

ORIGINAL ARTICLE

Ecallantide for the Treatment of Acute Attacks in Hereditary Angioedema

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ABSTRACT

BACKGROUND

Hereditary angioedema is a rare genetic disorder characterized by acute, intermittent, and potentially life-threatening attacks of edema of the skin and mucosa. We evaluated ecallantide, a newly developed recombinant plasma kallikrein inhibitor, for the treatment of acute attacks of angioedema.

METHODS

In this double-blind, placebo-controlled trial, patients with hereditary angioedema presenting with an acute attack were randomly assigned, in a 1:1 ratio, to receive subcutaneous ecallantide, at a dose of 30 mg, or placebo. Two measures of patient-reported outcomes were used to assess the response: treatment outcome scores, which range from +100 (designated in the protocol as significant improvement in symptoms) to -100 (significant worsening of symptoms), and the change from baseline in the mean symptom complex severity score, which range from +2 (representing a change from mild symptoms at baseline to severe symptoms after) to -3 (representing a change from severe symptoms at baseline to no symptoms after). The primary end point was the treatment outcome score 4 hours after study-drug administration. Secondary end points included the change from baseline in the mean symptom complex severity score at 4 hours and the time to significant improvement.

RESULTS

A total of 71 of the 72 patients completed the trial. The median treatment outcome score at 4 hours was 50.0 in the ecallantide group and 0.0 in the placebo group (interquartile range [IQR], 0.0 to 100.0 in both groups; $P=0.004$). The median change in the mean symptom complex severity score at 4 hours was -1.00 (IQR, -1.50 to 0.00) with ecallantide, versus -0.50 (IQR, -1.00 to 0.00) with placebo ($P=0.01$). The estimated time to significant improvement was 165 minutes with ecallantide versus more than 240 minutes with placebo ($P=0.14$). There were no deaths, treatment-related serious adverse events, or withdrawals owing to adverse events.

CONCLUSIONS

Four hours after administration of ecallantide or placebo for acute attacks of angioedema in patients with hereditary angioedema, patient-reported treatment outcome scores and mean symptom complex severity scores were significantly better with ecallantide than with placebo. (Funded by Dyax; ClinicalTrials.gov number, NCT00262080.)

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HEREDITARY ANGIOEDEMA IS AN AUTOSOMAL dominant disorder with an estimated prevalence ranging from 1 case in 10,000 to 1 case in 50,000 persons.¹⁻³ Patients with hereditary angioedema have intermittent acute attacks of edema involving the larynx, oropharynx, face, gastrointestinal mucosa, extremities, or genitalia.⁴ Attacks occur unpredictably and may persist for 2 to 5 days.^{5,6} Gastrointestinal attacks can cause incapacitating colic, vomiting, and diarrhea and can result in unnecessary abdominal surgery. Laryngeal attacks may be life-threatening because of the potential for airway obstruction.^{5,7} Attacks do not typically respond to antihistamines, corticosteroids, or epinephrine.

Hereditary angioedema is caused by mutations of the C1 esterase-inhibitor gene, resulting in reduced activity or quantity of the protein.⁸ The C1 esterase inhibitor is a major inhibitor of plasma kallikrein and coagulation factor XIIa.⁹⁻¹¹ Decreased levels of C1 esterase inhibitor in patients with hereditary angioedema lead to unrestrained plasma kallikrein activity, resulting in elevated levels of bradykinin.^{9,12,13} Bradykinin is a potent vasodilator that increases capillary endothelial permeability, causing the localized edema and painful swelling that are the hallmarks of an acute attack of angioedema in patients with this disease.⁹

Although approved therapies for treatment of acute attacks in patients with hereditary angioedema have been available to patients outside the United States for many years,¹⁴ approved, disease-specific therapies have only recently become available in the United States.^{15,16} The widely prescribed short- and long-term prophylactic treatments, including 17 α -alkylated androgens, antifibrinolytic agents, and fresh-frozen plasma, are often associated with considerable risks and adverse effects.^{8,17}

Ecallantide (Kalbitor [previously, DX-88]; Dyax, Cambridge, MA) is a recombinant protein synthesized in the yeast *Pichia pastoris*.¹⁸⁻²⁰ Ecallantide is a potent and specific inhibitor of plasma kallikrein.^{8,18-20} In phase 2 trials, symptoms of angioedema improved within 4 hours after treatment with ecallantide.^{18,21} The Evaluation of DX-88's Effects in Mitigating Angioedema (EDEMA) 3 trial was a randomized, placebo-controlled, phase 3 evaluation of ecallantide for the treatment of acute attacks of angioedema in patients with hereditary angioedema.

METHODS

STUDY DESIGN

The EDEMA3 trial was a multicenter, randomized, double-blind, placebo-controlled trial sponsored by Dyax. The study was designed by the sponsor, and the protocol was approved by the institutional review boards or ethics committees of the participating institutions. The study was conducted in accordance with the protocol (available with the full text of this article at NEJM.org). Data were gathered by study investigators, study staff, and Synergos (The Woodlands, TX), an independent contract research organization paid by the sponsor. All data analyses were performed by the contract research organization or the sponsor. Writing support for the first draft of the manuscript and editorial support for the modification of subsequent drafts before submission for publication were provided by Publication Connexion (Newtown, PA), a manuscript preparation company paid by the sponsor. The academic authors vouch for the integrity and completeness of the data and all analyses.

PATIENTS

Eligibility criteria were an age of at least 10 years and a documented diagnosis of hereditary angioedema. Exclusion criteria were pregnancy, breast-feeding, or receipt of an investigational drug other than ecallantide within 30 days before study enrollment or noninvestigational C1 esterase-inhibitor therapy or ecallantide within 7 days before enrollment. Prophylactic androgen therapy was permitted. At the screening visit, before any study procedures were performed, written informed consent was provided by each adult patient; patients who were children gave written consent, oral assent, or both and a parent or guardian gave written informed consent.

Eligible patients who had provided signed consent and who subsequently presented at the study site within 8 hours after the onset of moderate or severe symptoms of angioedema were enrolled. Moderate attacks were defined as those for which intervention is highly desirable for symptoms and that impede activities of daily living; severe attacks were defined as those necessitating treatment or intervention and that result in patients' inability to perform activities of daily living.

TRIAL PROCEDURES

We randomly assigned the trial participants, in a 1:1 ratio, to receive subcutaneously either ecallantide, at a dose of 30 mg, or placebo (phosphate-buffered saline, pH 7.0). Randomization was performed on the basis of a block design, with stratification according to use or nonuse of ecallantide in a previous EDEMA trial and the attack site (i.e., gastrointestinal, laryngeal, or peripheral). Patients were observed for at least 4 hours after study-drug administration. Symptoms were assessed every 15 minutes for the first 2 hours, every 30 minutes for the next 2 hours, and finally at 24 hours. Additional medical treatment (including fluids and pain relievers) was provided during the 24-hour period after study-drug administration, as deemed necessary by the investigators. An open-label dose of 30 mg of subcutaneous ecallantide was allowed for cases involving severe upper-airway compromise. Three follow-up visits were planned at study days 7, 30, and 90.

END POINTS

The primary end point was the treatment outcome score²² at 4 hours after study-drug administration. The treatment outcome score is a composite, patient-reported outcome measure based on the site or sites of symptoms, the symptom severity at baseline, and the response to treatment (see the Supplementary Appendix, available at NEJM.org). Values for the composite treatment outcome score range from +100 (designated in the protocol as significant improvement in symptoms) to -100 (significant worsening of symptoms).

The principal secondary end point was the change from baseline in the mean symptom complex severity score²² at 4 hours. The mean symptom complex severity score is another patient-reported outcome measure incorporating the symptom site or sites and symptom severity, before versus after treatment (see the Supplementary Appendix). Values for the mean symptom complex severity score range from 0 (no symptoms) to 3 (severe). The response to symptoms is assessed by calculating the change from the baseline score, with improvement reflected by a decrease in score and a range from a high of +2 (representing a change from mild symptoms at baseline to severe symptoms after) to a low of -3 (representing a change from severe symptoms at baseline to no symptoms after).

An additional secondary end point was the time to significant improvement in overall response, defined as the first time after administration of the study drug that the patient reported that, overall, his or her symptoms were “a lot better or resolved.” Possible categories of reported overall response were that symptoms were “a lot better or resolved,” “a little better,” “the same,” “a little worse,” or “a lot worse” relative to baseline. Other secondary end points included the treatment outcome score and the change in the mean symptom complex severity score at 24 hours after study-drug administration and the time to sustained improvement in overall response, defined as the first time within 4 hours after study-drug administration that the patient reported any improvement in symptoms (“a little better” or “a lot better or resolved”) for a period of at least 45 minutes.

Evaluations for safety included the assessment of adverse events, physical examination, electrocardiography, taking of vital signs, and laboratory testing, including assays to measure the levels of anti-ecallantide antibodies. Data on adverse events were collected starting at enrollment (day 1) through the third follow-up visit (day 90±7 days). Attacks of angioedema were recorded as serious adverse events if the patient was hospitalized for the presenting attack or as either an adverse event or a serious adverse event if there were subsequent attacks (through the time of the third follow-up visit).

STATISTICAL ANALYSIS

On the basis of data from the EDEMA1 trial,²¹ we calculated that with 62 patients, randomly assigned in a 1:1 ratio to receive either ecallantide or placebo, the study would have a statistical power of 90% to detect a difference in the distribution of treatment outcome scores at 4 hours after study-drug administration (the primary end point) between the two groups, using a two-sided Wilcoxon rank-sum test, at a P value of less than or equal to 0.05. This calculation was based on an estimated probability of 0.712 that the treatment outcome score for a patient in the ecallantide group would exceed the score for a patient in the placebo group. In September 2006, the decision was made to increase the sample size from 62 to 72 to enroll a sufficient number of patients for validation of the electronic diaries and to accommodate the use of a more conservative statistical

Table 1. Baseline Characteristics in the Intention-to-Treat Population, According to Study Group.*

Characteristic	Ecallantide (N=36)	Placebo (N=36)	Total (N=72)	P Value†
Age — yr				0.09
Mean	38.5±14.6	32.2±13.8	35.4±14.5	
Median (range)	37.4 (18.0–77.0)	30.4 (11.0–57.0)	33.7 (11.0–77.0)	
Weight — lb				0.11
Mean	177.7±43.6	166.9±54.0	172.3±49.0	
Median (range)	162.0 (123.0–283.0)	142.5 (92.0–325.0)	155.0 (92.0–325.0)	
Sex — no. (%)				1.00
Male	12 (33)	13 (36)	25 (35)	
Female	24 (67)	23 (64)	47 (65)	
Race or ethnic group — no. (%)‡				1.00
White	33 (92)	32 (89)	65 (90)	
Black	1 (3)	4 (11)	5 (7)	
Hispanic	2 (6)	0	2 (3)	
Symptom complex — no. (%)§				
Laryngeal	9 (25)	4 (11)	13 (18)	0.22
Gastrointestinal	20 (56)	21 (58)	41 (57)	1.00
Complex at peripheral site	25 (69)	21 (58)	46 (64)	
Genital or buttocks	2 (6)	4 (11)	6 (8)	0.67
External head or neck	4 (11)	9 (25)	13 (18)	0.22
Cutaneous	21 (58)	14 (39)	35 (49)	0.16

* Plus-minus values are means ±SD. To convert pounds to kilograms, multiply by 0.45359.

† P values were calculated with the use of Fisher's exact test (with, for race or ethnic group, the P value reflecting the difference between the two groups for the comparison between white and nonwhite classifications), except for age and weight, for which Wilcoxon's rank-sum test was used.

‡ Race or ethnic group was self-reported.

§ Patients could have had more than one symptom complex at baseline.

approach to the analysis of the primary end point. This increase was not based on study results, which remained blinded.

Results from the intention-to-treat population are presented here. Patients not reporting the overall response as “a lot better or resolved” at 15 minutes through 4 hours after study-drug administration had data censored at 4 hours. Patients who received an additional medical intervention, including open-label ecallantide, within 4 hours after study-drug administration had data censored at the time of the intervention. As prespecified in the statistical-analysis plan for the study, missing values were imputed in the efficacy analyses for patients receiving an additional medical intervention, including open-label ecallantide for severe upper-airway compromise. For

these patients, at 4 or 24 hours or both (depending on when the intervention was administered), the response was classified as “significant worsening” for calculation of the treatment outcome score, and the severity was classified as “severe” for calculation of the mean symptom complex severity score.

The effects of the study drug on the treatment outcome score and the mean symptom complex severity score were assessed by means of the nonparametric Wilcoxon rank-sum test. The original statistical-analysis plan did not specify a blocking strategy; however, a blocked Wilcoxon rank-sum test incorporating the stratification variables used in the randomization procedure — that is, previous exposure to ecallantide and primary attack site — was performed, and its

Table 2. Efficacy Analyses with Respect to Primary and Secondary End Points, According to Study Group.*

End Point	Ecallantide (N = 36)	Placebo (N = 36)	P Value†
TOS 4 hr after study-drug administration			0.004
Median (range)	50.0 (–100.0 to 100.0)	0.00 (–100.0 to 100.0)	
IQR	0.0 to 100.0	0.0 to 100.0	
Mean	46.8±59.3	21.3±69.0	
Change from baseline in MSCS score 4 hr after study-drug administration			0.01
Median (range)	–1.00 (–3.00 to 1.50)	–0.50 (–1.67 to 1.75)	
IQR	–1.50 to 0.00	–1.00 to 0.00	
Mean	–0.88±1.11	–0.51±0.68	
Significant improvement in overall response‡			
No. of patients (%)	18 (50)	12 (33)	
Estimated time to onset (min)			0.14
Median	165.0	>240	
IQR	83.0 to >240	135.0 to >240	
TOS 24 hr after study-drug administration§			0.007
No. of patients	33	34	
Median (range)	75.0 (–100.0 to 100.0)	0.00 (–100.0 to 100.0)	
IQR	0.0 to 100.0	–100.0 to 100.0	
Mean	44.3±70.4	–0.5±87.9	
Change from baseline in MSCS score 24 hr after study-drug administration¶			0.04
No. of patients	33	33	
Median (range)	–1.00 (–3.00 to 1.50)	–0.50 (–2.00 to 2.00)	
IQR	–2.00 to 0.00	–1.00 to 0.00	
Mean	–0.87±1.14	–0.46±1.07	
Sustained improvement in overall response			
No. of patients (%)	25 (69)	18 (50)	
Estimated time to onset — min			0.08
Median	67.0	165.0	
IQR	37.0 to >240	49.0 to >240	

* Plus–minus values are means ±SD. The treatment outcome score (TOS) can range from +100 (significant improvement in symptoms) to –100 (significant worsening of symptoms). The change in the mean symptom complex severity (MSCS) score can range from +2 (representing a change from mild symptoms at baseline to severe symptoms after) to –3 (representing a change from severe symptoms at baseline to no symptoms after). (See the Supplementary Appendix for more information about both types of scores.) IQR denotes interquartile range.

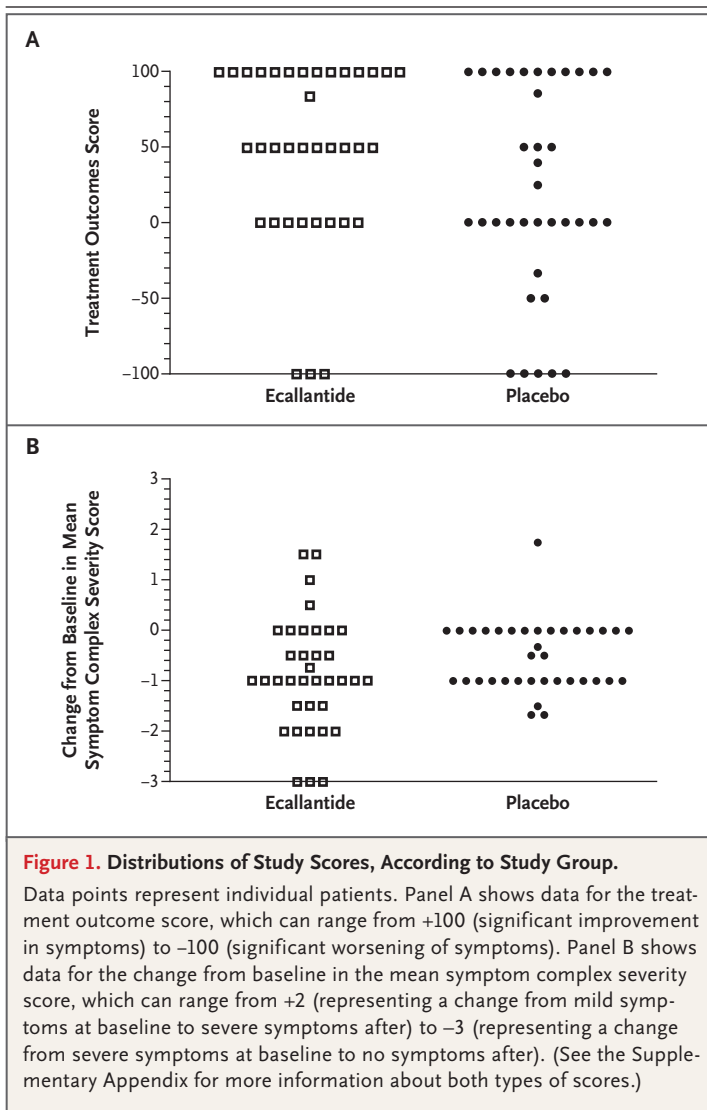
† P values were calculated with the use of the Wilcoxon rank-sum test blocked by the stratification variables of previous exposure to ecallantide and primary attack site, except for the estimated times to onset of first significant improvement and sustained improvement, for which the log-rank test was used.

‡ Onset of significant improvement is defined as the first time during the first 4 hours after study-drug administration that the patient reported the overall response assessment as “a lot better or resolved.”

§ Data were missing for three patients in the ecallantide group and two in the placebo group, owing to either a missed electronic-diary assessment or a faulty electronic diary.

¶ Data were missing for three patients in the ecallantide group and three in the placebo group, owing to either a missed electronic-diary assessment or a faulty electronic diary.

|| Onset of sustained improvement is defined as the first time during the first 4 hours after study-drug administration that a patient reported the overall response assessment as either “a little better” or “a lot better or resolved” for a period of at least 45 minutes.



results are presented here. In a blocked Wilcoxon rank-sum test, the data are ranked separately within each of the six groups formed on the basis of the stratification factors, rather than across the overall study population, as is done in a standard Wilcoxon rank-sum test. The times to significant improvement were analyzed with the use of the Kaplan–Meier method and the log-rank test. Proportions were compared between the two study groups by fitting prespecified logistic-regression models, with attack site and previous use of ecallantide as covariates. P values of less than 0.05, using a two-sided significance level, were considered to indicate statistical significance. No adjustments were made for multiple comparisons.

RESULTS

STUDY POPULATION

Between December 8, 2005, and February 10, 2007, 160 patients with hereditary angioedema were enrolled at 44 study sites in the United States, Canada, Europe, and Israel (see Fig. 1 in the Supplementary Appendix). Of these patients, 72 presented with an acute attack and were randomly assigned to a study group: 36 to the ecallantide group and 36 to the placebo group. Baseline characteristics were similar between the study groups (Table 1). Nine children, 10 to 17 years of age at the time a parent or guardian gave written informed consent, were enrolled (two in the ecallantide group and seven in the placebo group). At baseline, the most commonly reported symptom complexes were gastrointestinal and cutaneous. Some patients reported more than one symptom complex.

Over the course of the study, two patients who presented to the same study site at the same time were given the incorrect study drug: one patient randomly assigned to receive placebo instead received ecallantide, and one patient randomly assigned to receive ecallantide instead received placebo (see Fig. 1 in the Supplementary Appendix). One patient in the ecallantide group was lost to follow-up after the day 7 visit.

OUTCOME MEASURES

At 4 hours after study-drug administration, the median treatment outcome score was 50.0 (interquartile range [IQR], 0.00 to 100.0) for the ecallantide-treated group and 0.0 (IQR, 0.00 to 100.0) for the placebo-treated group ($P=0.004$) (Table 2 and Fig. 1A). At 4 hours after study-drug administration, the median change in the mean symptom complex severity score was -1.00 (IQR, -1.50 to 0.00) in the ecallantide group and -0.50 (IQR, -1.00 to 0.00) in the placebo group ($P=0.01$) (Table 2 and Fig. 1B). The median time to significant improvement in overall response was 165.0 minutes (IQR, 83.0 to >240) with ecallantide and >240 minutes (IQR, 135.0 to >240) with placebo ($P=0.14$) (Table 2 and Fig. 2).

At 24 hours after study-drug administration, the median treatment outcome score was 75.0 (IQR, 0.00 to 100.0) for the ecallantide group and 0.0 (IQR, -100.0 to 100.0) for the placebo group ($P=0.007$) (Table 2). The median change in the mean symptom complex severity score at 24 hours

was -1.00 (IQR, -2.00 to 0.00) with ecallantide and -0.50 (IQR, -1.00 to 0.00) with placebo ($P=0.04$). The median time to sustained improvement in overall response was 67.0 minutes (IQR, 37.0 to >240 minutes) in the ecallantide group and 165.0 minutes (IQR, 49.0 to >240 minutes) in the placebo group ($P=0.08$). Emerging symptoms and medical interventions occurring during the first 24 hours are summarized in the Supplementary Appendix.

ADVERSE EVENTS

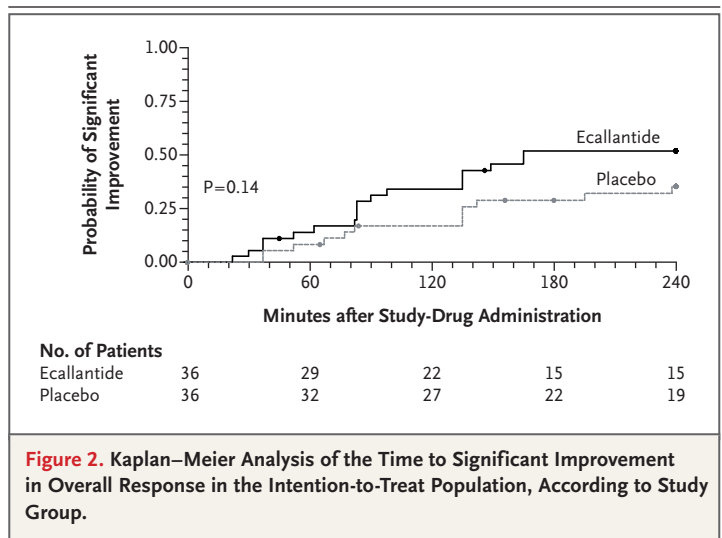
There were no deaths or withdrawals due to adverse events. Adverse events were experienced by 20 of the 36 patients (56%) receiving ecallantide and 12 of the 36 (33%) receiving placebo (Table 3). The most common adverse events occurring more often with ecallantide than with placebo included headache, diarrhea, pyrexia, and nasal congestion. A similar proportion of patients in the ecallantide group and the placebo group (4 [11%] and 5 [14%], respectively) had treatment-related adverse events.

A total of 41 of the 72 patients (57%) (20 of the 36 [56%] receiving ecallantide and 21 of the 36 [58%] receiving placebo) had at least one acute attack of angioedema during the 90-day follow-up period. Serious adverse events, all of which were acute attacks of angioedema, were reported in 3 ecallantide-treated patients (8%) and 2 placebo-treated patients (6%).

Mild, local injection-site reactions were reported in 1 patient in each group. No patients had seroconversion to positivity for anti-ecallantide antibodies. Two patients receiving ecallantide and 1 receiving placebo had seroconversion to positivity for anti-*P. pastoris* IgE antibodies. No episodes of potential hypersensitivity (e.g., urticaria, pruritus, or rhinitis) or anaphylaxis were noted in either group. For further details regarding adverse events, see the Supplementary Appendix.

DISCUSSION

In the EDEMA3 trial, we evaluated the effect of ecallantide in patients with hereditary angioedema presenting with acute attacks of angioedema. There was a significant reduction in the treatment outcome score at 4 hours (the primary end point) with ecallantide as compared with placebo, as well as in the change in the mean symp-



tom complex severity score at 4 hours and in both of these end points at 24 hours.

Attacks of angioedema in patients with hereditary angioedema manifest with a high degree of symptom variability and complexity, and no end points for measuring the response of an intervention have been validated. Therefore, two newly developed patient-reported outcome measures were used in this study: the treatment outcome score, which provides an assessment of the response to therapeutic intervention, and the mean symptom complex severity score, which provides a point-in-time estimate of symptom severity (see the Supplementary Appendix). Psychometric validation of these two measures has been described.²² The minimally important difference is estimated to be 30 for the treatment outcome score at 4 hours and -0.30 for the change from baseline in the mean symptom complex severity score at 4 hours.²²

Neither the median time to significant improvement in overall response nor the median time to sustained improvement in overall response differed significantly between the ecallantide group and the placebo group. The ability of these two end points to discriminate between the two study groups was influenced by the fact that no clinical assessments were performed between 4 hours and 24 hours after study-drug administration. For patients who had either significant or sustained improvement in overall response after 4 hours, the time to that end point was reported as >240 minutes. This limitation especially affected the time to significant

Table 3. Adverse Events in the Safety Population, According to Study Group.*

Adverse Event	Ecallantide (N=36)	Placebo (N=36)
	no. of patients (%)	
Any adverse event	20 (56)	12 (33)
Adverse events occurring more often with ecallantide (and in $\geq 3\%$ of either group)		
Headache	4 (11)	2 (6)
Diarrhea, not otherwise specified	3 (8)	0
Pyrexia	3 (8)	0
Nasopharyngitis	2 (6)	1 (3)
Tachycardia, not otherwise specified	2 (6)	1 (3)
Nasal congestion	2 (6)	0
Treatment-related adverse event†	4 (11)	5 (14)
Serious adverse event‡	3 (8)	2 (6)

* Patients reporting more than one event with the same preferred term are counted only once for that preferred term.

† Treatment-related adverse events were as follows. In the ecallantide group, one patient had pyrexia, fatigue, and influenza-like illness; one had burning at the injection site, sinus headache, nasal congestion, sneezing, and conjunctivitis; one had pyrexia, rigors, headache, and gastric disorder; and one had diarrhea. In the placebo group, one patient had tachycardia, one had swelling at the injection site, one had a prolonged prothrombin time, one had paresthesia of the tongue, and one had genital rash.

‡ All serious adverse events were acute attacks of angioedema considered to be unrelated to study treatment.

improvement in overall response; less than 50% of the subjects in the placebo group had reached this end point at 4 hours, and therefore the median is reported as >240 minutes. It is plausible that, had clinical assessments been made beyond 4 hours, significant differences in these two end points might have been detected.

No patients who had been seronegative for anti-ecallantide antibodies had seroconversion during the study. As noted in the Supplementary Appendix, two patients who had previously been treated with ecallantide were seropositive at baseline, but these patients nonetheless appeared to have a clinical response to study-drug treatment. Seroconversion to positivity for anti-*P. pastoris* IgE antibodies did occur in three patients who

had been seronegative at baseline, in addition to eight who were seropositive at baseline. No apparent hypersensitivity responses occurred. Thus, we found no evidence that seroconversion to ecallantide is associated with a decrease in efficacy or other adverse events, although the number of study participants is too small to allow for any definitive statement regarding such phenomena.

There are few established therapies for hereditary angioedema, although both C1 esterase-inhibitor therapy and ecallantide were recently approved in the United States. Anabolic androgens are used for long-term prophylaxis, but such use can be associated with hepatotoxicity and virilization. The antifibrinolytic agent tranexamic acid is also used for prophylaxis but is significantly less effective than androgens. Fresh-frozen plasma is used for the treatment of acute attacks of angioedema but can transmit viral pathogens and may actually increase symptoms in the short term because it contains proteins that mediate the pathogenesis of the edema. These limitations of currently available agents are the basis of the interest in new approaches. Though in this trial ecallantide was compared with placebo, rather than with an active control such as fresh-frozen plasma, future studies may help to clarify the relative benefit of this targeted form of disease management.

In summary, we compared the effect of the recombinant plasma kallikrein inhibitor ecallantide with that of placebo in treating acute attacks of angioedema in patients with hereditary angioedema. At 4 hours after study-drug administration, the treatment outcome score, a patient-reported outcome measure, was significantly better with ecallantide than with placebo.

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