# Efficacy and safety of ecallantide in treatment of recurrent attacks of hereditary angioedema: Open-label continuation study

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## ABSTRACT

*Hereditary angioedema (HAE) is a rare disorder characterized by recurrent attacks of potentially life-threatening edema. The plasma kallikrein inhibitor ecallantide is approved for treatment of acute HAE attacks. This study evaluates the efficacy and safety of ecallantide for treatment of multiple HAE episodes in the DX-88/19 (continuation) study. Patients received 30 mg of subcutaneous ecallantide for acute HAE attack symptoms, with no limit on number of episodes treated. Primary end point was change in patient-reported mean symptom complex severity (MSCS) score at 4 hours. Additional end points included change in MSCS score at 24 hours, treatment outcome score (TOS) at 4 and 24 hours, and time to response. Safety parameters included adverse events. Statistical analyses were conducted on qualifying treatment episodes (those with ≥12 patients). One hundred forty-seven patients received treatment for 625 episodes; analyses were conducted through 13 treatment episodes. Across 13 episodes at 4 hours, mean change in MSCS score ranged from −1.04 to −1.36, and mean TOSs ranged from 56.2 to 79.8. Median time to onset of sustained improvement ranged from 59 to 113 minutes. There was no indication of reduced efficacy with repeated ecallantide use. No new safety signals were detected. Eight patients (5.4%) reported potential hypersensitivity reactions, six of whom met the definition of anaphylaxis based on National Institute of Allergy and Infectious Diseases criteria. Ecallantide is effective for acute recurrent HAE attacks and maintains its efficacy and safety during multiple treatment episodes in patients with HAE. Potential hypersensitivity reactions were consistent with prior reports.*

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Hereditary angioedema (HAE) is a rare autosomal dominant disorder, with an estimated prevalence of ~1 in 50,000 persons, that is associated with functional deficiency of the C1-esterase inhibitor (C1-INH).[1–4] HAE is characterized by recurrent attacks of nonpruritic, nonpitting, submucosal, or subcutaneous swelling, and many patients will experience multiple recurrent attacks throughout their lifetime.[3] In a longitudinal study of HAE attacks, only 370 of 5736 patient-years were symptom free.[1] The mean number of episodes per year was 24.0 in women and 20.1 in men, and 60.7% of women and 43.6% of men experienced >12 attacks/year.[1]

Several agents are approved in the United States for the treatment of acute HAE attacks, including C1-INH (Berinert; CSL Behring, Kankakee, IL); icatibant (Firazyr; Shire Orphan Therapies, Lexington, MA), a bradykinin receptor antagonist; and ecallantide (Kalbitor; Dyax Corp., Burlington, MA), a specific antagonist of plasma kallikrein produced in *Pichia pastoris* yeast.[5–7] Plasma kallikrein, which is inhibited by C1-INH, is part of a proteolytic cascade that, when activated, leads to the generation of bradykinin, which induces vascular permeability, resulting in fluid leakage and the characteristic edema of HAE attacks.[3,8,9]

Ecallantide was approved based on the results of two randomized, double-blind, placebo-controlled, phase 3 clinical studies in the Evaluation of DX-88's Effects in Mitigating Angioedema (EDEMA) clinical development program:

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EDEMA3-double blind (EDEMA3-DB) and EDEMA4.[10,11] In both studies, ecallantide treatment was associated with significant symptomatic improvement within 4 hours of administration, as measured by two validated, patient-reported outcome measures, change in mean symptom complex severity (MSCS) score and treatment outcome score (TOS).[10,11] Because any agent used in the treatment of acute HAE attacks is likely to be used multiple times throughout the patient's life, we conducted an open-label study of recurrent use of ecallantide in patients with HAE to investigate whether any evidence exists for a change in the efficacy of ecallantide after repeated use.

## METHODS

Study DX-88/19 was an open-label continuation study of the safety and efficacy of ecallantide in patients with HAE. Patients who completed EDEMA4 were rolled over into DX-88/19 for follow-up and to allow continued access to ecallantide.[11] Patients who were ineligible for any other ecallantide clinical trial and who met the inclusion and exclusion criteria for this study were also eligible for enrollment.

### Patient Population

Patients aged ≥10 years with a confirmed diagnosis of type I or type II HAE were eligible for the study. Patients were to present at the study site within 8 hours of development of moderate or severe symptoms, or at any time after the development of mild symptoms. Symptom resolution must not have begun at the time of treatment. There were no limits on the number of attacks for which an enrolled patient could be treated.

Patients were excluded if they had received treatment with any investigational drug other than ecallantide within 30 days of dosing or treatment with ecallantide or C1-INH concentrate within 72 hours of dosing. Those who were pregnant or breastfeeding were also excluded.

### Treatments Administered

For each HAE attack, a single 30-mg subcutaneous dose of ecallantide (10 mg/mL of formulation), given *via* 2 or 3 subcutaneous injections not exceeding 1.7 mL each, was administered. Treated patients who failed to achieve a complete response or who relapsed were eligible to receive 1 additional 30-mg dose of ecallantide (dose B), administered in the same manner, between 4 and 24 hours after the initial dose. Patients were permitted to take emergency medications, including opioids, antiemetics, and alternate HAE therapies.

### Efficacy Assessments

Several patient-reported outcome instruments were used to assess attack severity and response to treatment: MSCS score, TOS, an overall response assessment, and a visual analog scale (VAS) for pain intensity. All patient-reported responses were captured *via* an electronic diary.

The MSCS score is a comprehensive point-in-time assessment of symptom severity. HAE symptom complexes were characterized by anatomic location (oropharyngeal head/neck [also referred to as laryngeal]; gastrointestinal/abdominal [abdominal]; and genital/buttocks, nonoropharyngeal head/neck, and/or cutaneous [collectively referred to as peripheral]). The severity of each affected symptom complex was rated at baseline by the patient on a categorical scale (mild = 1, moderate = 2, and severe = 3). Follow-up assessments were conducted at 4 and 24 hours postdosing (a rating of normal or no symptoms = 0 was added for follow-up). The ratings were averaged at each time point to calculate the MSCS score. A decrease from baseline in MSCS score represents symptomatic improvement; the minimally important difference (MID) for change in MSCS score is −0.30.[12] The primary end point of DX-88/19 was the change from baseline in MSCS score at 4 hours postdosing.

The TOS is a comprehensive measure of symptomatic response after treatment, which was assessed for each symptom complex at 4 and 24 hours postdosing. At each time point, response was rated by the patient on a categorical scale: significant improvement ("a lot better or resolved") = 100, improvement ("a little better") = 50, no change ("same") = 0, worsening ("a little worse") = −50, and significant worsening ("a lot worse") = −100. Each response score was weighted by baseline severity and averaged to generate the TOS. Positive TOS values represent improvement; the MID for TOS is 30.0.[12]

MSCS score and TOS response rates were defined as the proportion of patients achieving predefined thresholds in MSCS score or TOS (for change from baseline MSCS score, −0.3, −0.5, −0.7, or −1.0; for TOS, 30, 50, 70, or 100).

The overall response assessment used a categorical scale similar to that used for the TOS but was focused on overall, rather than symptom complex–specific, response. The overall response assessment was conducted at baseline and at 15, 30, 45, 60, 75, 90, and 105 minutes and at 2, 2.5, 3, 3.5, 4, and 24 hours postdosing. The time to significant improvement was defined as the first time the patient reported feeling "a lot better or resolved" on the overall response assessment within 4 hours of dosing. The time to onset of sustained improvement was defined as the first time the patient reported feeling "a little better" or "a lot better or resolved" on the overall response assessment for a continuous duration of ≥45 minutes within 4 hours of dosing.

The VAS pain intensity assessment was conducted at baseline and at 4 hours postdosing. Patients were asked to

indicate their overall pain level by drawing a slash through a 100-mm line (no pain = 0 and worst possible pain = 100).

### Safety

Treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs) were recorded after the start of treatment through 28 ± 2 days postdosing. The severity of TEAEs was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0 (CTCAE, National Institutes of Health, Bethesda, MD). All TEAEs were evaluated by the investigator for their possible relationship to study drug. TESAEs were defined as TEAEs that resulted in persistent or significant disability or incapacity, required inpatient hospitalization or prolongation of existing hospitalization, were potentially life-threatening, or resulted in death.

A brief physical examination, vital sign evaluation, and a 12-lead electrocardiogram were conducted predose, 4 hours postdosing, and 7 ± 2 days and 28 ± 2 days postdosing. Laboratory evaluations, including complete blood count with differential and platelet count, serum chemistry, coagulation parameters, and urinalysis were conducted at the same time points.

### Sample Size Determination and Statistical Methods

This study was expected to enroll up to 150 eligible patients. The anticipated sample size was based on pragmatic considerations (primarily the rarity of HAE), was similar to other open-label studies of this type, and was considered sufficient to assess the safety and efficacy of ecallantide in this population.

Analyses of efficacy and safety were conducted on the safety population, defined as all patients who received ≥1 dose of ecallantide in DX-88/19. All analyses were performed on a per episode basis; episodes for which there were ≥12 treated patients (referred to as "qualifying" episodes) were analyzed. Kaplan-Meier analysis was used to assess time-to-response end points; summary statistics were calculated for all other end points.

## RESULTS

A total of 207 patients were enrolled, of whom 147 (70 rollover patients from the EDEMA4 study; 77 non-rollover patients) received treatment and were included in the safety population (Fig. 1). Mean patient age was 35.8 years (range, 11–72 years); 67.1% of patients were women and 82.2% were white.

A total of 625 acute HAE episodes were treated. Follow-up was completed through 90 ± 7 days postdosing for 572 episodes (91.5%). The maximum number of treated attacks for any patient was 21 ($n$ = 1). Thirteen episodes qualified for analysis. Across the qualifying treatment episodes, the percentage of patients with a primary attack location classified as laryngeal ranged from 5.9 to 31.3%, as abdominal ranged from 30.8 to 66.7%, and as peripheral ranged from 13.3 to 53.8%.

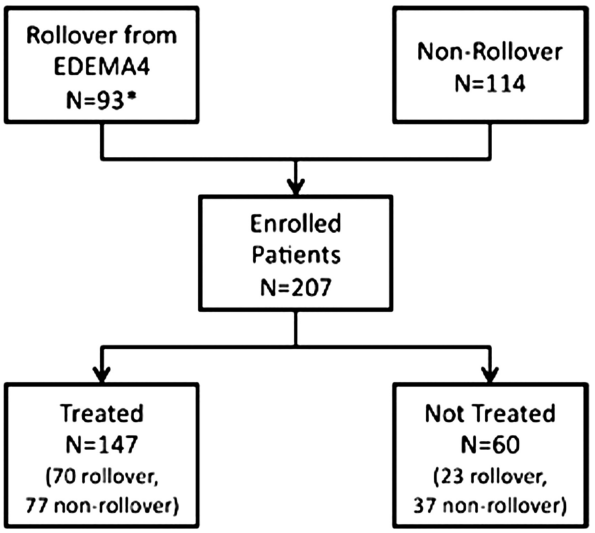


*Figure 1. Patient disposition. *Three patients from Evaluation of DX-88's Effects in Mitigating Angioedema (EDEMA4) did not roll over into DX-88/19.*

### MSCS Score End Points

Figure 2 presents the mean change in MSCS score for each of the 13 qualifying treatment episodes. At 4 hours, mean change from baseline ranged from −1.04 to −1.36 and exceeded the MID of −0.30 for all qualifying episodes. The proportion of patients with a change in MSCS score of at least −0.3 ranged from 76.8 to 93.8% across qualifying episodes, while the proportion of patients with a change in MSCS score of at least −1.0 ranged from 62.5 to 91.7%. There was no evidence of any trend efficacy across treatment episodes with respect to the proportion of patients achieving MSCS score change thresholds. At 24 hours, the mean change from baseline in MSCS score ranged from −1.31 to −1.99, with all qualifying treatment episodes exceeding the MID. There was no evidence of any decrease in across treatment episodes, with respect to 4- or 24-hour MSCS score outcomes.

### TOS End Points

Figure 3 presents the mean TOS values across the 13 qualifying episodes. At 4 hours, mean TOS ranged from 56.2 to 79.8; all mean values exceeded the MID of 30.0. The proportion of patients with a TOS value of at least 30 ranged from 76.9 to 100% across qualifying episodes, and 28.0–69.2% of patients had a TOS of 100. There was no evidence of any trend across treatment episodes with respect to the proportion of patients achieving TOS thresholds. At 24 hours postdosing,

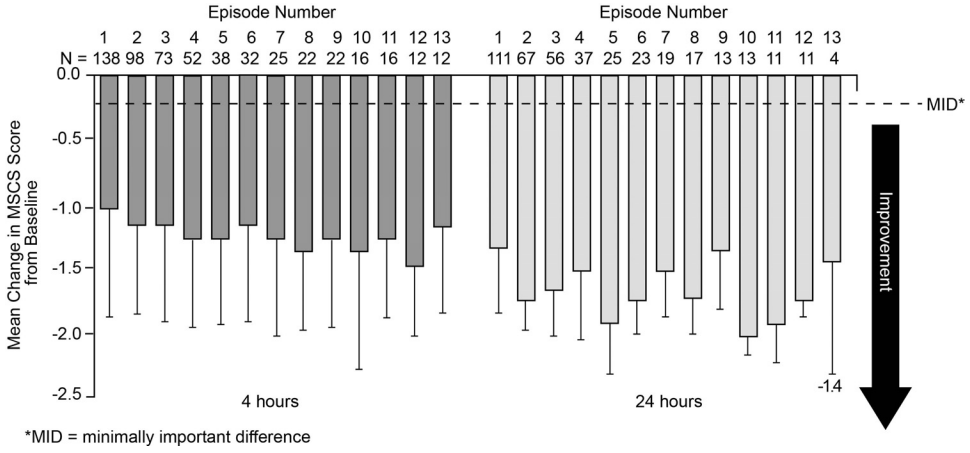


*Figure 2. Mean symptom complex severity (MSCS) score. Mean change in MSCS score at 4 and 24 hours postdosing by treatment episode. Negative values indicate improvement; error bars represent standard deviation. The minimally important difference (MID) is −0.3.*

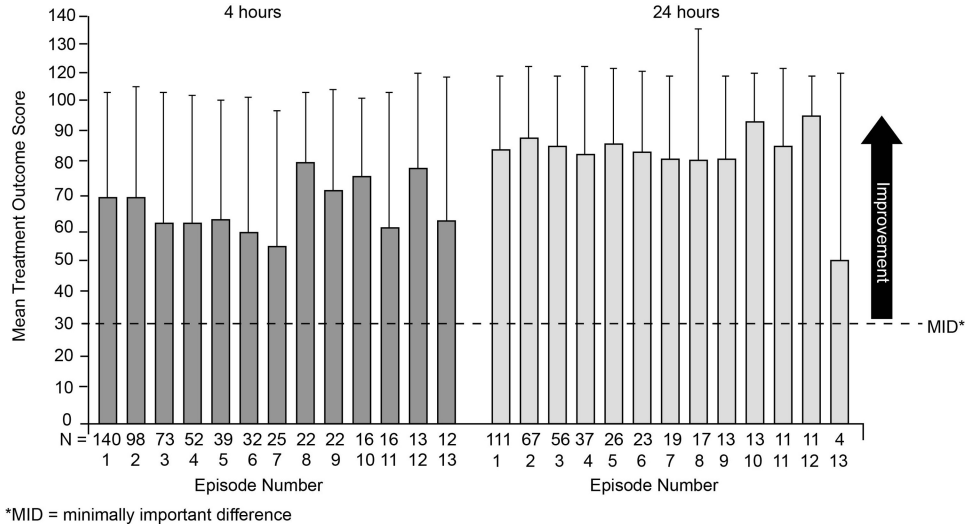


*Figure 3. Treatment outcome score (TOS). Mean TOS at 4 and 24 hours postdosing by treatment episode. Positive values indicate improvement; error bars represent standard deviation. The maximum possible score is 100, and the minimally important difference (MID) is 30.0.*

mean TOS ranged from 50.0 to 95.4 across qualifying episodes; again, mean TOS responses exceeded the MID in all qualifying episodes. As with the MSCS score, there was no evidence of any decrease in efficacy across treatment episodes with respect to TOS outcomes.

### Time-to-Response End Points

Across qualifying episodes, 43.8–65.2% of patients achieved significant improvement (*i.e.*, complete or near complete resolution) within 4 hours postdosing. The median time to significant improvement was estimable within 4 hours for 12 of the 13 qualifying treatment episodes and ranged from 169 to 240 minutes (Table 1). Across qualifying episodes, 69.2–100% of patients achieved onset of sustained improvement within 4 hours of dosing. The estimated median time to onset of sustained improvement ranged from 59 to 113 minutes (Table 1). Across treatment episodes, there were no evident trends with respect to either the proportion of patients or the median time required to achieve either end point.

### Additional Efficacy End Points

Across qualifying episodes, median percentage reductions in VAS pain scores at 4 hours postdosing ranged from 56.6 to 82.3% (Table 2). Across qualifying episodes, 7.1–26.8% of patients received medical intervention during 24 hours postdosing. The most frequent medical intervention was administration of dose B, which was received by 4.3–19.5% of patients across qualifying treatment episodes. Overall, dose B was administered for 11% of the 625 treated attacks.

### Safety Outcomes

Overall, 102 of 147 patients (69.4%) reported one or more TEAE during the study. Across qualifying episodes, 26.1–69.2% of patients reported one or more TEAE (Fig. 4). Most TEAEs were mild to moderate in severity and considered unrelated to study drug. No patient discontinued treatment or had an incomplete treatment episode because of a TEAE. Across qualifying episodes, no consistent changes were observed in the overall incidence of TEAEs or in the incidence of any

Table 1 **Kaplan-Meier estimates of time to response end points**

| Episode | *n** | Time to Onset of Sustained Improvement (min) | | Time to Significant Improvement (min) | |
|---|---|---|---|---|---|
| | | Median (95% CI) | IQR | Median (95% CI) | IQR |
| 1 | 145 | 67.9 (52.9, 97.7) | 37.7, 151.1 | 225.2 (164.5, 228.2) | 109.7, 240.0 |
| 2 | 102 | 58.8 (45.0, 82.8) | 37.7, 135.4 | 194.5 (165.2, 227.5) | 97.2, NR |
| 3 | 77 | 82.9 (67.8, 106.2) | 52.7, 165.2 | 225.4 (225.1, —) | 165.2, NR |
| 4 | 56 | 67.9 (52.8, 113.0) | 43.2, 180.3 | 198.1 (165.4, —) | 112.7, NR |
| 5 | 41 | 88.7 (67.7, 135.2) | 52.9, 165.7 | 240.0 (165.3, —) | 135.2, NR |
| 6 | 33 | 112.7 (60.0, 135.2) | 52.9, 179.3 | 225.2 (137.0, —) | 135.3, NR |
| 7 | 27 | 67.9 (52.7, 135.4) | 38.1, 135.5 | NR (195.3, —) | 120.8, NR |
| 8 | 23 | 90.3 (67.8, 113.5) | 67.7, 135.4 | 210.5 (135.3, —) | 120.0, 240.0 |
| 9 | 23 | 97.9 (53.8, 150.7) | 53.3, 165.2 | 169.3 (135.4, 240.0) | 113.2, 240.0 |
| 10 | 17 | 85.2 (82.7, 135.8) | 82.7, 135.8 | 170.5 (165.1, —) | 165.1, NR |
| 11 | 16 | 113.3 (64.7, 135.3) | 51.3, 150.3 | 226.5 (145.7, —) | 141.2, NR |
| 12 | 15 | 90.7 (52.9, 135.1) | 52.7, 135.1 | 177.2 (113.8, —) | 113.8, NR |
| 13 | 13 | 85.3 (37.9, 170.2) | 30.3, NR | 195.2 (135.1, —) | 120.3, NR |

**Number of evaluable patients, defined as those patients with one or more assessments of overall response at or before 4 hr.*
*— = Indicates that the parameter could not be determined; CI = confidence interval; IQR = interquartile range; min = minutes; NR = not reached within 4 hr.*

Table 2 **Percent change from baseline in pain score on VAS at 4 hr postdosing**

| Episode | *n** | Mean (SD) | Median | IQR | Min, Max |
|---|---|---|---|---|---|
| 1 | 137 | −58.85 (54.74) | −75.29 | −93.94, −37.33 | −100.0, 283.3 |
| 2 | 98 | −56.77 (57.80) | −74.12 | −92.00, −32.18 | −100.0, 300.0 |
| 3 | 73 | −57.03 (34.86) | −63.79 | −86.21, −36.36 | −100.0, 70.2 |
| 4 | 52 | −57.94 (35.77) | −65.69 | −90.67, −25.49 | −100.0, 19.6 |
| 5 | 39 | −53.60 (36.17) | −56.63 | −88.14, −23.08 | −100.0, 25.0 |
| 6 | 32 | −60.12 (38.56) | −69.27 | −90.91, −40.98 | −100.0, 52.2 |
| 7 | 25 | −62.69 (22.96) | −60.00 | −77.78, −51.85 | −100.0, −10.2 |
| 8 | 22 | −75.15 (20.43) | −82.25 | −86.96, −65.43 | −100.0, −12.5 |
| 9 | 22 | −60.22 (45.20) | −74.47 | −85.96, −50.00 | −100.0, 100.0 |
| 10 | 16 | −65.47 (29.75) | −72.23 | −81.62, −50.41 | −100.0, 16.3 |
| 11# | 15 | −63.95 (29.88) | −72.09 | −80.30, −59.02 | −100.0, 5.4 |
| 12 | 13 | −64.19 (48.17) | −68.00 | −83.82, −63.89 | −100.0, 87.5 |
| 13 | 12 | −54.74 (45.71) | −67.83 | −83.61, −28.96 | −100.0, 29.4 |

**Number of evaluable patients, defined as those patients with non-missing values for VAS.*
*#One outlier result was removed from this episode.*
*IQR = interquartile range; max = maximum; min = minimum; SD = standard deviation; VAS = visual analog scale.*

specific TEAE. There was also no evidence for a change in the severity of TEAEs or in relatedness to study drug.

Overall, 27 of 147 patients (18.4%) reported at least one TESAE. The most commonly reported TESAE was HAE (11.6%). Abdominal pain was reported by 2.7% of patients. No other TESAE was reported by more than one patient. During the study, one death occurred that was unrelated to study drug (homicide).

Potential hypersensitivity reactions were reported in eight patients (5.4%). Reactions in six of these patients (4.1%) met the criteria for anaphylaxis based on the National Institute of Allergy and Infectious Diseases.[13] These six cases had a variable clinical presentation. For example, one patient experienced mild hot flush, dyspnea, and pruritus, and another patient experienced life-threatening anaphylaxis with pruritus, erythema, dizziness, nausea, and confusion. All of these events resolved without sequelae. Treatments ranged from epinephrine (two patients) to no treatment (two patients).

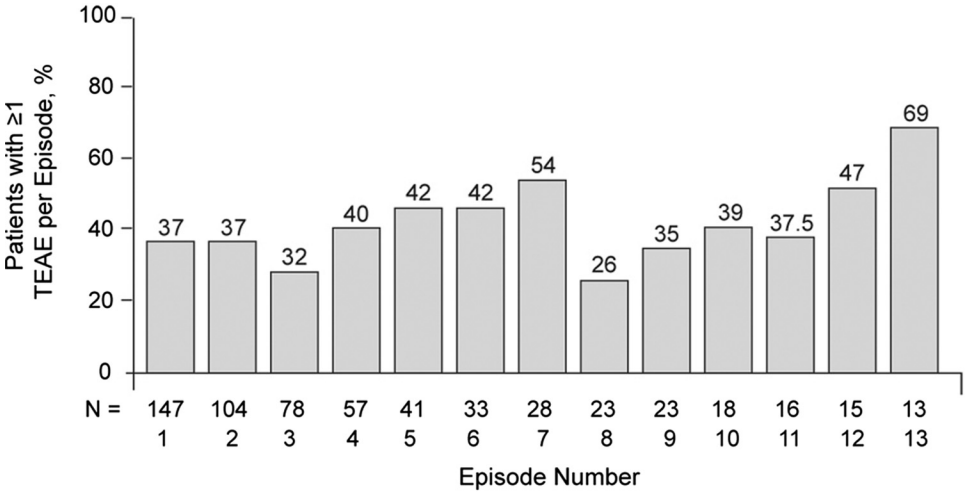


***Figure 4.*** *Treatment-emergent adverse events (TEAEs). Proportion of patients reporting one or more TEAE by treatment episode number.*

Table 3 **Comparison of 4-hr efficacy outcomes: EDEMA3-DB, EDEMA4, and DX-88/19**

| Study | Change in MSCS Score (mean ± SD) | | Treatment Outcome Score (mean ± SD) | |
|---|---|---|---|---|
| | Ecallantide | Placebo | Ecallantide | Placebo |
| EDEMA3-DB[10] | −0.88 ± 1.11 | −0.51 ± 0.68 | 46.8 ± 59.3 | 21.3 ± 69.0 |
| EDEMA4[11] | −0.8 ± 0.6 | −0.4 ± 0.8 | 53.4 ± 49.7 | 8.1 ± 63.2 |
| DX-88/19* | −1.04 ± 0.77 to −1.36 ± 0.68 | NA | 56.2 ± 34.2 to 79.8 ± 24.7 | NA |

**Results for DX-88/19 (current study) reported as range across 13 qualifying treatment episodes.*
*EDEMA = Evaluation of DX-88's Effects in Mitigating Angioedema; MSCS = mean symptom complex severity; NA = not applicable; SD = standard deviation.*

During the study, no clinically relevant or consistent mean changes from baseline were observed for any laboratory evaluation, electrocardiogram interval, physical examination, or vital sign parameter.

## DISCUSSION

This study evaluated the efficacy and safety of open-label ecallantide treatment for multiple, recurrent, acute HAE attacks over time in a "real-world" setting. A total of 625 attacks were evaluated. The maximum number of treated attacks for any patient was 21. Treatment response, measured by change in MSCS score and TOS, was clinically meaningful at 4 hours, indicating prompt response, and at 24 hours, indicating sustained response. For all efficacy measures examined, there was no evidence that the efficacy of ecallantide consistently changed or declined with repeated use.

Comparison of results of this study with those of the pivotal randomized, placebo-controlled clinical trials of ecallantide, EDEMA3-DB and EDEMA4, is facilitated by the use of the same patient-reported outcome measures in all three studies. As summarized in Table 3, mean 4-hour changes in MSCS score and TOS were similar in all three studies, suggesting that the efficacy of ecallantide under real-world conditions involving repeated treatment is at least comparable with its efficacy in the context of a controlled, single-treatment clinical study. This conclusion is reinforced by comparison of the 4-hour TOS responder rate at a threshold of >50, which was 68.8% in EDEMA4[11] compared with 73.1–100% across treatment episodes in this study. As in EDEMA3-DB and EDEMA4, symptomatic relief provided by ecallantide in this study was also sustained through 24 hours postdosing.

No obvious trends were observed with respect to the proportions of patients who achieved or failed to achieve specific response thresholds across qualifying treatment episodes. This study was not designed to evaluate possible associations between patient characteristics and the likelihood of response to ecallantide. However, a recent analysis of pooled results from EDEMA3-DB and EDEMA4 suggested the possibility of reduced effectiveness of the standard dose among obese or heavy patients (body mass index of >30 $kg/m^2$ or body weight >200 lb) compared with those with a body mass index of ≤30 $kg/m^2$ or body weight of ≤200 lb. Other factors (patient gender, attack location, and attack severity) did not appear to affect response to ecallantide.[14]

Ecallantide was generally safe and well tolerated during this study. As in the two placebo-controlled studies, most TEAEs were mild to moderate in intensity and

considered unrelated to ecallantide administration. The most frequently reported TEAEs were related to HAE. As with the efficacy results, there was no indication of systematic increase or decrease in the proportion of patients reporting TEAEs. Potential hypersensitivity reactions meeting the National Institute of Allergy and Infectious Diseases criteria for anaphylaxis were observed in 6 of 147 patients (4.1%).[13] This rate is comparable with the 3.9% rate reported for 255 patients who received i.v. or subcutaneous ecallantide during the clinical development program, but is somewhat higher than the 2.7% rate for the subgroup ($n$ = 187) of patients who were treated with subcutaneous administration.[6,15] Concern about the potential for anaphylaxis led to the inclusion of a boxed warning in the prescribing information for ecallantide,[6,15] highlighting the need for ecallantide to be administered by a health care professional with appropriate medical support to manage anaphylaxis and HAE.

Taken as a group, the results of this study, along with those from EDEMA3-DB and EDEMA4, validate the inhibition of plasma kallikrein as a valuable strategy in the treatment of acute HAE attacks. Although other therapeutic agents (including a plasma-derived formulation of C1-INH and a bradykinin receptor antagonist) have been approved for the treatment of acute HAE attacks, the use of different patient-reported efficacy measures in these studies precludes direct comparison of their respective efficacies regarding treatment for acute attacks. There are few reports on the repeated use of other therapies approved by the Food and Drug Administration for the treatment of acute HAE attacks. One study was conducted on the administration of C1-INH to 57 patients with 1085 attacks,[16] and another addressed long-term use of C1-INH administered prophylactically once weekly.[17] The current study provides an evaluation of repeated use of an acute HAE therapy in a large patient cohort ($n$ = 147 patients treated for 625 HAE attacks).

This study has some important limitations, including the constraint on study/sample size imposed by the rarity of HAE. A more important limitation involves the declining number of patients with an increasing number of episodes. The specific reasons underlying this decline remain unclear but probably include inherent variability in attack frequency, differing times of enrollment *vis-à-vis* the study timeline, and possible access to alternate therapies for the treatment or prevention of acute attacks. The efficacy and safety of ecallantide with repeated use should continue to be evaluated in long-term observational studies.

## CONCLUSIONS

The efficacy of ecallantide is consistently maintained with repeated use over time in the treatment of acute HAE attacks. This study confirms that ecallantide appears to be a safe and well-tolerated treatment for acute attacks of HAE. Results of this study support ecallantide as an effective and well-tolerated treatment for recurrent acute HAE attacks.


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