Common Drug Review
Clinical Review Report

January 2018

Drug	icatibant (Firazyr, subcutaneous)
Indication	For the treatment of acute attacks of hereditary angioedema (HAE) in adults with C1 esterase inhibitor deficiency.
Listing request	As per indication.
Manufacturer	Shire Human Genetics Therapies Canada Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in allergy and immunology who provided input on the conduct of the review and the interpretation of findings.

Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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ABBREVIATIONS

AE	adverse event
C1-INH	C1 esterase inhibitor
CHAEN	Canadian Hereditary Angioedema Network
CI	confidence interval
DB	double blind
EASSI	Evaluation of the Safety of Self-Administration with Icatibant (study)
EMEA	European Medicines Agency
HAE	hereditary angioedema
IQR	interquartile range
ITT	Intention to treat
LTP	long-term prophylaxis
LOCF	last observation carried forward
MCID	minimal clinically important difference
NR	not reported
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
TACSR	time to almost complete symptom relief
TISI	time to initial symptom improvement
TOSR	time to onset of symptom relief
TOSR-P	time to onset of primary symptom relief
VAS	visual analogue scale
WAO	World Allergy Organization
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Hereditary angioedema (HAE) is a rare autosomal dominant disorder caused by a deficiency (type I) or dysfunction (type II) of C1 esterase inhibitor (C1-INH). A third type of HAE with an unknown cause (type III) is unrelated to C1-INH. HAE is characterized by recurrent attacks of nonpruritic subcutaneous or submucosal edema, most commonly affecting the skin (cutaneous attacks), gastrointestinal tract (abdominal attacks), and respiratory tract (laryngeal attacks). HAE attacks can last from one to four days, and are unpredictable and self-limiting. The goal of therapy is to prevent attacks through prophylactic medications or to alleviate symptoms (e.g., swelling and pain) during an acute attack. The only therapy previously available and indicated for the treatment of HAE attacks in Canada is plasma-derived C1-INH (Berinert).

Icatibant is a synthetic peptide that is a selective competitive antagonist of the bradykinin B2 receptor. According to the Health Canada–approved product monograph, icatibant is administered by slow subcutaneous injection in the abdominal area at a recommended dose of 30 mg, with the option for patients to self-administer the injection. Additional doses may be administered at intervals of at least six hours if response is inadequate or if symptoms recur, with no more than three doses administered within a 24-hour period. Icatibant is available as 3 mL (10 mg/mL) single-dose, single-use, pre-filled syringes. The indication under review and requested listing criteria are listed below.

Indication under review
For the treatment of acute attacks of hereditary angioedema (HAE) in adults with C1 esterase inhibitor deficiency.
Listing criteria requested by sponsor
As per indication.

The objective of this systematic review is to examine the beneficial and harmful effects of subcutaneous icatibant in the treatment of acute attacks of HAE in adults with C1 esterase inhibitor deficiency (type I or type II).

Results and Interpretation

Included Studies

Two phase 3, randomized, double-blind, placebo-controlled studies met the inclusion criteria for this systematic review. FAST-3 (N = 98) and FAST-1 (N = 64) evaluated the efficacy and safety of subcutaneous icatibant 30 mg compared with placebo in patients with type I or type II HAE as confirmed by C4 levels or immunogenic or functional C1-INH deficiency who had experienced an acute attack in the cutaneous, abdominal, or laryngeal areas. Patients presenting with laryngeal symptoms were administered open-label icatibant in FAST-1 and initially in FAST-3. After a protocol amendment in FAST-3, patients presenting with mild to moderate laryngeal symptoms were also randomized to receive icatibant or placebo. Efficacy assessments were performed up to 120 hours after treatment, and safety assessments were performed up to 14 days after treatment, unless a new attack occurred prior to that. In the open-label extension phases of FAST-3 and FAST-1, subsequent attacks were treated with a maximum of three doses, administered at least six hours apart, of open-label subcutaneous (SC) icatibant 30 mg.

In both studies, the majority of enrolled patients were female, the mean age was 35 to 36 years, and over 86% of patients were Caucasian. In the six months prior to enrolment, patients experienced more cutaneous attacks (mean 6.7 to 9.9) than abdominal attacks (mean 3.8 to 6.8), with laryngeal attacks (mean 0.7 to 2.8) being the least common. A visual analogue scale (VAS) was used to measure symptom intensity, with 0 mm representing "no symptom" and 100 mm representing "worst possible symptom." In FAST-3, the primary efficacy end point was the time to onset of symptom relief (TOSR) as defined by a 50% reduction in the composite VAS-3 score (average of the VAS scores for skin swelling, skin pain, and abdominal pain). In FAST-1, the primary efficacy end point was the time to onset of primary symptom relief (TOSR-P). This was defined by a pre-specified reduction in the pre-treatment VAS score for the primary symptom (skin swelling or pain for cutaneous attacks; abdominal pain for abdominal attacks), according to the following equation: $y = 6 \div 7x - 16$ (x = pre-treatment VAS; y = post-treatment VAS), with $x \geq 30$ mm. The manufacturer demonstrated that the minimal clinically important difference (MCID) for the VAS scale was 9 mm, but did not state whether this applied to all symptoms. There was no literature identified that validated the use of the VAS-3 composite.

The limitations of the available evidence include the possibility of unblinding due to injection-site reactions associated with icatibant, which may have biased both patient and investigator-reported outcomes, including all time-to-event outcomes based on VAS and symptom scores. The sample sizes were small, relative to other studies of drug treatments for chronic conditions and, while this design limitation is common for studies of rare diseases, it limits the ability to assess long-term efficacy and harms. There was a lack of data in the assessment of outcomes in patients with laryngeal symptoms. The use of composite outcomes presented in FAST-3 was not validated. It remains unknown whether the improvement in time to symptom relief along with other drug-related side effects (e.g., injection-site reactions) would have resulted in an overall positive impact on a patient's quality of life, daily activities, physical functioning, and mental functioning. There is a lack of trials directly comparing icatibant with other available Health Canada–approved therapies for acute HAE attacks (i.e., Berinert).

Efficacy

Key efficacy outcomes identified in this CADTH Common Drug Review (CDR) were: non-laryngeal and laryngeal symptom relief, and health-related quality of life. Health-related quality of life was not measured in the double-blind phase of FAST-3 and FAST-1.

In FAST-3, the median TOSR was statistically significantly shorter in the icatibant group compared with the placebo group (2.0 hours versus 19.8 hours; $P < 0.001$) in the non-laryngeal population. In FAST-3, the TOSR-P was also statistically significantly shorter in the icatibant group compared with the placebo group (1.5 hours versus 18.5 hours; $P < 0.001$). In FAST-1, the median TOSR-P was numerically shorter in the icatibant group compared with the placebo group, but the difference was not statistically significant (2.5 hours versus 4.6 hours; $P = 0.142$). In FAST-3, the TOSR of individual VAS symptoms (skin swelling, skin pain, abdominal pain) as defined by a 50% reduction from pre-treatment VAS was statistically significantly shorter in the icatibant group compared with the placebo group for all individual symptoms. In FAST-1, the TOSR of individual VAS symptoms (as defined by the same equation as for the TOSR-P) was statistically significantly shorter in the icatibant group compared with the placebo group for skin swelling and skin pain.

The time to almost complete symptom relief (TACSR) was defined by the earliest of three consecutive VAS scores of less than 10 mm. In FAST-3, the median TACSR was statistically significantly shorter in the icatibant group compared with the placebo group (8.0 hours versus 36.0 hours; $P = 0.012$). In FAST-1,

the median TACSR was shorter in the icatibant group compared with the placebo group (8.5 hours versus 23.3 hours), but this difference was not statistically significant ($P = 0.069$).

Patients and investigators were asked to record the time at which they perceived initial improvement of symptoms. In FAST-3, the median time to initial symptom improvement (TISI) as assessed by the patient and investigator was statistically significantly shorter in the icatibant group compared with the placebo group (patient: 0.8 hours versus 3.5 hours [$P < 0.001$]; investigator: 0.8 hours versus 3.4 hours [$P < 0.001$]). In FAST-1, the median TISI as assessed by the patient was statistically significantly shorter in the icatibant group compared with the placebo group (0.8 hours versus 16.9 hours; $P < 0.001$). The median TISI as assessed by the investigator was 6.5 hours in the icatibant group and 14.0 hours in the placebo group, and this difference was not statistically significant ($P = 0.240$). As the judgment of initial symptom improvement is subjective, results need to be interpreted with caution.

In FAST-3, patients presenting with mild to moderate laryngeal symptoms were randomized to icatibant and placebo after a protocol amendment early in the study. Due to the small number of randomized patients with laryngeal attacks, and the fact both patients randomized to placebo were administered icatibant, there is a lack of data on the efficacy of icatibant and placebo in patients with laryngeal attacks.

FAST-3 and FAST-1 are limited by possible unblinding due to injection-site reactions associated with icatibant, and the use of patient-reported outcomes on symptom relief that may be subject to bias. There is also limited information on the validity of using the VAS for non-pain outcomes, and no validation of the use of composite outcomes in FAST-3. Both FAST-3 and FAST-1 had similar study designs, but FAST-3 had a composite primary end point and FAST-1 did not. FAST-1 did not meet its primary efficacy end point. A post-hoc analysis that calculated the TOSR in FAST-1 using the composite VAS-3 score as defined in FAST-3 found a statistically significant difference between the icatibant and placebo groups (2.5 hours versus 7.0 hours; $P = 0.02$). As the TOSR based on the composite VAS-3 in FAST-1 was determined post hoc, these results need to be interpreted with caution.

The open-label extension phases of FAST-3 and FAST-1 showed a similar TOSR for the first 5 icatibant-treated attacks in FAST-3 and the first 10 icatibant-treated attacks in FAST-1. Of the 435 attacks treated with icatibant in FAST-3, 19 (4.4%) required a second icatibant injection, and 1 attack required a third injection. Of the 340 attacks treated in FAST-1, 36 (10.6%) required a second icatibant injection and 4 (1.2%) required a third icatibant injection. For the majority of attacks, it appears that a single dose of icatibant is sufficient to alleviate symptoms.

Icatibant is approved for self-administration in North America and Europe. In FAST-3 and FAST-1, patients received their icatibant injections at a clinical site by a health care professional, which provided limited information on self-administration of icatibant. The Evaluation of the Safety of Self-Administration with Icatibant (EASSI) was a manufacturer-funded, non-randomized, open-label study of icatibant conducted to study the safety and efficacy of self-administration of icatibant for HAE attacks (APPENDIX 8: SUMMARY OF AN OPEN-LABEL STUDY USING SELF-ADMINISTERED ICATIBANT). In EASSI, the TOSR, according to the composite VAS-3, was similar to that of FAST-3.

The manufacturer provided a systematic review and indirect treatment comparison comparing treatment effects of icatibant with other treatments for HAE. The only relevant comparator in the Canadian context was Berinert and, due to heterogeneity between studies and confounding factors, the relative efficacy of icatibant and Berinert unclear.

Harms

No deaths were reported in the icatibant groups of FAST-3 and FAST-1 during the double-blind phase. In FAST-3, one patient randomized to the placebo group died from a myocardial infarction.

The proportion of patients reporting adverse events was slightly higher in the placebo group compared with the icatibant group (FAST-3: 54.3% versus 41.3%; FAST-1: 62.1% versus 40.7%). The most commonly reported adverse events included gastrointestinal disorders, general disorders, administration-site conditions, infections and infestations, and the worsening of a current HAE attack or occurrence of a new attack. No patient experienced a serious adverse event in either the FAST-3 and FAST-1 icatibant groups. In FAST-3, one patient in the placebo group withdrew from the study due to a non-fatal myocardial infarction related to underlying coronary heart disease and dyslipidemia.

The most common adverse events associated with icatibant were injection-site reactions. Almost all icatibant-treated patients experienced at least one injection-site reaction, with the most common being erythema, followed by swelling, burning, itching, a warm sensation, and skin pain. Injection-site reactions were experienced by a greater proportion of patients in the icatibant group compared with the placebo group (FAST-3: 100% versus 58.7%; FAST-1: 96.3% versus 27.6%). Patients with evidence of coronary artery disease (such as unstable angina pectoris, severe coronary heart disease, or congestive heart failure) were excluded from FAST-3 and FAST-1 due to studies in animal models that showed bradykinin 2 receptor inhibition can reduce coronary blood flow. Since these patients were excluded from these studies, there is a lack of efficacy data in this patient population. In both FAST-3 and FAST-1, no patients in the icatibant groups experienced cardiac or vascular disorders.

Pharmacoeconomic Summary

The manufacturer submitted a cost-minimization analysis in which similar clinical effectiveness for icatibant versus its comparator (a plasma-derived C1 esterase inhibitor [Berinert]) was assumed for the treatment of acute HAE attacks in adults, based on the results of a manufacturer-funded indirect treatment comparison. The analysis was conducted from the Canadian public payer perspective. Unit cost for Berinert was calculated from Canadian Blood Services annual reports. Unit costs for non-drug resources were derived from standard reference lists (Ontario Schedule of Benefits, Canadian Institute for Health Information Patient Cost Estimator), while costs for supportive medications were sourced from the Ontario Drug Benefit Formulary. Resource utilization for hospitalizations, supportive care, drug self-administration, and related training was derived from expert opinion. The time horizon for the analysis was the duration of one attack of HAE (estimated at 96 hours), which was expected to encompass the onset of symptom relief for all attacks (the primary end point of the majority of relevant trials). The manufacturer's base-case analysis assumed that one subcutaneous injection of icatibant would be required per attack. Berinert dosing was based on patient weight using the weight distribution of patients in the FAST-1 and FAST-2 trials.

At the confidential submitted price of $[redacted] per 30 mg syringe, when drug costs only per HAE attack are considered, icatibant is more expensive than three vials of Berinert ($2,169 for a patient weight > 50 kg and ≤ 75 kg) but less expensive than four vials of Berinert ($2,892 for a patient weight > 75 kg and ≤ 100 kg).

The comparative effectiveness of icatibant and Berinert is uncertain. Due to its more convenient route of administration (subcutaneous for icatibant versus intravenous for Berinert), icatibant is likely to be associated with lower costs of training, administration, monitoring, and supportive care compared with Berinert, but the true cost difference is unknown. CDR reanalyses varying the number of vials of Berinert

required per attack and the proportion of patients self-administering Berinert suggest the cost impact of icatibant could range from a cost saving of $564 per attack (in patients who weigh from 75 kg to 100 kg) to an additional cost of $159 per attack (in patients who weigh from 50 kg to 75 kg), when compared with Berinert.

Conclusions

Two randomized, double-blind placebo-controlled studies evaluating the efficacy and safety of subcutaneous icatibant 30 mg compared with placebo in patients with type I or type II HAE who experienced an acute attack in the cutaneous, abdominal, or laryngeal areas were included in the systematic review. The results of the included studies suggest that icatibant is superior to placebo in reducing the TOSR in patients presenting with non-laryngeal attacks. Only one study met the primary efficacy end point of TOSR. Across both studies, the icatibant group consistently had shorter time to symptom relief outcomes than the placebo group. In one study, patients with mild to moderate laryngeal attacks were also randomized to icatibant and placebo, but the small sample sizes and the eventual use of icatibant in both laryngeal patients in the placebo group makes it difficult to draw any conclusions on the effectiveness of icatibant compared to placebo for this outcome. A manufacturer-provided systematic review and indirect comparison reported that icatibant had a similar efficacy to Berinert. However, due to the heterogeneity between study designs and outcome definitions, the results of this indirect comparison must be viewed with caution. Repeated treatment with icatibant for subsequent attacks resulted in a similar TOSR, with no new safety concerns compared with the controlled phases. Few patients required a second or third dose of icatibant for each attack. The most common harms associated with icatibant were injection-site reactions, which included erythema, swelling, burning, itching, a warm sensation, and skin pain.

TABLE 1: SUMMARY OF RESULTS FOR NON-LARYNGEAL ATTACKS

	FAST-3		FAST-1	
	Icatibant (N = 43)	Placebo (N = 45)	Icatibant (N = 27)	Placebo (N = 29)
TOSR – VAS-3 (composite end point) – primary efficacy end point (FAST-3)				
Median TOSR, h (IQR)[a]	2.0 (1.0, 5.0)	19.8 (3.5, 37.0)	2.5 (NR)	7.0 (NR)
P value[b]	< 0.001		0.02	
HR (95% CI)[c]	3.17 (1.97, 5.11)		NR	
TOSR-P – primary symptom VAS – primary efficacy end point (FAST-1)				
Median TOSR-P, h (IQR)[a]	1.5 (1.0, 3.5)	18.5 (2.0, 30.9)	2.5 (1.1, 6.0)	4.6 (1.8, 10.2)
P value[b]	< 0.001		0.142	
HR (95% CI)[c]	2.76 (1.73, 4.39)		1.09 (0.57, 2.07)	
TOSR – skin swelling VAS				
Median TOSR, h (95% CI/IQR)[c]	3.0 (2.0, 5.0)	22.3 (12.0, 36.1)	3.1 (2.0, 10.0)	10.2 (4.0, 38.6)
P value[b]	< 0.001		0.039	
TOSR – skin pain VAS				
Median TOSR, h (95% CI/IQR)[d]	2.0 (1.5, 2.5)	8.0 (3.0, 23.9)	1.6 (1.5, 4.0)	9.0 (3.5, 32.4)
P value[b]	0.013		0.007	
TOSR – abdominal pain VAS				
Median TOSR, h (95% CI/IQR)[c]	1.8 (1.0, 2.5)	3.5 (2.0, 8.0)	2.0 (1.0, 3.1)	3.3 (1.5, 8.0)

	FAST-3		FAST-1	
	Icatibant (N = 43)	Placebo (N = 45)	Icatibant (N = 27)	Placebo (N = 29)
P value[b]	0.007		0.056	
TACSR				
Median TACSR, h (IQR)[a]	8.0 (2.5, 50.1)	36.0 (8.1, –)	8.5 (2.5, 31.5)	23.3 (10.2, 55.7)
P value[b]	0.012		0.069	
TISI — patient-assessed				
Median TISI, h (IQR)[a]	0.8 (0.4, 1.4)	3.5 (1.0, 8.3)	0.8 (0.5, 2.0)	16.9 (3.2, –)
P value[b]	< 0.001		< 0.001	
TISI — investigator-assessed				
Median TISI, h (IQR)[a]	0.8 (0.4, 1.8)	3.4 (1.0, 7.0)	6.5 (1.0, -)	14.0 (2.0, –)
P value[b]	< 0.001		0.240	
Harms, n (%)				
N (safety population)	46	46	27	29
Death	0	1 (2.2)	0	0
AEs	19 (41.3)	25 (54.3)	11 (40.7)	18 (62.1)
SAEs	0	5 (10.9)	0	0
WDAEs	0	1 (2.2)	0	0
Harms, n (%)				
Injection-site reactions	46 (100)	27 (58.7)	26 (96.3)	8 (27.6)
Erythema	45 (97.8)	12 (26.1)	26 (96.3)	4 (13.8)
Swelling	42 (91.3)	11 (23.9)	23 (85.2)	3 (10.3)
Burning	20 (43.5)	2 (4.3)	6 (22.2)	2 (6.9)
Itching	19 (41.3)	0	5 (18.5)	0
Warm sensation	24 (52.2)	1 (2.2)	18 (66.7)	1 (3.4)
Skin pain	15 (32.6)	4 (8.7)	5 (18.5)	1 (3.4)

AE = adverse event; CI = confidence interval; h = hours; HAE = hereditary angioedema; HR = hazard ratio; IQR = interquartile range; SAE = serious adverse event; TACSR = time to almost complete symptom relief; TISI = time to initial symptom improvement; TOSR = time to onset of symptom relief; TOSR-P = time to onset of primary symptom relief; VAS = visual analogue scale; WDAE = withdrawal due to adverse event.

Source: Clinical Study Reports,[1,2] US Food and Drug Administration.[3]

[a] Derived from Kaplan-Meier estimates.

[b] Peto-Peto Wilcoxon test (FAST-3) and log-rank Wilcoxon test (FAST-1).

[c] HR derived from Cox proportional hazards regression model with covariate adjustment for stratification factors, edema location, and previous use of C1-INH within five days.

[d] FAST-3 presented 95% CI; FAST-1 presented IQR.

1. INTRODUCTION

1.1 Disease History, Prevalence and Incidence

Hereditary angioedema (HAE) is a rare autosomal dominant disorder that is characterized by recurrent attacks of nonpruritic subcutaneous or submucosal edema, most commonly affecting the skin (cutaneous attacks), gastrointestinal tract (abdominal attacks), and respiratory tract (laryngeal attacks).[4-6] The estimated prevalence of HAE is 1 in 50,000, with reported ranges from 1:10,000 to 1:150,000.[5] HAE is caused by the deficiency or dysfunction of C1 esterase inhibitor (C1-INH) enzyme, a key regulator of the complement and contact systems, which leads to the activation of kallikrein and subsequent overproduction of the nanopeptide bradykinin.[4,5] Bradykinin binds to bradykinin type 2 receptors on endothelial cells, causing increased vascular permeability, which may lead to angioedema if present in excessive amounts.[4,5]

There are three types of HAE: type I (85% of patients) is caused by decreased production of C1-INH; type II (15%) is caused by normal or elevated production of functionally impaired C1-INH; type III (< 1%) is characterized by normal C1-INH level and function and may be caused by a mutation in coagulation factor XII.[4,5] Mutations in the *C1-INH* gene are inherited in approximately 75% of HAE patients, but mutations may appear de novo in 25% of patients.[5] Despite its genetic basis, genetic testing is not required to confirm a diagnosis of HAE. The diagnosis of type I and type II HAE is based on a detailed history and physical examination along with confirmatory laboratory diagnostic tests.[5] C1-INH inhibits the active form of C1; in its absence, C1 will auto-activate and cleave its substrates, C4 and C2. Laboratory tests indicate markedly decreased C1-INH activity and C4 levels, but normal C1 levels, with decreased (type I), normal, or supranormal but dysfunctional (type II) levels of C1-INH.[5,7] According to the World Allergy Organization (WAO), all patients suspected of having type I or type II HAE should be assessed for blood levels of C4, C1-INH protein, and C1-INH function. If abnormally low, tests should be repeated to confirm the diagnosis.

Although the age of onset in HAE patients is variable, the majority of patients will experience their first attack in childhood or adolescence, with approximately one-third of patients experiencing their first attack before the age of five.[7,8] Despite the early age of onset in the majority of HAE patients, a proper diagnosis of the condition may be delayed for several years, particularly if there is no family history.[7] Acute attacks are unpredictable and are often spontaneous without a clear precipitating factor.[5] However, dental procedures, medical procedures, emotional stress, menstruation, oral contraceptive use, infections, and the use of medications such as angiotensin-converting enzyme inhibitors have been known to trigger attacks.[5]

Cutaneous and abdominal attacks are the most frequent type of attack and reported in over 90% of HAE patients.[5,7,8] Cutaneous attacks may involve areas of the face, extremities, and genitals.[5] Facial swelling may involve the lips, tongue, oropharynx, and periorbital tissues, while extremity swelling can progress to affect large areas of the arms or legs. Abdominal attacks involve the gastrointestinal tract. They can be extremely painful and accompanied by nausea, vomiting, and diarrhea. Laryngeal attacks are the least frequent type of attack, but 50% of patients will experience one or more episodes during the course of their disease.[7,8] Laryngeal attacks are the primary cause of mortality in HAE patients due to the risk of asphyxiation.[5] The frequency of attacks in symptomatic, untreated patients can range from weekly to less than yearly.[5] Each attack may last one to four days and can involve one or more sites, severely affecting patient quality of life.[4,5]

1.2 Standards of Therapy

As there is currently no cure for HAE, the goal of therapy is to prevent attacks or to alleviate symptoms (swelling and pain) during an acute attack.

Long-term prophylaxis (LTP) aims to reduce the number and severity of acute attacks and is administered continuously to patients during symptom-free periods, potentially for life.[9,10] An LTP approach should be considered when patients, despite optimized on-demand treatment of acute attacks, continue to experience more than 12 moderate-to-severe attacks per year, or are affected by HAE more than 24 days per year.[9] The Canadian Hereditary Angioedema Network (CHAEN) recommends plasma-derived C1-INH (pdC1-INH), androgens (e.g., danazol), and antifibrinolytic drugs (e.g., tranexamic acid) as therapeutic options for LTP, though tranexamic acid is less effective than androgens.[11] The drug pdC1-INH (Cinryze) has received a Health Canada Notice of Compliance for the routine prevention of angioedema attacks in adults and adolescents with HAE in Canada, but has yet to be commercially available.[12] Androgen derivatives should be used with caution due to their androgenic and anabolic effects.[13] The WAO does not recommend antifibrinolytic drugs for LTP due to a lack of data supporting their efficacy.[13]

Short-term prophylaxis aims to reduce the risk of swelling in a patient undergoing a procedure likely to precipitate an attack. The WAO recommends that short-term prophylaxis be considered before dental surgeries, procedures where endotracheal intubation is required, procedures where the upper airway or pharynx is manipulated, and before bronchoscopy or endoscopy.[13] CHAEN recommends pdC1-INH be administered to HAE patients prior to major procedures or intubation; if not available, danazol or plasma may be used.[11] For lower-risk procedures, if safe on-demand drugs such as pdC1-INH are available, prophylaxis may be omitted.[11,13]

For the treatment of acute attacks, the WAO recommends that all attacks that result in debilitation or dysfunction and involve the face, neck, or abdomen should be considered for on-demand treatment, while the treatment of laryngeal attacks is mandatory.[13] The WAO and CHAEN recommend that acute attacks be treated with C1-INH, ecallantide, or icatibant.[11,13] In Canada, intravenous pdC1-INH (Berinert) has been licensed for use since 2010 and is available through Canadian Blood Services. Ecallantide (Kalbitor), a kallikrein inhibitor that is administered subcutaneously, is licensed in the United States as therapy for angioedema events. Intravenous recombinant human C1-INH (Rhucin, Ruconest), purified from the milk of transgenic rabbits, is approved for use in HAE patients in the European Union. Both ecallantide and recombinant C1-INH are not currently licensed for use in Canada.

As acute attacks are unpredictable and potentially life-threatening, timely administration of appropriate treatment is imperative and the WAO and CHAEN recommends that attacks be treated as early as possible.[11,13] Current therapy options are limited because they must be administered by a health care professional, possibly delaying treatment. Berinert is approved for self-administration, but the process of intravenous self-administration may be complex because the concentrate must be prepared and reconstituted before injection into a vein.[14] However, with proper training, patients appear able to overcome the barriers to self-administration.[15]

1.3 Drug

Icatibant (Firazyr) is a synthetic peptide that is a selective competitive antagonist of the bradykinin B2 receptor. Icatibant is administered by slow subcutaneous injection in the abdominal area at a recommended dose of 30 mg. If response is inadequate or if symptoms recur, additional doses may be administered at intervals of at least six hours, with no more than three doses administered within a

24-hour period. Icatibant is available as 3 mL (10 mg/mL) single-dose, single-use, pre-filled syringes. A Notice of Compliance was granted by Health Canada on June 4, 2014.[16]

Indication under review
For the treatment of acute attacks of hereditary angioedema (HAE) in adults with C1 esterase inhibitor deficiency.
Listing criteria requested by sponsor
As per indication.

TABLE 2: KEY CHARACTERISTICS OF TREATMENTS FOR ACUTE ATTACKS OF HEREDITARY ANGIOEDEMA

	Icatibant (Firazyr)	pdC1-INH (Berinert)
Mechanism of Action	Bradykinin B2 receptor antagonist	C1-INH replacement
Indication[a]	For the treatment of acute attacks of HAE in adults with C1-INH deficiency	For the treatment of acute abdominal, facial, or laryngeal attacks of HAE of moderate-to-severe intensity
Route of Administration	SC injection in the abdominal area	IV injection
Recommended Dose	30 mg Additional doses may be administered at intervals of ≥ six hours if response is inadequate or if symptoms recur. No more than three doses may be administered in a 24-hour period.	20 IU per kg body weight
Serious Side Effects/Safety Issues	Injection-site reactions, cardiovascular events	Thromboembolic events, possible infections transmitted through human plasma, severe hypersensitivity reactions

C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema; IU = international unit; IV = intravenous; pdC1-INH = plasma-derived C1-INH; SC = subcutaneous.
[a] Health Canada indication.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of subcutaneous icatibant for the treatment of acute attacks of hereditary angioedema (HAE) in adults with C1 esterase inhibitor deficiency (type I or type II).

2.2 Methods

Studies selected for inclusion in the systematic review included the pivotal studies in support of the Health Canada indication provided in the manufacturer's submission to CDR, as well as those meeting the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult patients with type I or type II HAE experiencing an acute attack Subgroups of interest: • Location of acute attack (subcutaneous, abdominal, laryngeal) • Number of previous treatments • Treatment with prophylactic drug (yes/no)
Intervention	Subcutaneous icatibant
Comparators	• Plasma-derived C1-INH (Berinert) • Placebo
Outcomes	**Key efficacy outcomes:** • Non-laryngeal symptom relief: skin swelling, erythema, skin irritation, skin pain, abdominal pain, nausea, vomiting, diarrhea • Laryngeal symptom relief: difficulty swallowing, voice change, breathing difficulties, stridor, asphyxia • HRQoL using a validated scale (e.g., SF-36) **Other efficacy outcomes:** • Durability of response • Use of rescue medication • Need for additional dose of icatibant • Hospitalization • Need for intubation (laryngeal attack) • Death **Harms outcomes:** • AEs, SAEs, WDAEs, mortality • Notable harms or harms of special interest (injection-site reaction, cardiovascular events)
Study Design	Published and unpublished RCTs

AE = adverse event; C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema; HRQoL = health-related quality of life; RCT = randomized controlled trial; SAE = serious adverse event; SF-36 = short form (36) health survey; WDAE = withdrawal due to adverse event.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates through Ovid; Embase (1974–) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Firazyr (icatibant).

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on July 11, 2014. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on November 19, 2014. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (www.cadth.ca/en/resources/finding-evidence-is/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Databases (free), Internet Search and Open Access Journals. Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

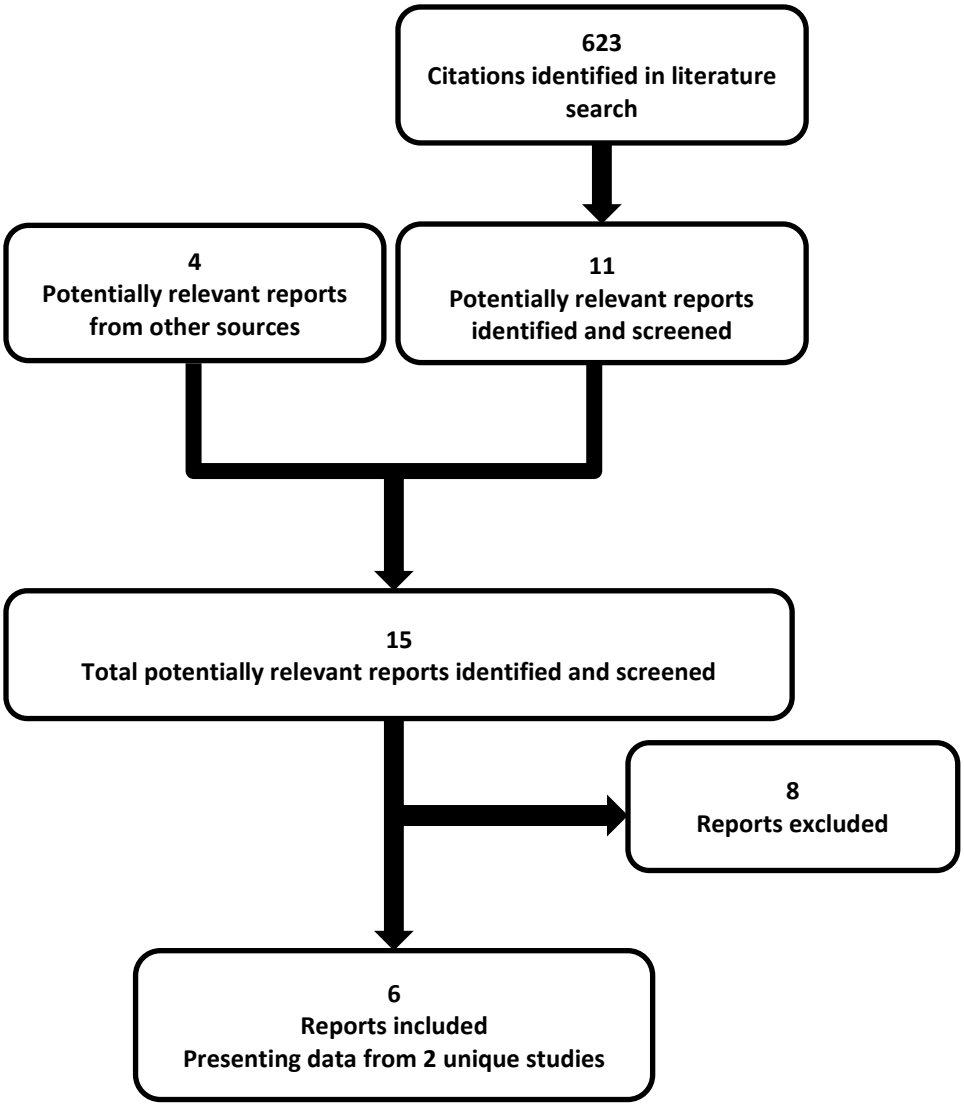
Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings from the Literature

A total of two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES



QUORUM = Quality of Reporting of Meta-analyses.

TABLE 4: DETAILS OF INCLUDED STUDIES

		FAST-3 (HGT-FIR-054)	FAST-1 (JE049-2103)
DESIGNS & POPULATIONS	**Study Design**	DB RCT	
	Locations	Multi-centre: 11 countries, 67 study centres; one patient in Canada and 65 patients in the US enrolled	Multi-centre: four countries, 26 study centres (including 5 in Canada, 17 in the US, 3 in Australia, and 1 in Argentina); 10 patients in Canada and 33 patients in the US enrolled
	Enrolled (N)	98	64
	Randomized (N)	93 (not including severe laryngeal attacks)	56 (not including laryngeal attacks)
	Inclusion Criteria	• Patients ≥ 18 years of age with a documented diagnosis of HAE type I or II confirmed either by decreased C4 levels or immunogenic or functional C1-INH deficiency (< 50% of normal levels). Inclusion was permitted initially based on medical history alone if a clear diagnosis had been made using all of the following criteria: family history; characteristic attack manifestations, recurrent attacks; historical functional C1-INH level < 50%; exclusion of other forms of angioedema • Acute attack in the cutaneous, abdominal, or laryngeal areas • Moderate to very severe cutaneous or abdominal attack • Study treatment must have commenced within six hours of the abdominal or cutaneous attack, becoming at least moderate in severity	
		• Study treatment must have commenced within six hours of the laryngeal attack, becoming at least mild in severity • Study treatment must have commenced within 12 hours after the onset of any attack (regardless of severity) • Patient must have reported at least one VAS score ≥ 30 mm	• For patients with abdominal and/or cutaneous symptoms only, patients must have reported VAS scores ≥ 30 mm for at least one primary symptom (skin swelling, skin pain, abdominal pain)
	Exclusion Criteria	• Diagnosis of angioedema other than HAE • Previous treatment with icatibant • Participation in a clinical trial of another investigational medicinal product within the past 30 days • Treatment with replacement therapy (e.g., C1-INH) < 3 days (FAST-1), or < 5 days (FAST-3) before the onset of the current attack (these patients were enrolled in FAST-3 after protocol amendment 2) • Treatment with pain medication since onset of current attack • Treatment with ACE inhibitors • Evidence of coronary artery disease (e.g., unstable angina pectoris, severe coronary heart disease, congestive heart failure) based on medical history or at screening examination	

		FAST-3 (HGT-FIR-054)	FAST-1 (JE049-2103)
DRUGS	**Intervention**	SC icatibant 30 mg: single dose for first attack. Open-label SC icatibant 30 mg was administered for all subsequent attacks; a maximum of three doses, administered ≥ six hours apart, was permitted	
		Open-label icatibant was administered for severe laryngeal attacks	Open-label icatibant was administered for all laryngeal attacks
	Comparator(s)	SC placebo	
DURATION	**Phase**		
	Double-blind	First attack: when patients presented with cutaneous and/or abdominal symptoms with at least moderate severity (according to an investigator-conducted global assessment using a symptom severity scale), or with laryngeal symptoms with mild to moderate severity	First attack: when patients presented with cutaneous and/or abdominal symptoms with at least moderate severity according to an investigator-conducted global assessment using a symptom severity scale
		• Efficacy assessments: up to 120 hours • Safety assessments: up to 14 days (if no new attack occurred)	
	Open-label extension	Patients could elect to continue to receive open-label icatibant for the treatment of subsequent attacks until such time as the study was discontinued by the sponsor or the investigational product became commercially available	
OUTCOMES	**Primary End Point**	TOSR: the earliest of three consecutive non-missing measurements for which there was a ≥ 50% reduction in the pre-treatment composite VAS score (VAS-3)	TOSR-P: the earliest of three consecutive non-missing measurements for which there was symptom relief in the primary symptom. (For cutaneous attacks, the primary symptom was cutaneous pain or swelling; for abdominal attacks, it was abdominal pain.)
	Other End Points	• TACSR • TISI (patient and investigator) • TOSR of individual VAS scores • Change from baseline in individual VAS scores over time • Change from baseline in individual symptom scores (patient and investigator) over time • Global assessment and clinical global impression or improvement post-treatment (investigator) • Use of rescue medication	
		• TOSR-P • TOSR for composite symptom scores (patient and investigator) • Change from baseline in composite VAS over time • Change from baseline in composite symptom scores (patient and investigator) over time • Time to any reduction in laryngeal VAS and symptoms scores (patient and investigator)	• Durable response to treatment

		FAST-3 (HGT-FIR-054)	FAST-1 (JE049-2103)
NOTES	**Publications**	Lumry et al. (2011)[17]	Cicardi et al. (2010)[18]

ACE = angiotensin-converting enzyme; C1-INH = C1 esterase inhibitor; C4 = complement component 4; DB = double blind; HAE = hereditary angioedema; RCT = randomized controlled trial; SC = subcutaneous; TACSR = time to almost complete symptom relief; TISI = time to initial symptom improvement; TOSR = time to onset of symptom relief; TOSR-P = time to onset of primary symptom relief; VAS = visual analogue scale.
Source: CDR submission.[19]
Note: three additional reports were included: Health Canada reviewer's report,[20] Food and Drug Administration Medical Review[3] and Statistical Review.[21]

3.2 Included Studies

3.2.1 Description of Studies

Two phase 3 randomized, double-blind, placebo-controlled studies met the inclusion criteria for this systematic review. FAST-3 (N = 98) and FAST-1 (N = 64) both included patients with type I or type II HAE who experienced an acute attack in the cutaneous, abdominal, or laryngeal areas. Patients presenting with cutaneous or abdominal symptoms were randomized, in a 1:1 ratio with stratification by symptom type and previous use of C1-INH (FAST-3 only), to receive a single dose of SC icatibant 30 mg or SC placebo. Multiple doses were not permitted for the first attack. In both studies, patients presenting with laryngeal symptoms were administered open-label icatibant. After a protocol amendment, patients in FAST-3 presenting with mild to moderate laryngeal symptoms were also randomized to icatibant and placebo. Efficacy assessments were performed up to 120 hours after treatment, and safety assessments were performed up to 14 days after treatment, unless a new attack occurred prior to that. In the open-label extension phase, subsequent attacks were treated with a maximum of three doses, administered at least six hours apart, of open-label SC icatibant 30 mg. (APPENDIX 8: SUMMARY OF AN OPEN-LABEL STUDY USING SELF-ADMINISTERED ICATIBANT).

3.2.2 Populations

a) Inclusion and Exclusion Criteria

Patients at least 18 years of age with a documented diagnosis of type I or II HAE based on decreased C4 levels or immunogenic or functional C1-INH deficiency were eligible for inclusion in the FAST-3 and FAST-1 studies. Enrolment and randomization in the studies occurred when patients presented with cutaneous or abdominal symptoms that were at least moderate in severity, as determined by an investigator global assessment at pre-treatment. In FAST-3, patients must have reported at least one VAS score ≥ 30 mm for any symptom. In FAST-1, patients must have reported VAS scores of ≥ 30 mm for at least one primary symptom (skin pain, skin swelling, abdominal pain). Patients presenting with laryngeal symptoms of any severity were treated. Patients had to be able to complete a baseline assessment and commence treatment no later than six hours after the attack had become at least moderate in severity, or mild in severity in the case of laryngeal attacks in FAST-3.

Patients were excluded if they had a diagnosis of angioedema other than HAE; had previously been treated with icatibant; had been treated with pain medication since the onset of the current attack; or were currently being treated with angiotensin-converting enzyme inhibitors. Patients were also excluded if there was any evidence of coronary artery disease.

In FAST-1, patients were excluded if they had received treatment with replacement therapy (e.g., C1-INH) less than three days prior to the onset of the current attack. In FAST-3, patients were initially excluded if

they received treatment with replacement therapy less than five days prior to the onset of the current attack. After protocol amendment 2, these patients were also enrolled in FAST-3.

b) Baseline Characteristics

Baseline characteristics are presented separately for the non-laryngeal intention-to-treat (ITT) population (Table 5) and the laryngeal population (Table 6). In general, the demographics were similar across treatments groups in both FAST-3 and FAST-1 in the non-laryngeal population. FAST-1 had a greater proportion of female patients in the placebo group compared with the icatibant group (72.4% versus 59.3%, respectively). The average age was 35 to 36 years, and over 86% of enrolled patients were Caucasian.

In the FAST-3 non-laryngeal population, 87.5% of patients reported a family history of HAE and 86.4% of patients had type I HAE, with an average time since diagnosis of 19.2 years, indicating a very experienced HAE population. The mean time since the last acute attack was slightly longer in the icatibant group compared with the placebo group (4.3 months versus 3.4 months, respectively).

In the non-laryngeal population of both FAST-3 and FAST-1, the mean number of cutaneous attacks during the six months prior to study entry was higher than the mean number of abdominal attacks, combined attacks, and laryngeal attacks. In addition, the majority of patients characterized previous attacks as moderate to severe for all attack types. The mean number of types of attacks was generally balanced across treatment groups in FAST-3. In FAST-1, the mean number of both cutaneous and abdominal attacks experienced in the last six months was higher in the icatibant group than the placebo group (7.3 versus 4.9).

In the FAST-3 non-laryngeal population, a third of patients reported prior use of C1-INH therapy in both the icatibant and placebo groups (37.2% and 31.1%). In FAST-3, approximately one-third of the patients received concomitant therapy with danazol. Two patients in the icatibant group received concomitant therapy with tranexamic acid.

In the FAST-3 laryngeal population, there were more differences between treatment groups for the patients presenting with mild to moderate laryngeal symptoms who were randomized, but this may be due to small sample sizes.

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS OF NON-LARYNGEAL ITT POPULATION

Characteristics	FAST-3		FAST-1	
	Icatibant (N = 43)	Placebo (N = 45)	Icatibant (N = 27)	Placebo (N = 29)
Mean age, years (SD)	36.1 (13.7)	36.6 (11.2)	34.8 (9.8)	34.9 (11.4)
Female sex, n (%)	27 (62.8)	29 (64.4)	16 (59.3)	21 (72.4)
Mean weight, kg (SD)	81.7 (25.1)	80.7 (20.9)	80.3 (21.1)	76.0 (21.9)
Race, n (%)				
White	38 (88.4)	40 (88.9)	25 (92.6)	25 (86.2)
Black	3 (7.0)	0	0	0
Asian	0	0	0	1 (3.4)
Other	2 (4.7)	5 (11.1)	2 (7.4)	3 (10.3)

Characteristics	FAST-3		FAST-1	
	Icatibant (N = 43)	Placebo (N = 45)	Icatibant (N = 27)	Placebo (N = 29)
Disease characteristics				
Family history of HAE, n (%)				
Yes	38 (88.4)	39 (86.7)	NR	NR
No	5 (11.6)	5 (11.1)	NR	NR
No answer	0	1 (2.2)	NR	NR
Type of HAE, n (%)				
Type I	37 (86.0)	39 (86.7)	NR	NR
Type II	6 (14.0)	6 (13.3)	NR	NR
Time since diagnosis				
Mean, years (SD)	20.2 (14.6)	18.3 (11.1)	NR	NR
Median, years (range)	15.3 (0.6, 64.7)	17.7 (0, 42.0)	NR	NR
Time since last attack				
Mean, months (SD)	4.3 (10.8)	3.4 (2.9)	NR	NR
Median, months (range)	1.8 (0.4, 71.5)	2.5 (0.1, 13.7)	NR	NR
Cutaneous attacks in the last six months				
n	43	43	20	21
Mean number (SD)	6.7 (7.7)	7.3 (11.8)	8.6 (10.2)	9.9 (12.8)
Average severity of previous cutaneous attacks				
Mild, n (%)	3 (7.0)	3 (6.7)	3 (11.1)	1 (3.4)
Moderate, n (%)	17 (39.5)	23 (51.1)	10 (37.0)	11 (37.9)
Severe, n (%)	15 (34.9)	11 (24.4)	9 (33.3)	12 (41.4)
Abdominal attacks in the last six months				
n	43	44	20	19
Mean number (SD)	4.2 (4.5)	3.8 (5.7)	5.1 (5.6)	6.8 (4.4)
Average severity of previous abdominal attacks				
Mild, n (%)	0	1 (2.2)	0	0
Moderate, n (%)	9 (20.9)	12 (26.7)	7 (25.9)	7 (24.1)
Severe, n (%)	17 (39.5)	22 (48.9)	15 (55.6)	16 (55.2)
Cutaneous and abdominal attacks in the last six months				
n	38	40	10	9
Mean number (SD)	3.6 (6.8)	3.8 (12.1)	7.3 (12.6)	4.9 (4.4)
Average severity of previous cutaneous and abdominal attacks				
Mild, n (%)	1 (2.3)	0	0	0
Moderate, n (%)	6 (14.0)	3 (6.7)	3 (11.1)	5 (17.2)
Severe, n (%)	2 (4.7)	4 (8.9)	9 (33.3)	6 (20.7)
Laryngeal attacks in the last six months				
n	38	40	6	5
Mean number (SD)	1.0 (2.3)	0.7 (1.4)	1.7 (1.2)	2.8 (3.5)
Average severity of previous laryngeal attacks				
Mild, n (%)	1 (2.3)	1 (2.2)	0	2 (6.9)
Moderate, n (%)	3 (7.0)	3 (6.7)	1 (3.7)	2 (6.9)
Severe, n (%)	10 (23.3)	8 (17.8)	6 (22.2)	5 (17.2)
Medication				
Previous use of C1-INH, n (%)				
Yes	16 (37.2)	14 (31.1)	NR	NR
No	27 (62.8)	31 (68.9)	NR	NR

Characteristics	FAST-3		FAST-1	
	Icatibant (N = 43)	Placebo (N = 45)	Icatibant (N = 27)	Placebo (N = 29)
Previous use of C1-INH within 5 days, n (%)				
Yes	1 (2.3)	1 (2.2)	NR	NR
No	41 (95.3)	41 (91.1)	NR	NR
Concomitant medications, n (%)				
Danazol	16 (37.2)	16 (35.6)	NR	NR
Tranexamic acid	2 (4.7)	0	NR	NR

C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema; NR = not reported; SD = standard deviation.
Source: Clinical Study Reports.[1,2]

TABLE 6: SUMMARY OF BASELINE CHARACTERISTICS OF LARYNGEAL POPULATION

Characteristics	FAST-3			FAST-1
	Icatibant (N = 3)	Placebo (N = 2)	OL icatibant (N = 5)	OL icatibant (N = 8)
Mean age, years (SD)	40.3 (6.7)	50.0 (22.6)	41.6 (11.8)	47.1 (13.9)
Female, n (%)	2 (66.7)	1 (50.0)	2 (40.0)	5 (62.5)
Mean weight, kg (SD)	86.6 (33.4)	70.3 (5.0)	96.9 (14.7)	92.3 (20.7)
Race, n (%)				
White	3 (100)	2 (100)	4 (80)	8 (100)
Other	0	0	1 (20)	0
Disease characteristics				
Family history of HAE, n (%)				
Yes	3 (100)	2 (100)	4 (80)	NR
No	0	0	1 (20)	NR
No answer	0	0	0	NR
Type of HAE, n (%)				
Type I	3 (100)	2 (100)	4 (80)	NR
Type II	0	0	1 (20)	NR
Time since diagnosis				
Mean, years (SD)	7.8 (10.1)	38.4 (31.2)	11.1 (7.8)	NR
Median, years (range)	3.3 (0.7, 19.4)	38.4 (16.4, 60.5)	10.3 (0.1, 21.6)	NR
Time since last attack				
Mean, months (SD)	2.3 (2.3)	6.9 (5.8)	11.6 (21.7)	NR
Median, months (range)	1.8 (0.3, 4.8)	6.9 (2.9, 11.0)	1.2 (0.5, 50.4)	NR
Medication				
Previous use of C1-INH, n (%)				
Yes	2 (66.7)	1 (50.0)	2 (40.0)	NR
No	1 (33.3)	1 (50.0)	3 (60.0)	NR
Previous use of C1-INH within five days, n (%)				
Yes	1 (33.3)	0	0	NR
No	2 (66.7)	2 (100)	5 (100)	NR

Characteristics	FAST-3			FAST-1
	Icatibant (N = 3)	Placebo (N = 2)	OL icatibant (N = 5)	OL icatibant (N = 8)
Concomitant medications, n (%)				
Danazol	0	0	3 (60.0)	NR
Tranexamic acid	0	0	0	NR

C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema; NR = not reported; OL = open label; SD = standard deviation.
Source: Clinical Study Reports.[1,2]

3.2.3 Interventions

a) First Attack

In FAST-3 and FAST-1, patients with abdominal or cutaneous symptoms judged to be of at least moderate severity were randomized in a 1:1 ratio to receive a single dose of SC icatibant 30 mg or SC placebo (Table 7). After a protocol amendment in FAST-3, patients with laryngeal symptoms judged to be of mild to moderate severity were also randomized in the same manner. Patients with laryngeal symptoms in FAST-1 and patients with severe laryngeal symptoms in FAST-3 were administered open-label treatment with SC icatibant 30 mg.

TABLE 7: TYPE OF ATTACK AND TREATMENT OF PATIENTS IN FAST-3 AND FAST-1

Type of Attack	FAST-3	FAST-1
Moderate-to-severe non-laryngeal	Randomized	Randomized
Mild laryngeal	Randomized	OL icatibant
Moderate laryngeal	Randomized	OL icatibant
Severe laryngeal	OL icatibant	OL icatibant

OL = open label.

b) Subsequent Attacks

If symptoms became worse more than 48 hours after the initial treatment, the event was to be considered a new attack. Subsequent cutaneous, abdominal, and laryngeal attacks were treated with SC icatibant 30 mg in the open-label extension phase (see APPENDIX 6: ADDITIONAL EFFICACY AND HARMS DATA FROM LONG-TERM EXTENSIONS OF INCLUDED STUDIES (FAST-3 and FAST-1)).

c) Timing of Dose

Treatment was to be administered no later than six hours after the attack had become at least moderate in severity, or mild in severity in the case of laryngeal attacks in FAST-3. In FAST-3, treatment was to be administered no more than 12 hours after the onset of the attack.

d) Concomitant Medication

The use of attenuated androgens for prophylactic treatment of HAE was permitted only if the dose was stable or decreased.

e) Rescue Medication

Rescue medication was defined as any medication that, in the opinion of the investigator, was immediately necessary to alleviate acute symptoms resulting from the current HAE attack. Rescue therapy for randomized patients was to be withheld for as long as possible, ideally for the first eight to nine hours after injection of the study drug. Rescue medications could include pain medication,

antiemetics, fresh frozen plasma, C1-INH, epinephrine, and intravenous or prescription-strength non-steroidal anti-inflammatory drugs (NSAIDs).

f) Prior Medication

In FAST-3, patients who received replacement therapy (e.g., C1-INH products, fresh frozen plasma) less than five days prior to the onset of the current attack were not initially eligible for enrolment in the study until amendment 2, which allowed for the enrolment of these patients. In FAST-3, patients who had received replacement therapy less than three days prior to the onset of any new attack were not to receive treatment with study medication for the new attack.

3.2.4 Outcomes

a) Timing of Assessments

The following visits were to occur after a patient exhibited symptoms of an acute attack.

Visit 1 (Day 1): Pre-randomization and pre-treatment assessments performed.

Visit 2 (Day 1): This visit was to take place immediately after receiving treatment. Patients were hospitalized and monitored for at least eight hours after treatment. Patients were discharged from the hospital a minimum of eight hours after treatment upon being deemed clinically stable by the investigator. In FAST-1, patients were hospitalized for up to 15 hours. Symptoms were assessed at 30-minute intervals for 4 hours after administration of study drug, and then 5, 6, 8, 10, and 12 hours after administration of study drug.

Visit 3 (days 2 to 5): This visit was to take place 24 to 48 hours after SC injection. Patients were to assess their symptoms three times daily during this period or until symptoms subsided.

Visit 4 (Day 14 ± 2): After the completion of assessments for the first attack on Visit 4, the double-blind treatment phase was to end for each patient. If a new attack occurred prior to this visit, the patient was to enter the open-label extension phase of the study, and the new attack would be assessed as Visit A1. The double-blind phase was a maximum of 14 days.

Visit 5 (Week 5 ± 1 week): Safety follow-up assessments were performed for all patients at Visit 5, and every six months following the first attack until the study ended. A safety follow-up phone call was performed every 12 weeks following the first attack, regardless of the patient's participation in the open-label extension phase.

b) Scales

Visual Analogue Scale

A VAS was used to measure symptom intensity in patients during an acute attack. The VAS consisted of a 100 mm horizontal line, with 0 mm representing "no symptom" and 100 mm representing "worst possible symptom." Patients were asked to draw a vertical line at the point along the scale representing the current status of the measured symptom. In FAST-3 and FAST-1, the symptoms measured using the VAS included skin swelling, skin pain, and abdominal pain. In FAST-3, patients with laryngeal attacks also assessed difficulty swallowing and voice change using the VAS.

Symptom Scores Assessing Interference With Daily Activities (Patient and Investigator)

A five-point scale was used to assess the severity of each symptom: 0 = none (absence of symptoms); 1 = mild (no to mild interference with daily activities); 2 = moderate (moderate interference with daily

activities); 3 = severe (severe interference with daily activities); 4 = very severe (very severe interference with daily activities). Both patients and investigators assessed the following symptoms: skin swelling, erythema, skin pain, abdominal pain, nausea, vomiting, diarrhea, difficulty swallowing, and voice change. The patient also assessed skin irritation, while the investigator also assessed abdominal tenderness, breathing difficulties, stridor, and asphyxia (Table 8).

TABLE 8: SYMPTOM SCORES

Assessed by Patient	Assessed by Investigator
Skin swelling Erythema Skin pain Abdominal pain Nausea Vomiting Diarrhea Difficulty swallowing[a] Voice change[a]	
Skin irritation	Abdominal tenderness Breathing difficulties[a] Stridor[a] Asphyxia[a]

[a] Laryngeal attacks only.

Composite Scores (FAST-3)

In FAST-3, the following composite scores were defined.

- **VAS-3:** The average of the VAS scores for three symptoms (skin swelling, skin pain, abdominal pain) for non-laryngeal attacks.
- **VAS-5:** The average of the VAS scores for five symptoms (skin swelling, skin pain, abdominal pain, difficulty swallowing, voice change) for laryngeal attacks.
- **Composite patient-assessed symptom scores:** For non-laryngeal attacks, the average of 8 patient-assessed non-laryngeal symptoms (NL-SSS-8). For laryngeal attacks, the average of 10 patient-assessed laryngeal symptoms (L-SSS-10).
- **Composite investigator-assessed symptoms scores:** For non-laryngeal attacks, the average of 8 investigator-assessed non-laryngeal symptoms (NL-ISS-8). For laryngeal attacks, the average of 13 investigator-assessed laryngeal symptoms (L-ISS-13).

Global Assessment (Investigator)

The investigator made a global assessment considering all abdominal symptoms combined, all cutaneous symptoms combined and all laryngeal symptoms combined using the same five-point scale used to score symptom severity.

Clinical Global Impression and Improvement (Patient and Investigator)

The investigator completed a clinical global impression at baseline based on a seven-point scale: 1 = normal (not at all ill); 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill patients. The patient completed a clinical global impression at baseline using a five-point scale to answer the question, “How severe do you consider this HAE attack to be?”: 1 = one of the mildest HAE attacks I have ever had; 5 = one of the most severe HAE attacks I have ever had.

On the visits following baseline in the double-blind phase of the study, global improvement was assessed by the investigator and patient using a seven-point scale: 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse.

c) Efficacy Outcomes

The outcomes of interest identified in the protocol are described subsequently. For a more detailed description of study outcomes, see APPENDIX 5: VALIDITY OF OUTCOME MEASURES.

TABLE 9: OUTCOMES IN FAST-3 AND FAST-1

FAST-3	FAST-1
• TACSR • TISI (patient and investigator) • TOSR of individual VAS scores • Change from baseline in individual VAS scores over time • Change from baseline in individual symptom scores (patient and investigator) over time • Global assessment and clinical global impression/improvement post-treatment (investigator) • Use of rescue medication	
• TOSR-P • TOSR for composite symptom scores (patient and investigator) • Change from baseline in composite VAS over time • Change from baseline in composite symptom scores (patient and investigator) over time • Time to any reduction in laryngeal VAS and symptoms scores (patient and investigator)	• Durable response to treatment

TACSR = time to almost complete symptom relief; TISI = time to initial symptom improvement; TOSR = time to onset of symptom relief; TOSR-P = time to onset of primary symptom relief; VAS = visual analogue scale.

Time to Onset of Symptom Relief

The primary efficacy end point in FAST-3 and FAST-1 was the time to onset of symptom relief (TOSR), which was defined as the time from study drug administration to the earliest of three consecutive non-missing measurements of documented symptom relief. In FAST-3, symptom relief was defined as a ≥ 50% reduction in the pre-treatment composite VAS score (VAS-3 for non-laryngeal attacks; VAS-5 for laryngeal attacks).

In FAST-1, symptom relief was defined as a reduction from the pre-treatment VAS in the primary symptom (time to onset of primary symptom relief [TOSR-P]). Symptom relief was achieved for any value to the right and below a line with the equation $y = 6 \div 7x - 16$ (x = pre-treatment VAS; y = post-treatment VAS), with $x \geq 30$ mm. This corresponds to a reduction of 30 mm from a baseline VAS of 100 mm, and a reduction of 20 mm from a baseline VAS of 30 mm. For cutaneous attacks, the primary symptom was skin swelling or skin pain, whichever was the most severe. If both skin swelling and skin pain were equally severe, skin pain was used as the primary symptom. For abdominal attacks, the primary symptom was abdominal pain. The TOSR-P was evaluated as a secondary end point in FAST-3 in the same manner as for FAST-1.

Time to Almost Complete Symptom Relief

The time to almost complete symptom relief (TACSR) was defined as the time from injection to the time of the first of three consecutive measures at which all VAS scores were less than 10 mm. For cutaneous

and abdominal attacks, the VAS score comprised skin swelling, skin pain, and abdominal pain. For laryngeal attacks, the VAS score comprised skin swelling, skin pain, abdominal pain, difficulty swallowing, and voice change. Patients who did not achieve symptom relief within the observation period were censored at the last observation time.

Time to Initial Symptom Improvement
Patients and investigators were asked to record the time at which they perceived initial improvement of symptoms. Patients were asked to provide this information as part of their patient diary, which was used to record specified outcome measures during hospitalization and at the time of discharge from the treatment centre (days 2 to 5). Patients whose symptoms did not improve within the observation period were censored at 48 hours.

Durable Response to Treatment
In FAST-1, a durable response was defined as an onset of symptom relief for the primary symptom within eight hours after treatment that lasted at least 24 hours.

d) Safety Outcomes
An adverse event was defined as any clinically relevant worsening of the signs and symptoms of a treated HAE attack. Symptoms recurring more than 48 hours after an initial attack were considered to be a new attack and were not reported as adverse events. Adverse events included worsening of conditions present at the onset of the study, intercurrent illnesses, drug interactions, abnormal laboratory values, abnormal electrocardiogram results, and clinically significant abnormalities in physical examination, vital signs, and weight. All adverse events that occurred from visit 1 to the end of study assessment were recorded, and patients were asked to report any adverse events experienced between study visits. Adverse events were monitored continuously from the time of randomization throughout the study until 14 days (± 2 days) after the patient's last dose of the study drug or until the event stabilized or resolved.

A serious adverse event was any adverse event occurring at any dose that was fatal, life-threatening, required in-patient hospitalization, prolonged existing hospitalization or resulted in persistent or significant disability or incapacity. It also included any congenital anomaly or important medical event.

3.2.5 Statistical Analysis

a) Sample Size Calculation
In FAST-3 and FAST-1, the sample size calculations included only patients who experienced abdominal or cutaneous symptoms. Patients with laryngeal symptoms did not contribute to the sample size.

In FAST-1, a sample size of 50 patients (25 patients per group) was planned to provide 80% power to detect a difference of 5.5 hours between treatment groups in time to symptom relief. A sample size of 56 patients in FAST-1 allowed for a 10% attrition rate while maintaining an evaluable 25 patients per treatment group. If the dropout rate was greater than the projected 10%, replacements were to be recruited according to the inclusion and exclusion criteria established for the study.

In FAST-3, using a log-rank test for equality of survival curve and assuming a 0.05 two-sided significant level, a sample size of 80 patients (40 patients per group) was planned to provide 80% power to detect a difference between treatment groups in time to symptom relief. A sample size of 88 patients allowed for a 10% discontinuation rate. The sample size calculation was based on the per cent of patients who did not achieve symptom relief at 1, 2, 4, 6, 12, or 24 hours after treatment in FAST-1.

b) Statistical Tests

Unless specified, the following statistical methods were used in both FAST-3 and FAST-1. In both FAST-3 and FAST-1, results for patients with laryngeal attacks were reported descriptively with no statistical comparisons.

Time-to-Event Outcomes

Time-to-event outcomes were summarized using the Kaplan-Meier method. The median time to event and corresponding sign-test based, two-sided 95% CI, as well as the number and percentage of patients achieving symptom relief, were summarized by treatment group for the non-laryngeal ITT, non-laryngeal per-protocol, ITT, and laryngeal populations.

Difference in Time to Onset of Symptom Relief Between Treatment Groups

For the primary and key secondary efficacy end points, the difference in TOSR between treatment groups was tested by the following hypothesis: H_0: $\lambda_{icatibant}/\lambda_{placebo} = 1$ versus H_1: $\lambda_{icatibant}/\lambda_{placebo} \neq 1$, where $\lambda_{icatibant}$ refers to the hazard rate under icatibant and $\lambda_{placebo}$ refers to the hazard rate under placebo. A Peto-Peto Wilcoxon test with a global two-sided significance level of 5% was used to test the null hypothesis.

To control for study-design factors, a comparison of hazard ratios for icatibant versus placebo was analyzed using a Cox proportional hazards model that included covariates for treatment and stratification factors, edema location, and previous use of C1-INH (FAST-3 only).

Individual and Composite Scores

The change from baseline in individual and composite VAS and symptom scores was analyzed using a non-parametric Wilcoxon rank-sum test without adjustment for covariates.

Rescue Medication

The proportion of patients receiving rescue medications was analyzed using the Fisher's exact test for categorical data. To evaluate the effect of using rescue medications, time to symptom relief was analyzed, censoring patients who took rescue medication before the onset of symptom relief. In FAST-3, this analysis was conducted using the non-laryngeal ITT population.

Missing Data

Missing individual VAS symptom scores were imputed. Protocol-specified assessment times with all individual symptom scores missing were excluded from the analysis (i.e., were ignored in the determination of three consecutive measurements). Patients without documented symptom relief were censored at the time of their last VAS assessment.

Multiplicity

No adjustments were made for multiple comparisons.

c) Analysis Populations

In the FAST-3 and FAST-1 studies, the following populations were defined.

First Attacks

Non-laryngeal ITT: This included all randomized patients with cutaneous or abdominal first attacks. Patients were analyzed according to their randomized treatment assignment, regardless of treatment actually received. This population was used for the primary efficacy analysis in FAST-3 and FAST-1.

Non-laryngeal per-protocol population: This included all patients in the non-laryngeal ITT population who had no major deviations from the protocol procedures and who had at least one pre-treatment VAS score of ≥ 30 mm for any symptom (FAST-3), or for the primary symptom (FAST-1). Patients had to have received treatment within six hours after the onset of moderate symptoms, but not more than 12 hours after the onset of the attack (FAST-3). This population was used as a sensitivity analysis for the primary and key secondary efficacy end points.

Laryngeal: This included all patients with laryngeal first attacks. In FAST-3, this included patients with mild to moderate laryngeal symptoms who were randomized to receive icatibant and placebo, and patients with severe laryngeal symptoms who received treatment with open-label icatibant. In FAST-1, this included all patients who received treatment with open-label icatibant due to laryngeal symptoms.

Safety

Safety: This included all patients who received the study drug. Safety analyses were performed according to the treatment patients actually received.

3.3 Patient Disposition

The disposition of patients in the double-blind phase of FAST-3 and FAST-1 is presented in Table 10 and Table 11.

Few patients discontinued the study in the double-blind phase of FAST-3 and FAST-1. In FAST-3, no patients in the icatibant group discontinued the study during the double-blind phase. Two patients randomized to the placebo group discontinued the study, one due to a fatal myocardial infarction and another due to a non-fatal myocardial infarction. In addition, one patient who received open-label icatibant for severe laryngeal attack was lost to follow-up. In FAST-1, one patient discontinued the study in the double-blind phase in the icatibant group due to an abdominal attack. One patient who received open-label icatibant withdrew consent.

TABLE 10: PATIENT DISPOSITION IN DOUBLE-BLIND PHASE

Criteria, N (%)	FAST-3		FAST-1	
	Icatibant | OL Icatibant	Placebo	Icatibant	Placebo
Screened	370		178	
Did not meet entry criteria	42		29	
No qualifying attack	230		149	
Enrolled	98		64	
	48	45	35	29
Randomized	93 (100)		56 (100)	
	46 (100)	47 (100)	27 (100)	29 (100)
Non-laryngeal attack	43 (93.5)	45 (95.7)	27 (100)	29 (100)
Cutaneous	26 (56.5)	26 (55.3)	14 (51.9)	13 (44.8)
Abdominal	17 (37.0)	19 (40.4)	13 (48.1)	16 (55.2)

Criteria, N (%)	FAST-3		FAST-1	
	Icatibant | OL Icatibant	Placebo	Icatibant	Placebo
Laryngeal attack	3 (6.5)	2 (4.3)	0	0
Discontinued from DB phase (14 days)	0	2 (4.3)	1 (3.7)	0
Medical condition	0	1 (2.1)	0	0
Death	0	1 (2.1)	0	0
Other	0	0	1 (3.7)	0
Completed DB phase	46 (100)	45 (95.7)	26 (96.3)	29 (100)
Non-laryngeal ITT	43 (93.5)	45 (95.7)	27 (100)	29 (100)
Non-laryngeal PP	40 (87.0)	42 (89.4)	24 (88.9)	27 (93.1)
Laryngeal population	3 (6.5) | 5 (100)	2 (4.3)	8 (100)	0
Safety	46 (100) | 6 (100)[a]	46 (100)[a]	27 (100)	29 (100)

DB = double blind; ITT = intention to treat; NR = not reported; OL = open label; PP = per protocol.
Source: Clinical Study Reports.[1,2]
[a] One patient classified as non-laryngeal and randomized was treated with open-label icatibant after developing severe laryngeal symptoms.

TABLE 11: PATIENT DISPOSITION OF OPEN-LABEL ICATIBANT-TREATED FIRST LARYNGEAL ATTACKS

Criteria, N (%)	FAST-3	FAST-1
	OL Icatibant (Severe Laryngeal Symptoms)[a]	OL Icatibant (All Laryngeal Symptoms)
Treated	5 (100)	8 (100)
Discontinued	1 (20)	1 (12.5)
Withdrew consent	0	1 (12.5)
Lost to follow-up	1 (20)	0

OL = open label.
Source: Clinical Study Reports.[1,2]
[a] One patient classified as non-laryngeal and randomized was treated with open-label icatibant after developing severe laryngeal symptoms.

3.4 Exposure to Study Treatments

The extent of exposure to the study drug in FAST-3 and FAST-1 is presented in Table 12 and Table 13.

In FAST-3, all patients in both the non-laryngeal and laryngeal populations received one dose of the study drug in the double-blind phase. In the non-laryngeal population, the median time from the onset of non-laryngeal first attacks until the administration of the study drug was similar between the icatibant and placebo groups (6.3 hours versus 5.5 hours). The mean and median time from the onset of first severe laryngeal attacks until the administration of open-label icatibant was shorter than for the randomized population (3.6 hours).

In FAST-1, one patient randomized to placebo received more than one dose of the study drug. This patient developed laryngeal symptoms approximately six hours after the randomized treatment for which icatibant was a permitted rescue medication and a waiver was provided to permit this additional administration. The median time from onset to treatment was determined in a post-hoc analysis by the Food and Drug Administration and was found to be longer in the placebo group compared with the icatibant group (10.0 hours versus 7.6 hours).

TABLE 12: EXTENT OF EXPOSURE OF FIRST NON-LARYNGEAL ATTACKS IN DOUBLE-BLIND PHASE; SAFETY POPULATION

	FAST-3		FAST-1	
	Icatibant (N = 46)	Placebo (N = 46)	Icatibant (N = 27)	Placebo (N = 29)
Number of doses, n (%)				
1	46 (100)	46 (100)	27 (100)	28 (96.6)
2	0	0	0	1 (3.4)
Mean time from onset to treatment, hours (SD)	6.9 (3.1)	6.1 (2.4)	NR	NR
Median time from onset to treatment, hours (range)	6.3 (2.2, 12.4)	5.5 (2, 14.0)	7.6[a]	10.0[a]

NR = not reported; SD = standard deviation.
Source: Clinical Study Reports.[1,2]
[a] Determined post hoc by the Food and Drug Administration.[3]

TABLE 13: EXTENT OF EXPOSURE OF OPEN-LABEL ICATIBANT-TREATED FIRST LARYNGEAL ATTACKS; SAFETY POPULATION

	FAST-3	FAST-1
	OL icatibant (N = 6)	OL icatibant (N = 8)
Number of doses, n (%)		
1	6 (100)	8 (100)
2	0	0
Mean time from onset to treatment, hours (SD)	3.8 (2.5)	NR
Median time from onset to treatment, hours (range)	3.6 (1.0, 7.4)	NR

NR = not reported; OL = open label; SD = standard deviation.
Source: Clinical Study Reports.[1,2]

3.5 Critical Appraisal

3.5.1 Internal Validity

- FAST-3 and FAST-1 were both randomized, placebo-controlled, double-blind trials. However, nearly all patients in the icatibant group experienced injection-site reactions compared with a much lower proportion of patients in the placebo group. This may have resulted in both the patient and investigator becoming aware of the treatment assignment, and possible bias in patient- and investigator-reported outcomes.
- Both the primary and secondary efficacy end point used patient-reported outcomes with limited validation in the context of HAE attacks. The VAS has often been used in pain studies, but not often in HAE studies. The manufacturer provided data that suggested the VAS has reasonable construct validity and discriminant validity, with a minimal clinically important difference (MCID) of 9 mm for HAE attacks. However, the manufacturer did not specify which symptoms this MCID applied to. The validity of the composite VAS outcomes used in FAST-3 is not known.
- In FAST-1, the median time from attack onset to the administration of the study drug was greater in the placebo group than the icatibant group (10.0 hours versus 7.6 hours), and was greater in the placebo group of FAST-1 compared with the placebo group of FAST-3 (10.0 hours versus 5.5 hours). As symptoms of an acute attack may resolve spontaneously over time, the later administration of placebo may have accounted for a shorter TOSR in the FAST-1 placebo group compared with the FAST-3 placebo group.

- In FAST-1, the manufacturers stated that the early use of rescue medication may have obscured the benefit of icatibant in the study. In FAST-1, 11 of the 14 patients who received rescue medication in the placebo group did so within 12 hours of receiving placebo. However, a sensitivity analysis showed the use of rescue medication had no significant impact on the primary efficacy end points. In the sensitivity analysis, patients were censored if they received rescue medication before the onset of symptom relief at the time they initiated use of rescue medication.
- Dropout rates were minimal in both FAST-3 and FAST-1 and nearly all patients received a single dose of icatibant for their first attack.
- The number of patients presenting with laryngeal attacks in FAST-3 who were randomized to icatibant and placebo were too few to make any conclusions on the effectiveness of icatibant compared with placebo. In addition, all laryngeal patients randomized to placebo were administered icatibant (one as rescue therapy, one because the patient developed laryngeal symptoms severe enough to warrant treatment with icatibant). Therefore, all results comparing icatibant with placebo in laryngeal patients must be interpreted with caution.

3.5.2 External Validity

- Because icatibant was administered by a health care professional in a hospital setting in both FAST-3 and FAST-1, the applicability of these studies to patient self-administration is limited.
- Both FAST-3 and FAST-1 were placebo-controlled studies. There are no head-to-head studies comparing icatibant to other relevant treatments for HAE (e.g., Berinert).
- Few patients from FAST-3 and FAST-1 were from Canada. The majority of patients in FAST-3 were from the United States, where different therapies are licensed for prophylaxis of HAE and treatment of acute attacks. This may have resulted in a patient population with a history of previous treatments different from what would be seen in a typical Canadian patient; however, both FAST-3 and FAST-1 had patient populations that were representative of a population with HAE, according to the clinical experts consulted for this review.
- The majority of patients enrolled in FAST-3 and FAST-1 were Caucasian, limiting the generalizability of results to other ethnic groups.
- All patients enrolled in FAST-3 and FAST-1 were adults who were at least 18 years of age, limiting the generalizability of findings to children and adolescents; however, the Health Canada–approved indication is specifically for adults.
- Composite outcomes were employed only in FAST-3 and not in FAST-1. The use of a primary symptom to define the primary efficacy end point in FAST-1 may not be a representative outcome of HAE, which is a disease that may involve several symptoms (see APPENDIX 5: VALIDITY OF OUTCOME MEASURES).
- HAE is a life-long disease with recurrent attacks. In FAST-3 and FAST-1, there was a lack of controlled data on the durability of beneficial effects beyond the first attack.
- Patients were administered icatibant in FAST-3 and FAST-1 only after their non-laryngeal symptoms became moderate to severe, limiting the generalizability of icatibant for use in pre-attack symptoms of HAE (e.g., paresthesia or erythema).
- There is a risk of off-label use of therapies as prophylaxis for HAE attacks; however, as the half-life of icatibant is too short (one hour), it is unlikely that icatibant will be used off-label as prophylaxis for HAE.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol (section 2.2, Table 3) are reported subsequently. For detailed efficacy data, see APPENDIX 4: DETAILED OUTCOME DATA.

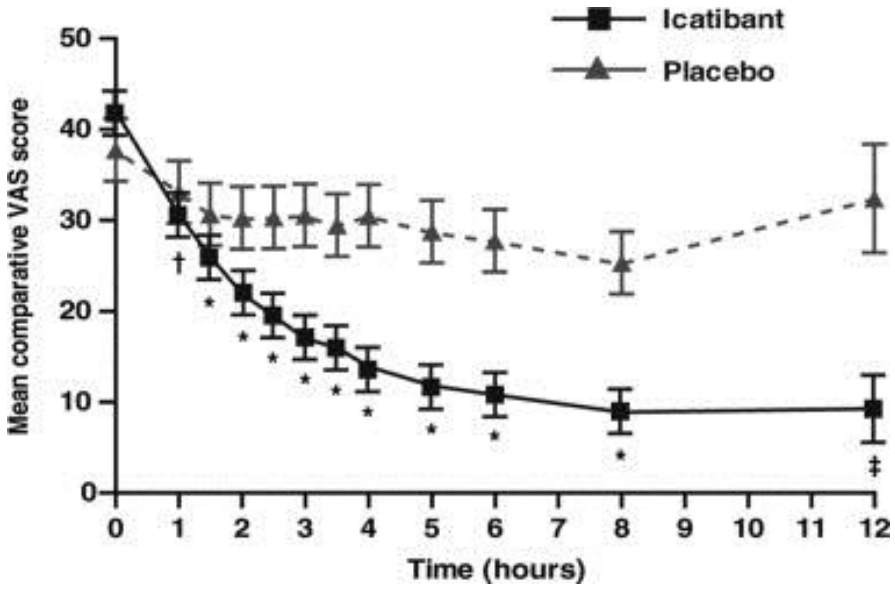
3.6.1 Non-Laryngeal Symptom Relief

a) Time to Onset of Symptom Relief

The time to onset of non-laryngeal symptom relief, defined as a 50% reduction from pre-treatment in composite VAS-3 score, was the primary efficacy end point in FAST-3 (Table 16). For the non-laryngeal ITT population, the median TOSR was statistically significantly shorter in the icatibant group compared with the placebo group (2.0 hours versus 19.8 hours, $P < 0.001$; hazard ratio 3.17 [95% CI, 1.97 to 5.11]). Similar results were seen using the non-laryngeal per-protocol population.

The reduction in mean VAS-3 score was statistically significantly greater for icatibant from one hour after treatment through eight hours after treatment (Figure 2). At eight hours post-treatment, the absolute difference in change from pre-treatment VAS between icatibant and placebo was approximately 20 mm.

FIGURE 2: MEAN COMPOSITE VAS-3 SCORE FOR THE FIRST 12 HOURS AFTER TREATMENT (NON-LARYNGEAL ITT)



Source: Lumry et al. (2011)[17]
*$P \leq 0.001$
†$P = 0.003$
‡$P = 0.041$

b) Time to Onset of Primary Symptom Relief

The TOSR-P was the key secondary end point in FAST-3 and the primary end point in FAST-1 (Table 17). For cutaneous attacks, the primary symptom was skin swelling or skin pain, whichever was the most severe symptom (skin pain was used if equally severe). For abdominal attacks, the primary symptom was abdominal pain. In FAST-3, four patients in the placebo group did not achieve symptom relief within the observation period and were censored. In FAST-3, the median TOSR-P was less statistically significantly in the icatibant group compared with the placebo group (1.5 hours versus 18.5 hours, $P < 0.001$; hazard ratio 2.76 [95% CI, 1.73 to 4.39]).

In FAST-1, one patient did not achieve symptom relief within the observation period. In FAST-1, the median TOSR-P was 2.5 hours in the icatibant group and 4.6 hours in the placebo group (hazard ratio 1.09 [95% CI, 0.57 to 2.07]). This difference was not statistically significant ($P = 0.142$).

c) Time to Almost Complete Symptom Relief

The TACSR was the earliest of three consecutive non-missing measurements for which VAS scores for all symptoms were less than 10 mm. In FAST-3 and FAST-1, a greater proportion of patients achieved almost complete symptom relief within the observational period in the icatibant group compared with the placebo group (FAST-3: 83.7% versus 68.9%; FAST-1: 88.9% versus 72.4%) (Table 18). In FAST-3, the median TACSR was statistically significantly shorter in the icatibant group compared with the placebo group (8.0 hours versus 36.0 hours; *P* = 0.012). In FAST-1, the median TACSR was shorter in the icatibant group compared with the placebo group (8.5 hours versus 23.3 hours), but this difference was not statistically significant (*P* = 0.069).

d) Time to Initial Symptom Improvement

Patients and investigators were asked to record the time at which they perceived initial improvement of symptoms. In FAST-3, patients who did not achieve symptom improvement within the observation period were censored at 48 hours. In FAST-1, investigators assessed visual symptoms only.

In FAST-3, the median time to initial symptom improvement (TISI) as assessed by the patient was statistically significantly shorter in the icatibant group compared with the placebo group (0.8 hours versus 3.5 hours; *P* < 0.001) (Table 19). The median TISI as assessed by the investigator was also statistically significantly shorter in the icatibant group compared with the placebo group (0.8 hours versus 3.4 hours; *P* < 0.001). In FAST-1, the median TISI as assessed by the patient was statistically significantly shorter in the icatibant group compared with the placebo group (0.8 hours versus 16.9 hours; *P* < 0.001). The median TISI as assessed by the investigator was 6.5 hours in the icatibant group and 14.0 hours in the placebo group. This difference was not statistically significant (*P* = 0.240).

e) Time to Onset of Symptom Relief of Individual VAS Symptoms

In FAST-3, symptom relief of individual VAS symptoms was defined as a 50% reduction from pre-treatment in the VAS score. In FAST-1, the symptom relief of individual VAS symptoms was defined as any value to the right and below a line with the equation $y = 6 \div 7x - 16$ (x = pre-treatment VAS; y = post-treatment VAS), with $x \geq 30$ mm. This corresponds to a reduction of 30 mm from a baseline VAS of 100 mm, and a reduction of 20 mm from a baseline VAS of 30 mm.

In FAST-3, the median TOSR was statistically significantly shorter in the icatibant group compared with the placebo group for skin swelling (3.0 hours versus 22.3 hours; *P* < 0.001), skin pain (2.0 hours versus 8.0 hours; *P* = 0.013), and abdominal pain (1.8 hours versus 3.5 hours; *P* = 0.007) (Table 20). In FAST-1, the median TOSR was statistically significantly shorter in the icatibant group compared with the placebo group for skin swelling (3.1 hours versus 10.2 hours; *P* = 0.039) and skin pain (1.6 hours versus 9.0 hours; *P* = 0.007). There was no statistically significant difference in the TOSR for abdominal pain (2.0 hours versus 3.3 hours; *P* = 0.056).

f) Time to Onset of Symptom Relief for Composite Symptom Scores (FAST-3)

In FAST-3, symptom relief in the non-laryngeal population according to the composite symptom scores was defined as a 50% reduction from the pre-treatment score. The TOSR for composite symptom scores was analyzed as an exploratory end point in FAST-3. The median TOSR for the composite patient-assessed symptom score was 2.0 hours in the icatibant group and 8.0 hours in the placebo group (Table 21). The median TOSR for the composite investigator-assessed symptom score was 1.6 hours in the icatibant group and not evaluable in the placebo group because less than 50% of patients achieved symptom relief. Both differences in TOSR according to composite symptom scores were statistically significantly different (*P* < 0.001).

g) Investigator Global Assessment

The investigator made a global assessment of all cutaneous symptoms combined, all abdominal symptoms combined, and all laryngeal symptoms combined using a five-point scale at pre-treatment and at specific time points post-treatment. At pre-treatment in both FAST-3 and FAST-1, a greater proportion of patients in the icatibant group had severe cutaneous symptoms than in the placebo group ([redacted]), though these differences were not statistically significant (Table 22). At four hours post-treatment in FAST-3, the distribution of cutaneous symptom-severity ratings was statistically significantly different between the icatibant and placebo groups. In FAST-1, there was no statistically significant difference between the icatibant and placebo groups in the global assessment of cutaneous symptoms at four hours post-treatment.

At four hours post-treatment in FAST-3, the distribution of abdominal symptom severity ratings at four hours post-treatment was statistically significantly different between the icatibant and placebo groups. In FAST-1, there was no statistically significant difference between the icatibant and placebo groups in the global assessment for abdominal symptoms at four hours post-treatment.

h) Clinical Global Impression and Improvement (Investigator)

Global investigator-based impressions were assessed at pre-treatment, and clinical global improvements were assessed periodically after study treatment using seven-point scales. Pre-treatment clinical global impressions were generally balanced between treatment groups in both FAST-3 and FAST-1, with the majority of patients ranked as moderately ill by the investigator (Table 24). In FAST-3, there were statistically significantly greater symptom improvements at four hours post-treatment in the icatibant group compared with the placebo group. Statistical significance was not assessed in FAST-1, but a greater number of patients exhibited symptom improvements at four hours post-treatment in the icatibant group compared with the placebo group.

3.6.2 Laryngeal Symptom Relief

In FAST-3, a total of 10 patients had a laryngeal attack. Of these, 3 patients were randomized to the icatibant group, 2 were randomized to the placebo group, and 5 received open-label icatibant for severe laryngeal symptoms.

The two patients in the placebo group also received icatibant. One patient developed laryngeal symptoms that investigators considered severe enough to warrant treatment with open-label icatibant. The other patient was treated with icatibant as a rescue medication 3.4 hours after receiving the original placebo treatment. Small sample numbers precluded a meaningful statistical comparison.

In FAST-1, eight patients received open-label icatibant for laryngeal symptoms.

a) Time to Onset of Symptom Relief

The time to onset of laryngeal symptom relief, defined as a 50% reduction from pre-treatment in composite VAS-5 score, was the primary efficacy end point in FAST-3 (Table 25). The median TOSR was 2.5 hours in the icatibant group and 3.2 hours in the placebo group. The median TOSR was 2.3 hours for the open-label icatibant group.

b) Time to Onset of Primary Symptom Relief

In FAST-3, all patients presenting with mild to moderate laryngeal symptoms who received blinded treatment achieved primary symptom relief (Table 26). The median TOSR-P was 2.5 hours in the icatibant group and 2.7 hours in the placebo group. The median TOSR was 2.3 hours for the open-label

icatibant group. In FAST-1, three patients who had a pre-treatment VAS of at least 30 mm and were included in the analysis had a median TOSR-P of 2.1 hours.

c) Time to any Reduction in Laryngeal Symptom Scores (FAST-3)

In FAST-3, the time to any reduction in laryngeal symptom scores as assessed by patients and investigators was measured. A reduction was defined as any reduction (from pre-treatment scores greater than zero) in all laryngeal symptom scores. As assessed by the patient and investigator, all patients who received blinded treatment achieved a reduction in laryngeal symptom score (Table 27). The median time to any reduction in laryngeal symptom score was 2.5 hours in the icatibant group and 3.7 hours in the placebo group, according to patient-assessed symptoms. The median time to any reduction in laryngeal symptom score was 2.5 hours in the icatibant group and 3.2 hours in the placebo group, according to investigator-assessed symptoms. For patients treated with open-label icatibant, the median time to any reduction in laryngeal symptom score was 2.2 hours as assessed by the patient, and 1.5 hours as assessed by the investigator.

d) Time to any Reduction in Laryngeal VAS-5 Scores (FAST-3)

In FAST-3, the time to any reduction in laryngeal VAS scores was measured. A reduction was defined as any reduction (from pre-treatment scores greater than zero) in all laryngeal VAS scores. Of the five patients in the laryngeal population who received blinded treatment, all patients achieved a reduction in laryngeal VAS scores (Table 28). The median time to any reduction in laryngeal VAS scores was 1.0 hours in the icatibant group and 2.7 hours in the placebo group. Two patients randomized to the placebo group received icatibant. All of the four patients who received open-label icatibant and who had pre-treatment and post-treatment scores achieved a reduction in laryngeal VAS scores. The median time to any reduction in laryngeal VAS score was 1.0 hour in the open-label icatibant group.

3.6.3 Health-Related Quality of Life

Health-related quality of life outcomes were not assessed in FAST-3. In FAST-1, a patient satisfaction questionnaire was administered to patients during the open-label extension phase (see APPENDIX 6: ADDITIONAL EFFICACY AND HARMS DATA FROM LONG-TERM EXTENSIONS OF INCLUDED STUDIES).

3.6.4 Durability of Response

In FAST-1, a durable response was defined as an onset of symptom relief for the primary symptom within eight hours after treatment that lasted at least 24 hours. In FAST-1, there was no statistically significant difference in durable response rates between the icatibant and placebo groups (51.9% versus 50.0%; P = 1.000) (Table 29).

3.6.5 Use of Rescue Medication

In FAST-3, the number and percentage of patients who received rescue medications at any time during the attack up to five days post-treatment were presented. In the non-laryngeal population, more patients required the use of rescue medication in the placebo group compared with the icatibant group (40.0% versus 7.0%) (Table 30). Eight patients in the placebo group and two patients in the icatibant group required the use of C1-INH products due to the worsening or recurrence of HAE symptoms. One additional patient in the placebo group required the infusion of fresh frozen plasma as rescue therapy. One patient in the placebo group was given open-label icatibant 2.5 hours after receiving blinded treatment due to worsening or recurrence of HAE symptoms.

In the FAST-3 laryngeal population, one patient in the icatibant group required C1-INH products and one patient in the placebo group was administered icatibant. No patients treated with open-label icatibant for laryngeal first attacks required rescue medication.

Of the non-laryngeal population in FAST-1, six patients (22.2%) in the icatibant group received rescue medication during the double-blind phase, all on the day of the administration of the study drug. Some patients required several different medications, multiple administrations, or both. In the placebo group, 15 patients (51.7%) required rescue medication in the double-blind phase of the study. Of these, 11 patients received rescue medication within 12 hours of receiving placebo. One patient in the placebo group experienced a laryngeal attack after study entry and was treated with open-label icatibant.

Of the eight patients presenting with laryngeal symptoms at baseline in FAST-1, three patients received rescue medication within 24 hours of receiving treatment with icatibant. One patient received one additional dose of icatibant, one patient received a single dose of rescue medication, and one patient received several rescue medications due to recurrent abdominal attacks.

To evaluate the effect of using rescue medications on the primary efficacy end points, post-hoc analyses were conducted in which patients were censored if they took rescue medications before the onset of symptom relief (Table 32). In FAST-3, the median TOSR was statistically significantly shorter in the icatibant group compared with the placebo group (2.0 hours versus 22.5 hours; $P < 0.001$). In FAST-1, there was still no statistically significant difference in TOSR between the icatibant and placebo groups (2.5 hours versus 5.0 hours; $P = 0.07$) when patients were censored at the time rescue medication was administered. In FAST-1, when patients who took rescue medication before the onset of symptom relief were censored at 120 hours, there was a statistically significant difference in TOSR between the icatibant and placebo groups (2.5 hours versus 9.0 hours; $P = 0.02$).

3.6.6 Additional Doses of Icatibant

In FAST-3, no patients were administered more than one dose of icatibant during the double-blind phase (i.e., for the first attack). In FAST-1, one patient randomized to placebo received more than one dose of the study drug. This patient developed laryngeal symptoms approximately six hours after the randomized treatment for which icatibant was a permitted rescue medication, and a waiver was provided to permit this additional administration.

3.6.7 Hospitalization

Hospitalization was not an outcome that was assessed in FAST-3 and FAST-1.

3.6.8 Need for Intubation (Laryngeal Attacks)

The need for intubation was not an outcome that was assessed in FAST-3 and FAST-1.

3.6.9 Death

In FAST-3, one death was reported in the placebo group. This patient died due to a myocardial infarction.

3.6.10 Subgroup Analysis

Only the subgroups of interest identified in the review protocol are reported subsequently. FAST-3 and FAST-1 did not perform subgroup analyses based on number of previous treatments and concomitant treatment with a prophylactic drug.

a) Location of Acute Attack

In FAST-3 and FAST-1, subgroup analyses were completed for the non-laryngeal ITT population according to the location of the acute attack (Table 33). For patients with cutaneous attacks in FAST-3, the median onset of symptom relief was statistically significantly shorter in the icatibant group compared with the placebo group (2.0 hours versus 23.9 hours; $P < 0.001$). For patients with abdominal attacks in FAST-3, the median onset of symptom relief was statistically significantly shorter in the icatibant group compared with the placebo group (1.5 hours versus 4.0 hours; $P < 0.003$), although this difference was not as pronounced as in the cutaneous group. For patients with cutaneous attacks in FAST-1, the medium TOSR-P was 3.4 hours in the icatibant group and 10.0 hours in the placebo group. For patients with abdominal attacks in FAST-1, the medium TOSR-P was 2.0 hours in the icatibant group and 3.0 hours in the placebo group. Neither of these differences were statistically significant.

b) Prior Use of C1 Esterase Inhibitor

After a protocol amendment in FAST-3, patients who had received C1-INH products within five days prior to the onset of the first on-study attack were permitted to enrol in the study. As only two patients had prior C1-INH use (one in each treatment group), no conclusions can be drawn from the subgroup analyses regarding prior C1-INH use (Table 34).

TABLE 14: KEY EFFICACY OUTCOMES, NON-LARYNGEAL ITT

	FAST-3		FAST-1	
	Icatibant (N = 43)	Placebo (N = 45)	Icatibant (N = 27)	Placebo (N = 29)
TOSR — VAS-3 (composite end point), primary efficacy end point (FAST-3)				
Median TOSR, hours (IQR)[a]	2.0 (1.0, 5.0)	19.8 (3.5, 37.0)	2.5 (NR)	7.0 (NR)
P value[b]	< 0.001		0.02	
Hazard ratio (95% CI)[c]	3.17 (1.97, 5.11)		NR	
TOSR-P — primary symptom VAS, primary efficacy end point (FAST-1)				
Median TOSR-P, hours (IQR)[a]	1.5 (1.0, 3.5)	18.5 (2.0, 30.9)	2.5 (1.1, 6.0)	4.6 (1.8, 10.2)
P value[b]	< 0.001		0.142	
Hazard ratio (95% CI)[c]	2.76 (1.73, 4.39)		1.09 (0.57, 2.07)	
TOSR — censoring patients who used rescue medication				
Median TOSR, hours (IQR)[a]	2.0 (1.0, 5.0)	22.5 (7.9, 36.1)	2.5	5.0
P value[b]	< 0.001		0.07	
TOSR — skin swelling VAS				
Median TOSR, hours (95% CI/IQR)[d]	3.0 (2.0, 5.0)	22.3 (12.0, 36.1)	3.1 (2.0, 10.0)	10.2 (4.0, 38.6)
P value[b]	< 0.001		0.039	
TOSR — skin pain VAS				
Median TOSR, hours (95% CI/IQR)[c]	2.0 (1.5, 2.5)	8.0 (3.0, 23.9)	1.6 (1.5, 4.0)	9.0 (3.5, 32.4)
P value[b]	0.013		0.007	
TOSR — abdominal pain VAS				
Median TOSR, hours (95% CI/IQR)[c]	1.8 (1.0, 2.5)	3.5 (2.0, 8.0)	2.0 (1.0, 3.1)	3.3 (1.5, 8.0)
***P* value[b]**	0.007		0.056	

	FAST-3		FAST-1	
	Icatibant (N = 43)	Placebo (N = 45)	Icatibant (N = 27)	Placebo (N = 29)
TACSR				
Median TACSR, hours (IQR)[a]	8.0 (2.5, 50.1)	36.0 (8.1, NE)	8.5 (2.5, 31.5)	23.3 (10.2, 55.7)
P value[b]	0.012		0.069	
TISI — patient-assessed				
Median TISI, hours (IQR)[a]	0.8 (0.4, 1.4)	3.5 (1.0, 8.3)	0.8 (0.5, 2.0)	16.9 (3.2, NE)
P value[b]	< 0.001		< 0.001	
TISI — investigator-assessed				
Median TISI, hours (IQR)[a]	0.8 (0.4, 1.8)	3.4 (1.0, 7.0)	6.5 (1.0, -)	14.0 (2.0, NE)
P value[b]	< 0.001		0.240	

CI = confidence interval; IQR = interquartile range; NE = not estimable; TACSR = time to almost complete symptom relief; TISI = time to initial symptom improvement; TOSR = time to onset of symptom relief; TOSR-P = time to onset of primary symptom relief; VAS = visual analogue scale.

[a] Derived from Kaplan-Meier estimates.

[b] Peto-Peto Wilcoxon test (FAST-3) and log-rank Wilcoxon test (FAST-1).

[c] Hazard ratio derived from Cox proportional hazards regression model with covariate adjustment for stratification factors, edema location, and previous use of C1-INH within five days.

[d] FAST-3 presented 95% CI; FAST-1 presented IQR.

3.7 Harms

Only those harms identified in the review protocol are reported subsequently (2.0 OBJECTIVES & METHODS). For detailed harms data, see APPENDIX 4: DETAILED OUTCOME DATA.

In FAST-3 and FAST-1, safety assessments during the double-blind phase were performed up until 14 days after administration of study drug.

3.7.1 Adverse Events

In FAST-3 and FAST-1, more patients experienced adverse events in the placebo group compared with the icatibant group (FAST-3: 54.3% versus 41.3%; FAST-1: 62.1% versus 40.7%). The most commonly reported adverse events included gastrointestinal disorders, general disorders, and administration-site conditions; infections and infestations; and the worsening of a current HAE attack or occurrence of a new attack.

3.7.2 Serious Adverse Events

In FAST-3, no patient reported a serious adverse event in the icatibant group. Five patients (10.9%) reported a serious adverse event in the placebo group. This included one case of myocardial infarction (fatal), one tracheostomy, two cases of worsening or recurrence of HAE, and one case of acute gastroenteritis. In FAST-1, no patient in either treatment group reported a serious adverse event.

3.7.3 Withdrawals Due to Adverse Events

In FAST-3, one patient in the placebo group discontinued from the study due to a non-fatal myocardial infarction related to underlying coronary heart disease and dyslipidemia. In FAST-1, no patients discontinued from the study due to an adverse event.

3.7.4 Mortality

In FAST-3, one death was reported in the placebo group. This patient died due to a myocardial infarction. In FAST-1, there were no deaths reported during the double-blind phase.

3.7.5 Notable Harms

Injection-site reactions were defined as local reactions occurring at the site of subcutaneous injection. In FAST-3, all patients randomized to the icatibant group experienced an injection-site reaction, compared with 58.7% of patients in the placebo group. In FAST-1, 96.3% of patients experienced an injection-site reaction, compared with 27.6% of patients in the placebo group. Symptoms at the injection site included erythema, swelling, burning, itching, a warm sensation, and skin pain, all of which were experienced in a greater number of patients in the icatibant group compared with the placebo group.

With regard to cardiovascular events, two patients in the placebo group of FAST-3 experienced a cardiac disorder. One patient experienced a myocardial infarction and another patient experienced heart palpitations. In FAST-3, one patient in the placebo group experienced hypotension.

TABLE 15: HARMS DURING THE DOUBLE-BLIND PHASE; SAFETY POPULATION

	FAST-3		FAST-1	
	Icatibant (N = 46)	Placebo (N = 46)	Icatibant (N = 27)	Placebo (N = 29)
AEs				
Patients with > 0 AEs, N (%)	19 (41.3)	25 (54.3)	11 (40.7)	18 (62.1)
Most common AEs				
Gastrointestinal disorders	6 (13.0)	3 (6.5)	1 (3.7)	5 (17.2)
General disorders and administration-site conditions	4 (8.7)	2 (4.3)	3 (11.1)	4 (13.8)
HAE attack[a]	5 (10.9)	11 (23.9)	3 (11.1)	5 (17.2)
Infections and infestations	6 (13.0)	5 (10.9)	3 (11.1)	4 (13.8)
SAEs				
Patients with > 0 SAEs, N (%)	0	5 (10.9)	0	0
WDAEs				
AEs leading to treatment withdrawal, N (%)	0	1 (2.2)	0	0
Deaths				
Number of deaths, N (%)	0	1 (2.2)	0	0
Notable harms				
Injection-site reactions	46 (100)	27 (58.7)	26 (96.3)	8 (27.6)
Erythema	45 (97.8)	12 (26.1)	26 (96.3)	4 (13.8)
Swelling	42 (91.3)	11 (23.9)	23 (85.2)	3 (10.3)
Burning	20 (43.5)	2 (4.3)	6 (22.2)	2 (6.9)
Itching	19 (41.3)	0	5 (18.5)	0
Warm sensation	24 (52.2)	1 (2.2)	18 (66.7)	1 (3.4)
Skin pain	15 (32.6)	4 (8.7)	5 (18.5)	1 (3.4)
Cardiac disorders	0	2 (4.3)	0	0
Vascular disorders	0	0	0	1 (3.4)

AE = adverse event; HAE = hereditary angioedema; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] Worsening of current attack or new attack.

4. DISCUSSION

4.1 Summary of Available Evidence

Two randomized, double-blind, placebo-controlled studies met the inclusion criteria for this systematic review. FAST-3 (N = 98) and FAST-1 (N = 64) evaluated the efficacy and safety of subcutaneous icatibant 30 mg compared with placebo in patients with type I or type II HAE who experienced an acute attack in the cutaneous, abdominal, or laryngeal areas.

Patients presenting with any laryngeal symptoms were administered open-label icatibant in FAST-1 and initially in FAST-3. After a protocol amendment in FAST-3, patients presenting with mild to moderate laryngeal symptoms were also randomized to receive icatibant or placebo.

The double-blind phase of both FAST-3 and FAST-1 encompassed the patients' first attack, which was to be treated with a single dose of icatibant. Subsequent attacks were treated in the open-label extension phase, where open-label icatibant 30 mg was administered up to a maximum of three doses at least six hours apart. See APPENDIX 6: ADDITIONAL EFFICACY AND HARMS DATA FROM LONG-TERM EXTENSIONS OF INCLUDED STUDIES (FAST-3 and FAST-1).

4.2 Interpretation of Results

4.2.1 Efficacy

a) Non-laryngeal Attacks

The results from FAST-3 and FAST-1 suggest that icatibant is effective for the treatment of non-laryngeal acute attacks in HAE, despite potential unblinding from injection-site reactions associated with icatibant. In FAST-3, the icatibant group had a statistically significantly shorter time to symptom relief end points according to composite and individual VAS scores, and investigator-assessed and patient-assessed symptom scores. In FAST-1, the icatibant group consistently had a shorter time to symptom relief end points than the placebo group, although the differences were not statistically significant.

Both FAST-3 and FAST-1 had patient populations that were representative of a population with HAE, according to the clinical experts consulted for this review. In the six months prior to study enrolment, the number of cutaneous attacks experienced by patients was higher than the number of abdominal attacks, with the number of laryngeal attacks being the most infrequent. These proportions were also reflected during the double-blind phases of FAST-3 and FAST-1, where the majority of patients' first attack were cutaneous, followed by abdominal, with very few laryngeal attacks. The effect of the concomitant administration of prophylactic medication was not analyzed in either study, even though the use of prophylactic medication was permitted if the dose at enrolment was stable or decreased. However, the proportion of patients taking danazol or tranexamic acid for prophylaxis was balanced between icatibant and placebo groups in FAST-3, with the majority of patients taking danazol. Few patients were receiving tranexamic acid as prophylaxis upon enrolment into FAST-3, but this may be due to the high proportion of patients who were in the United States, where tranexamic acid is not approved for use in patients with hereditary angioedema.[3]

Although the general study design of FAST-3 and FAST-1 is similar, both studies had different primary efficacy end points. Composite end points were employed in FAST-3 and not FAST-1. According to the manufacturer, the components of the VAS-3 (abdominal pain, skin pain, skin swelling) were specifically and consistently highlighted by patients as the most important symptoms when experiencing a non-laryngeal attack. The clinical expert consulted for this review agreed that abdominal pain, skin pain, and

skin swelling would be key symptoms for these patients; however, as the composite VAS-3 score was an average of these three symptoms, the clinical impact on the change in score would vary depending on what type of attack patients presented with. For example, a patient presenting with only abdominal symptoms who achieved symptom relief would only have an improvement in their abdominal pain symptoms and not skin swelling or pain. As there are few studies that have validated outcomes employed in HAE studies, the manufacturer attempted to validate the outcomes employed in the FAST studies. The MCID for onset of symptom relief was determined to be a 9 mm change in VAS (see APPENDIX 5: VALIDITY OF OUTCOME MEASURES), but this information came from unpublished sources that were not peer-reviewed and should be interpreted with caution. In FAST-3, the difference in the change from baseline composite VAS-3 scores between the icatibant and placebo groups was approximately 20 mm after four hours. Considering an MCID of 9 mm, this would be a clinically meaningful difference.

FAST-2 was a study with a design identical to FAST-1 that compared icatibant to tranexamic acid. In FAST-2, the TOSR-P was statistically significantly shorter in the icatibant group compared with the tranexamic acid group; however, tranexamic acid was not considered to be an appropriate comparator by the CDR review team as it is not recommended as treatment for acute attacks in HAE guidelines, and thus FAST-2 was not included in the CDR systematic review (see APPENDIX 7: SUMMARY OF A RANDOMIZED CONTROLLED TRIAL OF ICATIBANT VERSUS TRANEXAMIC ACID (FAST-2)). Fewer patients in the icatibant groups of FAST-3 and FAST-1 required rescue medication compared with placebo during the observation period and before the onset of symptom relief. Patients treated with icatibant are less likely to require rescue medication to treat their HAE attacks.

Patients were enrolled if they received the study drug within six hours of the non-laryngeal attack becoming moderate to severe and within 12 hours of the onset of the attack (FAST-3), meaning that patients could have waited several hours after symptom onset before receiving the study drug. The clinical expert consulted for this review said it is common for patients to wait several hours in the emergency room before receiving treatment; however, the median time from onset of the attack to administration of the study drug varied between the placebo groups of FAST-3 and FAST-1 (5.5 hours versus 10.0 hours). As an attack will spontaneously resolve over time, the later administration of placebo in FAST-1 could potentially have accounted for the shorter TOSR-P seen in the placebo group of FAST-1 compared with the placebo group of FAST-3.

b) Laryngeal Attacks

In FAST-3, patients presenting with mild to moderate laryngeal symptoms were randomized to icatibant and placebo after a protocol amendment early in the study. Due to the small number of randomized patients with laryngeal attacks, and the fact both patients randomized to placebo were administered icatibant, there is a lack of controlled data on the efficacy of icatibant and placebo in patients with laryngeal attacks; however, the TOSR according to the composite VAS-5 and the time to primary symptom relief for icatibant-treated laryngeal attacks were similar to that of the non-laryngeal population. Laryngeal attacks are the primary cause of mortality in HAE patients, but the impact of icatibant treatment in reducing suffocation or death in laryngeal attacks was not assessed in these studies.

c) Subsequent Attacks

Due to the recurrent nature of HAE attacks, it is important to determine the efficacy of icatibant dosing for repeated attacks. In FAST-3, efficacy results for the first five icatibant-treated attacks showed a similar time to onset of composite and primary symptom relief (see APPENDIX 6: ADDITIONAL EFFICACY

AND HARMS DATA FROM LONG-TERM EXTENSIONS OF INCLUDED STUDIES (FAST-3 and FAST-1), Table 38). In FAST-1, efficacy results for the first 10 icatibant-treated attacks also showed a similar TOSR-P (Table 39). While only a single dose was permitted during the double-blind phases of FAST-3 and FAST-1, up to three doses were permitted for subsequent attacks in the open-label extension phases. Of the 435 attacks treated with icatibant in the FAST-3 open-label extension phase, 19 (4.4%) required a second icatibant injection, and one attack required a third injection. Of the 340 attacks treated in the FAST-1 open-label extension phase, 36 (10.6%) required a second icatibant injection and 4 (1.2%) required a third icatibant injection. For the majority of attacks, it appears that a single dose of icatibant is sufficient to alleviate symptoms.

d) Self-administration

Icatibant is approved for self-administration in North America and Europe. In FAST-3 and FAST-1, patients received their icatibant injections at a clinical site by a health care professional, which provided limited information on self-administration of icatibant. EASSI was a manufacturer-funded, non-randomized, open-label study of icatibant conducted to study the safety and efficacy of self-administration of icatibant for HAE attacks (see APPENDIX 8: SUMMARY OF AN OPEN-LABEL STUDY USING SELF-ADMINISTERED ICATIBANT). In EASSI, the TOSR according to the composite VAS-3 was similar to that of FAST-3. The median time from onset of attack to icatibant administration was 5 hours, which was slightly shorter than what was observed in FAST-3 (6.3 hours) and FAST-1 (7.3 hours). Self-administration of icatibant may allow for earlier treatment of HAE attacks, which may impact the time to resolution of an attack. A prospective, observational study found that the duration of an attack was statistically significantly shorter in patients treated within one hour of attack onset compared with those treated over one hour after attack onset.[22] A potential concern with self-administration of icatibant is patients not seeking treatment from a health care professional when needed, and the need to properly educate patients on how to appropriately administer treatment. The manufacturer states that in countries where icatibant has been approved, third-party partners have been contracted to provide specially trained registered nurses to conduct in-clinic training for health care practitioners, and in-home training for patients and caregivers upon request.[20] In addition, injection-training kits containing materials and videos can be provided for use in training patients.

There is a lack of trials directly comparing icatibant to other drugs used for the treatment of HAE attacks. In Canada, plasma-derived C1 esterase inhibitor concentrate (Berinert) is the only other drug available for this indication. Berinert is indicated for the treatment of acute abdominal, facial, or laryngeal HAE attacks of moderate-to-severe intensity. The manufacturer provided a systematic review and indirect treatment comparison comparing treatment effects of icatibant with other treatments for HAE. Due to heterogeneity between studies and confounding factors, the relative efficacy of icatibant and Berinert was unclear.

The majority of patients will experience their first HAE attack in childhood or adolescence;[7,8] however, the safety and efficacy of icatibant in children and adolescents have not been evaluated as patients enrolled in FAST-3 and FAST-1 were over the age of 18 years. In addition, patients were administered icatibant in FAST-3 and FAST-1 only after their non-laryngeal symptoms became moderate to severe and, as such, icatibant is not to be injected if the patient has only pre-attack symptoms such as paresthesia or erythema, according to the Health Canada product monograph.[16]

4.2.2 Harms

The most common adverse events associated with icatibant were injection-site reactions. Almost all icatibant-treated patients experienced at least one injection-site reaction, with the most common being erythema, followed by swelling, burning, itching, a warm sensation, and skin pain. Injection-site reactions were experienced by a greater proportion of patients in the icatibant group compared with the placebo group.

Patients with evidence of coronary artery disease such as unstable angina pectoris, severe coronary heart disease, or congestive heart failure, were excluded from FAST-3 and FAST-1 due to studies in animal models that showed that bradykinin 2 receptor inhibition can reduce coronary blood flow. Since these patients were excluded from these studies, there is a lack of efficacy data in this patient population. In both FAST-3 and FAST-1, no patients experienced cardiac or vascular disorders in the icatibant groups. The Health Canada–approved product monograph includes a warning that the use of icatibant acetate in patients with acute ischemic heart disease or unstable angina pectoris could potentially lead to a decrease in coronary blood flow and a deterioration in cardiac function.[16] Post-market adverse reactions to icatibant have included one serious case each of acute myocardial infarction and chest pain.[20]

In the open-label extension phases of FAST-3 and FAST-1, there were no new safety concerns that arose from the controlled phases. As few patients required a second or third dose of icatibant for each attack, there is limited information on the safety of multiple icatibant doses per attack.

In both FAST-3 and FAST-1, increased transaminase levels (alanine transaminase and aspartate transaminase) were seen in icatibant-treated patients (data not shown), though these were not considered to be clinically significant by the investigator. During post-marketing, one case of serious alanine transaminase and aspartate transaminase increase was reported in a patient with multi-organ failure due to sepsis. As there is a lack of data on long-term harms for repeated use of icatibant, it is unclear whether liver disorders may develop as a result of continued icatibant use.

The safety and efficacy of Firazyr in children and adolescents have not been evaluated. Considering that the first clinical presentation of HAE is common during childhood or adolescence, there is a risk of off-label use in pediatric patients.

5. CONCLUSIONS

Two randomized, double-blind placebo-controlled studies evaluating the efficacy and safety of subcutaneous icatibant 30 mg compared with placebo in patients with type I or type II HAE who experienced an acute attack in the cutaneous, abdominal, or laryngeal areas were included in the systematic review. The results of the included studies suggest that icatibant is superior to placebo in reducing the TOSR in patients presenting with non-laryngeal attacks. Only one study met the primary efficacy end point of TOSR. Across both studies, the icatibant group consistently had shorter time to symptom relief outcomes than the placebo group. In one study, patients with mild to moderate laryngeal attacks were also randomized to icatibant and placebo, but the small sample sizes and the eventual use of icatibant in both laryngeal patients in the placebo group makes it difficult to draw any conclusions on the effectiveness of icatibant compared to placebo for this outcome. A manufacturer-provided systematic review and indirect comparison reported that icatibant had a similar efficacy to Berinert. However, due to the heterogeneity between study designs and outcome definitions, the results of this indirect comparison must be viewed with caution. Repeated treatment with icatibant for subsequent attacks resulted in a similar TOSR, with no new safety concerns compared with the controlled phases. Few patients required a second or third dose of icatibant for each attack. The most common harms associated with icatibant were injection-site reactions, which included erythema, swelling, burning, itching, a warm sensation, and skin pain.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CDR staff based on the input provided by patient groups. It has not been systematically reviewed. It has been reviewed by the submitting patient groups.

1. Brief Description of Patient Group(s) Supplying Input

HAE Canada is a national patient organization that provides education and support services for Canadian hereditary angioedema patients and their families. Founded in 2010, its mission is to partner with physicians, nurses, and other health care–related professionals to ensure all hereditary angioedema (HAE) patients have access to timely and appropriate treatment to improve their quality of life. HAE Canada has a membership of 207 people. HAE Canada organizes regional events, produces educational materials, works with health care providers to establish guidelines for a comprehensive standard of care, and provides individual support services to HAE patients.

HAE Canada declares that it relies on funding from pharmaceutical companies and has received unrestricted grants from CSL Behring, ViroPharma and Shire Canada. It declares no conflict of interest in the preparation of their submission.

2. Condition and Current Therapy-Related Information

Information for the submission included results of a survey to HAE Canada members (63 patients and 27 caregivers responded), a focus group of HAE patients and caregivers (four patients, one caregiver and three patients/caregivers) and one-to-one conversations with patients (including five patients with experience using Firazyr).

HAE is a rare and potentially life-threatening inherited blood disorder. People with HAE experience attacks of severe swelling that affect various body parts, including the hands, feet, face, airway (throat) and internal organs. Swelling of the throat is the most dangerous aspect of HAE because the airway can close and cause death by suffocation. Seventy-three per cent of surveyed patients reported experiencing throat swelling at some point in their lives.

Patients reported that attacks fluctuate significantly, both in frequency and severity, thereby introducing a significant element of uncertainty and risk into their daily lives. Living with unpredictable, extremely painful, and sometimes life-threatening attacks can have a significant impact on day-to-day living and quality of life for both HAE patients and their families. The most common impact of HAE cited by patients, was stress (98%). In addition, patients reported that HAE has a negative impact on the following facets of their lives: travel (89%), work or school productivity (83%), social life (78%), family life (73%), and financial situation (50%). Adverse impact on patients' financial situation, employability, and ability to plan social events were reported. Patients described HAE as a disease that affects every aspect of their lives, even when they are not experiencing an acute attack. A patient described the impact of HAE in this way: *"HAE is described by medical professionals as episodic but there is nothing episodic about living with this disease. I don't only have to deal with it when I am having an attack. I have to think about it all the time. I have to continually adjust my goals, plans, and dreams every day."*

Survey respondents reported using Berinert, danazol, tranexamic acid, and accessing Firazyr through the Special Access Programme. Berinert was a commonly used treatment among survey responders. Several patients reported high satisfaction with Berinert treatment and that it allowed them to return to work and normal social functioning. Some patients commented that Berinert's intravenous formulation is a

negative aspect of this product because of the complexities of mixing, needing a private space for administration, self-administration, and temperature-control requirements. Some patients commented that it is not always possible to administer a dose of Berinert at the first sign of an attack because of the need for a controlled setting, and they perceived that delayed administration reduces effectiveness. Difficult vein access was also cited as a significant problem in some instances. In addition to Berinert, some patients used danazol and several felt it controlled their symptoms to some degree but experienced side effects such as anxiety, depression, weight gain, mood swings, low sex drive, and excessive hair growth. Some patients reported poor responses to all of the current treatment options (Berinert, danazol, tranexamic acid).

Caregivers said that HAE has a high or very high impact on leisure activities, day-to-day family life, work or school productivity, social life, and financial situation. Because HAE is an inherited disease, many HAE patients are often also caregivers themselves, which can magnify the impact of the illness on a family.

3. Related Information About the Drug Being Reviewed

Five patients responding to the survey had experience with Firazyr, which they accessed through the Special Access Programme. Four reported a positive experience while one had a negative experience. Patients who had not tried Firazyr anticipated that Firazyr would provide a portable option for quick and simple administration during the onset of an attack. They also expressed an expectation that Firazyr could be an option for patients when other treatment options have been shown ineffective. Subcutaneous administration is expected to make administration easier for patients with poor vein access.

Patients who have used Firazyr cited its usefulness for preventing intubation and allowing adequate time for them to get to hospital for further intervention. One patient reported that "….*After I was discharged from the ICU [intensive care unit]and I needed to give myself Firazyr for the first time, I remember 30 minutes later that it was like a curtain was raised and I knew I was coming out of the attack."* Some patients expressed that Firazyr did not completely eliminate attacks, but reported symptom improvement. A patient noted: *"Firazyr slowed my attack but did not take it away completely. It obviously won't work for all of us but I think it should be an option for those that it does work for, especially for emergencies."*
Some patients reported improved work productivity and quality of life after using Firazyr.

Some patients who accessed Firazyr through the Special Access Programme expressed frustration because, when they lost access, they could not afford to purchase the product.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	July 11, 2014
Alerts:	Weekly search updates until November 19, 2014
Study Types:	Randomized controlled trials; controlled clinical trials; multicenter studies; cohort studies; cross-over studies; case control studies; comparative studies; epidemiologic studies; also costs and cost analysis studies, quality of life studies, and economic literature.
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
Line	**Strategy**
1	(Firazyr or icatibant* or hoe 140 or hoe140 or B06AC02 or Hoechst 140 or hoechst140 or JE049 or "JE 049").ti,ab,ot,sh,hw,rn,nm
2	(130308 48 4 or "130308484" or 13030848 4 or 13048 484 or 138614-30-9 or "138614309" or 13861430 9 or 138614 309 or C59-H89-N19-O13-S or UNII-7PG89G35Q7 or UNII7PG89G35Q7).rn,nm.
3	1 or 2
4	3 use pmez
5	exp *icatibant/
6	(Firazyr or icatibant* or hoe 140 or hoe140 or B06AC02 or Hoechst 140 or hoechst140 or JE049 or "JE 049").ti,ab.
7	5 or 6
8	7 use oemezd
9	4 or 8
10	exp animals/
11	exp animal experimentation/ or exp animal experiment/
12	exp models animal/
13	nonhuman/
14	exp vertebrate/ or exp vertebrates/
15	animal.po.
16	or/10-15
17	exp humans/
18	exp human experimentation/ or exp human experiment/
19	human.po.
20	or/17-19
21	16 not 20
22	9 not 21
23	22 not conference abstract.pt.
24	remove duplicates from 23

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for search:	To July 11, 2014
Keywords:	Firazyr, icatibant, HAE, angioedema
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Bas et al. (2013)[23]	Long-term extension
Malbran et al. (2014)[24]	
Maurer et al. (2013)[22]	Study design
Bouillet et al. (2011)[25]	
Bork et al. (2007)[26]	
Aberer et al. (2014)[27]	
Boccon-Gibod et al. (2012)[28]	Study design and population
Bas et al. (2010)[29]	

APPENDIX 4: DETAILED OUTCOME DATA

Non-laryngeal Symptom Relief

TABLE 16: TIME TO ONSET OF SYMPTOM RELIEF IN FAST-3 (PRIMARY END POINT) USING VAS-3; NON-LARYNGEAL ITT

	FAST-3	
	Icatibant (N = 43)	Placebo (N = 45)
Patients with pre-treatment VAS ≥ 30 mm, n (%)	43 (100)	45 (100)
Patients with symptom relief, n (%)	43 (100)	42 (93.3)
Number of censored patients[a]	0	3
Median TOSR, hours (IQR)[b]	2.0 (1.0, 5.0)	19.8 (3.5, 37.0)
Hazard ratio (95% CI)[c]	3.17 (1.97, 5.11)	
P value[c]	< 0.001	

CI = confidence interval; IQR = interquartile range; ITT = intention to treat; TOSR = time to onset of symptom relief; VAS = visual analogue scale.
Source: Clinical Study Report.[1]
[a] Patients who did not achieve symptom relief within the observation period were censored at the last observation time.
[b] Derived from Kaplan-Meier estimates.
[c] Hazard ratio and *P* value derived from Cox proportional hazards regression model with covariate adjustment for stratification factors, edema location, and previous use of C1-INH within five days.

TABLE 17: TIME TO ONSET OF PRIMARY SYMPTOM RELIEF IN FAST-3 (SECONDARY END POINT) AND FAST-1 (PRIMARY END POINT); NON-LARYNGEAL ITT

	FAST-3		FAST-1	
	Icatibant (N = 43)	Placebo (N = 45)	Icatibant (N = 27)	Placebo (N = 29)
Patients with pre-treatment VAS ≥ 30 mm, n (%)	43 (100)	45 (100)	27 (100)	28 (100)
Number of patients with symptom relief, n (%)	43 (100)	41 (91.1)	26 (96.3)	27 (96.4)
Number of censored patients[a]	0	4	1	1
Median TOSR-P, hours (IQR)[b]	1.5 (1.0, 3.5)	18.5 (2.0, 30.9)	2.5 (1.1, 6.0)	4.6 (1.8, 10.2)
P value[c]	< 0.001		0.142	
Hazard ratio (95% CI)[d]	2.76 (1.73, 4.39)		1.09 (0.57, 2.07)	
P value[d]	< 0.001		0.804	

CI = confidence interval; IQR = interquartile range; ITT = intention to treat; TOSR-P = time to onset of primary symptom relief; VAS = visual analogue scale.
Source: Clinical Study Reports.[1,2]
[a] Patients who did not achieve primary symptom relief within the observation period were censored at the last observation time.
[b] Derived from Kaplan-Meier estimates.
[c] Peto-Peto Wilcoxon test (FAST-3) and log-rank Wilcoxon test (FAST-1).
[d] Hazard ratio and *P* value derived from Cox proportional hazards regression model with covariate adjustment for stratification factors, edema location, and previous use of C1-INH (FAST-3 only) within five days.

TABLE 18: TIME TO ALMOST COMPLETE SYMPTOM RELIEF FOR ALL SYMPTOMS IN FAST-3 AND FAST-1 (SECONDARY END POINTS); NON-LARYNGEAL ITT

	FAST-3		FAST-1	
	Icatibant (N = 43)	Placebo (N = 45)	Icatibant (N = 27)	Placebo (N = 29)
Patients with almost complete symptom relief, n (%)	36 (83.7)	31 (68.9)	26 (88.9)	21 (72.4)
Number of censored patients[a]	7	14	3	8
Median TACSR, hours (IQR)[b]	8.0 (2.5, 50.1)	36.0 (8.1, -)	8.5 (2.5, 31.5)	23.3 (10.2, 55.7)
P value[c]	0.012		0.069	

IQR = interquartile range; ITT = intention to treat; TACSR = time to almost complete symptom relief.
Source: Clinical Study Reports.[1,2]
[a] Patients who did not achieve almost complete symptom relief within the observation period were censored at the last observation time.
[b] Derived from Kaplan-Meier estimates.
[c] Peto-Peto Wilcoxon test (FAST-3) and log-rank Wilcoxon test (FAST-1).

TABLE 19: TIME TO INITIAL SYMPTOM IMPROVEMENT IN FAST-3 AND FAST-1 (SECONDARY END POINTS); NON-LARYNGEAL ITT

	FAST-3		FAST-1	
	Icatibant (N = 43)	Placebo (N = 45)	Icatibant (N = 27)	Placebo (N = 29)
Patient-assessed				
Symptom improvement, n (%)	43 (100)	41 (91.1)	26 (96.3)	15 (51.7)
Number of censored patients[a]	0	4	1	14
Median TISI, hours (IQR)[b]	0.8 (0.4, 1.4)	3.5 (1.0, 8.3)	0.8 (0.5, 2.0)	16.9 (3.2, -)
P value[c]	< 0.001		< 0.001	
Investigator-assessed				
Symptom improvement, n (%)	42 (97.7)	44 (97.8)	16 (59.3)	15 (51.7)
Number of censored patients[a]	1	1	11	14
Median TISI, hours (IQR)[b]	0.8 (0.4, 1.8)	3.4 (1.0, 7.0)	6.5 (1.0, -)	14.0 (2.0, -)
P value[c]	< 0.001		0.240	

IQR = interquartile range; ITT = intention to treat; TISI = time to initial symptom improvement.
Source: Clinical Study Reports.[1,2]
[a] Patients who did not achieve symptom improvement within the observation period were censored at the last observation time.
[b] Derived from Kaplan-Meier estimates.
[c] Peto-Peto Wilcoxon test (FAST-3) and log-rank Wilcoxon test (FAST-1).

TABLE 20: TIME TO ONSET OF SYMPTOM RELIEF OF INDIVIDUAL VAS SYMPTOM SCORES IN FAST-3 (EXPLORATORY ANALYSIS) AND FAST-1 (EXPLORATORY POST-HOC ANALYSIS); NON-LARYNGEAL ITT

Symptom	FAST-3[a]		FAST-1[b]	
	Icatibant (N = 43)	Placebo (N = 45)	Icatibant (N = 27)	Placebo (N = 29)
Skin swelling				
Number of patients with symptom relief	39	38	18	19
Number of censored patients[c]	0	5	0	2
Patients with symptom relief, %	100	86.8	100	89.5
Median TOSR,[d] hours	3.0	22.3	3.1	10.2
95% CI	2.0, 5.0	12.0, 36.1	-	-
IQR	-	-	2.0, 10.0	4.0, 38.6
P value[e]	< 0.001		0.039	
Skin pain				
Number of patients with symptom relief	37	35	9	12
Number of censored patients[c]	0	2	0	1
Patients with symptom relief, %	100	94.3	100	91.7
Median TOSR,[d] hours	2.0	8.0	1.6	9.0
95% CI	1.5, 2.5	3.0, 23.9	-	-
IQR	-	-	1.5, 4.0	3.5, 32.4
P value[e]	0.013		0.007	
Abdominal pain				
Number of patients with symptom relief	30	31	15	18
Number of censored patients[c]	0	1	1	0
Patients with symptom relief, %	100	96.8	93.3	100
Median TOSR,[d] hours	1.8	3.5	2.0	3.3
95% CI	1.0, 2.5	2.0, 8.0	-	-
IQR	-	-	1.0, 3.1	1.5, 8.0
P value[e]	0.007		0.056	

CI = confidence interval; IQR = interquartile range; ITT = intention to treat; TOSR = time to onset of symptom relief.
Source: Clinical Study Reports.[1,2]

[a] Symptom relief is defined as a 50% reduction from pre-treatment in the VAS score.

[b] Symptom relief defined as any value to the right and below a line with the equation $y = 6 \div 7x - 16$ (x = pre-treatment VAS; y = post-treatment VAS), with $x \geq 30$ mm.

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

[d] Derived from Kaplan-Meier estimates.

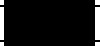
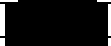
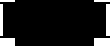
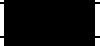
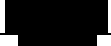
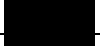
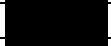
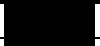
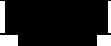
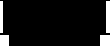
[e] Peto-Peto Wilcoxon test (FAST-3) and log-rank Wilcoxon test (FAST-1).

TABLE 21: TIME TO ONSET OF SYMPTOM RELIEF FOR COMPOSITE SYMPTOM SCORES IN FAST-3 (EXPLORATORY END POINT); NON-LARYNGEAL ITT

	FAST-3	
	Icatibant (N = 43)	Placebo (N = 45)
Patient-assessed symptom score		
Patients with symptom relief, n (%)	43 (100)	43 (95.6)
Number of censored patients[a]	0	2
Median TOSR, hours (IQR)[b]	2.0 (1.0, 3.5)	8.0 (2.5, 38.4)
P value[c]	< 0.001	
Investigator-assessed symptom score		
Patients with symptom relief, n (%)	38 (88.4)	21 (47.7)
Number of censored patients[a]	5	23
Median TOSR, hours (IQR)[b]	1.6 (1.0, 3.5)	- (2.5, -)[d]
P value[c]	< 0.001	

IQR = interquartile range; ITT = intention to treat; TOSR = time to onset of symptom relief.
Source: Clinical Study Report.[1]
[a] Patients who did not achieve symptom relief within the observation period were censored at the last observation time.
[b] Derived from Kaplan-Meier estimates.
[c] Peto-Peto Wilcoxon test (FAST-3) and log-rank Wilcoxon test (FAST-1).
[d] Not evaluable because less than 50% of patients achieved symptom relief.

TABLE 22: INVESTIGATOR GLOBAL ASSESSMENT FOR CUTANEOUS SYMPTOMS IN FAST-3 AND FAST-1 (SECONDARY END POINTS); NON-LARYNGEAL ITT

	FAST-3		FAST-1	
	Icatibant (N = 43)	Placebo (N = 45)	Icatibant (N = 27)	Placebo (N = 29)
Pre-treatment investigator global assessment, n (%)				
n				
0 Absence of symptoms				
1 Mild				
2 Moderate				
3 Severe				
4 Very severe				
P value[a]				
Investigator global assessment at four hours, n (%)				
n				
0 Absence of symptoms				
1 Mild				
2 Moderate				
3 Severe				
4 Very severe				
P value[a]				

ITT = intention to treat.
Source: Clinical Study Reports.[1,2]
[a] Fisher's exact test.

TABLE 23: INVESTIGATOR GLOBAL ASSESSMENT FOR ABDOMINAL SYMPTOMS IN FAST-3 AND FAST-1 (SECONDARY END POINTS); NON-LARYNGEAL ITT

	FAST-3		FAST-1	
	Icatibant (N = 43)	Placebo (N = 45)	Icatibant (N = 27)	Placebo (N = 29)
Pre-treatment investigator global assessment, n (%)				
n	[redacted]	[redacted]	[redacted]	[redacted]
0 Absence of symptoms	[redacted]	[redacted]	[redacted]	[redacted]
1 Mild	[redacted]	[redacted]	[redacted]	[redacted]
2 Moderate	[redacted]	[redacted]	[redacted]	[redacted]
3 Severe	[redacted]	[redacted]	[redacted]	[redacted]
4 Very severe	[redacted]	[redacted]	[redacted]	[redacted]
P value[a]	[redacted]		[redacted]	
Investigator global assessment at four hours, n (%)				
n	[redacted]	[redacted]	[redacted]	[redacted]
0 Absence of symptoms	[redacted]	[redacted]	[redacted]	[redacted]
1 Mild	[redacted]	[redacted]	[redacted]	[redacted]
2 Moderate	[redacted]	[redacted]	[redacted]	[redacted]
3 Severe	[redacted]	[redacted]	[redacted]	[redacted]
4 Very severe	[redacted]	[redacted]	[redacted]	[redacted]
P value[a]	[redacted]		[redacted]	

ITT = intention to treat.
Source: Clinical Study Reports.[1,2]
[a] Fisher's exact test.

TABLE 24: INVESTIGATOR-ASSESSED CLINICAL GLOBAL IMPRESSION/IMPROVEMENT IN FAST-3 AND FAST-1 (SECONDARY END POINTS); NON-LARYNGEAL ITT

	FAST-3		FAST-1	
	Icatibant (N = 43)	Placebo (N = 45)	Icatibant (N = 27)	Placebo (N = 29)
Pre-treatment clinical global impression, n (%)				
1 Normal, not ill	[redacted]	[redacted]	[redacted]	[redacted]
2 Borderline	[redacted]	[redacted]	[redacted]	[redacted]
3 Mildly ill	[redacted]	[redacted]	[redacted]	[redacted]
4 Moderately ill	[redacted]	[redacted]	[redacted]	[redacted]
5 Markedly ill	[redacted]	[redacted]	[redacted]	[redacted]
6 Severely ill	[redacted]	[redacted]	[redacted]	[redacted]
7 Among the most extremely ill	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]		[redacted]	
Clinical global improvement at four hours, n (%)				
1 Very much improved	[redacted]	[redacted]	[redacted]	[redacted]
2 Much improved	[redacted]	[redacted]	[redacted]	[redacted]
3 Minimal improvement	[redacted]	[redacted]	[redacted]	[redacted]
4 No change	[redacted]	[redacted]	[redacted]	[redacted]
5 Minimally worse	[redacted]	[redacted]	[redacted]	[redacted]
6 Much worse	[redacted]	[redacted]	[redacted]	[redacted]
7 Very much worse	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]		[redacted]	

ITT = intention to treat.
Source: Clinical Study Reports.[1,2]
[a] Fisher's exact test.

Laryngeal Symptom Relief

TABLE 25: TIME TO ONSET OF SYMPTOM RELIEF IN FAST-3 (PRIMARY END POINT) USING VAS-5; LARYNGEAL

	FAST-3		
	Icatibant (N = 3)	Placebo (N = 2)	OL Icatibant (N = 5)
Number of patients with symptom relief, n (%)	3	2	4[a]
Number of censored patients[b]	0	0	0
Median TOSR, hours (IQR)[c]	2.5 (1.3, 3.0)	3.2 (1.0, 5.4)	2.3 (1.6, 3.0)

IQR = interquartile range; OL = open label; TOSR = time to onset of symptom relief; VAS = visual analogue scale.
Source: Clinical Study Report.[1]
[a] One patient was excluded from analysis.
[b] Patients who did not achieve symptom relief within the observation period were censored at the last observation time.
[c] Derived from Kaplan-Meier estimates.

TABLE 26: TIME TO ONSET OF PRIMARY SYMPTOM RELIEF IN FAST-3 (SECONDARY END POINT) AND FAST-1 (PRIMARY END POINT); LARYNGEAL

	FAST-3			FAST-1
	Icatibant (N = 3)	Placebo (N = 2)	OL Icatibant (N = 5)	OL Icatibant (N = 8)
Number of patients with symptom relief, n (%)	3	2	4[a]	3[b]
Number of censored patients[c]	0	0	0	0
Median TOSR-P, hours (IQR)[d]	2.5 (1.3, 3.0)	2.7 (1.0, 4.4)	2.3 (1.8, 3.2)	2.1

IQR = interquartile range; OL = open label; TOSR-P = time to onset of primary symptom relief.
Source: Clinical Study Reports.[1,2]
[a] One patient was exclude from analysis.
[b] Number of patients with pre-treatment VAS ≥ 30 mm.
[c] Patients who did not achieve primary symptom relief within the observation period were censored at the last observation time.
[d] Derived from Kaplan-Meier estimates.

TABLE 27: TIME TO ANY REDUCTION IN LARYNGEAL SYMPTOM SCORES IN FAST-3 (SECONDARY END POINT); LARYNGEAL

	FAST-3		
	Icatibant (N = 3)	Placebo (N = 2)	OL Icatibant (N = 5)
Patient-assessed (10 symptoms)			
Patients excluded from analysis, n	0	0	2
Patients with a reduction, n	3	2	3
Number of censored patients[a]	0	0	0
Median time to reduction, hours (IQR)[b]	2.5 (1.3, 3.0)	3.7 (2.0, 5.4)	2.2 (2.1, 4.0)
Investigator-assessed (13 symptoms)			
Patients excluded from analysis, n	0	0	0
Patients with a reduction, n	3	2	5
Number of censored patients[a]	0	0	0
Median time to reduction, hours (IQR)[b]	2.5 (0.8, 3.0)	3.2 (1.0, 5.4)	1.5 (1.2, 2.6)

IQR = interquartile range; OL = open label.
Source: Clinical Study Report.[1]
[a] Patients who did not achieve reduction in laryngeal symptom scores within the observation period were censored at the last observation time.
[b] Derived from Kaplan-Meier estimates.

TABLE 28: TIME TO ANY REDUCTION IN LARYNGEAL VAS-5 SCORES IN FAST-3 (SECONDARY END POINT); LARYNGEAL

	FAST-3		
	Icatibant (N = 3)	Placebo (N = 2)	OL Icatibant (N = 5)
Patients excluded from analysis, n	0	0	1
Patients with a reduction, n	3	2	4
Number of censored patients[a]	0	0	0
Median time to reduction, hours (IQR)[b]	1.0 (1.0, 1.5)	2.7 (1.0, 4.4)	1.0 (1.0, 1.3)

IQR = interquartile range; OL = open label.
Source: Clinical Study Report.[1]
[a] Patients who did not achieve a reduction in laryngeal symptom scores within the observation period were censored at the last observation time.
[b] Derived from Kaplan-Meier estimates.

Durability of Response

TABLE 29: DURABLE RESPONSE RATES IN FAST-1 (SECONDARY END POINT); NON-LARYNGEAL ITT

	FAST-1	
	Icatibant (N = 27)	Placebo (N = 29)
Patients with pre-treatment VAS ≥ 30 mm, n (%)	27	28
Durable response, n (%)	14 (51.9)	14 (50.0)
95% CI	31.9, 71.3	30.6, 69.4
P value[a]	1.000	

CI = confidence interval; ITT = intention to treat; VAS = visual analogue scale.
Source: Clinical Study Report.[2]
[a] Fisher's exact test.

Use of Rescue Medication

TABLE 30: USE OF RESCUE MEDICATION IN FAST-3 AND FAST-1 (SECONDARY END POINTS); NON-LARYNGEAL ITT

	FAST-3		FAST-1	
	Icatibant (N = 43)	Placebo (N = 45)	Icatibant (N = 27)	Placebo (N = 29)
Rescue medication up to 120 hours post-treatment, n (%)	3 (7.0)	18 (40.0)	6 (22.2)	15 (51.7)
C1-INH products	2 (4.7)	8 (17.8)		
Rescue medication prior to onset of symptom relief, n (%)	0	16 (35.6)	NR	NR

C1-INH = C1 esterase inhibitor; NR = not reported.
Source: Clinical Study Reports.[1,2]

TABLE 31: USE OF RESCUE MEDICATION IN FAST-3 AND FAST-1 (SECONDARY END POINTS); LARYNGEAL

	FAST-3			FAST-1
	Icatibant (N = 3)	Placebo (N = 2)	OL icatibant (N = 5)	OL icatibant (N = 8)
Rescue medication up to 120 hours post-treatment, n (%)	1 (33.3)	1 (50.0)	0	3 (37.5)

OL = open label.
Source: Clinical Study Reports.[1,2]

TABLE 32: SENSITIVITY ANALYSIS FOR PRIMARY EFFICACY OUTCOMES IN FAST-3 AND FAST-1 CENSORING PATIENTS WHO USED RESCUE MEDICATIONS PRIOR TO ONSET OF SYMPTOM RELIEF; NON-LARYNGEAL ITT

	FAST-3		FAST-1	
	Icatibant (N = 43)	Placebo (N = 45)	Icatibant (N = 27)	Placebo (N = 29)
Number of patients with symptom relief, n (%)	43 (100)	29 (64.4)	24 (88.9)	17 (60.7)
Number of censored patients	0	16	3	11
Median TOSR, hours (IQR)[a]	2.0 (1.0, 5.0)	22.5 (7.9, 36.1)	2.5	5.0
P value[b]	< 0.001		0.07	

IQR = interquartile range; ITT = intention to treat; TOSR = time to onset of symptom relief.
Source: Clinical Study Reports.[1,2]
[a] Derived from Kaplan-Meier estimates.
[b] Peto-Peto Wilcoxon test.

Subgroup Analysis

TABLE 33: SUBGROUP ANALYSIS OF TIME TO ONSET OF SYMPTOM RELIEF IN FAST-3 AND FAST-1 BASED ON LOCATION OF ATTACK; NON-LARYNGEAL ITT

	FAST-3[a]		FAST-1[b]	
	Icatibant (N = 43)	Placebo (N = 45)	Icatibant (N = 27)	Placebo (N = 29)
Cutaneous attack				
Number of patients	26 (100)	26 (100)	14 (100)	13 (100)
Number of patients with symptom relief, n (%)	26 (100)	23 (88.5)	14 (100)	12 (92.3)
Number of censored patients[c]	0	3	0	1
Median TOSR, hours (IQR)[d]	2.0 (1.5, 6.0)	23.9 (8.0, 38.4)	3.4 (2.0, 10.0)	10.0 (3.5, 32.8)
P value[d]	< 0.001		0.221	
Abdominal attack				
Number of patients	17 (100)	19 (100)	13 (100)	15 (100)[e]
Number of patients with symptom relief, n (%)	17 (100)	19 (100)	12 (92.3)	15 (100)
Number of censored patients[c]	0	0	1	0
Median TOSR, hours (IQR)[d]	1.5 (1.0, 3.5)	4.0 (2.0, 31.5)	2.0 (1.0, 2.5)	3.0 (1.5, 6.0)
P value[d]	0.003		0.159	

IQR = interquartile range; ITT = intention to treat; TOSR = time to onset of symptom relief.
Source: Clinical Study Reports.[1,2]
[a] Symptom relief is defined as a 50% reduction from pre-treatment in the VAS score.
[b] Symptom relief defined as any value to the right and below a line with the equation $y = 6 \div 7x - 16$ (x = pre-treatment VAS; y = post-treatment VAS), with $x \geq 30$ mm.
[c] Patients who did not achieve primary symptom relief within the observation period were censored at the last observation time.
[d] Derived from Kaplan-Meier estimates.
[e] One patient did not have a pre-treatment VAS of ≥ 30 mm.

TABLE 34: SUBGROUP ANALYSIS OF TIME TO ONSET OF SYMPTOM RELIEF IN FAST-3 (PRIMARY END POINT) USING VAS-3 BASED ON PRIOR C1-INH USE; NON-LARYNGEAL ITT

	FAST-3	
	Icatibant (N = 43)	Placebo (N = 45)
Prior C1-INH (within five days)		
Number of patients	1	1
Patients with symptom relief	1	1
Number of censored patients	0	0
Median TOSR, hours	21.8	37.0
P value[b]	0.317	
No prior C1-INH		
Number of patients	41	41
Patients with symptom relief	41	38
Number of censored patients	0	3
Median TOSR, hours (IQR)[a]	2.0 (1.0, 4.0)	19.8 (3.6, 36.1)
P value[b]	< 0.001	

C1-INH = C1 esterase inhibitor; IQR = interquartile range; ITT = intention to treat; TOSR = time to onset of symptom relief; VAS = visual analogue scale.
Source: Clinical Study Report.[1]
[a] Derived from Kaplan-Meier estimates.
[b] Peto-Peto Wilcoxon test.

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Objective

To survey and summarize current literature describing validation of outcomes used for assessing treatment response in patients with hereditary angioedema (HAE).

Findings

Until recently, there have been very few therapeutic options to treat HAE attacks. Therefore, there are few studies that have sought to validate outcomes employed in HAE studies. Two common approaches to measuring treatment response have been time-based approaches and symptom-based approaches. Time-based approaches were used for the primary outcomes in the FAST-1 and FAST-2 studies, in which median time from treatment administration to improvement in symptoms was measured. The FAST-1 study used the concept of an index symptom, which was the symptom rated most severe at the onset of the attack. A visual analogue scale (VAS) system was used to score the single symptom. An equation was used to determine the definition of symptom relief in FAST-1, roughly equivalent to a 20 mm to 30 mm reduction on the VAS. The FAST-3 trial used a composite VAS outcome, which measured three symptoms. Symptom relief was defined as ≥ 50% reduction of the VAS composite score.

Even if comparisons are made between the FAST-1 and FAST-3 trials, significant differences are observed in the definitions of the primary outcome measures. HAE attack symptoms vary depending on the type of attack and HAE attacks may include multiple sites simultaneously. Because of the heterogeneity of HAE attacks, there are no universally accepted measures for evaluating treatment response in HAE studies. Caballero (2012) makes several observations about the challenges of standardizing and validating outcomes in HAE studies:[30]

- heterogeneity of attack location, time course and time to resolution (inter- and intra-patient)
- symptoms vary with attack location
- attack timing is unpredictable
- attack severity is likely best assessed by the patient (not a physician)
- attacks are self-limiting, therefore onset of symptom relief is an important aspect of study outcomes.

VAS techniques have been used in pain studies, but a literature search revealed there is very little research published on the use of VAS in HAE studies. A published study funded by a manufacturer of a C1 esterase inhibitor product describes the content validity of the VAS for HAE patients.[31] There were no quantitative analyses presented in the publication. Their qualitative analyses suggested that four VAS questionnaires (abdominal, oropharyngeal, peripheral, urogenital) had good content validity and were suitable for use in HAE studies. It is not clear if the same VAS scales were used in both the FAST-1 and FAST-3 trials.

The manufacturer provided unpublished data describing the analyses they performed related to validating the outcomes.[32] They reported using pooled data from both trials in their validation analyses. They made the following observations regarding the VAS and patient symptom scales used in FAST-1 and FAST-2:

- construct validity: 0.82 to 0.89 (correlation between VAS and patient symptom scores)
- discriminant validity: statistically significant differences between those experiencing a symptom and those not experiencing a symptom; $P < 0.0001$ for all VAS and symptom-severity measures
- clinical validity: statistically significant differences were noted between clinician ratings of severity in 10 out of 12 comparisons for VAS

- ability to detect change: effect sizes increase from small to moderate or large with greater clinical improvement as rated by the clinician
- test–retest reliability was difficult to assess because the patients' status changed quickly.

The manufacturer also reported the results of a study that was designed to estimate the minimum clinically important difference (MCID) in VAS scores as the basis for defining onset of symptom relief for skin swelling, skin pain, or abdominal pain in HAE patients experiencing an acute attack. The study was an observational study to evaluate the response to patient-reported reduction in symptom severity following a cutaneous or abdominal HAE attack using a VAS. Patients used a diary to complete the VAS and patient symptom scores at baseline. They also completed the VAS, patient symptom scores, and a verbal descriptor scale for skin swelling, skin pain, and abdominal pain at 12 fixed intervals for 48 hours after baseline, or until the VAS score was zero (no symptoms), whichever occurred first. The results demonstrated a 9 mm change in VAS as the MCID for onset of symptom relief using receiver operating characteristic curve analysis. This cut-point provided 88.24% specificity and 82.61% sensitivity at six hours post baseline. The manufacturer did not state whether the 9 mm figure applies to all symptoms, or only to selected symptoms of HAE attacks. Full reports were not provided; therefore, it was not possible to fully appraise the results provided.

CDR reviewers did not identify any literature that discussed the use of the VAS-3 or VAS-5 composite scales. The validity of this method of evaluating response to treatment for HAE attacks is unknown. There are some possible weaknesses inherent in these composite measures. For example, the VAS-3 was an average of the VAS scores of three symptoms (skin swelling, skin pain, abdominal pain). If a patient had an abdominal attack, the impact on score change could be different, relative to patients who have a peripheral attack.

Summary

Measuring treatment effects of HAE attacks in an objective fashion is a challenge because of the heterogeneity of the attack symptomatology. There are very few data that establish the validity of the outcomes used in the FAST-1 and FAST-3 trials, such as the VAS. The manufacturer provided summary results of some unpublished studies that were not peer-reviewed. These data suggest that the VAS has reasonable construct validity and discriminant validity, and that the minimal important difference in HAE attacks is 9 mm for the VAS. CDR reviewers were not able to perform full critical appraisal of the methods for deriving the MCID because full reports were not provided.

APPENDIX 6: ADDITIONAL EFFICACY AND HARMS DATA FROM LONG-TERM EXTENSIONS OF INCLUDED STUDIES (FAST-3 and FAST-1)

Objective

To summarize the open-label extension phases from the FAST-3 and FAST-1 studies.

Findings

In FAST-3, after the patient's first attack, they could choose to continue receiving open-label icatibant for the treatment of subsequent attacks. The treated population was used to evaluate repeated treatment with icatibant over time.

In FAST-1, patients who were screened and found to be eligible for enrolment, but either did not experience an attack or did not experience an attack severe enough to require treatment during the controlled phase, were allowed to directly enter the open-label extension (OLE) phase following closure of the controlled phase.

During the OLE phases of FAST-3 and FAST-1, a maximum of three subcutaneous injections of icatibant 30 mg, each administered at least six hours apart, could be given per attack. If symptoms became worse more than 48 hours after the initial treatment, the event was to be considered a new attack. No more than eight injections of icatibant were to be given in any four-week period.

TABLE 35: PATIENT DISPOSITION IN OPEN-LABEL EXTENSION PHASE

Criteria, N (%)	FAST-3	FAST-1
Total treated in open-label phase	82	72 (100)
From DB phase	78	52
Directly	4	20

DB = double blind.

FAST-3

In FAST-3, analyses for the patient's first five icatibant-treated attacks are summarized. The number of attacks summarized was capped at five due to the small number of patients expected to have more than five icatibant-treated attacks.

In total, 88 patients received icatibant for first attacks. This included 46 patients randomized to blinded treatment with icatibant and 36 patients who were randomized to placebo who subsequently received open-label icatibant, in addition to five patients with laryngeal first attacks treated with open-label icatibant, and one patient who developed severe laryngeal symptoms and was treated with open-label icatibant after randomization. In total, 435 attacks were treated in the open-label phase; of those, 19 attacks (4.4%) required a second icatibant injection and one attack (< 1%) required a third icatibant injection.

TABLE 36: NUMBER OF ICATIBANT-TREATED ATTACKS IN FAST-3 OPEN-LABEL EXTENSION

Attack Number	Icatibant-Treated Attack, N (%)
1	88 (100)[a]
2	70 (79.5)
3	55 (62.5)
4	37 (42.0)
5	31 (35.2)

Source: Clinical Study Report.[1]
[a] There were 46 patients treated in the double-blind phase.

TABLE 37: TYPE OF ATTACK AND EXTENT OF EXPOSURE OF ICATIBANT-TREATED ATTACKS IN FAST-3 OLE

	Attack 1 (N = 88)	Attack 2 (N = 70)	Attack 3 (N = 55)	Attack 4 (N = 37)	Attack 5 (N = 31)
Type of attack, n (%)					
Cutaneous	43 (48.9)	28 (40.0)	24 (43.6)	18 (48.6)	15 (48.4)
Abdominal	33 (37.5)	32 (45.7)	24 (43.6)	16 (43.2)	11 (35.5)
Laryngeal	11 (12.5)	10 (14.3)	7 (12.7)	3 (8.1)	5 (16.1)
Number of injections, n (%)					
1	85 (96.6)	70 (100)	51 (92.7)	36 (97.3)	31 (100)
2	2 (2.3)	0	4 (7.3)	1 (2.7)	0
3	1 (1.1)	0	0	0	0

OLE = open-label extension.
Source: Clinical Study Report.[1]

a) Time to Onset of Symptom Relief

Symptom relief was defined as a 50% reduction from pre-treatment VAS-3 for non-laryngeal attacks and VAS-5 for laryngeal attacks. Patients with all scores missing or zero at pre-treatment or all post-treatment scores missing were excluded from the analysis. In FAST-3, the median time to onset of symptom relief ranged from 1.9 hours to 2.1 hours for the first five icatibant-treated attacks (Table 38).

TABLE 38: TIME TO ONSET OF SYMPTOM RELIEF USING VAS-3 OF ICATIBANT-TREATED ATTACKS IN FAST-3 OLE

	Attack 1 (N = 88)	Attack 2 (N = 70)	Attack 3 (N = 55)	Attack 4 (N = 37)	Attack 5 (N = 31)
Patients with symptom relief, n (%)	85 (98.8)	69 (100)	55 (100)	35 (94.6)	31 (100)
Number of censored patients	1	0	0	2	0
Median TOSR, hours (IQR)[a]	2.0 (1.5, 3.5)	1.9 (1.0, 2.5)	2.0 (1.5, 3.5)	2.1 (1.5, 3.5)	2.0 (1.1, 2.5)

IQR = interquartile range; TOSR = time to onset of symptom relief; OLE = open-label extension; VAS = visual analogue scale.
Source: Clinical Study Report.[1]
[a] Derived from Kaplan-Meier estimates.

b) Time to Onset of Primary Symptom Relief

Primary symptom relief was defined as a reduction from pre-treatment in the score for a single primary VAS symptom. Symptom relief was defined as any value to the right and below a line with the equation $y = 6 \div 7x - 16$ (x = pre-treatment VAS; y = post-treatment VAS), with $x \geq 30$ mm. In FAST-3, the median

time to onset of primary symptom relief ranged from 1.5 hours to 2.0 hours for the first five icatibant-treated attacks (Table 39).

TABLE 39: TIME TO ONSET OF PRIMARY SYMPTOM RELIEF OF ICATIBANT-TREATED ATTACKS IN FAST-3 OLE

	Attack 1 (N = 88)	Attack 2 (N = 70)	Attack 3 (N = 55)	Attack 4 (N = 37)	Attack 5 (N = 31)
Patients with symptom relief, n (%)	85 (100)	67 (98.5)	54 (100)	33 (94.3)	30 (96.8)
Number of censored patients	0	1	0	2	1
Median TOSR, hours (IQR)[a]	2.0 (1.0, 3.0)	1.5 (1.0, 2.0)	2.0 (1.1, 4.0)	1.6 (1.0, 3.0)	1.5 (1.0, 2.5)

IQR = interquartile range; OLE = open-label extension; TOSR = time to onset of symptom relief.
Source: Clinical Study Report.[1]
[a] Derived from Kaplan-Meier estimates.

c) Safety

Among the first five icatibant-treated attacks, 39.8% of patients experienced at least one adverse event at the first attack, 35.7% at the second, 36.4% at the third, 21.6% at the fourth, and 22.6% at the fifth. One to two patients experienced a serious adverse event during each of the first five icatibant-treated attacks.

TABLE 40: HARMS IN FAST-3 OLE

	Attack 1 (N = 88)	Attack 2 (N = 70)	Attack 3 (N = 55)	Attack 4 (N = 37)	Attack 5 (N = 31)
AEs					
Patients with > 0 AEs, N (%)	35 (39.8)	25 (35.7)	20 (36.4)	8 (21.6)	7 (22.6)
Most common AEs (≥ 10% in at least one attack)					
Gastrointestinal disorders	11 (12.5)	1 (1.4)	0	2 (5.4)	0
HAE	7 (8.0)	3 (4.3)	7 (12.7)	1 (2.7)	0
Infections and infestations	7 (8.0)	9 (12.9)	6 (10.9)	2 (5.4)	1 (3.2)
Nervous system disorders	9 (10.2)	6 (8.6)	3 (5.5)	0	1 (3.2)
SAEs					
Patients with > 0 SAEs, N (%)	1 (1.1)	1 (1.4)	3 (5.5)	2 (5.4)	1 (3.2)
Arrhythmia	0	0	0	1 (2.7)	0
Cholecystitis	0	0	1 (1.8)	0	0
HAE	1 (1.1)	1 (1.4)	1 (1.8)	0	0
Non-cardiac chest pain	0	0	0	0	1 (3.2)
Pneumonia	0	0	1 (1.8)	0	0
Pulmonary embolism	0	0	0	1 (2.7)	0

AE = adverse event; HAE = hereditary angioedema; OLE = open-label extension; SAE = serious adverse event.
Source: Clinical Study Report.[1]

FAST-1

Results presented for attack 1 are from patients who experienced their first icatibant-treated attack in the OLE phase only. Other patients would have experienced their first treated attack during the double-blind phase.

In total, 340 attacks were treated in the FAST-1 OLE phase; of those, 36 (10.6%) required a second icatibant injection and 4 (1.2%) required a third icatibant injection. Of the 40 attacks that required additional icatibant injections, there were 12 cutaneous attacks, 23 abdominal attacks, and 5 laryngeal attacks. A summary of the extent of exposure of the first 10 attacks is presented in Table 41.

TABLE 41: EXTENT OF EXPOSURE OF THE FIRST 10 ICATIBANT-TREATED ATTACKS IN THE FAST-1 OLE

Attack Number	Number of Patients	One Icatibant Injection, n (%)	Two Icatibant Injections, n (%)	Three Icatibant Injections, n (%)
1	20	19 (95.0)	1 (5.0)	0
2	63	58 (92.1)	4 (6.3)	1 (1.6)
3	45	40 (88.9)	4 (8.9)	0
4	38	36 (94.7)	2 (5.3)	0
5	29	23 (79.3)	5 (17.2)	1 (3.4)
6	23	18 (78.3)	5 (21.7)	0
7	18	15 (83.3)	3 (16.7)	0
8	16	13 (81.25)	1 (6.25)	2 (12.5)
9	15	14 (93.3)	1 (6.7)	0
10	14	12 (85.7)	2 (14.3)	0

OLE = open-label extension.
Source: Clinical Study Report.[33]

a) Time to Onset of Primary Symptom Relief

Primary symptom relief was defined as a reduction from pre-treatment in the score for a single primary VAS symptom. Symptom relief was defined as any value to the right and below a line with the equation $y = 6 \div 7x - 16$ (x = pre-treatment VAS; y = post-treatment VAS), with $x \geq 30$ mm. In FAST-1, the median time to onset of primary symptom relief ranged from 1.0 hours to 2.0 hours for the first 10 icatibant-treated attacks (Table 42).

TABLE 42: TIME TO ONSET OF PRIMARY SYMPTOM RELIEF IN THE FAST-1 OLE PHASE

Attack Number	Icatibant-Treated Attacks[a]	Number of Censored Patients	Percentage of Patients With Symptom Relief	Median TOSR-P (95% CI)
1	11	1	90.9	1.0 (1.0, 2.5)
2	48	1	97.9	2.0 (1.5, 2.5)
3	36	0	100	1.8 (1.0, 2.5)
4	31	4	87.1	1.5 (1.0, 2.5)
5	21	2	90.5	1.3 (1.0, 2.0)
6	19	3	84.2	1.5 (1.0, 2.3)
7	16	3	81.3	1.5 (1.0, 3.6)
8	14	3	78.6	1.2 (1.0, 2.5)
9	12	2	83.3	1.3 (1.0, 2.0)
10	11	1	90.9	1.5 (1.0, 9.0)

CI = confidence interval; OLE = open-label extension; TOSR-P = time to onset of primary symptom relief.
Source: Clinical Study Report.[33]
[a] Number of patients with pre-treatment VAS ≥ 30 mm.

b) Rescue Medication

A total of 17 patients (23.6%) took rescue medication during the OLE phase. Fourteen patients received rescue medication for 18 attacks treated with icatibant. Of the 18 attacks treated with both icatibant and rescue medication, there were 9 abdominal, 7 cutaneous, and 2 laryngeal attacks.

c) Patient Satisfaction

A questionnaire was administered to patients at Week 24 of the FAST-1 OLE phase (Table 43). Of the 72 patients in the OLE phase, 53 responded to the questionnaire. The majority of patients (94.3%) were more satisfied or much more satisfied when asked how satisfied they were with icatibant for relieving symptoms compared with their usual treatment. When asked how likely they were to continue using icatibant after the study finishes, 69.8% responded that they would definitely use it.

TABLE 43: PATIENT SATISFACTION IN THE FAST-1 OLE PHASE AT WEEK 24

	Icatibant (N = 53), N (%)
How satisfied are you with the way this medication relieves your symptoms compared with your usual treatment for an HAE attack?	
Much less satisfied	0
Less satisfied	2 (3.8)
Equally satisfied	1 (1.9)
More satisfied	19 (35.8)
Much more satisfied	31 (58.5)
How bothersome is it for you to receive this medication compared with your usual treatment for an HAE attack?	
Much more bothersome	4 (7.5)
More bothersome	12 (22.6)
Equally bothersome	7 (13.2)
Less bothersome	15 (28.3)
Much less bothersome	15 (28.3)
To what degree would you prefer to self-administer the medication at home?	
Definitely prefer it	38 (71.7)
Somewhat prefer it	4 (7.5)
Makes no difference	1 (1.9)
Somewhat prefer not to	2 (3.8)
Definitely prefer not to	8 (15.1)
Overall, how satisfied are you with this medication compared with your usual treatment for an HAE attack?	
Much less satisfied	1 (1.9)
Less satisfied	3 (5.7)
Equally satisfied	3 (5.7)
More satisfied	18 (34.0)
Much more satisfied	28 (52.8)
How likely is it that you will continue to use this medication after the study finishes?	
Definitely use it	37 (69.8)
Very likely	10 (18.9)
Somewhat likely	4 (7.5)
Not sure	1 (1.9)
Somewhat unlikely	0
Very unlikely	0
Definitely not use it	1 (1.9)

OLE = open-label extension; HAE = hereditary angioedema.

d) Safety

During the FAST-1 OLE phase, 81.9% of patients experienced at least one adverse event and 4.2% of patients experienced at least one serious adverse event. Almost all patients experienced an injection-site reaction (97.2%).

TABLE 44: HARMS IN FAST-1 OLE PHASE

	Icatibant (N = 72)
AEs	
Patients with > 0 AEs, N (%)	59 (81.9)
Most common AEs (≥ 10%)	
General disorders and administration-site conditions	15 (20.8)
HAE	23 (31.9)
Infections and infestations	27 (37.5)
Investigations	8 (11.1)
Nervous system disorders	16 (22.2)
SAEs	
Patients with > 0 SAEs, N (%)	3 (4.2)
Notable harms	
Injection-site reactions, N (%)	70 (97.2)
Erythema	70 (97.2)
Swelling	66 (91.7)
Burning	21 (29.2)
Itching	22 (30.6)
Warm sensation	37 (51.4)
Skin pain	15 (20.8)

AE = adverse event; HAE = hereditary angioedema; OLE = open-label extension; SAE = serious adverse event.
Source: Clinical Study Report.[33]

Summary

Icatibant demonstrated consistent efficacy across repeated treatment of acute HAE attacks. The majority of patients only required a single dose of icatibant for each acute attack. In FAST-3, the median time to onset of symptom relief according to the composite VAS scores was similar across all attacks. In FAST-3 and FAST-1, the time to onset of primary symptom relief was also similar across subsequent attacks. No new safety concerns arose during the OLE phases.

APPENDIX 7: SUMMARY OF A RANDOMIZED CONTROLLED TRIAL OF ICATIBANT VERSUS TRANEXAMIC ACID (FAST-2)

Objective

To summarize the results of the double-blind phase of FAST-2, a randomized controlled trial that compared icatibant to tranexamic acid.[18,34]

Findings

A summary of study characteristics and findings from FAST-2 is presented in Table 45.

TABLE 45: SUMMARY OF FAST-2

Design	DB RCT, parallel group; patients with laryngeal symptoms received OL icatibant
Population	Adults with HAE type 1 or 2, N = 74 randomized
Interventions	Subcutaneous icatibant 30 mg (N = 36) versus oral tranexamic acid 1,000 mg t.i.d. × 2 days (N = 38); open-label icatibant for laryngeal symptoms (N = 3)
Duration of double-blind phase	Treatment of a single HAE attack
Follow-up period	14 days after attack
N (%) male	27 (37)
Mean age (SD)	41 (13)
Mean number of attacks during previous six months, n (SD)	Cutaneous: • Icatibant: 7.4 (6.3) • Tranexamic acid: 7.9 (6.5) Abdominal: • Icatibant: 4.2 (3.8) • Tranexamic acid: 8.7 (18) Laryngeal: • Icatibant: 2.4 (1.9) • Tranexamic acid: 2.2 (2.0)
Years study performed	2005–2006
Clinical sites	31 sites in Europe and Israel
Primary outcome	Time to onset of symptom relief (VAS). For cutaneous attacks, swelling or skin pain was used. For abdominal attacks, abdominal pain was used.
Patients experiencing a cutaneous attack during the trial, n (%)	47 (64)
Patients experiencing an abdominal attack during the trial, n (%)	27 (36)
Patients who took C1-INH during the study for rescue or prophylaxis, n (%)	Icatibant: 11 (31) Tranexamic acid: 4 (11) Laryngeal attack patients: 0
Results of primary outcome: median time to onset of symptom relief (IQR)	Icatibant: 2.0 hours (1.0–3.5) Tranexamic acid: 12.0 hours (3.5–25.4); $P < 0.001$
Results: median time to almost complete symptom relief (IQR)	Icatibant: 10.0 hours (2.8–23.2) Tranexamic acid: 51.0 hours (12.0–79.5); $P < 0.001$

Incidence of SAEs, n (%)	Icatibant: 3 (8%) (severe laryngeal HAE attack, cystitis, gastroenteritis with hypertensive crisis) Tranexamic acid: 1 (3%) (death due to aortic valve stenosis)
Incidence of AEs, n (%)	Icatibant: 18 (50%) Tranexamic acid: 14 (37%)
Worsening of HAE symptoms, n (%)	Icatibant: 5 (14%) Tranexamic acid: 7 (18%)

AE = adverse event; C1-INH = C1 esterase inhibitor; DB = double blind; HAE = hereditary angioedema; IQR = interquartile range; OL = open label; RCT = randomized controlled trial; SAE = severe adverse event; SD = standard deviation; t.i.d. = three times daily; VAS = visual analogue scale.

Some patient and study characteristics appeared to be different in FAST-2 compared with the FAST-1 and FAST-3 trials. Patients were slightly older in FAST-2 than in FAST-1 and FAST-3. In FAST-2, the majority of attacks were cutaneous attacks (64%), whereas in FAST-1 and FAST-3, a smaller proportion of the attacks were cutaneous.

The primary outcome was assessed for a single primary symptom: cutaneous swelling, cutaneous pain, or abdominal pain. The VAS reduction associated with symptom relief had to be 30% (i.e., 30 mm change on a baseline VAS of 100 mm). This was similar to the primary end point definition for the FAST-1 study. The results for the primary outcome were statistically significant in favour of icatibant.

Significant numbers of patients used C1 esterase inhibitor treatment during the study. More patients used this treatment in the icatibant group, compared with the tranexamic acid group. This may have biased the results in favour of the icatibant group.

Summary

The FAST-2 study was performed in 2005–2006 and tranexamic acid was selected as a comparator drug. The use of tranexamic acid was not well justified by the FAST-2 investigators.[18] Tranexamic acid for treatment of HAE attacks is not recommended in any current guidelines. Two Canadian clinical experts consulted for this review stated this drug is not an appropriate comparator for icatibant. The results for the primary outcome were statistically significant in favour of icatibant, but the chosen comparator has no place in the current treatment paradigms; therefore, the results have limited usefulness for understanding the effects of icatibant relative to appropriate comparators.

APPENDIX 8: SUMMARY OF AN OPEN-LABEL STUDY USING SELF-ADMINISTERED ICATIBANT

Objective

To summarize the results of the EASSI (Evaluation of the Safety of Self-administration with Icatibant) study. In this manufacturer-funded, non-randomized, open-label study of icatibant, patients were permitted to self-administer the drug (study JE049-3101C).[27,35]

Findings

A summary of the study characteristics and findings from EASSI is presented in Table 46. A total of 151 adults were enrolled in the study and given training in self-administration; 104 patients were treated at least once during the study for an attack. Non-naive patients were to self-administer icatibant for their first on-study icatibant-treated hereditary angioedema (HAE) attack, while naive patients were to have the first HAE attack treated at the clinical site and self-administer icatibant for a subsequent HAE attack. There were 22 patients who had not previously used icatibant and thus received icatibant from a health care professional for a first attack and were trained in self-administration. Subsequently, 19 out of 22 patients from this previously naive cohort joined 78 non-naive patients, forming the self-administration cohort who self-administered icatibant during the study (N = 97). Self-administered icatibant consisted of a single dose for 90 of 97 patients (92.8%); 5 patients returned to the site for a second injection, while 2 patients used commercial icatibant as rescue medication.

TABLE 46: SUMMARY OF THE EVALUATION OF THE SAFETY OF SELF-ADMINISTRATION WITH ICATIBANT STUDY

Study locations	Argentina, Europe, Israel
Main objective	To study the safety of self treatment with icatibant for HAE attacks
Secondary objective	To determine local tolerability, convenience, efficacy
Dose of icatibant used	Single 30 mg subcutaneous dose. Up to 2 additional doses could be given within 6 to 48 hours after the first dose, with ≥ 6 hours between subsequent injections
Population that self-administered icatibant	N = 97
Mean age, years (SD)	41 (14)
% male	34%
Concomitant medications, n (%)	Danazol, 27 (28%); tranexamic acid, 3 (3%)
Patients with ≥ 1 laryngeal attack in prior 6 mos, n (%)	23 (23%)
Patients with 1–5 cutaneous attacks in prior 6 mos, n (%)	38 (39%)
Patients with 1–5 abdominal attacks in prior 6 mos, n (%)	39 (40%)
Median (range) time from attack onset to icatibant administration (first dose), hours	5 (0–47)
Median (range) time from attack onset to icatibant administration (second dose, 7 patients), hours	24 (10–51)
Patients who found self-administration preferable to clinic administration, n (%)	89 (92%)
Patients reporting laryngeal symptoms, n (%)	2 (%)
Patients reporting adverse events, n (%)	33 (34%)

Patients who reported the AE of worsening HAE, n (%)	22 (23%)
Median (range) time from icatibant administration to worsening or recurrence of HAE symptoms, hours	14 (0.5–27)
Patients who returned to physician after self-administration for additional icatibant, n (%)	5 (5%)
C1-inhibitor used as rescue medication, n (%)	7 (9%)
Efficacy after self-administration (all patients had tried icatibant on at least one prior occasion)	
Median time to onset of symptom relief (using VAS 3)	3.8 hours
Patients who considered attack resolved at 48 hours, n (%)	75 (77%)

AE = adverse event; HAE = hereditary angioedema; mos = months; SD = standard deviation.

The only AE that occurred in at least 10% of patients overall was worsening or recurrence of HAE, reported in 22 (23%) patients. Other AEs were comparatively uncommon. Overall, in the self-administration phase these were: headache, experienced by three patients (one severe, one moderate, and one mild event) and abdominal pain, experienced by two patients (one severe event and one moderate event). There were no deaths or SAEs reported in patients who received icatibant.

After self-administration, 22 out of 97 patients (23%) experienced worsening or recurrence of HAE symptoms. The majority of patients with worsening or recurrence did not return to the study site for assessment. The reasons for returning to the study site were persistent (N = 2), worsening (N = 2), or new HAE symptoms (N = 3); all of these events were treated with a second icatibant injection (administered by a health care professional); no attacks required a third injection.[27]

Ninety-four of the 97 patients who self-treated with icatibant had at least one injection-site reaction (self-assessment). Among non-naive patients, the severity of most local reactions at the injection site by two hours post-dose was mild or moderate, with the following exceptions: three patients with severe skin redness, two patients with severe swelling, one patient with severe itching, and two patients with a severe warm sensation. The severity of symptoms at the injection site decreased over time and, by 10 hours, no patients had any symptoms considered severe. Recurrences of swelling, burning, and itching were each observed in one patient at 36 hours post-dose. Among naive patients, severe skin redness and severe swelling were each observed in one patient at one hour post-dose; other symptoms at the injection site were mild or moderate. At 48 hours post-dose, approximately 20% of patients still had injection-site reactions present, as assessed by the investigator.

Seventeen (17.5%) patients who self-administered icatibant used rescue medication, and rescue medication was used by 13 of the 22 (59.1%) patients who experienced worsening or recurrence of HAE after self-administration. Commonly used medications were palliative drugs for either pain (ibuprofen, paracetamol, metamizole sodium, diclofenac) or gastrointestinal symptoms (metoclopramide, buscopan plus, hyoscine). Other rescue medications included C1-INH in six patients, and icatibant in three patients.

Summary

Icatibant is approved for self-administration in North America and Europe and the primary objective of the EASSI trial was to examine the safety of icatibant self-administration. The rate of adverse events (other than HAE symptoms) was low; however, 23% of patients reported worsening or recurrence of HAE symptoms. It is not known whether these symptoms represented a new attack, or worsening of the

original attack. Icatibant has a short half-life (one to two hours) and it is hypothesized that this may explain the worsening of symptoms in some patients during the follow-up period.[27] The authors of the EASSI publication suggest that in real-world usage, around 15% of patients who use icatibant will require some form of follow-up treatment, including additional icatibant therapy or other therapies.[27]
Patient satisfaction was higher for icatibant self-administration, relative to having the drug administered in the clinic. Efficacy evaluation was not the primary objective of this study; nevertheless, the outcome "median time to onset of symptom relief" in EASSI was defined similarly in FAST-3 and the results were similar between the trials (EASSI: 3.8 hours; FAST-3: 2.0 hours).

APPENDIX 9: SUMMARY OF MANUFACTURER-SUBMITTED INDIRECT COMPARISON

Objective

The objective of this review is to summarize the methods and results, and to conduct a critical appraisal of the manufacturer-provided systematic review[36] and indirect treatment comparison,[37] comparing the treatment effects of icatibant with other treatments.

Summary of Analysis

Rationale

The manufacturer indicated that the systematic review and indirect comparison was undertaken to estimate the relative efficacy of icatibant to Berinert and to provide inputs to the cost-effectiveness model. There are no trials that compare icatibant to Berinert directly.

Methods

a) Eligibility Criteria

To be eligible for inclusion in the primary analysis of the systematic review, studies had to include patients with hereditary angioedema (type I or II) and must be randomized controlled trials (RCTs) comparing icatibant directly with the comparators, and studies comparing icatibant or a comparator with a common control or placebo. There were three icatibant trials and one Berinert trial that met the inclusion criteria for the indirect comparison.

b) Intervention and Comparators

The included treatment comparators were C1 esterase inhibitors (Berinert and Cinryze), ecallantide, recombinant human C1 esterase inhibitor (Ruconest) and tranexamic acid. The doses had to have been at a licensed dose, or a dose expected to be used in clinical practice.

While several comparators were selected by the manufacturer in their analyses, the focus of this summary and critical appraisal will be the comparison between icatibant and the approved dose of Berinert (20 IU/kg).

c) Outcomes

The outcomes of interest for the manufacturer's analyses were mortality, symptom relief (time to onset and proportion of patients, using the VAS), C1 esterase inhibitor level and activity, symptom improvement, and physician global assessment. However, the main outcome of interest for the manufacturer was time to onset of symptom relief and the other outcomes were not reported.

Sources of Results From the Icatibant Trials and the Berinert Trial

The manufacturer attempted to obtain hazard ratios for the time to onset of symptom relief data because they stated it would be inappropriate to compare median time to onset of symptom relief between the icatibant and Berinert trials. These hazard ratios were readily available from the manufacturer's databases for icatibant, but were not available from the Berinert publication. Therefore, the manufacturer derived the hazard ratios using a published method for visualization of the Kaplan-Meier plots from the Berinert publication.

Analysis

The manufacturer did not perform a study-quality assessment of the included trials.

Indirect comparisons were undertaken using the Bucher method, in which the common comparator (placebo) is used to statistically link the competing treatments. The complexities in this comparison stem from the different outcome definitions used in the icatibant and Berinert trials.

From the icatibant trials, the manufacturer extracted three outcomes related to the onset of symptom relief:

A. Time to onset of primary symptom relief
B. Time to initial symptom improvement assessed by patient
C. Time to onset of symptom relief based on composite VAS score.

The manufacturer selected outcome definition A to compare with the outcome reported in the Berinert trial. In the Berinert trial, it was defined as, "Time from the start of treatment to the onset of relief of symptoms (acute abdominal or facial hereditary angioedema [HAE] attacks) (as) determined by patient responses to a standard question posed at appropriate time intervals for as long as 24 hours after the start of treatment."

In the icatibant trials, there were three different types of analysis to adjust for the use of rescue medication. In the Berinert publication, the author performed two analyses that corresponded to two out of three methods from the icatibant trials.

TABLE 47: INCLUDED TRIALS AND VOLUME OF RESULTS GENERATED TO INFORM THE INDIRECT COMPARISON

Trials With Icatibant Versus Placebo (or Tranexamic Acid in FAST-2)		Trials With Berinert Versus Placebo	
Combinations of Trial Analyses Used in the Indirect Comparison	**Number of Hazard Ratios Generated for Icatibant 30 mg Versus Placebo**	**Trial Used for the Indirect Comparison**	**Number of Hazard Ratios Generated for Berinert 20 IU Versus Placebo**
FAST-1	45	Impact-1	3
FAST-2			
FAST-3			
FAST-1 and FAST-3 meta-analysis			
FAST-1, FAST-2 and FAST-3 meta-analysis			

IU = international units.

Therefore, for the outcome of onset of symptom relief, there were 45 hazard ratios produced for icatibant versus placebo. The large number of hazard ratios produced is because of the five different study combinations, three end point definitions, and three censoring methods. There were only three hazard ratios for Berinert 20 IU/kg versus placebo from one study.

Results

a) Patient Characteristics

The three icatibant RCTs and one Berinert RCT represented 361 patients. The number of patients per study group ranged from 27 to 47. All four studies used placebo as a comparator except for the FAST-2

study, which used tranexamic acid as a comparator. All four studies used double-blind methodology. All trials were designed to study the impact of treatment on one attack.

There was heterogeneity among the patient populations enrolled in the trials. There were variations in mean age, gender proportion, and type of index attack (cutaneous or abdominal), and the trial sites were located in North America, South America, Europe, Asia, and Australia.

b) Results of the Indirect Comparison

The manufacturer presented the results for the indirect comparison of icatibant versus Berinert 20 IU/kg in the form of hazard ratios and 95% confidence intervals. There were 45 hazard ratios presented for this comparison based on the five different study combinations, three end point definitions and three censoring methods. The manufacturer took these 45 indirect comparison hazard ratios and summarized them (Table 48).

Table 48 presents the number of hazard ratios that were above a value of 1 (favouring icatibant) and below 1 (favouring Berinert), as well as the mean of all hazard-ratio estimates and the number of comparisons in which icatibant was significantly more or less effective (i.e., where the 95% confidence intervals [CIs] for the hazard ratio did not encompass a value of 1).

TABLE 48: HAZARD RATIO ESTIMATES

	Number of Hazard Ratio Estimates[a] < 1 / ≤ 1	Mean Hazard Ratio	Median Hazard Ratio	Minimum Hazard Ratio	Maximum Hazard Ratio	Icatibant Significantly Better / Worse[b]
Icatibant versus Berinert 20 IU/kg	8 / 37	1.381	1.387	0.717	2.099	2 / 0

IU = international unit.

[a] Hazard ratio (HR) estimates greater than 1 imply a result in favour of icatibant, while HR estimates less than 1 favour the comparator.

[b] "Significantly better" is the number of comparisons (out of 45) where the entire 95% confidence interval for the HR lies above 1 (favours icatibant), whereas "Significantly worse" is the number of comparisons (out of 45) where the 95% confidence interval for the HR lies below 1 (favours comparator).

CDR reviewers performed a simple sensitivity analysis of the 45 indirect comparison estimates that were generated by the manufacturer. All results using the FAST-2 trial were removed because this trial used an inappropriate comparator (tranexamic acid). In addition, only the results that compared end points with similar definition were used. Applying these filters on the 45 indirect comparisons, there were 9 indirect comparison hazard ratios remaining. Four of nine indirect comparisons had hazard ratios < 1 (favours Berinert) and five of nine indirect comparisons had hazard ratios ≥ 1 (favours icatibant). Among the nine indirect comparisons, no hazard ratios were statistically significant.

Limitations

There are many limitations related to the indirect comparison estimates generated in the manufacturer's analysis. These likely have introduced significant heterogeneity into the analysis and include:

- Different definitions for "time to onset of symptom relief" were used between the trial.
- The trials were relatively small and were performed at clinical sites across all five continents. Clinical practice standards and approaches will differ widely across the multiple sites.
- There were different methods used for censoring data in the time-to-event analyses.

- The rules for rescue medication use differed in the trials (timing and type of medication used).
- The estimation of events and censor times was performed from the Berinert publication's Kaplan-Meier plots. While this method has been published and used elsewhere.[38] it is not a precise method for generating hazard ratios.

As a result of these limitations, a very large number of point estimates (drug versus placebo) and indirect comparison estimates (icatibant versus Berinert) were generated. The result was a very complex presentation of data. The authors could have been more selective in their data presentation, presenting only the results that were more likely to provide robust estimates. For example, they could have eliminated estimates based on outcome definitions or censoring methods that did not match. In addition, the FAST-2 study could have been eliminated from the analysis for clarity. The manufacturer assumed that the comparator in FAST-2 (tranexamic acid) was equivalent in efficacy to placebo, but there was no RCT evidence provided to demonstrate this assumption. Tranexamic acid is not cited in current guidelines as a treatment option for HAE attacks.

In addition, the systematic review and indirect comparison contained estimates for several comparator drugs other than Berinert. Berinert was the only comparator of interest in the manufacturer's economic submission and, therefore, the data from the other comparators could have been omitted, creating a more focused indirect comparison report.

Strengths

Strengths of the manufacturer-provided systematic review and indirect comparison included transparency of methods and clear presentation of results. Another strength of the reports is that the manufacturer provided a critical appraisal of their own analyses. The Bucher method is an established and straightforward method for indirect comparison and was appropriate for the comparison of interest.

TABLE 49: CRITICAL APPRAISAL POINTS FOR THE MANUFACTURER'S SYSTEMATIC REVIEW AND INDIRECT COMPARISON

Item	Details and Comments
Are the rationale for the study and the study objectives stated clearly?	• Rationale stated; need to determine comparative effectiveness for an economic analysis
Does the methods section include the following? • Description of eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction (validity/quality assessment of individual studies)	• Literature search strategy, search terms presented • Inclusion/exclusion criteria presented • No critical appraisal performed of included studies • Data extraction presented • The FAST-3 study was not included in the systematic review but it was included in the indirect comparison. Lack of transparency related to the apparently late insertion of this pivotal study
Are the outcome measures described?	• Outcomes of interest were clearly defined and data was extracted into the systematic review report. However, many of the outcomes were not presented in the indirect comparison report, and the reasons for this were not clearly stated
Is there a description of methods for analysis/synthesis of evidence? Do the methods described include the following? • Description of analyses	• Descriptions of their analyses and methods were provided, including methods for deriving hazard ratios from visualization of the Kaplan-Meier plots in the Berinert publication • Bucher method used for the indirect comparisons

Item	Details and Comments
methods/models • Handling of potential bias/inconsistency • Analysis framework	
Are sensitivity analyses presented?	• Sensitivity analyses were performed by presenting numerous hazard ratios for various combinations of trials, end point definitions, and censoring methods. However, the manufacturer made no attempt to perform sensitivity analyses of their summary table (Table 48)
Do the results include a summary of the studies included?	• Table/list of studies with information regarding study design and patient characteristics presented • A clear network diagram of studies was provided (despite the fact they did not perform network meta-analysis)
Are the results of the indirect comparison presented clearly?	• Hazard ratio point estimates and measures of uncertainty (95% CIs) were presented for drug versus placebo and icatibant versus Berinert, and an attempt was made to summarize the multiple hazard ratios by pooling
Does the discussion include the following? • Description/summary of main findings • Internal validity of analysis • External validity • Implications of results for target audience	• The manufacturer provided relevant comments regarding the limitations of their analysis, including internal validity • No discussion about external validity of the trials

CI = confidence interval.

Summary

Due to the absence of head-to-head trials between icatibant and other drugs currently used to treat HAE attacks, the manufacturer undertook a systematic review of RCTs and performed an indirect comparison using the Bucher method. For the outcome of time to symptom relief, some estimates indicated lower efficacy and some estimates indicated higher efficacy for icatibant relative to Berinert 20 IU/kg. The manufacturer stated there is some evidence to suggest that icatibant reduces time to symptom onset compared with Berinert; however, due to the large number of limitations of the presented analyses, the relative efficacy of icatibant versus Berinert remains unclear.

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