Reduction in VAS (Primary Symptom = Abdominal pain)

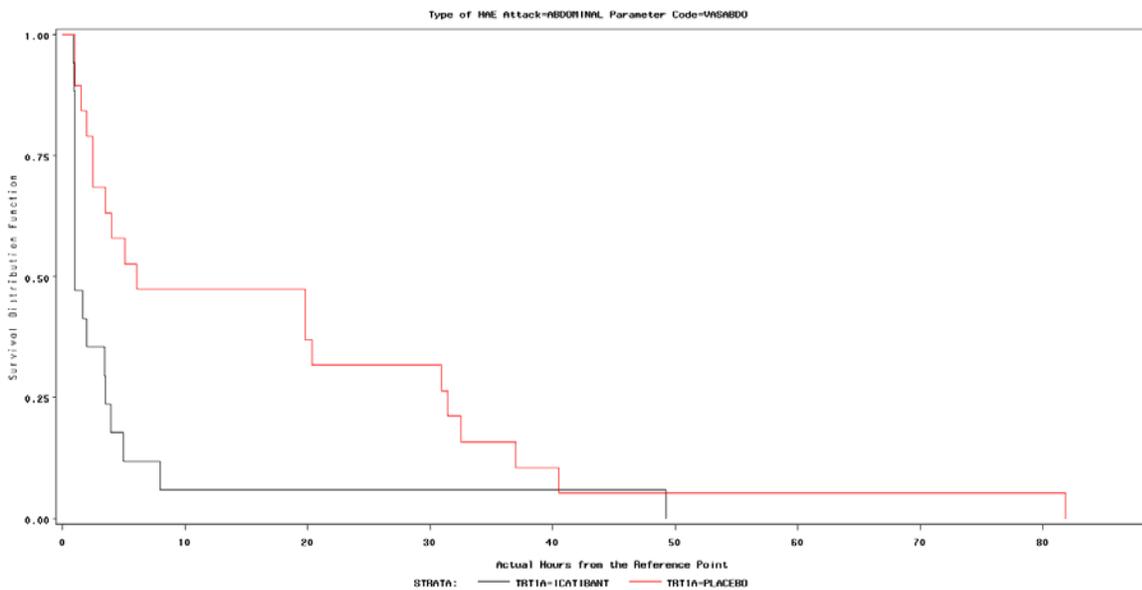


Figure 8: Time to 50% Reduction in VAS (Primary Symptom = Skin Pain)

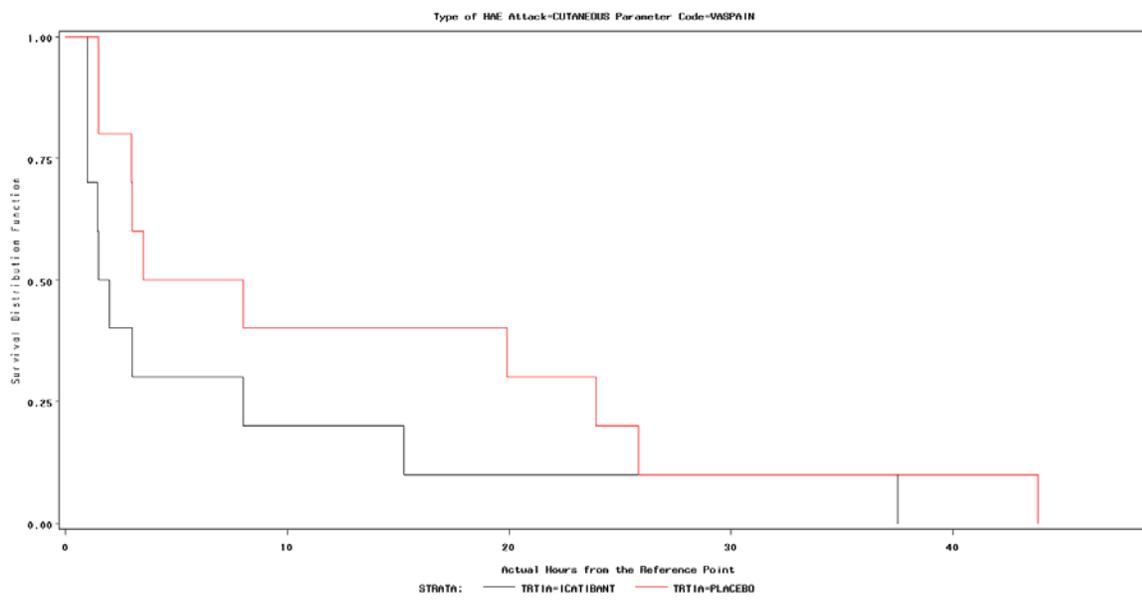
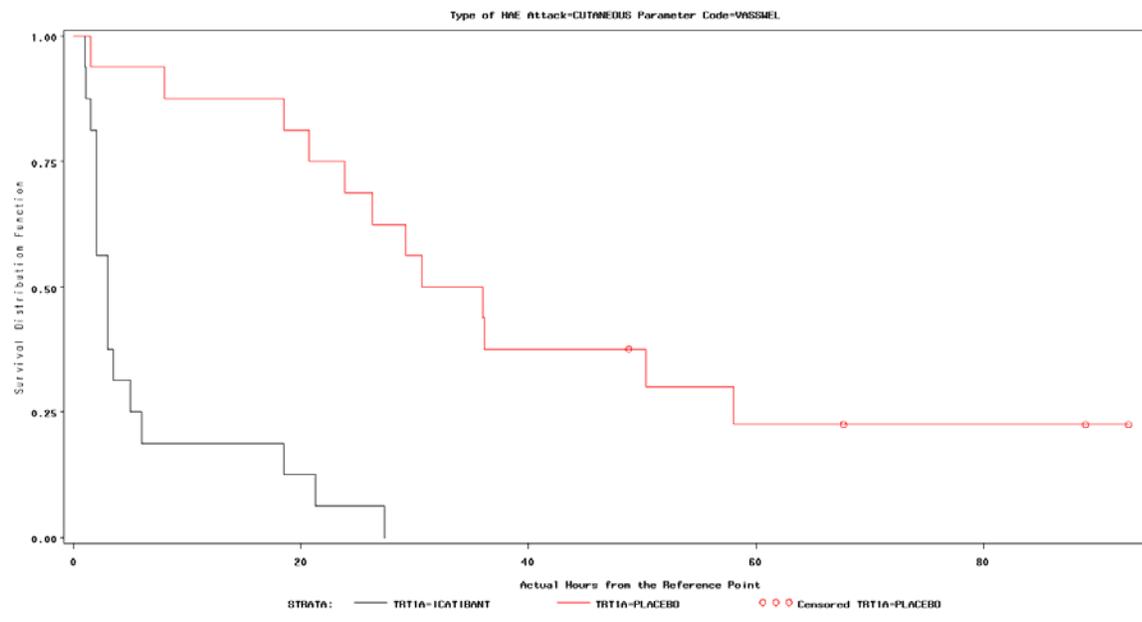


Figure 9: Time to 50% Reduction in VAS (Primary Symptom = Skin Swelling)



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

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

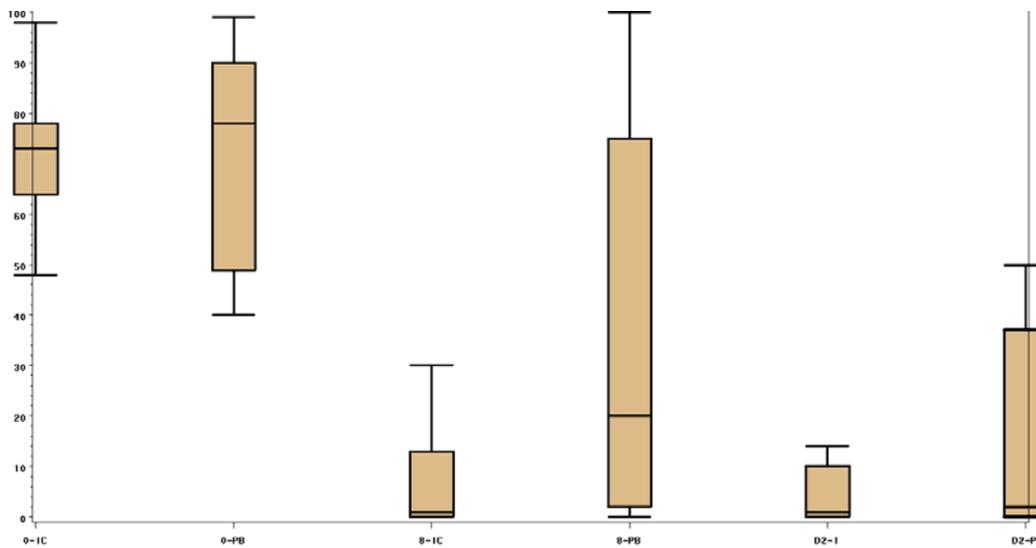


Figure 11: VAS Scores at Pretreatment, 8 Hours, and Day 2 Evening – Skin Pain

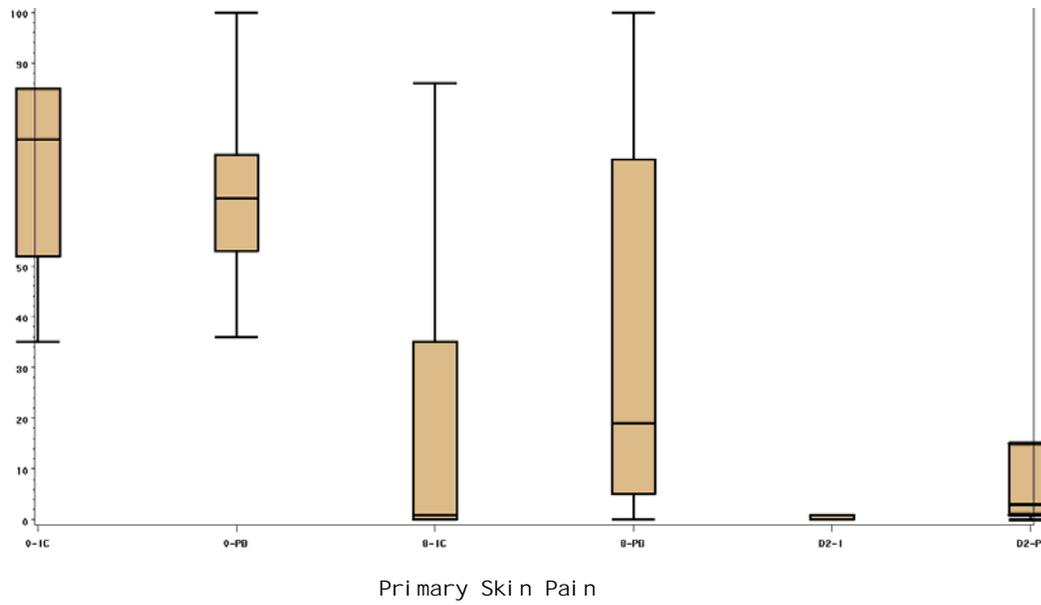
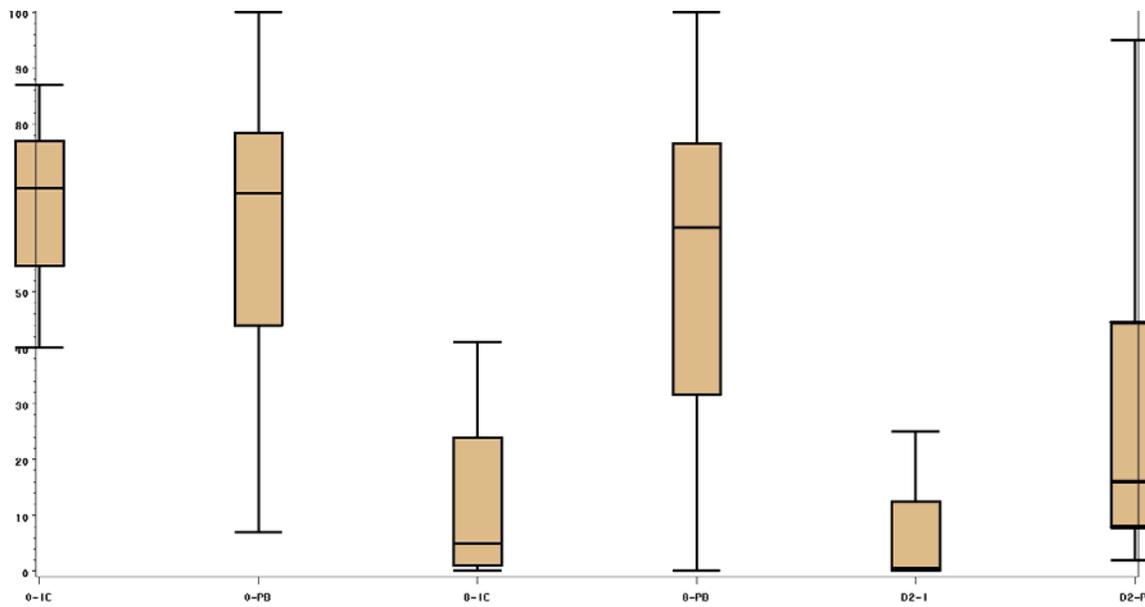


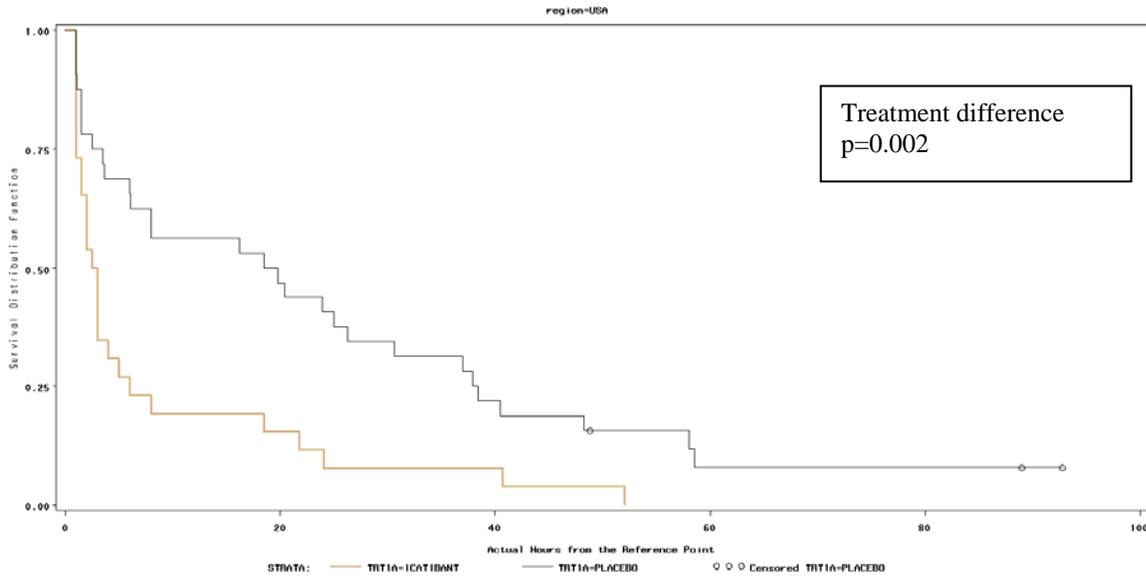
Figure 12: VAS Scores at Pretreatment, 8 Hours, and Day 2 Evening – Skin Swelling



4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

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

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



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

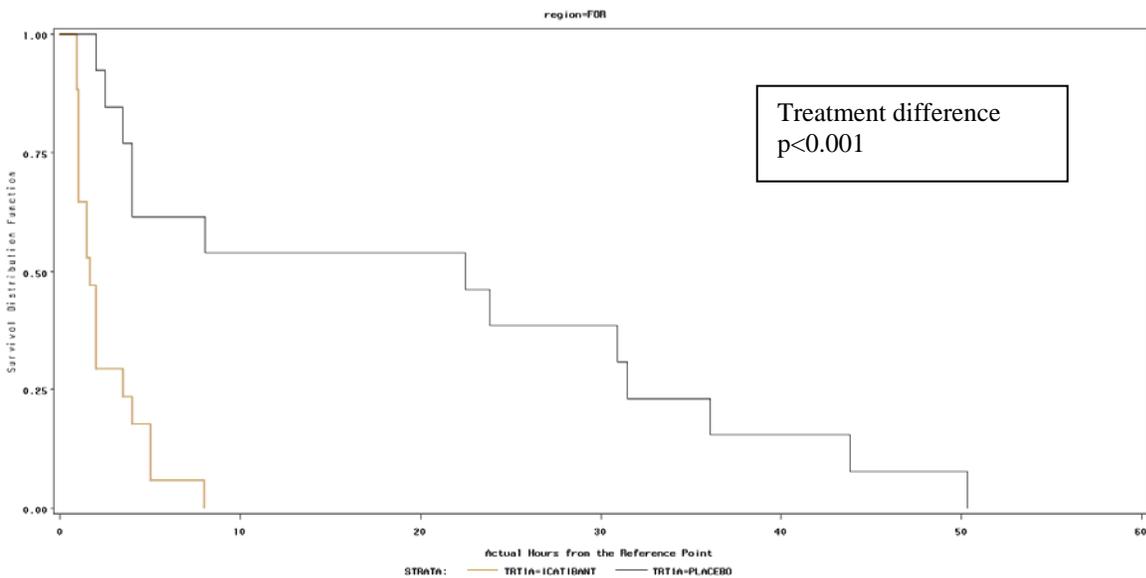
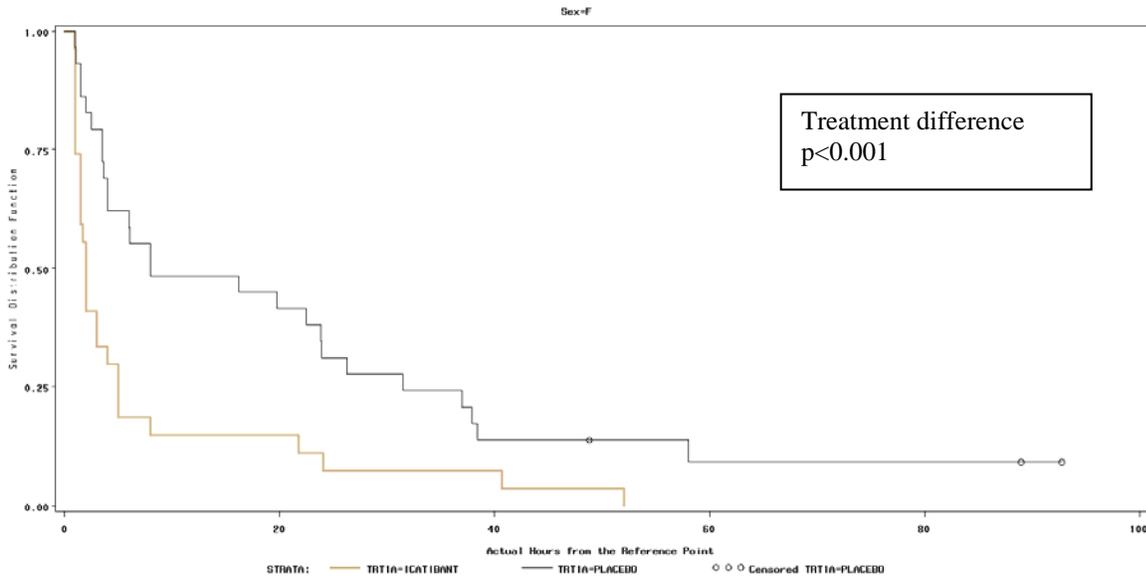
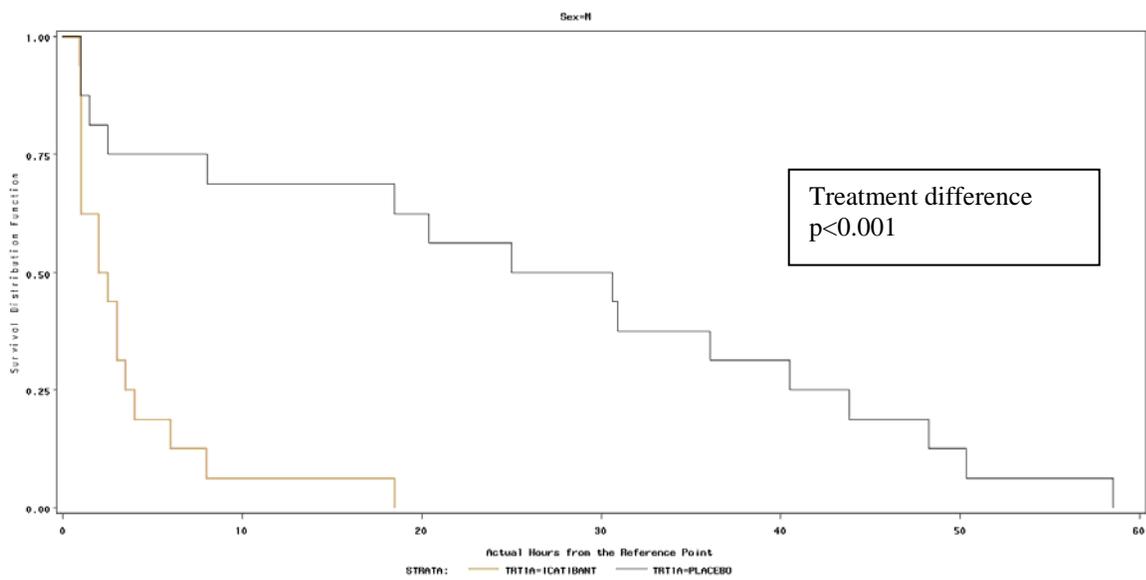


Figure 15: Time to 50% Reduction in VAS (Composite Symptom Score: all subjects) - FEMALE



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



5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

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

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

Note: The median time to onset was calculated using Kaplan-Meier methodology.

The Wilcoxon version of the log-rank test of SAS was used

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

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

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

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

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

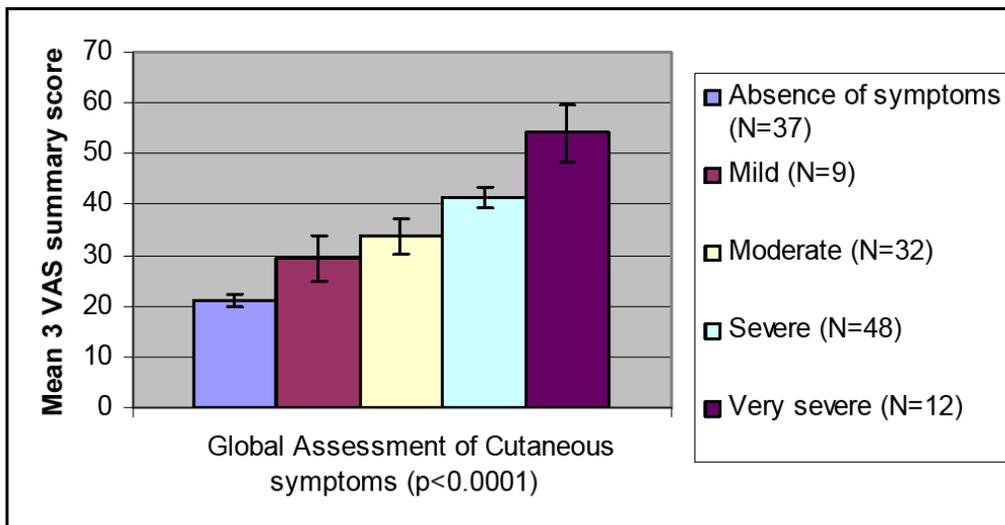
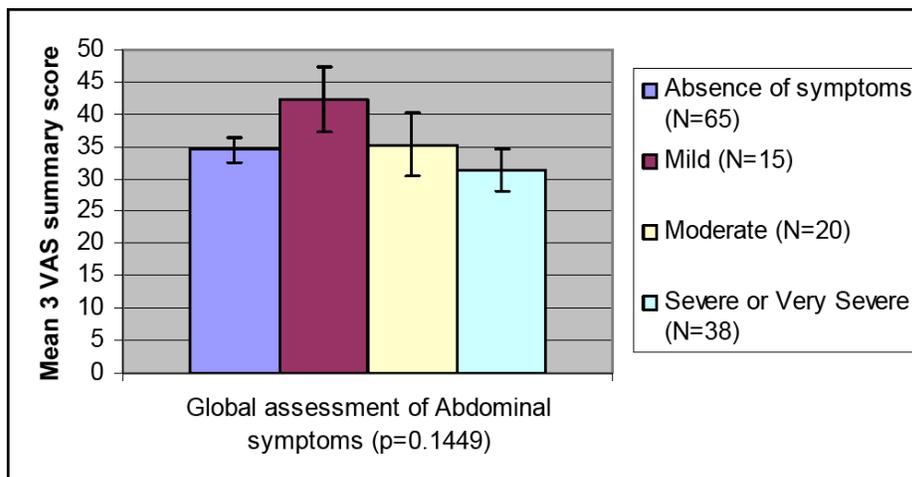


Figure 6. Clinical validity of the VAS-3 according to the global assessment of abdominal symptoms



5.2 Conclusions and Recommendations

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

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/s/

DAVID HOBERMAN
06/29/2011

JOAN K BUENCONSEJO
06/29/2011

I concur with Dr. Hoberman's review and recommendation.

THOMAS J PERMUTT
06/29/2011
concur



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

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number: N22-150/000
Drug Name: Icatibant 30 mg solution for subcutaneous injection
Proposed Indication(s): Treatment of hereditary angioedema attack
Applicant: Jerini US Inc.
Date(s): Received October 22, 2007
Review Priority: Priority

Biometrics Division: Division of Biometrics II/Office of Biostatistics
Statistical Reviewer: Qian H. Li, Sc.D.
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Medical Division: Division of Pulmonary and Allergy Products
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Project Manager: Carol Hill

Keywords: NDA review

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

In this NDA submission, Jerini US Inc. submitted icatibant 30 mg solution for injection for the treatment of hereditary angioedema (HAE) attack. The treatment is a single-dose administrated subcutaneously (s.c.). The efficacy evaluation of icatibant 30 mg was based on two randomized, double-blind, and multicenter phase 3 studies; Study 2102 with an active-control and Study 2103 with a placebo-control.

In the two studies, patients who experienced HAE attacks in either the abdominal region, cutaneous region, or both were randomized in a 1:1 ratio to either icatibant or control. The randomized patients should have symptoms of at least 30 mm in visual analogue scale (VAS) ranging from 0 to 100 mm. The primary efficacy endpoint was the time from treatment to the onset of symptom relief which was defined as a minimum reduction of 14 percent of the baseline score plus a further reduction of 16 mm.

Study 2102 randomized 74 patients, with 36 to icatibant and 38 to tranexamic acid, which was the active control. Study 2103 randomized 56 patients, with 27 to icatibant and 29 to placebo. According to the defined symptom relief, the icatibant showed statistically significantly faster relief of symptoms in comparison to tranexamic acid in Study 2102. The median response time was 2 hours in icatibant and 12 hours in tranexamic acid. However, the treatment difference between icatibant and placebo did not reach statistical significance in Study 2103. The median response time was 2.5 hours in icatibant and 4.6 hours in placebo.

Cross-study comparisons indicated that the two icatibant treatment groups shared a similar response pattern in the pre-specified symptom relief. It took more time to achieve the defined symptom relief in the tranexamic acid group than the placebo group. In turn, it took more time in placebo to achieve the symptom relief than the two icatibant groups. The treatment difference between tranexamic acid and placebo was greater than the differences between placebo and either of the two icatibant treatment groups. Given such observations in the two phase 3 studies and the lack of understanding in the treatment effect of tranexamic acid in treating HAE attack, this reviewer reached the following conclusions:

- If it was a valid statement that tranexamic acid was no worse than placebo, given the observations that the difference between tranexamic acid and placebo was greater than the difference between placebo and icatibant, it was fair to conclude that placebo was no worse than icatibant. Therefore, icatibant was no better than placebo.
- If tranexamic acid was in fact worse than placebo, Study 2102 would no longer be a valid study to support the efficacy evaluation of icatibant. With only one placebo-controlled study which did not show significant treatment difference at the level of 0.05 for the 2-sided p-value, there was no convincing evidence to support that icatibant was efficacious in treating patients with HAE attacks.

1.2 Statistical Issues and Findings

Several statistical issues were assessed and discussed in this review and are summarized in this section.

Unblinding

The sponsor discussed the concern of unblinding the treatments due to irritating reactions in the injection sites of the icatibant treatment groups. However, the sponsor did not find a solution to this problem. Based on the reviewer's analyses, compared with less than 10% in the control groups, close to 90% of the patients in the icatibant treatment groups in both studies showed at least 2 reaction symptoms out of six symptoms assessed. These symptoms included erythema, irritation, pain, pruritus, swelling, and warmth. As the efficacy assessment was based on the subjective measurements using VAS, it was possible that bias was introduced in the assessment when the treatments could be unblinded easily. If the reaction at the injection site is unavoidable, covering the injection site during the period of symptom assessments might help to reduce the potential bias.

Endpoints

Several problems in the definition of the primary endpoint made it difficult in understanding the treatment differences between icatibant and controls. The primary endpoint was defined as the time from the treatment to the onset of symptom relief in one primary symptom. The symptom relief was defined as a minimum reduction of 14 percent of the baseline score plus a further reduction of 16 mm in the primary symptom which was at least 30 mm at baseline.

As an attack could manifest several symptoms including abdominal pain, skin swelling, skin pain, and nausea, the information was wasted if the primary endpoint only focused on one primary symptom. Overall assessments on all the symptoms that a patient experienced during an attack should be more meaningful than just one symptom. To understand the treatment effect on all symptoms that patients experienced during the attacks, this reviewer explored analysis using all symptoms reported at the baseline prior to the treatment. The Anderson-Gill model for multivariate survival analysis was applied to assess all available symptom jointly. This reviewer considered this only an exploratory analysis since there were concerns on if it was appropriate to assess all the symptoms using VAS. Furthermore, it was not clear how to capture the symptoms that manifested after the administration of the treatment in the model.

The definition of the symptom relief was perceived inadequate as a reduction from 100 mm to 70 mm in VAS was considered to be symptom relief in a patient while the patient was still suffering from the severe symptom. Even if statistically significant treatment difference was demonstrated using such an endpoints, it is questionable if the patients would indeed benefit from the icatibant treatment. The sponsor explored a relatively stringent definition for symptom relief which was discussed in this review. This exploratory definition actually showed a larger treatment difference than the specified definition in the placebo-controlled study.

1.3 Data Sources

All documents and data were available in the electronic document room.

2. STATISTICAL EVALUATION OF INDIVIDUAL STUDIES

2.1 Study Design of Studies 2102 and 2103

Study Objectives

The primary objective of the two studies was to evaluate the efficacy of icatibant compared with control on the onset of symptom relief resulting from moderate to very severe acute cutaneous and abdominal edema attacks in patients with HAE.

The secondary objectives were:

- To evaluate the rate of response, time to almost complete relief, global outcome, and severity of each symptom
- To evaluate the safety and tolerability of icatibant

General Design

The two phase 3 studies were randomized, controlled, parallel groups, multi-center, and double-blind studies. Patients older than 18 years of age and with documented diagnosis of HAE Type I or II and current edema attack in cutaneous and abdominal and/or laryngeal areas were recruited. Patients with laryngeal attack were treated with open label icatibant and not randomized. Patients with moderate or severe cutaneous and/or abdominal symptoms were randomized in 1:1 ratio to receive either one dose of icatibant or control subcutaneously. The randomization was stratified by the symptom locations -- abdominal or cutaneous regions. Patients with both cutaneous and abdominal symptoms were allocated to the abdominal stratum if the abdominal symptom was moderate to very severe irrespective of the severity of cutaneous symptoms. A stochastic minimization randomization scheme was used to maintain balance between treatments within centers and edema locations. Patients completing the randomized treatment phase were enrolled to open-label treatment extension for future attacks. The results from the open-label phase were not covered in this review.

Efficacy evaluation and endpoints

The symptom assessed included abdominal pain, nausea, cutaneous pain, and cutaneous swelling. The symptoms were measured using a visual analogue scale (VAS) ranging from 0 to 100 mm. The symptom was assessed at Hours 0 (baseline), 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, and three times a day in the morning, midday, and evening in Day 2 to Day 5 post-treatment. The symptom relief, based on the statistical analysis plan, was defined as a minimum reduction of 14 percent of the baseline score plus a further reduction of 16 mm in the primary symptom which

was at least 30 mm at baseline. Furthermore, such reduction needed to be maintained in three consecutive time points.

The primary efficacy endpoint was the time from treatment to the first time point with onset of symptom relief. For the cutaneous stratum, the time to onset of symptom relief was based on the most severe symptoms among swelling or pain (skin). If both were equally severe, pain was used. For the abdominal stratum, the time to onset of symptom relief was based on the abdominal pain. The symptom relief was censored in patients with no symptom relief at the time of their last symptom assessment.

Secondary endpoints:

- Response rate at 4 hours after start of treatment -- defined as the proportion of patients with onset of symptom relief for the primary symptom within 4 hours after treatment.
- Time to the relief of each symptom presented in pre-dose VAS including the all symptoms.
- Time to almost complete symptom relief which was defined as a score between 0 and 10 mm on the VAS for at least three consecutive measurements for all symptoms (present at pre-dose or not).
- Patient and investigator's symptom score which was obtained using a 5-point scale: 0=none, 1=mild, 2=moderate, 3=severe, and 4=very severe.
- Global assessment which considered all abdominal, cutaneous, and/or laryngeal symptoms combined. They were performed by the investigator using the same 5-point scale defined for the symptom score.
- More ...

Analysis populations

Three analysis populations were defined, including safety population, intent-to-treat (ITT) population, and per-protocol (PP) population. The efficacy analyses were performed using the ITT and PP populations.

The ITT population included all randomized patients who received double-blind treatments.

The PP population included all ITT patients who had no major deviations from the protocol procedures and who received treatment within 6 hours after onset of moderate symptoms. Patients with a pre-dose VAS of less than 30 mm for the primary symptom were excluded. The major protocol deviation criteria were listed in Appendix 1 of the statistical analysis plan.

The safety population included all randomized patients who received trial medication and for whom a safety assessment was available.

Statistical methods and handling of missing data

Wilcoxon log-rank test was used to analyze the time from treatment to the symptom relief.

The sponsor also planned to conduct a supportive analysis for the time to onset of symptom relief taking into account the rescue medication used before the onset of symptom relief and the time

from the first symptom became moderate until treatment start. A proportional hazard model was used including the rescue medication use and the time from the first symptom to treatment start as covariates. This reviewer did not think that this analysis was appropriate as the use of rescue medication was the consequence of the treatments.

The sponsor assessed subgroup analyses by the primary symptom locations, gender, and body weights.

2.2 Study Results of Studies 2102 and 2103

Study 2102 was conducted during the period of March 1st, 2005 and July 25th, 2006 in Europe including Austria, France, Germany, Hungary, Ireland, Israel, Italy, Lithuania, Poland, Sweden, Switzerland, and United Kingdom. Study 2103 was conducted during the period of December 28th, 2004 and July 17th, 2006 at 25 sites in US, Canada, Australia and Argentina.

Patient disposition

Study 2102 enrolled 77 patients, of which 3 patients with laryngeal symptoms were treated with icatibant in open label. The rest of the 74 patients were randomized to either icatibant (36 patients) or placebo (38 patients). All of the randomized patients were included in the safety and ITT patient populations. Four patients in the icatibant group and 3 from the placebo group were excluded from the PP population.

Study 2103 enrolled 64 patients, of which eight of the 64 patients received open label icatibant treatment for laryngeal symptoms. The rest of 56 patients were randomized to receive either icatibant (27 patients) or placebo (29 patients). All of the randomized patients were included in the safety and ITT patient populations. Three patients from icatibant and 2 from placebo were excluded from the PP population due to major protocol violations. Only 1 patient discontinued the study in the icatibant group prematurely.

The numbers of patients in the ITT populations are summarized in Table 1.

Demographic and baseline information in the ITT populations

In Study 2102, all randomized patients were Caucasians. The majority of the patients were female (64%). The mean age was 41 years. In Study 2103, there were more male patients in the icatibant group (41%) than that in the placebo group (28%). The majority was female. The mean age was 35 years, ranging from 18 to 58 years. The majority of patients were Caucasians.

There were some imbalances observed in the medical history information between treatment groups in both studies. Given the sample sizes in each study, it was possible to observing some imbalances in many body systems and preferred terms that were examined. However, it was not clear if any of the imbalances could influence the efficacy assessment of the treatment difference.

The numbers of patients experienced attacks during the last 6 months are also summarized in Table 1.

Table 1: Patient disposition and baseline information.

	Study 2103		Study 2102	
	Icatibant	Placebo	Icatibant	Tranexamic
#of ITT patients	27	29	36	38
Cutaneous stratum	14	13	24	23
Abdominal stratum	13	15	12	15
Number of patients experienced attacks during the last 6 months				
Cutaneous	20	21	35	32
Abdominal	20	19	26	22
Cutaneous and abdominal	10	9	12	15

Blinding

The sponsor mentioned that blinding treatment could be compromised as some patients had local reactions such as erythema, swelling, itching, burning, warm sensation, and cutaneous pain after s.c. injection of icatibant. The sponsor stated that this problem could not be avoided because of reasons including ethical concerns. The local tolerability of the injection site was assessed half hour after the injection.

To understand the seriousness of the unblinding issue due to irritating reactions at the injection site, data collected at the injection sites 30 minutes after the injection were analyzed for the double-blind phase by the reviewer. Table 2 summarizes the number of patients had reactions by the six symptoms assessed. As can be seen from Table 2, almost every icatibant patients in both studies experienced erythema, compared with about 10% in the control groups. The majority of the icatibant patients also experienced swelling while only few in the control groups. More than half of the icatibant patients also experienced warmth sensation, compared with only 1 patient in each control group of the two studies.

Table 2: Number of patients experienced reactions at injection site by reaction symptoms.

Local reactions at injection site	Study 2103		Study 2102	
	Icatibant (n=27)	Placebo (n=29)	Icatibant (n=36)	Tranexamic (n=38)
Erythema	26	4	35	3
Irritation	5	2	14	2
Pain	3	1	5	0
Pruritus	4	0	9	0
Swelling	21	3	24	6
Warmth	17	1	17	1

To understand the scope of the reaction at the injection sites, data were also analyzed by the number of symptoms which were manifested at the injection site by this reviewer. The results are summarized in Table 3. As it can be seen from Table 3, closed to 90% of the icatibant patients in both studies, compared with less than 10% patients in the control groups, experienced at least 2 symptoms at the injection site.

Based on these analyses, the blinding of the treatments could be broken easily by examining the number of symptoms and the types of the symptoms at the rejection sites.

Table 3: Number of patients experienced the local reactions by number of symptoms.

Number of reactions at injection site	Study 2103		Study 2102	
	Icatibant (n=27)	Placebo (n=29)	Icatibant (n=36)	Tranexamic (n=38)
6	0	0	3	0
5	3	0	3	0
4	5	0	5	0
3	7	0	6	0
2	9	3	14	2
1	2	5	3	8
0	1	21	2	28

Concomitant medicine

Every one in the placebo group used concomitant medication, compared with 78% in the icatibant group in Study 2103 during the double-blind treatment phase. Fewer patients in the tranexamic acid group (61%) than the icatibant group (72%) used concomitant medication during the double-blind treatment phase in Study 2102. Both studies showed that more patients in the control groups than the icatibant groups used rescue medication during the double-blind treatment. The concomitant and rescue medication use is summarized in Table 4.

Table 4: Number of patients used concomitant and rescue medication during double-blind treatment.

	Study 2103		Study 2102	
	Icatibant (n=27)	Placebo (n=29)	Icatibant (n=36)	Tranexamic (n=38)
Concomitant medication	21 (78%)	29(100%)	26 (72%)	23 (61%)
Concomitant rescue medication	6 (22%)	14 (48%)	7 (19%)	12 (32%)

Results of efficacy analyses

1) Primary endpoint

In Study 2102, one patient in icatibant and two in tranexamic acid groups did not have baseline VAS ≥ 30 mm, therefore, were removed from the analysis (not included in the risk set for the survival analysis). Two patients in the tranexamic acid group did not show symptom relief based on the definition and were counted as censored. The median time to the onset of symptom relief was 2 hours in icatibant and 12 hours in the tranexamic acid group. The treatment difference was highly statistically significant based on the Wilcoxon log-rank test.

In Study 2103, one patient in the placebo group was removed from the analyses because the baseline VAS was below 30 mm at the treatment. Almost all patients except one in each treatment group had symptom relief during the observed time. The median time to the onset of symptom relief was 2.5 hours in the icatibant treatment group vs. 4.6 hour in the placebo

treatment group. The Wilcoxon log-rank test for the time from the start of treatment to the onset of symptom relief yielded a p-value of 0.142 for the treatment difference.

The primary efficacy results are summarized in Table 5. Additional analyses performed by this reviewer are also displayed in Table 5, including Log-rank tests, stratified Wilcoxon and Log-rank tests which were stratified by the primary symptom locations (abdominal or cutaneous regions). In Study 2103, it was observed that the Wilcoxon tests yielded relatively smaller p-values compared with the log-rank tests. This observation further confirmed that there was larger separation between treatments in early response time. The relatively smaller p-values in the stratified tests also revealed what was observed in the data. That is, the symptom relief response overtime in the placebo group depended upon the location of the attack which can be seen in the analyses by strata. As the treatment difference was large in Study 2102, the strata effect become less prominent.

As the location of attack was a stratification factor in randomization, the primary analyses by attack locations are also presented in Table 5. The results indicated that in the control groups in both studies, the abdominal symptoms appeared to respond faster than the cutaneous symptoms. Such difference between strata in the icatibant groups was much smaller.

Table 5: Summary of the primary efficacy results.

	Study 2103		Study 2102	
	Icatibant (n=27)	Placebo (n=29)	Icatibant (n=36)	Tranexamic (n=38)
All Strata				
Responder	26	27	35	34
Censored	1	1	0	2
Median (hr)	2.5	4.6	2.0	12.0
Wilcoxon (Sponsor's analysis)	0.142		<0.001	
Log-rank	0.358		<0.001	
Stratified Wilcoxon	0.065		<0.001	
Stratified Log-rank	0.192		<0.001	
Cutaneous Stratum	(n=14)	(n=13)	(n=24)	(n=23)
Responder	14	12	23	21
Censored	0	1	0	2
Median (hr)	3.4	10.0	2.5	18.2
Wilcoxon p-value	0.221		<0.001	
Abdominal Stratum	(n=13)	(n=16)	(n=12)	(n=15)
Responder	12	15	12	13
Censored	1	0	0	0
Median (hr)	2.0	3.0	1.6	3.5
Wilcoxon p-value	<0.159		0.026	

2) Secondary endpoints

Among the many secondary endpoints specified and more explored, it was not clear which secondary endpoints should be reviewed thoroughly. For the purpose of understanding the effect of icatibant, this review included a few secondary endpoints which might provide more insights into the treatment effect.

Response rate at 4 hours after the start of the treatment:

The results of the analyses by the sponsor on this endpoint are summarized in Table 6 and were considered consistent with what was shown in the primary endpoint.

Table 6: Analyses on response rate at 4 hours.

	Study 2103		Study 2102	
	Icatibant (n=27)	Placebo (n=29)	Icatibant (n=36)	Tranexamic (n=38)
# of patients with baseline VAS \geq 30 mm	27	28	35	36
Responders	18 (66.7%)	13 (46.4%)	28 (80.0%)	11 (30.6%)
Fisher's exact test	0.176		<0.001	

Time to relief of each symptom presented in pre-dose:

The results of analyses by the sponsor are summarized in Table 7. The sponsor performed the analyses in each symptom. In addition to the sponsor's analyses, this reviewer explored to perform multivariate survival analyses including all the symptoms at pre-dose. Anderson-Gill model was used appropriate for these analyses. The results of the multivariate survival analyses are also displayed in Table 7.

Table 7: Analyses on time to the relief of all symptoms presented in pre-dose.

	Study 2103		Study 2102	
	Icatibant (n=27)	Placebo (n=29)	Icatibant (n=36)	Tranexamic (n=38)
Abdominal pain	15	18	12	13
Censored	1	0	0	0
Median (hr)	2.0	3.3	1.2	3.5
p-values	0.056		0.026	
Skin swelling	18	19	27	26
Censored	0	2	0	2
Median (hr)	3.1	10.2	2.6	18.1
p-values	0.039		<0.001	
Skin pain	9	12	16	16
Censored	0	1	0	0
Median (hr)	1.6	9.0	1.6	3.5
p-values	0.007		0.003	
Nausea	10	8	4	7
Censored	0	0	0	0
Median (hr)	1.1	2.3	1.3	1.5
p-values	0.080		0.550	
Anderson-Gill model	<0.001		<0.001	

3) Sponsor's post-hoc analyses

A more stringent definition of the symptom relief than the one pre-specified was explored. The post-hoc symptom relief was defined as a minimum reduction of 3/7 of the baseline score plus a

further reduction of 50/7 mm in the primary symptom, which required 50 mm reduction in a symptom when baseline score was 100 mm to qualify for a responder. By this definition, a larger treatment differences were seen in both studies in comparison to the pre-specified definition.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In addition to the subgroup analyses by attack location, the sponsor performed subgroup analyses by gender which are summarized in Table 8. In addition, the region differences were assessed by conducting subgroups analyses by US and non-US region for Study 2103 only. These subgroup analyses are displayed in Table 9. The results of these subgroup analyses should not be over interpreted for the small sizes.

Table 8: Subgroup analyses by genders.

	Study 2103		Study 2102	
	Icatibant (n=11)	Placebo (n=8)	Icatibant (n=12)	tranexamic (n=15)
Male in ITT population				
Responder	10	7	11	14
Censor	1	1	0	1
Median time to symptom relief (hr)	2.7	23.0	3.5	14.0
Wilcoxon log-rank p-value	0.160		0.013	
Female in ITT population	(n=16)	(n=21)	(n=24)	(n=23)
Responder	16	20	24	20
Censor	0	0	0	1
Median time to symptom relief (hr)	2.0	3.3	1.6	10.0
Wilcoxon log-rank p-value	0.273		<0.001	

Table 9: Reviewer’s US and non-US subgroup analyses for Study 2103.

	US subgroup		Non-US subgroup	
	Icatibant (n=16)	Placebo (n=14)	Icatibant (n=11)	Placebo (n=15)
Responder	15	13	11	14
Censored	1	1	0	0
Median (hr)	2.25	7.0	2.5	3.6
Wilcoxon	0.129		0.550	

5. Collective Evidence and Label Recommendation

5.1 Collective Evidence

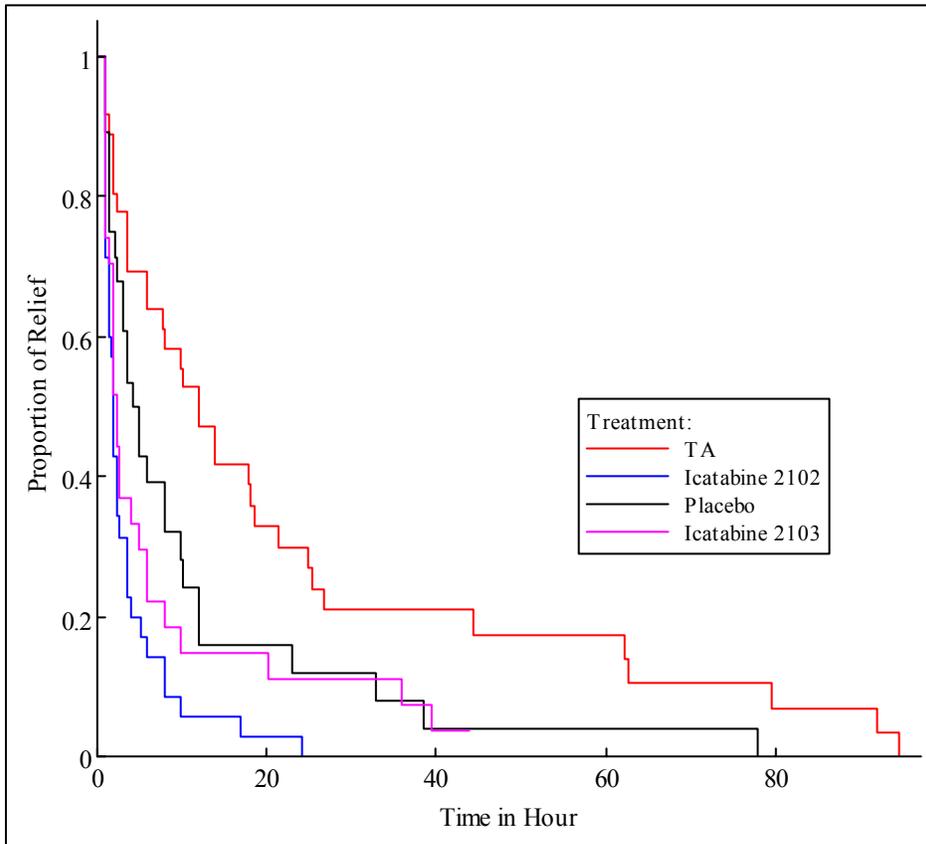
In this review process, many thoughts were given in hope to understand if the active-controlled study could be used to support the efficacy evaluation of icatibant. The sponsor believed that tranexamic acid was no worse than placebo. However, there was no supporting evidence to show that tranexamic acid did not harm patients. This reviewer did cross-study comparisons to gain better understanding of the performance of all the treatment arms. Figure 1 shows the response of the symptom relief over time for the four treatments from the two studies.

As can be seen from Figure 1, the two icatibant treatment groups shared a similar response pattern. As the two studies were similarly designed and conducted in the same patient

population, this observation further validated that this cross comparisons between the two studies was appropriate.

Figure 1 shows that it took more time to achieve the defined symptom relief in the tranexamic acid group than the placebo group. In turn, it took more time in the placebo to achieve the symptom relief than the two icatibant groups. The treatment difference between tranexamic acid and placebo was greater than the differences between placebo and either of the two icatibant treatment groups.

Figure 1 Symptom Relief Time



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/s/

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