

Assessment of rebound and relapse following ecallantide treatment for acute attacks of hereditary angioedema

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Keywords

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Abstract

Background: Hereditary angioedema (HAE) is a rare genetic disease characterized by unpredictable and recurring attacks of angioedema. This study assessed potential attack rebound and relapse following treatment with ecallantide, a plasma kallikrein inhibitor approved for HAE attack treatment.

Methods: Results were integrated from 2 double-blind, placebo-controlled studies of ecallantide treatment for HAE: EDEMA3-DB and EDEMA4. Symptoms were assessed by treatment outcome score (TOS), mean symptom complex severity (MSCS) score, and global response. Patients with improvement at 4 h post-dosing in all three measures followed by any sign of worsening at 24 h were considered to show potential rebound if worsening was beyond baseline or potential relapse if not beyond baseline. Likelihood of rebound or relapse was determined by the number of measures showing worsening and the magnitude of worsening. Patients receiving placebo who met the criteria for rebound/relapse were evaluated for descriptive comparison only.

Results: Significantly more ecallantide-treated patients (42 of 70) compared to placebo (26 of 71) showed improvement in three measures at 4 h and were thus eligible for rebound/relapse ($P = 0.006$). Of the nine ecallantide-treated patients with signs of worsening at 24 h, none were likely rebound, one was assessed as possible rebound, one as likely relapse, and two as possible relapse. No patient with potential rebound/relapse experienced new symptoms after dosing. Medical intervention was required in one ecallantide-treated patient.

Conclusion: Ecallantide was efficacious for treating acute HAE attacks. Relapse was observed in a small proportion of patients, and there was little evidence of rebound.

Hereditary angioedema (HAE) is a rare autosomal dominant disorder characterized by recurring episodes of angioedema. Type I HAE is attributed to a deficiency of C1 esterase inhibitor (C1-INH); type II to defective C1-INH. With C1-INH deficient or defective, the kallikrein-kinin cascade is subject to over-activation, leading to excess bradykinin, the key mediator of the angioedema (1–4).

HAE attacks are unpredictable and can affect the upper airway, face, abdomen, genitourinary tract, and extremities (5, 6). Though the course and duration of attacks can be highly variable, they typically last several days. Peripheral attacks are the most common and typically take the longest to resolve (7–9). Abdominal attacks, the next most common, have been reported to endure for an average of 3 days (range: 1–6 days) (9, 10).

Ecallantide is approved for acute treatment of HAE attacks affecting any anatomic site. Efficacy was demonstrated in two pivotal trials in the EDEMA (evaluation of DX-88s effect in mitigating angioedema) development program (7, 11–13). A 60-amino-acid protein, ecallantide is a potent ($K_i = 25$ pM), selective, and reversible inhibitor of kallikrein (13–15). Its half-life is approximately 2 h; plasma concentrations of the approved 30 mg subcutaneous dose exceed the inhibition constant for at least 10 h (16, 17). While the efficacy of ecallantide at 4 and 24 h after dosing has been demonstrated (11, 12), further insights into the relationship between the pharmacokinetic profile and the durability of efficacy should enhance the clinical understanding of this drug. Given ecallantide's relatively short half-life, this study aims to assess the potential for attack rebound or relapse following ecallantide treatment.

Methods

This post-hoc analysis is based on the integrated population from the two pivotal double-blind, placebo-controlled ecallantide studies: EDEMA3-DB and EDEMA4 (18). The study protocols were reviewed and approved by the appropriate Institutional Review Board and/or Independent Ethics Committee at each site; all patients provided written informed consent. Patients with documented HAE diagnosis, age ≥ 10 , presenting within 8 h of moderate-to-severe HAE-attack symptoms affecting any anatomic location were enrolled. One treatment episode per patient was included in the analysis (18).

In both studies, patients were randomized 1 : 1 to receive 30 mg subcutaneous (SC) ecallantide or placebo. At baseline, patients identified and rated the severity of all affected sites based on five symptom complexes: stomach/gastrointestinal (abdominal), internal head/neck (laryngeal), genital/buttocks, external head/neck, and cutaneous. Efficacy was assessed 4 and 24 h after dosing with three patient-reported outcome (PRO) measures: mean symptom complex severity (MSCS) score, treatment outcome score (TOS), and global response. MSCS score is a point-in-time assessment of symptom severity; values range from 0 (no symptoms) to 3 (severe) (19). A decrease in MSCS score from baseline indicates improvement; the greatest possible improvement (-3) indicates a change from severe baseline symptoms to no symptoms post-dosing. TOS is a composite measure of symptom response; values range from -100 (significant worsening) to 100 (significant improvement) (19). The global response assesses how patients were feeling overall compared to baseline, using the following categories: 'a lot better or resolved'; 'a little better'; 'same'; 'a little worse'; 'a lot worse.'

Potential rebound/relapse was identified based on patients' 4- and 24-h efficacy results. Patients who showed improvement in all three efficacy measures at 4 h followed by worsening at 24 h in ≥ 1 measure were considered to have potential rebound/relapse. Thus, the first step in the analysis was to identify patients showing improvement in all three measures at 4 h. Potential rebound/relapse cases were then identified from this pool based on their 24-h outcomes. Both treatment arms were examined for qualitative comparison.

Cases were considered potential rebound if 4-h improvement was followed by worsening beyond baseline severity levels at 24 h. Rebound was considered likely if the worsening was shown in all three measures, possible if in two measures, and unlikely if shown in only one measure.

Cases were considered potential relapse if 4-h improvement was followed by worsening at 24 h that was not beyond baseline severity. A minimum threshold of worsening equivalent to one severity level (i.e., MSCS score ≥ 1 , TOS ≥ 50 , global response ≥ 1 category) was used to guide assessment of likelihood. Relapse was considered likely if the worsening met the minimum threshold in all three measures; possible if in two measures; and unlikely if in one measure or if the worsening did not meet the threshold in any measure. Cases identified as unlikely rebound/relapse were those in which the

majority of 24-h efficacy evidence pointed to durability of response.

For borderline cases (i.e., cases that showed signs of both rebound and relapse, or cases showing relapse both above and below the minimum threshold), the magnitude of worsening across the three measures was assessed to determine rebound/relapse likelihood.

For each case of potential rebound/relapse, available individual patient data were qualitatively assessed to identify potentially predisposing characteristics.

Open-label doses

Both study protocols permitted the administration of open-label ecallantide up to 4 h following treatment if there was risk of severe upper airway compromise (SUAC). Patients who received a SUAC dose were excluded from this analysis.

In EDEMA4, Dose B (open-label, 30 mg SC ecallantide) was permitted 4–24 h after initial dosing if, according to the investigator, there was incomplete or no response to study drug, or if attack symptoms 'relapsed,' defined in the protocol as 'an attack between 4 and 24 h after an initial improvement postdosing.'

Any patient who received a Dose B for an investigator-determined 'relapse' was to be reviewed as a case of potential rebound/relapse. If a patient received a Dose B for incomplete or no response, the patient's 4-h efficacy results were to be reviewed to confirm the patient had not met the three-efficacy-measure improvement criteria.

Results

The integrated analysis included 70 ecallantide-treated and 71 placebo-treated patients. Patient dispositions are summarized in Fig. 1.

At 4 h, improvement in at least one of three efficacy measures was seen in 51 (72.9%) ecallantide-treated and 37 (52.1%) placebo-treated patients ($P = 0.01$). Improvement in all three measures – TOS, MSCS score, and global response – was seen in 42 (60%) ecallantide-treated and 26 (37%) placebo-treated patients ($P < 0.01$).

Of the 42 ecallantide-treated patients showing three-efficacy-measure improvement, a total of 9 (21.4%) showed signs of worsening at 24 h and were thus considered potential rebound/relapse. There were no cases of likely rebound, 1 (2.4%) possible rebound, 1 (2.4%) likely relapse, and 2 (4.8%) possible relapse (Table 1). The remaining five were unlikely rebound/relapse.

Of the 26 placebo-treated patients showing three-efficacy-measure improvement, a total of 7 (26.9%) showed worsening at 24 h: 2 (7.7%) met the definition for possible rebound, 2 (7.7%) likely relapse, 1 (3.8%) possible relapse, and two unlikely rebound/relapse.

Figure 2 presents mean efficacy outcomes for all patients with potential rebound/relapse; outcomes from the original integrated analysis are shown for context. In patients with potential rebound/relapse, the mean change in MSCS score

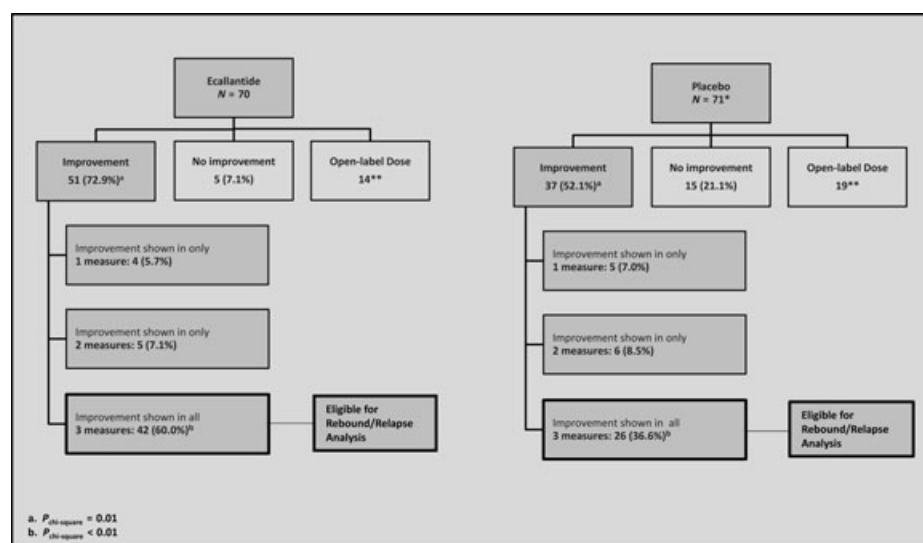


Figure 1 Summary of patient disposition and rebound/relapse eligibility. Patients categorized by 4-h efficacy outcomes with respect to the three efficacy measures: mean symptom complex severity score, treatment outcome score, and global response. Patients showing improvement in all three efficacy measures at 4 h were considered eligible for relapse or rebound. Patients treated with open-label ecallantide include those treated for severe upper airway compromise (SUAC) within 4 h of treatment and those treated with Dose B

between 4 and 24 h of treatment. Dose B was allowed in EDEMA4 only. Patients treated for SUAC were excluded from the rebound/relapse analysis. Patients treated with Dose B were considered separately to assess for potential signs of rebound/relapse. *Two additional patients received placebo but were not included in this analysis due to missing 4-h data. **Because Dose B was not available for all patients included in this analysis, the number of patients receiving open-label doses is not presented with a percentage.

at 4 and 24 h following ecallantide was -1.11 and -0.72 , respectively, and -1.00 and -0.50 , respectively, following placebo. Mean TOS at 4 and 24 h following ecallantide was 81.48 and 46.11, respectively, and 73.00 and -14.86 , respectively, following placebo.

Individual efficacy outcomes for ecallantide-treated patients with potential rebound/relapse are presented in Fig. 3. The greatest degree of worsening was seen in Patient E1 with moderate improvement at 4 h (change in MSCS score -1.0 , TOS 50; global response 'a little better'), followed at 24 h by a return to baseline-level severity in MSCS score, and worsening beyond baseline in TOS and global response (-50 and 'a lot worse,' respectively). This case met the definitions for rebound and relapse; the case was assessed as possible rebound because there were more signs of rebound than relapse. One other border-line case (Patient E4) showed worsening from 4 to 24 h in three measures. The worsening did not meet the minimum threshold for two measures, but because all three measures worsened, this case was assessed as possible relapse.

Dose B

Dose B was administered to 11 ecallantide-treated patients and 16 placebo-treated patients. In all cases, Dose B was administered for incomplete or no response. None were given for investigator-determined relapse. No patient administered a Dose B met the three-efficacy-measure improvement criteria at 4 h (Table 2).

Table 1 Summary of potential rebound and potential relapse by treatment

	Ecallantide (N = 70)	Placebo (N = 71)
Patients eligible for relapse or rebound*	42 (60%)	26 (37%)
Rebound [†]		
Likely	0	0
Possible	1	2
Unlikely	1	0
Total potential rebound	2	2
Relapse [‡]		
Likely	1	2
Possible	2	1
Unlikely	4	2
Total potential relapse	7	5
Total likely or possible rebound/relapse	4	5
Total potential rebound/relapse	9	7

*Patients were eligible for relapse or rebound if they showed improvement in three measures at 4 h.

[†]Rebound defined as improvement in all three efficacy measures at 4 h postdosing followed by worsening beyond baseline-level severity at 24 h. Likelihood assessed by number of measures showing signs of rebound or relapse.

[‡]Relapse defined as improvement in all three efficacy measures at 4 h postdosing followed by worsening, but not worse than baseline, at 24 h. Likelihood assessed by number of measures showing signs of relapse that met or exceeded a minimum threshold.

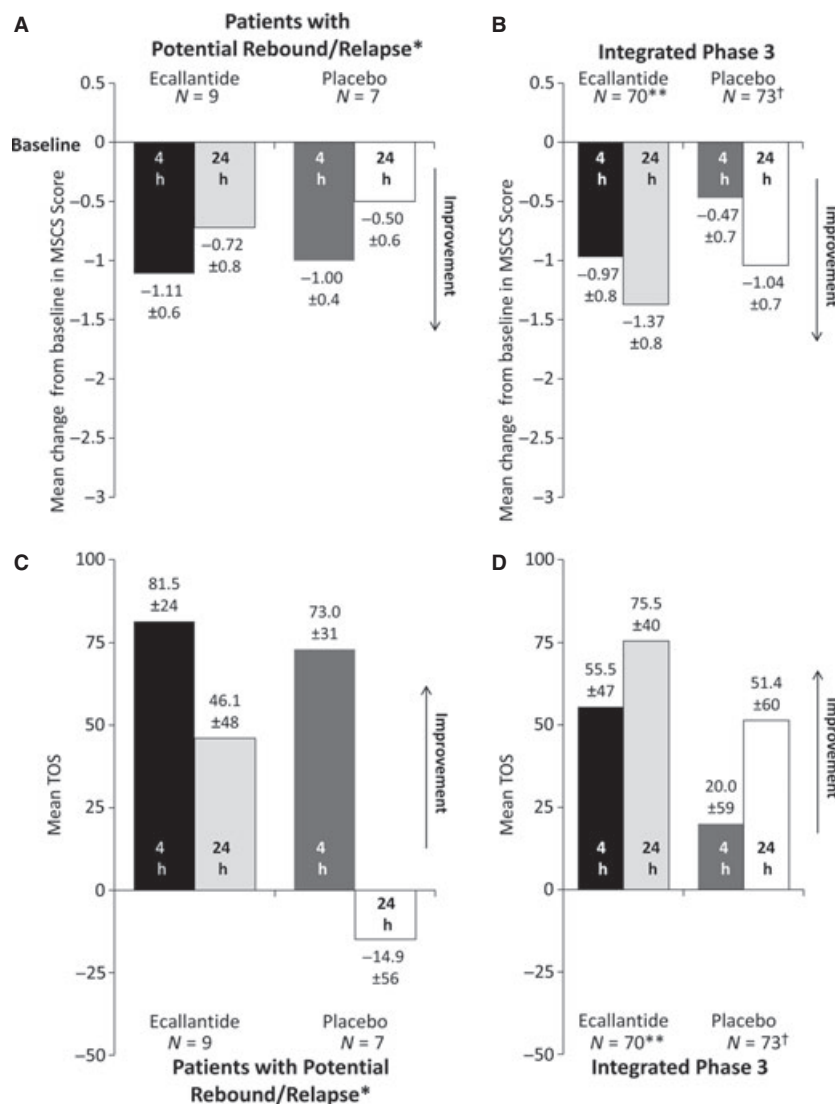


Figure 2 Mean efficacy outcomes at 4 and 24 h. (A) Mean change in mean symptom complex severity (MSCS) Score from baseline to 4 and 24 h: patients with potential rebound/relapse. Negative change in MSCS score indicates improvement; the minimally important difference (MID) is estimated to be 30 (19). (B) Mean change in MSCS Score from baseline to 4 and 24 h: integrated phase 3 study population. Results from integrated phase 3 study, reported elsewhere (18), are presented to provide context of efficacy. (C) Treatment outcome score (TOS) at 4 and 24 h: Patients with potential rebound/relapse. Higher scores indicate greater improvement; MID is estimated to be 0.30 (19). (D) TOS

at 4 and 24 h: integrated phase 3 study population. Results from integrated phase 3 study, reported elsewhere (18), are presented to provide context of efficacy. *Potential rebound/relapse defined as improvement in all three efficacy measures at 4 h postdosing, followed by worsening in any measure at 24 h. **Not all 70 ecallantide-treated patients had valid 4- and 24-h data available: three were missing 4-h data for MSCS score and TOS; 19 were missing 24-h data. †Not all 73 placebo-treated patients had valid 4- and 24-h data available: six were missing 4-h data for MSCS score and TOS; 24 were missing 24-h data for MSCS score; 23 were missing 24-h data for TOS.

Emerging symptoms and medical interventions

No patients with potential rebound/relapse reported new symptoms that emerged postdosing. Medical intervention was required in one ecallantide-treated patient: Patient E3 (likely relapse) received danazol for an abdominal attack.

Attack locations and patient characteristics

Attack locations and patient characteristics for all patients with potential rebound/relapse are summarized in Table 3. Of the nine ecallantide-treated patients, five (56%) had symptoms at multiple sites; abdominal symptoms, all of

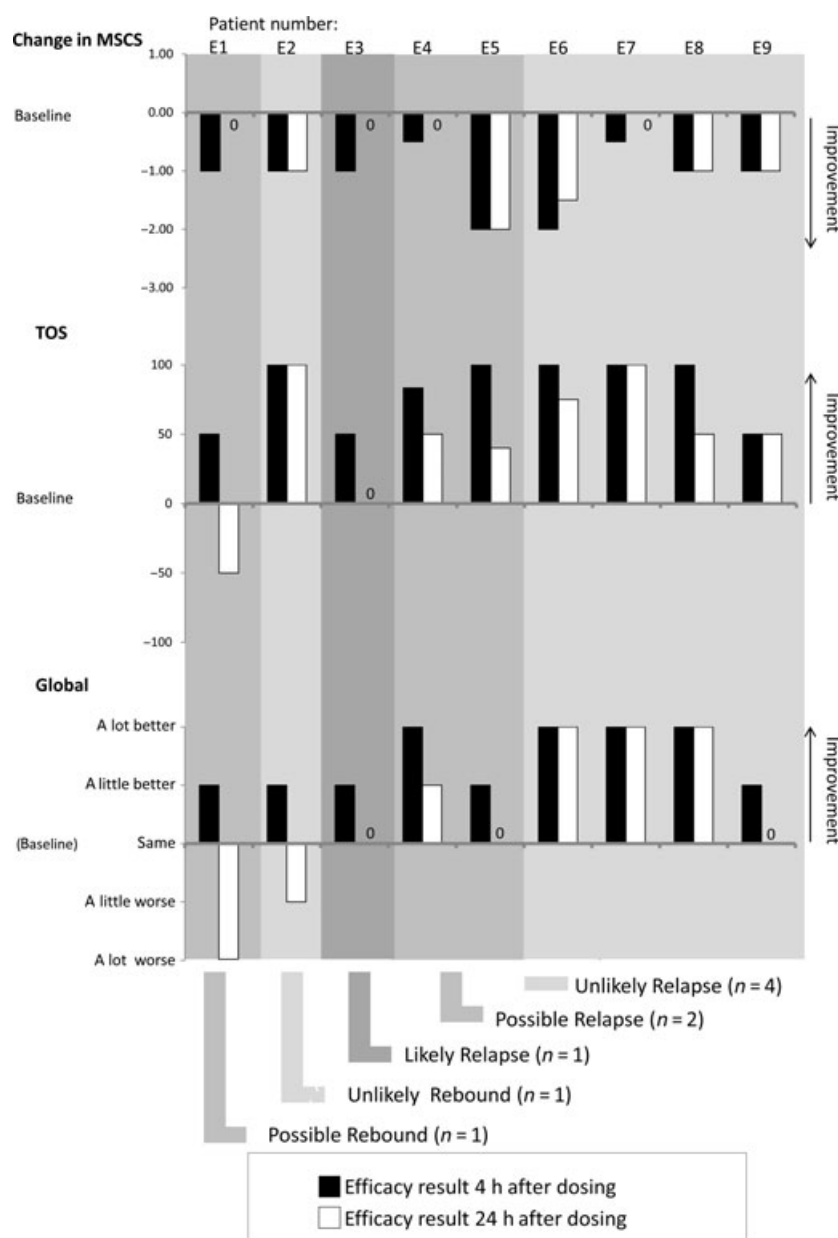


Figure 3 Efficacy outcomes at 4 and 24 h following ecallantide, by patient and relapse category. Efficacy outcomes at 4 and 24 h after dosing for: top panel: the change in mean symptom complex severity score (negative values indicate improvement from baseline), middle panel: the treatment outcome score (positive values indicate improvement from baseline), and bottom panel: global

response (bars above the x-axis indicate improvement from baseline). For each efficacy measure, distance from the x-axis represents a change from baseline severity, and '0' value represents a return to baseline severity. Patients are categorized as likely, possible, or unlikely rebound or relapse, per definitions presented in the text.

moderate severity, were present in seven (78%) patients, including all of those with likely or possible rebound/relapse. In the placebo-treated patients, three (43%) had symptoms at multiple sites; five (71%) had abdominal symptoms.

Of the nine ecallantide-treated patients with potential rebound/relapse, 5 (56%) received ecallantide ≥ 6 h after onset of moderately severe symptoms.

Additional treatment-episode information is available and noteworthy for patients E1 and E5. Patient E1 (possible rebound) had a BMI of 40; across all studies within the EDEMA program, this patient showed a strong and durable response for the majority of other ecallantide-treated attacks (39 overall; 27 after the attack included in this analysis) but showed potential relapse in one other ecallantide-treated

Table 2 Summary of open-label doses in the integrated study population

	Ecallantide (N = 70)	Placebo (N = 71)
<i>Patients treated with open-label dose</i>	14	19
For SUAC*	3	4
Dose B	11	16
Patients treated with Dose B following SUAC	0	1
Patients treated with Dose B following improvement at 4 h in all 3 efficacy measures (TOS, MSCS score, and global response)	0	0
Reason for dose B		
Incomplete or no response	11	16
Investigator-determined relapse†	0	0

MSCS, mean symptom complex severity; SUAC, severe upper airway compromise; TOS, treatment outcome score.

*Patients treated for SUAC were removed from 4-h efficacy evaluations.

†Investigator-determined relapse defined in the protocol as 'an attack between 4 and 24 h after an initial improvement postdosing.'

episode and required medical intervention in four others, including Dose B. Patient E5 (possible relapse) was treated >7 h after moderate symptom onset for an attack affecting all five symptom complexes. This patient experienced several subsequent similar attacks with similar 4- and 24-h responses; although Dose B was available for all subsequent episodes, it was never administered.

Discussion

To assess the occurrence of rebound or relapse of HAE attacks following a response to treatment, we first identified patients with sufficient enough improvement at 4 h that a decline at 24 h would be indicative of an attack rebound or relapse. Confirming the previously reported efficacy benefit of ecallantide (7, 11, 12, 18, 20), the proportion of patients eligible for rebound/relapse – i.e., showing symptom improvement by three efficacy measures – was significantly higher for patients treated with ecallantide vs placebo.

Taking a conservative approach, we then considered any sign of symptom worsening at 24 h to be a case of potential rebound/relapse. Of the nine ecallantide-treated patients meeting the criteria for potential rebound, five were considered unlikely rebound or relapse. There was one case of possible rebound and three cases of likely or possible relapse.

A qualitative review of patient characteristics identified no clear predictors or predisposing factors for potential rebound/relapse. Nevertheless, notable case details – including attack locations, time to treatment, BMI, and treatment-response history – may provide clinical insights relevant to the variability of HAE attacks and treatment response.

Of the four ecallantide-treated patients with likely or possible rebound/relapse, three had symptoms affecting more than one anatomic site, and all four had abdominal symptoms. Patients with abdominal attacks tend to have combinations of symptoms, can have fairly long crescendo and maximum phases of colicky symptoms (10), and may be more likely to show signs of worsening following reports of symptom improvement. C1-INH therapy and icatibant have each also shown a need for second doses for worsening symptoms in patients with abdominal attacks (second doses of icatibant have also been needed for other symptoms sites) (21, 22).

In ecallantide-treated patients, five (56%) of the nine potential rebound/relapse cases (including three of the four likely/possible cases) were in patients treated ≥ 6 h after moderate symptom onset. In contrast, among the ecallantide-treated patients who showed durable improvement in all three measures at 4 and 24 h, the majority (29 of 33; 88%) were treated within 6 h of onset. Earlier treatment has been correlated with improved efficacy and is thus recommended by treatment guidelines (23–25). The cases of potential rebound/relapse following late treatment may be examples of attacks that would have benefited from treatment before attacks progressed to multiple sites or reached maximum severity.

Of the four patients with likely or possible rebound/relapse following ecallantide, two have treatment-response histories available for multiple ecallantide-treated attacks. Both have disease profiles suggesting they may be prone to severe attacks. One patient (possible relapse) was treated for frequent attacks, all affecting multiple sites, including the larynx. The other (possible rebound), with a very high BMI, has shown strong response to the majority of ecallantide treatments, but occasionally has required medical intervention, including Dose B. The episode included in the current analysis occurred in EDEMA3-DB and was thus not eligible for Dose B; the patient's profile suggests the patient should be monitored for the possible benefit of Dose B, especially in the case of attacks that include multiple symptom sites, severe abdominal symptoms, or laryngeal symptoms.

Patients who were treated with placebo and met the criteria for potential rebound/relapse may be seen as a testament to the inherent variability of the time course of HAE-attack symptoms, with occasional clear signs of improvement followed by worsening. On the basis of a qualitative comparison, the occurrence of potential rebound/relapse in patients who showed improvement following treatment is similar in ecallantide- and placebo-treated patients. It is important, however, to keep in mind that the structure and scope of the analysis preclude a statistical comparison of rates of potential rebound/relapse. A comparison of incidence rates based on the patients who were eligible for rebound – i.e., showed improvement in all three measures – is not based on a random sampling of patients, which confounds any statistical comparisons. On the other hand, a comparison based on the full integrated study population would be misleading as it would not account for the fact that more ecallantide patients showed improvement and were thus eligible for analysis of rebound/relapse.

This study is also limited by being a post-hoc analysis. Furthermore, not all treatment episodes that were included in the

Table 3 Patient demographics and baseline symptoms: patients with potential rebound/relapse

Patient/Assessment	Sex	Age	BMI	Baseline symptoms*	Time to treatment† (h: min)	Average attack duration‡
E1	M	17	40	Abdominal	3.3	1–4 days
Possible rebound				Cutaneous		
E2	F	40	23.5	Cutaneous	3.6	2 days
Unlikely rebound						
E3	F	21	19.3	Abdominal	6.0	3 days
Likely relapse						
E4	F	31	23.8	Abdominal	6.5	3 days
Possible relapse				Cutaneous (mild)		
E5	F	34	25.3	Laryngeal	7.3	NR§
Possible relapse				Abdominal		
				Genital/Buttock		
				Ext head/neck		
				Cutaneous		
E6	F	37	23.9	Abdominal	9.3	4 days
Unlikely relapse				Cutaneous		
E7	M	42	26.2	Laryngeal	1.7	1–2 days
Unlikely relapse				Cutaneous		
E8	F	20	22.3	Abdominal	7.9	3 days
Unlikely relapse						
E9	M	31	22.8	Abdominal	2.7	2 days
Unlikely relapse						
P1	F	13	25.8	Cutaneous	2.9	2–3 days
Possible rebound						
P2	F	32	20.6	Abdominal	2.6	1–2 days
Possible rebound						
P3	F	42	23.8	Cutaneous	6.7	2–3 days
Likely relapse						
P4	M	11	22.7	Abdominal	8.4	3 days
Likely relapse						
P5	M	49	30.8	Abdominal	2.4	2.5 weeks
Possible relapse				Ext head/neck (mild)		
				Cutaneous		
P6	M	18	19.9	Abdominal	5.0	2–3 days
Unlikely relapse				Cutaneous		
P7	F	30	33.5	Abdominal	2.9	3 days
Unlikely relapse				Genital/Buttock (severe)		
				Cutaneous		

BMI, body mass index; NR, not reported.

*All baseline symptoms were moderate in severity, unless otherwise noted.

†Time to treatment defined as time from patient-reported onset of symptoms of at least moderate severity to dosing.

‡Patient-reported average attack duration, based on medical history, for the symptom complex included in this analysis.

§Patient E5 had not reported previous attacks affecting the symptom complexes present in this attack. However, the patient had reported that the duration of previous attacks affecting other symptom complexes averaged 8 h.

integrated analysis had a Dose B available. While the administration of a Dose B did not affect the rate of potential rebound/relapse in this analysis, the potential benefit of a Dose B for averting symptom worsening could not be adequately assessed.

As has been demonstrated by the efficacy reported at 4 and 24 h following ecallantide treatment (7, 11, 12, 18), despite a relatively short half-life, ecallantide's ability to inhibit plasma kallikrein activity and thereby suppress bradykinin production is sufficient to block the progression of the majority of attacks. With no clear indication of a rebound effect and a small incidence of possible or likely relapse, this analysis confirms that the degree of suppression of plasma kallikrein effects a

meaningful duration of action for the treatment of an acute HAE attack.

Conclusion

As defined in this integrated analysis of patients from the EDEMA3-DB and EDEMA4 studies, relapse was observed in only a small proportion of acute HAE attacks treated with ecallantide, and there was little evidence of rebound. These data contribute to the body of evidence demonstrating a durable response to ecallantide treatment of acute HAE attacks. Attack details and individual patient data reinforce

the clinical importance of monitoring patient responses and individualizing therapeutic intervention.

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Authors' contribution

J.B., E.S., R.I., and W.P. contributed to the conception and/or design of the study; J.B., E.S., and R.I. contributed to the analysis and interpretation of data; J.B., E.S., J.K., R.I., and W.P. contributed to the drafting of the article or critical revision for intellectual content; J.B., E.S., J.K., R.I., and W.P. approved the final version of the manuscript.

Conflict of interest

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) J.B., J.K., R.I., and W.P. have support from Dyax Corp. as follows: J.B. receives consulting fees, E.S., J.K., and R.I. are full-time employees, and W.P. is a former full-time employee; (2) J.B. has received grants from Dyax Corp., CSL Behring, Shire, ViroPharma, and Pharming; has received consulting fees or honoraria from Dyax Corp., CSL Behring, Shire, and ViroPharma; has received payment for lectures, including speakers' bureau activity, from TEVA, Dyax, ViroPharma, Shire, and; and has no ownership interests related to this research; (3) the authors' spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) J.B., E.S., J.K., R.I., and W.P. have no nonfinancial interests that may be relevant to the submitted work.

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