

Response time for ecallantide treatment of acute hereditary angioedema attacks

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Background: Hereditary angioedema (HAE) is a rare, debilitating, and potentially fatal disease characterized by acute attacks of swelling that can affect the abdomen/gastrointestinal tract, larynx, face, genitals, and extremities. Ecallantide is a novel plasma kallikrein inhibitor developed for the treatment of acute HAE attacks.

Objective: To examine the speed of effect of ecallantide vs placebo.

Methods: Data were integrated from 2 randomized, double-blind, placebo-controlled phase 3 trials of ecallantide in patients with HAE. Eligible patients presented within 8 hours of onset of a moderate to severe HAE attack for 1:1 randomization to receive a single dose of 30 mg of subcutaneous ecallantide or placebo. End points included time to beginning of improvement, time to sustained overall improvement, and time to significant overall improvement.

Results: A total of 143 participants (70 receiving ecallantide and 73 receiving placebo) were included. The distribution curves for time to beginning of improvement demonstrated a trend in favor of ecallantide vs placebo within 4 hours ($P_{\log \text{ rank}} = .09$). For time to onset of sustained improvement, the difference in the distribution of the curves between the 2 groups reached significance by 2 hours after dosing ($P_{\log \text{ rank}} = .04$). For time to significant overall improvement, the difference in the distribution of the curves reached significance in favor of ecallantide by 90 minutes ($P_{\log \text{ rank}} = .04$). The beneficial effect of ecallantide was demonstrated earliest for abdominal attacks, followed by laryngeal and peripheral attacks.

Conclusions: Ecallantide provides relief of acute HAE attack symptoms, with rapidity of response commensurate with therapeutic needs for HAE attack locations.

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INTRODUCTION

Hereditary angioedema (HAE) is a rare, debilitating, and potentially fatal disease characterized by unpredictable acute attacks of swelling that can affect the abdomen/gastrointestinal tract, larynx, face, genitals, and extremities.^{1–4} It is caused by reduced levels of or functionally abnormal C1-esterase inhibitor, a major inhibitor of contact system proteases. During acute HAE attacks, reduced C1-esterase inhibitor activity results in high levels of unopposed plasma kallikrein and overactivation of the kallikrein-kinin cascade, which then leads to excess bradykinin production, increased vascular permeabil-

ity, and swelling.^{4–6} Ecallantide (KALBITOR; Dyax Corp) is a novel plasma kallikrein inhibitor approved in the United States in December 2009 for the treatment of acute attacks of HAE.^{6,7}

Although typically attacks worsen during the first 24 hours and can last up to 5 days,^{2,4,8} individual HAE attacks are highly variable. Untreated attacks may progress unpredictably, becoming more severe or spreading to other anatomical locations.¹

A retrospective analysis of the time course profiles of multiple abdominal attacks in 153 patients identified 5 distinct attack phases: a prodromal phase, an early phase with mostly painless symptoms lasting from less than 1 hour to 24 hours, a crescendo phase with increasing severity across 0.5 to 18 hours (average, 2.4 hours), a maximum phase of pain and intensity enduring for 0.5 to 60 hours (average, 23.5 hours), and a decrescendo phase enduring for 12 to 84 hours.⁹ Although detailed time course profiles of other attack locations have not been published, attacks of different locations have demonstrated different time courses of resolution; overall attack duration and time to relief is often longer for peripheral attacks than for laryngeal or abdominal attacks.^{10–14}

As therapeutic options expand and clinical practice continues to demand a comprehensive understanding of the variations and complexities of HAE attacks, more detailed data regarding attack course by anatomical location and response to available therapy is needed. This analysis of integrated

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results from the phase 3 trials of the Evaluation of DX-88's Effects in Mitigating Angioedema (EDEMA) development program uses 3 distinct end points to examine the speed of effect of ecallantide and placebo overall and by primary attack location.

METHODS

These analyses integrate data from 2 similarly designed, multicenter, double-blind, placebo-controlled phase 3 studies in the EDEMA program: EDEMA3 double-blind portion (EDEMA3-DB) and EDEMA4. Both studies included patients 10 years or older with documented type I or II HAE who presented within 8 hours of a moderate to severe HAE attack affecting any anatomical location. Before initiation, the study protocols were reviewed and approved by the appropriate institutional review board or independent ethics committee at each site; all the patients provided written informed consent.

In both studies, patients with HAE attacks were randomized 1:1 to receive 30 mg of subcutaneous ecallantide or placebo. The randomization was stratified by anatomical location of the attack and by previous exposure to ecallantide. Both study protocols permitted the administration of an open-label dose of 30 mg of subcutaneous ecallantide up to 4 hours after initial treatment in the case of severe upper airway compromise (SUAC). In EDEMA4, an open-label dose of 30 mg of subcutaneous ecallantide (dose B) was also permitted 4 to 24 hours after initial dosing if there was an incomplete or no response to study drug or if attack symptoms recurred.

Time-to-response information was collected via a global improvement measure, a single-item response assessment by which patients reported how they were feeling overall compared with baseline using the following 5 categories: "a lot better or resolved," "a little better," "unchanged," "a little worse," and "a lot worse." Patients were asked every 15 minutes for the first 2 hours after dosing (hours 0-2), every 30 minutes for the next 2 hours (hours 2-4), and again at 24 hours. Based on the patients' responses, *time to beginning of improvement* was defined as the first time after dosing that the patient reported a response of "a little better" or "a lot better or resolved" within 4 hours of treatment. *Time to onset of sustained improvement* was defined as the first time after dosing that the patient reported a response of "a little better" or "a lot better or resolved" that endured for at least 45 minutes. *Time to significant overall improvement* was defined as the first time after dosing that the patient reported a response of "a lot better or resolved," reflecting complete or near-complete symptom resolution. Time to significant overall improvement was a secondary end point in EDEMA3-DB and EDEMA4. Time to onset of sustained improvement was a tertiary end point in both studies. Time to beginning of improvement was a post hoc analysis.

Time-to-improvement end points were analyzed overall and by primary attack location. In both studies, patients identified affected body sites based on 5 predefined anatomical locations, or symptom complexes, which were then con-

solidated into the 3 attack locations used in this analysis. Abdominal attacks include the "stomach/gastrointestinal" symptom complex, laryngeal attacks include the "internal head/neck," and peripheral attacks include the "genital/buttocks," "external head/neck," and "cutaneous" symptom complexes. Because attacks could affect multiple anatomical locations, primary attack location was determined in a hierarchical manner: as laryngeal if the internal head/neck symptom complex was identified as moderate/severe at baseline, as abdominal if the stomach/gastrointestinal symptom complex was moderate/severe at baseline (in the absence of moderate/severe laryngeal symptoms), and as peripheral if the external head/neck, genital/buttocks, or cutaneous symptom complex was moderate/severe at baseline (in the absence of moderate/severe laryngeal or abdominal symptoms).

Time-to-improvement end points were analyzed using Kaplan-Meier methods using a log-rank test to compare the distributions between the treatment groups. A $P=.05$, using a 2-sided significance level, denoted statistical significance. If the end point had not been reached by 4 hours after dosing, the patient's time to response was censored at the time of their last assessment. If a patient received an open-label dose (SUAC or dose B), the time to response was censored at the time of intervention. No adjustments were made for multiplicity.

The proportion of patients who achieved significant improvement by 4 and 24 hours after dosing was also assessed using the Fisher exact test. Patients who received a SUAC dose before 4 hours had neither the 4-hour nor the 24-hour evaluation; patients who received a dose B between 4 and 24 hours did not have a 24-hour evaluation. Patients missing the 4- or 24-hour evaluation were excluded from the proportion analyses.

RESULTS

Study Population

A total of 143 patients (70 receiving ecallantide and 73 receiving placebo) were included in this analysis. This integrated analysis includes only results from the initial treatment episode for the 25 patients treated in EDEMA3-DB and EDEMA4 to maintain treatment group independence. Baseline patient demographics are presented in Table 1. Treatment groups were well balanced with respect to age, sex, and race. At baseline, the abdomen was the most frequently reported primary attack location (44.8%), followed by peripheral attacks (38.5%) and laryngeal attacks (16.8%). Relative to the placebo group, the ecallantide group had more peripheral attacks (45.7% vs 31.5%) and laryngeal attacks (21.4% vs 12.3%) and fewer abdominal attacks (32.9% vs 56.2%).

Time to Improvement

Beginning of improvement within 4 hours was experienced by 51 ecallantide-treated patients (72.9%) vs 42 placebo-treated patients (57.5%). The median (interquartile range) time was 67.0 (37.0-225.0) minutes for ecallantide-treated patients and 105.0 (37.0-not reached [NR]) minutes for pla-

Table 1. Baseline Patient Demographics

Characteristic	Ecallantide group (n = 70)	Placebo group (n = 73)	Total (N = 143)
Age, y ^a			
Mean (SD)	36.5 (13.34)	36.1 (13.54)	36.3 (13.40)
Median	34.8	37.1	35.9
Range	16–77	10–72	10–77
Sex, No. (%)			
Female	49 (70.0)	45 (61.6)	94 (65.7)
Male	21 (30.0)	28 (38.4)	49 (34.3)
Race, No. (%)			
White	58 (82.9)	65 (89.0)	123 (86.0)
Black	4 (5.7)	6 (8.2)	10 (7.0)
Hispanic	6 (8.6)	1 (1.4)	7 (4.9)
Asian	1 (1.4)	1 (1.4)	2 (1.4)
Other	1 (1.4)	0	1 (0.7)
Primary attack location, No. (%)			
Abdominal	23 (32.9)	41 (56.2)	64 (44.8)
Laryngeal	15 (21.4)	9 (12.3)	24 (16.8)
Peripheral	32 (45.7)	23 (31.5)	55 (38.5)

^a Age at time of informed consent for the hereditary angioedema episode used in the integrated analysis.

cebo-treated patients (Supplementary Table 1). The distribution of the curves demonstrated a trend in favor of the ecallantide group, but significance was not reached ($P_{\log \text{ rank}} = .09$). The curves began to diverge approximately 1 hour after dosing (Fig 1A).

Sustained improvement was experienced by 48 ecallantide-treated patients (68.6%) and 30 placebo-treated patients (41.1%) within 4 hours after dosing. The median (interquartile range) time to onset of sustained improvement was 98.0 (52.0–NR) minutes for ecallantide-treated patients and was NR (52.0 minutes–NR) within 4 hours for placebo-treated patients (Supplementary Table 1). The difference between the ecallantide and placebo groups was significant ($P_{\log \text{ rank}} = .005$) (Fig 1B); a significant difference was noted by 2 hours after dosing ($P_{\log \text{ rank}} = .04$) (Supplementary Table 2).

Significant overall improvement (ie, complete or near-complete symptom resolution) was experienced by 33 ecallantide-treated patients (47.1%) and 19 placebo-treated patients (26.0%) within 4 hours after dosing. The median time was not reached by 4 hours in either group (Supplementary Table 1). However, the curves began to diverge approximately 60 minutes after dosing; the distribution of the curves was significant in favor of ecallantide ($P_{\log \text{ rank}} = .02$) (Fig 1C); significance was reached by 90 minutes after dosing ($P_{\log \text{ rank}} = .04$) (Supplementary Table 3).

Analysis by Primary Attack Location

Abdominal attacks. In patients whose primary attack location was abdominal, beginning of improvement within 4 hours after dosing was experienced by 19 of 23 ecallantide-treated patients (82.6%) vs 25 of 41 placebo-treated pa-

tients (61.0%). By 75 minutes, almost twice as many ecallantide-treated patients as placebo-treated patients with abdominal attacks had experienced beginning of improvement.

Sustained improvement within 4 hours for an abdominal attack was experienced by 19 of 23 ecallantide-treated patients (82.6%) vs 18 of 41 placebo-treated patients (43.9%); the distribution of the curves was significantly different ($P_{\log \text{ rank}} = .002$). By 1 hour after treatment, almost twice as many ecallantide-treated patients with abdominal attacks experienced onset of sustained improvement vs placebo-treated patients (Fig 2A).

Significant overall improvement within 4 hours was experienced by 15 of 23 ecallantide-treated patients (65.2%) vs 13 of 41 placebo-treated patients (31.7%) with an abdominal attack; the distribution of the curves was significantly different ($P_{\log \text{ rank}} = .01$). Within 2.75 hours, twice as many ecal-

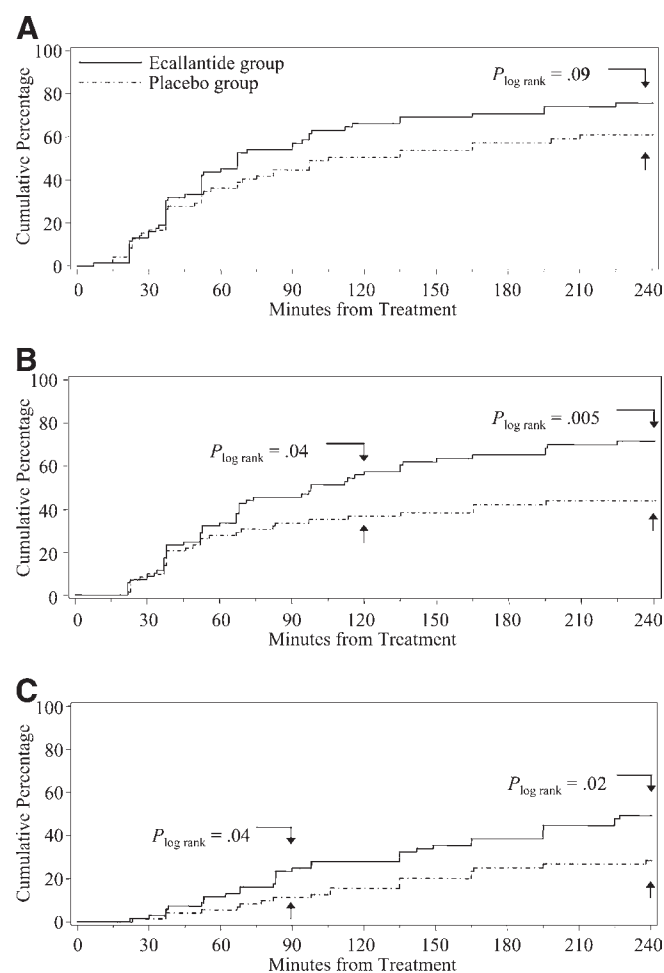


Figure 1. Kaplan-Meier analyses of time-to-response end points for the overall analysis population by treatment group. A, Time to beginning of improvement. B, Time to onset of sustained improvement. C, Time to significant improvement. Censoring of an individual patient's time-to-response data was conducted as described in the "Methods" section.

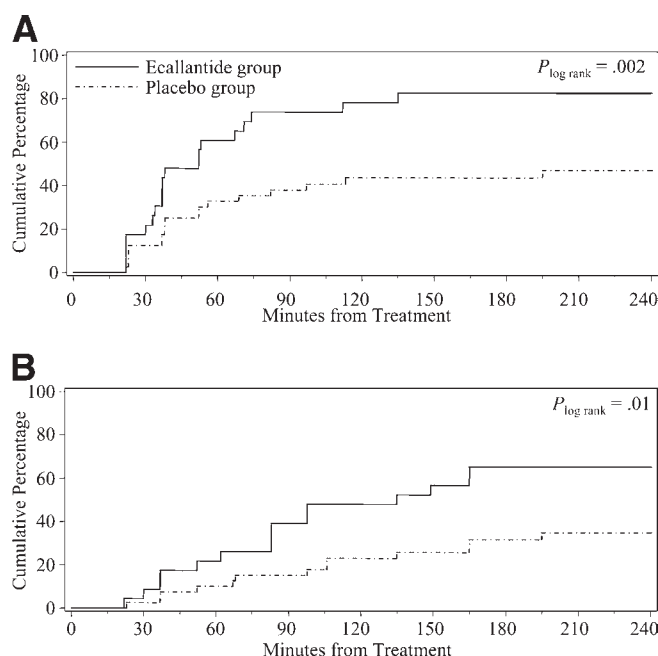


Figure 2. Kaplan-Meier analyses of the time to sustained (A) and significant (B) improvement for abdominal attacks. Censoring of an individual patient's time-to-response data was conducted as described in the "Methods" section.

lallantide-treated as placebo-treated patients experienced significant improvement (Fig 2B).

Laryngeal attacks. In patients whose primary attack location was laryngeal, beginning of improvement within 4 hours after dosing was experienced by 10 of 15 ecallantide-treated patients (66.7%) and by 4 of 9 placebo-treated patients (44.4%). Sustained improvement within 4 hours for a laryngeal attack was experienced by 10 of 15 ecallantide-treated patients (66.7%) vs 2 of 9 placebo-treated patients (22.2%). For patients with laryngeal attacks, the curves for time to onset of sustained improvement begin to diverge at approximately 1 hour (Fig 3A). By 2 hours, 3 times as many ecallantide-treated patients as placebo-treated patients had experienced sustained improvement. However, the difference in the distribution of the curves did not reach significance ($P_{\log \text{ rank}} = .10$).

Significant overall improvement within 4 hours for a laryngeal attack was experienced by 9 of 15 ecallantide-treated patients (60.0%) and by 1 of 9 placebo-treated patients (11.1%) (Fig 3B). The distribution of the curves was significant ($P_{\log \text{ rank}} = .03$).

Of patients with primary laryngeal attack symptoms, 1 in each treatment group demonstrated sustained improvement but not significant improvement within 4 hours. Of the 7 placebo-treated patients with a laryngeal attack who experienced neither sustained nor significant overall improvement within 4 hours, 3 received a SUAC dose. Of the 5 ecallantide-treated patients who experienced neither sustained nor significant improvement, 3 received a SUAC dose.

Peripheral attacks. In patients whose primary attack location was peripheral, beginning of improvement within 4 hours after dosing was experienced by 22 of 32 ecallantide-treated patients (68.8%) and by 13 of 23 placebo-treated patients (56.5%). Onset of sustained improvement within 4 hours was experienced by 19 of 32 ecallantide-treated patients (59.4%) and by 10 of 23 placebo-treated patients (43.5%). The curve for time to onset of sustained improvement rises somewhat more rapidly for ecallantide-treated patients than for placebo-treated patients (Fig 4A). Significant overall improvement was experienced by 9 of 32 ecallantide-treated patients (28.1%) and by 5 of 23 placebo-treated patients (21.7%) within 4 hours after treatment (Fig 4B).

Proportion of Significant Overall Improvement

Figure 5 presents the proportion of patients with significant overall improvement 4 and 24 hours after dosing. Of the 67 ecallantide-treated patients with a 4-hour evaluation, 31 (46.3%) had significant improvement vs 16 of 67 placebo-treated patients (23.9%). The percentage of ecallantide-treated patients with significant improvement at 4 hours, and the percentage difference between ecallantide and placebo, was greatest among laryngeal attacks (ecallantide, 66.7%; placebo, 16.7%), followed by abdominal attacks (ecallantide, 60.9%; placebo, 28.2%) and peripheral attacks (ecallantide, 28.1%; placebo, 18.2%). Overall, at 24 hours, 32 of 51 ecallantide-treated patients (62.7%) and 24 of 50 placebo-treated patients (48.0%) showed significant improvement. The percentage of ecallantide-treated patients with significant

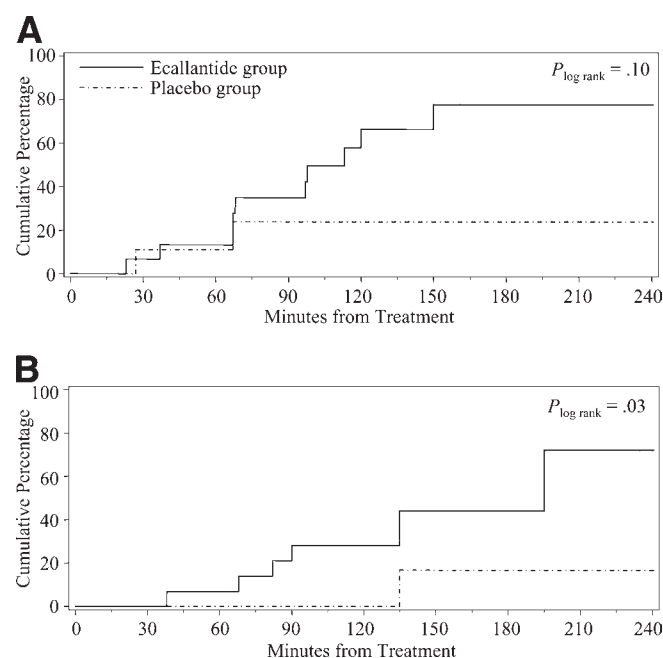


Figure 3. Kaplan-Meier analyses of the time to sustained (A) and significant (B) improvement for laryngeal attacks. Censoring of an individual patient's time-to-response data was conducted as described in the "Methods" section.

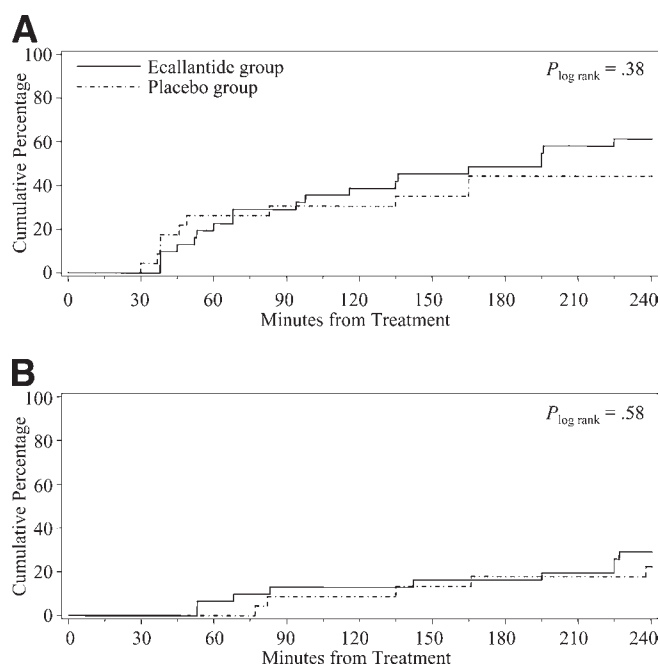


Figure 4. Kaplan-Meier analyses of the time to sustained (A) and significant (B) improvement for peripheral attacks. Censoring of an individual patient's time-to-response data was conducted as described in the "Methods" section.

improvement at 24 hours was highest among laryngeal attacks (ecallantide, 81.8%; placebo, 33.3%), followed by peripheral attacks (ecallantide, 61.9%; placebo, 29.4%) and abdominal attacks (ecallantide, 52.6%; placebo, 60.0%).

DISCUSSION

The goal of managing an acute attack of HAE is to achieve rapid, consistent, and sustained resolution of attack symptoms while preventing attack progression to other anatomical areas, especially the larynx, which could result in asphyxiation. Speed and extent of attack resolution were evaluated in this integrated analysis of the 2 double-blind, placebo-controlled, phase 3 studies of ecallantide in patients with HAE experiencing acute attacks.

The 3 time-to-improvement end points—beginning of improvement, onset of sustained improvement, and significant overall improvement—represent increasingly stringent clinical hurdles and address the most relevant clinical efficacy concerns of patients and physicians. Because HAE attacks are associated with significant pain, disability, and concern for potential asphyxiation, the rapidity of initial onset of action is an important determination. However, onset of sustained improvement and significant overall improvement address clinical efficacy questions highly relevant to patient therapy: at what point is durable improvement achieved and how quickly are HAE symptoms minimized enough for patients to resume normal daily activities? The characterization of sustained improvement ensures that therapeutic impact is not

biased by transient symptom improvement, as may occur with colicky, episodic abdominal symptoms during an HAE attack. The time to significant overall improvement, which reflects complete or near-complete symptom resolution, is the most stringent clinical measure providing strong evidence that the attack has resolved and is unlikely to proceed to other attack sites. Kaplan-Meier analyses demonstrated the benefit of ecallantide over placebo for all 3 hurdles, with statistical significance in favor of ecallantide demonstrated for the more stringent hurdles of onset of sustained improvement and significant improvement, thus supporting the clinical efficacy and usefulness of ecallantide.

Time-to-response analyses by attack location demonstrated that abdominal attacks respond most rapidly, followed by laryngeal and peripheral attacks. Abdominal attacks had the earliest onset of sustained and significant improvement and showed pronounced improvement over placebo: twice as many ecallantide-treated patients experienced sustained improvement within 1 hour after dosing and significant im-

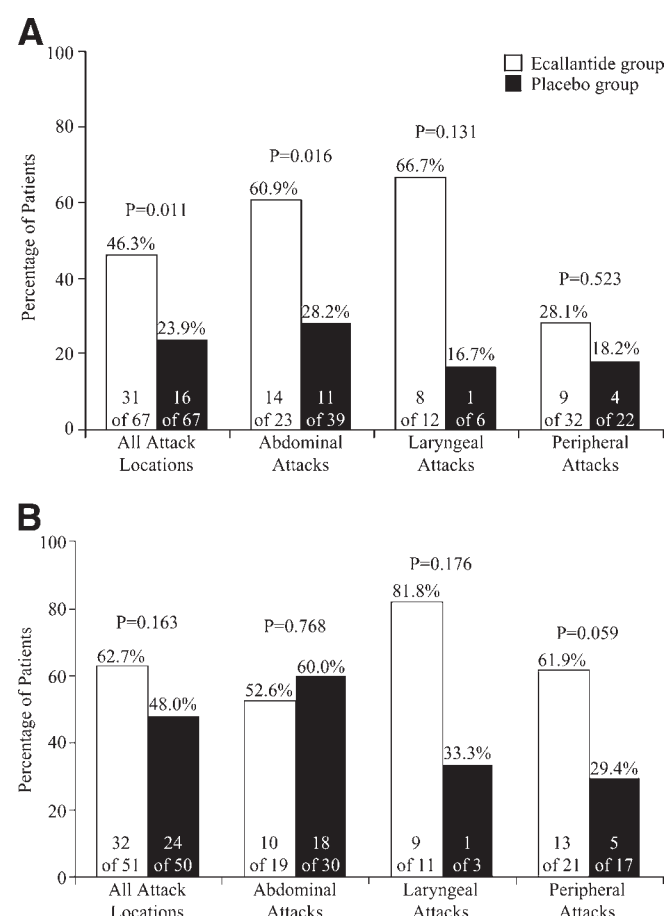


Figure 5. Proportion of patients with significant improvement at 4 hours (A) and at 24 hours (B). Patients missing the 4- or 24-hour evaluation were excluded from these analyses, as described in the "Methods" section. The P values are from the Fisher exact test.

provement by 2.75 hours. For abdominal attacks, statistically significant benefit for ecallantide over placebo was demonstrated by 4 hours after dosing. Early onset of relief of abdominal symptoms is clinically important given the pain, disability, and duration of typical abdominal episodes that frequently necessitate emergency medical care for narcotic analgesics, antiemetics, and intravenous fluids for progressive symptoms. Early effective intervention with ecallantide or other HAE-specific therapies is expected to alleviate the need for such emergency treatment and to prevent the occasional unnecessary surgical intervention for unresolved abdominal attacks.

Laryngeal attacks also showed rapid and pronounced improvement over placebo: twice as many ecallantide-treated patients experienced sustained improvement within 2 hours, and more than 3 times as many experienced significant overall improvement by 4 hours. Despite the relatively small number of patients with laryngeal attacks and the consequent difficulty of drawing statistical inferences, the Kaplan-Meier curves of time to sustained improvement within 4 hours demonstrated statistically significant benefit for ecallantide over placebo. Consistent rapid treatment efficacy is essential for laryngeal attacks given the associated mortality and the opportunity to prevent aggressive interventions sometimes required for progressive laryngeal edema, such as intubation or tracheotomy and intensive care unit stays.

The Kaplan-Meier analyses showed that peripheral attacks were the slowest to respond to treatment. The proportions analysis at 4 and 24 hours demonstrated that the benefit of ecallantide over placebo occurred after 4 hours for peripheral attacks. That is, at the 4-hour assessment, the percentage of ecallantide-treated patients with significant overall improvement was lower for patients with peripheral attacks compared with patients with abdominal and laryngeal attacks. However, at 24 hours, the percentage of ecallantide-treated patients with peripheral attacks demonstrating significant overall improvement caught up with the overall population and demonstrated benefit over placebo. This attack course and treatment response for peripheral attacks is consistent with other clinical experiences with HAE, which have shown that cutaneous angioedema is slower to resolve compared with angioedema at other anatomical sites.^{12–14} The underlying reason for the longer duration of cutaneous symptoms compared with gastrointestinal or laryngeal swelling has not been clearly identified but presumably relates to a greater capacity of mucosal tissues to rapidly resorb extravasated fluid once the vasodilatory effects of bradykinin have been halted. Nonetheless, the treatment response for peripheral swelling demonstrates the clinical benefits of stopping the progression of skin swelling, reducing the potential for attack progression to other anatomical sites, and potentially shortening the overall period of discomfort and disability that can be associated with moderate to severe cutaneous angioedema. The overall clinical benefit of treating cutaneous

HAE early in attack progression warrants further study.

This study is limited by the relatively small numbers of patients in some analyses, especially the analyses of laryngeal attacks. Furthermore, the study was a retrospective analysis of a combined data set, and one end point—time to beginning of improvement—was not prespecified in the trial designs, whereas the other end points were.

In summary, the data presented herein analyzing time to improvement for 3 levels of clinically relevant resolution, overall and by primary attack location, contribute to the growing base of empirical evidence and the growing understanding of the complexities and variations of acute HAE attacks. Physicians and patients using ecallantide for the treatment of acute HAE attacks can expect a rapid treatment effect. Onset of sustained symptom relief demonstrated statistically significant improvement for ecallantide over placebo by 2 hours after treatment; onset of significant overall improvement demonstrated statistically significant improvement for ecallantide over placebo by 90 minutes after treatment. Given the natural history and substantial morbidity of HAE attacks that can last up to 5 days without therapy, the symptom relief demonstrated with ecallantide should provide significant clinical benefit against acute attack symptoms, with rapidity of response commensurate with the therapeutic needs for HAE attack locations.

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SUPPLEMENTARY DATA

Additional tables accompany the on-line version of this article (available at <http://www.annallergy.org>).

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Supplementary Table 1. Time to Beginning of Improvement, Onset of Sustained Improvement, and Significant Improvement in Overall Response

	Ecallantide group (n = 70)	Placebo group (n = 73)	P value ^a
Beginning of improvement			
Began to improve within 4 h, No. (%)	51 (72.9)	42 (57.5)	NA
Time to beginning of improvement			.09
Estimated median	67.0	105.0	
95% CI	52.0–98.0	67.0–ND	
IQR	37.0–225.0	37.0–NR	
Onset of sustained improvement			
Sustained improvement within 4 h, No. (%)	48 (68.6)	30 (41.1)	NA
Time to onset of sustained improvement			.005
Estimated median	98	NR	
95% CI	68.0–136.0	165.0–ND	
IQR	52.0–NR	52.0–NR	
Significant improvement			
Significant improvement, No. (%)	33 (47.1)	19 (26.0)	NA
Time to significant improvement ^b			.02
Estimated median	NR	NR	
95% CI	165.0–ND	ND–ND	
IQR	98.0–NR	166.0–NR	

Abbreviations: CI, confidence interval; IQR, interquartile range; NA, not applicable; ND, could not be determined; NR, not reached within 4 hours.

^a Kaplan-Meier log-rank *P* values comparing the distributions for the time-to-improvement endpoint.

^b If the endpoint had not been reached by 4 hours post-dosing, the patient's time to response was censored at the time of their last assessment. If a patient received an open-label dose, the time to response was censored at the time of intervention.

Supplementary Table 2. Patients Achieving Sustained Improvement by Time

Minutes after dose	Patients, No. (%)		P value ^a
	Ecallantide group (n = 70)	Placebo group (n = 73)	
45	17 (24.3)	15 (20.5)	.58
60	23 (32.9)	20 (27.4)	.49
75	31 (44.3)	22 (30.1)	.12
90	31 (44.3)	24 (32.9)	.19
105	35 (50.0)	25 (34.2)	.09
120	39 (55.7)	26 (35.6)	.04
150	43 (61.4)	27 (37.0)	.01
180	44 (62.9)	29 (39.7)	.02
210	47 (67.1)	30 (41.1)	.008
240	48 (68.6)	30 (41.1)	.005

^a *P* values are from the log-rank test comparing distributions for the time to onset of sustained improvement based on Kaplan-Meier analysis.

Supplementary Table 3. Patients Achieving Significant Improvement by Time

Minutes after dose	Patients, No. (%)		<i>P</i> value ^a
	Ecallantide group (n = 70)	Placebo group (n = 73)	
45	5 (7.1)	3 (4.1)	.43
60	8 (11.4)	4 (5.5)	.20
75	11 (15.7)	6 (8.2)	.17
90	17 (24.3)	8 (11.0)	.04
105	19 (27.1)	9 (12.3)	.03
120	19 (27.1)	11 (15.1)	.08
150	24 (34.3)	14 (19.2)	.05
180	26 (37.1)	17 (23.3)	.07
210	30 (42.9)	18 (24.7)	.03
240	33 (47.1)	19 (26.0)	.02

^a *P* values are from the log-rank test comparing distributions for the time to significant improvement based on Kaplan-Meier analysis.