

Open-label, multicenter study of self-administered icatibant for attacks of hereditary angioedema

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Abstract

Background: Historically, treatment for hereditary angioedema (HAE) attacks has been administered by healthcare professionals (HCPs). Patient self-administration could reduce delays between symptom onset and treatment, and attack burden. The primary objective was to assess the safety of self-administered icatibant in patients with HAE type I or II. Secondary objectives included patient convenience and clinical efficacy of self-administration.

Methods: In this phase IIIb, open-label, multicenter study, adult patients were trained to self-administer a single 30-mg icatibant subcutaneous injection to treat their next attack. Icatibant-naïve patients were treated by an HCP prior to self-administration. Evaluations included adverse event (AE) reporting, a validated questionnaire for convenience, and visual analog scale for efficacy.

Results: A total of 151 patients were enrolled; 104 had an attack requiring treatment during the study, and 97 patients (19 naïve) were included in the self-administration cohort. Recurrence or worsening of HAE symptoms (22 of 97) was the most commonly reported AE; rescue medications including icatibant ($N = 3$) and C1-inhibitor concentrate ($N = 6$) were used in 13 cases. Overall, 89 of 97 patients used a single injection of icatibant. No serious AEs or hospitalizations were reported. Most patients (91.7%) found self-administration preferable to administration in the clinic. The median time to symptom relief (3.8 h) was comparable with results from controlled trials of icatibant.

Conclusions: With appropriate training, patients were successfully able to recognize HAE attacks and decide when to self-administer icatibant. This, coupled with the patient-reported high degree of satisfaction, convenience and ease of use supports the adoption of icatibant self-administration in clinical practice.

Hereditary angioedema (HAE) is a rare autosomal dominant disorder characterized by attacks of nonpruritic edema typically affecting the abdomen, extremities, and upper airways (1–3). HAE types I and II are caused by quantitative or functional C1-inhibitor (C1-INH) deficiency, with consequent angioedema attacks mediated by local bradykinin accumulation, vascular bradykinin B₂ receptor activation, and fluid extravasation (3–5).

The natural course and severity of individual HAE attacks varies (3, 6, 7), but all attacks have the potential to become disabling and/or develop life-threatening laryngeal symptomatology (3, 6), resulting in frequent hospitalizations (8). Given that many patients also require administration of treatment by an HCP, the burden of HAE on both healthcare resources and patients is significant (9, 10). According to a recent study, however, successful management of HAE

does not appear to depend on limited efficacy of the drugs, but on their limited use (11). The development of home- and self-treatment protocols could facilitate access to treatment (12), and this is reflected in recent guidance that states that patients should be trained to self-administer on-demand therapy wherever possible (1, 6).

Icatibant, a subcutaneously injected bradykinin B₂ antagonist, is licensed in 40 countries for the symptomatic treatment of HAE type I and II attacks. It was approved for self-administration in 2011 by the European Medicines Agency and the United States Food and Drug Administration and, at the time of this study, was the only HAE treatment licensed for self-administration. Three phase III trials have demonstrated the safety and efficacy of icatibant administered by healthcare professionals (HCPs) in patients with HAE (13, 14), while other investigators have reported successful treatment of HAE attacks with icatibant administered by patients and HCPs in the home setting (15, 16). Here, we present data from EASSI (Evaluation of the Safety of Self-administration with Icatibant; Clinicaltrials.gov identifier: NCT00997204), a phase IIIb, international, multicenter, open-label study of the safety, patient convenience, and efficacy of icatibant self-administration in adults with HAE types I and II.

Methods

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines and FDA Institutional Review Board regulations and approved by the Institutional Review Board/Independent Ethics Committee at each study site (Supporting Information Table S1).

Study design

Evaluation of the Safety of Self-administration with Icatibant (EASSI) was an international prospective open-label study conducted at 23 sites. All patients were trained to self-administer icatibant, with initial treatment by an HCP for naïve patients and unsupervised self-administration for non-naïve patients (Fig. 1). Following both HCP administration and self-administration, patients with worsening or recurrence of HAE symptoms 6–48 h after initial treatment were asked to return to the study site for assessment by the investigator and consideration for additional icatibant injections (up to a maximum of three injections per attack). Patients who experienced laryngeal symptoms or any cutaneous swelling affecting the face or neck were instructed to return to the study site immediately after icatibant self-administration or to seek immediate medical attention at the nearest emergency care facility.

Objectives

The primary objective was to assess the clinical safety of a single self-administered open-label icatibant injection for an

HAE attack. Local tolerability of injection, patient convenience, and efficacy of self-administered icatibant were assessed as secondary objectives.

Patients

Adult patients with a documented diagnosis of HAE type I or II were eligible to participate. Exclusion criteria included diagnosis of angioedema other than HAE type I or II; evidence of symptomatic coronary artery disease based on medical history (in particular, unstable angina pectoris or severe coronary heart disease); congestive heart failure (New York Heart Association Class III or IV) (17); stroke within the previous 6 months; treatment with an angiotensin converting enzyme inhibitor; and pregnancy and/or breastfeeding.

Icatibant self-administration training

All patients were trained to self-administer icatibant as a subcutaneous injection into the abdominal skin using a syringe prefilled with 3 ml isotonic, sterile saline solution (acetate-buffered solution for injection, pH 5.5 ± 0.3). Patients received comprehensive educational materials and instructions to illustrate the method of self-administration and were trained to use a patient diary to record attack characteristics and outcomes. The training materials included instructions on how to self-diagnose an HAE attack, decide on the necessity to treat, and what to do in the event of a laryngeal attack.

Procedure for administration of icatibant

Treatment-relevant HAE attacks (i.e., attacks that the patient considered to require treatment) were treated with single injections of icatibant (30 mg in 3 ml solution). First HAE attacks following enrollment in naïve patients were administered by an HCP at the study site. Non-naïve patients (including those who had completed the naïve treatment phase) self-administered icatibant for their first treatment-relevant attack. All patients were asked to return to the study site for follow-up 48 h (or within 7 days) after self-administration.

Safety

Adverse events (AEs) were assessed by investigators at scheduled study visits up to 28 days post-treatment. Patients were asked to record any AEs that occurred between study visits. All AEs were assessed by investigators for severity (mild [no limitation of usual activities], moderate [some limitation of usual activities], or severe [inability to carry out usual activities]) and causality (not related, possibly related, probably related, or definitely related) to study drug. A serious AE (SAE) was defined as an AE that resulted in death, was life-threatening, or caused hospitalization/prolongation of an existing hospitalization, persistent or significant disability/incapacity, or congenital anomaly/birth defect. Any worsening or recurrence of HAE symptoms that occurred within 48 h of treatment with icatibant was reported as an AE.

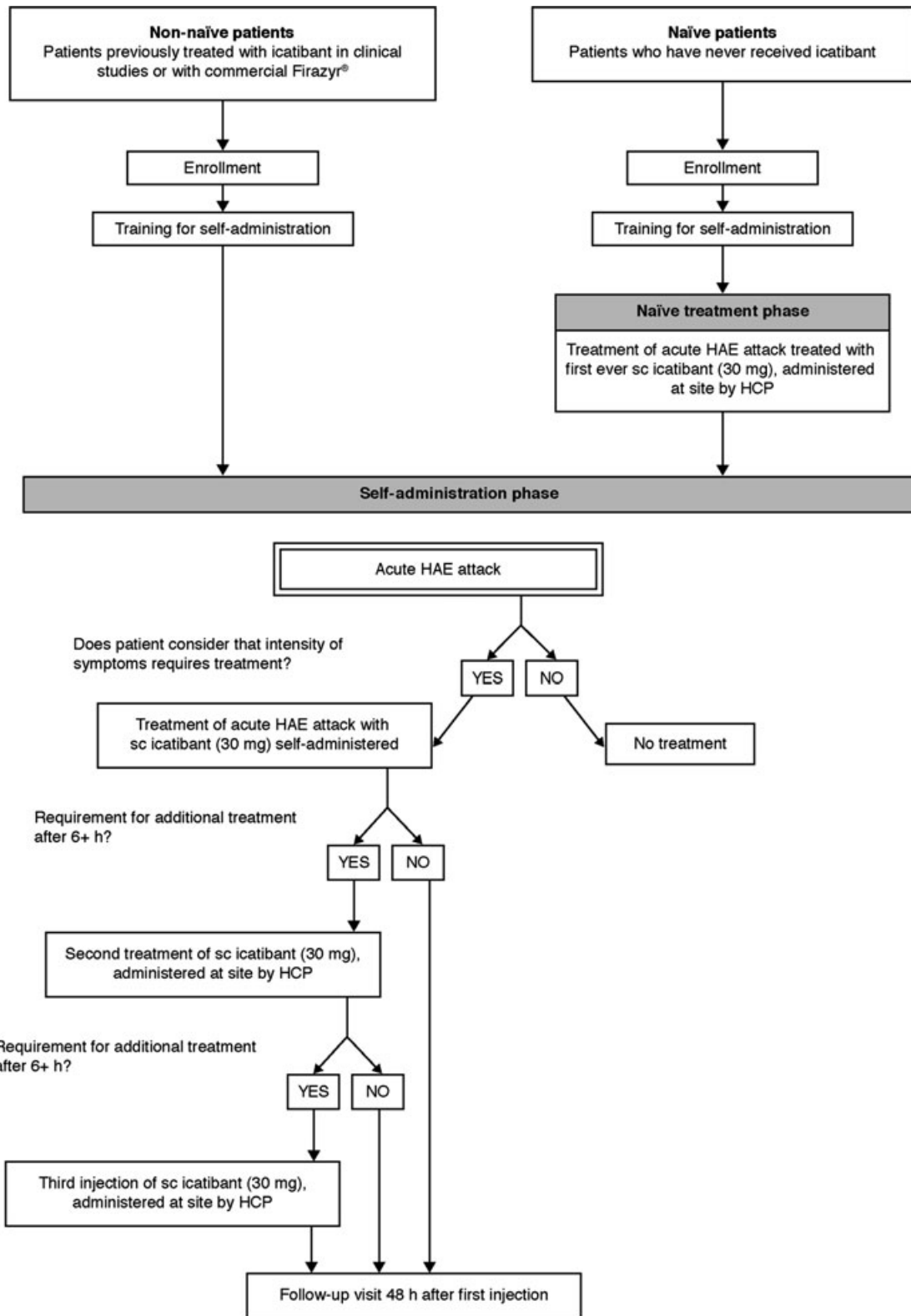


Figure 1 Study design. All enrolled patients were trained to self-administer icatibant; those that experienced a treatment-relevant HAE attack were treated with HCP- or self-administered icatibant

depending on whether they were icatibant-naïve at enrollment. HAE, hereditary angioedema; HCP, healthcare professional; sc, subcutaneous.

Injection site reactions were assessed by patients and investigators. These were not recorded as AEs unless they met the criteria for an SAE.

Efficacy and patient convenience

Efficacy evaluations were based on patient-assessed symptom severity over time, measured using a visual analog scale (VAS) for the symptoms skin pain, skin swelling, and abdominal pain. VAS scores (0 mm = absent, 100 mm = worst possible severity) were recorded in the patient diary at predefined intervals up to 48 h; patients also recorded whether they considered their attack resolved and over at 48 h. Severity of skin edema, abdominal symptoms, and laryngeal attacks (0 = absent, 4 = very severe) were assessed by investigators as a global assessment. Patients in the self-administration phase completed a (nonvalidated) convenience questionnaire consisting of eight questions; following a protocol amendment, patients were also asked to complete a validated Treatment Satisfaction Questionnaire for Medication (TSQM) (18). The TSQM consisted of 14 questions in four domains: effectiveness, adverse effects, convenience, and global satisfaction (Supporting Information Table S2). Domain scores ranged from 0 to 100, with higher scores representing higher satisfaction.

Concomitant medications considered to be rescue medications were identified by retrospective medical review and categorized as definitive HAE therapies (i.e., icatibant or C1-INH concentrate) or palliative therapies (e.g., analgesics).

Statistical methods

Enrollment of approximately 150 subjects was planned to obtain ≥ 25 evaluable, self-administered icatibant injections in ≥ 25 patients (a formal sample size calculation was not performed). Descriptive analyses were performed for safety, local tolerability, and patient convenience data. For efficacy analyses, attacks were categorized as cutaneous or abdominal based on the symptom with the highest pretreatment VAS score. Onset of symptom relief was defined as (i) $\geq 50\%$ reduction in the pretreatment composite three-symptom VAS score (VAS-3); and (ii) a reduction in primary symptom VAS score of ≤ 6 of 7 of the pretreatment VAS minus 16 mm (i.e., equivalent to a reduction of approximately 30% for a pretreatment VAS of 100 mm and of 60% for a pretreatment VAS of 30 mm). Times to onset of symptom relief were determined as the earliest of the three consecutive scheduled measurements at which symptom relief was documented. Median and 95% confidence intervals were calculated using Kaplan–Meier methodology. Patients without documented symptom relief were censored at the time of their last non-missing scheduled assessment.

Results

Patient population

Between 25 September 2009 (first patient enrolled) and 22 June 2011 (final patient completed), 151 patients were

enrolled and trained to self-administer icatibant. In total, 97 patients self-administered icatibant and 22 received HCP-administered icatibant (19 patients who were naïve to icatibant at enrollment received both HCP- and self-administered treatment). Demographic and baseline characteristics are summarized in Table 1.

Safety of self-administered icatibant

Thirty-three patients (34.0%) experienced at least one AE following icatibant self-administration, and 11 patients (50.0%) experienced at least one AE following HCP administration (Supporting Information Table S3). The majority of AEs were mild or moderate: eight patients experienced AEs considered by the investigator to be severe (seven following self-administration and one following HCP administration). There were no SAEs or discontinuations due to AEs, and no clinically important changes were observed in either vital signs or physical examinations.

The most common AE was worsening or recurrence of HAE symptoms within 48 h of icatibant treatment, reported in six patients (27.2%) in the naïve treatment phase and 22 (22.6%) patients in the self-administration phase (Supporting Information Table S3). Most of these were assessed as mild or moderate (Table 2), and no patient required hospitalization. Median (range) times from attack onset to icatibant self-administration in patients with and without worsening or recurrence of HAE symptoms were 5.0 ([0.0–47.0]; $N = 22$) and 5.0 ([0.1–30.8]; $N = 75$) hours, respectively. The majority of patients with worsening or recurrence did not return to the study site for assessment and treatment as per the study protocol. 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 (HCP-administered) icatibant injection (Table 3); no attacks required a third injection.

Table 1 Patients' baseline characteristics

	Naïve treatment phase* ($N = 22$)	Self-administration phase† ($N = 97$)
Mean (SD) age, years	44.4 (16.4)	40.9 (13.6)
Sex, N (%)		
Male	7 (31.8)	33 (34.0)
Female	15 (68.2)	64 (66.0)
Race, N (%)		
Caucasian	22 (100.0)	97 (100.0)
Mean (SD) weight, kg	75.1 (19.0)	73.4 (18.4)
Mean (SD) height, cm	167.4 (8.9)	169.2 (9.6)

SD, standard deviation; HCP, healthcare professional.

*The naïve treatment phase included patients that had not previously received icatibant (naïve patients). These patients received icatibant administered by an HCP.

†The self-administration phase included naïve patients who had completed the naïve treatment phase and non-naïve patients who had previously received HCP-administered icatibant.

Table 2 Attack characteristics in patients with worsening or recurrence of HAE symptoms

	Naïve treatment phase* (N = 22)	Self-administration phase† (N = 97)
Patients with worsening or recurrence of HAE symptoms, N (%)	6 (27.3)	22 (22.7)
Median (range) time from attack onset to icatibant administration, h	6.5 (1.5–51.3)	5.0 (0.0–47.0)
Median (range) time from icatibant administration to worsening or recurrence of HAE symptoms‡	24.0 (15.6–44.5)	14.0 (0.5–26.8)
Intensity of initial attack based on primary symptom VAS score, N		
0–29	1	3
30–59	2	6
60–100	3	13
Intensity of worsening or recurrence of HAE symptoms, N		
Mild (no interference with daily activities)	3	5
Moderate (interference with daily activities)	2	12
Severe (major interference with daily activities)	1	5
Used rescue medication, N		
Yes	2	13
Type of rescue medication used, N§		
Bismuth	0	1
C1-INH concentrate	2	6
NSAID	0	3
Antispasmodic	0	2
Icatibant	0	3
Analgesic	0	3

HAE, hereditary angioedema; VAS, visual analog scale; C1-INH, C1-inhibitor concentrate; NSAID, nonsteroidal anti-inflammatory drug; HCP, healthcare professional.

*The naïve treatment phase included patients that had not previously received icatibant (naïve patients). These patients received icatibant administered by an HCP.

†The self-administration phase included naïve patients who had completed the naïve treatment phase and non-naïve patients who had previously received HCP-administered icatibant.

‡In case of multiple events, the time from icatibant administration to the earliest event was used.

§Patients could be counted in >1 category.

Table 3 Overview of symptoms and times to initial and second icatibant injections in patients that returned to the study site for worsening or recurrence of HAE symptoms

Patient identifier	Primary symptom of initial attack	Reason for returning to the study site	New HAE symptoms	Time to injection, h	
				Attack onset to first injection	Attack onset to second injection
Naïve treatment phase*					
A	Abdominal pain	New HAE symptoms developed	Abdominal colics	6.4	24.0
B	Skin swelling	New HAE symptoms developed	Left orbital edema attack	1.5	47.4
Self-administration phase†					
A	Abdominal pain	Symptoms worsened	–	2.9	10.2
C	Abdominal pain	Symptoms persisted	–	8.8	36.7
D	Abdominal pain	Symptoms worsened	–	1.8	23.1
E	Skin swelling	Symptoms persisted	–	9.3	23.1
F	Skin swelling	New HAE symptoms developed	Abdominal pain, tightness in throat	5.4	51.5

HAE, hereditary angioedema; HCP, healthcare professional.

*The naïve treatment phase included patients that had not previously received icatibant (naïve patients). These patients received icatibant administered by an HCP.

†The self-administration phase included naïve patients who had completed the naïve treatment phase and non-naïve patients who had previously received HCP-administered icatibant.

The only other AEs reported in >1 patient were headache ($N = 3$) and abdominal pain ($N = 2$). Drug-related AEs occurred in seven patients (7.2%) following icatibant self-administration and in two patients (9.1%) following HCP administration (Supporting Information Table S4).

Rescue medication usage

Rescue medication was used by two of six patients (33.3%) with worsening or recurrence of HAE symptoms in the naïve treatment phase (both C1-INH concentrate) and by 13 of 22 patients (59.1%) with worsening or recurrence in the self-administration phase (six patients used C1-INH concentrate, three patients used icatibant, and the remaining patients used palliative medications) (Table 2). Four patients without reported worsening or recurrence of HAE symptoms used rescue medications, including C1-INH concentrate in two patients.

Additional icatibant injections

Eighty-nine patients (91.8%) used a single icatibant injection during the self-administration phase; eight patients (8.2%) required an additional icatibant injection for new, persistent, or worsening HAE symptoms (three patients used icatibant as rescue medication, and five returned to the study site for an additional injection of icatibant as per protocol). In the naïve treatment phase, two patients (9.1%) returned to the study site and received an additional icatibant injection for new HAE symptoms.

Local tolerability

Injection site reactions, including reddening, swelling, burning, itching, warming, and pain, were reported by 94 of 97 patients (96.9%) during the self-administration phase. By 6 h after injection, injection site reactions were absent or mild in 87 of 90 patients (96.7%) who completed the assessments. Seventeen patients (17.5%) in the self-administration phase reported severe injection site reaction symptoms; no intervention was needed, and none was reported as an SAE.

Patient convenience assessment

All 97 patients who self-administered icatibant completed the treatment satisfaction questionnaire, and 23 completed the TSQM. Based on the treatment satisfaction questionnaire, the majority of patients were satisfied with the results of self-administered icatibant, convenience, and ease of use (Fig. 2A). The results of the TSQM were broadly consistent with those of the treatment satisfaction questionnaire indicating a high degree of satisfaction for all four domains (Fig. 2B).

Efficacy assessments

Mean VAS-3 scores following both HCP- and self-administered icatibant declined over time (Supporting Information Fig. S1). Median times to onset of symptom relief were 3.8 and

2.0 h by VAS-3 and primary symptom VAS, respectively (Table 4).

Three patients self-administered icatibant for laryngeal attacks, all of which were considered by the patients to be satisfactorily resolved by 48 h.

Discussion

Evaluation of the Safety of Self-administration with Icatibant (EASSI) is the largest evaluation to date of the safety of a self-administered on-demand HAE treatment. With appropriate training, patients were successfully able to recognize HAE attacks and decide when to self-administer icatibant, reporting a high degree of satisfaction, convenience, and ease of use. Safety, tolerability, and efficacy outcomes following icatibant self-administration were comparable with HCP administration and broadly consistent with the phase III controlled trials (13, 14).

The natural history of an HAE attack is variable, with waxing and waning symptoms over several days being common, and as might be expected, some patients (23–27%) in EASSI experienced symptom worsening or recurrence, or emergence of new symptoms, after reporting initial symptom improvement. For these patients, additional icatibant injections have been effective, and up to three icatibant injections may be administered within a 24-h period if needed (although, notably, no patient in EASSI required a third injection).

In considering the observed recurrence rate, it is important to note that the 48-h time frame for reporting worsening or recurrence events allowed in this study compared with the 4- to 24-h follow-up periods used in other studies of on-demand HAE therapies (19–22) and also the fact that patients in EASSI were not required to have a minimum VAS score to treat their attack. The data may therefore be more reflective of 'real-world' experience. However, it is also of note that, of the 28 reported recurrence or worsening events, only seven resulted in patients returning to the study site for assessment by the investigator as per study protocol requirements, precluding robust clinical evaluation of the majority of reported recurrence events.

While the relatively short plasma half-life of 1–2 h following subcutaneous icatibant administration (23) might be considered as potentially contributing to worsening or recurrence, icatibant has been shown to provide a sustained duration of action of <8 h (13, 14).

In this study, the median times from icatibant administration to worsening or recurrence of HAE symptoms was 24.0 and 14.0 h in the naïve ($N = 6$) and self-administration ($N = 22$) phases, respectively. One (3.6%) patient reported a time of 0.5 h from icatibant administration to worsening of HAE symptoms; this was a severe and prolonged abdominal attack for which the patient took various palliative rescue medications (hyoscine, metoclopramide, and tranexamic acid), but did not return to the study site for investigator assessment. This patient might be considered an outlier and perhaps highlights the need for better patient education in identifying and managing HAE events.

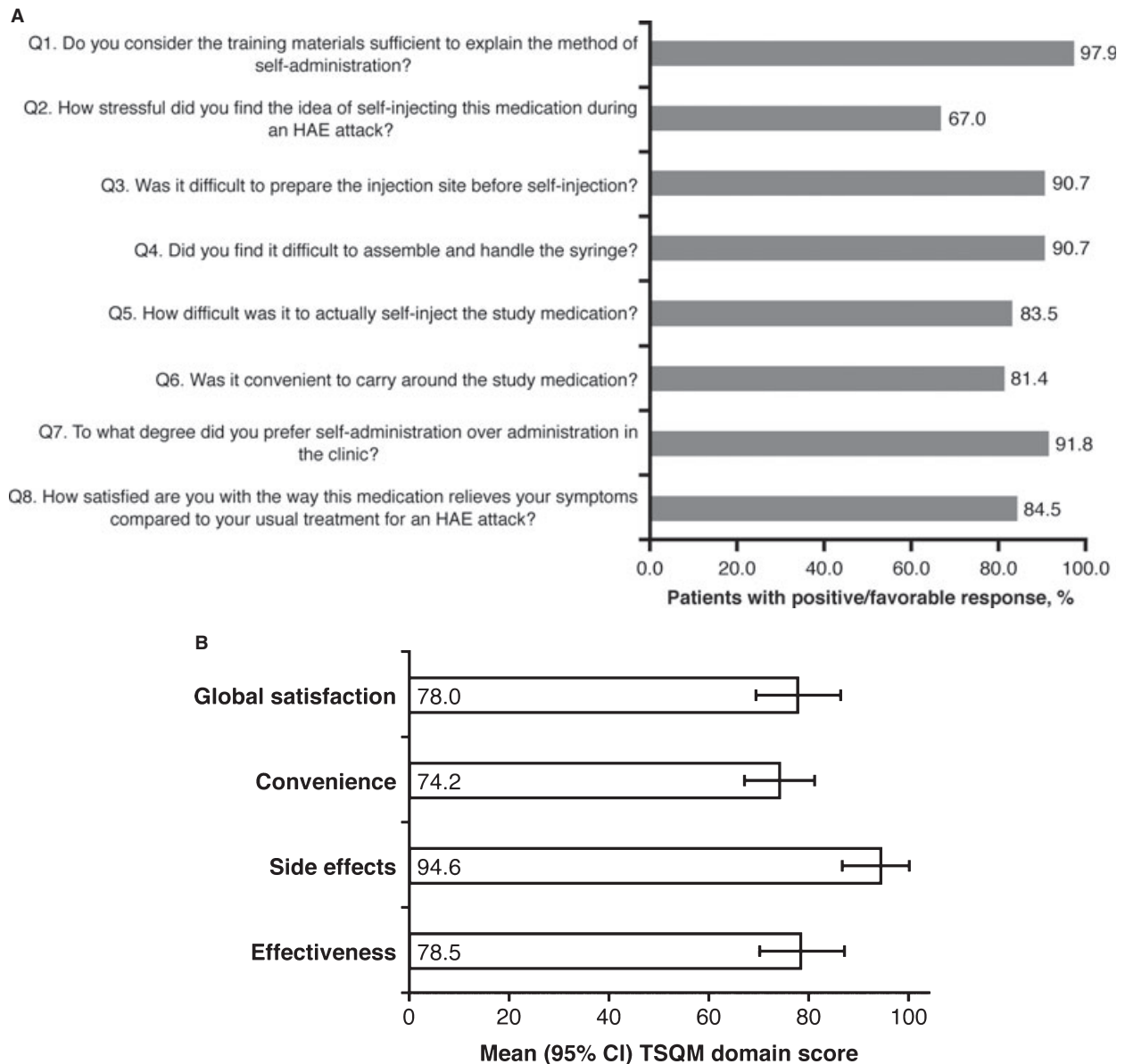


Figure 2 Convenience and satisfaction with icatibant self-administration: (A) summary of responses to the convenience and satisfaction questionnaire ($N = 97$); (B) mean and 95% CI TSQM domain scores ($N = 23$). (A) Global Clinical Research. Patients provided answers to eight questions regarding convenience and satisfaction of icatibant self-administration, with five possible responses (ranging from very positive/favorable through neutral to very negative/unfavorable) for each question. The proportions of patients with

very positive/positive or favorable/very favorable responses (i.e., in support of icatibant self-administration) to each question are shown. (B) The Treatment Satisfaction Questionnaire for Medication (TSQM) consisted of 14 questions categorized in the domains effectiveness, side-effects, convenience, and global satisfaction. Domain scores range from 0–100, with higher scores representing higher satisfaction. CI, confidence interval.

The value of a clear definition of worsening or recurrence is evident from the thorough clinical assessment made of the six patients (seven attacks) who returned to the study site for additional icatibant injections and was a key limitation of the study. Two of these patients experienced new HAE symptoms, three experienced persistent or worsening symptoms, and one patient experienced separate events of new

HAE symptoms and worsening symptoms. Of the recurrence events involving new symptoms, the second icatibant injection was administered within 18–46 h of the initial treatment (compared with 7–28 h for events involving persistent or worsening symptoms); thus, we cannot exclude the possibility that some of these recurrence events were actually new attacks.

Table 4 Times to onset of symptom relief assessed by composite VAS-3 and primary symptom VAS scores

	Naïve treatment phase* (N = 22)		Self-administration phase† (N = 97)	
	Composite VAS-3	Single primary symptom VAS	Composite VAS-3	Single primary symptom VAS
Number of evaluable patients‡	21	17	91§	87¶
Patients with symptom relief, %	100	100	95.6	97.7
Median time (95% CI) to onset of symptom relief, h	2.0 (1.1–4.0)	2.0 (1.0–4.2)	3.8 (2.0–4.0)	2.0 (2.0–2.0)

VAS, visual analog scale; CI, confidence interval; HCP, healthcare professional.

The time to onset of symptom relief was defined as the first of the three consecutive assessments at which symptom relief was observed. Symptom relief was defined using VAS-3 scores ($\geq 50\%$ reduction from predose in the VAS-3 score) and primary symptom VAS scores (post-dose primary symptom VAS score $\leq 6/7$, predose primary symptom VAS score – 16 mm).

*The naïve treatment phase included patients that had not previously received icatibant (naïve patients). These patients received icatibant administered by an HCP.

†The self-administration phase included naïve patients who had completed the naïve treatment phase and non-naïve patients who had previously received HCP-administered icatibant.

‡VAS-3 score-evaluable patients included all patients with at least the predose VAS assessment for each of the three components (skin swelling, skin pain, and abdominal pain). Single primary-symptom VAS score-evaluable patients included all patients with ≥ 1 predose VAS assessment ≥ 30 mm.

§Four patients were censored without symptom relief.

¶Two patients were censored without symptom relief.

Rescue medication usage in EASSI predominantly occurred in patients who reported worsening or recurrence of symptoms. The pattern of rescue medication usage suggests that some patients may have chosen to use readily available treatments (including commercially available icatibant and C1-INH concentrate in approximately 50% of cases) rather than returning to the clinic. It is possible that clinicians and patients might differ in their perception of the need to administer definitive therapy, and factors such as time of day, weekends vs week days, and physician availability may also contribute, reinforcing the need for comprehensive education of patients in self-managing HAE attacks.

Although not prespecified in the protocol, the combination of patients requiring definitive rescue medication and those receiving an additional icatibant injection per protocol is perhaps a useful proxy of the true recurrence rate. Using this measure, 15 of 97 patients (15.4%) following self-administration and four of 22 patients (18.2%) following HCP administration required definitive follow-up treatment. In real-life practice, it will be of interest to see whether patient experience and education in self-administration can help to optimize future timing of treatments and reduce the need for additional injections.

Our findings regarding patients' perception of convenience and ease of icatibant self-administration complement previous observations where self-administration of intravenous C1-INH concentrate was well-tolerated and associated with improved quality of life and independence and was popular with patients (24, 25). Further studies using novel instruments for assessing disease activity and quality of life in patients with HAE (26, 27) should be implemented to confirm these findings.

Efficacy was a secondary objective, and this noncomparative study was not powered to rigorously evaluate efficacy outcomes. However, the median times to onset of symptom relief were generally consistent with the FAST controlled trials of icatibant (13, 14), and the 48-h assessments by patients and investigators support the durability of responses to icatibant for most patients.

In conclusion, the safety and tolerability profile of self-administered icatibant observed in EASSI, coupled with the levels of satisfaction reported by patients with self-treatment, and efficacy similar to HCP administration, support adoption of icatibant self-administration in clinical practice. By using self-treatment protocols for acute HAE attacks, treatment decisions can be delegated from physician to patient, thereby enhancing patients' autonomy.

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Author contributions

All authors made equal contributions to the study and publication.

Conflicts of interest

W. Aberer has acted as a medical advisor and speaker for Shire and CSL Behring, received funding to attend conferences and other educational events, received donations to his departmental fund, and participated in clinical trials for Shire. M. Maurer has received speaker/consultancy fees from Shire/Jerini AG and ViroPharma. A. Reshef has received consultancy fees from Shire/Jerini AG and research support from CSL Behring. H. Longhurst has received funding for research and staff support from CSL Behring, Shire, and Pharming; is a consultant for CSL Behring, Shire, and Swedish Orphan; and is a speaker for CSL Behring, Shire, Swedish Orphan, and ViroPharma. S. Kivity has received research support from Shire/Jerini AG. A. Bygum has received speakers' fees from Shire/Jerini AG and consultancy fees from ViroPharma and CSL Behring, has participated in a clinical trial for Jerini AG, and is an advisor for the HAE Danish Patient Organization. T. Caballero has received speaker and

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Mean (\pm SEM) change in composite VAS-3 score over time during the naïve treatment phase ($n = 22$) and the self-administration phase ($n = 97$).

Table S1. Institutional Review Board/Independent Ethics Committee information.

Table S2. Treatment Satisfaction Questionnaire for Medication (TSQM) domains, questionnaire items and assessment scales (Adapted from Atkinson et al. [18]).

Table S3. Adverse events by system organ class and MedDRA preferred term.

Table S4. Drug-related adverse events by system organ class and MedDRA preferred term.

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