Advisory Committee Meeting Briefing Package

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Firazyr® (icatibant)

NDA 22,150

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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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LIST OF ABBREVIATIONS

Term	Definition
ACE	angiotensin-converting enzyme
ADR	adverse drug reaction
AE	adverse event
AUC	area under the plasma concentration-time curve
AUC_{inf}	area under the serum concentration-time curve from 0 to infinity
B2	bradykinin receptor type 2
BK	bradykinin
BMI	body mass index
C1-INH	complement 1 esterase inhibitor
CDF	cumulative distribution function
CGI	clinical global impression/ improvement
CI	confidence interval
C_{max}	maximum observed plasma concentration
CL/F	clearance uncorrected for bioavailability
CYP405	cytochrome 450
ECG	electrocardiogram
EU	European Union
F	bioavailability
FDA	United States Food and Drug Administration
GFR	glomerular filtration rate
GI	gastrointestinal
h	hour
HAE	hereditary angioedema
HCP	healthcare provider
HGT	(Shire) Human Genetic Therapies, Inc., the parent company of Jerini US, Inc. (the applicant of NDA 22,150)
HMWK	high molecular weight kininogen
IgG	immunoglobulin G
IOS	Icatibant Outcome Survey
IV	intravenous(ly)
MCSD	minimum clinically significant difference
MedDRA	Medical Dictionary of Regulatory Activities
NDA	New Drug application
ng/mL	nanogram per milliliter

NYHA	New York Heart Association
PD	pharmacodynamics
PIP	pediatric investigational plan
PK	pharmacokinetics
PRO	patient-reported outcome
PT	preferred term
PVRM	Shire's Global Pharmacovigilance and Risk Management
QT	total time for ventricular depolarization and repolarization
ROC	receiver operating characteristic
SAP	statistical analysis plan
SC	subcutaneous(ly)
SD	standard deviation
SGSS	Shire's Global Safety System
$t_{1/2}$	terminal half-life
TA	tranexamic acid
TIA	transient ischemic attack
US	United States of America
VAS	visual analog scale

GLOSSARY OF TERMS

A summary of terms used throughout this document is provided below, with brief definitions to aid reader comprehension.

Term	Definition
Clinical global impression/ improvement (CGI)	The investigator used a 7-point scale to score the severity of the attack from 1 for "normal, not at all ill" to 7 for "among the most extremely ill patients" at pretreatment. The subjects used a 5-point scale to assess the severity of the attack using the question "How severe do you consider this HAE attack to be?" at pretreatment. Following treatment, the subject and investigator used a 7 point scale to indicate levels of improvement in severity of the attack.
EASSI	**E**v**a**luation of the **S**afety of **S**ubcutaneous **I**catibant (self-administration study, Study JE049-3101)
FAST	**F**or **A**ngioedema **S**ubcutaneous **T**reatment (controlled Phase III studies FAST-1, FAST-2, FAST-3))
Global assessment	A global assessment of symptoms in 3 areas (cutaneous symptoms, abdominal symptoms and laryngeal symptoms) was performed by the investigator using a 5-point scale.
Laryngeal treated population	The laryngeal treated population included all patients with laryngeal attacks who were treated with double-blind or open label icatibant and used data from the patient's first laryngeal attack to explore the efficacy of icatibant for the treatment of laryngeal attacks. Analyses were limited to data corresponding to the subject's first icatibant-treated laryngeal attack regardless of whether that attack occurred in the controlled or open label phase of the studies.
Non-laryngeal population	The non-laryngeal population included all randomized patients whose first attack on study was either cutaneous or abdominal; randomized patients with laryngeal first attacks were excluded. This is considered the intent-to-treat population used data resulting from the randomized, double-blind treatment with icatibant or control for the main analysis of each efficacy endpoint and allowed comparisons to comparator treatment. Analyses were limited to data corresponding to the subject's first attack.
Observation period adverse event	For safety analyses in pooled Phase III populations, adverse events were monitored continuously from study drug administration through the Day 14 visit for each study drug-treated attack. Observation period adverse events were defined as treatment emergent adverse events occurring prior to or on the Day 14 visit or study discontinuation, which ever occurred first, for each study drug-treated attack.
Phase III safety population	The Phase III safety population included all (both non-laryngeal and laryngeal) randomized and treated patients from the controlled Phase III studies and used data from double-blind treatment (icatibant or control) of the patient's first attack for analyses of safety and allowed safety comparisons for icatibant and comparator treatment.
Phase III treated population	The Phase III treated population included all patients (with either non-laryngeal or laryngeal attacks) from the controlled Phase III studies who were treated with double-blind, as well as open-label icatibant. The Phase III treated population was used to explore efficacy and safety of repeated treatment with icatibant. Although all repeat attacks were analyzed, most analyses conducted with this population were focused on data corresponding to the patient's first 5 icatibant-treated attacks due to the small number of patients with more than 5 icatibant treated attacks. Results were summarized by icatibant-treated attack number.

Rescue medication	Rescue medication was any medication immediately necessary to alleviate acute symptoms which were judged by the investigator as resultant from the current HAE attack.
Symptom scores	Attack symptoms were evaluated by the subject (skin swelling, erythema, irritation, skin pain, abdominal pain, nausea, vomiting, diarrhea, difficulty swallowing, and voice change) and investigator (skin swelling, erythema, skin pain, abdominal pain, nausea, abdominal tenderness, vomiting, diarrhea, difficulty swallowing, voice change, breathing difficulties, stridor, and asphyxia) using a 5-point scale for each individual symptom.
Time to almost complete symptom relief (TACSR)	**T**ime to **a**lmost **c**omplete **s**ymptom **r**elief was calculated from the time of treatment administration to the onset of almost complete symptom relief. Almost complete symptom relief was determined as the earliest of 3 consecutive non-missing measurements for which all VAS scores were less than 10 mm.
Time to initial symptom improvement (TISI)	**T**ime to **i**nitial **s**ymptom **i**mprovement (TISI) was the time at which initial improvement of the symptoms was noticed, and was reported separately by the patient and the investigator.
Time to onset of symptom relief (TOSR)	**T**ime to **o**nset of **s**ymptom **r**elief (TOSR) was calculated from the time of treatment administration to the onset of symptom relief. Symptom relief was determined as the earliest of three consecutive non-missing measurements in which there is at least a 50% reduction in the pretreatment composite VAS score. TOSR was the primary endpoint in FAST-3 and was calculated post hoc for FAST-1 and FAST-2 based on prospectively collected single VAS data in those trials.
Time to onset of primary symptom relief (TOSR-P)	**T**ime to **o**nset of **s**ymptom **r**elief for the **p**rimary attack symptom was calculated from the time of treatment administration to the onset of primary symptom relief. Primary symptom relief was determined as the earliest of 3 consecutive non-missing measurements in which there is a reduction to less than $Y = 6/7 X - 16$ in the pretreatment primary VAS score, where X = pretreatment VAS for the symptom and Y = post-treatment VAS TOSR-P was the primary efficacy endpoint in FAST-1 and FAST-2.
Treatment-emergent adverse event	Treatment-emergent adverse events were defined as those adverse events which occurred or worsened after the time of the first study drug administration.
Visual analog scale (VAS)	The VAS is a scale used to measure the intensity of each symptom of the attack at baseline and at the pre-determined time points throughout the treatment period. It consists of a horizontal 10 centimeter line, with the 0 point corresponding to a state where the patient experiences no symptoms at all and the 10 cm point represents the worst symptoms ever experienced by the patient. The patient indicates his or her current state of symptoms by drawing a mark across the horizontal line. The VAS was the chief patient reported outcome (PRO) symptom assessment tool used in the Phase III studies. Unless otherwise specified, VAS refers to a VAS for a single symptom.
VAS-3 (3-symptom composite VAS)	For attacks classified as abdominal or cutaneous, this composite VAS score (VAS-3) was calculated as the average of 3 symptoms: skin pain, skin swelling, and abdominal pain. This endpoint allows for comprehensive evaluation of the heterogenous symptoms experienced by patients across abdominal and cutaneous attacks.

VAS-5 (5-symptom composite VAS	The composite VAS score for laryngeal attacks (VAS-5) was calculated as the average of 5 symptoms: skin pain, skin swelling, abdominal pain, difficulty swallowing, and voice change. This endpoint allows for comprehensive evaluation of the heterogenous symptoms experienced by patients across abdominal, cutaneous, and laryngeal attacks.
Worsening or recurrence of HAE	As delineated in the Phase III study protocols, investigators were asked to report worsening or recurrence of HAE symptoms within 48 hours of study drug administration as an adverse event. If symptoms worsened or recurred more than 48 hours after study drug administration, the attack was considered to be a new attack and was not reported as an AE.

1 EXECUTIVE SUMMARY

Icatibant Proposed Use

Icatibant is a bradykinin receptor antagonist with a proposed indication for the treatment of acute attacks of hereditary angioedema (HAE) in adults.

Background Information

HAE is a rare, debilitating, autosomal dominant disorder characterized clinically by recurrent, unpredictable and complex attacks of edema, inflammation and pain of the face, larynx, extremities, genitals and gastrointestinal tract that is fatal in some patients.

HAE prevalence is estimated at 1:10,000 to 1:50,000, with 6,000 to 30,000 patients in the United States.[1] Known attack stimuli include stress, trauma, surgical procedures, and hormonal changes. However, many attacks occur without an observable triggering factor, which adds to the overall complexity of the disease and creates anxiety for the patient. HAE typically presents as edematous attacks that are non-pitting, non-erythematous and non-pruritic. The frequency of HAE attacks ranges from less than 1 per year to more than 100 per year and attacks typically last 2 to 5 days if untreated.[2] The most serious of HAE attacks result in laryngeal edema, causing obstruction of the upper airways that may lead to death by asphyxiation if undiagnosed and/or untreated.[3, 4]

As a chronic disease, patients become attuned to the initial signs of an HAE attack and play an active role in their treatment.[5] HAE research suggests that early intervention can lessen attack severity and duration, as well as limit progression to other anatomical locations.[6] As a result, all available HAE guidelines and recommendations support prompt intervention when an attack begins.[5] Patient feedback suggests that the symptomatology for HAE attacks is significantly different and distinguishable from other emergent medical conditions.[5]

Bradykinin is the key mediator of the clinical symptoms of HAE.

The result of functional deficiencies in the kallikrein-bradykinin pathway is a rapid accumulation of bradykinin (BK). Bradykinin is directly responsible for the clinical symptoms of HAE, causing increased vascular permeability, vasodilation, and contraction of visceral smooth muscle. Deficiencies in this pathway cause either a quantitative (Type I) or functional (Type II) deficiency of complement 1 inhibitor (C1-INH).

Icatibant is a novel, potent and specific antagonist of the BK type 2 receptor with the same affinity for the receptor as endogenous bradykinin.

Icatibant is a synthetic decapeptide with a similar structure to BK, but with 5 non-proteinogenic amino acids. It is a competitive antagonist developed to specifically and selectively block the B2 receptor. Icatibant is prepared as sterile, isotonic, acetate buffered solution (pH 5.5±0.3). The product is supplied as a 10 mg/mL (free base) solution in a 3-mL pre-filled syringe. The product is to be stored below 25°C (77° F).

Icatibant offers the potential for early access to treatment of acute HAE attacks.

While prophylactic and acute treatments are currently available for the treatment of HAE in adults, these treatments do not completely fulfill the medical needs of many HAE patients. In treating HAE, a need exists for a medication that will facilitate early intervention for most patients and allow self-administration for treatment of their attacks when they occur. This will give patients increased independence and an improved quality of life.

Icatibant provides the opportunity for early intervention and, as such, icatibant offers the potential to address this unmet medical need.

Icatibant Clinical Trial Overview

A comprehensive clinical dataset has been created to establish the efficacy and safety of icatibant, despite the rarity of HAE.

In clinical studies, a total of 1055 HAE attacks have been treated with 30 mg subcutaneous (SC) icatibant. Subcutaneously administered 30 mg icatibant has been administered by a healthcare provider (HCP) to 129 healthy subjects and 236 patients with HAE and has been self-administered by 56 patients with HAE. In addition to exposure in clinical studies, over 8,000 patient exposures to Firazyr® have occurred cumulatively in the postmarketing setting from European Union regulatory approval on 11 July 2008 through January 2011.

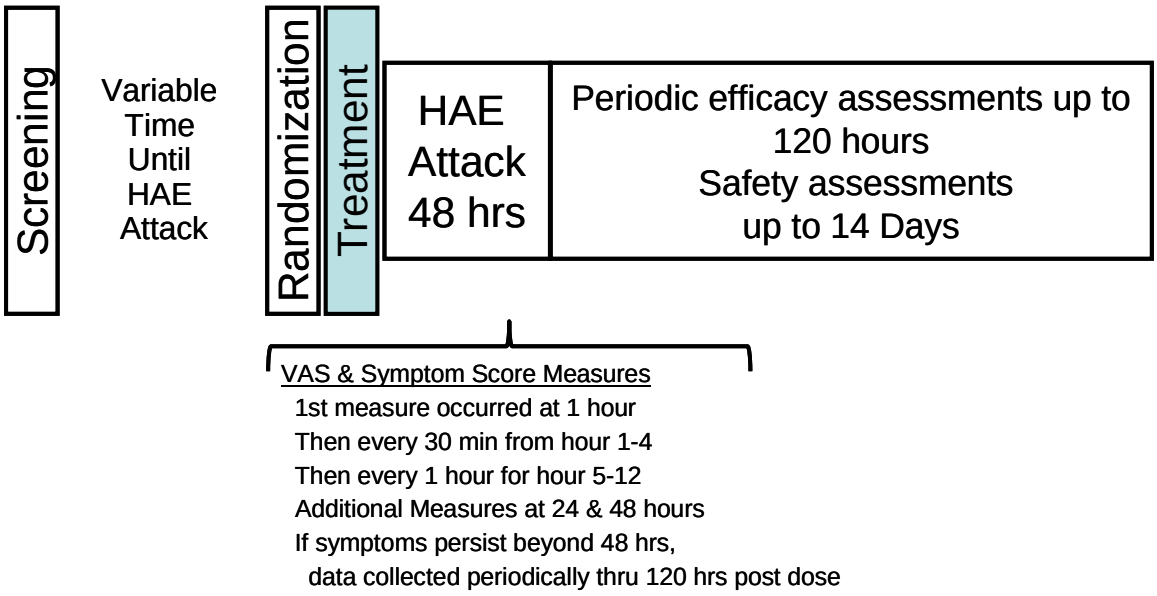
Efficacy and safety were assessed in 3 controlled Phase III studies that used similar clinical designs.

Three double-blind, randomized, controlled Phase III studies (FAST-1, FAST-2, and FAST-3) have been conducted in patients with Type I or Type II HAE following initial findings of safety and efficacy in Phase I and Phase II clinical studies. FAST-3 represents the definitive Phase III study for icatibant and is supported by FAST-1 and FAST-2.

The FAST studies were similar in design; each had a controlled phase to assess efficacy and safety in a randomized, controlled, double-blind setting and an open-label extension phase to assess treatment of subsequent HAE attacks. FAST-1 and FAST-3 were placebo-controlled; FAST-2 used tranexamic acid as a comparator.

As shown in Figure 1-1, eligible patients consented to participate in the study and were instructed to return to the investigational site when their next HAE attack began. At that time, enrolled patients were randomized and received study drug. Patients and investigators were asked to rate their symptoms using validated efficacy measures, the visual analog score (VAS), clinical global impression/improvement (CGI), investigator global assessment, and symptoms score measurements, through 48 hours after the administration of study drug. Patients were followed for up to 14 days after study drug administration or until the onset of another HAE attack, whichever came first. After receiving treatment for their first on-study attack, patients could participate in the open-label phase of the studies for treatment of subsequent attacks. In FAST-1 and FAST-2, patients who were screened but did not have an attack while the controlled phase was open for randomization were also eligible to participate in the open-label phase.

Figure 1-1 Phase III Study Design: Controlled Phase



The Phase III studies used patient-reported outcomes (PROs) as the instruments to measure outcomes on patient-reported symptoms such as abdominal pain and skin pain/swelling.

Following endpoint design precedent for HAE studies, icatibant Phase III studies used a VAS and symptom score measurements that examined the symptoms of primary importance to patients (eg, skin and abdominal pain and skin swelling in cutaneous and abdominal attacks as well as voice change and difficulty swallowing in laryngeal attacks). These symptoms were identified using literature review, expert input, qualitative and quantitative market research, and post hoc patient qualitative research. The efficacy measures were validated per FDA guidance as part of comprehensive patient reported outcome (PRO) validation studies.

The key study endpoints measured "time to a clinically relevant effect" from the patient's perspective.

The primary endpoint in the 3 controlled Phase III studies was "Time to onset of symptom relief". In FAST-1 and FAST-2, Time to Onset of Symptom Relief was based on a pre-specified reduction (relative to VAS pretreatment) in the VAS score for a single identified primary symptom (TOSR-P). The primary symptom was identified based on the type of attack (cutaneous or abdominal).

Upon evaluation of the results of these studies it was determined that use of a single primary symptom lacked the ability to capture the full clinical picture of disease activity during an acute attack, and as suggested by FDA, a composite endpoint was developed.

The primary endpoint for the definitive Phase III study, FAST-3, was the Time to Onset of Symptom Relief (TOSR) based on a pre-specified reduction (relative to VAS pretreatment) in a 3-component (cutaneous pain, cutaneous swelling and abdominal pain) composite VAS score (VAS-3). The VAS-3 was considered to be a more comprehensive and clinically relevant measure of treatment effect than the primary symptom VAS, as patients may experience multiple concomitant symptoms during an HAE attack. To facilitate cross-study comparisons, the primary endpoint used in FAST-1 and FAST-2, the time to onset of symptom relief, TOSR-P, was specified as the key secondary endpoint for FAST-3. The prospectively collected single VAS data from the FAST-1 and FAST-2 studies were also used to calculate the 3-component VAS-3 post hoc to facilitate comparison with the definitive FAST-3 study.

Because reduction in attack duration and severity is a key goal of HAE attack management, the Phase III studies also analyzed the Time to Almost Complete Symptom Relief (TACSR) (ie, first of 3 consecutive measures where all VAS measures <10 mm) as a key supportive endpoint.

A listing of other supportive endpoints collected during these Phase III studies can be found in Appendix 2.

Icatibant Efficacy Data

The Phase III clinical studies demonstrate that icatibant is an effective treatment for acute HAE attacks in adults, including cutaneous, abdominal, and laryngeal attacks, as demonstrated by reproducible and consistent efficacy across multiple endpoints.

As shown in Table 1-1, patients treated with icatibant demonstrated a statistically significant improvement in TOSR for cutaneous and abdominal attacks relative to placebo in FAST-3 ($p<0.0001$) and a significantly faster TOSR-P than tranexamic acid in FAST-2 ($p<0.0001$). While the median TOSR-P in FAST-1 was shorter for the icatibant group than for the placebo group, the difference was not statistically significant ($p=0.1217$).

Significant benefit in TOSR was also observed in FAST-1 and FAST-2 when these studies were analyzed according to the primary endpoint as defined in FAST-3. In addition, significant benefit in TOSR-P was observed in FAST-2 and FAST-3 studies ($p<0.0001$ for each). All 3 FAST studies also demonstrated a consistent reduction in Time to Almost Complete Symptom Relief (TACSR) with icatibant treatment, with statistical significance shown in FAST-2 ($p=0.0001$) and FAST-3 ($p=0.0116$) (Section 7.1.3.3). Consistent evidence for the efficacy of icatibant is also demonstrated by the secondary endpoints shown in Appendix 5.

Table 1-1 Summary of Efficacy Across the Phase III Controlled Studies

	FAST-3		FAST-1		FAST-2	
Endpoint	**Icatibant N=43**	**Placebo N=45**	**Icatibant N=26**	**Placebo N=29**	**Icatibant N=33**	**Tranexamic Acid N=38**
TOSR						
Median (h)	2.0	19.8	2.3	7.9	2.0	12.0
(95% CI)	(1.5, 3.0)	(6.1, 26.3)	(1.5, 5.1)	(5.0, 19.8)	(1.5, 3.5)	(6.0, 22.3)
p-value[a]	<0.0001		0.0136		<0.0001	
TOSR-P						
Median (h)	1.5	18.5	2.3	5.0	2.0	10.1
(95% CI)	(1.0, 2.0)	(3.6, 23.9)	(2.0, 5.0)	(3.0, 8.0)	(1.5, 2.6)	(3.5, 18.1)
p-value[a]	<0.0001		0.1217		<0.0001	
TACSR						
Median (h)	8.0	36.0	10.5	19.4 (12.0,	10.0	42.5
(95% CI)	(5.0, 42.5)	(29.0, 50.9)	(3.0, 31.5)	55.7)	(3.5, 12.1)	(26.0, 59.8)
p-value[a]	0.0116		0.1195		0.0001	

TACSR=time to almost complete symptom relief; TOSR= time to onset of symptom relief; TOSR-P=time to onset of primary symptom relief

TOSR is defined as at least 50% reduction from pretreatment in the 3-symptom VAS score (VAS-3).

TOSR-P is defined as a reduction from pretreatment in the score for a single, primary VAS symptom. Symptom relief is defined as any reduction below 6/7 pretreatment value -16 mm 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 30 mm. For subjects with a pretreatment VAS <30 mm, symptom relief was defined as a 68% reduction from pretreatment.

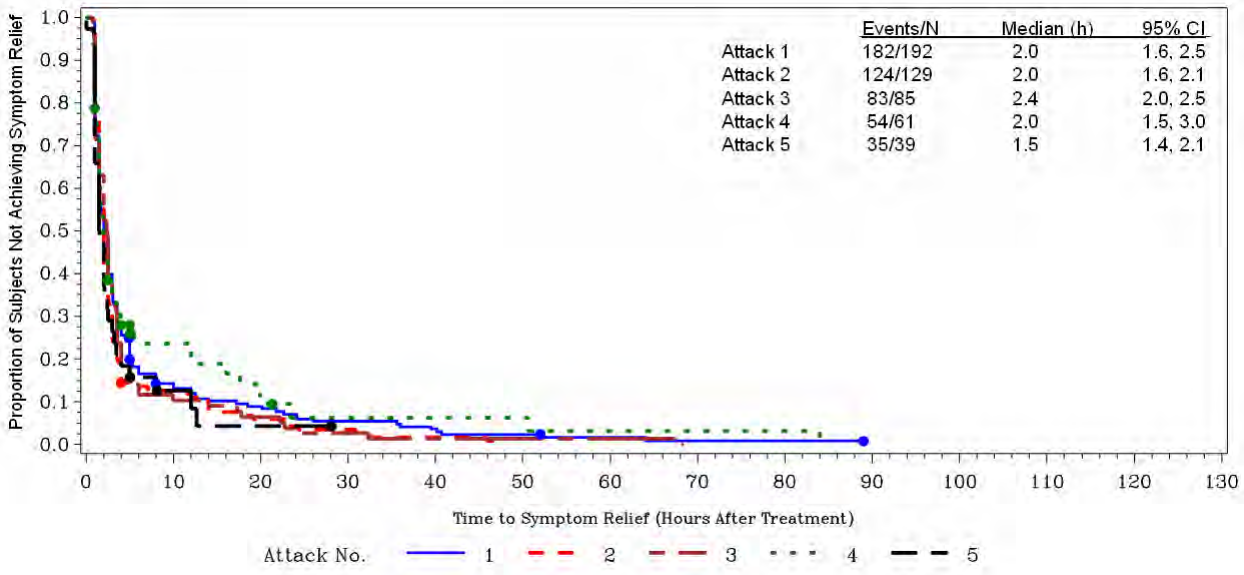
TACSR is defined as all VAS scores <10 mm.

[a] Peto-Peto Wilcoxon p-value

Source: ISE Tables 6.1.1, 8.1.1, and 10.1.

After participating in the controlled phase of the study, patients could elect to enter the open-label extension phase where they were eligible for treatment with icatibant for subsequent attacks. In total, 225 patients participated in the open-label extensions. Open-label efficacy data demonstrated that the response to treatment for repeated attacks was similar to that observed in the controlled phase of the studies, and also consistent when analyzed for each attack. Figure 1-2 presents the TOSR for the first 5 icatibant-treated attacks in the Phase III treated population, showing consistent median TOSR ranging from 1.5 to 2.4 hours, which was consistent with the TOSR for each of the controlled Phase III trials (2.0, 2.3, 2.0 hours for FAST-3, FAST-1, FAST-2, respectively). Thirty eight (38) patients have also been treated for more than 5 HAE attacks, with one patient treated for 142 attacks. In these patients with repeat exposure, the efficacy remained consistent from attack to attack (Section 7.3).

Figure 1-2 Time to Onset of Symptom Relief (First 5 Icatibant-Treated Attacks)- Phase III Treated Population



Symptom relief is defined as a 50% reduction from pretreatment in the 3-symptom composite VAS score.
Only non-laryngeal attacks are summarized since FAST-2 and FAST-1 did not collect VAS scores for laryngeal symptoms.
For patients previously randomized to placebo or tranexamic acid, their second on-study attack will be their first icatibant-treated attack.
Data from patients who did not achieve symptom relief within the observation period were censored at the last observation time. Dot indicates censoring.
Source: ISE Figure 1.4 and ISE Table 6.4

The median Time to Initial Symptom Improvement (TISI) for laryngeal attacks was 0.6 hours.

Laryngeal attacks were experienced by 60 patients over the course of the controlled Phase III studies. Because VAS-based laryngeal symptoms were not collected in FAST-1 and FAST-2, the Time to Initial Symptom Improvement (TISI) as judged by the patient was used across the 3 studies to assess onset of response for laryngeal attacks. Results for patient with laryngeal attacks were consistent with the icatibant-treated subjects in the controlled Phase III studies. The median patient–reported TISI was 0.6 hours for all first on-study laryngeal attacks treated with icatibant across the controlled Phase III studies, compared with a median TISI of 0.8 hours for each of the icatibant treated non-laryngeal attack groups in the controlled phases of FAST-3, FAST-2, and FAST-1 (Section 7.4).

Icatibant Safety Data

Icatibant 30 mg SC was well tolerated for the treatment of acute HAE attacks, with a consistent safety profile across all clinical studies.

Although almost all patients treated with SC icatibant experienced localized injection site reactions, these reactions were mostly mild or moderate in severity, and resolved quickly after icatibant administration without the need for intervention (Section 8.1.4).

Excluding localized injection site reactions, the overall occurrence of adverse events was lower for the icatibant group than for the placebo group (42.5% and 54.7% of patients, respectively, experienced AEs within 14 days of study drug administration). There were no deaths or discontinuations due to AE reported for patients receiving icatibant in the Phase III studies (Section 8.1.2).

Worsening/recurrence of HAE was expected to occur in the course of an HAE attack due to the continuously evolving nature of HAE attacks. In all three trials, the protocol designated that any worsening/recurrences were to be reported as an AE. It was reported in 15.9% of icatibant-treated patients during the controlled phase of the Phase III studies. The majority of worsenings/recurrences of HAE were considered mild or moderate and resolved with no or limited intervention (Section 8.1.5.4).

No hypersensitivity or anaphylactic reactions were reported in patients treated with icatibant. Three patients tested positive for anti-icatibant antibodies (IgG). The positive results were transient and all 3 patients maintained efficacy over the treatment period (Section 8.1.6.3).

No clinically relevant trends were observed in the safety profile by age, sex, body weight category, race, geographic region, concomitant medication, attack severity, or edema location. The safety profile seen across treatment of subsequent attacks was consistent with that seen for the icatibant groups in the controlled Phase III studies, and it is consistent with the post-marketing safety observed to date in countries outside the United States.

The safety profile of self-administered icatibant was consistent with that seen in the controlled Phase III studies.

Self-administration of icatibant was evaluated in the EASSI study, a multicenter, open-label Phase IIIb study, which assessed the clinical safety and effect of self-administration of 30 mg SC injections of icatibant for acute HAE attacks. In the ongoing, EASSI study, 56 patients have received training on and have self-administered icatibant. The safety profile of self-administered icatibant was consistent with that seen in the controlled Phase III studies and the integrated safety analyses. No new safety issues have been identified in this ongoing study. The TOSR was consistent with that observed in the controlled Phase III studies (Section 9.3).

Icatibant Benefit-Risk

Treatment with 30 mg SC icatibant produces a rapid and predictable response for acute cutaneous, abdominal and laryngeal attacks of HAE with an acceptable safety profile.

Icatibant is a first-in-class B2 bradykinin receptor antagonist with a proposed indication for the treatment of acute attacks of hereditary angioedema (HAE) in adults.

Patients suffering from an acute HAE attack are in need of a safe and effective treatment that offers fast access, portability, and the opportunity for earlier intervention than currently approved

therapies. Subcutaneously administered 30 mg icatibant has been shown to be a safe and efficacious treatment for acute HAE attacks including cutaneous, abdominal, and laryngeal attacks, as demonstrated by reproducible and consistent efficacy for icatibant across multiple endpoints in the double-blind treatment phases of 3 controlled Phase III studies, and upon repeated open-label use for treatment of subsequent HAE attacks.

Icatibant demonstrated a consistent adverse event profile across the 3 controlled Phase III studies. The majority of events were reported at an incidence similar to that observed in the active comparator (tranexamic acid) group and lower than in the placebo group. The Phase III safety data confirmed the safety profile seen in the Phase I and II studies. Additionally, over 8,000 patient exposures to Firazyr® have occurred cumulatively in the post-marketing setting from European Union regulatory approval on 11 July 2008 through January 2011. Post-marketing data are consistent with that observed in the clinical studies, and no safety concerns have been identified.

Treatment of HAE, including self-administration, is a patient-physician partnership. Existing international treatment guidelines recommend that every patient with HAE be considered for self-administration.[5] With proper training, patients with HAE are able to detect the unique signs and symptoms of their disease that allow them to distinguish an acute attack from other medical conditions and to remain actively involved in ongoing treatment and attack management.[5] Patient disease awareness, appropriate training, and active participation in the treatment of their HAE attack symptoms support the benefit of a prompt self-administered treatment following the onset of an attack. The results of the EASSI study demonstrate that patients were able to decide when initiation of treatment was appropriate, and they were able to safely self-administer icatibant to treat their attacks. The safety of self-administered icatibant was similar to HCP-administered icatibant seen in the controlled Phase III studies, and these patients experienced a similar TOSR after administration of icatibant.

Shire has proposed specific instructions within the "Patient Counseling Information" section of the draft labeling for use by physicians in the education of their patients regarding the safe use of icatibant, including information about when to administer icatibant, when to seek clinical assistance, and correct injection administration.

Subcutaneously administered 30 mg icatibant was demonstrated to be efficacious in the treatment of acute HAE attacks with an overall acceptable safety profile.

2 HEREDITARY ANGIOEDEMA

2.1 Disease Description and Epidemiology

Hereditary angioedema (HAE) is a rare, autosomal dominant disorder characterized clinically by recurrent and self-limiting attacks of edema. Its prevalence is estimated at 1:10,000 to 1:50,000.[1] HAE attacks can strike at several anatomical locations, generally categorized into 3 primary areas, cutaneous, abdominal, and laryngeal. Individuals can experience symptoms for attacks that differ between attacks. Known stimuli include stress, surgical procedures, and hormonal changes. However, many attacks occur without a known triggering factor, which adds to the overall complexity of the disease and burden to the patient. The frequency of HAE attacks ranges from less than 1 per year to more than 100 per year and attacks typically last 2 to 5 days.[2] The most serious of HAE attacks result in laryngeal edema, causing obstruction of the upper airways that may lead to death by asphyxiation in 30-50% of patients if undiagnosed and/or untreated.[3, 4] Proper diagnosis, patient education, and management have led to a decrease in the number of patient deaths due to laryngeal edema. However, even among properly diagnosed and informed patients, HAE attacks can be fatal. [3, 4, 7]

2.2 Pathophysiology

Bradykinin is widely accepted to be responsible for the clinical symptoms of HAE, causing increased vascular permeability, vasodilation and contraction of visceral smooth muscle.[8] The disease is caused by either a quantitative (Type I) or qualitative (Type II) deficiency of C1 inhibitor (C1-INH). A third type of HAE (Type III) has been described, but its pathophysiology has not been well-elucidated; this condition, therefore, has not been the subject of clinical studies. The functions of C1 inhibitor include the prevention of C1 complement autoactivation, inactivation of coagulation factors XIIa, XIIf, XIa, and inhibition of activated kallikrein. After a triggering event, the deficiency in C1 inhibitor results in accelerated release of bradykinin, the principal mediator of the increased vascular permeability characteristic of HAE, through its cleavage from high molecular weight kininogen by dysregulated, activated kallikrein. As the level of circulating BK increases, vasodilation and progressive edema occur at variable anatomical locations (Figure 3-1).

2.3 Overall Burden of Disease

The unpredictable nature of and need for frequent medical intervention in the acute and long-term management of attacks of HAE are associated with significant personal and healthcare-related costs. HAE may affect a patient's ability to work full time or may increase the amount of time absent from work, school, or leisure activities that is directly related to the clinical manifestations of HAE.[9] Physical pain from an attack often leads to missed work or school.[9, 10] The potential for a life-threatening laryngeal attack may result in continual anxiety.[5] Swelling caused from a cutaneous attack can be embarrassing as well as both disfiguring and disabling.[5, 11] Patients with HAE are more likely to have depressive symptoms than the general population and report taking psychotropic or antidepressant medication at a rate nearly twice the national average.[9]

The current treatment paradigm also requires trips to healthcare providers, including emergency care which leads to delays in initiation of HAE treatment. Thus patients' lives and attack resolution are often dictated by timing and proximity of appropriate medical care.[5]

2.4 Currently Available Treatments for HAE and Unmet Medical Need

Current medical management of HAE is multi-faceted, including: long-term prophylaxis to prevent attacks, short-term prophylaxis before elective surgical procedures, and treatment for acute attacks. Such treatment strategies include therapies that are both approved and unapproved in the US.

2.4.1 Currently Approved Therapies for HAE in the US

Treatments currently approved in the US for the treatment of HAE are limited to a C1-INH product, Cinryze®, for prophylaxis of HAE attacks (short versus long term prophylaxis is not specified in its product labeling), another C1-INH product, Berinert®, for treatment of acute facial or abdominal attacks of HAE, and a kallikrein inhibitor, Kalbitor® (ecallantide), for the treatment of acute attacks of HAE (types of attacks not specified in product labeling). In addition, a variety of therapies are commonly used "off-label" for HAE. Both the approved and unapproved treatments form part of a general treatment strategy that can be further divided into prophylaxis (both short and long term) and treatment of acute attacks.

2.4.2 Treatment for the Prophylaxis of HAE Attacks

C1 inhibitor replacement is approved for prophylaxis and used as such in short and long term situations. Because currently available C1-INH products are blood-derived, however, they carry a potential risk of transmission of infectious agents and the potential for hypersensitivity reactions. They also must be infused intravenously. Despite the availability of C1 inhibitor replacement and other prophylactic agents, breakthrough attacks still occur.[12, 13]

Antifibrinolytics (eg, tranexamic acid, ε-aminocaproic acid) have also been used for short and long term prophylaxis. Their utility in acute attacks has not been studied in clinical trials; however, they are commonly used for treatment of acute attacks, and such use has historically been part of therapeutic guidelines. The use of antifibrinolytics in HAE has not been approved in the United States.

Another class of agents for long-term prophylaxis is the attenuated androgens (eg, danazol or stanozolol) and plasma-derived C1 inhibitor replacement. Though capable of reducing the frequency and severity of HAE attacks over time, attenuated androgens have the potential for significant side effects with chronic use, such as masculinization, hyperlipidemia and hepatic adenomas.

Icatibant is not intended for use as a prophylactic agent.

2.4.3 Treatment of Acute Attacks of HAE

The indication sought for icatibant in the US is for the treatment of acute attacks of HAE in adults.

In the US, C1 and kallikrein inhibitors are available for the treatment of acute attacks of HAE. Though C1 inhibitor products can provide relief of symptoms in acute attacks, they require IV infusion and refrigerated storage, and thus may not always be convenient to administer. A kallikrein inhibitor (ecallantide) has been approved in the United States for treatment of acute attacks; however, there is a risk of drug hypersensitivity associated with its use. The product labeling states that ecallantide should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis.[14]

While acute treatments are available for HAE, they require intravenous administration and supervision by a healthcare professional which can result in initiation delays that may lessen the potential therapeutic benefit. No treatment is approved for self-administration for acute HAE attacks in the United States. Other treatments for acute attacks are primarily palliative and are intended to ameliorate the symptoms (eg, pain, gastrointestinal manifestations such as nausea and vomiting) of angioedema rather than to control the HAE attack itself.

2.4.4 Accessibility of Therapy for Self-Management of HAE

Publications support that with proper training and experience, HAE patients are able to detect the unique signs and symptoms of HAE that allow them to distinguish an acute attack and remain actively involved in ongoing treatment and attack management.[5]

Prompt intervention has been linked with lessened attack severity, lessened likelihood to progress to another anatomical site, and sooner symptom resolution; as supported by HAE clinical data.[6, 15] Current treatment guidelines specify that patients with HAE should initiate treatment as soon as the patient recognizes the signs and symptoms of an acute attack in order to arrest the attack cycle, thereby helping to increase personal safety and minimize disruption in living a healthy and productive life.[5] These guidelines, together with patient familiarity with their condition and ability to recognize and treat attacks, support the ongoing need for self-administration.

There remains a need for a novel HAE treatment that is readily accessible. Inhibition of bradykinin action through use of a bradykinin receptor (B2) antagonist is a novel therapeutic strategy for treatment of clinical symptoms of HAE, and represents the rationale for use of icatibant, a potent B2 receptor antagonist, in treatment of acute attacks of angioedema in patients with HAE.

3 OVERVIEW OF ICATIBANT

3.1 Description of Icatibant

Icatibant is a bradykinin antagonist indicated for treatment of acute attacks of HAE in adults. It is a highly selective direct inhibitor of bradykinin action, the key mediator of edema in HAE.

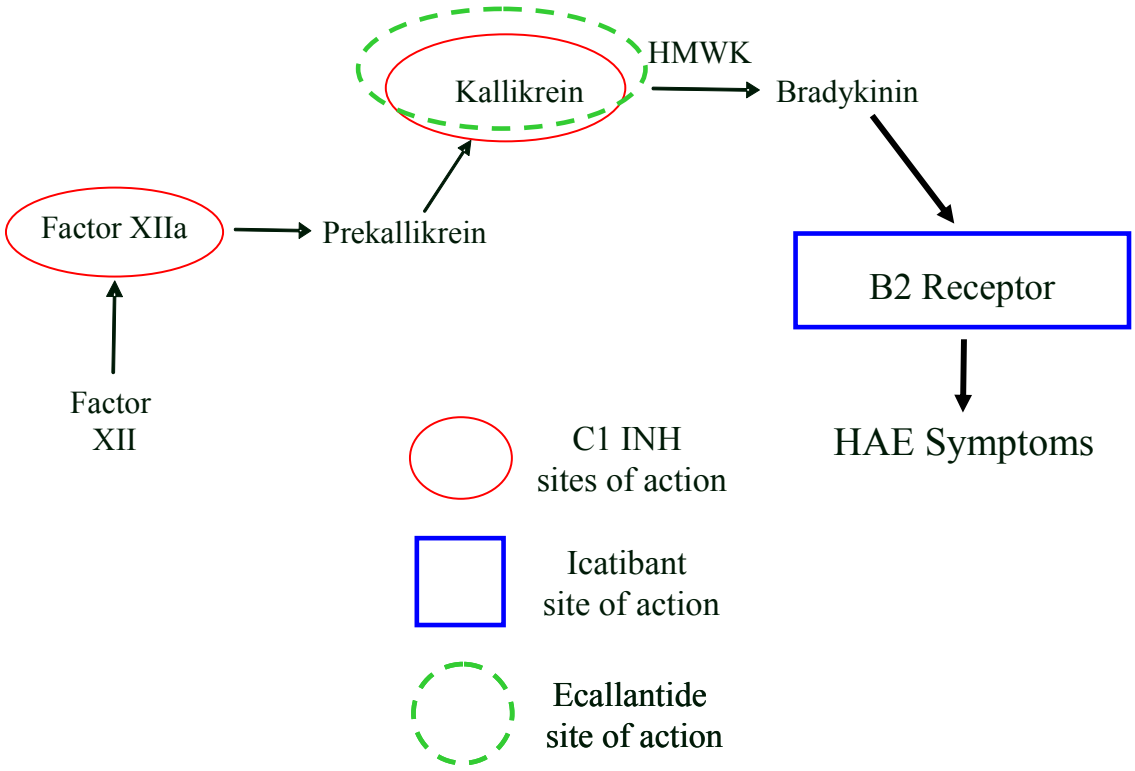
Icatibant is a synthetic decapeptide with a similar structure to bradykinin, but with 5 non-proteinogenic amino acids. Icatibant is prepared as a sterile, isotonic, acetate buffered solution containing sodium chloride, acetic acid, sodium hydroxide, and water for injection, adjusted to pH 5.5 ± 0.3. The solution does not contain any preservative. The product is supplied as a 10 mg/mL (free base) solution in a 3-mL pre-filled syringe. The product is to be stored below 25°C (77° F).

3.2 Mechanism of Action

Icatibant is a potent and selective antagonist of the B2 receptor, and can alleviate the symptoms of an acute release of bradykinin.[16] The B2 receptor is a G coupled protein receptor that is expressed in multiple tissues, which once bound and activated in the vascular endothelium, leads to the production of nitric oxide, prostacyclin and cGMP.[17] The released signaling molecules cause disruptions in both inter and intra cellular transport, specifically in the cytoskeletal elements leading to the opening of tight junctions between cells.[18] The resulting vascular leakage and edema are the most recognizable symptom of HAE and are directly attributable to increases in bradykinin formation. Icatibant has an affinity for the B2 receptor that is equal to that of bradykinin and is a competitive antagonist of the human B2 receptor.

Bradykinin is produced as a result of a series of proteolytic events that begins with the auto activation of factor XII which converts pre-kallikrein to kallikrein. Once sufficient kallikrein is formed, it catalyzes the formation of bradykinin from high molecular weight kininogen.[19] C1-inhibitor therapies which act on at least two targets, plasma kallikrein and factor XIIa, act to reduce the production of plasma kallikrein and the subsequent formation of bradykinin.[20] In contrast, icatibant directly inhibits the action of bradykinin at its receptor target. Thus icatibant represents a logical and scientifically sound therapeutic approach for the treatment of acute HAE attacks.

Figure 3-1 Sites of Action for Icatibant and Approved Treatments for Acute HAE



HMWK = high molecular weight kininogen

Bradykinin is elevated during and after an ischemic insult and has been shown to have beneficial effects on tissues following ischemia-reperfusion events.[21-24]

Laboratory studies have shown that perfusion with bradykinin into the heart after periods of cardiac ischemia reduces the infarct size as well as the duration and incidence of ventricular fibrillation, improves cardiodynamics, reduces release of cytosolic enzymes, and preserves energy-rich phosphates and glycogen stores in models of myocardial infarction.[25-27] However, in animal models blockade of B2 receptors with icatibant worsened ischemia-induced effects in the heart tissue of rats.[28, 29] While there is a risk of aggravating the deleterious effects of ischemia-reperfusion during exposure to icatibant there is no evidence that antagonizing the bradykinin 2 receptor leads to ischemia.

Other molecules such as adenosine and opioids have been shown to have similar benefits as bradykinin on ischemia-reperfusion injury and operate through distinct yet converging mechanisms.[30-33] These convergent pathways potentially mitigate the risks posed by the presence of icatibant during the reperfusion phase of a myocardial infarction. Additionally, the clinical duration of action of icatibant is less than 12 hours, which is a narrow window of time in which a myocardial infarction would have to occur to realize the potential negative effects of icatibant on an ischemic event.

3.3 Regulatory History

Icatibant received Orphan Drug Designation status on 25 November 2003. The development program was granted Fast Track status by the United States Food and Drug Administration (FDA) on 15 June of 2004.

Clinical development of icatibant was initiated by Hoechst AG in the early 1990s. Jerini AG continued clinical development of icatibant after in-licensing the drug from Hoechst Marion Roussel in 2001. In October 2007, following completion of 2 randomized, blinded, controlled Phase III studies (FAST-2 and FAST-1) in patients with HAE, a New Drug Application (NDA) for icatibant (NDA 22,150) was submitted for the treatment of acute attacks of HAE. Following completion of the review in April 2008, the FDA determined that an additional Phase III study would be necessary. FAST-1 failed to demonstrate a statistically significant treatment difference between placebo and icatibant, and there were concerns regarding the use of tranexamic acid as a comparator in FAST-2 because it was not approved for the treatment of HAE in the United States. Shire completed its acquisition of Jerini in 2009.

In response to the concerns of the FDA, Shire HGT conducted a third randomized, blinded, controlled Phase III study, FAST-3, designed to definitively evaluate the efficacy and safety of icatibant for treatment of acute attacks of HAE.

Data from the FAST-3 study, supported by data from the previously submitted Phase III studies (FAST-2 and FAST-1), plus data from a self-administration study (EASSI) and PRO validation studies demonstrating the validity of the visual analog scales (VAS) used in the primary and key secondary endpoints, form the basis of the application that is currently under review by the FDA.

Icatibant was approved for use in the European Union (EU) on 11 July 2008 and is currently approved in 37 countries worldwide for the treatment of acute attacks of HAE in adults. In February 2011, the European Commission granted approval for self-administration of icatibant in the EU.

4 NONCLINICAL RESULTS

4.1 Summary of Nonclinical Safety

The completed nonclinical data package included single and repeated dose studies, embryofoetal toxicity studies in rats and rabbits, and the reproductive toxicity package was completed with fertility and pre-/post-natal studies based in rats and rabbits with subcutaneous administration. All studies were supported by integrated toxicokinetic measurements. The nonclinical safety package was completed with genotoxicity testing consistent with current guidelines and appropriate safety pharmacology studies. All impurities have been qualified by nonclinical safety assessments. The icatibant-related safety findings observed in the clinic were also present in the preclinical safety studies. In addition, carcinogenicity testing is ongoing.

4.2 Summary of Nonclinical Pharmacology

The pharmacologic activity of B2 receptor antagonism by icatibant has been demonstrated in in vitro and in vivo models. Icatibant is a potent antagonist of B2 receptors, with an affinity similar to bradykinin. In vivo icatibant has been shown to attenuate bradykinin-induced decreases in blood pressure, as well as increases in bronchoconstriction and nociception. In vitro studies have shown that icatibant can act as a partial B2 receptor agonist at concentrations greater than 300 μM. Additional studies done in human skin mast cells have also shown that concentrations greater than 100 μM led to histamine release. The concentrations of icatibant that led to agonism of the receptor or histamine release exceed the maximal clinical systemic exposure by 300 and 100 fold respectively; however such concentrations are likely achieved at the site of injection. This transient local concentration at the injection site may trigger histamine release and partial agonism, and may be responsible for the observed injection site reactions. The interaction of icatibant with human bradykinin 1 and 2 receptors was investigated in a binding assay (JE049-003). Icatibant bound to the B1 and B2 receptors with an IC_{50} of 6μM and 4.3 μM, respectively.

Absorption of icatibant from the subcutaneous injection site and time to peak concentration in plasma are rapid. Catabolism of icatibant results in cleavage of the molecule, forming 2 principal moieties, icatibant (1-5) (M1) and icatibant (7-10) (M2) which are common to rat, dog and man, thus validating the choice of species used for toxicology. Following administration of ^{3}H-icatibant to rats, with the radiolabel in either the M1 or M2 portions of the molecule, excretion of radioactivity was predominantly urinary with the major radioactive components in urine being the M1 or M2 metabolite, depending on the position of the radiolabel. Very little unchanged icatibant (<10%) was recovered in urine.

5 PHASE I/II CLINICAL DEVELOPMENT PROGRAM IN HAE

5.1 Summary of Clinical Studies

In clinical studies, a total of 1055 HAE attacks (including 115 laryngeal attacks) have been treated with 30 mg SC icatibant. SC icatibant 30 mg has been administered by a healthcare provider to 129 healthy subjects and 236 patients with HAE. Icatibant has also been self-administered by 56 patients with HAE in the EASSI (**E**v**a**luation of the **S**afety of **S**ubcutaneous **I**catibant) study (Study JE049-3101).

A summary of the clinical development program for icatibant supporting HAE is presented in Table 5-1.

Table 5-1 Icatibant Phase I/II Clinical Development Program for HAE

Study Number (Name)	Design	Dose(s)	N Study population
Phase I Studies			
JE049-1001	Part 1/Panel 0: open SD sb S&T, PK/PD, BK challenge Part 1/Panels A&B: 2 rotating panels, 4-period , sb co S&T, PK/PD, BK challenge Part 1/Panel C: 4-period db co, placebo S&T, PK/PD, renal function	0.005, 0.01, 0.025, 0.05, 0.4, 0.8 mg/kg 4-h IV infusion. 0.8, 1.6,3.2 mg/kg 1-h IV infusion 0.15 mg/kg, 24-h IV infusion	26 NHV
JE049-1101	Db, placebo-controlled, sequential groups, S&T, PK	0.04 mg/kg/1 h, 0.4 mg/kg/0.5 h, 0.4 mg/kg/ 0.25 h, IV infusion	10 NHV
JE049-1102	Part 1: db, ascending SC dose, placebo-controlled Part 2: Randomized, open-label co S&T, PK/PD	Part 1: SC injection of 0.05(40 mg/mL), 0.2 (40 mg/mL), 0.2 (20 mg/mL) and 0.4 (20 mg/mL) mg/kg icatibant or placebo Part 2: SC injection of 0.4 mg/kg (10 or 20 mg/mL) or IV infusion of 0.4 mg/kg icatibant	Part 1: 16 Part 2: 24 NHV
JE049-1103	Db, placebo-controlled S&T, PK/PD	SC icatibant 30 mg or placebo; 3 doses day 1, single dose days 8 and 15	32 NHV
JE049-2001	Randomized,db, placebo-controlled, 2-way co, S&T, PK/PD, 2 parallel panels	0.15 mg/kg/day continuous IV infusion of icatibant or placebo over 3 days	Panel A: 8 patients with hepatic insufficiency Panel B: 8 NHV
JE049-2002	Panel A: Randomized, db, placebo-controlled, escalating dose Panel B: Open-label, escalating	0.15, 0.3, 0.6, or 1.2 mg/kg/day continuous IV infusion of icatibant or placebo over 5 days 0.15, 0.3, or 0.6 mg/kg/day continuous	Panel A: 37 patients with hepatic cirrhosis

Table 5-1 Icatibant Phase I/II Clinical Development Program for HAE

Study Number (Name)	Design	Dose(s)	N Study population
	dose Efficacy, S&T, PK/PD	IV infusion of icatibant over 5 days	Panel B: 4 patients with hepatorenal syndrome
HGT-FIR-061	Randomized, placebo-active controlled, co Safety, effect of single SC dose on QT prolongation, PK	4 treatment periods; SC icatibant 30 mg or placebo single dose, SC icatibant 90 mg 3 injections, moxifloxacin 400 mg PO single dose	71 NHV
HGT-FIR-065	Open-label, uncontrolled S&T, PK of icatibant and metabolites M1 and M2	SC icatibant 30 mg (3 ×10 mg 3-mL injections); multiple dose (3 doses at 6-h intervals)	21 NHV
Phase II Study			
JE049-2101	Open-label, uncontrolled, proof of concept Sequential dosing of IV and SC icatibant Efficacy, S&T, PK/PD	IV icatibant: 0.4 mg/kg (2 h or 30 m infusion); 0.8 mg/kg (30 m infusion); single dose SC icatibant: 30 mg and 45 mg; single dose	15 HAE

Abbreviations: co = crossover; db = double blind; HAE = hereditary angioedema; IV = intravenous; NHV = normal healthy volunteers; sb = single blind; SC = subcutaneous; SD = single dose; S&T = safety and tolerance; PD = pharmacodynamics; PE = pharmacoeconomics; PK = pharmacokinetics

5.2 Summary of Clinical Pharmacology

Data on the pharmacokinetics (PK) and pharmacodynamics (PD) of icatibant were obtained from 3 early studies using IV administration (JE049 9101, JE049 9103, and JE049 9106), 6 studies in healthy subjects using IV and SC administration (JE049-1001, JE049-1101, JE049 1102, JE049 1103, HGT-FIR-061 and HGT-FIR-065), and one study in patients with HAE using both IV and SC administration (JE049-2101). In addition, the pharmacokinetics of IV icatibant in non-HAE patients with hepatic and/or renal impairment was investigated in two studies (JE049-2001 and JE049-2002).

5.2.1 Drug Metabolism and Excretion

Icatibant is extensively metabolized to 2 inactive metabolites, M1 and M2, probably by NADPH-independent proteolytic enzymes, with no involvement of cytochrome 450 (CYP450) enzymes. In humans, it was shown that only about 5% (range from 2 to 10%) of icatibant is excreted unchanged in urine. Given the high recovery of both metabolites (up to greater than 90%) excreted in urine, there are no theoretical concerns about inclusion of icatibant-derived peptides and amino acids in the amino acid pool.

5.2.2 Protein Binding and Drug-Drug Interactions

The in vitro binding of icatibant to human serum plasma proteins is low (44%). No information is available on the type of proteins that may bind to icatibant or its metabolites.

In vitro studies investigating the effects of icatibant on human CYP450 isoenzymes showed no evidence that clinically relevant inhibition or induction of these enzymes would be expected. Accordingly, no drug-drug interaction studies were performed in humans during the clinical development program. The inhibition of bradykinin degradation by angiotensin-converting enzyme (ACE) inhibitors, leading to an increased bradykinin concentration, may contribute to the antihypertensive effect of these drugs. Since icatibant acts as a bradykinin receptor antagonist, there is a theoretical possibility, though considered remote, of a PD interaction whereby icatibant may attenuate the antihypertensive effect of ACE inhibitors. Because some patients receiving ACE inhibitors are known to develop angioedema due to increased bradykinin levels, use of ACE inhibitors is contraindicated in patients with a history of any type of angioedema. For this reason, subjects on ACE inhibitors were excluded from the Phase III trials.

5.2.3 Pharmacokinetics

The PK properties of subcutaneously administered icatibant have been thoroughly characterized in healthy subjects and in subjects with HAE. There is no indication from existing data or any physiologically-based expectation that the PK properties of SC icatibant overall would differ significantly between healthy subjects and subjects with HAE.

In the 3 early Phase I clinical studies, icatibant was given by IV infusion at rates and durations that were constant within a given study, but varied by study, in a series of placebo-controlled, double-blind studies to healthy male volunteer subjects over a dose range from 0.03 mg/kg to approximately 0.26 mg/kg (JE049-9101, JE049-9103, JE049-9106). In subsequent IV infusion studies (JE049-1001 and JE049-1101), doses from 0.005 to 3.2 mg/kg over 1 hour were tested. All doses up to 1.6 mg/kg over 1 hour were well-tolerated, with 0.4 mg/kg being identified as the minimum dose having a clinically useful duration of action of about 6-8 hours. In JE049-1001, which investigated the exposure-response (PK/PD) for icatibant using a human bradykinin challenge model in healthy subjects, the PD response of icatibant was shown to be relatively insensitive to dose. At a dose of 0.4 mg/kg, mean peak plasma concentrations of icatibant are rapidly achieved that are about 50- to 100-fold above the EC50 values necessary for inhibition of bradykinin-induced effects on blood pressure, heart rate and cutaneous blood flow, making this a clinically relevant dose. The principal effect of increasing or decreasing dose by as much as 2-fold is a modest change in the duration of effect of approximately 1.5-2 hours.

Overall across IV studies, there was a linear, dose proportional relationship between the administered dose and plasma exposure as measured by C_{max} and AUC. Elimination of icatibant was multiphasic with the majority of the drug being eliminated with $t_{1/2}$ ranging from approximately 0.6 hours to 1.5 hours. The clearance of icatibant was similar across studies, though increasing slightly with increased IV dose. In a study in healthy subjects, the absolute bioavailability of icatibant after SC administration (10 mg/mL formulation) was determined to be 97.2% (JE049-1102), thus establishing the equivalence in exposure of 0.4 mg/kg IV and 30 mg SC doses (0.4 mg/kg in a 75 kg subject).

In single- and repeated-dose Phase I studies in healthy male and female subjects in which doses of 30 or 90 mg (HGT-FIR-061 and HGT-FIR-065) were characterized, approximately dose proportional increases in the mean values for C_{max}, and AUC were seen between the 30 mg and 90 mg doses. Following SC administration of a single 30 mg dose of icatibant to healthy subjects (N=96; HGT-FIR-061, HGT-FIR-065), a mean (± standard deviation) maximum plasma concentration (C_{max}) of 974 ± 280 ng/mL was observed after approximately 0.75 hours. The mean area under the concentration-time curve ($AUC_{0-\infty}$) after a single 30 mg SC dose was 2165 ± 568 ng·hour/mL, with no evidence of accumulation of icatibant following three 30 mg SC doses administered 6 hours apart. Plasma clearance (CL/F) after SC administration was 245 ± 58 mL/min with a mean elimination half-life ($t_{1/2}$) of 1.4 ± 0.4 hours and volume of distribution at steady state (V_{ss}) of 29.0 ± 8.7 L.

The effect of age and sex on icatibant PK was investigated in a repeated-dose SC administration study in healthy subjects (JE049-1103; n=6 on treatment/group). In this study, there was an approximately 2.5-fold greater C_{max} and approximately 4-fold greater AUC in elderly females compared to young males. In this small study, the differences seen between males and females, and young and elderly subjects could not be fully explained by differences in body weight or body mass index (BMI). In order to more comprehensively address potential demographic effects on PK, a population PK analysis based on data from 210 treatments representing a total of 98 male and 42 female subjects (age range 19 to 83 years) was then conducted. This analysis indicated that there was a modest but statistically significant effect of age on icatibant clearance which is equivalent in magnitude to the known effects of age on renal function. Sex was not a significant covariate for clearance in this analysis and there was no difference in weight-corrected clearance values between males and females. Integrated analysis of PK data from 2 recent Phase I studies in healthy subjects (HGT-FIR-061, HGT-FIR-065; N=103, 51 males, 52 females) showed that over the 18 to 50 year age range for subjects in these studies, there were no statistically significant trends toward increases or decreases in CL/F (clearance uncorrected for bioavailability, F) or $t_{1/2}$. There were statistically significant positive correlations between clearance, volume of distribution and body weight. The magnitude of the observed differences are not expected to be clinically relevant given the overall variability in PK parameter estimates and the broad exposure-response profile of icatibant, where the main impact of demographic effects on exposure would be to modestly affect the duration of effect rather than its magnitude.

The PK properties of icatibant in patients with HAE were investigated in a Phase II study (JE049-2101). Two males and 2 females were enrolled into each of the 30 mg and 45 mg SC dose groups (8 patients total). The mean C_{max} and AUC were consistent overall with those derived in other studies, including studies with healthy volunteers.

Studies in patients with impairment of renal or hepatic function (JE049-2002; (glomerular filtration rate [GFR] 30-60 mL/min and Child-Pugh score ≥7 and ≤15) did not show any significant differences in the PK of icatibant or its metabolites compared to healthy subjects, indicating that no adjustment to the proposed 30 mg dose is necessary in populations with mild to moderate renal or hepatic impairment. Extrinsic factors, such as smoking and concomitant drugs, were not specifically studied for their effect on icatibant pharmacokinetics during the clinical development program.

5.2.4 Pharmacodynamics and Dose Selection

The PD properties of subcutaneously administered icatibant have been characterized in healthy subjects and in subjects with HAE.

The pathophysiology of HAE attacks and the mechanism of action of icatibant are well understood, but relevant PD endpoints are not available in clinical studies of HAE subjects because of the local character and variable pattern of HAE symptomatology. Consequently, a traditional approach to prediction/estimation of a clinically effective dose in patients using the exposure-response (PK/PD) relationship represented a significant challenge for icatibant. The approach used to address this critical drug development issue included the use of a human bradykinin challenge model in healthy subjects that confirmed a dose-, concentration-, and time-dependent inhibition of the effect of bradykinin on blood pressure, heart rate and cutaneous blood flow by IV infused icatibant. The scientific consensus regarding the pivotal role of bradykinin in the pathophysiology of HAE strongly supports the validity of the human bradykinin challenge model for elucidating the PK/PD relationships in HAE.

Several Phase I studies and a Phase II study were conducted to select the optimal route and dose to take forward into the pivotal Phase III efficacy studies. The Phase I dose-ranging bradykinin challenge study (JE049-1001; dose range tested: from 0.005 to 3.2 mg/kg over 1 h), and PK/PD modeling of the resulting data identified the minimum dose with a clinically useful duration of action of about 6-8 hours as 0.4 mg/kg (IV) and a maximum tolerated dose of 1.6 mg/kg. After confirming SC as the most favorable route of administration with almost complete bioavailability in a separate Phase I study (JE049-1102), a small, dose-ranging Phase II study in HAE subjects (JE049-2101; N=15, 20 cutaneous or abdominal attacks) evaluated 0.4 and 0.8 mg/kg doses via IV infusion, as well as SC doses of 30 mg and 45 mg (0.4 mg/kg and 0.6 mg/kg in a 75 kg subject, respectively). This study showed no differences in safety or tolerability between dose groups and equivalent efficacy between dose groups as assessed by symptom relief at 4 hours post-treatment (VAS scale). The 30 and 45 mg SC doses showed equivalent efficacy and safety and a shorter time to first improvement of symptoms (subject reported) over IV infusion. Since confirmed in study JE049-2101 where the efficacy of 30 and 45 mg SC was equivalent, the 30 mg SC dose was selected and consistently employed in the controlled phases of the Phase III studies.

6 DESCRIPTION OF CONTROLLED PHASE III STUDIES

The efficacy and safety of SC icatibant have been evaluated in 3 controlled Phase III studies in patients with Type I or Type II HAE. These studies are collectively known as the FAST studies (**F**or **A**ngioedema **S**ubcutaneous **T**reatment). In FAST-1, FAST-2, and FAST-3, icatibant was administered to patients by HCPs. The controlled phases of these 3 studies are completed. The open-label extensions to FAST-1 and FAST-2 have concluded, while the open-label extension phase of FAST-3 is ongoing. Additionally, an open-label uncontrolled Phase IIIb study (EASSI, **E**v**A**luation of the **S**afety of **S**ubcutaneous **I**catibant) of the safety and efficacy of self-administered icatibant in treatment of acute attacks of HAE is ongoing at this time. Results presented in this document are based on the 56 patients who had self-administered icatibant at the time of data cutoff (16 October 2010).

The FAST studies were similar in design; each had a controlled phase to assess efficacy and safety in a randomized, controlled, double-blind setting, and an open-label extension phase to assess treatment of subsequent HAE attacks. A summary of the icatibant Phase III clinical studies is in Table 6-1.

Table 6-1 Phase III Clinical Studies with Icatibant

Study Number (Name)	Design	Dose(s)	N Study population
Double-blind Controlled Studies			
JE049-2103 (FAST-1)	Randomized, db, controlled, parallel group Efficacy, S&T, PE	30 mg icatibant or placebo; 1 SC dose	64 (56 randomized, 8 treated open-label[a]) HAE
JE049-2102 (FAST-2)	Randomized, db, controlled, parallel group Efficacy, S&T, PE	30 mg icatibant; 1 SC dose or tranexamic acid; 1 dose PO	77 (74 randomized, 3 treated open-label[a]) HAE
HGT-FIR-054 (FAST-3)	Randomized, db, controlled, parallel group Efficacy, S&T	30 mg icatibant or placebo; 1 SC dose	98 (93 randomized, 5 treated open-label) HAE
Open-Label Extension Studies			
JE049-2103 (FAST-1)	Open-label extension	SC icatibant 30 mg; up to 3 doses at 6-h intervals permitted per attack	69 HAE
JE049-2102 (FAST-2)	Open-label extension	SC icatibant 30 mg; up to 3 doses at 6-h intervals permitted per attack	50 HAE

Table 6-1 Phase III Clinical Studies with Icatibant

Study Number (Name)	Design	Dose(s)	N Study population
HGT-FIR-054 (FAST-3)	Open-label extension	SC icatibant 30 mg; up to3 doses at 6-h intervals permitted per attack	58 HAE Ongoing
Phase III Self-administration Study			
JE049-3101 (EASSI)	Open-label, uncontrolled	30 mg icatibant 1 SC dose	56 HAE Ongoing

Abbreviations: co = crossover; db = double blind; HAE = hereditary angioedema; IV = intravenous; NHV = normal healthy volunteers; sb = single blind; SC = subcutaneous; SD = single dose; S&T = safety and tolerance; PD = pharmacodynamics; PE = pharmacoeconomics; PK = pharmacokinetics

[a] In FAST-1, FAST-2, and FAST-3 patients with laryngeal symptoms who were enrolled during the controlled phase were not randomized and received open label icatibant. FAST-3 was amended (Amendment 1) and patients with mild to moderate laryngeal symptoms were randomized received blinded treatment.

6.1 Patient-Reported Outcomes (PRO)

Consistent with precedent from previous HAE studies, icatibant Phase III studies used a visual analog scale (VAS) and symptom score measurements that examined the symptoms of primary importance to patients (eg, skin and abdominal pain followed by skin swelling in cutaneous and abdominal attacks; voice change and difficulty swallowing in laryngeal attacks).

The use of PROs is an accepted approach to directly measure patient symptoms in registration trials. The FDA issued a guidance on use of PRO in clinical trials[34] commenting that "A PRO instrument (ie, a questionnaire plus the information and documentation that support its use) is a means to capture PRO data used to measure treatment benefit or risk in medical product clinical trials". "A PRO is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else. The outcome can be measured in absolute terms (eg, severity of a symptom, sign, or state of a disease) or as a change from a previous measure."

The FDA guidance outlines the Agency's expectations for validation and the efficacy measures used within the icatibant clinical trials have been validated as per this guidance. A summary of the validation is provided in Appendix 1.

6.2 Efficacy Measures

Efficacy measures were similar across the controlled Phase III studies and included patient- and investigator- reported outcome measures. These measures were selected to capture the symptoms of primary importance to patients (eg, skin and abdominal pain, and skin swelling for cutaneous attacks, for the primary and key secondary endpoints) and were identified using literature review, expert input, qualitative and quantitative market research and post hoc patient qualitative research.

The patient-assessed or investigator-assessed efficacy measures summarized in Table 6-2 were included across the controlled Phase III studies.

Table 6-2 Efficacy Measures Assessed Across Phase III Studies (FAST-1, FAST-2, FAST-3)

	Patient -Assessed	Physician-Assessed
Visual Analogue Scale (VAS)	Skin Swelling Skin Pain Abdominal Pain Nausea[a] Diarrhea[a] Difficulty Swallowing[c] Voice change[c]	
Symptom scores	Skin swelling[b] Erythema (skin redness) Skin irritation Skin pain Abdominal pain Nausea Vomiting Diarrhea Difficulty Swallowing Voice change	Skin swelling Erythema (skin redness) Skin pain Abdominal pain Nausea Abdominal tenderness Vomiting Diarrhea Difficulty swallowing Voice change Breathing difficulties Stridor Asphyxia
Global Assessment		Cutaneous symptoms Abdominal symptoms Laryngeal symptoms
Clinical Global Impression/Improvement (CGI)	Global[c]	Global

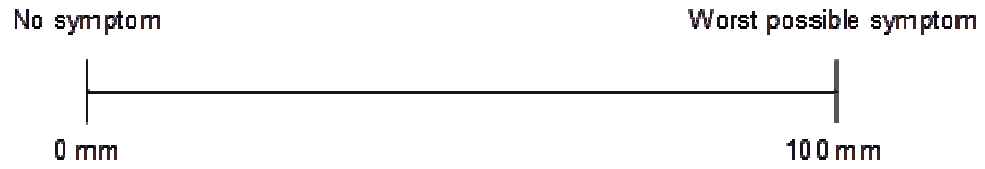
[a] Nausea and diarrhea were not assessed by VAS in FAST-3 and was not included as a primary symptom VAS in FAST-1 and FAST-2.
[b] These were the terms included in the FAST-3 patient diary, the terminology in studies FAST-1 and FAST-2 was clarified as the patient diary was developed and validated.
[c] FAST-3 only

FAST-3 included additional assessments unique to that study, which included clinical global impression/improvement (patient-assessed global measure) and VAS for laryngeal symptoms (patient-assessed difficulty swallowing and voice change).

6.2.1 Visual Analog Scale

The assessment of patient symptoms was based on the visual analog scale (VAS), which is an accepted method by which to capture PROs (Appendix 1). The symptoms of an HAE attack considered most important by patients and physicians (skin pain, skin swelling and abdominal pain) were assessed by the VAS instrument. A VAS utilizes a scorecard with a 100 mm horizontal line, with extreme values and associated verbal descriptors at the beginning and end of the line.

The patient draws a vertical line at the point along the scale that represents the current intensity of the measured symptom. Each symptom was assessed with its own VAS and was referred to as a "single VAS". The VAS appears as follows:



The scale was used to measure the intensity of each symptom of the attack at prior to treatment with study drug and at pre-determined post-treatment time points throughout the treatment period.

A single predominate, or "primary" symptom VAS was used for the FAST-1 and FAST-2 endpoints and is detailed further in Section 6.3.1. In FAST-3, a composite VAS was also used and is detailed further in Section 6.3.2. The composite VAS-3 comprised the average of individual VAS scores for 3 primary non-laryngeal symptoms experienced by a patient during an acute HAE attack: skin pain, skin swelling, and abdominal pain.

In addition, a 5-symptom composite VAS was calculated for patients with laryngeal attacks in FAST-3. The composite VAS-5 comprised the average of individual VAS scores for 5 hallmark symptoms potentially experienced by a patient during an acute laryngeal HAE attack: difficulty swallowing, voice change, skin pain, skin swelling, and abdominal pain.

Since pain is a major component of HAE, the use of PROs is appropriate in assessing patient outcome. It has been well-established in the literature for PROs that a VAS change between 10 and 20 mm represents a clinically meaningful change in the perception of pain. This consistency in minimum clinically significant difference (MCSD) for the VAS for pain is also seen with other symptoms, such as nausea, dyspnea in congestive heart failure, and dyspnea in asthma.[2, 13, 35-41] In addition, the FDA agreed that receiver operating characteristic (ROC) analyses were appropriate to determine MCSD (FDA correspondence September 2006). ROC analyses indicated that absolute changes as small as 9 mm in a primary symptom VAS differentiated improved patients (defined by patient response on a verbal descriptor scale rating change from baseline in symptom severity) from unimproved patients with a sensitivity of 82.61% and a specificity of 88.24% (ref report JE049-4102). A subsequent report summarizing the similar analyses to estimate MCSD for the VAS-3 composite score indicated an improvement as small as 5 mm on the VAS-3 composite differentiated improved from unimproved patients with a sensitivity of 90% and a specificity of 90.24% (Report JE049-5129). Thus, any person who had a baseline VAS-3 score of 10 mm or higher could potentially meet the FDA definition of a responder (50% improvement) in a clinically meaningful way (more than 5 mm change).

In qualitative and quantitative validation studies conducted per the FDA guidance, the single symptom VAS measures and the VAS composite scores have been shown to be valid, reliable and responsive and appropriate to use in studies of HAE (see Appendix 1).

These studies also demonstrated that the subject symptom score secondary endpoints were valid, reliable and responsive and appropriate for use in the assessment of HAE symptoms during a clinical study.

6.2.2 Symptom Score

Other symptoms frequently reported during HAE attacks were assessed by patient- and investigator- reported severity scores (see Table 6-2). All HAE attack symptoms were scored using a 5-point scale that ranged from 0 (no symptoms, absence of symptoms) to 4 (very severe, severe interference with daily activities).

6.2.3 Investigator –Assessed Clinical Global Impression/Improvement

The Clinical Global Impression/Improvement (CGI) score is an accepted and widely used tool for assessing patient response across a number of conditions (eg, psychiatric disorders).[42, 43] The investigator used a 7-point scale to score the severity of the attack from 1 for "normal, not at all ill" to 7 for "among the most extremely ill patients" at pretreatment. Following treatment, the investigator used a 7-point scale to score levels of improvement in severity of the attack following study drug administration from 1 (very much improved) to 7 (very much worse).

6.2.4 Investigator's Global Assessment

A global assessment of symptoms in 3 areas (cutaneous symptoms, abdominal symptoms and laryngeal symptoms) were performed by the investigator using a following 5-point scale that ranged from 0 (no symptoms, absence of symptoms) to 4 (very severe, very severe interference with daily activities).

6.3 Study Endpoints

6.3.1 Primary Efficacy Endpoint: FAST-1 and FAST-2

In FAST-1 and FAST-2, the primary endpoint was the Time to Onset of Symptom Relief, based on a pre-specified reduction from pretreatment VAS score for a single identified Primary symptom (TOSR-P).

The primary symptom was identified based on the type of attack (Section 6.5.3.2). For abdominal attacks, the single primary symptom was based on the VAS for "abdominal pain". For cutaneous attacks, the single primary symptom was based on the most severe VAS for "skin swelling" or "skin pain." If both were equally severe, the VAS for "skin pain" was used.

In order to facilitate cross-study comparisons, the primary endpoint for FAST-1 and FAST-2, TOSR-P, was specified as the key secondary endpoint for FAST-3.

6.3.2 Primary Efficacy Endpoint: FAST-3

Following discussions with the FDA during the design of FAST-3, the primary endpoint was defined as the Time to Onset of Symptom Relief (TOSR) based on a prespecified reduction from pretreatment in a 3-component composite VAS score (VAS-3).

The VAS-3 was considered to be a more comprehensive and clinically relevant measure of treatment effect than the primary symptom VAS, as patients may experience multiple concomitant symptoms during an HAE attack, and VAS-3 better reflected the overall burden on the patient. Further, VAS-3 was closely related to the original FAST-1 and FAST-2 primary endpoint, since it measures the same symptoms (ie, skin pain, skin swelling and abdominal pain) and employs the same assessment tool.

The VAS-3 composite score was calculated as the average of 3 individual VAS scores.

- Skin swelling
- Skin pain
- Abdominal pain

Symptom relief was conservatively defined as a 50% reduction from pretreatment in the composite VAS score. TOSR was calculated as the time of the first of three consecutive measures which symptom relief was observed.

To maintain continuity with FAST-3 and to facilitate cross-study comparisons and subgroup analyses, TOSR was calculated in post hoc analyses from prospectively acquired VAS data from the FAST-1 and FAST-2 studies.

6.3.3 Secondary Endpoints

A number of additional secondary endpoints were also assessed across the controlled Phase III studies. This document focuses on 4 secondary endpoints that assess the continuum of effect of icatibant on the broad spectrum of symptoms in acute attacks of HAE and demonstrate the onset of clinically relevant efficacy and resolution of attack. These include:

- Change from baseline in composite VAS over time
- Time from treatment administration to subject- and investigator-assessed Initial Symptom Improvement (TISI)
- Time from treatment administration to Almost Complete Symptom Relief (TACSR), defined as the time of the first of 3 consecutive measures at which all VAS scores were less than 10 mm
- Use of rescue therapy

A complete list of secondary endpoints is included in Appendix 2 and results are summarized in Appendix 5.

6.3.4 Safety Evaluations

Safety assessments included:

- Adverse events, including any AE and SAE, reported by relation to treatment and

severity

- Symptoms at injection site: Injection site reactions were documented in the "local tolerability" page (or form) of the patient diary and in the eCRF. An injection site reaction that did not meet the criteria of a serious adverse event did not need to be additionally reported as an adverse event
- Antibody assay results
- Laboratory results
- Electrocardiogram (ECG)
- Vital signs
- Physical examination findings

6.4 Study Design

The 3 controlled Phase III studies were similar in design; each had a controlled phase for a single acute attack followed by an open-label treatment phase for subsequent attacks. Key elements of their study design are described in Table 6-3.

Table 6-3 Summary of Study Design for FAST Studies

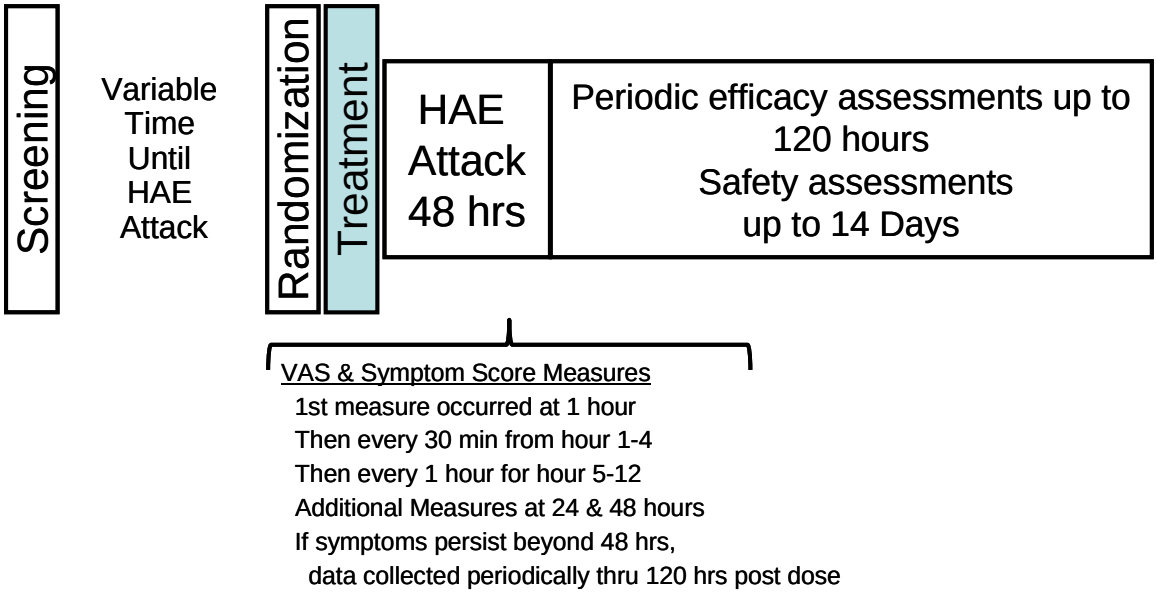
	FAST-1	FAST-2	FAST-3
Study Design	Randomized double-blind, controlled Open-label extension	Randomized double-blind, controlled Open-label extension	Randomized double-blind, controlled Open-label extension
Location(s)	Multicenter: US, Ex US	Multicenter:Ex-US	Multicenter:US, Ex US
Icatibant dose and administration	Icatibant 30 mg SC	Icatibant 30 mg SC	Icatibant 30 mg SC
Control	Placebo	Tranexamic acid	Placebo
Number of injections	Single injection during the controlled phase, up to 3 injections per attack during the open-label phase	Single injection during the controlled phase, up to 3 injections per attack during the open-label phase	Single injection during the controlled phase, up to 3 injections per attack during the open-label phase
Primary Efficacy Objective	Efficacy of icatibant compared to placebo on Time to Onset of Symptom Relief for HAE – Primary symptom VAS (TOSR-P)	Efficacy of icatibant compared to tranexamic acid on Time to Onset of Symptom Relief for HAE – Primary symptom VAS (TOSR-P)	Efficacy of icatibant compared to placebo on Time to Onset of Symptom Relief for HAE – composite VAS (TOSR)
Key Secondary Efficacy Objective	n/a	n/a	Efficacy of icatibant compared to placebo on Time to Onset of Symptom Relief for HAE – Primary symptom VAS

Table 6-3 Summary of Study Design for FAST Studies

	FAST-1	FAST-2	FAST-3 (TOSR-P)
Safety Objectives	Safety, tolerability	Safety, tolerability	Safety, tolerability
Study Population	Adult patients with HAE	Adult patients with HAE	Adult patients with HAE

A schematic of study design for the controlled phase of the FAST studies is presented in Figure 6-1. Patients with HAE were identified and screened for eligibility. Eligible subjects who consented to participate in the study were instructed to return to the site when their next HAE attack began. At that time, patients with moderate to severe cutaneous or abdominal attacks were enrolled and randomized to receive one 30 mg SC dose of icatibant or control. After implementation of protocol amendment 1 in FAST-3, patients with mild or moderate laryngeal attacks were randomized to blinded treatment.

Figure 6-1 Phase III Study Design: Controlled Phase



Study entry criteria were similar across the controlled Phase III studies and are summarized in Appendix 3. Subjects were male or female, at least 18 years of age and with a documented diagnosis of HAE Type I or II (confirmed by medical history and/or laboratory confirmation of immunogenic or functional C1-INH deficiency).

The current attack had to be moderate to very severe and subjects must have completed baseline assessments and commenced treatment no later than 6 hours after the time the current attack became moderate. Patients who had received previous treatment with icatibant were excluded from enrollment in FAST-3.

Patients and investigators were asked to rate attack symptoms using the VAS and symptom score measurements through 48 hours after the administration of study drug. If symptoms continued, symptom assessment continued at predefined intervals up to 120 hours. Patients were followed for up to 14 days for safety after study drug administration or until the onset of another HAE attack, whichever came first.

After receiving treatment for their first on-study attack, patients could participate in the open-label, repeated treatment phase of the study for subsequent attacks. In FAST-1 and FAST-2, screened patients who did not have an attack until after the controlled phase of the study was completed were permitted to receive treatment in the open-label phase.

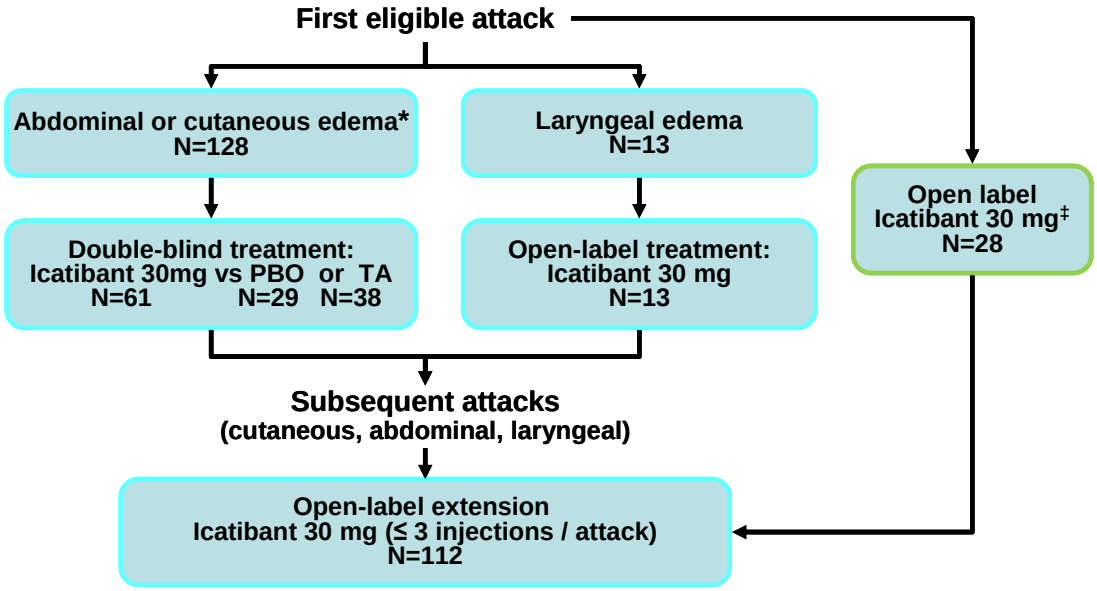
Because laryngeal attacks are potentially life-threatening, patients who presented with a laryngeal attack of any severity were to receive open-label icatibant (single 30 mg SC injection) in all 3 studies. After implementation of protocol amendment 1 in FAST-3, patients with mild or moderate laryngeal attacks were randomized to blinded treatment.

Placebo (FAST-1 and FAST-3) was an isotonic, sterile, and buffered solution formulated to match the study drug (3.0 ml, acetate-buffered solution for injection, pH 5.5±0.3). Tranexamic acid (FAST-2) was provided as a hard capsule containing 500 mg tranexamic acid encapsulated with methyl cellulose and magnesium stearate; placebo for tranexamic acid was similar in presentation with the same excipients.

During the open-label phase subjects received 1 SC injection of 30 mg icatibant. Repeat dosing of icatibant was permitted within 48 hours of the initial treatment if the attack worsened or if, in the opinion of the subject and the investigator, symptoms remained severe enough to warrant further treatment. A maximum of 3 injections that were at least 6 hours apart could be given per attack. If symptoms became worse more than 48 hours after the initial treatment, the event was considered a new attack.

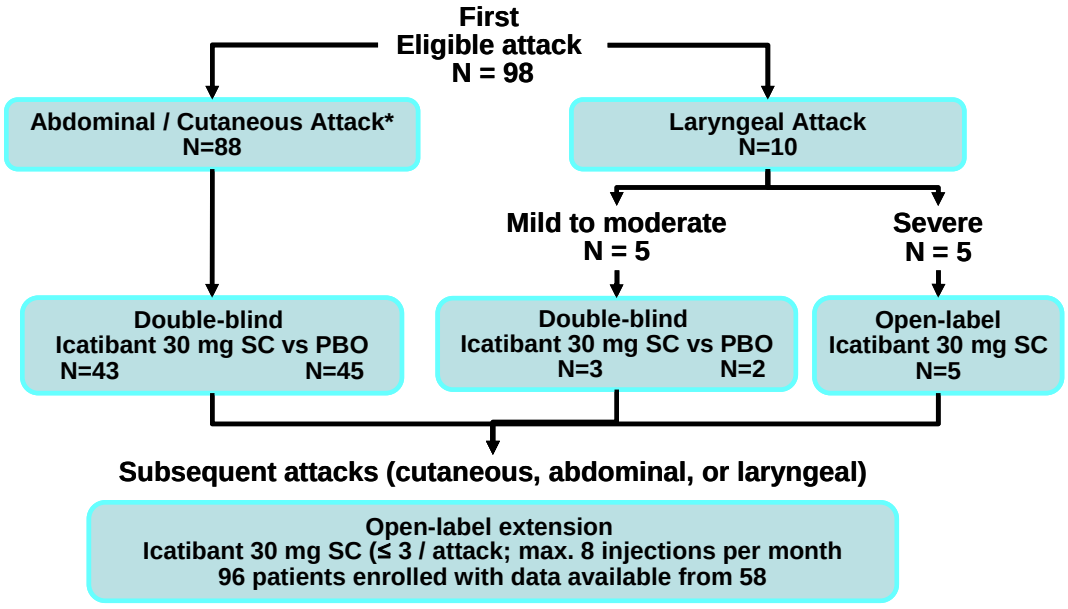
Figure 6-2 depicts the study schema for FAST-1/FAST-2 and Figure 6-3 depicts the study schema for FAST-3 after the implementation of protocol amendment 1.

Figure 6-2 Treatments Administered in FAST-1 and FAST-2



* Moderate to very severe
‡ Patients who presented with laryngeal symptoms during the controlled phase received open label treatment with icatibant
Note: 28 patients who had been screened but not enrolled in the double blind phase were allowed to enter the study after the double blind phase was completed. They received open-label icatibant as part of a modified open-label extension phase.

Figure 6-3 Treatments Administered in FAST-3 (post Amendment 1)



Note: No patients with mild to moderate laryngeal first attacks were enrolled prior to amendment 1.
* Moderate to very severe

6.5 Statistical Methods

6.5.1 Analysis Populations

Populations were defined for analyses of efficacy and safety by study and in integrated analyses, and are based on data collected from the controlled, phase III studies. The criteria used to define the analysis populations are summarized in Table 6-4.

6.5.1.1 Efficacy Analyses Populations

- The Non-laryngeal Population
    - This is the intent-to-treat population, which included all randomized patients whose first attack on study was either cutaneous or abdominal; randomized patients with laryngeal first attacks were excluded
    - Used data resulting from the randomized, double-blind treatment with icatibant or control for the main analysis of each efficacy endpoint and to allow comparisons to comparator treatment
    - Analyses were limited to data corresponding to the subject's first attack
- The Phase III Treated Population (for repeated treatment analysis)
    - Included all patients (with either non-laryngeal or laryngeal attacks) from the controlled Phase III studies who were treated with double-blind as well as open-label icatibant
    - Used data from the patient's repeated treatment with icatibant to explore the efficacy and safety of repeated treatment
    - Analyses conducted with this population were generally focused on data corresponding to the subject's first 5 icatibant-treated attacks, although data from all repeat attacks were analyzed. Results were summarized by icatibant-treated attack number

      NOTE: It should be noted that the first icatibant-treated attack may not have been the subject's first on-study attack. Specifically, patients randomized to placebo had their first icatibant-treated attack recorded as their second on-study attack; ie, their second on-study attack counted as their first icatibant-treated attack.
- The Laryngeal Treated Population
    - Included all patients with laryngeal attacks who were treated with double-blind or open-label icatibant
    - Used data from the patient's first laryngeal attack to explore the efficacy of icatibant for the treatment of laryngeal attacks
    - Analyses were limited to data corresponding to the subject's first icatibant-treated laryngeal attack regardless of whether that attack occurred in the controlled or open-label phase of the studies

6.5.1.2 Safety Populations

Data from the controlled Phase III studies were pooled to evaluate safety. Three safety populations were defined:

- The Phase III Safety Population
    - Included all (both non-laryngeal and laryngeal) randomized and treated patients from the controlled Phase III studies
    - Used data from double-blind treatment (icatibant or control) of the patient's first attack for analyses of safety, allowing safety comparisons for icatibant and comparator treatment
- The Phase III Treated Population (for repeated treatment analysis), as defined in Section 6.5.1.1.
- The Phase I and II Safety Population, included all subjects from Phase I and II studies. Supplemental analyses of safety were conducted with this population according to the treatment actually received.

Table 6-4 Criteria for Phase III Analysis Population Definitions

	Type of Attack		Study Treatment		Type of Analysis	
Analysis Population	**Non-laryngeal**	**Laryngeal**	**Randomized Double blind**	**Open-label**	**Efficacy**	**Safety**
Non-laryngeal N=88	•		•		•	
Laryngeal treated N=60		•[a]	•	•	•	
Phase III Safety N=223	•	•	•			•
Phase III Treated N=225	•	•	•	•	•[b]	•

[a] Limited to the first icatibant-treated laryngeal attack, which may have occurred in either the controlled or open-label phases of the studies

[b] Generally limited to the first 5 attacks

6.5.2 Sample Size Calculations

Sample size calculations are detailed in Appendix 4.

6.5.3 Efficacy Analyses

6.5.3.1 Time to Onset of Symptom Relief (TOSR)

The Time to Onset of Symptom Relief was defined as the time from study drug administration to the onset of symptom relief (TOSR), where symptom relief was defined as a 50% reduction from the pretreatment composite VAS-3 score (Section 6.3.2). The onset of symptom relief was calculated as the earliest of 3 consecutive non-missing measurements in which there was at least a 50% reduction from the pretreatment composite VAS score. Missing individual symptom scores were imputed using last observation carried forward for calculating the composite VAS. Protocol-specified assessment times with all individual symptom scores missing were excluded from the analysis (ie, were ignored in the determination of three consecutive measurements). Patients without documented symptom relief were censored at the time of their last VAS assessment. For the non-laryngeal population, the composite VAS-3 was used to evaluate TOSR; for patients with first laryngeal attacks, the composite VAS-5 was used to evaluate TOSR. TOSR was the primary endpoint in FAST3 and was calculated post hoc for FAST-1 and FAST-2 based on prospectively collected single VAS data in those studies.

The TOSR was summarized using the Kaplan-Meier method. The Peto-Peto Wilcoxon test with a global 2-sided significance level of 5% was used to test the null hypothesis. The Peto-Peto Wilcoxon test was selected for this analysis as it gives more weight to earlier achievement of symptom relief.

Sensitivity Analyses

A number of sensitivity analyses were performed in the non-laryngeal population. To control for study design factors, time to symptom relief was analyzed using a Cox proportional hazards model, which included covariates for treatment and the stratification factors used in the randomization, edema location and previous use of C1-INH (the latter applies to FAST-3 only). The hazard ratio (icatibant - control), the corresponding 95% confidence interval, and the p-value assessing differences among treatment groups were determined. These analyses also assessed whether results were sensitive to the use of the Peto-Peto Wilcoxon test, rather than proportional hazards. In addition, the p-value from the stratified Peto-Peto Wilcoxon test was presented as a parallel to primary analysis.

The use of rescue medications following treatment with icatibant was allowed during the studies to alleviate acute symptoms which were judged by the investigator as resultant from the current HAE attack. Time to symptom relief was analyzed censoring patients who took rescue medications before the onset of symptom relief to evaluate the use of rescue medications. This analysis was conducted using the non-laryngeal population. Patients were censored at the time of administration of rescue medication, if symptom relief had not already occurred. The analysis was conducted using the same methods as for the primary analysis.

Time to Onset of Symptom Relief was explored using different criteria to define symptom relief. Specifically, 30%, 40%, 60%, and 70% reductions from pretreatment in composite VAS were assessed, using the same analysis methods as for the primary analysis for TOSR-P.

6.5.3.2 Time to Onset of Symptom Relief for the Primary Symptom of the Attack (TOSR-P)

Time to Onset of Symptom Relief for the Primary Symptom of the Attack (TOSR-P) was determined using the subject-assessed VAS score for a single primary symptom (determined by edema location) and was defined as a reduction from the pretreatment value as follows:

Any value below the line $Y = 6/7\ X - 16$ with $X \geq 30$ mm, where X = pretreatment VAS for the primary symptom and Y = the post-treatment VAS, was considered to be relief. 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 30 mm, and the line defining the criterion interpolates between these 2 points for other baseline VAS scores between 30 mm and 100 mm. If the pretreatment primary VAS score was <30 mm, primary symptom relief was defined as at least a 68% reduction from pretreatment.

The single primary symptom VAS was programmatically assigned based on the edema location of the attack. For abdominal attacks, the primary symptom VAS was based on abdominal pain. For cutaneous attacks, the primary symptom VAS was based on the more severe pretreatment score of skin pain or skin swelling; if both are equally severe at pretreatment, then skin pain was used. For laryngeal attacks, the primary symptom VAS was based on the more severe pretreatment score of difficulty swallowing or voice change; if both were equally severe at pretreatment then difficulty swallowing was used.

Time to Onset of Primary Symptom Relief (TOSR-P) was calculated from the time of study drug administration to the onset of primary symptom relief. Primary symptom relief was determined as the earliest of 3 consecutive non-missing measurements meeting the criterion specified above. Missing primary symptom scores were not imputed. Protocol-specified assessment times with primary symptom scores missing were excluded from the analysis (ie, were ignored in the determination of three consecutive measurements). Patients without documented primary symptom relief were censored at the time of their last VAS assessment. TOSR-P was the primary endpoint in FAST-1 and FAST-2 and the key secondary endpoint in FAST-3. TOSR-P was the primary endpoint in FAST-1 and FAST-2 and the secondary endpoint in FAST-3.

All of the analyses performed for the primary endpoint, TOSR, were repeated for the key secondary endpoint, TOSR-P.

Subgroup Analyses

TOSR and TOSR-P were explored further within subgroups using the Non-laryngeal Population. The same analysis methods as for the primary analysis were used. In addition, the interactions between treatment and the subgroup factors were explored using a proportional hazards regression model with study, treatment, and the subgroup factors as additional explanatory variables. The estimated hazard ratio (icatibant:control) within each subgroup and the corresponding 95% confidence interval were presented.

6.5.3.3 Change from Baseline in Composite VAS over Time

The actual value, change from pretreatment, and number and percentage of subjects with at least a 50% reduction from pretreatment were summarized by study time point and treatment groups for the non-laryngeal population, by icatibant-treated attack for the Phase III Treated population, and by protocol for the laryngeal population. The treatment groups will be compared using the Wilcoxon rank-sum test for change from pretreatment to each time point in the composite VAS, and using Fisher's exact test for the proportion of patients with at least a 50% reduction from pretreatment.

6.5.3.4 Time to Initial Symptom Improvement (TISI)

The secondary endpoint, Time to Initial Symptom Improvement (TISI), was reported by both subjects and investigators as the time at which initial symptom improvement was noted. It was summarized using the Kaplan-Meier method. The Peto-Peto Wilcoxon test with a global 2-sided significance level of 5% was used to test the null hypothesis.

6.5.3.5 Time to Almost Complete Symptom Relief (TACSR)

The secondary endpoint, Time to Almost Complete Symptom Relief (TACSR), was defined as the time between injection and the first documentation of almost complete symptom relief. Almost complete symptom relief was defined as a score <10 mm on each individual VAS score for 3 consecutive non-missing measurements. Patients who did not achieve documented almost complete symptom relief were censored at the time of their last symptom assessment. TACSR was summarized using the Kaplan-Meier method. The Peto-Peto Wilcoxon test with a global 2-sided significance level of 5% was used to test the null hypothesis.

6.5.3.6 Use of Rescue Therapy

The number and percentage of subjects who received rescue therapy before the onset of symptom relief, as well as at anytime during the HAE attack (within 120 hours of initial study drug administration), were summarized by treatment group, and the treatment difference was tested using a Fisher's exact test.

6.5.3.7 Other Efficacy Analyses

Analyses of other secondary efficacy endpoints were performed and are summarized in Appendix 2. Results are detailed in Appendix 5.

6.5.3.8 Multiple Comparisons in FAST-3

FAST-3 had a pre-specified primary endpoint, TOSR, and a pre-specified key secondary endpoint, TOSR-P. While not explicitly stated in the statistical analysis plan (SAP), there was an implicit gatekeeper approach to multiple comparisons. That is, the trial would only be considered successful if there was a statistically significant difference at the 5% significance level for the icatibant group relative to the placebo group.

If so, then consideration would be given to the significance of the treatment comparison for the key secondary endpoint, also at the 5% significance level. All other efficacy endpoints were secondary and not controlled for multiple comparisons.

6.5.4 Safety Analyses

Observation period AEs were defined as treatment emergent AEs occurring from the time of study drug administration to the Day 14 visit or study discontinuation, whichever occurred first, for each study-drug treated attack. Data from the early clinical studies demonstrated that injection site reactions were common with icatibant administration; therefore injection site reactions were identified as events of interest prospectively, and were reported separately from AEs.

7 EFFICACY

In the following discussion, the results for FAST-3 are presented first, as this is the definitive Phase III trial. The results from FAST-1 and FAST-2 are then presented as supportive trials. The discussion presented in this section focuses on the primary and key secondary endpoints from the FAST studies, and where appropriate, other important secondary endpoints. Symptom scores, the investigator's global assessment, and CGI results are not discussed, although a tabular summary of results can be found in Appendix 5. In addition, the Phase IIIb study of self-administration of icatibant (EASSI) is discussed in Section 9.

7.1 Controlled Phase III Studies

7.1.1 FAST-3

FAST-3 was designed as a randomized, double-blind, placebo-controlled Phase III study to examine the efficacy of icatibant for the treatment of acute HAE attacks. The study included key design elements suggested by the FDA including the utilization of a composite measure of HAE symptoms. A composite measure was selected to more adequately address the variable nature of HAE attacks and provide a more comprehensive assessment of the effect of icatibant across the spectrum of symptoms that occur during an attack, instead of focusing on a single symptom. The primary endpoint of FAST-3 was defined as the Time to Onset of Symptom Relief (TOSR) as measured by the composite VAS (VAS-3 for non-laryngeal attacks). The VAS-3 was defined as the average of the 3 individual VAS scores for the symptoms of skin swelling, skin pain, and abdominal pain and was the tool used to determine the primary efficacy. The Time to Onset of Symptom Relief (TOSR) was defined as the time to the first of three consecutive measurements at which the 3-component, composite VAS was at least 50% less than the baseline composite VAS score.

The primary endpoint of FAST-1 and FAST-2, the Time to Onset of Primary Symptom Relief (TOSR-P), was included as the key secondary endpoint in FAST-3 to enable cross-study comparisons.

During the controlled phase of FAST-3, a total of 88 patients were randomized; 43 patients received icatibant and 45 patients received placebo.

The disposition of FAST-3 is summarized in Table 7-1. Nine of the 10 patients in the icatibant group and 6 of the 8 patients in the placebo group who did not complete assessments up to Day 14 had an additional HAE attack and were not able to complete the study assessments.

The demographics for FAST-3 are summarized in Table 7-2.

Table 7-1 Patient Disposition-Non-laryngeal Population (FAST-3)

Parameter	Icatibant (N=43)	Placebo (N=45)
Completed assessments up to Day 14		
Yes	33 (76.7)	37 (82.2)
No	10 (23.3)	8 (17.8)
Reason for not completing assessments up to Day 14		

Table 7-1 Patient Disposition-Non-laryngeal Population (FAST-3)

Parameter	Icatibant (N=43)	Placebo (N=45)
Withdrawal of consent	0	0
Significant medical conditions	0	1 (2.2)
Additional HAE attack	9 (20.9)	6 (13.3)
Lost to Follow-up/Other	1 (2.3)	0
Death	0	1 (2.2)
Had a subsequent attack treated with icatibant in the open-label extension		
Yes	29 (67.4)	22 (48.9)
No	14 (32.6)	23 (51.1)

Source: ISE Table 1.2

Table 7-2 Demographic and Baseline Characteristics- Non-laryngeal Population (FAST-3)

	Icatibant (N=43)	Placebo (N=45)
Age[a] (years)		
Mean (SD)	36.1 (13.69)	36.6 (11.18)
Age[a] group		
≤30 years- n (%)	16 (37.2)	13 (28.9)
>30 to ≤40 years- n (%)	13 (30.2)	16 (35.6)
>40 to ≤50 years- n (%)	10 (23.3)	11 (24.4)
>50 years n (%)	4 (9.3)	5 (11.1)
Sex		
Male n (%)	16 (37.2)	16 (35.6)
Female n (%)	27 (62.8)	29 (64.4)
Race		
White	38 (88.4)	40 (88.9)
Non-White	5 (11.6)	5 (11.1)
Weight (kg)		
Mean (SD)	81.73 (25.07)	80.66 (20.87)
Weight Group		
≤50 kg- n (%)	4 (9.3)	2 (4.4)
>50 to ≤75 kg- n (%)	16 (37.2)	20 (44.4)
>75 to ≤100 kg- n (%)	14 (32.6)	13 (28.9)
>100 kg n (%)	9 (20.9)	10 (22.2)
Geographic Region		
North American- n (%)	27 (62.8)	32 (71.1)
Eastern Europe n (%)	8 (18.6)	4 (8.9)
Other n (%)	8 (18.6)	9 (20.0)
Location of First On-study Attack		

Table 7-2 Demographic and Baseline Characteristics- Non-laryngeal Population (FAST-3)

	Icatibant (N=43)	Placebo (N=45)
Cutaneous n (%)	26 (60.5)	26 (57.8)
Abdominal n (%)	17 (39.5)	19 (42.2)
Severity of First On-Study Attack		
Moderate n (%)	27 (62.8)	28 (62.2)
Severe n (%)	16 (37.2)	17 (37.8)
Baseline VAS-3 mean (SD)	41.67 (15.774)	37.74 (19.211)
Hours from attack onset to study drug administration- mean (SD)	7.07 (3.157)	6.18 (2.316)

SD = standard deviation

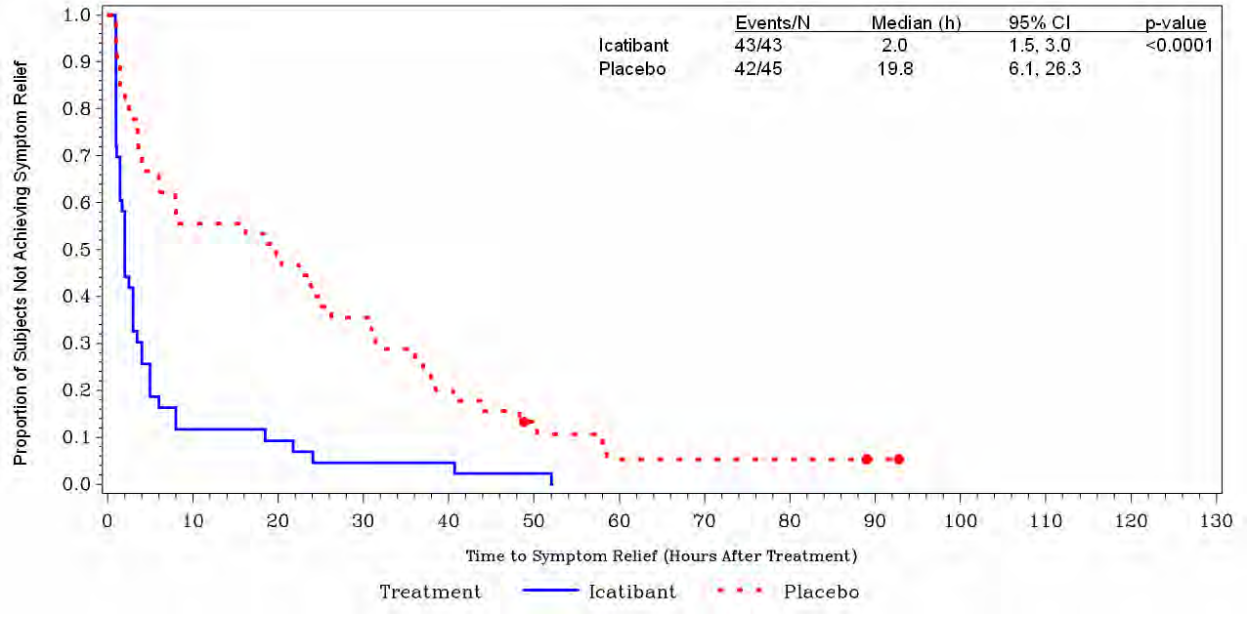
[a] Age at first administration of study medication.

Source: ISE Table 2.1, ISE Table 5.1, and ISE Table 13.1

7.1.1.1 Primary Efficacy Endpoint- TOSR (based on VAS-3)

In FAST-3, icatibant demonstrated a statistically significantly faster TOSR for cutaneous and abdominal attacks than placebo in FAST-3 (p<0.0001) (Figure 7-1).

Figure 7-1 Time to Onset of Symptom Relief (TOSR)- Non-laryngeal Population (FAST-3)



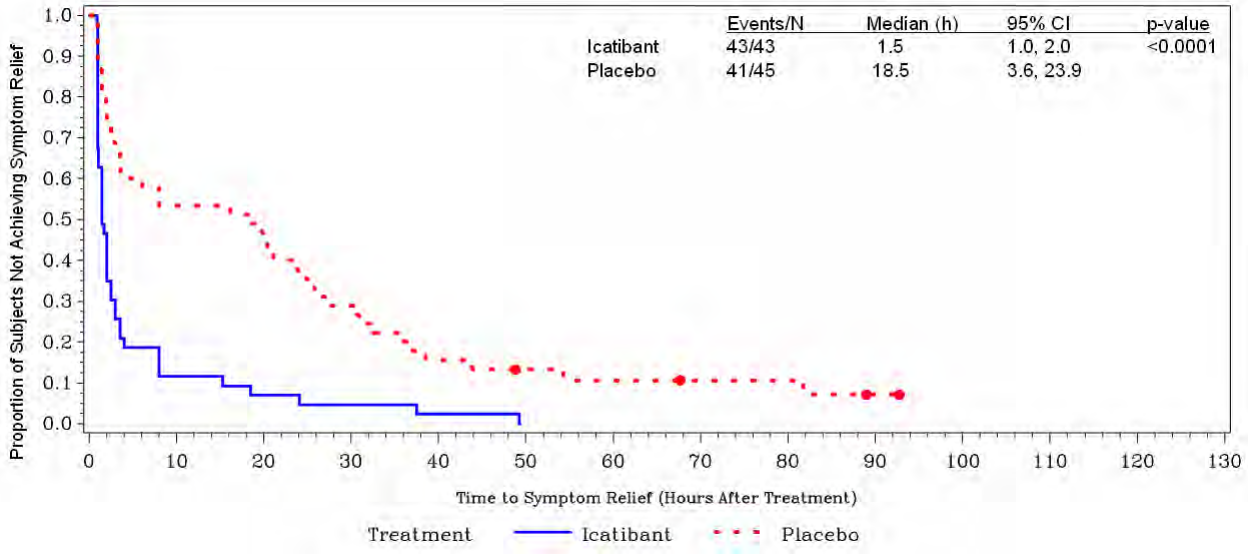
Symptom relief is defined as a 50% reduction from pretreatment in the 3-symptom composite VAS score. Patients who did not achieve symptom relief within the observation period were censored at the last observation time. Dot indicates censoring.

Source: ISE Figure 1.1.1 and ISE Table 6.1.1

7.1.1.2 Key Secondary Endpoint-TOSR-P (based on the single primary symptom VAS)

In FAST-3, icatibant demonstrated a statistically significantly faster TOSR-P (based on the identified single primary VAS symptom) for cutaneous and abdominal attacks than placebo in FAST-3 ($p<0.0001$) (Figure 7-2).

Figure 7-2 Time to Onset of Primary Symptom Relief (TOSR-P) Based on the Single, Primary VAS -Non-laryngeal Population (FAST-3)



Primary symptom relief is defined as a reduction from pretreatment in the score for a single primary VAS symptom. Detailed definition of TOSR-P in Section 6.5.3.2.
Patients who did not achieve symptom relief within the observation period were censored at the last observation time. Dot indicates censoring.
Source: ISE Figure 3.1.1 and Table 8.1.1

7.1.2 FAST-1 and FAST-2

The primary endpoint for both FAST-1 and FAST-2 was the TOSR-P, which was the key secondary endpoint in FAST-3.

During the controlled phase of FAST-1, a total of 55 patients were randomized; 26 patients received icatibant and 29 patients received placebo. During the controlled phase of FAST-2, a total of 73 patients were randomized; 35 patients received icatibant and 38 patients received tranexamic acid.

The disposition for FAST-1 and FAST-2 is summarized in Table 7-3. The demographics for FAST-1 and FAST-2 are summarized in Table 7-4.

Table 7-3 Disposition-Non-laryngeal Population (FAST-1 and FAST-2)

	FAST-1		FAST-2	
Parameter	**Icatibant (N=26)**	**Placebo (N=29)**	**Icatibant (N=35)**	**Tranexamic Acid (N=38)**
Completed assessments up to Day 14				
Yes n (%)	20 (76.9)	27 (93.1)	29 (82.9)	31 (81.6)
No n (%)	6 (23.1)	2 (6.9)	6 (17.1)	7 (18.4)
Reason for not completing assessments up to Day 14				
Withdrawal of consent	0	0	0	0
Additional HAE attack n (%)	4 (15.4)	2 (6.9)	6 (17.1)	6 (15.8)
Significant medical conditions	0	0	0	0
Lost to Follow-up/Other n (%)	2 (7.7)	0	0	1 (2.6)
Death	0	0	0	0
Had a subsequent attack treated with icatibant in the open-label extension				
Yes n (%)	22 (84.6)	26 (89.7)	22 (62.9)	21 (55.3)
No n (%)	4 (15.4)	3 (10.3)	13 (37.1)	17 (44.7)

Source: ISE Table 1.2

Table 7-4 Demographic and Baseline Characteristics- Non-laryngeal Population (FAST-1 and FAST-2)

	FAST-1		FAST-2	
	Icatibant (N=26)	**Placebo (N=29)**	**Icatibant (N=35)**	**Tranexamic Acid (N=38)**
Age[a] (years)				
Mean (SD)	35.0 (9.95)	34.9 (11.37)	40.0 (13.62)	41.9 (12.36)
Age[a] group				
≤30 years- n (%)	8 (30.8)	11 (37.9)	9 (25.7)	10 (26.3)
>30 to ≤40 years- n (%)	9 (34.6)	8 (27.6)	13 (37.1)	6 (15.8)
>40 to ≤50 years n (%)	7 (26.9)	8 (27.6)	4 (11.4)	12 (31.6)
>50 years n (%)	9 (25.7)	10 (26.3)	9 (25.7)	10 (26.3)
Sex				
Male- n (%)	11 (42.3)	8 (27.6)	12 (34.3)	15 (39.5)
Female n (%)	15 (57.7)	21 (72.4)	23 (65.7)	23 (60.5)
Race				
White n (%)	26 (100.0)	27 (93.1)	35 (100.0)	38 (100.0)
Non-White n (%)	0	2 (6.9)	0	0
Weight (kg)				
Mean (SD)	79.73 (21.27)	76.04 (21.88)	79.78 (16.25)	74.22 (15.61)
Weight Group				
≤50 kg- n(%)	2 (7.7)	1 (3.4)	1 (2.9)	1 (2.6)
>50 to ≤75 kg- n (%)	10 (38.5)	16 (55.2)	15 (42.9)	21 (55.3)

Table 7-4 Demographic and Baseline Characteristics- Non-laryngeal Population (FAST-1 and FAST-2)

	FAST-1		FAST-2	
	Icatibant (N=26)	**Placebo (N=29)**	**Icatibant (N=35)**	**Tranexamic Acid (N=38)**
>75 to ≤100 kg n (%)	9 (34.6)	8 (27.6)	16 (45.7)	14 (36.8)
>100 kg n (%)	5 (19.2)	4 (13.8)	3 (8.6)	2 (5.3)
Geographic Region				
North American- n (%)	17 (65.4)	18 (62.1)	0	0
Western Europe n (%)	0	0	27 (77.1)	27 (71.1)
Eastern Europe n (%)	0	0	5 (14.3)	7 (18.4)
Other n (%)	9 (34.6)	11 (37.9)	3 (8.6)	4 (10.5)
Location of First On-study Attack				
Cutaneous n (%)	13 (50.0)	13 (44.8)	23 (65.7)	23 (60.5)
Abdominal n (%)	13 (50.0)	16 (55.2)	12 (34.3)	15 (39.5)
Severity of First On-Study Attack				
Moderate n (%)	10 (38.5)	12 (41.4)	9 (25.7)	11 (28.9)
Severe n (%)	16 (61.5)	17 (58.6)	26 (74.3)	27 (71.1)
Baseline VAS-3- mean (SD)	34.09 (15.149)	41.55 (23.251)	32.89 (16.309)	32.13 (16.157)
Hours from attack onset to study drug administration- mean (SD)	11.95 (11.133)	12.94 (9.632)	10.15 (6.125)	9.74 (10.037)

SD = standard deviation

[a] Age at first administration of study medication.

Source: ISE Table 2.1, ISE Table 5.1, and ISE Table 13.1

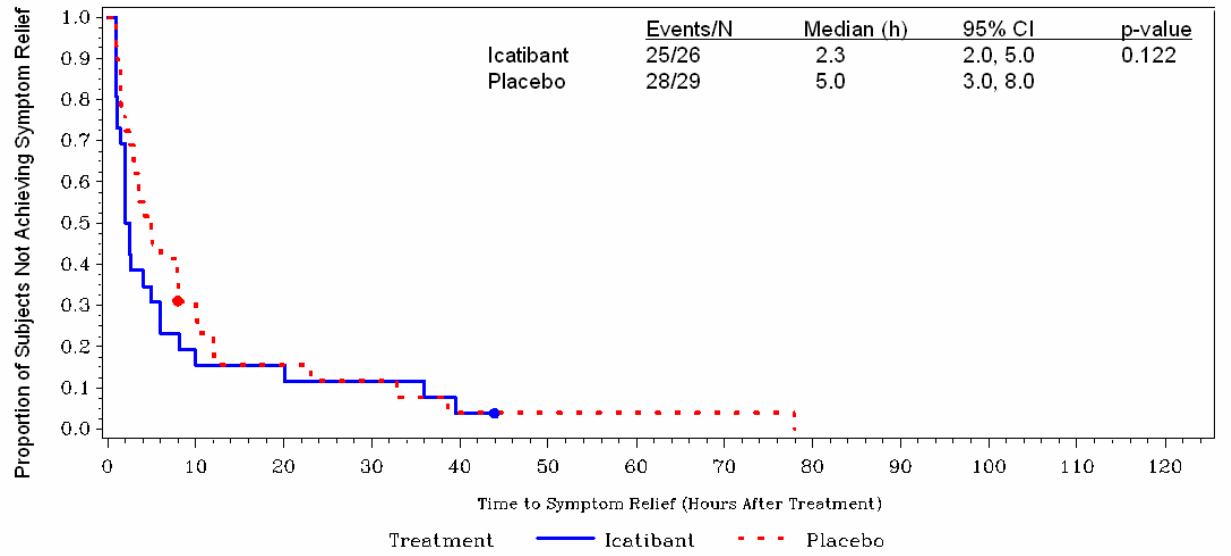
7.1.2.1 Primary Endpoint- TOSR-P (based on the Single Primary Symptom VAS)

In FAST-1 and FAST-2, the primary endpoint was the TOSR-P. This endpoint was defined as a reduction from pretreatment in the score for an identified single, primary VAS symptom.

In FAST-1, while the median TOSR-P in FAST-1 was shorter for the icatibant group than for the placebo group, the difference was not statistically significant (p=0.122) (Figure 7-3).

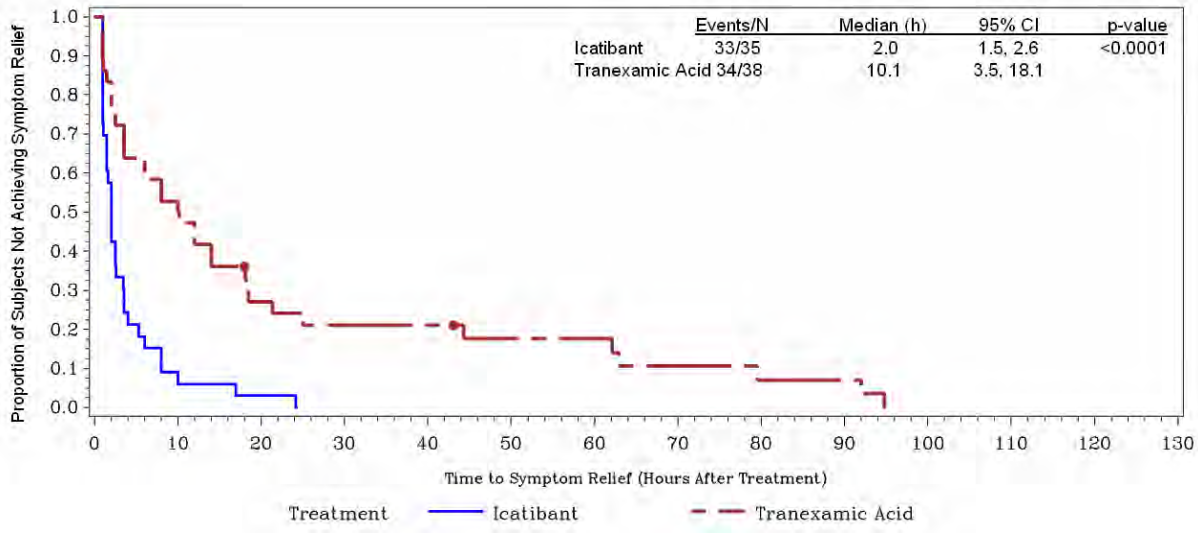
In FAST-2, icatibant demonstrated a statistically significantly faster TOSR-P (based on the identified single primary VAS symptom) for cutaneous and abdominal attacks than placebo (p<0.0001) (Figure 7-4).

Figure 7-3 Time to Onset of Primary Symptom Relief (TOSR-P)- Non-laryngeal Population (FAST-1)



Primary symptom relief is defined as a reduction from pretreatment in the score for a single primary VAS symptom. Detailed definition of TOSR-P in Section 6.5.3.2.
Patients who did not achieve symptom relief within the observation period were censored at the last observation time. Dot indicates censoring.
Source: ISE Figure 3.1.1 and Table 8.1.1

Figure 7-4 Time to Onset of Primary Symptom Relief (TOSR-P)- Non-laryngeal Population (FAST-2)

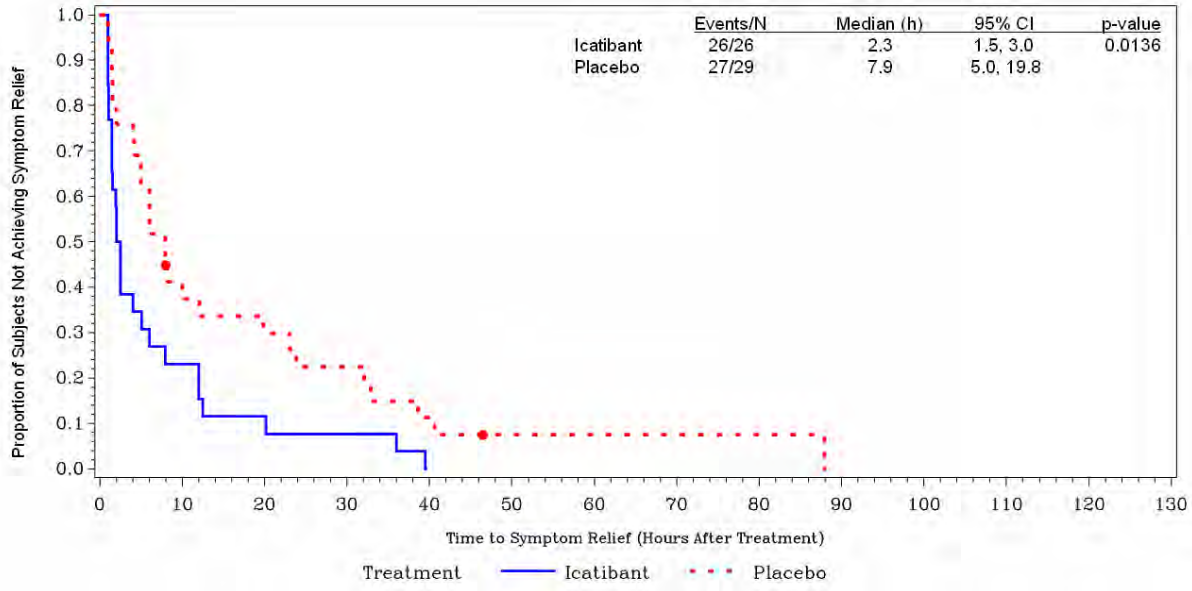


Primary symptom relief is defined as a reduction from pretreatment in the score for a single primary VAS symptom. Detailed definition of TOSR-P in Section 6.5.3.2
Data from patients who did not achieve symptom relief within the observation period were censored at the last observation time. Dot indicates censoring.
Source: ISE Figure 3.1.1 and Table 8.1.1

7.1.2.2 TOSR (based on the composite VAS-3)

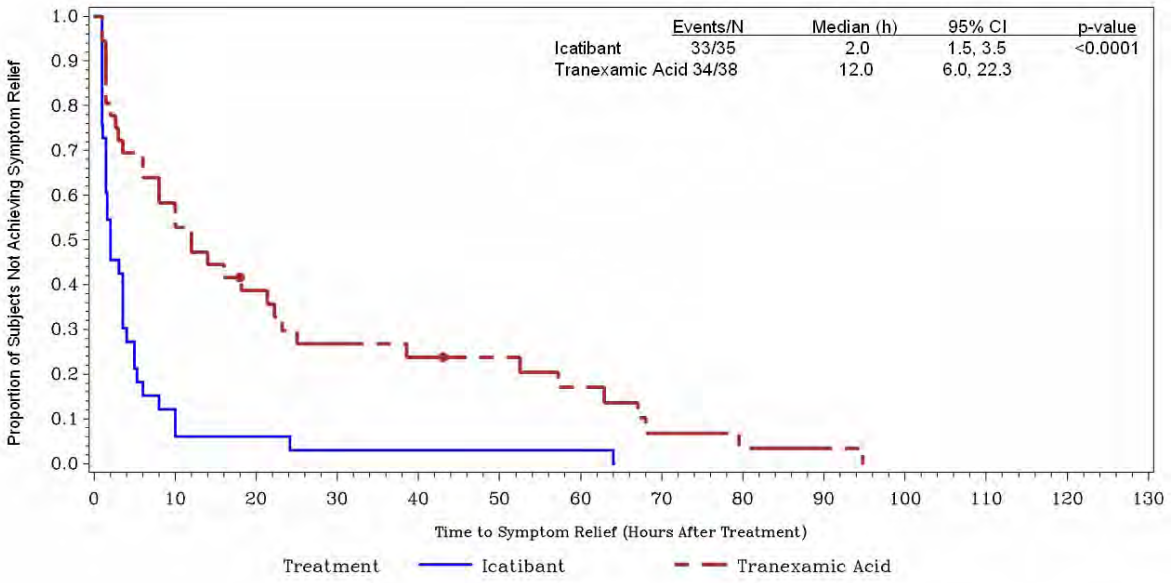
Although the TOSR was not a predefined endpoint in the FAST-1 and FAST-2 studies, it was possible in post hoc analyses to calculate the composite VAS-3 score from the individual VAS scores collected prospectively in FAST-1 and FAST-2. Significant benefit in TOSR was observed in FAST-1 and FAST-2 when these studies were analyzed according to the primary endpoint as defined in FAST-3. The difference in TOSR between icatibant and placebo was statistically significant in FAST-1 (medians of 2.3 and 7.9 hours, respectively; p = 0.0136) (Figure 7-5) as well as for the difference in TOSR between icatibant and tranexaic acid in FAST-2 (medians of 2.0 and 12.0 hours, respectively; p <0.0001) (Figure 7-6).

Figure 7-5 Time to Onset of Symptom Relief (TOSR)- Non-laryngeal Population (FAST-1)



Symptom relief is defined as a 50% reduction from pretreatment in the 3-symptom composite VAS score. Data from patients who did not achieve symptom relief within the observation period were censored at the last observation time. Dot indicates censoring.
Source: ISE Figure 1.1.1 and ISE Table 6.1.1

Figure 7-6 Time to Onset of Symptom Relief (TOSR)- Non-laryngeal Population (FAST-2)



Symptom relief is defined as a 50% reduction from pretreatment in the 3-symptom composite VAS score. Data from patients who did not achieve symptom relief within the observation period were censored at the last observation time. Dot indicates censoring.
Source: ISE Figure 1.1.1 and ISE Table 6.1.1

7.1.2.3 Points to Consider in Evaluating FAST-1 and FAST-2

Overall the data from the 3 controlled Phase III studies show that icatibant produces a consistent TOSR of approximately 2 hours. However, the TOSR in the placebo arm was unexpectedly shorter in FAST-1 than in FAST-3, which may explain why the difference between icatibant and placebo for the primary endpoint of TOSR-P was not statistically significant.

POTENTIAL EXPLANATIONS FOR THE DIFFERENCES IN RESPONSE IN THE PLACEBO ARMS FOR FAST-1 AND FAST-3

It is generally well accepted that comparisons across studies should be interpreted with caution and require careful consideration of all study details to avoid misleading conclusions. While the applied study methodologies, inclusion criteria, and the investigational treatments in all FAST studies were similar (with the exception of the control group in FAST-2 and that patients in FAST-3 only were required to be treated within 12 hours of the onset of the attack), some of the characteristics of the presenting HAE attack symptoms differed between the randomized patient populations in FAST-1 and FAST-3. These differences may have affected the observed responses in the placebo groups.

Post hoc analyses demonstrate differences between the FAST-1 and the FAST-3 study populations, which may have contributed to the different results in their respective placebo groups. As shown in Table 7-5, a larger proportion of the placebo patients in FAST-1 had abdominal attacks than in FAST-3.

Abdominal HAE attacks are painful, disabling and bothersome to patients but, in the FAST trials, tended to recover more quickly than cutaneous attacks. The typical severe colicky pain associated with abdominal attacks is often difficult to tolerate without pharmacological intervention.[37, 44] Patients in the FAST-1 placebo group used rescue medications such as pain medications more often than placebo patients in FAST-3, which may have influenced the evolution of the primary VAS scores in the placebo group in FAST-1.

Attacks in FAST-1 were also more likely to be severe and of longer duration prior to study drug administration than those in FAST-3. These factors may have increased the likelihood that rescue medications were administered early in FAST-1. A higher proportion of patients in FAST-1 used rescue medication than in FAST-3. This is evident either when considering rescue medication prior to onset of symptom relief, within 12 hour of placebo administration, or at any time during the attack (Table 7-5). In order to examine the potential impact of the use of rescue medication, a sensitivity analysis of FAST-1, which censored data from patients who received rescue medication, was performed. This analysis suggested a benefit of icatibant (median 2.3 hours) compared with placebo (median 5.0 hours) for the TOSR-P, although the difference was not statistically significant (p=0.0693) (ISE Table 8.1.2). As discussed in Section 7.1.2.1 and shown in Figure 7-5, post hoc analyses of TOSR based on the composite VAS-3 were completed for FAST-1, which demonstrated statistically significant differences between icatibant and placebo.

Table 7-5 Attack Characteristics for the FAST-1 and FAST-3 Placebo Groups- Non-laryngeal Population

Attack Characteristic	FAST-1 Placebo N=29	FAST-3 Placebo N=45
Primary Attack n (%)		
Cutaneous	13 (44.8)	26 (57.8)
Abdominal	16 (55.2)	19 (42.2)
Severity n (%)		
Moderate	12 (41.4)	28 (62.2)
Severe	17 (58.6)	17 (37.8)
Median time from attack onset to moderate symptoms- hours	6.0	2.5
Median time from moderate symptoms to dose administration- hours	3.2	3.3
Median time from attack onset to dose administration- hours	10.0	5.5
Used rescue medication prior to onset of symptom relief n (%)	10 (37.0)	13 (31.0)
Used rescue medication within 12 hours of drug administration n (%)	13 (44.8)	13 (28.9)
Used rescue medication any time during attack n (%)	15 (51.7)	18 (40.0)

Sources: ISE Tables 5.1 and 27.1

CHOICE OF TRANEXAMIC ACID AS COMPARATOR

Though not approved in the US, tranexamic acid is approved in Europe for the prophylactic management of HAE.[36, 41, 45] Although its effectiveness in acute attacks has not been assessed in controlled trials, it was commonly used as a treatment for acute attacks of HAE at the time FAST-2 was designed, and such use was reflected in contemporaneous consensus guidelines.[45] It is theorized that antifibrinolytic agents such as tranexamic acid work in HAE by inhibiting plasminogen activation with consequent "sparing" of C1-INH usage.[45] Also, advice from the European Medicines Agency indicated a preference for the use of an approved and widely available treatment over placebo for a registration study.

Overall, the results from FAST-2 show statistically significant differences between the icatibant and tranexamic acid groups, thereby demonstrating the effectiveness of icatibant in the treatment of acute HAE attacks and contributing to the safety database. The tranexamic acid group in FAST-2 had similar results compared with the placebo group in FAST-3.

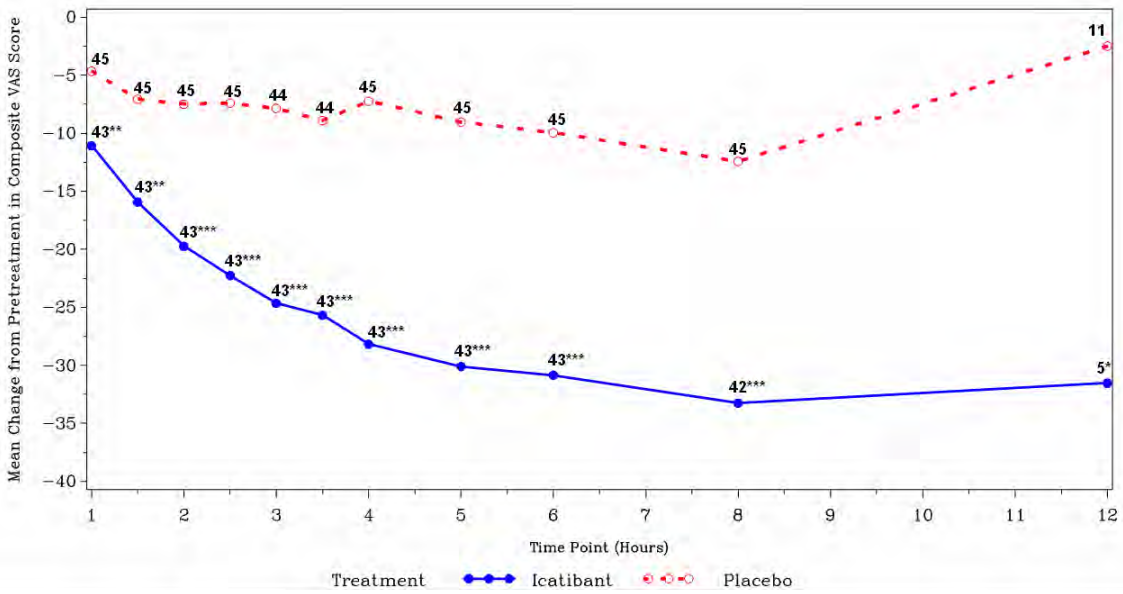
7.1.3 Other Important Findings Based on Secondary Endpoints in the 3 Controlled Phase III Studies

7.1.3.1 Mean Change in Composite VAS (VAS-3) over Time

Because both FAST-1 and FAST-2 prospectively collected individual VAS measurements for the symptoms of HAE, the sponsor has calculated the composite VAS for FAST-1 and FAST-2 post hoc to allow for comparison across the 3 studies.

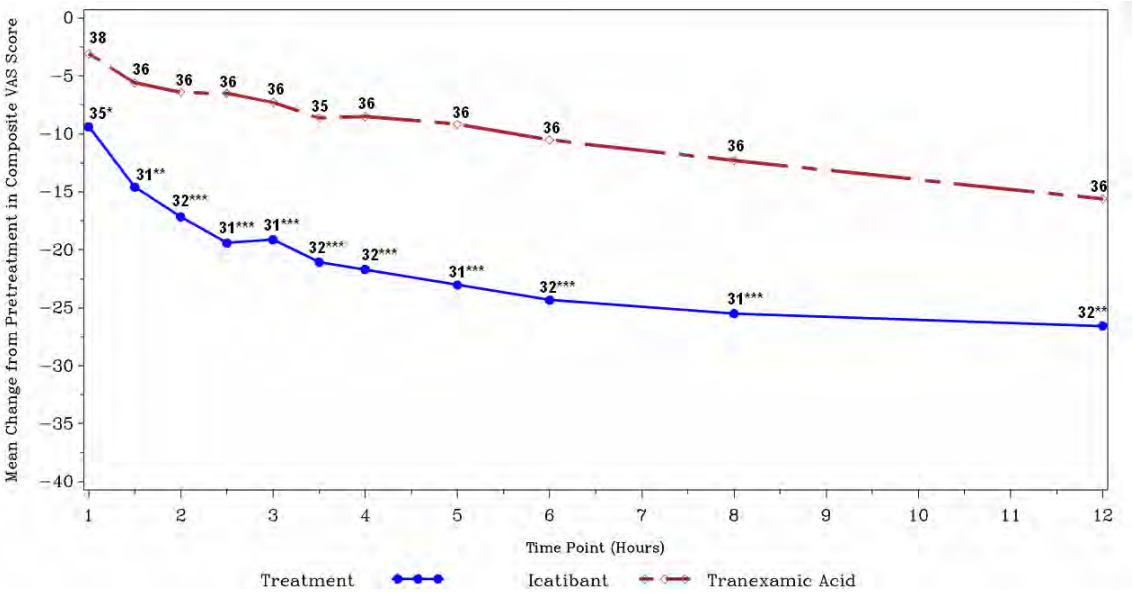
Across the controlled Phase III studies, the icatibant group had a more rapid decrease in VAS-3 scores compared to control. The treatment difference for the change from baseline in VAS-3 was statistically significant between the icatibant and placebo group in FAST-3 at all assessments ($p \leq 0.0032$ at all time points through 8 hours; $p = 0.041$ at 12 hours, which was not a required assessment and had reduced sample size) (Figure 7-7) and between icatibant and tranexamic acid in FAST-2 at all assessments between 1 hour post-treatment and 12 hours post-treatment ($p<0.0001$ to $p=0.0142$) (Figure 7-8). The treatment difference between icatibant and placebo in FAST-1 was statistically significant only at 1 hour post-treatment ($p=0.00129$) (Figure 7-9).

Figure 7-7 Mean Change from Pretreatment in Composite VAS-3 Scores by Treatment Group- Non-laryngeal Population (FAST-3)



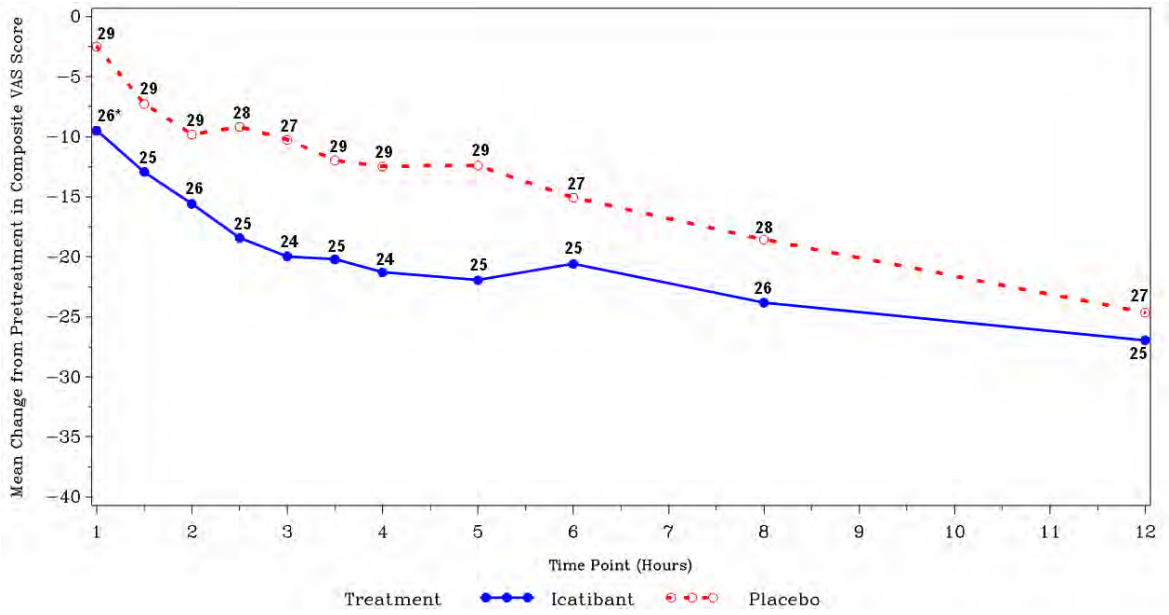
Note: The number of subjects is listed above each time point.
For comparison of icatibant to placebo groups (Wilcoxon rank sum p-value):
*** p ≤0.0001; ** 0.001 < p ≤0.01; * 0.01 <p ≤0.05
Source: Figure A99.ISE.322.1 and ISE Table 13.1

Figure 7-8 Mean Change from Pretreatment in Composite VAS-3 Scores by Treatment Group-Non-laryngeal Population (FAST-2)



Note: The number of subjects is listed above each time point.
For comparison of icatibant to placebo groups (Wilcoxon rank sum p-value):
*** p ≤0.0001; ** 0.001 < p ≤0.01; * 0.01 <p ≤0.05
Source: Figure A82.ISE.322 and ISE Table 13.1

Figure 7-9 Mean Change from Pretreatment in Composite VAS-3 Scores by Treatment Group-Non-laryngeal Population (FAST-1)



Note: The number of subjects is listed above each time point.
For comparison of icatibant to placebo groups (Wilcoxon rank sum p-value):
*** p ≤0.0001; ** 0.001 < p ≤0.01; * 0.01 <p ≤0.05
Source: Figure A82.ISE.322 and ISE Table 13.1

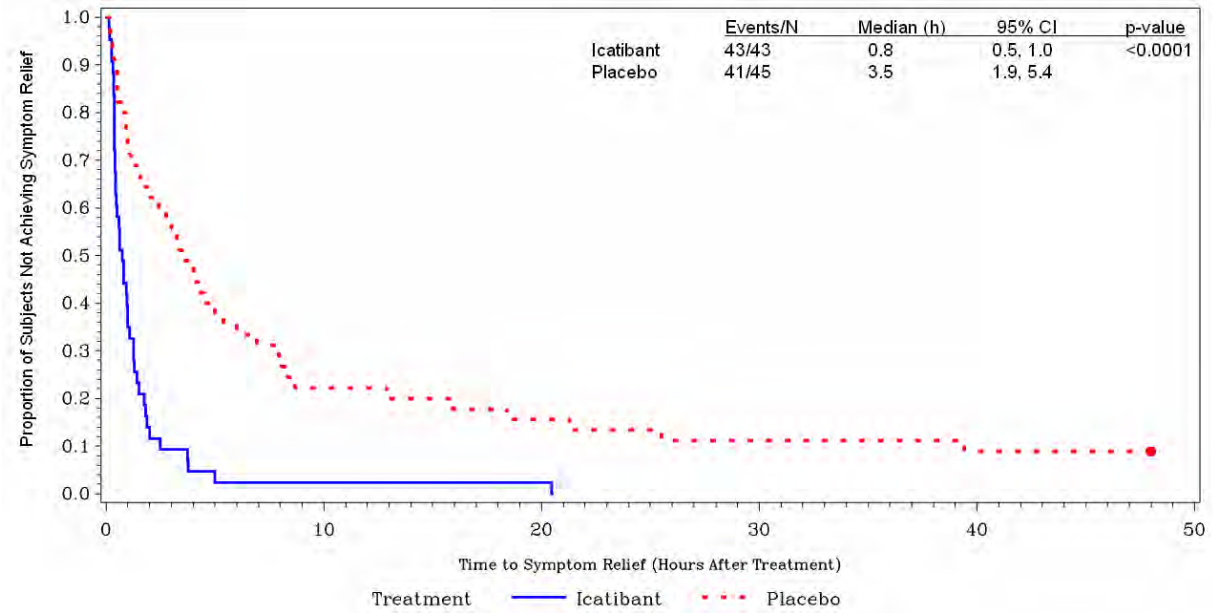
7.1.3.2 Time to Initial Symptom Improvement (TISI)

The TISI was calculated based on the recorded time at which a perceived initial improvement in symptoms occurred. The TISI was recorded by both the patient and the investigator for both laryngeal attacks and non-laryngeal (cutaneous and abdominal) attacks, allowing for comparison across attack location. Laryngeal attacks are discussed in Section 7.4.

Patient-assessed TISI is presented in Figure 7-10, Figure 7-11, and Figure 7-12 for FAST-3, FAST-2, and FAST-1 respectively. The median TISI was 0.8 hours each for the icatibant group in FAST-3, FAST-2, and FAST-1. The median TISI was 3.5 hours for the placebo group in FAST-1, 7.9 hours for the tranexamic acid group in FAST-2, and 10.1 hours for the placebo group in FAST-3. The differences between icatibant and control for TISI were statistically significantly in all 3 studies.

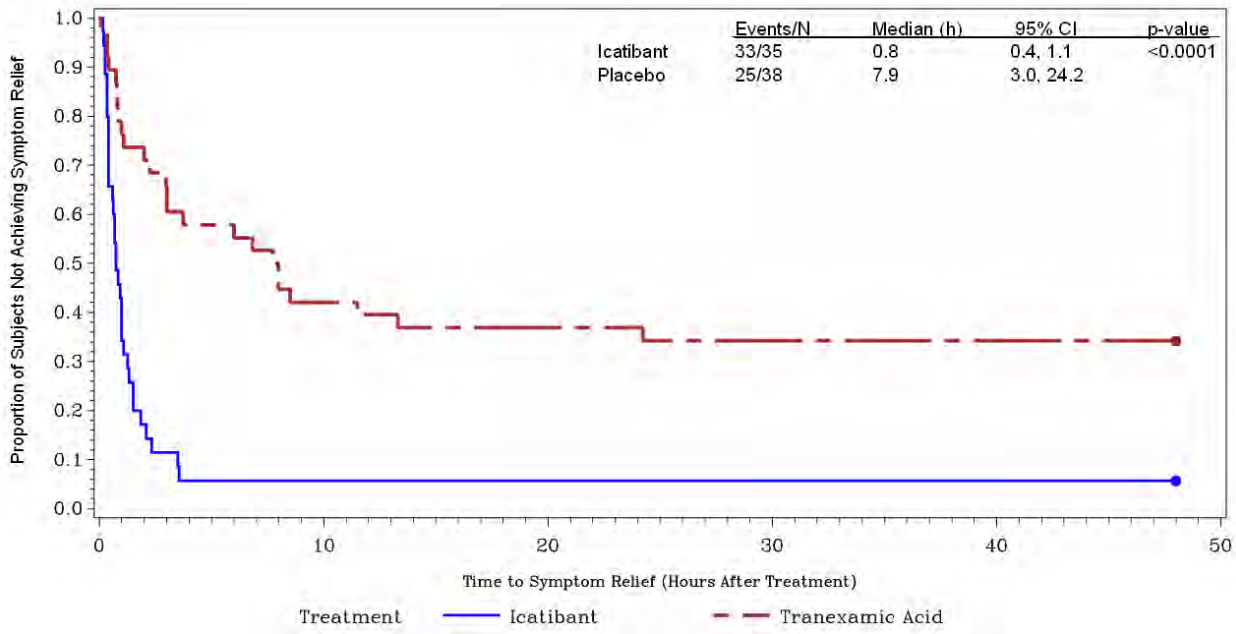
The results for the investigator-assessed TISI were consistent with those seen for the patient-assessed TISI.

Figure 7-10 Patient-Assessed Time to Initial Symptom Improvement (TISI)-Non-laryngeal Population (FAST-3)



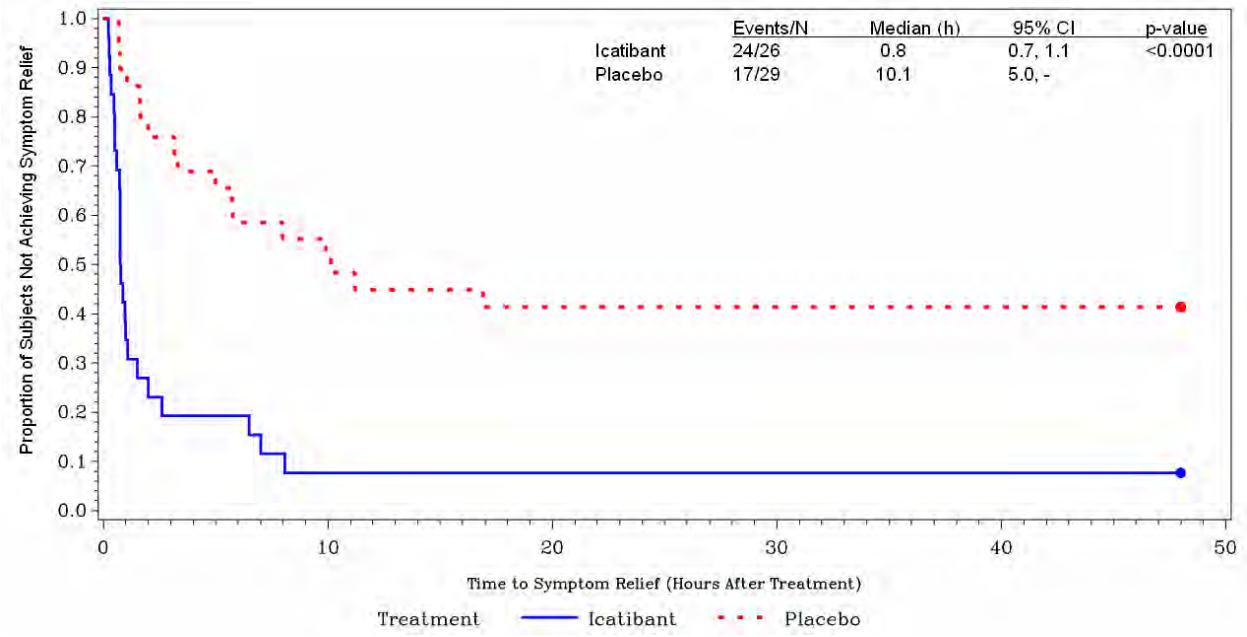
Data from patients who did not achieve symptom relief within the observation period were censored at 48 hours.
Dot indicates censoring.
Source: ISE Figure 6.1 and ISE Table 11.1

Figure 7-11 Patient-Assessed Time to Initial Symptom Improvement (TISI)-Non-laryngeal Population (FAST-2)



Data from patients who did not achieve symptom relief within the observation period were censored at 48 hours.
Dot indicates censoring.
Source: ISE Figure 6.1 and ISE Table 11.1

Figure 7-12 Patient-Assessed Time to Initial Symptom Improvement (TISI)-Non-laryngeal Population (FAST-1)



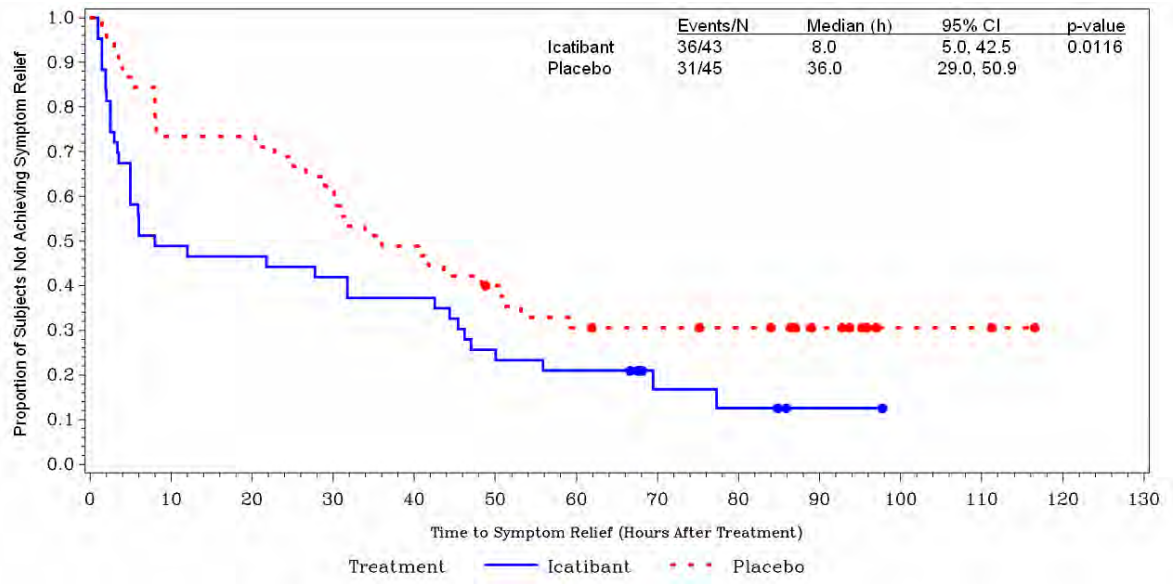
Data from patients who did not achieve symptom relief within the observation period were censored at 48 hours.
Dot indicates censoring.
Source: ISE Figure 6.1 and ISE Table 11.1

7.1.3.3 Time to Almost Complete Symptom Relief (TACSR)

The TACSR evaluates the time when the HAE essentially resolves, and is defined as the earliest of 3 consecutive non-missing measurements for which all VAS scores are less than 10 mm.

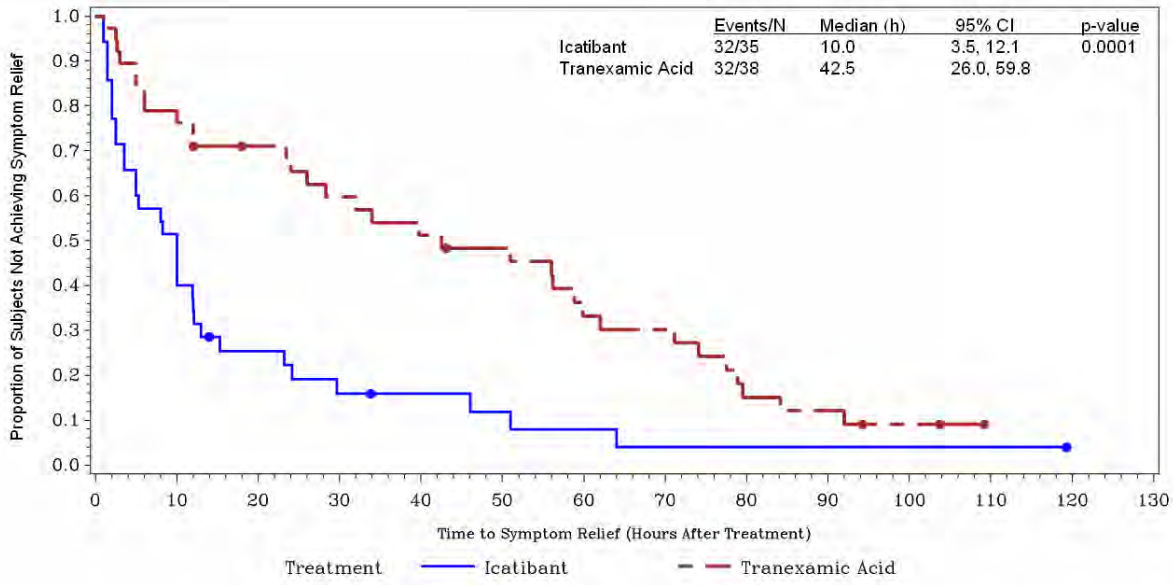
All 3 FAST studies also demonstrated a consistent reduction in TACSR with icatibant treatment, with statistical significance shown in FAST-2 (p=0.0001) and FAST-3 (p=0.0116) (Figure 7-13 and Figure 7-14, respectively). The difference in TACSR between the icatibant and placebo groups in FAST-1 was not statistically significant (p=0.1195) (Figure 7-15).

Figure 7-13 Time to Almost Complete Symptom Relief (TACSR)-Non-laryngeal Population (FAST-3)



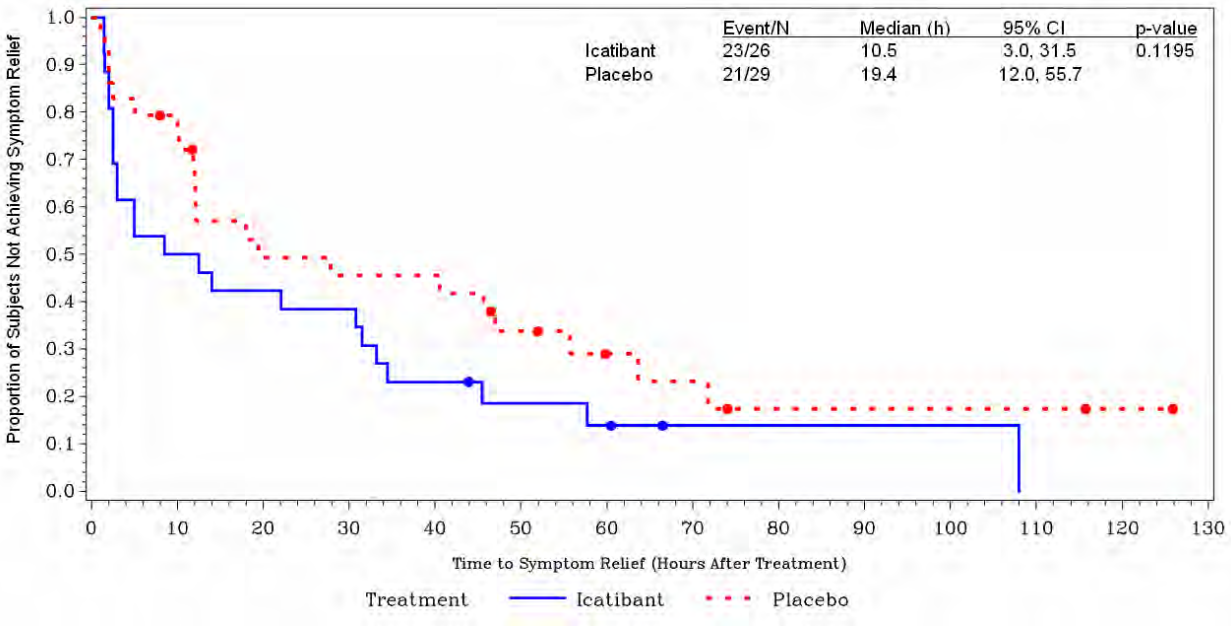
Almost complete symptom relief is defined as all VAS scores <10 mm.
Data from patients who did not achieve symptom relief within the observation period were censored at the last observation time. Dot indicates censoring.
Source: ISE Figure 5.1 and ISE Table 10.1

Figure 7-14 Time to Almost Complete Symptom Relief (TACSR)-Non-laryngeal Population (FAST-2)



Almost complete symptom relief is defined as all VAS scores <10 mm.
Patients who did not achieve symptom relief within the observation period were censored at the last observation time. Dot indicates censoring.
Source: ISE Figure 5.1 and ISE Table 10.1

Figure 7-15 Time to Almost Complete Symptom Relief (TACSR)-Non-laryngeal Population (FAST-1)



Almost complete symptom relief is defined as all VAS scores <10 mm.
Data from patients who did not achieve symptom relief within the observation period were censored at the last observation time. Dot indicates censoring.
Source: ISE Table 5.1 and ISE Table 10.1

7.1.3.4 Use of Rescue Therapy

The use of rescue therapy was examined across the FAST studies (Table 7-6). HAE attacks typically last from 2-5 days, and use of rescue medication was assessed through 120 hours after study drug administration. For this analysis, rescue medications were classified into gastrointestinal (GI, eg anti-emetics and agents to decrease motility) or pain medications, plasma protein or C1 inhibitors, or other. Patients could use medications from more than one group. A statistically significantly higher proportion of control patients used rescue therapy prior to the onset of symptom relief ($p<0.0001$, $p=0.0050$, and $p=0.0021$ for FAST-3, FAST-1, and FAST-2, respectively).

Table 7-6 Numbers of Patients who Used Non-Icatibant Rescue Therapy Across the Controlled Phase III Studies- Non-laryngeal Population

	FAST-1		FAST-2		FAST-3	
	Icatibant (N=26) n (%)	Placebo (N=29) n (%)	Icatibant (N=35) n (%)	Tranexamic Acid (N=38) n (%)	Icatibant (N=43) n (%)	Placebo (N=45) n (%)
Used rescue therapy prior to onset of symptom relief						
Yes	1 (3.8)	10 (37.0)	0	9 (26.5)	0	13 (31.0)
GI or Pain	1	7	0	1	0	9
Plasma Protein	0	5	0	7	0	7

Table 7-6 Numbers of Patients who Used Non-Icatibant Rescue Therapy Across the Controlled Phase III Studies- Non-laryngeal Population

	FAST-1		FAST-2		FAST-3	
	Icatibant (N=26) n (%)	Placebo (N=29) n (%)	Icatibant (N=35) n (%)	Tranexamic Acid (N=38) n (%)	Icatibant (N=43) n (%)	Placebo (N=45) n (%)
or C1-INH						
Icatibant	0	0	0	0	0	0
Other	1	1	0	1	0	4
Fisher's Exact p-value	0.0050		0.0021		<0.0001	
Used rescue therapy anytime during attack (within 120 hours of study drug administration)						
Yes	6 (23.1)	15 (51.7)	5 (14.3)	12 (31.6)	3 (7.0)	18 (40.0)
GI or Pain	6	9	1	2	0	11
Plasma Protein or C1-INH	2	5	4	9	2	9
Icatibant	0	1	0	0	0	1
Other	1	5	1	3	1	5
Fisher's Exact p-value	0.0507		0.1010		0.0003	

C1-INH = C1 inhibitor, GI = gastrointestinal

Fisher's exact p-value is for the comparison of patients who received rescue medications versus those who did not.

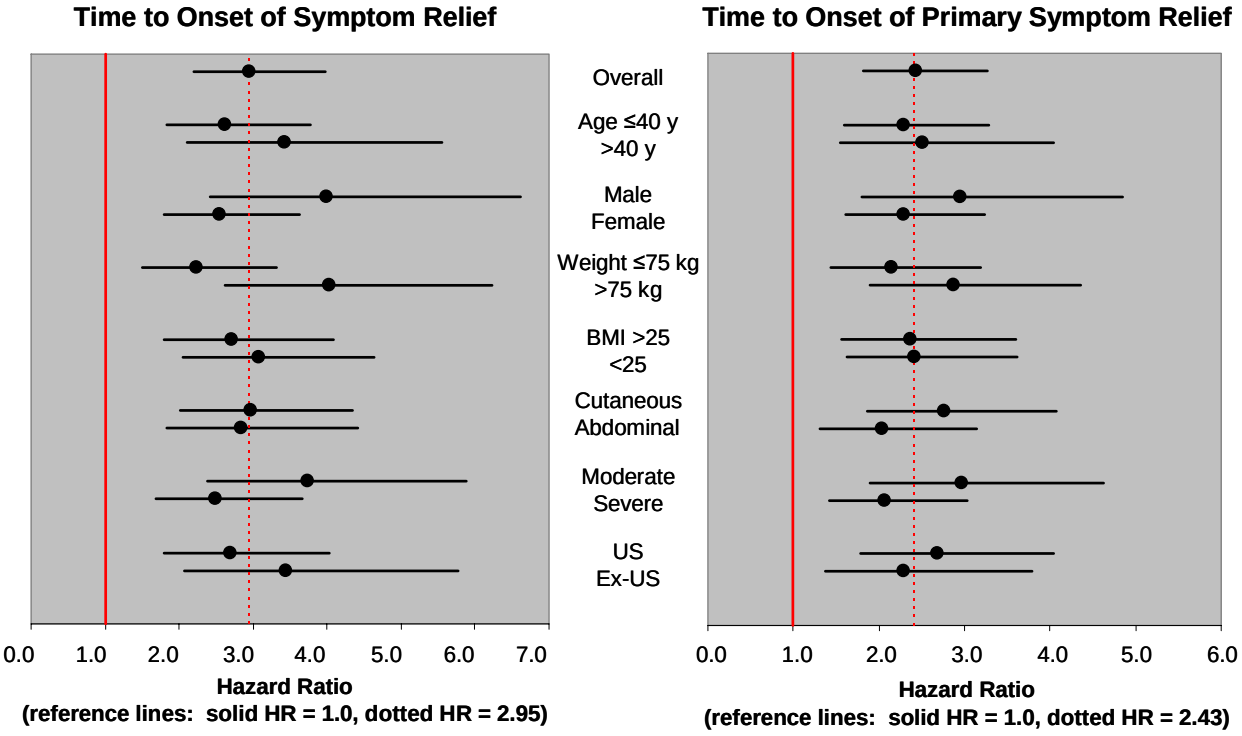
Source: ISE Table 27.1 and Table A32.ISE.186.1

7.2 Subgroup Analyses

Pooled data from the controlled Phase III studies were used to examine treatment effects within various patient subgroups. These analyses used a Cox proportional hazards regression model with adjustment for study effect and the study stratification factors (site of attack and, for FAST-3 ,C1 inhibitor use). Figure 7-16 depicts the hazard ratios and corresponding 95% confidence intervals for the TOSR (based on VAS-3) and TOSR-P by subgroup. A consistent and statistically significant treatment benefit of icatibant is seen across all subgroups.

Because only 12 of the 216 patients in the pooled non-laryngeal population were non-white, the analyses of the TOSR and the TOSR-P by race were not conducted.

Figure 7-16 Hazard Ratios for Time to Onset of Symptom Relief (TOSR) and Time to Onset of Primary Symptom Relief (TOSR-P) by Subgroup-Non-Laryngeal Pooled Population



7.3 Repeated Treatment

A total of 225 patients participated in the open-label extensions of the FAST studies, 76 patients were from FAST-3, 81 patients were from FAST-2, and 68 patients were from FAST-1. The open-label phase allowed for the collection of data during subsequent attacks. Because the frequency of attacks is unpredictable, the number of patients receiving repeated treatment for subsequent attacks diminishes over the time course of the studies.

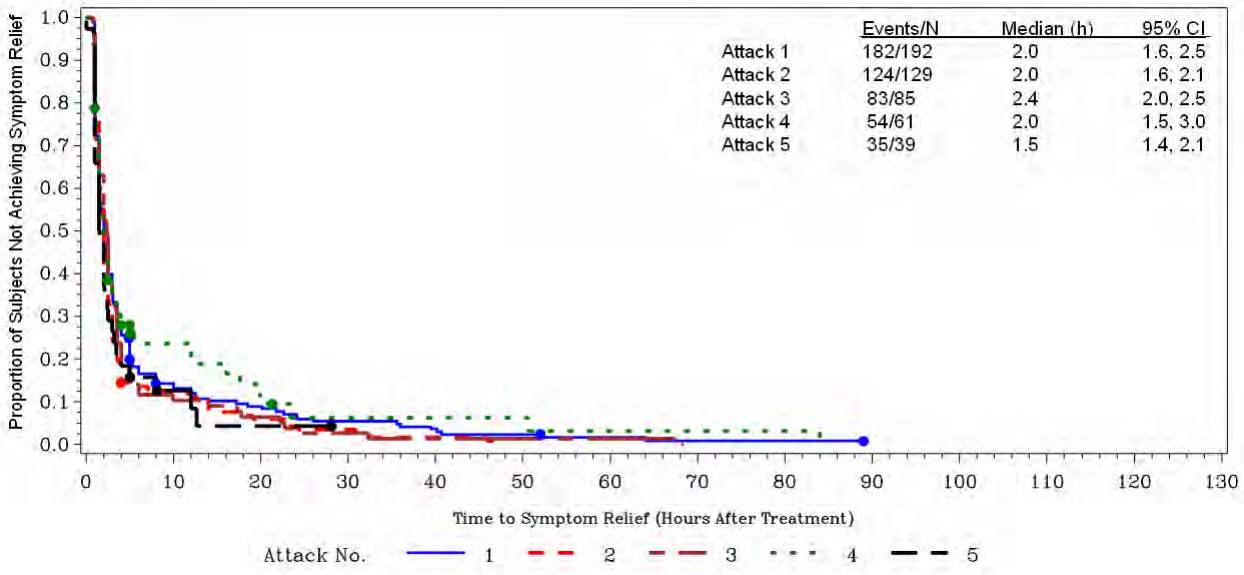
Note that in the open-label extension phase, for subjects previously randomized to placebo or tranexamic acid, the first icatibant-treated attack reflects their second on-study attack.

The figures below summarize data available for patients through 5 attacks.

7.3.1 Time to Onset of Symptom Relief (TOSR) (VAS-3) Across the First 5 Icatibant-Treated Attacks

A consistent treatment effect as measured by the TOSR was observed across the first 5 icatibant-treated attacks (Figure 7-17).

Figure 7-17 Time to Onset of Symptom Relief (TOSR) (First 5 Icatibant-Treated Attacks)-Phase III Treated Population

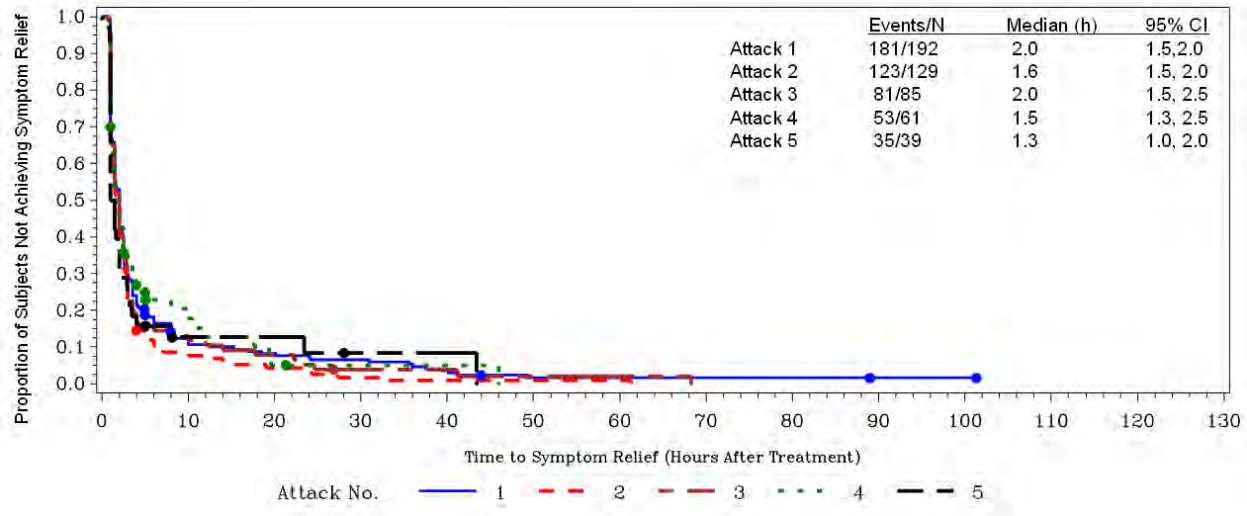


Symptom relief is defined as a 50% reduction from pretreatment in the 3-symptom composite VAS score.
Only non-laryngeal attacks are summarized since FAST-2 and FAST-1 did not collect VAS scores for laryngeal symptoms.
For patients previously randomized to placebo or tranexamic acid, their second on-study attack will be their first icatibant-treated attack.
Data from patients who did not achieve symptom relief within the observation period were censored at the last observation time. Dot indicates censoring.
Source: ISE Figure 1.4 and ISE Table 6.4

7.3.2 Time to Onset of Primary Symptom Relief (TOSR-P) (Single VAS) Across the First 5 Icatibant-Treated Attacks

A consistent treatment effect as measured by the TOSR-P was observed across the first 5 icatibant-treated attacks (Figure 7-18).

Figure 7-18 Time to Onset of Primary Symptom Relief (TOSR-P) (First 5 Icatibant-Treated Attacks)- Phase III Treated Population

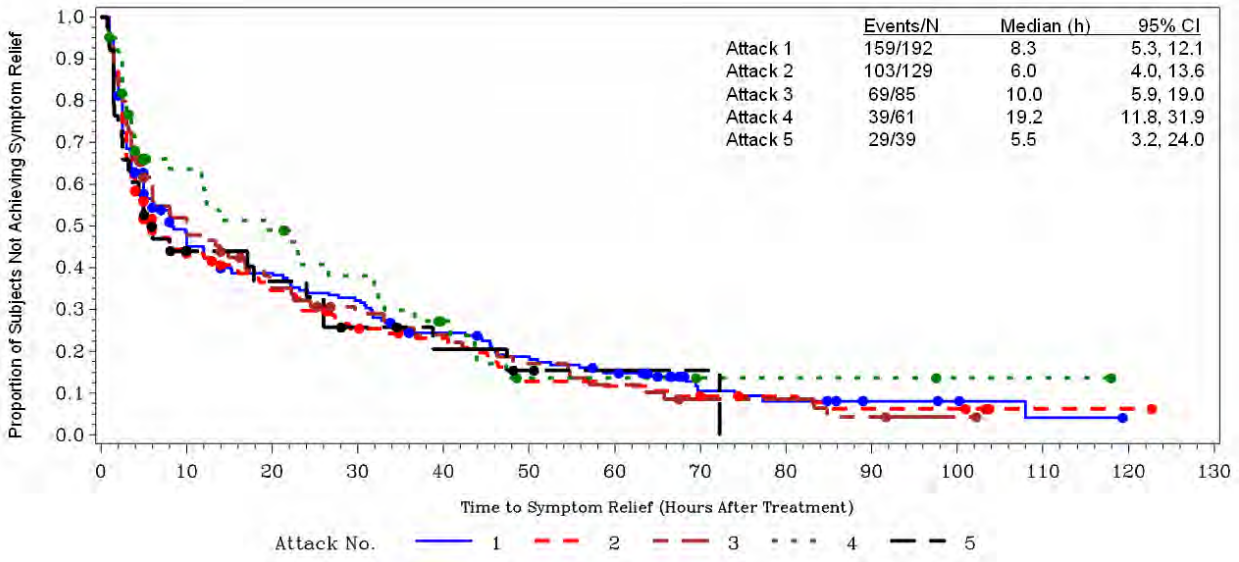


Primary symptom relief is defined as a reduction from pretreatment in the score for a single primary VAS symptom.
Detailed definition of TOSR-P in Section 6.5.3.2
Only non-laryngeal attacks are summarized since FAST-2 and FAST-1 did not collect VAS scores for laryngeal symptoms.
For patients previously randomized to placebo or tranexamic acid, their second on-study attack will be their first icatibant-treated attack.
Data from patients who did not achieve symptom relief within the observation period were censored at the last observation time. Dot indicates censoring.
Source: ISE Figure 3.4 and ISE Table 8.4

7.3.3 Time to Almost Complete Symptom Relief (TACSR) Across the First 5 Icatibant-Treated Attacks

The Kaplan-Meier curves for TACSR across the first five attacks were similar (Figure 7-19). Although there was some variability from attack to attack, the median TACRs were generally similar, with overlapping confidence intervals.

Figure 7-19 Time to Almost Complete Symptom Relief (TACSR) (First 5 Icatibant-Treated Attacks)- Phase III Treated Population

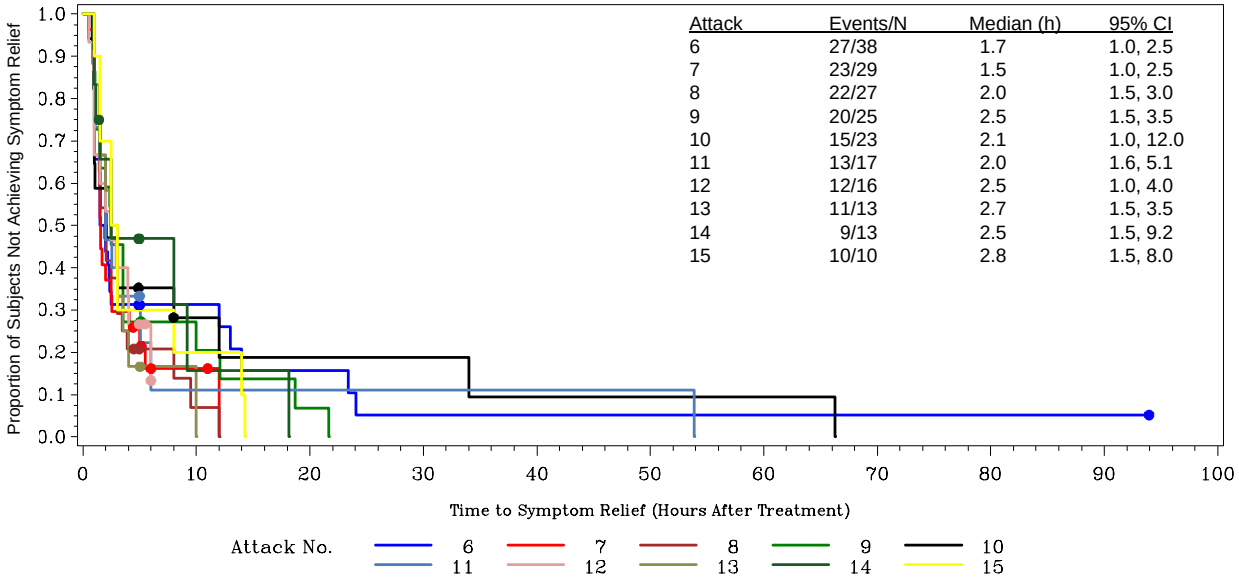


Almost complete symptom relief is defined as all VAS scores <10 mm.
For subjects previously randomized to placebo or tranexamic acid, their second on-study attack will be their first icatibant-treated attack.
Only non-laryngeal attacks are summarized since FAST-2 and FAST-1 did not collect VAS scores for laryngeal symptoms.
Data from patients who did not achieve symptom relief within the observation period were censored at the last observation time. Dot indicates censoring.
Source: ISE Figure 5.3 and ISE Table 10.3

7.3.4 Treatment for More Than 5 Attacks

Thirty eight (38) patients were treated for >5 HAE attacks, with one patient treated for 142 attacks. While the data are limited after the fifth attack, the efficacy remained consistent from attack to attack. Figure 7-20 presents the TOSR for icatibant-treated attacks 6 – 15.

Figure 7-20 Time to Onset of Symptom Relief (TOSR) (Icatibant-Treated Attacks 6 to 15)-Phase III Treated Population



Symptom relief is defined as a 50% reduction from pretreatment in the 3-symptom composite VAS score.
Only non-laryngeal attacks are summarized since FAST-2 and FAST-1 did not collect VAS scores for laryngeal symptoms.
For subjects previously randomized to placebo or tranexamic acid, their second on-study attack will be their first icatibant-treated attack.
Subjects who did not achieve symptom relief within the observation period were censored at the last observation time. Dot indicates censoring.
Source: Figure A18.ISE.155.1.1

7.4 Laryngeal Attacks

Given the seriousness of laryngeal attacks, in FAST-1, FAST-2, and, initially in FAST-3, all patients with laryngeal attacks were treated with open-label icatibant. In an attempt to obtain blinded, placebo comparison data, a protocol amendment to FAST-3 permitted patients with mild or moderate laryngeal attacks to be randomized to icatibant or placebo.

7.4.1 First Laryngeal Attacks in FAST-3

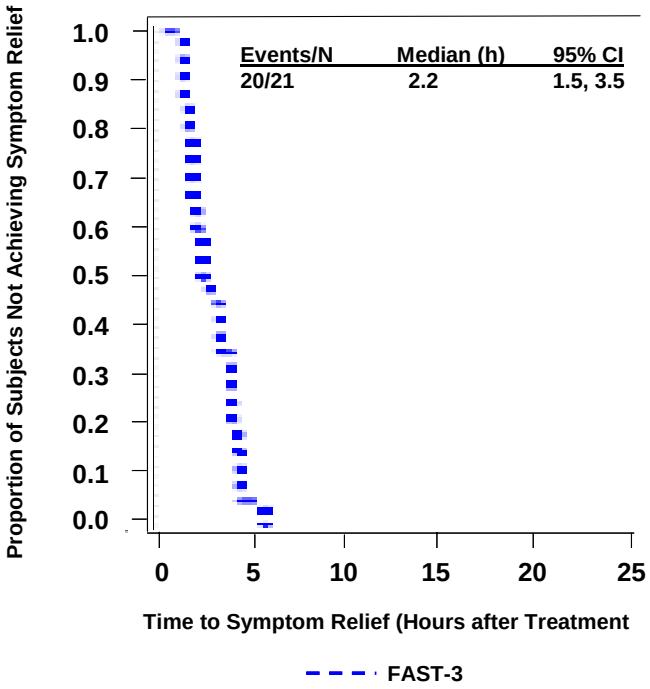
In FAST-3, 10 patients presented with laryngeal attacks during the controlled phase of the trial; 5 of whom received open-label icatibant and 5 of whom had mild to moderate laryngeal attacks and were randomized to receive icatibant or placebo. Of these 5 randomized patients, 3 were randomized to receive icatibant and 2 were randomized to placebo. The laryngeal symptoms of the 2 placebo patients progressed, and because open-label treatment of severe laryngeal attacks was permitted in the protocol, these patients were treated with icatibant following discussion between the investigators and the sponsor. All 5 patients achieved onset of symptom relief within 3.5 hours of icatibant administrations.

Because all laryngeal attacks in FAST-3 were ultimately treated with icatibant, the data for the patients with first on-study laryngeal attacks were pooled.

A total of 21 patients had first on-study laryngeal attacks, including the 10 patients from the controlled phase of the study and 11 patients who had first laryngeal attacks during the open-label extension phase.

For the 21 patients with laryngeal attacks in FAST-3, the median TOSR by VAS-5 was 2.2 hours (Figure 7-21).

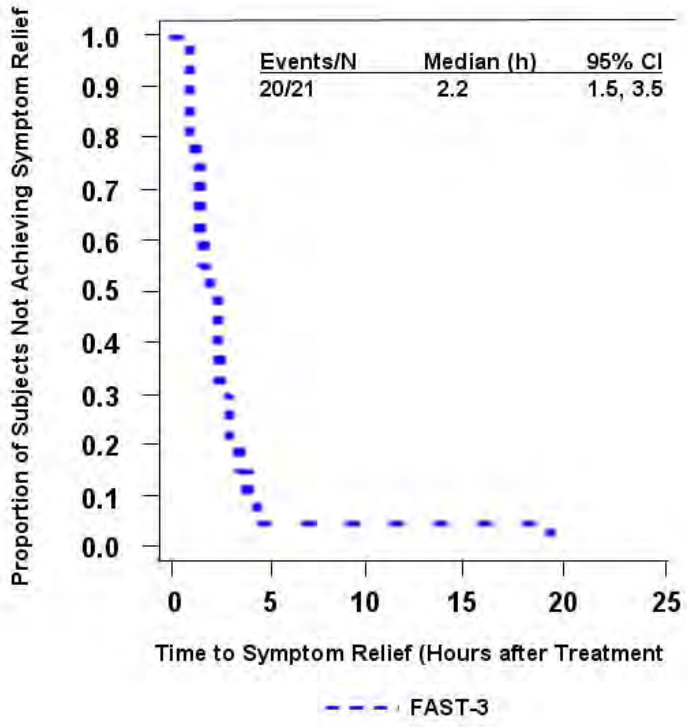
Figure 7-21 Time to Onset of Symptom Relief (TOSR) as Measured by the VAS-5-Laryngeal Treated Population (FAST-3)



Symptom relief is defined as a 50% reduction from pretreatment 5-symptom composite VAS score for laryngeal attacks.
FAST-2 and FAST-1 did not collect VAS scores for laryngeal symptoms thus symptom relief could not be determined for laryngeal attacks.
Data from patients who did not achieve symptom relief within the observation period were censored at the last observation time. Dot indicates censoring.
Source: ISE Figure 1.5 and ISE Table 6.5

The median TOSR-P was 2.2 hours for the 21 patients with laryngeal attacks in FAST-3 (Figure 7-22).

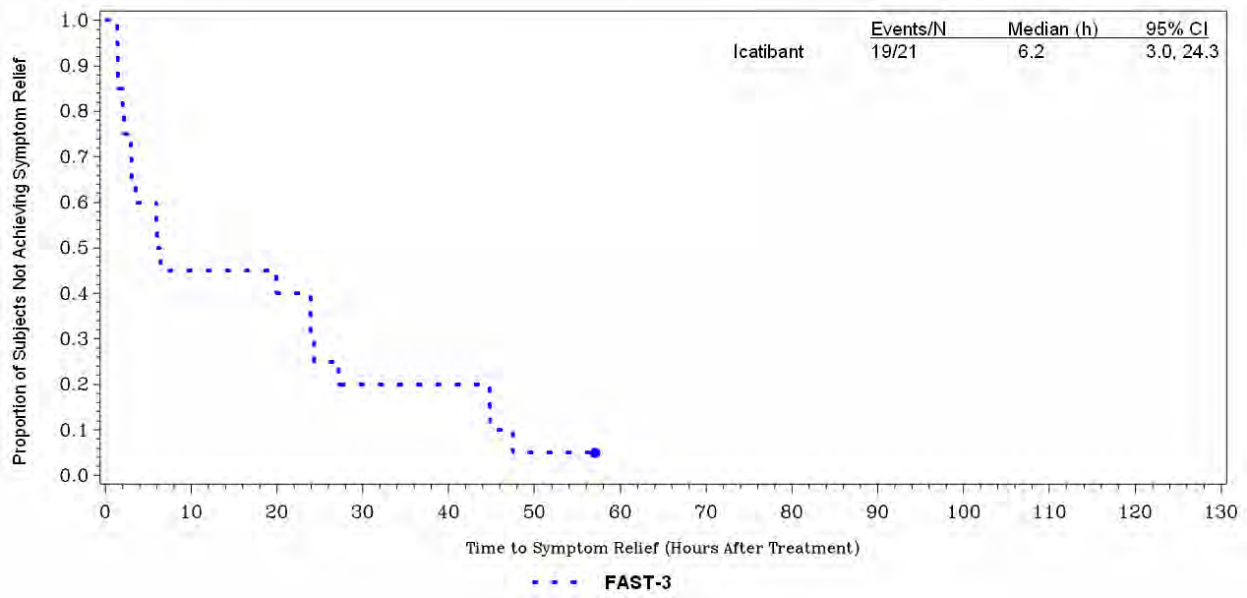
Figure 7-22 Time to Onset of Primary Symptom Relief (TOSR-P)- Laryngeal Treated Population (FAST-3)



Primary symptom relief is defined as a reduction from pretreatment in the score for a single primary VAS symptom. Symptom relief is classified as any reduction below (6/7) × pretreatment value − 16 mm 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 30 mm. For patients with a pretreatment VAS <30 mm, symptom relief was defined as 68% reduction from pretreatment.
FAST-2 and FAST-1 did not collect VAS scores for laryngeal symptoms thus symptom relief could not be determined for laryngeal attacks.
Data from patients who did not achieve symptom relief within the observation period were censored at the last observation time. Dot indicates censoring.
Source: ISE Figure 3.5 and ISE Table 8.5

The median TACSR was 6.2 hours for the 21 patients with laryngeal attacks in FAST-3 (Figure 7-23).

Figure 7-23 Time to Almost Complete Symptom Relief (TACSR)- Laryngeal Treated Population (FAST-3)



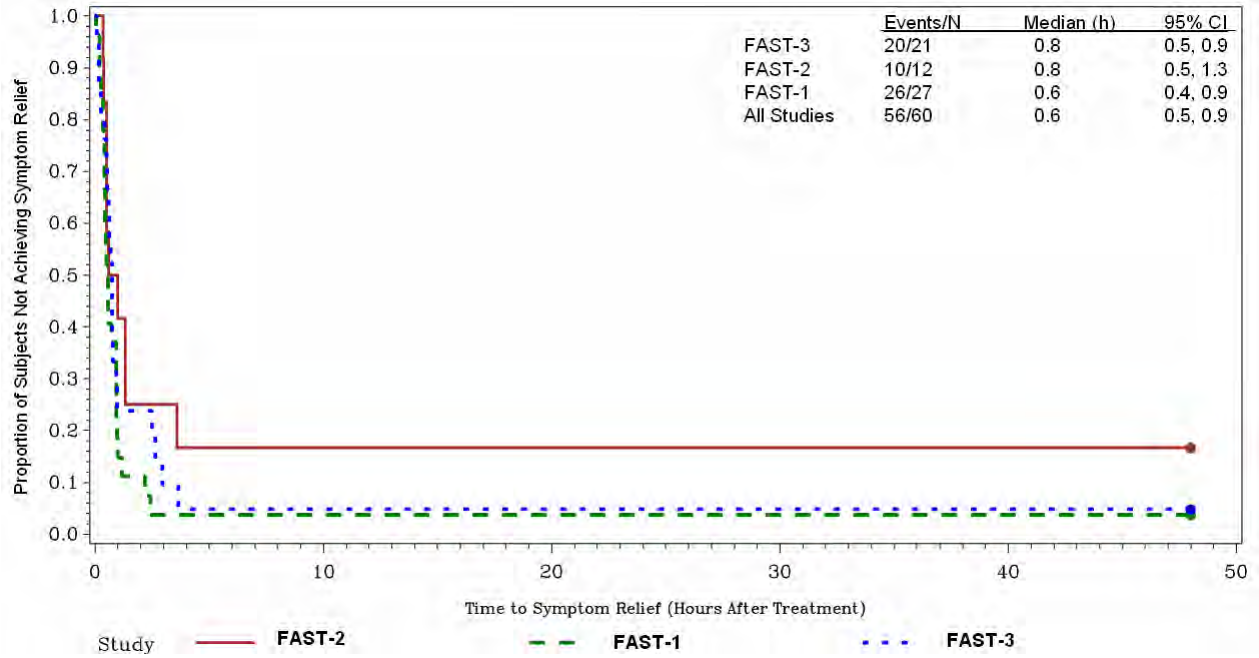
Almost complete symptom relief is defined as all VAS scores <10 mm.
For subjects previously randomized to placebo or tranexamic acid, their second on-study attack will be their first icatibant-treated attack.
FAST-2 and FAST-1 did not collect VAS scores for laryngeal symptoms thus symptom relief could not be determined for laryngeal attacks.
Data from patients who did not achieve symptom relief within the observation period were censored at the last observation time. Dot indicates censoring.
Source: ISE Figure 5.4 and ISE Table 10.4

7.4.2 Pooled Laryngeal Results from the Controlled Phase III Studies

All patients with laryngeal attacks in the controlled Phase III studies received icatibant, and an analysis of all 60 patients who had laryngeal attacks (21 from FAST-3, 12 from FAST-2, and 27 from FAST-1) was conducted to examine the effect of icatibant on these attacks. The VAS-5 was collected only in the FAST-3 study, and therefore the one endpoint that spans all 3 studies for laryngeal attacks is the Time to Initial Symptom Improvement (TISI).

The TISI for the laryngeal treated population (median 0.6 hours; Figure 7-24) was similar to that seen in the icatibant groups for the non-laryngeal populations in FAST-3, FAST-2, and FAST-1 (median 0.8 hours each) (Section 7.1.3.2).

Figure 7-24 Patient-Assessed Time to Initial Symptom Improvement (TISI)- Laryngeal Treated Pooled Population



Data from patients who did not achieve symptom relief within the observation period were censored at 48 hours.
Dot indicates censoring.
Source: ISE Figure 6.5 and ISE Table 11.5

7.5 Efficacy Conclusions

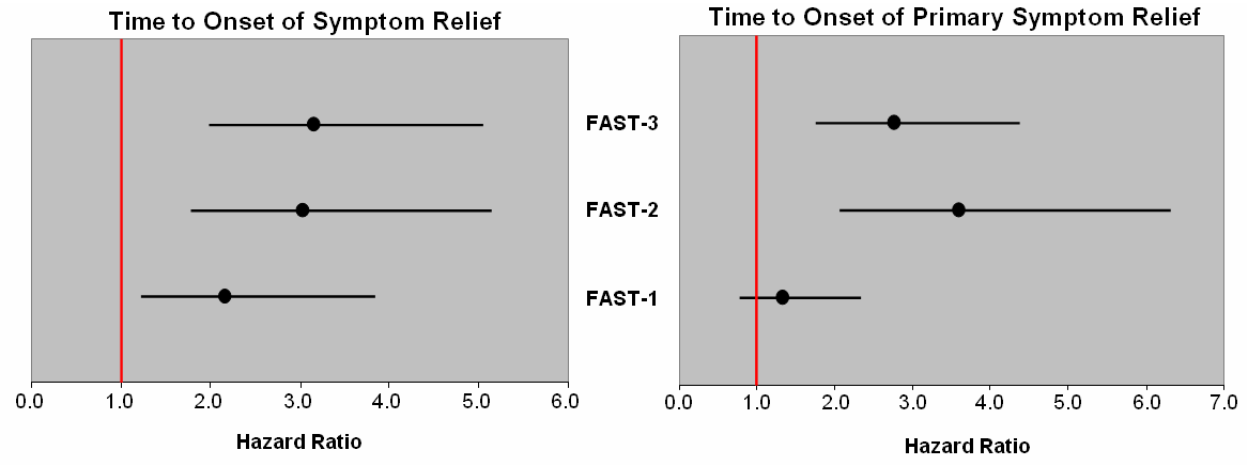
The Phase III clinical trials demonstrate that icatibant is an effective treatment for acute HAE attacks in adults with Type I or Type II HAE, including cutaneous, abdominal, and laryngeal attacks, as demonstrated by reproducible and consistent efficacy across multiple endpoints in a randomized, double-blind setting.

Across all 3 controlled studies, icatibant consistently produced a TOSR of approximately 2 hours following administration. This consistent response was seen across subgroups, attack types (including cutaneous, abdominal and laryngeal attacks), and following repeated treatment. The primary endpoint of FAST-3 was met; icatibant significantly decreased the TOSR compared with placebo (median 2.0 hours v 19.5 hours, respectively, $p < 0.0001$). Additionally the primary endpoint in FAST-2 was met; icatibant significantly decreased the TOSR-P compared with tranexamic acid in FAST-2 (median 2.0 hours v 10.1 hours, respectively, $p<0.0001$). Though not statistically significant, a difference in favor of icatibant was seen for the TOSR-P in FAST-1 compared with placebo (median 2.3 hours v 5.0 hours, respectively, $p=0.122$).

Sensitivity analyses used the Cox proportional hazards regression model with adjustment for study effect and the study stratification factors (site of attack and, for FAST-3, C1 inhibitor use) to assess the treatment effects. Figure 7-25 shows the hazard ratios and 95% confidence intervals from the models for each of the three studies for the TOSR and TOSR-P.

For the TOSR, the hazard ratios (icatibant:control) were greater than 1 for all three studies, indicating superiority of icatibant relative to the control group, although there were some differences in the magnitude of these ratios. For TOSR-P, the hazard ratios for FAST-2 and FAST-3 show a statistically significant difference between the icatibant and control groups. In FAST-1, the hazard ratio for TOSR-P favors icatibant, but the difference between icatibant and placebo is not statistically significant.

Figure 7-25 Hazard Ratios (Icatibant:Control) for the TOSR, Based on the VAS-3, and TOSR-P Across the Controlled Phase III Studies-Non-laryngeal Populations



The secondary endpoints of TACSR and TISI achieved similar patterns of statistical significance across the 3 double-blind controlled studies. Statistically significant differences in mean VAS scores for the first 12 hours after dosing were seen between the icatibant and control groups in FAST-3 and FAST-2. Significantly fewer icatibant-treated patients used rescue medications prior to the onset of symptom improvement compared to control ($p<0.0001$ for FAST-3, $p=0.0021$ for FAST-2, and $p=0.0050$ for FAST-1.)

Statistically significant differences between icatibant and placebo were seen for the TOSR and TOSR-P across the subgroup analyses, including age, sex, body weight, BMI, attack severity, attack location, and geographic location.

Repeated use of icatibant over time for treatment of multiple acute HAE attacks produces a consistent response at each attack, with no diminution of efficacy.

For laryngeal attacks, the efficacy of icatibant was consistent with that of the non-laryngeal attacks. The median TISI was 0.6 hours for all first on-study laryngeal attacks across the controlled Phase III studies, compared with median TISI of 0.8 hours each for the non-laryngeal icatibant groups in FAST-3, FAST-2, and FAST-1.

8 SAFETY AND TOLERABILITY

8.1 Safety in Controlled Phase III Studies

Data from the 3 controlled Phase III studies (FAST-1, FAST-2, and FAST-3) were pooled to evaluate safety. Two safety populations were defined:

The Phase III Safety Population, as defined in Section 6.5.1.2, included all (non-laryngeal and laryngeal) randomized and treated patients from the controlled Phase III studies and used data from double-blind treatment (icatibant or control) of the patient's first attack for analyses of safety, allowing safety comparisons for icatibant and comparator treatment.

The Phase III Treated Population, as defined in Section 6.5.1.1, included all patients (with either non-laryngeal or laryngeal attacks) from the controlled Phase III studies who were treated with double-blind, as well as open-label icatibant. The Phase III treated population was used to explore the safety of repeated treatment with icatibant. Although all repeat attacks were analyzed, most safety analyses conducted with this population were focused on data corresponding to the patient's first 5 icatibant-treated attacks due to the small number of patients with more than 5 icatibant-treated attacks. Results were summarized by icatibant-treated attack number.

Safety evaluations included analyses of observation period adverse events (AEs), defined as treatment-emergent AEs occurring from the time of study drug administration to the Day 14 visit or study discontinuation, whichever occurred first, for each treated attack.

8.1.1 Extent of Exposure

8.1.1.1 Phase III Safety Population

Across the 3 controlled Phase III studies, 113 patients with first attacks were treated with icatibant, 38 with tranexamic acid, and 75 with placebo.

8.1.1.2 Phase III Treated Population

On-study HAE attacks and cumulative exposure across the first 5 icatibant-treated attacks are presented in Table 8-1. Most patients experienced attacks that were cutaneous or abdominal, and a majority of attacks were moderate or severe. No trends in attack severity were seen by attack number.

Only 1 injection of icatibant was permitted for double-blind treatment of the patient's first attack; whereas, during the open-label phase patients were permitted to receive treatment with up to 3 injections of icatibant over a 24-hour period per attack. Across the first 5 icatibant-treated attacks, in most cases a single injection of icatibant was used. Two injections were used for 33 attacks, and 3 injections were used for 3 attacks.

Table 8-1 On-Study HAE Attack and Cumulative Exposure — Phase III Treated Population

	Icatibant 30 mg Treated Attack				
Parameter	**Attack 1 (N = 225)**	**Attack 2 (N = 146)**	**Attack 3 (N = 96)**	**Attack 4 (N = 67)**	**Attack 5 (N = 48)**
Type of attack [n (%)]					
Cutaneous	105 (46.7)	59 (40.4)	40 (41.7)	30 (44.8)	18 (37.5)
Abdominal	87 (38.7)	70 (47.9)	45 (46.9)	31 (46.3)	21 (43.8)
Laryngeal	33 (14.7)	17 (11.6)	11 (11.5)	6 (9.0)	9 (18.8)
Attack severity [n (%)]					
Mild	14 (6.2)	3 (2.1)	7 (7.3)	2 (3.0)	4 (8.3)
Moderate	105 (46.7)	74 (50.7)	42 (43.8)	28 (41.8)	19 (39.6)
Severe	106 (47.1)	69 (47.3)	47 (49.0)	36 (53.7)	25 (52.1)
Number of injections [n (%)][a]					
1	217[b] (96.4)	137 (93.8)	86 (89.6)	65 (97.0)	41 (85.4)
2	8 (3.6)	7 (4.8)	10 (10.4)	1 (1.5)	7 (14.6)
3	0	2 (1.4)	0	1 (1.5)	0

For patients initially randomized to placebo or tranexamic acid, their second on-study attack is their first icatibant-treated attack.

[a] Only 1 injection of icatibant was permitted for double-blind treatment of the patient's first attack; whereas, during the open-label phase patients were permitted to receive treatment with up to 3 injections of icatibant over a 24-hour period per attack.

[b] A total of 125 of the 217 patients given 1 injection of icatibant at attack 1 received double-blind treatment and were therefore permitted only 1 injection of icatibant

Source: ISS Table 7.2

8.1.2 Deaths and Discontinuations Due to Adverse Events in Controlled Phase III Studies

8.1.2.1 Deaths

No patient treated with icatibant died during a study. One patient in the placebo group died of myocardial infarction. This event was assessed as not related to study drug by the investigator.

8.1.2.2 Discontinuations Due to Adverse Events

There were no discontinuations due to observation period AEs among patients treated with icatibant for up to 5 attacks.

One patient in the placebo group discontinued, and later died, as a result of myocardial infarction. One patient in the tranexamic acid group discontinued due to pregnancy.

8.1.3 Serious Adverse Events

8.1.3.1 Phase III Safety Population

As presented in Table 8-2, observation period SAEs were reported for 1 patient in the icatibant group, 1 patient in the tranexamic group, and 3 patients in the placebo group. None of these SAEs was assessed as treatment-related by the investigator.

Table 8-2 Observation Period SAEs — Phase III Safety Population

Treatment Group	Event	Time from Last Icatibant Dose (ddd:hh;mm)	Patient No.	n/N (%)	No. Events	Related to Treatment
Icatibant	Cystitis	008:12:05	JE2102-090-004	1/113 (0.9)	1	No
Tranexamic acid	Pregnancy	-	JE2102-082-005	1/38 (2.6)	1	No
Placebo	Myocardial Infarction	-[a]	HGT054-320-010	1/75 (1.3)	1	No
Placebo	HAE Worsening/Recurrence	-	HGT054-338-002	1/75 (1.3)	1	No
Placebo	Gastroenteritis	-	HGT054-409-004	1/75 (1.3)	1	No

Only those AEs occurring after study drug administration until the earlier of the Day 14 visit, study discontinuation, or study drug administration for a new attack are summarized.

Investigators in the controlled Phase III studies were asked to report worsening/recurrence of HAE symptoms within 48 hours of study drug administration as an AE.

[a] The event occurred approximately 11 days after study drug (placebo) administration.

Source: ISS Tables 12.1 and 13.1 and ISS Listing 2

8.1.3.2 Phase III Treated Population

Observation period SAEs across the first 5 icatibant-treated attacks are presented in Table 8-3. None of these SAEs was assessed as treatment-related by the investigator. Worsening/ recurrence of HAE was the only SAE that was reported in more than 1 patient across the first 5 icatibant-treated attacks. Two patients experienced SAEs of worsening/recurrence of HAE. One event was a laryngeal attack during which the patient experienced worsening/recurrence 5 minutes after receiving icatibant. The other events of worsening/recurrence of HAE were reported in a single patient with a medical history of chronic pancreatitis. Narratives for both of these patients are provided in Section 8.1.5.4.

Table 8-3 Observation Period SAEs — Phase III Treated Population

Event	Icatibant-treated Attack No.	Time from Last Icatibant Dose (ddd:hh;mm)	Patient No.	n/N (%)	No. Events	Related to Treatment
Hereditary angioedema	Attack 1	000:05:00	JE2102-075-014	1/225 (0.4)	1	No
	Attack 4	<24 h[a]	JE2102-021-002	1/67 (1.5)	1	No
	Attack 5	011:09:05	JE2102-021-002	1/48 (2.1)	2	No
Cystitis	Attack 1	008:12:05	JE2102-090-004	1/225 (0.4)	1	No
Pancreatitis	Attack 2	009:01:11	JE2103-015-007	1/146 (0.6)	2	No
Chest Pain	Attack 2	05:08:30	JE2103-018-002	1/146 (0.6)	1	No
Road traffic accident (with head injury & wound)	Attack 2	001:10:23	JE2102-040-001	1/146 (0.7)	1	No
Head injury	Attack 2	001:10:23	JE2102-040-001	1/146 (0.7)	1	No
Wound	Attack 2	001:10:23	JE2102-040-001	1/146 (0.7)	1	No
Cholecystitis	Attack 3	003:14:30	HGT054-359-002	1/96 (1.0)	1	No
Pneumonia	Attack 3	007:14:30	HGT054-359-002	1/96 (1.0)	1	No
Tooth extraction	Attack 3	002:04:50	JE2102-020-005	1/96 (1.0)	1	No
Urinary tract infection bacterial	Attack 3	019:11:20	JE2102-020-001	1/96 (1.0)	1	No
Pulmonary embolism	Attack 4	009:14:00	HGT054-316-003	1/96 (1.0)	1	No

For each attack, only those AEs occurring after study drug administration until the earlier of the Day 14 visit, study discontinuation, or study drug administration for a new attack are summarized.

For patients initially randomized to placebo or tranexamic acid, their second on-study attack is their first icatibant-treated attack.

Investigators in the controlled Phase III studies were asked to report worsening/recurrence of HAE symptoms within 48 hours of study drug administration as an AE.

[a] The event onset time was not recorded, but occurred on the same day as dosing.

Source: ISS Tables 12.2 and 13.2 and ISS Listing 2

8.1.4 Injection Site Reactions

8.1.4.1 Phase III Safety Population

Because injection site reactions were common with icatibant administration in Phase I and II studies (Section 8.2.1), the site of study drug administration (injection site) was examined for the presence or absence of symptoms related to injection site reactions, including erythema, swelling, burning sensation, itching/pruritus, warm sensation, and pain at 0.5, 1, 2, 4, 8, 12, 24 hours and 14 days post-treatment. Injection site reactions were graded as absent, mild, moderate, or severe by the investigator or patient, as appropriate. Per the study protocols, injection site reactions were collected separately and were not generally reported as AEs unless they met the criteria for an SAE.

Local injection site reactions were seen in almost all icatibant-treated patients in the Phase III studies. As presented in Table 8-4, 110 of 113 patients (97.3%) in the icatibant group, 10 of 38 (26.3%) patients in the tranexamic acid group, and 25 of 75 patients (33.3%) in the placebo group experienced any injection site reaction. In the icatibant group, the most frequent injection site reactions (occurring in >80% of patients) were erythema and swelling. Warm sensation occurred in approximately one-half of the patients, burning and itching occurred in approximately one-third of the patients, and cutaneous (skin) pain occurred in approximately one-quarter of the patients. Most of the injection site reactions were mild to moderate in severity; 30 patients (26.5%) in the icatibant group had severe injection site reactions. The most frequent severe injection site reaction in the icatibant group was erythema, experienced by 28 patients (24.8%). All other severe injection site reactions in the icatibant group were experienced by <7% of patients.

There were no SAEs of injection site reactions and no discontinuations due to injection site reactions; all injection site reactions were non-serious, self-resolving, and none required hospitalization or additional intervention.

Table 8-4 Summary of Injection Site Reactions — Phase III Safety Population

Injection Site Reaction	Icatibant 30 mg (N= 113) n (%)	Tranexamic Acid[a] (N= 38) n (%)	Placebo (N= 75) n (%)
Any injection site reaction	**110 (97.3)**	**10 (26.3)**	**25 (33.3)**
Erythema	108 (95.6)	4 (10.5)	15 (20.0)
Swelling	93 (82.3)	6 (15.8)	12 (16.0)
Burning	41 (36.3)	2 (5.3)	3 (4.0)
Itching	35 (31.0)	0	0
Warm Sensation	60 (53.1)	1 (2.6)	2 (2.7)
Cutaneous (Skin) Pain	29 (25.7)	0	3 (4.0)
Severe injection site reactions	**30 (26.5)**	**0**	**2 (2.7)**
Erythema	28 (24.8)	0	0
Swelling	7 (6.2)	0	0
Burning	5 (4.4)	0	1 (1.3)
Itching	3 (2.7)	0	0
Warm Sensation	0	0	1 (1.3)
Cutaneous (Skin) Pain	2 (1.8)	0	1 (1.3)
Serious injection site reactions	**0**	**0**	**0**
Injection site reactions leading to withdrawal	**0**	**0**	**0**

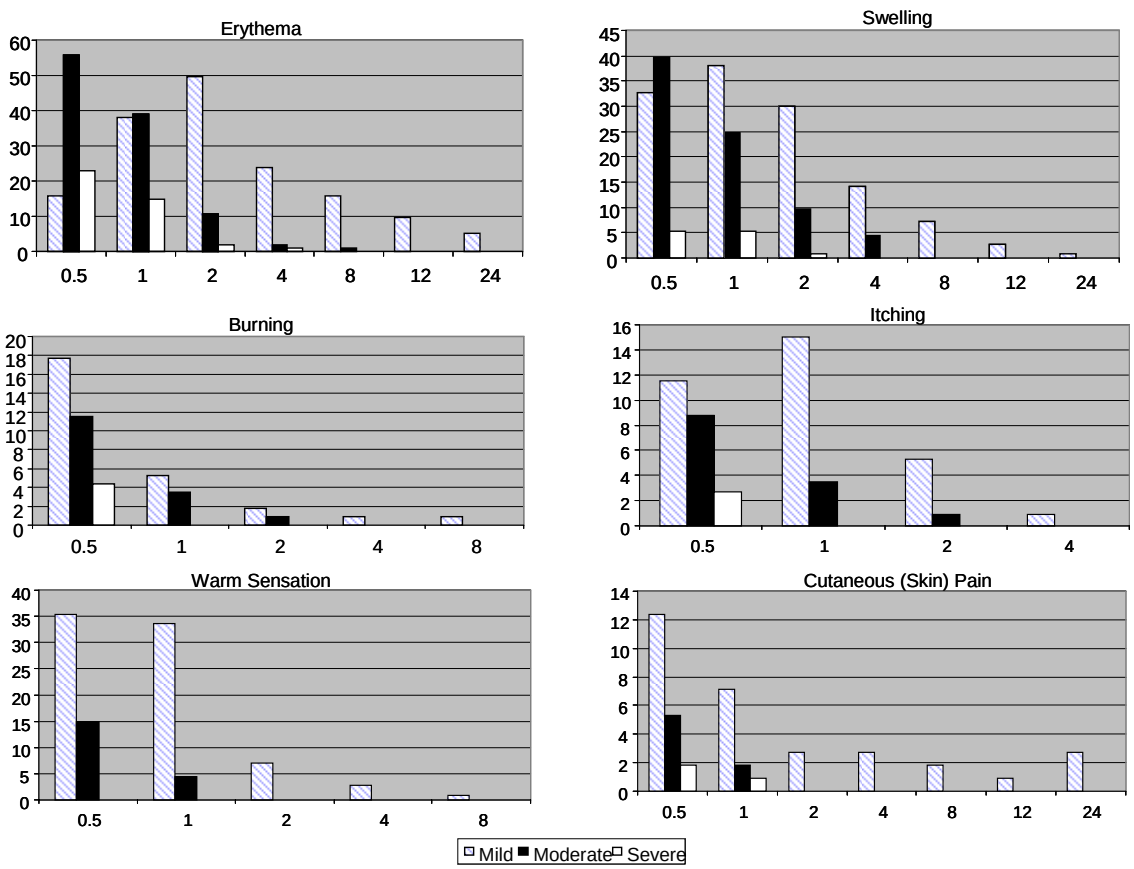
Three patients randomized to placebo received icatibant as a rescue medication and are counted in both the icatibant and placebo groups.

[a] Patients who received tranexamic acid also received a placebo injection to maintain blinding in the study.

Source: ISS Table 24.1

Overall, injection site reactions were transient (Figure 8-1). By 2 hours after treatment, most cases of erythema, the most frequently reported severe injection site reaction, reduced intensity to mild, and most cases (approximately 85%) were completely resolved within 8 hours after treatment. Most other injection site symptoms were completely resolved within 1 to 4 hours after injection.

Figure 8-1 Percent of Icatibant-Treated Patients with Injection Site Reactions by Symptom and Time Point-Phase III Safety Population



X-axis is time after administration in hours and Y-axis is percent of icatibant-treated patients with the specified symptom.
Source: ISS Table 26.1

8.1.4.2 Phase III Treated Population

The incidence of local injection site reactions across the first 5 icatibant-treated attacks is summarized in Table 8-5. Consistent with results seen for the first icatibant-treated attack in the icatibant group (see Table 8-4), injection site reactions were reported by almost all patients through the first 5 icatibant-treated attacks. The types and severities of injection site reactions were similar across the first 5 icatibant-treated attacks. Most of the injection site reactions were mild to moderate in severity; approximately one-quarter of patients had severe injection site reactions across the first 5 icatibant-treated attacks. The most frequent severe injection site reaction was erythema, experienced by 10.4% to 20.0% of patients across the first 5 icatibant-treated attacks. All other severe injection site reactions across the first 5 icatibant-treated attacks were experienced by <7% of patients.

All injection site reactions were non-serious, self resolving, and none required hospitalization or additional intervention.

Table 8-5 Summary of Injection Site Reactions — Phase III Treated Population

Injection Site Reaction	Icatibant 30 mg Treated Attack				
	Attack 1 (N= 225) n (%)	Attack 2 (N= 146) n (%)	Attack 3 (N= 96) n (%)	Attack 4 (N= 67) n (%)	Attack 5 (N= 48) n (%)
Any injection site reaction	219 (97.3)	143 (97.9)	94 (97.9)	62 (92.5)	44 (91.7)
Erythema	216 (96.0)	140 (95.9)	94 (97.9)	59 (88.1)	44 (91.7)
Swelling	184 (81.8)	117 (80.1)	76 (79.2)	52 (77.6)	38 (79.2)
Burning	70 (31.1)	39 (26.7)	20 (20.8)	17 (25.4)	8 (16.7)
Itching	67 (29.8)	30 (20.5)	18 (18.8)	14 (20.9)	7 (14.6)
Warm Sensation	115 (51.1)	58 (39.7)	36 (37.5)	25 (37.3)	14 (29.2)
Cutaneous (Skin) Pain	52 (23.1)	23 (15.8)	12 (12.5)	12 (17.9)	4 (8.3)
Severe injection site reaction	51 (22.7)	17 (11.6)	11 (11.5)	9 (13.4)	7 (14.6)
Erythema	45 (20.0)	15 (10.3)	10 (10.4)	8 (11.9)	7 (14.6)
Swelling	13 (5.8)	5 (3.4)	3 (3.1)	2 (3.0)	3 (6.3)
Burning	12 (5.3)	0	1 (1.0)	2 (3.0)	1 (2.1)
Itching	3 (1.3)	1 (0.7)	0	0	0
Warm Sensation	0	1 (0.7)	0	1 (1.5)	1 (2.1)
Cutaneous (Skin) Pain	2 (0.9)	1 (0.7)	1 (1.0)	0	0
Serious injection site reaction	0	0	0	0	0

For patients initially randomized to placebo or tranexamic acid, their second on-study attack is their first icatibant-treated attack.

Source: ISS Table 24.2

8.1.5 Adverse Events

8.1.5.1 Overall Summary of Adverse Events

PHASE III SAFETY POPULATION

The overall incidence of observation period AEs (excluding local injection site reactions) is presented in Table 8-6. Forty-eight of the 113 patients (42.5%) in the icatibant group experienced a total of 80 observation period AEs, 13 of 38 patients (34.2%) in the tranexamic acid group experienced a total of 17 observation period AEs, and 41 of 75 patients (54.7%) in the placebo group experienced a total of 61 observation period AEs. A higher proportion of patients in the icatibant group (12.4%) experienced investigator-assessed treatment-related observation period AEs compared with the proportion of patients in the tranexamic acid (10.5%) and placebo (5.3%) groups. There were no SAEs related to icatibant by investigator assessment.

No patient in the icatibant group died, was hospitalized, or discontinued a study due to an observation period AE. In the placebo group, 2 patients were hospitalized due to an observation period AE, and 1 patient died (myocardial infarction). In the tranexamic acid group, 1 patient discontinued the study due to an observation period AE (pregnancy).

Table 8-6 Summary of Observation Period Adverse Events — Phase III Safety Population

	Icatibant 30 mg (N = 113)		Tranexamic Acid (N = 38)		Placebo (N = 75)	
Parameter	**Patients (%)**	**Events**	**Patients (%)**	**Events**	**Patients (%)**	**Events**
Any AE[a]	48 (42.5)	80	13 (34.2)	17	41 (54.7)	61
Any serious AE	1 (0.9)	1	1 (2.6)	1	3 (4.0)	3
Any related serious AE	0	0	0	0	0	0
Any severe AE[a]	7 (6.2)	7	4 (10.5)	5	14 (18.7)	14
Deaths due to AE	0	-	0	-	1 (1.3)	-
Hospitalizations due to AE	0	0	0	0	2 (2.7)	2
Study discontinuation due to AE	0	-	1 (2.6)	-	1 (1.3)	-

Three patients randomized to placebo received icatibant as a rescue medication and are counted in both the icatibant and placebo groups. For these patients, AEs occurring prior to icatibant administration appear in the placebo column and AEs occurring after icatibant administration appear in the icatibant column.

Only those AEs occurring after study drug administration until the earlier of the Day 14 visit, study discontinuation, study drug administration for a new attack, or, if not randomized to icatibant, subsequent treatment with icatibant for the same attack, are summarized.

[a] Injection site reactions were reported separately, and per protocol were not generally reported as AEs.

Source: ISS Table 9.1

PHASE III TREATED POPULATION

The overall incidence of observation period AEs (excluding local injection site reactions) is presented in Table 8-7. The proportion of patients reporting any observation period AE decreased over the first 5 icatibant-treated attacks; 42.2% of patients had observation period AEs during icatibant-treated attack 1, whereas 25.0% of patients had observation period AEs during icatibant-treated attack 5. There were no SAEs across the first 5 icatibant-treated that were considered treatment related by the investigator. The proportion of patients with a severe observation period AEs ranged from 1.5% to 7.3% across the first 5 icatibant-treated attacks.

No patient died or discontinued a study due to an observation period AE across the first 5 icatibant-treated attacks. One patient was hospitalized due to 2 observation period AEs (cholecystitis, pneumonia) during icatibant-treated attack 3, and 1 patient was hospitalized due to an observation period AE (pulmonary embolism) during icatibant-treated attack 4. These events were reported as SAEs and are listed in Table 8-3.

Table 8-7 Summary of Observation Period Adverse Events — Phase III Treated Population

	Icatibant 30 mg Treated Attack				
	Attack 1 (N = 225)	**Attack 2 (N = 146)**	**Attack 3 (N = 96)**	**Attack 4 (N = 67)**	**Attack 5 (N = 48)**
Parameter	**Patients n (%)**	**Patients n (%)**	**Patients n (%)**	**Patients n (%)**	**Patients n (%)**
Any AE[a]	95 (42.2)	56 (38.4)	34 (35.4)	20 (29.9)	12 (25.0)
Any serious AE	2 (0.9)	3 (2.1)	3 (3.1)	2 (3.0)	1 (2.1)
Any related serious AE	0	0	0	0	0
Any severe AE	14 (6.2)	9 (6.2)	7 (7.3)	1 (1.5)	2 (4.2)
Deaths due to AE	0	0	0	0	0
Hospitalizations due to AE	0	0	1 (1.0)	1 (1.5)	0
Study discontinuation due to AE	0	0	0	0	0

For patients initially randomized to placebo or tranexamic acid, their second on-study attack is their first icatibant-treated attack.

For each attack, only those AEs occurring after study drug administration until the earlier of the Day 14 visit, study discontinuation, or study drug administration for a new attack are summarized.

[a] Injection site reactions were reported separately, and per protocol were not generally reported as AEs.

Source: ISS Table 9.2

8.1.5.2 Most Common Adverse Events

PHASE III SAFETY POPULATION

The most common observation period AE was worsening/recurrence of HAE, which was reported for 18 of 113 patients (15.9%) in the icatibant group, 6 of 38 (15.8%) patients in the tranexamic acid group, and 15 of 75 (20.0%) patients in the placebo group (Table 8-8).

Table 8-8 Most Common (Reported in ≥2 Patients in Any Treatment Group) Observation Period Adverse Events — Phase III Safety Population

	Icatibant 30 mg (N = 113)	Tranexamic Acid (N = 38)	Placebo (N = 75)
Preferred Term	**Patients n (%)**	**Patients n (%)**	**Patients n (%)**
Any Adverse Event[a]	48 (42.5)	13 (34.2)	41 (54.7)
Hereditary angioedema	18 (15.9)	6 (15.8)	15 (20.0)
Headache	4 (3.5)	2 (5.3)	4 (5.3)
Pyrexia	4 (3.5)	0	0
Sinusitis	3 (2.7)	0	1 (1.3)
Abdominal pain	3 (2.7)	0	0
Nausea	2 (1.8)	0	3 (4.0)
Nasopharyngitis	2 (1.8)	1 (2.6)	0
Rash	2 (1.8)	0	0
Abdominal distension	2 (1.8)	0	0
Diarrhea	2 (1.8)	0	0
Injection site pain	2 (1.8)	0	0
Injection site reaction	2 (1.8)	0	0
Urinary tract infection	2 (1.8)	0	1 (1.3)
Dizziness	2 (1.8)	0	1 (1.3)
Nasal congestion	2 (1.8)	0	0
Pharyngitis	1 (0.9)	0	2 (2.7)
Pruritus	0	0	3 (4.0)

Three patients randomized to placebo received icatibant as a rescue medication and are counted in both the icatibant and placebo groups. For these patients AEs occurring prior to icatibant administration appear in the placebo column and AEs occurring after icatibant administration appear in the icatibant column.

Only those AEs occurring after study drug administration until the earlier of the Day 14 visit, study discontinuation, study drug administration for a new attack, or, if not randomized to icatibant, subsequent treatment with icatibant for the same attack, are summarized.

Investigators were asked to report worsening/recurrence of HAE symptoms within 48 hours of study drug administration as an AE. If symptoms worsened/recurred more than 48 hours after study drug administration, the attack was considered to be a new attack and was not reported as an AE.

[a] Injection site reactions were reported separately, and per protocol were not generally reported as AEs.

Source: ISS Table 10.1

PHASE III TREATED POPULATION

Across the first 5 icatibant-treated attacks, observation period AEs were reported by 25.0% to 42.2% of patients. As shown in Table 8-9, the most common observation period AEs were worsening/recurrence of HAE and headache.

Table 8-9 Most Common Events (Reported in ≥2 Patients in Any Treatment Group) Observation Period Adverse Events — Phase III Treated Population

	Attack 1 (N = 225)	Attack 2 (N = 146)	Attack 3 (N = 96)	Attack 4 (N = 67)	Attack 5 (N = 48)
Preferred Term	**Patients n (%)**	**Patients n (%)**	**Patients n (%)**	**Patients n (%)**	**Patients n (%)**
Any Adverse Event[a]	95 (42.2)	56 (38.4)	34 (35.4)	20 (29.9)	12 (25.0)
Hereditary angioedema	32 (14.2)	11 (7.5)	9 (9.4)	3 (4.5)	5 (10.4)
Headache	10 (4.4)	9 (6.2)	9 (9.4)	1 (1.5)	1 (2.1)
Pyrexia	7 (3.1)	1 (0.7)	1 (1.0)	0	0
Abdominal pain	5 (2.2)	1 (0.7)	1 (1.0)	0	0
Nausea	4 (1.8)	1 (0.7)	0	1 (1.5)	0
Diarrhea	4 (1.8)	1 (0.7)	0	0	0
Vomiting	4 (1.8)	1 (0.7)	1 (1.0)	1 (1.5)	0
Nasopharyngitis	3 (1.3)	5 (3.4)	1 (1.0)	1 (1.5)	0
Upper respiratory tract infection	3 (1.3)	4 (2.7)	1 (1.0)	2 (3.0)	0
Dizziness	3 (1.3)	2 (1.4)	0	1 (1.5)	0
Urinary tract infection	3 (1.3)	1 (0.7)	2 (2.1)	3 (4.5)	0
Sinusitis	3 (1.3)	0	1 (1.0)	0	0
Injection site pain	3 (1.3)	0	0	0	0
Conjunctivitis	2 (0.9)	2 (1.4)	0	0	0
Blood creatine phosphokinase increased	2 (0.9)	2 (1.4)	1 (1.0)	2 (3.0)	0
Hypertension	2 (0.9)	1 (0.7)	1 (1.0)	0	0
Nasal congestion	2 (0.9)	1 (0.7)	1 (1.0)	0	0
Alanine aminotransferase increased	2 (0.9)	1 (0.7)	0	0	0
Abdominal distension	2 (0.9)	0	0	1 (1.5)	0
Dyspepsia	2 (0.9)	1 (0.7)	0	0	0
Rash	2 (0.9)	0	0	0	0
Injection site reaction	2 (0.9)	0	0	1 (1.5)	0
Chest pain	1 (0.4)	2 (1.4)	0	0	0
Urticaria	1 (0.4)	2 (1.4)	0	0	0
Cough	1 (0.4)	1 (0.7)	2 (2.1)	0	0
Acne	0	2 (1.4)	0	1 (1.5)	0

Table 8-9 Most Common Events (Reported in ≥2 Patients in Any Treatment Group) Observation Period Adverse Events — Phase III Treated Population

	Attack 1 (N = 225)	Attack 2 (N = 146)	Attack 3 (N = 96)	Attack 4 (N = 67)	Attack 5 (N = 48)
Preferred Term	**Patients n (%)**	**Patients n (%)**	**Patients n (%)**	**Patients n (%)**	**Patients n (%)**

For patients initially randomized to placebo or tranexamic acid, their second on-study attack is their first icatibant-treated attack.

For each attack, only those AEs occurring after study drug administration until the earlier of the Day 14 visit, study discontinuation, or study drug administration for a new attack are summarized.

Investigators were asked to report worsening/recurrence of HAE symptoms as an AE within 48 hours. If symptoms worsened/recurred more than 48 hours after study drug administration, the attack was considered to be a new attack and symptoms were not reported as an AE.

[a] Injection site reactions were reported separately, and per protocol were not generally reported as AEs.

Source: ISS Table 10.2

8.1.5.3 Severe Adverse Events

PHASE III SAFETY POPULATION

The majority of severe observation period AEs consisted of events of worsening/recurrence of HAE. As shown in Table 8-10, a lower percentage of patients in the icatibant group (5 of 113 patients, 4.4%) experienced severe worsening/recurrence of HAE during the observation period than in the tranexamic acid (3 of 38 patients, 7.9%) or placebo (11 of 75 patients, 14.7%) groups. Further discussion of worsening/recurrence of HAE is presented in Section 8.1.5.4. All other severe observation period AEs were experienced by 1 patient each.

Severe injection site reactions were reported separately from AEs and are summarized in Table 8-4.

Table 8-10 Severe Observation Period Adverse Events — Phase III Safety Population

System Organ Class Preferred Term	Icatibant N =113 n (%)	Tranexamic Acid N = 38 n (%)	Placebo N = 75 n (%)
Any Severe Adverse Event[a]	**7 (6.2)**	**4 (10.5)**	**14 (18.7)**
Hereditary angioedema	5 (4.4)	3 (7.9)	11 (14.7)
Dyspepsia	1 (0.9)	0	0
Headache	1 (0.9)	0	0
Pain	0	1 (2.6)	0
Pregnancy	0	1 (2.6)	0
Aphonia	0	0	1 (1.3)
Migraine	0	0	1 (1.3)
Myocardial infarction	0	0	1 (1.3)

Table 8-10 Severe Observation Period Adverse Events — Phase III Safety Population

System Organ Class Preferred Term	Icatibant N =113 n (%)	Tranexamic Acid N = 38 n (%)	Placebo N = 75 n (%)

Three patients randomized to placebo received icatibant as a rescue medication and are counted in both the icatibant and placebo groups. For these patients, AEs occurring prior to icatibant administration appear in the placebo column and AEs occurring after icatibant administration appear in the icatibant column.

Patients are counted only once within each PT by reporting the AE with the maximum severity.

Only those AEs occurring after study drug administration until the earlier of the Day 14 visit, study discontinuation, study drug administration for a new attack, or, if not randomized to icatibant, subsequent treatment with icatibant for the same attack, are summarized.

Investigators were asked to report worsening/recurrence of HAE symptoms within 48 hours of study drug administration as an AE. If symptoms worsened/recurred more than 48 hours after study drug administration, the attack was considered to be a new attack and symptoms were not reported as an AE.

[a] Injection site reactions were reported separately, and per protocol were not generally reported as AEs.

Source: ISS Table 14.1

PHASE III TREATED POPULATION

Across the first 5 icatibant-treated attacks, severe observation period AEs were reported by 1.5% to 7.3% of patients. Excluding injection site reactions, the majority of severe observation period AEs consisted of events of worsening/recurrence of HAE. A discussion of worsening/recurrence of HAE is presented in Section 8.1.5.4.

Additionally, 3 patients experienced a severe observation period AE of headache during attack 1 (2 patients) and attack 3 (1 patient), 2 patients experienced a severe observation period AE of dyspepsia during attack 1, and 2 patients experienced a severe observation period AE of chest pain during attack 2. One of the events of chest pain, assessed as not related by the investigator, was an SAE and occurred approximately 6 days after icatibant administration (see Table 8-3). The other event of chest pain, also assessed as not related by the investigator, was non-serious and occurred approximately 2 days after icatibant administration. All other severe events were experienced by 1 patient each across the first 5 icatibant-treated attacks.

Severe injection site reactions were reported separately from AEs and are summarized in Table 8-5.

8.1.5.4 Worsening/Recurrence of HAE

WORSENING/RECURRENCE OF HAE — PHASE III SAFETY POPULATION

Investigators in the controlled Phase III studies were asked to report worsening or recurrence of HAE symptoms within 48 hours of study drug administration as an AE. If symptoms worsened/recurred more than 48 hours after study drug administration, the attack was considered to be a new attack and was not reported as an AE.

All reports of worsening/recurrence of HAE were non-serious for icatibant-treated patients in the Phase III Safety Population (indicating that they were not hospitalized).

Eighteen of 113 icatibant-treated patients (15.9%) reported a worsening/recurrence of HAE within 48 hours of study drug administration at their first attack (Table 8-8). The majority of these events were mild or moderate in severity (13 of 18 patients, 72.2%). As shown in Table 8-11, a higher percentage of patients in the tranexamic acid (3 of 6, 50.0%) and placebo (11 of 15, 73.3%) groups reported severe worsening/recurrence of HAE than in the icatibant group (5 of 18, 27.8%).

A similar difference was seen among treatment groups within the first 12 hours of study drug administration, when worsening/recurrence of HAE was reported by 5 of 18 patients (27.8%) in the icatibant group compared to 6 of 6 patients (100.0%) in the tranexamic acid group, and 13 of 15 patients (86.7%) in the placebo group (Table 8-11).

Table 8-11 Worsening/Recurrence of HAE — Phase III Safety Population

	Icatibant 30 mg (N= 113) n (%)	Tranexamic Acid[a] (N= 38) n (%)	Placebo (N= 75) n (%)
Patients with worsening/recurrence of HAE	18 (15.9)	6 (15.8)	15 (20.0)
Subset of these patients with severe worsening/recurrence of HAE	5 (27.8)	3 (50.0)	11 (73.3)
Subset of these patients with worsening/recurrence of HAE within 12 hours of study drug administration	5 (27.8)	6 (100.0)	13 (86.7)

As delineated in the protocols, investigators were asked to report worsening/recurrence of HAE symptoms as as AE within 48 hours. If symptoms worsened/recurred more than 48 hours after study drug administration, the attack was considered to be a new attack and symptoms were not reported as an AE.

Source: ISS Table 14.1

Of the patients who had worsening/recurrence of HAE, rescue medications were used by 10 of 18 patients (55.6%) in the icatibant group, 6 of 6 patients in the tranexamic acid (100.0%) group, and 11 of 15 patients in the placebo (73.3%) group. It is noteworthy that a majority of the icatibant-treated attacks with associated worsening/recurrence of HAE were treated either with no medication at all (44.4%) or with palliative medication for pain or gastrointestinal symptoms only (16.7%).

WORSENING/RECURRENCE OF HAE — PHASE III TREATED POPULATION

Most events of worsening/recurrence of HAE reported across the first 5 icatibant-treated attacks were mild or moderate in severity (Table 8-12). However, 2 patients experienced events of worsening/recurrence of HAE that were assessed by the investigator as SAEs, unrelated to treatment. These events are described in the narratives below.

Table 8-12 Worsening/Recurrence of HAE within 48 Hours of Study Drug Administration — Phase III Treated Population

	Severity of Event			
Icatibant-treated Attack Number	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**	**Total n (%)**
Attack 1 (N=225)	7 (3.1)	15 (6.7)	10 (4.4)	32 (14.2)
Attack 2 (N=146)	4 (2.7)	4 (2.7)	3 (2.1)	11 (7.5)
Attack 3 (N=96)	0	5 (5.2)	4 (4.2)	9 (9.4)
Attack 4 (N=67)	1 (1.5)	1 (1.5)	1 (1.5)	3 (4.5)
Attack 5 (N=48)	2 (4.2)	2 (4.2)	1 (2.1)	5 (10.4)

For patients initially randomized to placebo or tranexamic acid, their second on-study attack is their first icatibant-treated attack.

As delineated in the protocols, investigators were asked to report worsening/recurrence of HAE symptoms as an AE within 48 hours. If symptoms worsened/recurred more than 48 hours after study drug administration, the attack was considered to be a new attack and symptoms were not reported as an AE.

Source: ISS Tables 10.2 and 14.2

Patient JE2102-075-014 had worsening/recurrence of a laryngeal attack 5 minutes after treatment with icatibant. The patient was intubated due to the progression of laryngeal edema and was ventilated for 8 hours. No additional treatment was initiated. As reported by the investigator, first symptom improvement was at 0.7 hours after icatibant, and regression of all laryngeal symptoms was recorded at 4 hours after treatment with icatibant. Due to the patient's medical condition, no patient-rated scores were recorded until 24 hours after icatibant treatment, when the patient considered all symptoms to be completely resolved. There was no further recurrence or worsening of HAE symptoms and no further icatibant or other therapies were needed, other than sedation to maintain mechanical ventilation until the patient stabilized.

Patient JE2102-021-002, with a medical history of chronic pancreatitis, had 2 events of worsening/recurrence of HAE. On both occasions, the patient had severe abdominal attacks, and did not respond to treatment with icatibant or C1 inhibitor. Both attacks resolved with overnight hospitalization for supportive care and pain relief with narcotic agents. The patient had another attack of HAE approximately 12 days after the second event, for which she did not receive icatibant. None of the events were assessed as related to icatibant by the investigator.

8.1.6 Laboratory and Other Safety Evaluations

8.1.6.1 Laboratory Evaluations

Samples for laboratory evaluations (hematology and coagulation, clinical chemistry, and urinalysis) were analyzed at pretreatment, and 2 and 14 days post-treatment for the Phase III Safety Population, and at pretreatment and 14 days post-treatment for the Phase III Treated Population.

PHASE III SAFETY POPULATION

Moderate (up to 2.5 times the upper limit of normal [ULN]) elevations of alanine transaminase (ALT), generally present at baseline, were seen more often in the icatibant group (16.7% of patients at 2 days compared to 13.6% before treatment) than in the placebo group (5.9% of patients at 2 days compared to 7.1% before treatment). Three patients in the icatibant group had ALT elevation of more than 2.5 the ULN both at baseline and after treatment, none with any associated increase in bilirubin. As a majority of these elevations were present before treatment, a contributory effect of icatibant was not evident.

PHASE III TREATED POPULATION

Isolated abnormalities in treated patients were observed in the following laboratory tests: glucose, bilirubin, creatine kinase, and uric acid. However, the rates of abnormalities were similar to that seen in the placebo group of the Phase III Safety Population, were more often present at baseline than after treatment with icatibant, and were generally considered to be clinically insignificant and of low Common Toxicity Criteria (CTC) grade. One patient had a clinically relevant CTC Grade 4 (>10 × ULN) elevation from pretreatment in creatine kinase in association with a back trauma and fall (>5 to 10 × ULN; >10 × ULN) and 1 patient had a clinically relevant CTC Grade 3 (>5 to 20 × ULN) elevation from pretreatment in aspartate transaminase (AST) twice (2 days after treatment with icatibant) in association with exacerbation of cholelithiasis.

8.1.6.2 Potential Effects on ECG and QT Interval

Apart from a single report in FAST-3 of transient sinus bradycardia approximately 30 minutes after icatibant administration, there were no clinically relevant electrocardiogram (ECG) findings related to icatibant in the controlled Phase III studies.

Additionally, icatibant showed no effect on ventricular repolarization in a separate, Phase I clinical pharmacology study (HGT-FIR-061), fully compliant with FDA/ICH E14 guidance, to investigate potential effects of icatibant on the QT/QTc intervals in healthy volunteer subjects. In this randomized, placebo- and active-controlled (moxifloxacin 400 mg orally), crossover-design study, SC icatibant at doses of 30 and 90 mg did not prolong the QT interval or significantly affect QTcF and QTcB. No subject had a maximum on-treatment observed value greater than 480 milliseconds or a change from baseline >60 ms based on QTcI, QTcF, and QTcB while receiving icatibant. In addition, there was no relationship between icatibant concentrations and placebo-corrected, change-from-baseline QTcI values. Thus, icatibant did not show any potential for QT/QTc prolongation, and did not influence cardiac electrophysiology and cardiac repolarization. Neither the 30 mg nor the 90 mg dose of icatibant produced any relevant changes in heart rate, systolic or diastolic blood pressure.

8.1.6.3 Immunogenicity

IMMUNOGENICITY IN FAST-1 AND FAST-2

A 3-tiered assay strategy was used for testing of serum samples from patients in FAST-1 and FAST-2 for the presence of anti-icatibant antibodies. As a first step, all samples were analyzed in an ELISA screening assay for IgG antibodies.

Samples scoring positive in this screening assay were subsequently analyzed in a confirmatory assay. If a sample was confirmed ELISA-positive in the confirmatory assay, then this sample was recorded as positive. Finally, the titer of samples recorded as positive was determined in a titration assay to semi-quantitatively measure the sample-icatibant interaction.

Immunogenicity generally remained negative in patients for up to 82 attacks over 2 years. An analysis of 129 patients treated with icatibant during the controlled and/or the open-label extension phases of FAST-2 and FAST-1 included 170 pre-treatment samples and 683 post-treatment samples. Of samples drawn prior to the initial treatment with icatibant, 2 out 170 tested positive; and, of the post-treatment samples, 5 of 683 tested positive. The positive post-treatment samples derived from 3 different patients, 1 patient from FAST-1 and 2 patients from FAST-2.

- One patient in FAST-1 had a single positive post-treatment sample from Day 14 after his first icatibant-treated attack. The 4 additional samples taken over a period of more than 5 months after the positive sample was obtained (including 2 samples following further icatibant treatment) were confirmed negative. The efficacy of icatibant in this patient was maintained throughout the open-label extension, thus confirming no loss of activity.
- One patient in FAST-2 who was treated for 11 HAE attacks over a 14 month period had 2 positive samples, 1 obtained on Day 14 after his third icatibant-treated attack and 1 obtained 3 months after his fourth attack. Two samples taken after treatment for his fifth attack were negative, indicating no occurrence of an antibody response towards icatibant. Moreover, the efficacy of icatibant was maintained over the treatment period.
- One patient in FAST-2 who was treated for 4 HAE attacks had a positive sample 5 months after his second attack. Additional samples obtained 6 and 9 months after the positive sample were negative. However, the Day 14 sample after the patient's third attack was positive, followed by negative samples obtained 10 and 12 weeks later (during the patient's fourth attack). No signs of an increasing titer were observed. The efficacy of icatibant was maintained over the entire period of 19 months.

IMMUNOGENICITY IN FAST-3

Serum samples from patients in the controlled and/or the open-label extension phases FAST-3 were analyzed to determine the presence of anti-icatibant antibodies. All samples were tested using validated ELISA screening assays for IgG and IgE antibodies. Samples scoring positive in either of the screening assays were subsequently analyzed in a confirmatory assay. A total of 529 samples were tested for anti-icatibant antibodies, 93 samples obtained prior to initial treatment with icatibant and 439 samples obtained after initial icatibant treatment.

No patient in the controlled phase of FAST-3 tested positive for the presence of anti-icatibant antibodies, nor was there any antibody response towards icatibant post treatment among patients who received treatment with icatibant for up to 5 attacks.

8.1.6.4 Hypersensitivity Reactions

No patients in any icatibant study, including the Phase III clinical studies, reported systemic hypersensitivity or an anaphylactic reaction. Using the criteria outlined by the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis and specified by Sampson et al[46], a review of the data for the existence of hypersensitivity reactions among all AEs from the relevant clinical studies with icatibant was completed. No event was identified as fulfilling the criteria of hypersensitivity.

8.1.6.5 Vital Signs and Physical Examination

No clinically relevant findings were seen with regard to vitals signs or physical examination results in the controlled Phase III studies.

8.1.6.6 Long-term Safety in Controlled Phase III Studies

Patients in the controlled Phase III clinical studies were followed until end of study or study discontinuation, whichever came first. The open-label extension phases of the FAST-1 and FAST-2 studies have concluded, while the open-label extension phase of FAST-3 is ongoing. The number of attacks experienced by patients in the studies varies widely, and ranges from 1 attack to 142 attacks (over approximately 3 years). Across the studies, 38 patients were treated with icatibant for more than 5 attacks. The safety profile of these patients was similar to that of the overall Phase III Treated Population. No icatibant-treated patient died during a study, and no patient discontinued due to an observation period AE. There were no trends observed in SAEs, no SAE was reported as related to icatibant, and there were no reports of systemic hypersensitivity during long-term use of icatibant. The pattern of AEs after the first 5 icatibant-treated attacks was similar to that observed during the first 5 icatibant-treated attacks.

8.1.6.7 Pregnancies

Four patients who participated in the Phase III studies conceived from 1 week to 12 months after icatibant exposure; all 4 delivered healthy babies. In the Phase I studies, there was 1 pregnancy reported, with elective termination at 8 weeks (HGT-FIR-061).

8.2 Other Studies

8.2.1 Safety in Phase I and II Studies

The Phase I and II Safety Population, as defined in Section 6.5.1.2, included all subjects from Phase I and II studies. Supplemental analyses of safety were conducted with this population according to the treatment actually received.

8.2.1.1 Deaths and Discontinuations Due to Adverse Events

No subject in the Phase I and II safety population died or was hospitalized due to an observation period AE. One subject who was in the SC icatibant group discontinued the study due to an observation period AE of vomiting.

8.2.1.2 Serious Adverse Events

Observation period SAEs were reported for 1 subject in the IV icatibant group (mania in a subject with pre-existing schizoaffective psychosis) and 1 subject in the SC icatibant group (recurrence/worsening of HAE).

8.2.1.3 Most Common Adverse Events

In Phase I and Phase II studies, observation period AEs were reported by 46 of the 108 subjects (42.6%) in the IV icatibant group, 20 of the 59 subjects (33.9%) in the IV placebo group, 85 of the 166 subjects (51.2%) in the SC icatibant group, and 16 of the 91 subjects (17.6%) in the SC placebo group.

In the SC icatibant group, the most frequent events were related to injection site reactions (including injection site burning, injection site erythema, injection site pruritis, injection site swelling, and injection site warmth). Erythema was reported by subjects in both the IV and SC icatibant groups (5.6% and 4.8%, respectively) but not by any subjects in either of the placebo groups. Additionally, headache was reported by >5% of subjects in all treatment groups, except in the SC placebo group, in which it was reported by 2.2% of subjects.

8.3 Safety in Special Populations

8.3.1 Patients with Hepatic and/or Renal Insufficiency

The safety of icatibant in patients with renal and/or hepatic insufficiency was explored in 2 studies, JE049-2001 and JE049-2002:

JE049-2001 was a Phase IIa study to explore the safety, tolerance, PK and PD profile of multiple doses of icatibant administered intravenously to patients with hepatic insufficiency. Systemic and local tolerance was good, without indication of labile blood pressure or orthostatic hypotension. No prolongation of QTc and no hepatic or renal toxicity were documented. Renal function (glomerular filtration rate [GFR]) was well-preserved throughout the 3-day treatment with IV icatibant.

JE049-2002 was a Phase IIa study to assess the safety and tolerance of icatibant in patients with cirrhosis with refractory ascites (with or without hepatorenal syndrome), and to explore pharmacokinetics and metabolism in patients with severe hepatic insufficiency. Systemic and local tolerance was good, without indication of labile blood pressure or orthostatic hypotension in this very sensitive population. No prolongation of QTc and no hepatic or renal toxicity were documented. Renal function (GFR) was well-preserved throughout the 5-day treatment with IV icatibant.

Icatibant was used safely in patients with mild to moderate hepatic and renal impairment. No accumulation with repeated doses occurred in these special patient populations.

8.3.2 Patients with Cardiac Risk Factors

Patients with New York Heart Association (NYHA) Grade 3 and 4 cardiac disease were excluded from the controlled Phase III studies. However, a review of the medical history showed that 79 of 225 patients in the clinical trials had at least 1 cardiac risk factor (eg, hypertension, hypercholesterolemia, diabetes mellitus).

One patient, a 44-year old male randomized to the placebo group, died of myocardial infarction 11 days after study drug (placebo) administration. This patient had a history of a transient ischemic attack (TIA) and ongoing hypertension when entering the trial. A potential cardiovascular event was reported as an SAE during the observation period in an icatibant-treated patient. This concerned a 59-year-old male who had a history of hypertension and experienced chest pain approximately 6 days after exposure to icatibant. The patient's medical workup was negative; the chest pain was considered by the reporter to be due to progression of underlying HAE disease.

8.4 Worldwide Marketing Experience

Icatibant was initially approved for the treatment of acute HAE in the European Union (EU) on 11 July 2008 and is currently approved in 37 countries. In addition, icatibant was approved for self-administration in the EU on 28 February 2011.

As of January 2011, over 8300 patient exposures have been estimated in the global post-marketing setting. A total of 13 spontaneous case reports were received, including 12 from spontaneous sources and 1 from the literature. These 13 cases reported a total of 25 adverse events. Of the 13 cases, 3 reported serious, unexpected spontaneous events:

- A 23-year-old male, who was admitted with necrotic, infected tonsils and acute suppurative inflammation affecting the subcutaneous connective tissue of the throat, received icatibant as an attempted rescue treatment. The infection led to septic shock and multi-organ failure. Due to the throat swelling, HAE was suspected, and icatibant was administered subcutaneously as a rescue treatment once daily for 5 days. The patient continued to experience multi-organ failure and died 16 days after discontinuation of icatibant.
- A 23-year-old male patient with confirmed C1 deficiency suffered a non-fatal myocardial infarction 1 day after treatment with icatibant for a cutaneous HAE attack. He had risk factors of obesity (BMI 33.5), smoking (15 to 20 cigarettes/day), history of deep vein thrombosis after knee arthroscopy, as well as a disrupted fibrinolysis in testing for hereditary thrombophilia (fibrin D-dimer level >32 mg/L upon admission), and a family history of myocardial infarction (father with MI). The diagnosis of myocardial infarction was confirmed after a second cardiac catheterization showing an occluded left anterior descending coronary artery; the thrombus was removed. A drug-eluting intra-arterial stent was placed and the patient was subsequently discharged.
- A 39-year-old female patient with a history of tooth extraction and preventative treatment with C1 inhibitor presented with an HAE attack and was hospitalized.

Fifteen minutes after icatibant administration, the patient experienced edema in the extremities, arthralgia, and numbness and pain in hands and feet. The following morning the attack had resolved.

8.5 Global Risk Management Activities

8.5.1 Education to Assure Safe Use

HAE is a life-long disorder and patients are very knowledgeable about their disease. As HAE attacks precede correct diagnosis and treatment, the patients are familiar with the symptoms of the attack and can discern these attacks from other events. The proposed education materials will build upon this knowledge base and patient-physician treatment collaboration to support the safe use of icatibant.

Shire has proposed specific instructions within the "Patient Counseling Information" section of the draft labeling for use by physicians in the education of their patients regarding the safe use of icatibant, including information about when to administer icatibant, when to seek clinical assistance, and correct injection administration. A toll-free service will be available to educate physicians and patients concerning administration of icatibant.

Most importantly, patients with laryngeal symptoms will be instructed to seek medical attention immediately after administration of icatibant. It will be recommended that they be managed in an appropriate medical institution until discharge is considered safe. In addition, the proposed labeling includes information for product storage as well as information about injection site reactions and their management.

8.5.2 Measures to Address Identified and Potential Risks

Routine pharmacovigilance activities will be supplemented with intensive data collection and follow up aimed at obtaining comprehensive information from spontaneously reported adverse events pertaining to identified and potential risks as outlined below.

In addition, the Icatibant Outcomes Survey (IOS) is a voluntary registry which will serve as a further source of safety data in the post-marketing setting. IOS is an international, multicenter, prospective, observational study open to all patients receiving icatibant treatment. The registry has been developed to gain a better understanding of the long-term safety of icatibant treatment in clinical practice. The objectives of the registry are to monitor the safety of icatibant during long-term treatment with focus on cardiac ischaemic events in patients predisposed to such events, effects related to attenuation of bradykinin, laryngeal attacks and hypersensitivity reactions.

8.5.2.1 Injection Site Reactions

The most common adverse events in clinical trials of icatibant are related to local reactions at the site of injection, which have been well categorized in the clinical development program.

Reactions may be moderate to severe but are self-limited and no serious reactions have been reported. Shire proposes to continue to monitor injection site reactions in the post-marketing setting to assure that any rare occurrences of more severe reactions or those with longer-term sequelae are promptly detected. The IOS will provide an additional source safety data from which to evaluate these events.

8.5.2.2 Potential Cardiac Risk under Ischemic Conditions

Bradykinin has been characterized experimentally as a tissue hormone with cardioprotective, antiproliferative, antihypertrophic, and antihypertensive effects. In acute cardiac ischemia (eg, acute coronary syndrome), accelerated release of bradykinin plays a cardioprotective role in concert with the other convergent mechanisms of cardioprotection described in Section 3.2).

Icatibant has not been shown to cause ischemia by itself and has no relevant effect on heart rate and blood pressure. As discussed in Section 3.2 attenuation by icatibant of the cardioprotective role of bradykinin is theoretically possible. It is expected, that due to the short systemic exposure to icatibant during treatment of an acute attack of HAE, any potential cardiovascular risk in humans would be limited to patients with pre-existing severe acute cardiac ischemia.

Because patients with NYHA Grade 3 and 4 cardiac disease were excluded from the controlled Phase III studies, no data exist in this sub-population. One post-marketing case of non-fatal myocardial infarction in a patient with multiple risk factors has been reported and the role of icatibant cannot be excluded (Section 8.4). Consistent with the draft labeling, Shire proposes that icatibant be used only under careful observation in patients with known ongoing ischemia or unstable angina, and only when potential benefit outweighs theoretical risk. Pharmacovigilance aimed at obtaining detailed case information from spontaneous reports in post-marketing, as well as from the IOS, will aid in further elucidating the potential for cardiac risk.

8.5.2.3 Hypersensitivity Reactions

Preclinical data suggest that icatibant is a weak sensitizer with negative antibody results in rat, dog and monkey and positive antibody results in guinea pig and rabbit; therefore, a theoretical risk of antibody induction cannot be ruled out. No seroconversion was observed in healthy subjects and only a weak antibody response was detected in 3 HAE patients. There was no evidence of hypersensitivity or lack of efficacy during clinical trials or in the post-marketing setting. No severe systemic reactions have been reported in marketed use. Post-marketing surveillance will be a useful tool to detect the potential for rare reactions when icatibant is used in a larger patient population.

8.5.2.4 Use in Pregnancy and Lactation

The safety of icatibant when used in pregnant and nursing mothers is unknown. Since the target population will include women of childbearing age, it is likely that exposures in pregnant women will occur. Consistent with the draft labeling, icatibant is only recommended during pregnancy if the potential benefit justifies the potential risk to the fetus, and that caution should be exercised when administered to nursing women.

Shire proposes to fully evaluate all known exposures in pregnant women by collecting detailed exposure history and to obtain follow-up information regarding fetal outcomes. Reports of pregnancy exposures will be collected though Drug Information requests, the IOS, and through direct reports to the pharmacovigilance department.

8.5.2.5 Pediatric Use

Currently, there are no data available concerning the use of icatibant in children. Shire plans to conduct a study to investigate the tolerability, safety, and pharmacokinetics of icatibant in pediatric patients with HAE. This study is designed to fulfill a commitment to the EMA under a pediatric investigational plan.

8.6 Safety Summary and Conclusions

Icatibant demonstrated a consistent AE profile across the 3 controlled Phase III studies (FAST-3, FAST-2, and FAST-1). Review of AEs in the controlled phase of these studies indicated that, apart from injection site reactions, a majority of events were reported at a frequency not different from the active (tranexamic acid) comparator group and lower than in the placebo control group. The Phase III safety data confirmed the safety profile seen previously in Phase I and II studies.

Local injection site reactions were seen in almost all icatibant-treated patients. In the Phase III studies, injection site reactions were summarized separately from general reports of AEs; the site of study drug administration (injection site) was examined at protocol-specified post-treatment time points for the presence or absence of erythema, swelling, burning sensation, itching/pruritus, warm sensation, and pain. Most injection site reactions were transient, mild to moderate in severity, and completely resolved within 4 to 8 hours of treatment. All events were considered non-serious and no patient required hospitalization or additional treatment due to injection site reactions.

Excluding local injection site reactions, observation period AEs were experienced by 42.5% of patients in the icatibant group, 34.2% of patients in the tranexamic acid group, and 54.7% of patients in the placebo group. A higher percentage of patients in the placebo (18.7%) and tranexamic acid (10.5%) groups experienced severe observation period AEs compared to the icatibant group (6.2%). No trends were observed in AE profiles by patient age group, sex, body weight category, race, or geographic region.

There were no deaths or discontinuations due to observation period AEs reported for patients receiving icatibant in the controlled Phase III studies, and there were no SAEs assessed as related to icatibant.

There were no clinically important findings in laboratory values or physical examination results related to icatibant, and no clinical effects on the heart or vital signs were observed.

No hypersensitivity or anaphylactic reactions were reported with icatibant. Only 3 patients tested positive for anti-icatibant antibodies (IgG). The positive test results were transient, and all 3 patients maintained efficacy over the treatment period.

The safety profile seen across repeated treatment with icatibant for multiple attacks was consistent with that seen for the icatibant group at the patients' first attack. Further, the post-marketing safety observed to date in countries outside of the United States is consistent with the safety profile observed in clinical trials.

Risk management activities, including data collection in areas of identified or potential risk, will allow for continued evaluation of the safety profile of icatibant. Education of physicians and patients through product labeling and outreach is proposed to ensure its safe use.

9 SELF-ADMINISTRATION OF ICATIBANT

9.1 Description of Study

In the 3 controlled Phase III studies, all SC injections of icatibant were administered by a healthcare provider (HCP). An ongoing Phase IIIb study, EASSI, assesses the use of self-administered icatibant for an acute HAE attack.

The primary objective of EASSI was to explore the clinical safety of self-treatment of HAE attacks. In addition, efficacy data was also collected using the same primary and key secondary endpoints as in FAST-3.

Patients with a documented diagnosis of HAE Type I or II were eligible to participate in this trial. Eligible patients included those who had received treatment for HAE with icatibant in previous clinical trials, patients who had been previously treated with the marketed product Firazyr®, and patients who were naïve to icatibant treatment.

For icatibant-naïve patients, the first on-study HAE attack was treated at the study site, where a HCP administered icatibant to the patient and educated the patient concerning self-administration; the patient received a patient diary to complete. Patients were permitted to use up to 3 doses of icatibant to treat an acute attack; during the self-administration phase the first dose was self-administered and, if needed, the second and third doses were to be administered by a HCP. After receiving their first treatment with icatibant under HCP supervision, icatibant-naïve patients were eligible for self-administration.

Patients were trained on SC self injection technique and then given a syringe containing icatibant to use in the event of an acute HAE attack. The decision to treat an attack was made by the patient based on their perceived necessity for acute treatment. Patients self-administered the icatibant injection at home or other location convenient to the patient, neither at the investigational site nor under HCP-supervision. Patients then completed a diary to capture data related to the safety and effect of self-administered icatibant. They returned to the investigative site for follow-up 48 hours after icatibant administration. After self-administration, patients with laryngeal attacks were instructed to go directly to their HCP, in case additional treatment was required.

The safety of self-administered icatibant was evaluated through the assessment of AEs, physical examination, measurement of vital signs, and assessment of local tolerability at the injection site. Adverse events were collected from dosing through study closeout. Patients recorded injection site reactions (reddening, swelling, burning, itching, warm sensation, skin pain) in the diary as an assessment of local tolerability. Laboratory assessments were not completed in this study.

Similar to the controlled Phase III studies, the TOSR was defined as the time from self-administration to the first documented time point out of 3 consecutive points at which the patient experienced at least 50% reduction in the pre-dose VAS-3 score (Section 6.3). The earliest of the 3 measurements was to be taken as the point of symptom relief.

A total of sixty-six 30 mg SC doses of icatibant study medication were administered during EASSI. Each of the 56 patients self-administered 1 dose, each of the 8 icatibant-naïve patients also received 1 HCP-administered dose. In addition, 2 patients (1 icatibant-naïve and 1 non-naïve) also received an additional dose of icatibant for the treatment of a single attack.

The disposition and demographics of subjects in EASSI are presented in Table 9-1 and Table 9-2, respectively.

Table 9-1 Summary of Subject Disposition by Subject Cohort Treated Population - Self-administered Subjects

	Non-naïve n (%)	Icatibant-naïve n (%)	Overall n (%)
Total number of subjects	48 (100.0)	8 (100.0)	56 (100.0)
Completed the study	47 (97.9)	8 (100.0)	55 (98.2)
Discontinued from the study	1 (2.1)	0	1 (1.8)
Main reason for premature discontinuation			
Withdrawal of consent	0	0	0
Significant medical conditions	0	0	0
Lost to follow-up	1 (2.1)	0	1 (1.8)
Death	0	0	0

Non-naïve subjects= subjects who were previously treated with icatibant at enrollment
Icatibant-naïve subjects = subjects not previously treated with icatibant at enrollment; these subjects had 1 HAE attack treated with icatibant by the site before self-administration

Source: JE049-3101 B CSR Table 10.1.1

Table 9-2 Baseline Demographic Characteristics by Subject Cohort Treated Population – Self-administered Subjects

Characteristics	Non-naïve (N=48)	Icatibant-naïve (N=8)	Overall (N=56)
Age (years)			
n	48	8	56
Mean (Std Dev.)	39.2 (12.45)	40.9 (14.95)	39.4 (12.70)
Median	37.5	39.0	37.5
Sex [n(%)]			
Male	16 (33.3)	2 (25.0)	18 (32.1)
Female	32 (66.7)	6 (75.0)	38 (67.9)
Race [n(%)]			
Caucasian	47 (97.9)	8 (100.0)	55 (98.2)
Other	1 (2.1)	0	1 (1.8)
Country [n(%)]			
Austria	9 (18.8)	3 (37.5)	12 (21.4)
Israel	11 (22.9)	0	11 (19.6)
Argentina	9 (18.8)	1 (12.5)	10 (17.9)

Table 9-2 Baseline Demographic Characteristics by Subject Cohort Treated Population – Self-administered Subjects

Characteristics	Non-naïve (N=48)	Icatibant-naïve (N=8)	Overall (N=56)
Germany	8 (16.7)	1 (12.5)	9 (16.1)
Spain	5 (10.4)	2 (25.0)	7 (12.5)
United Kingdom	6 (12.5)	1 (12.5)	7 (12.5)
Weight (kg)			
Mean (Std Dev.)	73.10 (18.446)	77.50 (23.707)	73.73 (19.097)
Median	69.25	68.50	69.25
Height (cm)			
Mean (Std Dev.)	169.5 (10.01)	166.8 (6.56)	169.1 (9.59)
Median	168.5	168.0	168.5

Non-naïve subjects= subjects who were previously treated with icatibant at enrollment
Icatibant-naïve subjects = subjects not previously treated with icatibant at enrollment; these subjects had 1 HAE attack treated with icatibant by a HCP at the site before self-administration

Note: Percentages are based on total number of subjects within each cohort

Source: JE049-3101 B CSR Table 10.1.2

9.2 Safety of Self-administered Icatibant

9.2.1 Injection Site Reactions

Patients were asked to assess the severity of injection site reactions including symptoms of skin redness, swelling, burning, itching, warm sensation, and skin pain for self-treated attacks.

Out of 56 patients, 53 (95%) had at least a mild injection site reaction. Among the 48 patients who had previously received icatibant, the severity of most reactions at 2 hours post-dose was mild or moderate; however several patients recorded severe injection site reactions as follows: 2 patients with severe skin redness, 2 patients with severe swelling, 1 patient with severe itching, and 1 patient with a severe warm sensation. The severity of injection site reactions decreased over time and by 10 hours no patients had any symptoms considered severe; 2 patients had a recurrence of burning and itching at 36 hours post-dose.

None of the 8 icatibant-naïve patients experienced any symptoms considered severe. Four of the 8 patients experienced moderate skin redness, otherwise all other symptoms were either mild or absent after self-administration of icatibant.

9.2.2 Adverse Events

During the self-administration phase, excluding injection site reactions, 18 of 56 (32.1%) patients overall experienced at least 1 AE; this total included 16 of 48 (33.3%) non-naïve patients and 2 of 8 (25.0%) icatibant-naïve patients.

A summary of all AEs by patient cohort for the self-administration phase is in Table 9-3. The most commonly reported AE during the self-administration phase was HAE. During the self-administration phase, 4 (7.1%) patients had AEs considered severe. Severe AEs included recurrence/worsening of hereditary angioedema (2 patients, 4.2%), abdominal pain, gastrointestinal pain, and headache (1 patient each, 2.1%). There were no deaths, early discontinuations, or SAEs during the study.

Table 9-3 Summary of All Adverse Events by System Organ Class, Preferred Term and Patient Cohort: Self-administration Phase Safety Population – Self-administered Patients

	Patients n (%)		
Preferred Term[a]	**Non-Naïve N = 48**	**Icatibant-Naïve N = 8**	**Total Self-administered N = 56**
Any Adverse Event	**16 (33.3)**	**2 (25.0)**	**18 (32.1)**
Hereditary angioedema	12 (25.0)	1 (12.5)	13 (23.2)
Abdominal pain	2 (4.2)	0	2 (3.6)
Headache	1 (2.1)	1 (12.5)	2 (3.6)
Gastrointestinal pain	1 (2.1)	0	1 (1.8)
Dizziness	1 (2.1)	0	1 (1.8)
Migraine	1 (2.1)	0	1 (1.8)
Rhinitis	1 (2.1)	0	1 (1.8)
Back pain	1 (2.1)	0	1 (1.8)
Skin swelling	1 (2.1)	0	1 (1.8)

[a] Patients are counted only once within each Preferred Term.

Adverse events are coded using the MedDRA Dictionary (Version 8.1).

Source: CSR JE049-3101-B Table 10.3.1.3.1.1

During the naïve treatment phase, 3 of the 8 (37.5%) patients had AEs of HAE recurrence or worsening after HCP-administered icatibant. In the self-administration phase, 13 of 56 (23.2%) patients experienced an AE of HAE recurrence or worsening after self-administration of icatibant (1 of these patients was the same patient that had an AE of HAE recurrence or worsening during the self-administration phase).

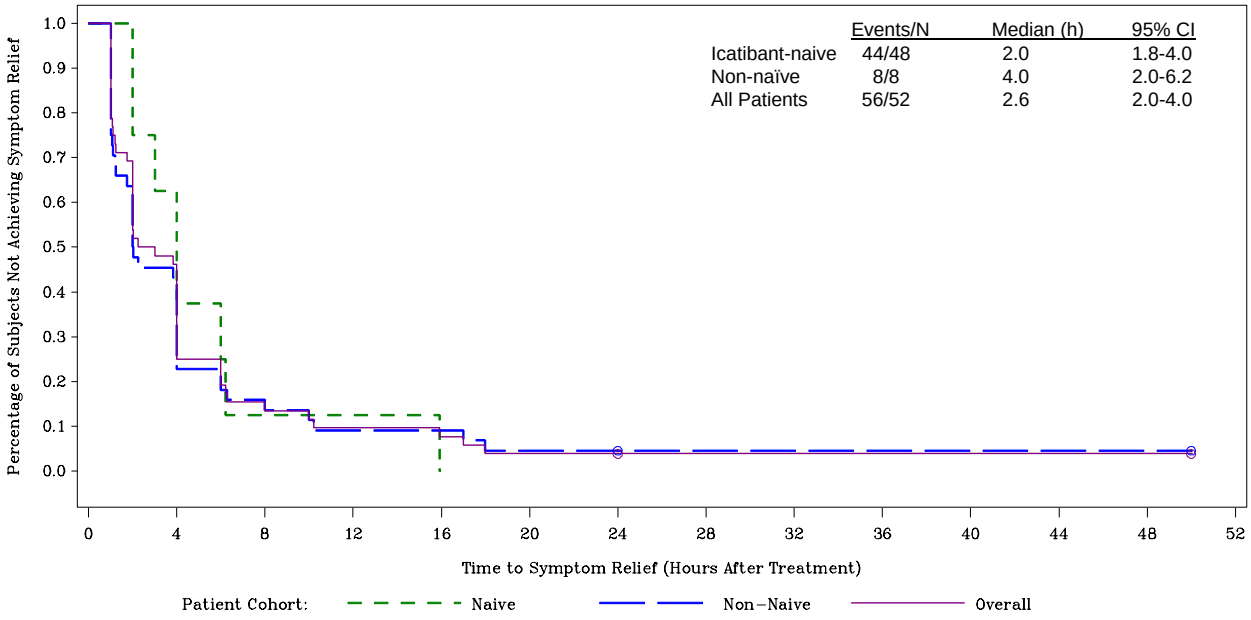
In the self-administration phase, the majority (11 of 13; 84.6%) of the recurrence or worsening of HAE events were considered mild (5 patients) and moderate (6 patients) in severity, the other 2 patients had events that were considered severe. Of the 2 patients with severe worsening/recurrence of HAE, one patient took C1-INH 16 hours after icatibant administration and the attack resolved 48 hours after icatibant administration, and one patient did not take any rescue medication and the attack resolved 48 hours after icatibant administration.

9.3 Effect of Self-administered Icatibant

The results from the endpoints collected in EASSI were consistent with the controlled Phase III studies.

The median TOSR using VAS-3 for icatibant-naïve and non-naïve subjects was 2.6 hours (95% CI 2.0, 4.0). Figure 9-1 shows the cumulative proportion of subjects with symptom relief, defined as at least 50% reduction in the pre-dose VAS-3 score, over time for non-naïve subjects, naïve subjects and subjects overall during the self-administration phase.

Figure 9-1 Time to Onset of Symptom Relief (TOSR) as measured by VAS-3- Self-administered Patients (EASSI)



Source: Figure F-VAS3-KM-SF-3

An analysis was completed to examine the time from attack onset to the time of icatibant administration. As presented in Table 9-4, the time to icatibant administration tended to be shorter for patients who were able to self-administer in the EASSI study than for those in the controlled Phase III studies, who had to travel to the clinical site to receive treatment.

Table 9-4 Time from Onset of HAE Attack to Icatibant Treatment (FAST-1, FAST-2, FAST-3, and EASSI)

Study	N	Mean (SD)	Median	Range
EASSI	56	6.7 (8.3)	4.5	0-47.0
FAST-3	43	7.1 (3.2)	6.5	2.2-12.4
FAST-2	35	10.2 (6.1)	10.5	3.4-27.1
FAST-1	24	12.0 (11.1)	7.6	3.7-53.4

9.4 Summary of Self-administration Study Findings

Overall, self-administrated icatibant was well tolerated and has a safety profile similar to that seen in the controlled Phase III studies.

No SAEs were seen with self-administrated icatibant. Patients were trained and were experienced with identifying relevant HAE attacks and presenting HAE symptoms. They were able to decide when it was appropriate to treat an acute HAE attack themselves. The effect of self-administered icatibant was similar to HCP-administered icatibant seen in the controlled Phase III studies. Patients were able to self-administer icatibant as soon as they noticed the signs and symptoms of an HAE attack or when the symptoms reached the level where treatment was indicated. Therefore, self-administration of icatibant provides patients the option of early access to treatment.

The patient and his/her physician can evaluate the appropriateness of self-administration based on the patient's knowledge of disease and ability to self treat. The inclusion of appropriate guidance information regarding self-administration will assist in timely treatment of these patients.

10 CONCLUSIONS

Icatibant is a first-in-class B2 bradykinin receptor antagonist with a proposed indication for the treatment of acute attacks of hereditary angioedema (HAE) in adults.

Patients suffering from an acute HAE attack are in need of a safe and effective treatment that offers fast access, portability, and the opportunity for earlier intervention than currently approved therapies. Subcutaneously administered 30 mg icatibant has been shown to be a safe and efficacious treatment for acute HAE attacks including cutaneous, abdominal, and laryngeal attacks, as demonstrated by reproducible and consistent efficacy for icatibant across multiple endpoints in the double-blind treatment phases of 3 controlled Phase III studies, and upon repeated open-label use for treatment of subsequent HAE attacks.

Icatibant demonstrated a consistent adverse event profile across the 3 controlled Phase III studies. The majority of events were reported at an incidence similar to that observed in the active comparator (tranexamic acid) group and lower than in placebo group. The Phase III safety data confirmed the safety profile seen in the Phase I and II studies. Additionally, over 8000 patient exposures to Firazyr® have occurred cumulatively in the post-marketing setting from European Union regulatory approval on 11 July 2008 through January 2011. Post-marketing data are consistent with that observed in the clinical studies, and no safety concerns have been identified.

Treatment of HAE, including self-administration, is a patient-physician partnership. Existing international treatment guidelines recommend that every patient with HAE be considered for self-administration.[5] With proper training, patients with HAE are able to detect the unique signs and symptoms of their disease that allow them to distinguish an acute attack from other medical conditions and to remain actively involved in ongoing treatment and attack management.[5] Patient disease awareness, appropriate training, and active participation in the treatment of their HAE attack symptoms support the benefit of a prompt self-administered treatment following the onset of an attack. The results of the EASSI study demonstrate that patients were able to decide when initiation of treatment was appropriate, and they were able to safely self-administer icatibant earlier in their attacks. The safety of self-administered icatibant was similar to HCP-administered icatibant seen in the controlled Phase III studies, and these patients experienced a similar TOSR after administration of icatibant.

Subcutaneously administered 30 mg icatibant was demonstrated to be efficacious in the treatment of acute HAE attacks with an overall acceptable safety profile.

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Appendix 1: Patient Reported Outcome Validation

At the time the studies were designed, no specific guidance in relation to patient-reported outcome (PRO) symptom assessments had been provided by the regulatory authorities. Since the completion of the studies, a specific guidance on the research needed to support PROs used in clinical trials has been issued by the Food and Drug Administration (FDA).[34] The PROs used in the controlled Phase III studies (FAST studies) and EASSI study were evaluated against the key elements outlined in this guidance, including demonstration of face and content validity, clinical validity, responsiveness, and interpretation of clinical trial results. Literature review, expert input, qualitative and quantitative market research and post hoc patient qualitative research supports the face and content validity of the diary used in the FAST studies and the EASSI study. All three types of attack (cutaneous, abdominal and laryngeal) and the relevant symptoms for those attacks were assessed. Though the primary endpoints were developed initially through clinical expert opinion, the subsequent patient qualitative research suggests that the most important symptoms as reported by patients were indeed covered in primary endpoints across the FAST studies and the EASSI study.

Cognitive debriefing interviews conducted with HAE patients demonstrated that the primary endpoint in the Phase III diaries captured the symptoms of primary importance to patients (ie, skin and abdominal pain followed by skin swelling for cutaneous patients). The remaining symptoms of importance reported by patients were captured in the secondary endpoints. Therefore, the primary and secondary endpoints in the Phase III diary have achieved face and content validity.

Psychometric properties of the symptom assessments were established prior to the FAST-3 trial using blinded, pooled FAST-1 and FAST-2 data, and replicated using FAST-3 data. In spite of common issues with assessing test retest reliability using clinical trial data, the abdominal pain, cutaneous pain, cutaneous swelling, and nausea VAS scores, and the composite VAS (VAS-3) and composite patient symptom score (NL-SSS-8) were shown to have adequate test retest reliability. The score's validity and ability to detect change has also been demonstrated.

As suggested in the PRO guidance, a number of different methods were used to estimate the Minimum Clinically Significant Difference (MCSD) for the VAS scores as well as the composite scores.

Anchor based results indicate absolute changes as small as 5-6 mm in the VAS-3 composite differentiated improved patients from unimproved patients with a sensitivity of 90% and a specificity of 90.24% (Report JE049-5129); in blinded pooled FAST-1 and FAST-2 data, "minimal improvement" at 4 hours was associated with an effect size of 0.60SD (Report JE049-5128). In FAST-3, relative changes of 30-40% in the VAS-3 composite were associated with "minimal improvement" reported by clinician and patient global assessments (Report HGT-FIR-RE002).

Distributional estimates for MCSD using 1/2SD change and standard error of measurement range from 12.7% to 36.2% improvement in FAST-3 data.

In the literature it is well-established that a VAS change of between 10 and 20 mm represents a clinically meaningful change in the perception of pain. This consistency in MCSD for the VAS for pain is also seen with other symptoms, such as nausea, dyspnea in congestive heart failure, and shortness of breath in asthma.[47-49]

For FAST-1 and FAST-2, the cut-off of a change of 20mm or more for the primary symptom VAS endpoint is supported by the available information as described above.

In the FAST-3 study, a responder was defined as at least 50% decrease in VAS-3 composite score, which represents a more stringent definition of a responder for the primary endpoint than was suggested based on analysis and literature.

Finally, results of cumulative distribution function (CDF) analyses on data from the FAST-1, FAST-2 and FAST-3 studies indicate that more patients treated with icatibant experienced symptom relief than when treated with either placebo (FAST-1 and FAST-3) or tranexamic acid (FAST-2), regardless of the level of improvement considered as a responder criteria. This result was consistently observed at all time points, and supports the efficacy of icatibant over placebo or tranexamic acid.

In summary, the symptom VASs and the composite scores have been shown to be reliable, valid and responsive and are appropriate to use in trials of HAE. In addition, the responder definition has been shown to be appropriately stringent in its measurement. The supportive secondary endpoints have also proven to be reliable, valid, and of relevance to patients.

A summary of the validation for patient reported outcomes is presented in Table A1.

Table A1 Validation of Patient Reported Outcomes

Validation Activity (FDA PRO Guidance Chapter)	Report Number (Date)	Report Title	Conclusions
Rationale for choice of PRO instrument	JE049-5111 (June 2007) JE049-5115 (Jan 2008) JE049-4104 (Oct 2008) HGT-FIR-RE003 (Jan 2011)	• Literature review of patient-reported outcomes used to assess abdominal pain, skin pain and skin swelling in angioedema. • Evaluation of market research reports in Hereditary Angioedema to support PRO submission package. • Hereditary Angioedema patient interviews to support PRO submission package. • KOL Opinion. • Assessment of Signs, Symptoms and Patient Reported Outcome Endpoints in Hereditary Angioedema Clinical Trials.	Decision to use VAS assessments to measure the severity of key symptoms were based on physician input and supported by literature review and patient interviews; inclusion of items in symptom severity score also based on physician input and supported by literature review and patient input.
Content Validity	JE049-5111 (June 2007) JE049-5115 (Jan 2008) JE049-4104 (Oct 2008) JE049-4105 (Jan 2010) HGT-FIR-RE003 (Jan 2011)	• Literature review of patient-reported outcomes used to assess abdominal pain, skin pain and skin swelling in angioedema. • Evaluation of market research reports in Hereditary Angioedema to support PRO submission package. • Hereditary Angioedema patient interviews to support PRO submission package. • Hereditary Angioedema patient interviews for face and content validation of the HGT-FIR-045 diary. • KOL Opinion. • Assessment of Signs, Symptoms and Patient Reported Outcome Endpoints in Hereditary Angioedema Clinical Trials.	Overall findings show FAST diaries have a good level of face and content validity and support the use of the diary in assessing the symptoms and course of HAE attacks during a clinical trial.
Endpoint Model	HGT-FIR-RE003 (Jan 2011)	• Assessment of Signs, Symptoms and Patient Reported Outcome Endpoints in Hereditary Angioedema Clinical Trials.	Model displays all study endpoints assessing concepts of interest in hierarchical order of consideration by trial.

Table A1 Validation of Patient Reported Outcomes

Validation Activity (FDA PRO Guidance Chapter)	Report Number (Date)	Report Title	Conclusions
Conceptual framework of PRO Instrument	HGT-FIR-RE003 (Jan 2011)	• Assessment of Signs, Symptoms and Patient Reported Outcome Endpoints in Hereditary Angioedema Clinical Trials.	Comprehensive information on conceptual framework and linkage of PRO claims to the concepts. Detail of how PRO items combine to form composite scores in the FAST-3 trial.
Assessment of Reliability, Other Validity and Ability to Detect Change	JE049-5110 (June 2007) JE049-5128 (Dec 2008) JE049-5130 (Sept 2009) HGT-FIR-RE002 (Dec 2010) HGT-FIR-RE003 (Jan 2011)	• Validation of PRO endpoints using pooled clinical trial data from the FAST Hereditary Angioedema studies (FAST-1 & FAST-2). • Psychometric Validation of a three-item Visual Analogue Scale Composite Endpoint (VAS-3) for Patients with Hereditary Angioedema (FAST-1 & FAST-2 data). • Psychometric Validation of a three-item Visual Analogue Scale Composite Endpoint (VAS-3) for Patients with Hereditary Angioedema LOCF (Last Observation Carried Forward) (FAST-1 & FAST-2 data). • Assessment of Psychometric Properties of the PRO Endpoints and Cumulative Distribution Functions in Trial HGT-FIR-054. • Assessment of Signs, Symptoms and Patient Reported Outcome Endpoints in Hereditary Angioedema Clinical Trials.	Demonstration of construct validity, known groups validity, clinical validity and responsiveness of VAS and symptom severity scales. Test-retest reliability detected for “abdominal pain” and “skin pain” VASs when sufficient number of stable patients was available. TheVASs and the VAS composite scores have been shown to be valid and responsive and are appropriate to use in trials of HAE.
Instrument Modification	JE049-4105 (Jan 2010) HGT-FIR-RE003 (Jan 2011)	• Hereditary Angioedema patient interviews for face and content validation of the HGT-FIR-045 diary. • Assessment of Signs, Symptoms and Patient Reported Outcome Endpoints in Hereditary Angioedema Clinical Trials.	Results of cognitive debriefing of the FAST-3 diaries indicated that the changes made were understandable to patients and allowed them to provide an accurate rating of the severity and location of their skin swelling.
Clinical Trial Interpretation	JE049-4102 (May 2007) JE049-5128 (Dec 2008) JE049-5129 (Aug	• Study to estimate the Minimum Clinically Significant Difference (MCSD) in Visual Analogue Scale (VAS) scores for skin swelling, skin pain, and abdominal pain in subjects with Hereditary Angioedema (HAE). • Psychometric Validation of a three-item Visual Analogue	Determination of 9mm change in VAS as MCSD for onset of symptom relief. Anchor based results indicate absolute changes as small as 5-6 mm in the VAS-3 composite differentiated improved

Table A1 Validation of Patient Reported Outcomes

Validation Activity (FDA PRO Guidance Chapter)	Report Number (Date)	Report Title	Conclusions
	2009) HGT-FIR-RE002(Dec 2010)	Scale Composite Endpoint (VAS-3) for Patients with Hereditary Angioedema. • Study to estimate the Minimum Clinically Significant Difference (MCSD) in Composite Visual Analogue Scale Score (VAS-3) for Skin Swelling, Skin Pain, and Abdominal Pain in Subjects with Hereditary Angioedema (HAE). • Assessment of psychometric Properties of the PRO Endpoints AND Cumulative Distribution Functions in Trial HGT-FIR-54	patients from unimproved patients with a sensitivity of 90% and a specificity of 90.24%. In blinded pooled FAST-1 and FAST-2 data, "minimal improvement" at 4 hours was associated with an effect size of 0.60SD. In FAST-3, relative changes of 30-40% in the VAS-3 composite were associated with "minimal improvement" reported by clinician and patient global assessments. Distributional estimates for MCSD using 1/2SD change and standard error of measurement range from 12.7% to 36.2% improvement in FAST-3 data.

Appendix 2: Summary of Primary and Secondary Endpoints in Controlled Phase III Studies

Numerous endpoints were selected and validated to assess the safety and efficacy of icatibant in the treatment of acute HAE attacks in the controlled Phase III studies. The endpoints for the controlled Phase III studies which are not discussed in this document are presented in Table A2, and results for selected endpoints are in Appendix 5.

Table A2 Endpoints Across the Controlled Phase III Studies

	FAST-1	FAST-2	FAST-3
Secondary Endpoints			
Time to investigator-assessed initial symptom improvement	X	X	X
Response rate 4 h post treatment	X	X	NA
Time to onset of symptom relief of each symptom present in pre dose VAS other than the primary symptom	X	X	NA
Composite VAS, change from pretreatment, AUC at 2, 4, 8 h post-treatment	NA	NA	X
Individual VAS scores, change from pretreatment, AUC at 2, 4, 8 h post-treatment	NA	NA	X
Composite subject-assessed symptom scores, change from pretreatment, AUC at 2, 4, 8 h post-treatment	NA	NA	X
Composite investigator-assessed symptom scores, change from pretreatment, AUC at 2, 4, 8 h post-treatment	NA	NA	X
Individual subject-assessed symptom scores, change from pretreatment, AUC at 2, 4, 8 h post-treatment	X	X	X
Individual investigator-assessed symptom scores, change from pretreatment, AUC at 2, 4, 8 h post-treatment	X	X	X
Investigator global assessment at 2, 4, 8h post treatment	X	X	X
Investigator clinical global impression/improvement at 4 &8 h post-treatment	X	X	X
Regression of symptoms (subject and investigator)	X	X	NA
Overall subject improvement	X	X	NA
Time to any reduction in subject assessed laryngeal symptom scores (laryngeal attacks)	NA	NA	X
Time from treatment administration to any reduction in investigator-assessed laryngeal symptom scores (laryngeal attacks)	NA	NA	X
Subject satisfaction	X	X	NA
Incidence and use of permitted rescue medications	X	X	X
Durable response to treatment	X	X	X
Safety Endpoints			

Table A2 Endpoints Across the Controlled Phase III Studies

	FAST-1	FAST-2	FAST-3
AEs, SAEs, local tolerability, laboratory values, vital signs, physical exam, ECG, immunogenicity	X	X	X

Abbreviations: AE = adverse events; ECG = electrocardiogram; h = hours; SAE = serious adverse event; VAS = visual analog scale

Appendix 3: Summary of Study Entry Criteria for the Controlled Phase III Studies

Entry criteria for the 3 controlled Phase III studies is detailed in Table A3.

Table A3 Key Study Entry Criteria for the Phase III Studies Controlled Phase

	FAST-1	FAST-2	FAST-3
Inclusion Criteria			
≥18 years at informed consent	X	X	X
Documented diagnosis Type I or II HAE	X	X	X
Moderate to very severe cutaneous, abdominal, laryngeal attack	X	X	X
Complete Baseline assessments and receive treatment w/in 6 h of attack becoming at least moderate	X	X	X
Complete Baseline assessments and receive treatment w/in 12 h of attack onset	-	-	X
VAS for primary symptom ≥30mm at randomization (cutaneous and abdominal attacks only)	X	X	X
Mild to moderate laryngeal attack	-	-	X
Exclusion Criteria			
Any other form of angioedema than Type I or II HAE	X	X	X
Received pain medication since onset of attack	X	X	X
Received replacement therapy (including C1-INH) w/in 3 days of attack	X	X	-
Received treatment with ACE inhibitors	X	X	X
Evidence of coronary artery disease, unstable angina pectoris, severe coronary heart disease, or congestive heart failure (NYHA class 3 or 4)	X	X	X
Serum creatinine ≥250 µmol/mL	-	X	-
Pregnant or breastfeeding	X	X	X
Contraindicated for tranexamic acid treatment	X	-	-
Previous treatment with icatibant	-	-	X

Abbreviations: ACE = angiotensin converting enzyme; C1 INH = ; HAE = hereditary angioedema; VAS = visual analog scale

Appendix 4: Sample Size Calculations for the Controlled Phase III Studies

FAST-2 (Comparator: Tranexamic Acid)

The sample sizes for FAST-2 and FAST-1 were calculated using the data that had been captured to date in the (then) ongoing study JE049-2101 from the 7 treated subjects and 8 treated attacks with icatibant. The estimated mean and variance of time from treatment to onset of relief were 1.9 h and 1.4 h, respectively. The estimated mean and variance for the time to onset of relief based on recall of previous attacks from these same subjects were 16.8 h and 44.8 h.

Because these estimates were based on small numbers of subjects, power calculations assumed a more pessimistic variance of 4 h for subjects treated with icatibant and 46 h for subjects in the control group. Using these variance assumptions, 27 subjects per arm were required to provide at least 80% power to detect a difference of 4 h between treatment groups. The sample size is based on a 2-sample t-test with a 5% significance level, and assuming standard deviations of 2 in the icatibant group and 6.78 in the tranexamic acid group.

Inflating the sample size by 20% to adjust for the use of a non-parametric Wilcoxon test, 33 subjects per arm were required to have at least 80% power to detect a difference of 4 h between treatment groups in time to relief. With this sample size, a 5% 2-sided log-rank test for equality of survival curves would have a power of 80% to detect a difference between a success rate of 80% in the icatibant group and 46% in the control group 12 hours after treatment of attack.

It was anticipated that a total enrollment of 74 randomized subjects with cutaneous and/or abdominal edema would be required to yield 66 evaluable subjects for the intent-to-treat (ITT) population (37 in both the icatibant and tranexamic acid groups in the controlled phase, to yield 33 evaluable subjects in each group), assuming a drop-out rate of 10%.

No defined number of laryngeal subjects was required, as these data were to be reported descriptively.

FAST-1 (Comparator: Placebo)

The power calculations for the FAST-1 study assumed a variance of 4 h for subjects treated with icatibant and 64 h for subjects in the control group. With these assumptions, 20 subjects per arm were required to provide at least 80% power to detect a difference of 5.5 h between treatment groups (for example 2.5 h for treated subjects and 8 hours for untreated subjects): The sample size was based on a 2-sample t-test with 5% alpha level and 80% power, assuming a difference of 5.5 h in time to onset of relief between the 2 treatment groups and standard deviations of 2 in the icatibant group and 8 in the placebo group.

Inflating the sample size by 20% to adjust for the use of a non-parametric Wilcoxon test, 25 subjects per arm was required to have at least 80% power to detect a difference of 4 h between treatment groups in time to relief. With this sample size, the study had a power of 80% to detect a difference in the success rate of 50% in the icatibant group versus 10% in the control.

It was anticipated that a total enrollment of 56 randomized subjects with cutaneous and/or abdominal edema would be required to yield 50 evaluable subjects for the ITT population (28 in both the icatibant and placebo groups in the double blind phase, to yield 25 evaluable subjects in each group), assuming a drop-out rate of 10%.

No defined number of laryngeal subjects was required, as these data were to be reported descriptively.

FAST-3 (Comparator: Placebo)

The sample size calculations requirements were focused on those subjects who experienced abdominal and/or cutaneous symptoms. The subjects experiencing mild to moderate laryngeal symptoms were analyzed separately and were not accounted for in the sample size calculations.

Sample size calculations were performed using nQuery Advisor software based on the percent of patients who did not achieve symptom relief at 1, 2, 4, 6, 12, and 24 h obtained in the FAST-1 study. This estimate of power was based on 10,000 simulation runs using the survival distributions specified in Table A4. Using the log-rank test for equality of survival curves and assuming a 5% 2-sided significance level, a total of 80 evaluable subjects (40 per treatment group) , would be required in the randomized controlled phase of the study to have at least 80% to detect the difference in survival curves. The sample size was increased by 10% to 88 subjects to account for potential dropouts.

Table A4 Percent of Patients Who Did Not Achieve Symptom Relief (FAST-1)

Time (hours)	Percent of Icatibant Patients Remaining	Percent of Control Patients Remaining
0	100	100
1	85.2	92.9
2	51.9	75.0
4	37.0	71.4
6	25.9	50.0
12	14.8	38.7
24	7.4	23.2

Appendix 5: Summary of Results: Selected Secondary Endpoints Across the Controlled Phase III Studies

Table A5 Efficacy Results for Selected Secondary Endpoints Across the Controlled Phase III Studies

	FAST-1		FAST-2		FAST-3	
	Icatibant (N=26)	Placebo (N=29)	Icatibant (N=35)	Tranexamic Acid (N=38)	Icatibant (N=43)	Placebo (N=45)
Non-laryngeal Population						
VAS-Based Endpoints:						
Median time to onset of symptom relief for the individual VAS score of:						
Skin swelling (h)	4.3	7.9	3.7***	21.3***	3.0***	22.3***
Skin pain (h)	4.0	6.0	1.5**	18.1**	2.0*	8.0*
Abdominal pain (h)	2.0	4.9	1.8	3.5	1.8**	3.5**
Mean change in composite VAS score at 2 hours after treatment (mm)	-15.59	-9.80	-17.16***	-6.42***	-19.74***	-7.49***
Median time to almost complete symptom relief (TACSR) (h)	10.5	19.4	10.0***	42.5***	8.0*	36.0*
Symptom-Score Based Endpoints:						
Median time to onset of symptom relief for the subject-assessed composite symptom score (h)	---	---	---	---	2.0***	8.0***
Median time to onset of symptom relief for the investigator-assessed composite symptom score (h)	---	---	---	---	1.6***	---[a]
Mean change in subject-assessed composite symptom score at 2 h	-0.54	-0.39	-0.49***	-0.20***	-0.53***	-0.22***
Mean change in investigator-assessed composite symptom score at 2 h	-0.50	-0.24	-0.59***	-0.23***	-0.44***	-0.19***
Other Endpoints:						
Median time to subject-assessed initial symptom improvement (h)	0.8***	10.1***	0.8***	7.9***	0.8***	3.5***
Median time to investigator-assessed initial symptom improvement (h)	7.3	14.0	1.8***	8.0***	0.8***	3.4***

Table A5 Efficacy Results for Selected Secondary Endpoints Across the Controlled Phase III Studies

	FAST-1		FAST-2		FAST-3	
	Icatibant (N=26)	Placebo (N=29)	Icatibant (N=35)	Tranexamic Acid (N=38)	Icatibant (N=43)	Placebo (N=45)
Number of subjects who used rescue medications prior to the onset of symptom relief	1 (3.8)**	10 (37.0)**	0**	9 (26.5)**	0***	13 (31.0)***
Number of subjects who had a durable response	14 (53.8)	12 (44.4)	23 (69.7)*	14 (41.2)*	35 (81.4)***	16 (38.1)***
Investigator global assessment at 4 hours (cutaneous symptoms)						
n	23	28	35	38	43	43
0 Absence of symptoms	9 (39.1)	10 (35.7)	11 (31.4)***	11 (28.9)***	13 (30.2)**	14 (32.6)**
1 Mild	6 (26.1)	5 (17.9)	17 (48.6)***	3 (7.9)***	19 (44.2)**	5 (11.6)**
2 Moderate	7 (30.4)	7 (25.0)	7 (20.0)***	10 (26.3)***	10 (23.3)**	16 (37.2)**
3 Severe	1 (4.3)	5 (17.9)	0***	12 (31.6)***	1 (2.3)**	7 (16.3)**
4 Very severe	0	1 (3.6)	0***	2 (5.3)***	0**	1 (2.3)**
Subject-assessed clinical global improvement score at 4 hours						
n	---	---	---	---	43	45
1 Very much improved	---	---	---	---	11 (25.6)***	2 (4.4)***
2 Much improved	---	---	---	---	21 (48.8)***	9 (20.0)***
3 Minimal improvement	---	---	---	---	9 (20.9)***	13 (28.9)***
4 No change	---	---	---	---	2 (4.7)***	6 (13.3)***
5 Minimally worse	---	---	---	---	0***	8 (17.8)***
6 Much worse	---	---	---	---	0***	4 (8.9)***
7 Very much worse	---	---	---	---	0***	3 (6.7)***
Investigator-assessed clinical global improvement score at 4 hours						
n	24	29	35	38	43	43
1 Very much improved	10 (41.7)**	1 (3.4)**	17 (48.6)***	3 (7.9)***	15 (34.9)***	4 (9.3)***
2 Much improved	8 (33.3)**	10 (34.5)**	15 (42.9)***	7 (18.4)***	16 (37.2)***	4 (9.3)***
3 Minimal improvement	5 (20.8)**	7 (24.1)**	3 (8.6)***	11 (28.9)***	10 (23.3)**	15 (34.9)***

Table A5 Efficacy Results for Selected Secondary Endpoints Across the Controlled Phase III Studies

	FAST-1		FAST-2		FAST-3	
	Icatibant (N=26)	Placebo (N=29)	Icatibant (N=35)	Tranexamic Acid (N=38)	Icatibant (N=43)	Placebo (N=45)
4 No change	1 (4.2)**	4 (13.8)**	0***	10 (26.3)***	2 (4.7)***	7 (16.3)***
5 Minimally worse	0**	5 (17.2)**	0***	5 (13.2)***	0***	7 (16.3)***
6 Much worse	0**	2 (6.9)**	0***	1 (2.6)***	0***	3 (7.0)***
7 Very much worse	0**	0**	0***	1 (2.6)***	0***	3 (7.0)***
Laryngeal Treated Population	(N=27)		(N=12)		(N=21)	
VAS-Based Endpoints:						
Median time to onset of symptom relief for the individual VAS score of:						
Difficulty Swallowing (h)	---	---	---	---	1.7	---
Voice Change (h)	---	---	---	---	2.0	---
Skin Swelling (h)	3.0	---	6.0	---	1.8	---
Skin Pain (h)	2.0	---	5.0	---	1.8	---
Abdominal Pain (h)	3.1	---	1.5	---	2.2	---

For the comparison of icatibant to the control group: *** indicates that $p \leq 0.001$; ** indicates that $0.001 < p \leq 0.01$; and * indicates that $0.01 < p \leq 0.05$.

[a] Fewer than half of subjects achieved onset of symptom relief based on the investigator assessment, therefore, the median is not estimable

Sources: ISE Table 6.1.1, ISE Table 8.1.1, ISE Table 8.2, ISE Table 10.1, ISE Table 11.1, ISE Table 12.1, ISE Table 12.4, ISE Table 13.1, ISE Table 17.1, ISE Table 21.1, ISE Table 25.1, ISE Table 26.1, ISE Table 27.1, ISE Table 28.1, and HGT-FIR-054 CSR