Ecallantide for treatment of acute hereditary angioedema attacks: Analysis of efficacy by patient characteristics

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ABSTRACT

Hereditary angioedema (HAE) is characterized by episodic attacks of edema. HAE is caused by low levels of the protein C1 esterase inhibitor, which inhibits plasma kallikrein, the enzyme responsible for converting high-molecular-weight kininogen to bradykinin. Unregulated production of bradykinin leads to the characteristic clinical symptoms of swelling and pain. Ecallantide is a novel plasma kallikrein inhibitor effective for treatment of acute HAE attacks. This study was designed to analyze the efficacy of ecallantide for treating HAE attacks by attack location, attack severity, patient gender, and body mass index (BMI). An analysis of integrated data from two double-blind, placebo-controlled trials of ecallantide for treatment of acute HAE attacks was undertaken. For the purpose of analysis, symptoms were classified by anatomic location and, for each location, by the patient-assessed severity of the attack. Efficacy versus placebo was examined using two validated patient-reported outcomes: treatment outcome score and mean symptom complex severity score. One hundred forty-three attacks were analyzed (73 ecallantide and 70 placebo). Ecallantide was equally effective in both male and female subjects. Ecallantide had decreased efficacy for patients with BMI > 30 kg/m^2. Ecallantide showed efficacy for treatment of severe and moderate attacks, and was effective for abdominal, internal head and neck, external head and neck, and cutaneous locations. In summary, ecallantide is effective for treatment of acute HAE attacks of different symptom locations and severity; outcomes were similar for men and women. However, the standard dose was less effective for obese patients.

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Hereditary angioedema (HAE) is characterized by episodic attacks of edema typically involving the skin, gastrointestinal (GI) tract, genitals, and oropharynx/larynx.[1–3] Attacks typically increase in severity over 1–2 days and then resolve over a similar time period. HAE attacks may be extremely painful and laryngeal attacks are potentially fatal; 9% of patients in one large series required intubation or tracheostomy.[2] In addition, there are substantial costs associated with HAE, including both direct medical costs and indirect costs due to missed work and other activities.[4,5]

HAE results from mutations in the C1 esterase inhibitor (C1-INH) gene, resulting in decreased plasma C1-INH function.[6] C1-INH inhibits a number of enzymes including C1, factor XII, and plasma kallikrein.[7] Extensive data indicate that HAE symptoms are caused by deficient regulation of plasma kallikrein leading to increased generation of bradykinin.[7–9] Bradykinin mediates increased vascular permeability, which underlies the swelling that characterizes HAE.

For many years, in the United States, treatment options for HAE were limited, but more effective medicines for HAE have recently become available in the United States.[10,11] Two preparations of C1-INH purified from human plasma are now available. One (Cinryze; ViroPharma, Exton, PA) is approved for prophylaxis,[12] and a second (Berinert; CSL-Behring, King of Prussia, PA) is approved for treatment of acute abdominal and facial attacks.[13] In addition, icatibant (Firazyr; Shire, Lexington, MA), a bradykinin receptor antagonist, was recently approved for treatment of acute HAE attacks.[14]

Ecallantide (Kalbitor; Dyax Corp., Burlington, MA), a novel, potent, and highly selective plasma kallikrein inhibitor that blocks bradykinin generation, is approved in the United States for the treatment of acute attacks of HAE in patients aged ≥16 years old.[15,16] Ecallantide has increased potency and selectivity for plasma kallikrein when compared with C1-INH.[15,16] Two randomized, double-blind, placebo-controlled studies of ecallantide for treatment of acute HAE attacks, and an integrated analysis of those studies showed significant efficacy and satisfactory safety, both individually and in integrated analyses.[17–20] Here, we analyze the effectiveness of ecallantide versus placebo by individual symptom location and severity,

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Table 1 **Symptom complex definitions**

Symptom Complex	Affected Areas
Cutaneous	Chest, back, shoulder, arm, hand, finger, hip, leg, ankle, foot, and toe
External head/neck	Face, ear, nose, jaw, chin, forehead, eye, and neck
Genital/buttocks	Genitals, buttocks, testicles, scrotum labia, and groin
Internal head/neck	Lip, palate, tongue, mouth, throat, and larynx
Stomach/GI	Stomach, intestines, and bowel

Symptoms were assigned to one or more specific symptom complexes as shown.
GI = gastrointestinal.

gender, and by patient weight and body mass index (BMI).

METHODS

Patients

Data are from evaluation of DX-88's effects in mitigating angioedema (EDEMA3) and EDEMA4, two randomized double-blind, placebo-controlled trials of ecallantide enrolling 168 total patients.[17–20] Analyses, here, are based on 143 patients; only the first treatment was included for the 25 patients treated in both trials.[20] Patients in both studies presented within 8 hours of development of moderate or severe HAE symptoms in at least one anatomic location. They were randomized to receive either 30 mg of ecallantide or placebo subcutaneously. Randomization was stratified by attack location and previous exposure to ecallantide. Patient symptom severity and response to treatment were recorded using an electronic diary both immediately before and at specific intervals after treatment. Patients with severe upper airway compromise were eligible for an open-label dose of ecallantide between 0 and 4 hours after initial treatment. In EDEMA4, patients with no or incomplete response or who relapsed were eligible for an open-label dose of ecallantide between 4 and 24 hours after initial treatment.[18]

Institutional Review Board approval was obtained at each participating site; each patient provided written informed consent.

Symptom Evaluation

On presentation, patient's symptoms were classified into one or more of five predefined symptom complexes: internal head/neck, stomach/GI, external head/neck, genital/buttocks, and cutaneous (Table 1). Patients also reported the severity of each identified symptom complex, defined as follows: mild symptoms were noticeable but did not affect activities of daily living, moderate symptoms affected activities of daily living and medical assistance was highly desirable, and/or severe symptoms prevented activities of daily living and required medical intervention.[17,18] All symptoms were included in this analysis.

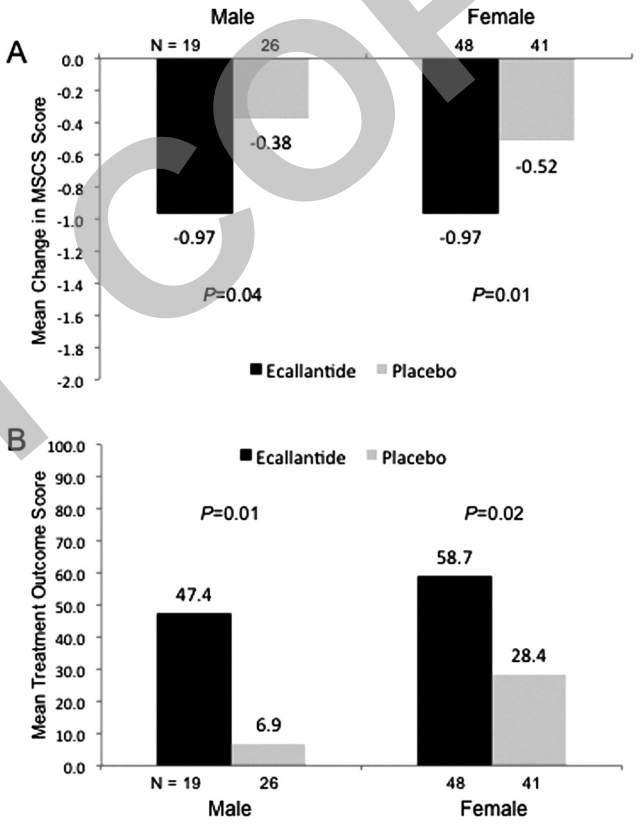

Figure 1. *Efficacy outcomes by gender. (A) Change in MSCS score at 4 hours and (B) TOS at 4 hours for ecallantide versus placebo. The p values from Wilcoxon rank sum test. MSCS, mean symptom complex severity; TOS, treatment outcome score.*

Two validated HAE-specific, patient-reported outcome measures were used to evaluate response to treatment—the mean symptom complex severity (MSCS) score and the treatment outcome score (TOS).[21] The MSCS score provides a point-in-time analysis of symptom burden. At baseline, patients identified symptom location(s) and rated the severity of each using a 3-point scale (1 = mild, 2 = moderate, and 3 = severe). Subsequently, 4 and 24 hours postdosing, patients reported severity of symptoms (as aforementioned, with the addition of normal = 0) and identified any new symptom locations. The MSCS

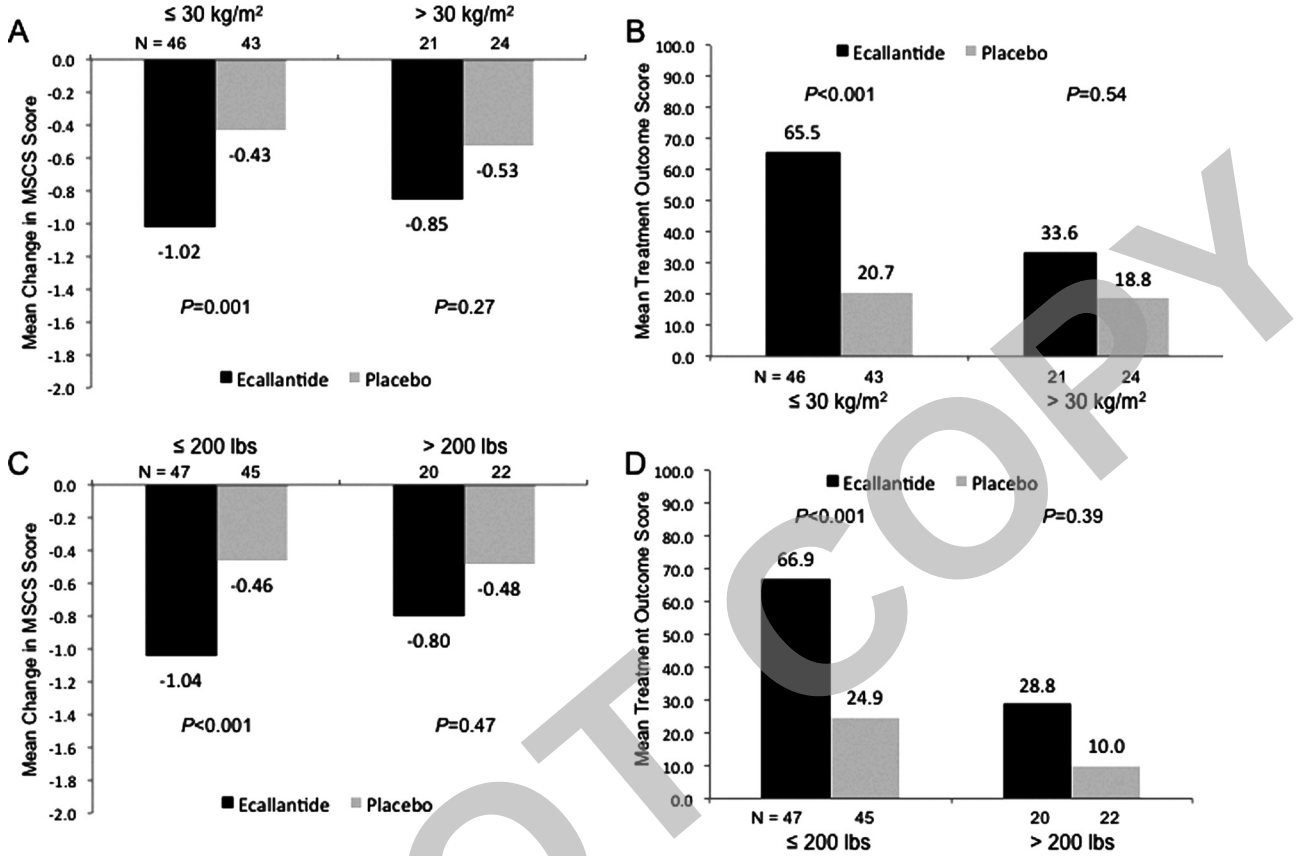

Figure 2. *Efficacy outcomes by BMI and weight. (A) Change in MSCS score at 4 hours and (B) TOS at 4 hours for ecallantide versus placebo by BMI (nonobese, BMI ≤ 30 kg/m²; obese, BMI > 30 kg/m²). (C) Change in MSCS score at 4 hours and (D) TOS at 4 hours for ecallantide versus placebo by body weight (≤200 lb; >200 lb). The p values from Wilcoxon rank sum test. BMI, body mass index; MSCS, mean symptom complex severity; TOS, treatment outcome score.*

score is the arithmetic mean of symptom severity across all affected locations. A decrease in MSCS score from baseline indicates improvement in symptom severity; a change in MSCS score of −0.3 is estimated to be the minimally important difference.[21]

TOS is a measure of response to treatment over time. For each symptom location, patients identified their response to treatment at 1, 2, 3, 4, and 24 hours postdosing using a categorical scale: significant improvement (100 points), improvement (50 points), no change (0 points), worsening (−50 points), or significant worsening (−100 points), with "significant improvement" being defined as the symptoms being "a lot better or resolved" per the patient and "significant worsening" as "a lot worse." TOS is calculated as a weighted average, with more severe baseline symptoms weighted more heavily. A positive TOS indicates improvement, with 30 as the estimated minimally important difference.[21]

A third end point, time to onset of sustained improvement, was also assessed. For individual symptom complexes, which were assessed at 1, 2, 3, 4, and 24 hours, it was defined as the first time within 4 hours postdosing that the patient reported the symptom complex was feeling "a little better" or "a lot better or resolved" for at least two consecutive time points.[17,18]

Analysis

For efficacy analyses by symptom location, each of the five individual symptom complexes was analyzed independently, using the outcomes specific for each location. Patients experiencing symptoms at more than one location were analyzed for each site. For severity analyses, if a patient recorded two or more symptom locations with the same severity, the MSCS score and TOS were averaged across those locations, and time to sustained improvement was calculated using both the shortest and the longest reported time to improvement for that severity.

The Wilcoxon rank sum test comparing active treatment and placebo groups at 4 hours was used to determine *p* values for TOS and change in MSCS score. Although randomization in both studies was stratified by prior ecallantide exposure and attack location, the attack location strata differed between the two studies. Therefore, blocking for prior ecallantide exposure was

included in the statistical methodology for analyses within the individual symptom complexes but otherwise was not used. Attacks missing the 4-hour assessment were excluded from the MSCS score and TOS analyses. The *p* values for percentage of patients showing sustained improvement within 4 hours were calculated using Fisher's exact test. Time to onset of sustained improvement was analyzed using Kaplan-Meier methodology; differences between groups were assessed with the log-rank test.

Safety

A comprehensive analysis of safety parameters and adverse events in this patient data set has been previously reported.[19] Because patients could be represented in more than one symptom complex location and severity group, safety analyses by subset were not conducted because of the difficulty in analyzing adverse events by individual symptom complex designation.

Role of the Funding Source

Dyax Corp. funded and designed both EDEMA3 and EDEMA4 with input from outside HAE and clinical trial experts. Data were gathered by study investigators at multiple sites. An independent contract research organization analyzed the data based on input from Dyax and the authors. The integrity of the analyses is backed by both the authors and the sponsor.

RESULTS

Patients

Overall, the 143 patients included in these analyses reported 229 total symptom complexes including 80 cutaneous, 73 stomach/GI, 31 internal head/neck, 29 external head/neck, and 16 genital/buttocks. The distribution of symptoms was similar between the ecallantide and placebo groups although there were more ecallantide-treated patients with cutaneous symptoms (48 versus 32; $p = 0.004$) and a trend toward more stomach/GI symptoms in placebo-treated patients (43 versus 30; $p = 0.07$).

Symptom severity was most commonly reported to be moderate ($n = 149$ symptom complexes; 65%), followed by severe ($n = 48$; 21%) and mild ($n = 32$; 14%). Symptom severity distribution was similar between the two treatment groups, although there were more patients in the ecallantide group with symptom complexes classified as severe ($n = 28$ versus $n = 20$).

Gender

Of the 143 patients analyzed, 94 (49 ecallantide treated; 45 placebo treated) were female and 49 (21 ecallantide treated; 28 placebo treated) were male subjects. Ecallantide was similarly effective for both genders (Fig. 1). For ecallantide-treated women, the TOS at 4 hours was 58.7 (versus 28.4 for placebo; $p = 0.02$) and the change in MSCS score was −0.97 (versus −0.52 for placebo; $p = 0.01$). For ecallantide-treated men, the TOS was 47.4 and the change in MSCS score was −0.97, versus 6.9 ($p = 0.01$) and −0.38 ($p = 0.04$), respectively.

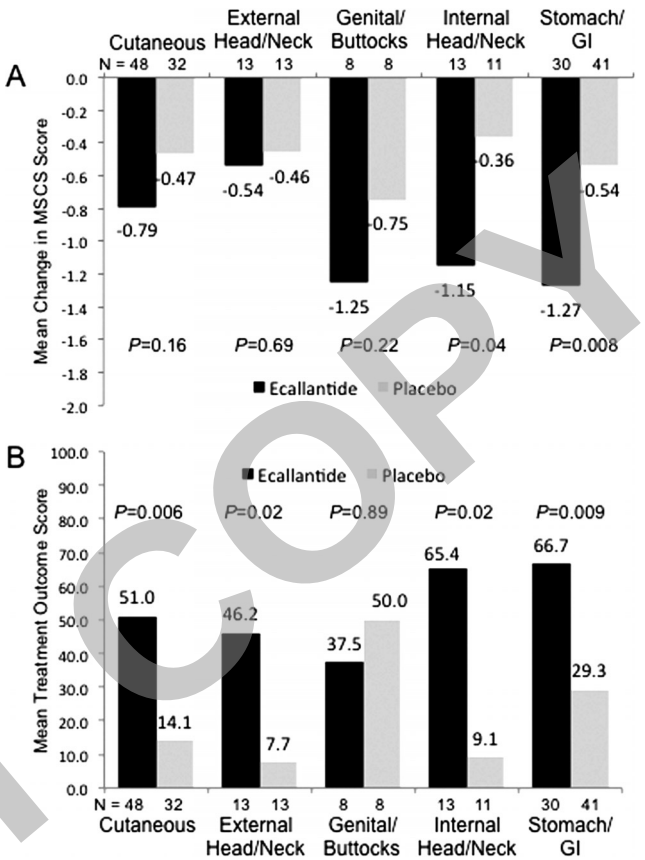

Figure 3. *Efficacy outcomes by individual symptom complex. (A) Change in MSCS score at 4 hours and (B) TOS at 4 hours for ecallantide versus placebo for the five prespecified symptom complexes reported by patients. Patients may have reported more than one symptom complex. Patients who received open-label ecallantide for severe upper airway compromise did not complete the 4-hour assessment and were excluded from the analysis as follows: four patients with internal head/neck symptoms (one ecallantide and three placebo) and three patients with both internal and external head/neck symptoms (two ecallantide and one placebo). Two placebo patients with stomach/GI symptoms were missing 4-hour data. The p values from Wilcoxon rank sum test blocked by prior exposure to ecallantide. MSCS, mean symptom complex severity; TOS, treatment outcome score.*

BMI and Weight

Ecallantide is given as a fixed 30-mg subcutaneous dose regardless of weight or BMI. To address concerns that ecallantide might be less effective for larger patients, we analyzed efficacy by separating patients into

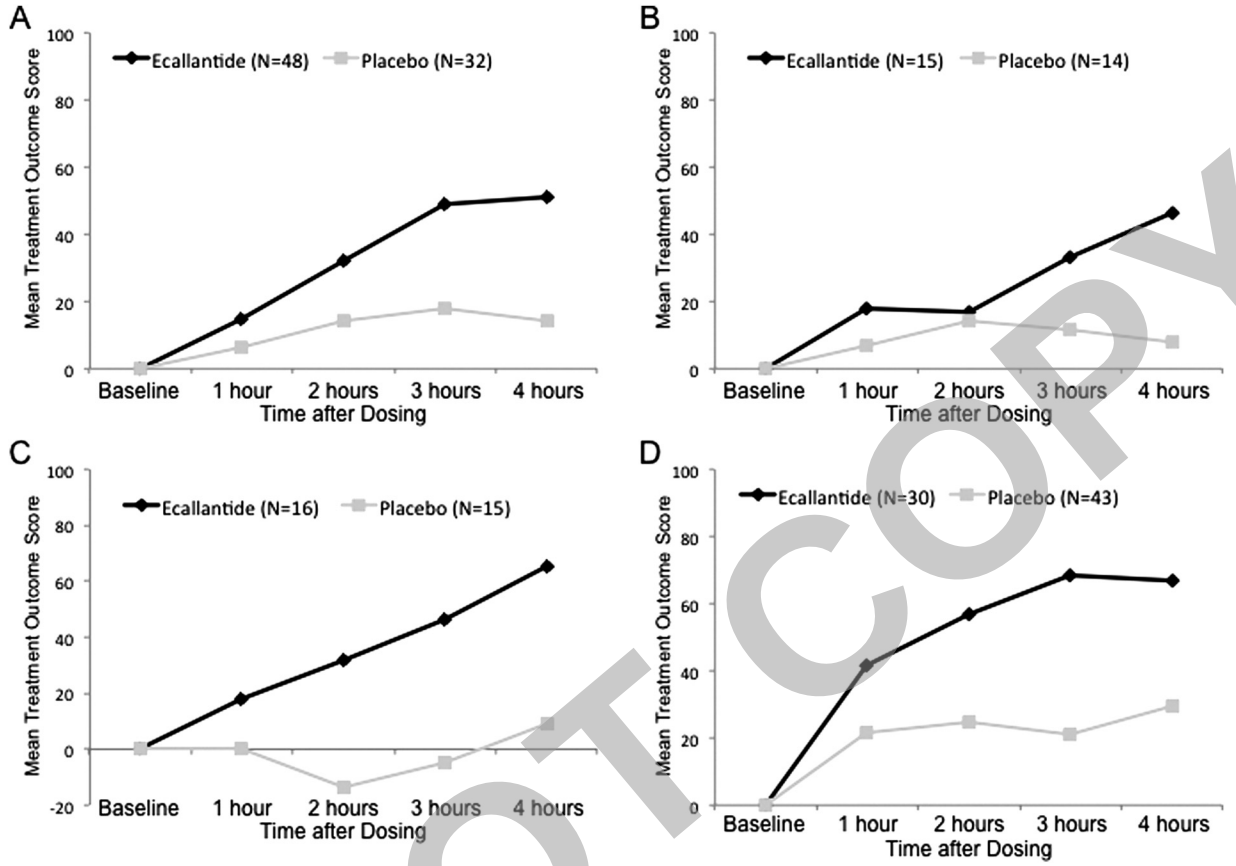

Figure 4. *TOS over time. TOS outcomes at 1, 2, 3, and 4 hours posttreatment for (A) cutaneous, (B) external head/neck, (C) internal head/neck, and (D) stomach/GI symptom complexes. Patients may have reported more than one symptom complex. The genital/buttocks symptom complex was not evaluated because of the small patient numbers. TOS, treatment outcome score.*

Table 2 **Onset of sustained improvement within 4 hours by symptom complex**

Symptom Complex Location	Patients with Sustained Improvement, *n* (%)			Median Time (IQR) to Onset of Sustained Improvement (min)		
	Ecallantide	Placebo	*p* Value*	Ecallantide	Placebo	*p* Value#
Cutaneous	*n* = 48	*n* = 32				
	32 (66.7)	12 (37.5)	0.01	165 (112, —)	— (114, —)	0.03
External head/neck	*n* = 15	*n* = 14				
	8 (53.3)	5 (35.7)	0.46	227 (166, —)	— (114, —)	0.29
Genital/buttocks	*n* = 8	*n* = 8				
	3 (37.5)	4 (50.0)	> 0.99	— (197, —)	— (58.5, —)	0.43
Internal head/neck	*n* = 16	*n* = 15				
	10 (62.5)	3 (20.0)	0.03	122 (56, —)	— (230, —)	0.02
Stomach/GI	*n* = 30	*n* = 43				
	24 (80.0)	19 (44.2)	0.003	62 (53, 115)	— (59, —)	0.001

Times are in minutes. Data were collected only until 4 hr. Patients may be included in more than one symptom location category.

**The p value from Fisher's exact test.*

#The p value from log-rank test.

IQR = interquartile range; GI = gastrointestinal; "—" = median or 75th percentile was not reached within 4 hr post–treatment.

obese (BMI > 30 kg/m^2; n = 47) and nonobese (BMI ≤ 30 kg/m^2; n = 96) categories (Fig. 2).

Ecallantide showed efficacy for the nonobese group with a change in MSCS score of −1.02 versus −0.43 for placebo (p = 0.001) and TOS of 65.5 versus 20.7 for placebo (p < 0.001). However, in the obese group, neither change in MSCS score (−0.85 for ecallantide versus −0.53 for placebo) nor TOS (33.6 for ecallantide versus 18.8 for placebo) were significantly different between groups (p = not significant [NS] for both).

Similarly, when analyzed by body weight, ecallantide was significantly more effective than placebo in patients weighing ≤200 lb (n = 97), with a TOS of 66.9 versus 24.9 for placebo (p < 0.001) and change in MSCS score of −1.04 versus −0.46 for placebo (p = < 0.001; Fig. 2). However, for patients weighing >200 lb (n = 46), TOS was 28.8 for ecallantide versus 10.0 for placebo and change in MSCS score was −0.80 versus −0.48, respectively (p = NS for both).

Attack Location

Figure 3 shows change in MSCS score (1A) and TOS (1B) at 4 hours by symptom complex. For stomach/GI symptoms, ecallantide was significantly more efficacious than placebo as assessed by both change in MSCS score (−1.27 versus −0.54; p = 0.008) and TOS (66.7 versus 29.3; p = 0.009). Similarly, internal head/neck symptoms showed significantly greater symptom resolution (change in MSCS score, −1.15 versus −0.36; p = 0.04) and patient-reported treatment efficacy (TOS, 65.4 versus 9.1; p = 0.02) when treated with ecallantide, despite relatively few patients being studied.

Cutaneous attacks showed a significantly improved outcome with ecallantide based on TOS (51.0 versus 14.1; p = 0.006) and a numerically greater response in symptom improvement (change in MSCS score, −0.79 versus −0.47) that was not statistically significant (p = 0.16). Similarly, for external head/neck symptoms, TOS (46.2 versus 7.7; p = 0.02), but not change in MSCS score (−0.54 versus −0.46; p = 0.69), showed statistically significantly greater improvement with ecallantide treatment. There were relatively few patients who reported genital/buttock swelling, and no significant difference was seen for either change in MSCS score or TOS (−1.25 versus −0.75 and 37.5 versus 50.0, respectively; p = NS] for both). Thus, our data confirm the efficacy of ecallantide at different anatomic locations, consistent with previous reports in which attacks were analyzed by primary attack location.[19,20]

We examined the time course of improvement in TOS by symptom complex location through 4 hours postdosing. As shown in Fig. 4, ecallantide led to rapid and sustained improvement in symptoms for stomach/GI, cutaneous, and both external and internal head/neck symptom locations relative to placebo.

Time to the onset of sustained improvement is shown in Table 2. Significantly more patients showed sustained improvement within 4 hours for stomach/GI, internal head/neck, and cutaneous symptom complexes, with the most rapid improvement shown for stomach/GI attacks.

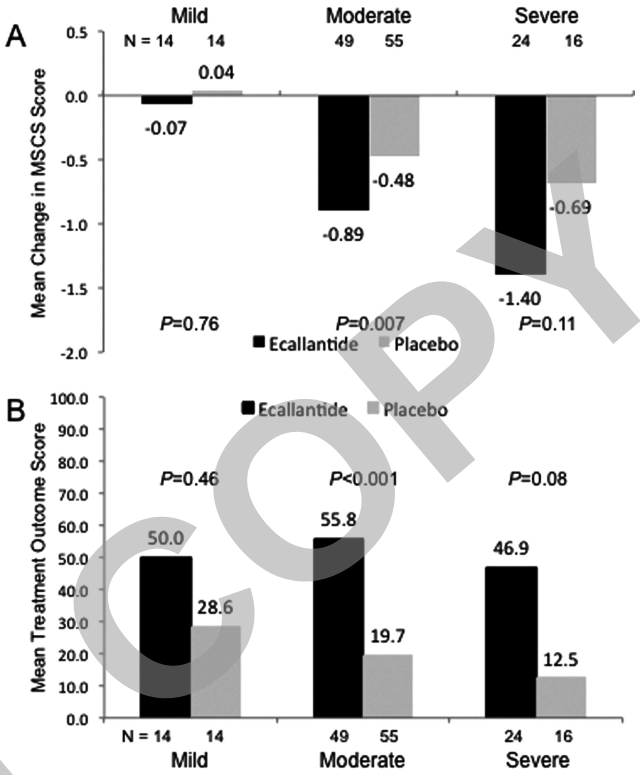

Figure 5. Efficacy outcomes by symptom severity. (A) Change in MSCS score at 4 hours and (B) TOS at 4 hours for ecallantide versus placebo by symptom severity. Patients may have reported more than one symptom complex and thus be included in more than one symptom severity category. Patients with more than one symptom complex of the same severity were only counted once within that severity; for these patients, MSCS score and TOS were determined by averaging the outcomes for the individual symptoms. Patients who received open-label ecallantide for severe upper airway compromise did not complete the 4-hour assessment and were excluded from the analysis as follows: two patients with mild symptoms (one per group), six patients with moderate symptoms (three per group), and one placebo patient with severe symptoms. Two placebo patients with severe symptoms were missing 4-hour data. The p values from Wilcoxon rank sum test blocked by prior exposure to ecallantide. MSCS, mean symptom complex severity; TOS, treatment outcome score.

Severity of Attack

For the analyses by symptom severity, each patient was only counted once within each severity category. Overall, the 143 patients were evaluated for 43 severe, 110 moderate, and 30 mild symptoms.

Symptoms rated as moderate or severe responded very well to ecallantide treatment (Fig. 5). For moderate symptoms, ecallantide treatment showed a change

Table 3 **Onset of sustained improvement within 4 hr by symptom severity**

Symptom Complex Severity	Patients with Sustained Improvement, *n* (%)			Median Time (IQR) to Onset of Sustained Improvement (min)		
	Ecallantide	Placebo	*p* Value*	Ecallantide	Placebo	*p* Value#
Mild	$n = 15$	$n = 15$				
	9 (60.0)	5 (33.3)	0.27	122 (54, —)	— (114, —)	0.07
Moderate	$n = 52$	$n = 58$				
	36 (69.2)	27 (46.6)	0.02	114 (58, —)	— (59, —)	0.02
Severe	$n = 24$	$n = 19$				
	14 (58.3)	3 (15.8)	0.006	118.5 (55, —)	— (—, —)	0.02

Times are in minutes. Data were collected only until 4 hr. Patients may be included in more than one symptom severity category. Patients with more than one symptom complex of the same severity were only counted once within that severity and onset of sustained improvement was determined based on the symptom complex with the shortest reported time to reach the endpoint. Overall, 32 mild symptom complexes were reported by 30 patients, 149 moderate symptom complexes were reported by 110 patients, and 48 severe symptom complexes were reported by 43 patients.

**The p value from Fisher's exact test.*

#The p value from log-rank test.

IQR = interquartile range; "—" = median or IQR was not reached within 4 hr posttreatment.

in MSCS score of −0.89 versus −0.48 for placebo and a TOS of 55.8 versus 19.7 for placebo ($p = 0.007$ and $p < 0.001$, respectively). For severe symptoms neither change in MSCS score (−1.40 versus −0.69; $p = 0.11$) nor TOS (46.9 versus 12.5; $p = 0.08$) reached statistical significance, although ecallantide showed a numerical improvement. Few mild symptoms were treated (15 per group) and differences in outcomes were not statistically significant (change in MSCS score, −0.07 versus 0.04; TOS, 50.0 versus 28.6; p = NS for both).

As shown in Table 3, for moderate and severe symptoms an increased proportion of ecallantide-treated patients showed onset of sustained improvement within 4 hours versus placebo-treated patients (moderate, 69.2% versus 46.6% and $p = 0.02$; severe, 58.3% versus 15.8% and $p = 0.006$) when the analysis used the shortest reported time to improvement for patients with more than one symptom complex of the same severity. Analysis of data using longest time to improvement yielded similar results (data not shown).

Safety

As reported by Sheffer *et al.*, ecallantide and placebo-treated patients in this data set reported a similar percentage of treatment-emergent adverse events (36% for ecallantide versus 35% for placebo).[19] Most treatment-emergent adverse events were mild or moderate in severity and unrelated to ecallantide. No hypersensitivity reactions, including anaphylaxis, were reported in this patient population.

DISCUSSION

Ecallantide is a potent and highly selective novel plasma kallikrein inhibitor recently approved in the United States for treatment of acute HAE attacks. We examined the efficacy of ecallantide versus placebo by patient characteristics including weight, BMI, and gender.

Although some response to ecallantide was noted in heavier and obese patients, they showed less response than smaller and nonobese patients. Whether this is caused by a larger volume of distribution in heavier patients or some other factor is not clear. The ecallantide product label indicates that a second dose may be administered, and this should be considered for patients, including heavier ones, who have an inadequate response to the initial 30-mg dose.[22] Icatibant is also given as a fixed dose and published data have not examined differences in efficacy by weight. Acute therapy with C1-INH has been examined using both a fixed dose (1000 U)[12] and a weight-based dose (20 U/kg), with the latter showing better efficacy than a lower dose.[12,13] Our analysis showed equal efficacy of ecallantide for men and women.

In this study, consistent with the findings of Bork *et al.* in a retrospective analysis of >100,000 attacks,[23] cutaneous and abdominal symptoms were the most often reported (35 and 32% of all symptoms, respectively). In our analysis, ecallantide was effective for treatment of attacks at all anatomic sites by at least one measure, except for genital/buttocks, where few symptoms were reported. This is consistent with analysis of this data by primary attack site.[19,20]

In a recent online survey of 457 HAE patients, 26% of respondents classified the overall severity of their most recent attack as mild, 46% as moderate, and 27% as severe.[5] In the present study, 14% of attack symptoms were mild, 65% were moderate, and 21% were severe. However, enrollment in EDEMA3 and EDEMA4 required at least one moderate or severe symptom, explaining the higher percentage of moderate attacks in this study. Ecallantide showed benefit for both moderate and severe attack locations, but no significant difference between ecallantide and placebo was seen for the few mild symptoms treated. Furthermore, a significant placebo response was noted, consistent with other HAE trials.[12–14] Trials of other HAE therapies have been limited to moderate and severe attacks[12–14] and, when reported, have had a majority of attacks classified as moderate.[13]

Our data suggest rapid onset of action with the majority of attacks improving in 4 hours, with an overall median time to improvement of 2 hours. This is similar to published data for C1-INH (2 hours for Cinryze and 2.9 hours for Berinert) and icatibant (2.0 and 2.5 hours in two trials), although differences in the exact criteria used to define the onset of improvement preclude direct comparisons.[12–14]

In the patient population analyzed here, ecallantide was not associated with an increased rate of treatment-emergent AEs compared with placebo;[19] however, there are reports of hypersensitivity reactions and anaphylaxis after ecallantide administration.[16,22] Ongoing surveillance to identify hypersensitivity reactions and consequences of antibody seroconversion will be helpful in further quantifying this risk.

There is a wide variation in the frequency and severity of HAE attacks shown by individual patients. However, all patients are at risk for severe and/or life-threatening attacks, even if their pattern of disease has been relatively mild, to date, or they are maintained on C1-INH prophylaxis. Furthermore, it is impossible to predict whether a mild attack will progress to a more severe state. Each HAE patient, therefore, should work with their health care provider to develop an action plan for the treatment of acute HAE attacks. Ecallantide, with its established effectiveness across all attack locations and severities, and its subcutaneous administration, represents an important option to fill this clinical need.

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