Original Article

Randomized Trial of Icatibant for Angiotensin-Converting Enzyme Inhibitor–Induced Upper Airway Angioedema

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What is already known about this topic? Angiotensin-converting enzyme inhibitors (ACE-Is) are associated with the risk of acute angioedema, a rapid swelling of subcutaneous and submucosal tissue, characteristically involving the lips, tongue, and larynx. No known pharmacologic agents effectively treat this potentially life-threatening condition.

What does this article add to our knowledge? In our randomized double-blind trial of patients with ACE-I–induced angioedema of the upper airway, icatibant was no more efficacious than placebo in shortening time to meeting discharge criteria, nor time to onset of symptom relief.

How does this study impact current management guidelines? Findings suggest that multiple pathways and genetic factors may potentially be involved in the underlying pathophysiology of ACE-I–induced angioedema attacks, necessitating the continuing search for effective pharmacologic options beyond bradykinin B2 receptor antagonists.

BACKGROUND: Upper airway angioedema is a rare, unpredictable, and at times life-threatening adverse effect of angiotensin-converting enzyme inhibitors (ACE-Is) with no existing effective pharmacologic treatment. Icatibant is a bradykinin B2 receptor antagonist that may be beneficial in patients with ACE-I–induced angioedema.

OBJECTIVE: We aimed to evaluate the efficacy of icatibant in subjects with ACE-I–induced angioedema.

METHODS: At 31 centers in 4 countries, adults on ACE-Is who presented within 12 hours of the onset of at least moderately severe angioedema were randomized 1:1 to icatibant 30 mg or placebo administered subcutaneously. The primary efficacy end point was time to meeting discharge criteria after study drug administration, based on the severity of airway symptoms assessed hourly by a blinded physician using clinical ratings across 4 domains.

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This clinical study was sponsored and funded by Shire HGT. The study was designed by the sponsor (Shire) with considerations of expert advice received. Data were collected by study sites in collaboration with the sponsor. Shire Biostatistics & Statistical Programming Department conducted the statistical analyses. R. Body was supported by the National Institute for Health Research (NIHR) in the United Kingdom via the Clinical Research Network (UK CRN 16860) and a personal fellowship (NIHR PDF-2012-05-193). Medical writing support was funded by Shire HGT.

Conflicts of interest: P. Levy has received consultancy fees and travel support from Shire. J.A. Bernstein has received research support from Shire; is a principal investigator, consultant, and speaker for Shire and CSL Behring; is a principal investigator for Dyax and Biocryst; is a consultant for Salix; has received consultancy and lecture fees from Shire, CSL Behring, Novartis, and Genentech; and is an unpaid member of the medical advisory board for the Hereditary Angioedema Association organization. R. Body has received research support from Shire, Novartis, Portola, Boehringer Ingelheim, Abbott Laboratories, Abbott Point of Care, Roche Diagnostics, and Bayer; has received travel support from Roche Diagnostics; and received a donation of reagents for research from Roche Diagnostics, Abbott Point of Care, Alere, FABPulous, Randox Laboratories, Siemens, and Abbott Laboratories. M.L.A. Sivilotti has received travel and research support from Shire. J. Schranz, J. Baptista, and W. Nothaft are employed by and have stock in Shire. A. Kimura was employed by and has stock in Shire. R. Sinert and J. Moellman declare that they have no relevant conflicts of interest.

Received for publication September 26, 2016; revised February 2, 2017; accepted for publication March 8, 2017.

Available online ■■

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2213-2198

http://dx.doi.org/10.1016/j.jaip.2017.03.003

Abbreviations used
ACE-I- Angiotensin-converting enzyme inhibitor
AE- Adverse event
AMACE- Amelioration of angiotensin-converting enzyme inhibitor—induced angioedema
IQR- Interquartile range
TOSR- Time to onset of symptom relief

RESULTS: A total of 121 subjects were randomized (icatibant, n = 61; placebo, n = 60); 118 received treatment a median of 7.8 hours from symptom onset. We observed no difference in time to meeting discharge criteria between groups (median, 4.0 hours in each group; $P = .63$). There also was no difference in time to onset of symptom relief (median, icatibant, 2.0 hours; placebo, 1.6 hours; $P = .57$) or any other secondary end point. Similar findings were noted in prespecified and post hoc subgroup analyses stratified by symptom severity, time interval to treatment, age, and other clinical covariates. No new safety signals were detected.

CONCLUSIONS: Icatibant was no more efficacious than placebo in at least moderately severe ACE-I—induced angioedema of the upper airway. **(J Allergy Clin Immunol Pract 2017;■:■-■)**

Key words: *Angiotensin-converting enzyme inhibitor; Angioedema; Upper airway; Icatibant*

Introduced into clinical practice in the 1980s, angiotensin-converting enzyme inhibitors (ACE-Is) remain a first-line agent for hypertension, heart failure, and diabetic nephropathy.[1-3] ACE-Is decrease the production of angiotensin II and block bradykinin degradation, resulting in vasodilation. Unfortunately, ACE-Is also can cause acute angioedema, a rapid swelling of subcutaneous and submucosal tissue, characteristically involving the lips, tongue, and larynx.[4] Although uncommon, edema of the tongue and larynx can lead to upper airway obstruction.[5] An estimated 1 in 150 to 1000 patients treated with ACE-Is will develop angioedema.[6-8]

ACE-I—induced angioedema may be caused by accumulation of bradykinin resulting from ACE-I—mediated blockade of bradykinin degradation, in concert with deficient alternative pathways of bradykinin inactivation.[9,10] There is no known effective pharmacologic treatment for ACE-I—induced angioedema. Corticosteroids, antihistamines, and epinephrine, used in allergic disorders, have no clear benefit in ACE-I—induced angioedema, yet are often administered empirically. Consensus guidelines emphasize close monitoring, airway intervention as required, and lifetime avoidance of all ACE-Is.[11-13]

Icatibant is a selective bradykinin B2 receptor antagonist[14] approved to manage hereditary angioedema (types I and II), in which bradykinin accumulates owing to a genetic deficiency in C1 inhibitor activity. In a phase II randomized controlled trial including subjects with ACE-I—induced angioedema, time to complete resolution of edema and to onset of symptom relief following a single icatibant dose were substantially shorter versus standard therapy.[15] We conducted a larger phase III trial using a validated and reliable scale for assessing ACE-I—induced angioedema that was clinically meaningful in the emergency department setting.[16] We aimed to evaluate the efficacy of icatibant in subjects with ACE-I—induced angioedema of at least moderate severity.

METHODS

This phase III, 2-armed, randomized double-blind clinical trial was conducted at 59 centers, mainly in the United States, with 11 sites in the United Kingdom, Israel, and Canada (ClinicalTrials.gov identifier, NCT01919801). Local ethics committees approved the study, which was conducted according to International Conference on Harmonisation Good Clinical Practice guidelines and the ethical principles in the Declaration of Helsinki. All subjects provided written informed consent.

Subjects

We enrolled adults 18 years or older who were currently being treated with an ACE-I and presented with ACE-I—induced angioedema of the head and/or neck. Patients with a diagnosis of angioedema of other etiology were excluded, that is, hereditary angioedema, acquired angioedema, or allergic angioedema (food, insect bite or sting, evident clinical response to antiallergy medications). Patients with a family history of recurrent angioedema or a history of angioedema attacks before starting ACE-I treatment also were excluded. Other exclusion criteria were anaphylaxis, trauma, abscess or infection or associated disease, local inflammation, local tumor, postoperative or postradiogenic edema, salivary gland disorders, non-ACE-I drug-induced angioedema, and acute urticaria.

Patients with a vascular condition that, in the investigator's judgment, was a contraindication to study participation and anyone requiring immediate airway intervention, such as endotracheal intubation, could not participate.

The severity of the ACE-I—induced angioedema attack was determined by the subject's worst severity rating at baseline among 4 clinical domains (difficulty breathing, difficulty swallowing, voice changes, and tongue swelling), as assessed by the enrolling physician (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Enrolled subjects had at least moderately severe ACE-I—induced angioedema of less than 12 hours' duration.

Conventionally administered drugs, namely, antihistamines, corticosteroids, and epinephrine, were allowed at any time before or after study drug administration. These medications are generally recognized as having little effect on bradykinin-mediated angioedema. However, as per common clinical practice in an emergency setting, many subjects were expected to have been administered these medications by emergency care providers before enrolling in the study. Patients with an evident clinical response to 1 of these medications were excluded.

Study interventions and assessments

Eligible subjects were randomly assigned 1:1 by a computer-generated randomization schedule to icatibant 30 mg (Firazyr; Shire, Lexington, Mass) or placebo (isotonic acetate-buffered solution) administered as a single subcutaneous injection. Randomization (permuted blocks of random sizes) was performed centrally and stratified by severity of attack at baseline (moderate vs severe or very severe) and by race (black or African American vs other). Syringes were prefilled to deliver 3 mL of solution and identically labeled regardless of the solution contained (icatibant or placebo). To conceal the treatment assignment from the subject,

investigator, and study staff, the study drug was identified only by a unique study drug kit number. Treatment assignments were linked to study drug kit numbers and randomization was performed by assigning a number to each subject.

For each subject, a single physician blinded to the treatment assignment assessed the severity of the 4 primary symptoms (see Table E1) at baseline, 30 minutes, and 60 minutes after study drug administration and hourly thereafter until hour 8 using a validated clinical rating scale. The rating scale and proposed discharge criteria used in this study were developed using qualitative analysis of interviews with clinicians to confirm clinical relevance and validity. The rating scale had good interrater reliability, demonstrated by an intraclass correlation coefficient of more than 0.80.[16] Investigators were trained on scoring and applying the discharge criteria measure. For subjects who had not met the primary end point or were not discharged by hour 8, symptom assessments continued every 2 hours up to hour 24, and every 3 hours thereafter.

In addition to comprehensive physician evaluation at baseline and 8 hours posttreatment, blood and urine samples were collected for hematology, biochemistry, pharmacokinetics, and urinalysis; electrocardiography also was performed. An independent external laboratory performed the pharmacokinetic assays and kept the results confidential until study unblinding.

Injection sites also were monitored for local reactions. The individual administering the study drug and assessing injection site reactions was different from and was not permitted to communicate findings with the physician assessing severity of angioedema symptoms and the study personnel performing all other safety assessments. To help maintain blinding, an opaque dressing was placed over the injection site, given the possibility of local injection site reactions with icatibant.[15]

A safety follow-up phone call was made on day 3 (with a window of +2 days) after study drug administration to query any adverse events (AEs) occurring after discharge and to determine recurrence of angioedema attack symptoms. If a subject was discharged on or after day 3, the safety follow-up phone call was made approximately 2 days after discharge.

End points

The primary efficacy end point was *time to meeting discharge criteria*, defined as time from study drug administration to earliest time that difficulty breathing and difficulty swallowing were absent (rating of 0 out of 4), and voice change and tongue swelling were mild or absent (0 or 1). The key secondary efficacy end point was *time to onset of symptom relief* (TOSR), defined as time from study drug administration to earliest time at which symptoms of at least moderate severity (pretreatment rating $\geq$2) improved by a minimum of 1 severity grade, and mild or absent symptoms (pretreatment rating of 0 or 1) were again assessed as mild or absent. We also calculated these time intervals for each of the 4 individual domains of the symptom score.

Other secondary efficacy end points were occurrence of airway intervention, admission to hospital (inpatient or intensive care unit), use of corticosteroids, antihistamines, or epinephrine for symptomatic relief after study drug administration, and number and proportion of subjects achieving the primary end point by 4, 6, and 8 hours after study drug administration.

Time to meeting discharge criteria and TOSR also were examined by prespecified exploratory subgroups: age, sex, race, body weight, body mass index, baseline attack severity, and geographic region. We conducted 2 post hoc subgroup analyses excluding subjects who received epinephrine previously and grouping subjects by time from symptom onset to study drug administration, to see whether any treatment effect could have been modified by these factors.

Safety signals examined included adverse events, injection site reactions, clinical laboratory test results, and electrocardiograms.

Statistical analysis

The statistical analyses were performed using SAS version 9.3 or higher (SAS Institute, Cary, NC). The primary end point, key secondary end point, and time-to-event results for individual symptoms were all tested using a weighted log-rank test (Peto-Prentice test) with a 2-sided α of 0.05 after adjustment for the stratification factors (race and baseline attack severity). For subgroup analyses, there was no covariate adjustment and *P* values were presented as descriptive statistics. Time-to-event data (time to meeting discharge criteria and TOSR) were summarized using Kaplan-Meier curves and Kaplan-Meier estimates of the 25th, 50th (median), and 75th percentiles with associated 2-sided 95% CIs. Fisher exact test was used to examine between-group differences in the proportion of subjects meeting each of the other secondary end points.

The efficacy analyses were conducted in the intention-to-treat population (Figure 1) unless otherwise stated.

The sample size calculation used Kaplan-Meier estimates from the amelioration of angiotensin-converting enzyme inhibitor—induced angioedema (AMACE) study (see Table E2 in this article's Online Repository at www.jaci-inpractice.org).[15] Using the log-rank test for evaluating equality of survival curves and a 2-sided significance level of .05, we calculated that 100 subjects (50 subjects per treatment group) would yield at least 95% power to detect a 2-fold difference in the primary efficacy end point and at least 90% power to detect a difference in the key secondary efficacy end point given similar distributions of events as observed in the previous study. Assuming that 15% of subjects would not achieve the end point, the requisite study sample size was estimated at 118 subjects.

Safety analyses were performed in the safety population (Figure 1). No formal hypothesis testing for safety assessments was planned.

RESULTS

Between December 2013 and August 2015, 121 subjects with presumed ACE-I—induced angioedema were randomized at 31 of 59 opened sites. No subjects withdrew from the study because of AEs, but 3 subjects did not receive the study drug and 1 subject could not be contacted for the day 3 follow-up (Figure 1).

Demographics and baseline characteristics were generally comparable between groups (Table I). More than 90% of the subjects received corticosteroids, antihistamines, or epinephrine before the study drug; the interval to treatment with these conventional medications averaged 3.5 hours. One notable difference was the higher percentage of patients weighing 75 kg or less in the placebo group versus the icatibant group.

Median time from symptom onset to study drug administration was 7.8 hours (interquartile range [IQR], 5.5-9.6 hours; Table II). Fifty-five subjects received antihistamines after study drug administration, 26 (43%) in the icatibant group and 29 (50%) in the placebo group.

Fifty-three subjects received a nonsteroidal anti-inflammatory drug within 21 days before their angioedema attack, including 28 subjects receiving icatibant and 25 subjects receiving placebo. Four subjects receiving icatibant (7%, type not defined) but no subjects receiving placebo had a history of angioedema.

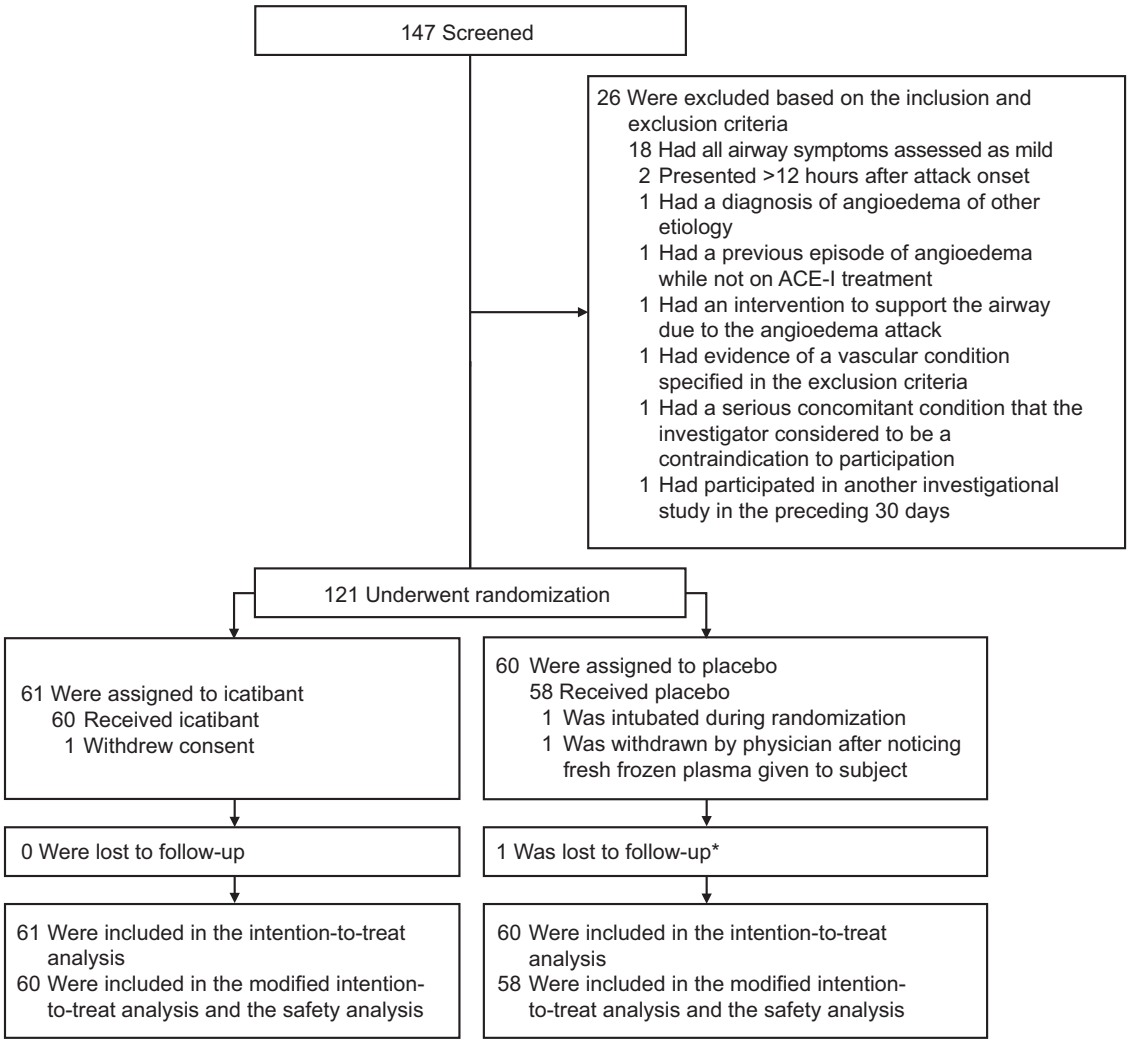

FIGURE 1. Flow diagram of subjects. The intention-to-treat population comprised all randomized subjects (N = 121). The modified intention-to-treat population comprised all randomized subjects who received the study drug (n = 118). The safety population comprised all subjects who received the study drug (n = 118). *Discharged from hospital approximately 13 hours after treatment having met discharge criteria, but could not be reached for the day 3 safety follow-up.

Efficacy

There were no statistically significant differences between the 2 treatment groups in the primary efficacy end point of time to meeting discharge criteria ($P = .63$), the key secondary end point of TOSR ($P = .57$), or any other secondary end point (see Tables E3 and E4 in this article's Online Repository at www.jaci-inpractice.org).

In both groups, median time to meeting discharge criteria was 4.0 hours (IQRs, 2.0-6.0 hours for icatibant and 1.0-6.0 hours for placebo). Median TOSR was 2.0 hours (IQR, 0.6-3.1 hours) with icatibant and 1.6 hours (IQR, 0.5-3.9 hours) with placebo (Figure 2). Of 121 randomized subjects, 34 receiving icatibant and 32 receiving placebo were admitted to hospital as inpatients; of these, 14 subjects receiving icatibant and 16 receiving placebo were admitted to an intensive care unit.

No apparent treatment differences were observed in planned or post hoc subgroup analyses (see Table E5 in this article's Online Repository at www.jaci-inpractice.org). When data on conventional medications administered before study drug administration were reviewed, it was noticed that more subjects in the icatibant group had received epinephrine than in the placebo group (16 vs 11, respectively). However, there was no apparent treatment benefit of icatibant in the subgroup of subjects who had not been given epinephrine.

One subject underwent endotracheal intubation 1.5 hours after receiving icatibant and 4.75 hours after attack onset. The symptoms were deemed moderate at baseline. The subject was admitted to an intensive care unit and met the primary end point 96 hours after treatment.

Safety

Mild or moderate injection site reactions were common in both groups (Table III). Other AEs occurring at or after study drug administration included headache (12%), angioedema (12%), and dysphonia (5%) with icatibant, and headache (7%), dyspnea (5%), and nausea (5%) with placebo. Three mild

TABLE I. Demographic and baseline characteristics by treatment group (intention-to-treat population)

Characteristic	Icatibant 30 mg (n = 61)	Placebo (n = 60)	Total (N = 121)
Age (y), mean ± SD	60.9 ± 12.1	61.8 ± 13.4	61.4 ± 12.7
Age >65 y, n (%)	22 (36.1)	25 (41.7)	47 (38.8)
Sex: male, n (%)	34 (55.7)	25 (41.7)	59 (48.8)
Black or African American, n (%)	41 (67.2)	43 (71.7)	84 (69.4)
Weight (kg), n (%)			
≤75	9 (14.8)	20 (33.3)	29 (24.0)
>75-100	31 (50.8)	24 (40.0)	55 (45.5)
>100	21 (34.4)	16 (26.7)	37 (30.6)
Body mass index (kg/m^2), mean ± SD	33.5 ± 8.9	30.5 ± 7.4	32.0 ± 8.3
Attack severity, n (%)			
Moderate	45 (73.8)	42 (70.0)	87 (71.9)
Severe or very severe	16 (26.2)	18 (30.0)	34 (28.1)
ACE-I taken, n (%)			
Lisinopril	40 (65.6)	44 (73.3)	84 (69.4)
Ramipril	6 (9.8)	2 (3.3)	8 (6.6)
Lisinopril and hydrochlorothiazide	5 (8.2)	3 (5.0)	8 (6.6)
Enalapril	4 (6.6)	1 (1.7)	5 (4.1)
Perindopril	3 (4.9)	2 (3.3)	5 (4.1)
Other	3 (4.9)	6 (10.0)	9 (7.4)
ACE-I treatment started within 90 d of the attack, n (%)*			
Yes	16 (26.7)	15 (24.6)	31 (25.6)
No	38 (63.3)	35 (57.4)	73 (60.3)
Missing data	6 (10.0)	8 (13.1)	14 (11.6)

*If the start date for the ACE-I was truncated (missing month, day, or both), the dates were imputed using an algorithm.

TABLE II. Medications and time delays preceding study drug administration

Parameter assessed	Icatibant 30 mg	Placebo	Total
Conventional medication administered before study drug administration, n (%)*	n = 61	n = 60	N = 121
All conventional medications	55 (90.2)	55 (91.7)	110 (90.9)
Antihistamines	52 (85.2)	53 (88.3)	105 (86.8)
Corticosteroids	49 (80.3)	51 (85.0)	100 (82.6)
Epinephrine	16 (26.2)	11 (18.3)	27 (22.3)
Time from attack onset to conventional medication administration (h)†	n = 55	n = 55	n = 110
Median	3.4	3.6	3.5
Range	0.0-9.7	0.0-11.7	0.0-11.7
IQR	1.8-5.8	2.5-5.1	2.1-5.3
Time from conventional medication to study drug administration (h)‡	n = 54	n = 53	n = 107
Median	3.7	3.1	3.3
Range	0.8-10.2	0.3-10.3	0.3-10.3
IQR	2.0-5.4	1.6-4.4	1.8-5.1
Time from attack onset to study drug administration (h)§	n = 60	n = 58	n = 118
Median	7.9	7.8	7.8
Range	2.0-12.4	1.7-12.2	1.7-12.4
IQR	5.5-9.7	5.6-9.4	5.5-9.6

Conventional medications include corticosteroids, antihistamines, and epinephrine.
*Intention-to-treat population.
†Intention-to-treat population, subjects who received conventional medication.
‡Modified intention-to-treat population, subjects who received conventional medication.
§Modified intention-to-treat population.

cardiac AEs were reported in 3 subjects receiving icatibant: atrial fibrillation (assessed as unrelated to study drug; history of atrial fibrillation), tachycardia (possibly related to study drug; received epinephrine concomitantly), and ventricular extrasystoles (possibly related to study drug; history of anxiety, breast cancer, nontoxic goiter, and hypertension). Three mild or moderate cardiac events were reported in 2 subjects receiving placebo: tachycardia (history of aortic stenosis, congestive heart failure, and coronary artery bypass graft) and 2 events of angina pectoris (history of angina and QTc prolongation); all 3 events were considered unrelated to the study drug. The most common AEs deemed treatment-related in the icatibant group were increased serum uric acid concentration, increased neutrophil percentage, dysphonia (2 subjects each), and angioedema (3 subjects). No treatment-related AEs were considered severe or serious.

DISCUSSION

In this phase III study, icatibant had no appreciable benefit in treating ACE-I–induced angioedema. These data contrast with the investigator-initiated AMACE study (27 subjects in per-protocol population; icatibant 30 mg vs standard therapy of intravenous prednisolone plus clemastine), which reported a substantially shorter median time to complete resolution of edema in the icatibant group (8.0 vs 27.1 hours; $P = .002$), as well as a shorter median time to TOSR (2.0 vs 11.7 hours; $P = .03$).[15] The reasons for the lack of concordance between our results and those of the earlier study remain unclear. Other than a possible type I error in the original study, multiple potential contributing factors merit consideration.

A notable difference between our findings and those in the AMACE study[15] was the substantially shorter time to improvement in the control group. The sample size calculation for the primary end point, time to meeting discharge criteria, was based on observed data from the AMACE study. The estimated icatibant response was comparable to that observed in this study. However, the placebo group recovered more quickly than estimated on the basis of AMACE data, and recovery time was considerably shorter than the typical 24 to 72 hours reported for patients with ACE-I–induced angioedema.[17-19] This finding, coupled with the fact that most subjects received corticosteroids, antihistamines, or epinephrine before study entry and only approximately 25% had started the ACE-I within 3 months of the attack, suggests that some enrolled subjects may have had histamine-mediated rather than ACE-I–induced angioedema. This possibility of a mixed angioedema population is an

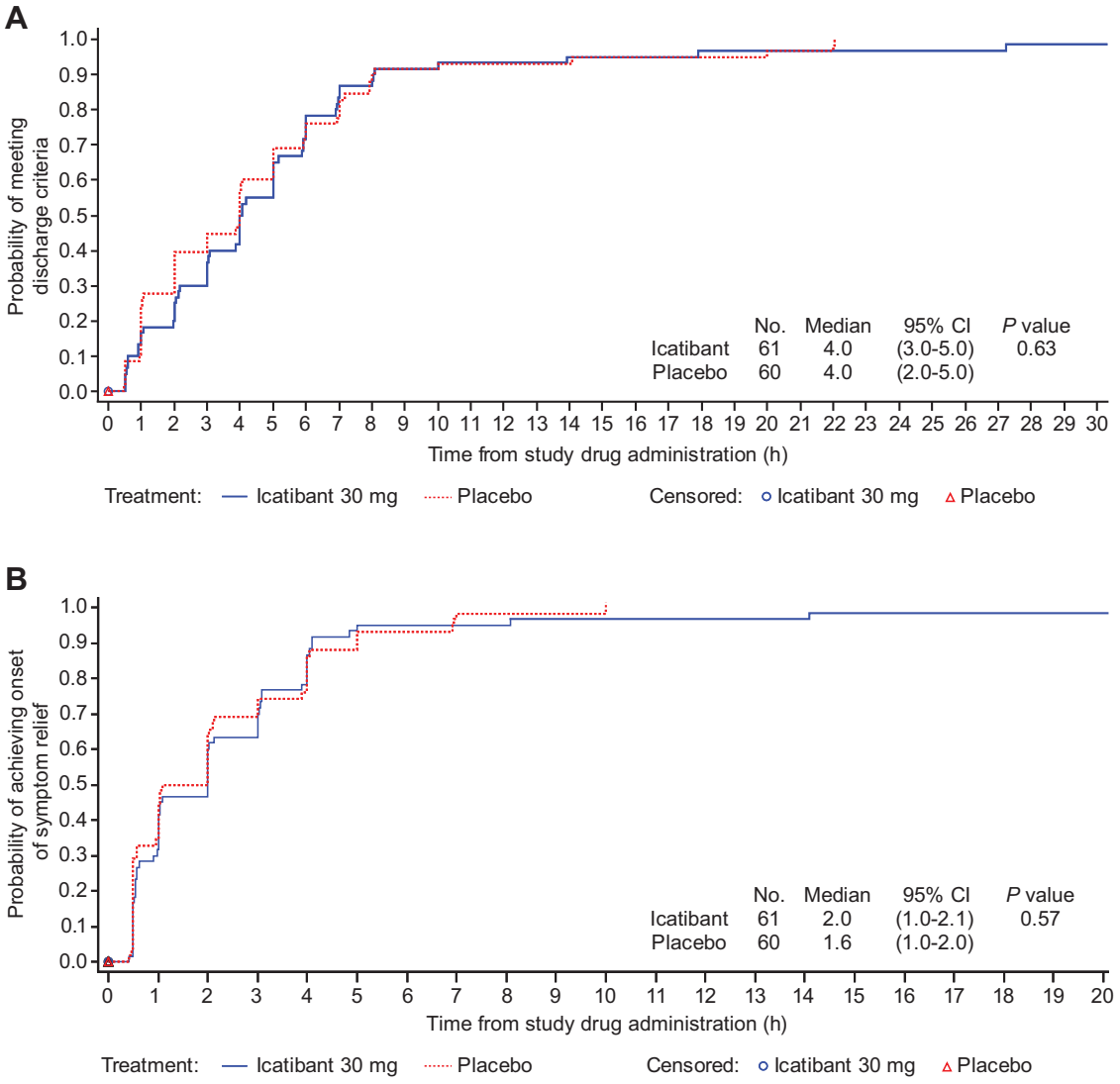

FIGURE 2. Kaplan-Meier plots. **A**, Time to meeting discharge criteria by treatment group. **B**, TOSR by treatment group (intention-to-treat population). Subjects who did not achieve the end point within the observation period were censored at the last observation time. One subject (icatibant group) who achieved the end points at 96 hours posttreatment was not plotted in this graph.

underlying limitation of a pragmatic study design; our patients represent those we would typically treat in the emergency department in a real-world setting. Although we acknowledge this possible limitation, our strict exclusion criteria reduced the likelihood of enrolling patients with other etiologies, particularly the exclusion of subjects with evident clinical response to antihistamines and/or corticosteroids. In addition, though many of our enrolled subjects did not follow the typical disease course for ACE-I–induced angioedema, reports in the literature vary considerably with regard to the timing of symptom onset after ACE-I exposure (1 day to ≥10 years),[12,17,18,20] as well as the duration of ACE-I–induced angioedema symptoms (a few hours to a few days),[21,22] and response to histamine-targeted agents.[17,18,22]

Another factor that may have contributed to a shorter recovery trajectory in the placebo group in our study was the prolonged median time from attack onset to study drug administration (7.9 [range, 2.0-12.4] and 7.8 [range, 1.7-12.2] hours in the icatibant group and the comparator group, respectively, in this study vs 6.1 [range, 3.0-10.0] and 5.1 [range, 2.0-9.3] hours in the AMACE study).[15] The time delay between symptom onset and study drug administration in any interventional study is multifactorial, and includes time taken for subjects to seek medical attention, be identified, and undergo study enrollment procedures. Although we explicitly excluded subjects with either mild angioedema or the most severe angioedema (who could not wait to undergo study procedures), eligible subjects who were rapidly worsening also were likely underrepresented in the study population. Therefore, the logistics of consent and enrollment may have led to a study population in whom the angioedema attack was plateauing, possibly contributing to an overall shorter duration of symptoms than is typically seen with ACE-I–induced angioedema attacks. Such considerations underline the challenges of performing clinical trials in a resuscitation

TABLE III. Treatment-emergent AEs and injection site reactions by treatment group (safety population)

	Icatibant 30 mg (n = 60)		Placebo (n = 58)	
AEs and injection site reactions	**n (%)**	**No. of events**	**n (%)**	**No. of events**
AEs				
Any event	27 (45.0)	70	21 (36.2)	40
Any treatment-related event	11 (18.3)	28	8 (13.8)	16
Any serious event	2 (3.3)	2	1 (1.7)	1
Fatal event	0		0	
Any treatment-related serious event	0		0	
Any severe event	1 (1.7)	1	1 (1.7)	1
Any treatment-related severe event	0		0	
Any event related to the angioedema attack	15 (25.0)	26	10 (17.2)	19
Injection site reactions				
Any injection site reaction	39 (65.0)		18 (31.0)	
Erythema	31 (51.7)		13 (22.4)	
Swelling	17 (28.3)		13 (22.4)	
Cutaneous pain	10 (16.7)		7 (12.1)	
Burning sensation	15 (25.0)		7 (12.1)	
Itching	13 (21.7)		6 (10.3)	
Warm sensation	16 (26.7)		8 (13.8)	
Any severe injection site reaction	0		0	

setting, and the need for solutions such as pragmatic trials and studies with waiver of consent.[23] However, an additional, pragmatic trial of icatibant in patients with rapidly progressing angioedema would be challenging to design and to enroll eligible patients into, even with exception from informed consent, because the need to exclude other common causes of angioedema would limit the promptness with which the investigational drug could be administered.

The primary end points also differed. The primary end point in the AMACE study was time to complete resolution of edema (based on composite scores and determined in part by visual examination), whereas the primary end point in this trial was based on explicit multilevel scoring in 4 distinct domains. Ishoo et al[24] previously described upper airway angioedema in 4 incremental stages that related the anatomic site of angioedema at presentation with the subject's risk of airway obstruction and thus decisions regarding hospital admission. The Ishoo et al criteria were not used in this trial because they require the use of invasive laryngoscopy to evaluate the upper airway and, critically, have not been validated,[25] unlike the rating scale and proposed discharge criteria used in this study.[16] The primary end point of this study was used to represent a feasible real-world assessment in the emergency department of the symptoms most concerning to physicians and patients, including tongue edema, which can lead to asphyxiation,[5] and voice change and difficulty breathing (dyspnea and stridor), which can signal the need for active airway intervention.[24]

Other between-study differences merit mention. The AMACE study[15] was conducted in a white European population, whereas there was a predominance of blacks or African Americans in this study, who may have a higher sensitivity to bradykinin than do whites.[26] In addition, the most frequently taken ACE-I in this study was lisinopril (69%), versus ramipril (48%) in the AMACE study. Although there is no clear differential risk for angioedema among ACE-Is, ramipril has a longer half-life,[27] possibly contributing to a prolonged duration of signs and symptoms. Unlike the AMACE study, the icatibant group in this study was allowed to receive concomitant conventional medications. Finally, in this study, 7% of subjects receiving icatibant had a history of angioedema (type not defined), whereas in the AMACE study, 5 (38%) subjects in the icatibant group and 5 (36%) in the control group had a history of ACE-I angioedema.[15] Repeat attacks were, therefore, more prevalent in the AMACE study, but there is no indication that this reflects a difference in the type of subjects enrolled or their potential response to treatment.

In our study, there was a higher percentage of patients weighing 75 kg or more in the icatibant group versus the placebo group. Weight has been shown to influence angioedema outcomes in some reports but not others. For instance, in patients with hereditary angioedema enrolled in the prospective, observational Icatibant Outcome Survey, obese patients had more severe attacks, and a higher percentage of obese patients required icatibant reinjection compared with patients with lower body mass index.[28] However, in a retrospective analysis of 875 patients with angioedema (of whom 496 [56.6%] had ACE-I–induced angioedema), body weight was not shown to increase the risk of severe angioedema.[22] In our study, no apparent treatment differences were observed when time to meeting discharge criteria and TOSR were examined by prespecified exploratory subgroups of body weight ($\leq$75 kg, 75-100 kg, >100 kg) and body mass index (<25 kg/m^2, 25-<35 kg/m^2, $\geq$35 kg/m^2).

There are likely multiple pathways and genetic factors involved in the development of ACE-I–induced angioedema.[29] The purported pathophysiologic mechanism suggests that icatibant should be efficacious,[30] but the results of this study cast doubt on the importance of bradykinin and B2 receptor interaction, or at least its importance several hours after symptom onset. Although our negative findings may have resulted from the presence of a mixed angioedema population (as mentioned previously), the possibility of alternative factors is important to consider. Previous studies of ecallantide, an inhibitor of the protease plasma kallikrein that liberates bradykinin from high-molecular-weight kininogen, also lead to questions regarding the importance of targeting bradykinin activity or its production.[31,32] There is research interest around bradykinin, substance P, and des-Arg^9-bradykinin and the peptidases involved in their metabolism, as well as an interest in the genes for their receptor sites. Further investigations could explore whether the pathophysiology of ACE-I–induced angioedema involves elevations in des-Arg^9-bradykinin or substance P, because des-Arg^9-bradykinin may interact with the B1 receptor and substance P through the neurokinin 1 receptor, neither of which is blocked by icatibant. Ultimately, ACE-I–induced angioedema may come to be defined by distinct patient subtypes considered susceptible to angioedema attacks because of variations in enzyme activity and ethnic predisposition.[29]

In conclusion, icatibant was no more effective than placebo in treating at least moderately severe ACE-I–induced angioedema in this phase III trial.

Acknowledgements

We thank the subjects, investigators, and study personnel for their participation in this study. Research was funded by the sponsor, Shire HGT. Under the direction of the authors, Clare Guni, BMBS, Sally Hassan, PhD, and Sophia Shumyatsky, PharmD, employees of Excel Scientific Solutions, provided writing assistance for this publication. Editorial assistance in formatting, proofreading, copy editing, and fact checking also was provided by Excel Scientific Solutions. Shire HGT provided funding to Excel Scientific Solutions for support in writing and editing this manuscript. Although employees of the sponsor were involved in the design, collection, analysis, interpretation, and fact checking of information, the content of this manuscript, the interpretation of the data, and the decision to submit the manuscript for publication was made independently by the authors.

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APPENDIX
STUDY INVESTIGATORS WHO ENROLLED AT LEAST 1 SUBJECT

Canada

- Marco Sivilotti (Kingston General Hospital, Kingston, Ontario)
- Sam Campbell (Queen Elizabeth II Health Sciences Center, Halifax, Nova Scotia)

Israel

- Osamah Hussein (Ziv Medical Center, Safed)

United Kingdom

- Richard Body (Manchester Royal Infirmary, Manchester)
- Andrew Appelboam (Royal Devon and Exeter Hospital NHS Trust, Exeter)
- Maria Finn (Brighton and Sussex University Hospitals NHS Trust, Brighton)
- Christopher Gough (Nottingham University Hospitals NHS Trust, Nottingham)

United States

- John Kowalski (Albert Einstein Medical Center, Philadelphia, Pennsylvania)
- Phillip Levy (Wayne State University and Sinai-Grace Hospital, Detroit, Michigan)
- Kurt Weber (Orlando Health, Orlando, Florida)
- Diane Sauter (Washington Hospital Center, Washington, District of Columbia)
- Marie-Carmelle Elie (UF Health Shands Hospital, Gainesville, Florida)
- John Garrett (Baylor University Medical Center, Dallas, Texas)
- Gregory Jay (Rhode Island Hospital, Providence, Rhode Island)
- David Burt (University of Virginia, Charlottesville, Virginia)
- Lawrence Lewis (Barnes-Jewish Hospital, Saint Louis, Missouri)
- Richard Sinert (Kings County Hospital Center, Brooklyn, New York)
- James Miner (Hennepin County Medical Center, Minneapolis, Minnesota)
- Jonathan A. Bernstein (University of Cincinnati, Cincinnati, Ohio)
- Samaresh Dasgupta (Inspira Health Network, Vineland, New Jersey)
- Megan Healy (Temple University Hospital, Philadelphia, Pennsylvania)
- Jacob Samuel (John H. Stroger Jr Hospital of Cook County, Chicago, Illinois)
- Jason Wilson (Tampa General Hospital, Tampa, Florida)
- Aveh Bastani (William Beaumont Hospital, Troy, Michigan)
- Chad Cannon (University of Kansas Cancer Center, Fairway, Kansas)
- Sharon Mace (Cleveland Clinic, Cleveland, Ohio)
- Gentry Wilkerson (University of Maryland School of Medicine, Baltimore, Maryland)
- Rana Bonds (University of Texas Medical Branch, Galveston, Texas)
- Howard Klausner (Henry Ford Health System, Detroit, Michigan)
- Arvind Venkat (Allegheny General Hospital, Pittsburgh, Pennsylvania)

TABLE E1. Symptom severity ratings: Difficulty breathing, difficulty swallowing, voice changes, and tongue swelling*

Symptom	Rating	Description of rating
Difficulty breathing	0 = absence of symptoms	Normal breathing
	1 = mild	Mild additional effort required for breathing by subject, but no audible wheezing or no stridor heard with stethoscope
	2 = moderate	Audible wheezing and/or stridor heard with stethoscope only, with uncomfortable breathing and moderate additional effort required for breathing by subject
	3 = severe	Audible wheezing and/or stridor audible without stethoscope, with subject in moderate distress
	4 = very severe	Audible severe wheezing and audible marked stridor, with subject in severe distress and tripod posturing (sitting or standing, leaning forward and supporting the upper body with hands on the knees or on another surface)
Difficulty swallowing	0 = absence of symptoms	Normal swallowing
	1 = mild	Mild sensation of difficulty swallowing (fullness in throat), but can swallow solids and liquids
	2 = moderate	Marked difficulty or unable to swallow solids, but can swallow liquids
	3 = severe	Unable to swallow solids or liquids, but can swallow saliva
	4 = very severe	Unable to swallow solids, liquids, or saliva (drooling)
Voice changes	0 = absence of symptoms	Normal voice
	1 = mild	Audible speech, but mild disruption of normal voice (hoarseness)
	2 = moderate	Audible speech, but moderate disruption of normal voice (muffled voice)
	3 = severe	Very difficult to hear speech or for subject to articulate
	4 = very severe	Unable to speak at all
Tongue swelling	0 = absence of symptoms	No swelling
	1 = mild	Mild anterior or lateral tongue swelling, uvula completely visible
	2 = moderate	Moderate anterior or lateral tongue swelling, uvula only partially visible
	3 = severe	Severe diffuse swelling of tongue, soft palate and uvula not visible at all
	4 = very severe	Very severe diffuse tongue swelling that completely fills mouth orifice

*The investigator was asked to rate each of the symptoms on the basis of a discussion with the subjects about their usual function and current function/symptoms, and on the basis of investigator's observation of certain signs. The descriptions provided in the table were used as a guide, along with the investigator's clinical judgment to determine the most representative severity rating.

TABLE E2. Kaplan-Meier estimates of the primary and key secondary end points used for the sample size calculation as observed in the AMACE study

	Percentage of subjects not meeting discharge criteria		Percentage of subjects not achieving onset of symptom relief	
Time (h)	Icatibant	Control	Icatibant	Control
2	89	91	44	91
4	67	82	11	73
6	33	73	10	55
8	22	60	9	36
12	12	55	8	9
24	11	27	0	0

TABLE E3. Kaplan-Meier estimates of time-to-event statistics for individual symptoms (modified intention-to-treat population)

Events	Icatibant 30 mg		Placebo	
Median time to meeting the discharge criterion (h) (95% CI)				
Difficulty breathing	n = 30	2.0 (0.9-3.0)	n = 26	1.5 (1.0-3.0)
Difficulty swallowing	n = 50	4.0 (2.1-5.0)	n = 49	3.9 (2.0-5.0)
Voice change	n = 51	0.6 (0.5-1.0)	n = 54	0.9 (0.5-1.0)
Tongue swelling	n = 49	2.0 (1.0-3.1)	n = 48	2.0 (0.6-3.0)
Median time to onset of relief for individual symptoms (h) (95% CI)				
Difficulty breathing	n = 30	0.5 (0.5-0.5)	n = 26	0.5 (not estimable*)
Difficulty swallowing	n = 50	0.5 (0.5-0.6)	n = 49	0.5 (0.5-0.6)
Voice change	n = 51	0.6 (0.5-1.0)	n = 54	0.5 (0.5-1.0)
Tongue swelling	n = 49	1.0 (0.9-2.0)	n = 48	0.8 (0.5-1.1)

All *P* values for between-group difference were ≥.08.
*Because of the large number of subjects who achieved relief at the same time point.

TABLE E4. Differences between the 2 treatment groups in secondary end points (modified intention-to-treat population)

Endpoint	Icatibant 30 mg (n = 60)	Placebo (n = 58)
Occurrence of airway intervention after study drug administration, n (%)	1 (1.7)	0
Occurrence of hospitalization after study drug administration, n (%)*	22 (45.8)	22 (45.8)
Use of corticosteroids, antihistamines, or epinephrine after study drug administration, n (%)	35 (58.3)	35 (60.3)
Achievement of time to meeting discharge criteria by time from study drug administration, n (%)		
4 h	33 (55.0)	35 (60.3)
6 h	47 (78.3)	44 (75.9)
8 h	55 (91.7)	53 (91.4)

All *P* values for between-group differences were ≥.58 and obtained from Fisher exact test.
*Subjects who were hospitalized before study drug administration were excluded from this analysis (48 subjects from each treatment group were included in this analysis).

TABLE E5. Kaplan-Meier estimates of time to meeting discharge criteria for subjects treated within or after 3, 4, 5, 6, 7, and 8 h of symptom onset (post hoc analysis; modified intention-to-treat population)

Subgroup by time from attack onset to treatment	Time to meeting discharge criteria	Icatibant 30 mg	Placebo
≤3 h	n	2	4
	Median (95% CI)	3.8 (0.6-7.0)	6.0 (3.0-22.0)
≤4 h	n	6	6
	Median (95% CI)	6.0 (0.6-96.0)	7.0 (3.0-22.0)
≤5 h	n	10	13
	Median (95% CI)	5.6 (0.6-6.9)	5.9 (3.0-8.0)
≤6 h	n	19	18
	Median (95% CI)	3.1 (2.0-6.9)	4.5 (3.0-6.0)
≤7 h	n	26	24
	Median (95% CI)	4.0 (2.1-5.2)	4.5 (3.0-6.0)
≤8 h	n	32	33
	Median (95% CI)	4.0 (2.1-5.0)	4.0 (2.0-5.9)
>3 h	n	58	54
	Median (95% CI)	4.0 (3.1-5.0)	4.0 (2.0-5.0)
>4 h	n	54	52
	Median (95% CI)	4.0 (3.0-5.0)	3.9 (2.0-4.1)
>5 h	n	50	45
	Median (95% CI)	4.0 (3.0-5.0)	3.0 (1.1-4.1)
>6 h	n	41	40
	Median (95% CI)	4.1 (3.1-5.0)	3.0 (1.0-4.1)
>7 h	n	34	34
	Median (95% CI)	4.0 (3.0-5.9)	2.5 (1.0-4.0)
>8 h	n	28	25
	Median (95% CI)	4.0 (3.0-5.9)	4.0 (1.0-5.0)

All *P* values for between-group difference were ≥.16.