

CLINICAL REVIEW

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Reviewer Name Susan Limb, MD
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Established Name Ecallantide
(Proposed) Trade Name Kalbitor
Therapeutic Class Kallikrein inhibitor
Applicant Dyax Corp.

Priority Designation P

Formulation Solution for injection
Dosing Regimen 30 mg SC; may repeat dose
Indication Treatment of acute HAE attacks
Intended Population HAE patients 10 years and older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical recommendation for this application is Complete Response. The Applicant's proposed indication for ecallantide is "the treatment of acute attacks of hereditary angioedema (HAE) in patients 10 years of age and older." The application contains evidence of efficacy to support this indication in patients ages 18 years of age and older, but a safety signal of anaphylaxis was identified. The application lacks an adequate risk management program to balance the significant risk of anaphylaxis. The application does not contain sufficient evidence of efficacy and safety to support approval for a pediatric population (10 to 17 years of age) because the clinical program included a limited number of patients in this age group.

This is a 505(b)(1) application for ecallantide solution for injection for the treatment of acute attacks of HAE. HAE is a rare, inherited condition characterized by intermittent, unpredictable attacks of angioedema. HAE is estimated to affect 1 in 10,000 to 50,000 individuals worldwide and is categorized as an orphan disease. The acute attacks of HAE are potentially life-threatening, particularly in cases of airway compromise. Attacks at other anatomic sites can cause disabling pain and significant morbidity. These attacks are highly variable in frequency and location among individuals and even within a given individual. Currently, there are no drug products approved for the treatment of acute attacks of HAE and the standard of care remains supportive therapy. Several drug products are available for prophylaxis, but acute attacks can still occur.

Ecallantide is a new molecular entity. The clinical development program included two small, randomized, placebo-controlled Phase 3 studies, EDEMA3 and EDEMA4. Both studies consisted of a single-dose double-blind phase followed by an open-label, uncontrolled extension study of repeat doses for new acute HAE attacks. Since no gold standard exists for the measurement of HAE symptoms, the pivotal studies relied on two novel patient-reported outcome measures, the Treatment Outcome Score (TOS) and the Mean Symptom Complex Score (MSCS). The Applicant developed the TOS and MSCS specifically for the ecallantide development program. Although numerically favorable, EDEMA3 did not show a statistically significant difference for ecallantide over placebo for the primary efficacy endpoint, TOS at 4 hours (47 vs. 21; $p=0.10$) for the intention-to-treat population. In EDEMA3, 1 patient randomized to receive ecallantide mistakenly received placebo and 1 patient randomized to placebo received ecallantide instead. When the analysis is corrected for these treatment administration errors, the results are statistically significant in favor of ecallantide and are in agreement with the per protocol population analysis (50 vs. 19; $p=0.04$). Similar results were seen for the key secondary efficacy endpoint, Change from Baseline MSCS at 4 hours. Based on the pre-specified analysis, the change in MSCS values was not statistically significant (-0.9 vs. -0.5; $p=0.09$). When corrected for the dosing error, the MSCS treatment difference is statistically

significant (-0.9 vs. -0.5; $p=0.04$). These post hoc analyses support ecallantide's efficacy but also demonstrate the limitations of the small sample size.

Since EDEMA3 results were not robust, confirmation of efficacy from a second placebo-controlled study, EDEMA4, was necessary. EDEMA4 was conducted under a Special Protocol Assessment (SPA) agreement. EDEMA4 demonstrated a statistically significant benefit for ecallantide over placebo both for the change in MSCS (-0.8 vs. -0.4; $p=0.01$) and the TOS at 4 hours (53 vs. 8; $p=0.003$). Notably, the MSCS treatment difference was comparable between EDEMA4 and EDEMA3, even though the latter study's findings were not statistically significant. A smaller sample size and the use of the TOS as a primary efficacy endpoint may have contributed to the non-significant results of EDEMA3.

However, additional analysis of EDEMA4 suggested that the treatment benefit may not have been consistent across the duration of the study. The Applicant amended EDEMA4 once the study had already been initiated, increasing the sample size from 52 to 96 patients. The Division agreed to the increase at the time, provided that the amendment was not based on an unblinded assessment of efficacy data collected up until that timepoint. The Division also stipulated that the sample size change should not alter patient enrollment or study conduct. To assess the impact of the protocol amendment, the Division requested that the Applicant provide an analysis of efficacy pre- and post-sample size change in the BLA submission. When the primary efficacy results of EDEMA4 are examined pre- and post-amendment, only the results for the latter 44 patients enrolled after the sample size increase show a statistically significant benefit for ecallantide over placebo. The pre-amendment change in MSCS from baseline was -0.7 vs. -0.6 ($p=0.83$). In comparison, the post-amendment change in MSCS from baseline was -0.9 vs. -0.1 ($p<0.001$). Notably, the placebo patients in the latter half of the study performed more poorly; in particular, 6 outlier patients in the placebo group appeared to drive the results. These patients were treated at 6 separate US study sites that had enrolled other HAE patients for EDEMA4 and previous EDEMA studies. Review of the demographics, baseline HAE history, and attack presentation did not reveal any clear factors to distinguish the outlier patients from the rest. This discrepancy in the results may be a reflection of the inherent variability of the disease. There is no evidence to suggest that study conduct or patient recruitment was altered by the amendment. Nevertheless, since the cause for this discrepancy is uncertain, the clinical review relied more heavily on secondary endpoints for additional evidence of efficacy. Secondary endpoints of particular interest included patients' global self-assessment scores and medical intervention patterns. These other endpoints were independent of the TOS and MSCS calculations and provided additional support for the efficacy of ecallantide in acute HAE attacks. When taken all together, the totality of data presented in the application supports ecallantide's efficacy for the proposed indication in patients 18 years of age and older.

The safety of ecallantide at the proposed 30 mg SC dose is supported in part by the submitted clinical study data, but an adequate risk management program is necessary to balance the safety concern of anaphylaxis. Safety data showed that ecallantide is most commonly associated with headache, nausea, diarrhea, pyrexia, and injection site reactions. The most concerning adverse events were anaphylaxis and other hypersensitivity reactions. Nine anaphylactic events were identified using anaphylaxis diagnostic criteria outlined by the 2006 Joint NIAID/FAAN Second

Symposium on anaphylaxis. Based on a population of 243 unique HAE patients and 846 ecallantide doses administered, the anaphylaxis rate is estimated as 3.7% of HAE patients or 1.1% of doses. An additional anaphylactic event was identified in the cardiothoracic surgery study, but given confounding comorbidities and other differences between the surgical patients and the HAE population, the cardiothoracic patients were excluded from the anaphylaxis rate calculation. As a more general concern, ecallantide appears to be highly immunogenic with an estimated seroconversion rate of 30% after 8 doses. The long-term consequences of seroconversion are not known at this time. Also, potential cross-reactivity with human tissue factor pathway inhibitor (TFPI) has not yet been studied. In knock-out mouse models, TFPI deficiency results in hypercoagulability and lethal thromboembolic events. Based on this literature, TFPI cross-reactivity may theoretically predispose to thrombotic events in humans. Although review of the safety data identified only one thrombotic event, the limitations of the safety database due to the orphan indication prevent drawing any conclusions about thrombotic events with ecallantide.

A Pulmonary and Allergy Drug Advisory Committee (PADAC) Meeting was held on February 4, 2009, to discuss the efficacy and safety results with a panel of outside experts. In general, the committee acknowledged the limitations of the efficacy and safety data, particularly in children. The PADAC was split on the vote regarding approval of ecallantide (6 Yes, 5 No, 2 Abstain). However, the comments from the PADAC suggested that given the unmet medical need and difficulty in conducting prospective trials in HAE, the Committee felt that there was enough information to support approval in adult HAE patients with the caveat of close monitoring and the Applicant's safe use plan. The Applicant's presentation at the PADAC meeting indicated plans for a mandatory registry for patients with restricted distribution via a central pharmacy, but details of the safe use plan were not submitted for review in the application. The clinical review agrees with the recommendations of the Committee, noting that the safety profile for the proposed dose would be acceptable with appropriate risk evaluation and management strategies. However, since the Applicant did not provide a detailed risk management program in the application, a Complete Response action is recommended by the clinical review.

Regarding the proposed pediatric indication, 25 patients between the ages of 10 to 17 years received some formulation of ecallantide during the development program, but only 15 pediatric patients were treated with the 30 mg SC dose. Furthermore, only 4 pediatric patients (two 16-year-old and two 17-year-old patients) received ecallantide during the double-blind phase of the studies. While there is no evidence from the available data that pediatric patients respond differently to ecallantide, the application lacks sufficient efficacy or safety data to make an assessment in patients under the age of 18 years for the proposed indication. Extrapolation of adult data to children is problematic. Although HAE is an autosomal dominant disease and the symptomatic manifestations of HAE are the same across age groups, the disease typically does not manifest until late childhood or early adolescence. The delay in symptomatic disease suggests that human development may influence the vasoactive mediator cascades responsible for HAE symptoms. Furthermore, at the time of this review, the validity of the pharmacokinetic exposure data in children for ecallantide remains in question. Without validated estimates of drug exposure in children, extrapolation of adult data to children is not possible.

In summary, the Applicant has provided evidence of safety and efficacy for ecallantide for the treatment of acute HAE attacks in adult patients ages 18 years of age and older. However, a safety signal of anaphylaxis was identified and the application lacks an adequate risk management program to balance the significant risk of anaphylaxis. Detailed and appropriate risk management strategies are necessary to balance the significant risk of anaphylaxis and other hypersensitivity reactions. While some data in pediatric patients is available, the data are not sufficient to draw conclusions about safety or efficacy in this population. Therefore, the recommendation of the clinical review is a Complete Response.

1.2 Risk Benefit Assessment

Given the nature of HAE attacks and the absence of other kallikrein-modifying drugs, off-label self-administration for HAE and use in non-HAE indications are anticipated. In the BLA submission, the Applicant included patient self-administration as an option at the discretion of the healthcare provider and the patient but the submission did not include data to support this mode of administration. In light of the anaphylaxis risk, the Division communicated concern about self-administration in the 60-day filing letter. Dyax outlined general risk evaluation and management strategies (REMS) to limit inappropriate and off-label use, including use of a central pharmacy for restricted distribution and a post-marketing pharmacovigilance program to track adverse events of special interest, namely anaphylaxis and other hypersensitivity reactions. Details of the REMS plan were not included. For the purposes of the PADAC discussion, the Applicant presented plans for a mandatory registry of patients, restricted distribution, and a pharmacovigilance program, but detailed plans have not been submitted to the Division at the time of this review.

Anaphylaxis and hypersensitivity reactions are the most serious potential adverse event associated with use of ecallantide. Anaphylaxis reactions are unpredictable and life-threatening events. However, HAE is also unpredictable and life-threatening and there are currently no approved therapies for use in acute attacks. Medical care facilities equipped to treat manifestations of acute HAE attacks such as laryngeal edema are an appropriate setting for administering ecallantide and monitoring for anaphylaxis. In addition, HAE patients, given the nature of their disease and the rarity of the condition, tend to be a relatively sophisticated patient population that would be receptive to patient education about anaphylaxis and drug hypersensitivity. Therefore, the clinical review concludes that the risks of ecallantide would be balanced by the potential efficacy benefit of ecallantide and the unmet medical need for this serious, potentially life-threatening condition when used in a controlled setting with healthcare provider supervision. However, the application did not include a detailed risk management program for review. Therefore, the risk: benefit ratio is unbalanced pending the submission and agreement on an appropriate risk management program.

1.3 Recommendations for Postmarketing Risk Management Activities

No formal recommendations for post-marketing risk management activities are made at this time due the recommendation for a Complete Response.

Reviewer's comment: While the following are not formal recommendations, the clinical review believes that future risk management proposals to promote use of ecallantide under appropriate medical supervision should include these elements:

- *Boxed warning on package insert highlighting risk of anaphylaxis and warning against self-administration.*
- *Medication Guide regarding the risk of hypersensitivity reactions, appropriate management of anaphylaxis, and the unknown risk of long-term anti-drug antibody seroconversion.*
- *Registration of healthcare providers and patients.*
- *Anaphylaxis and hypersensitivity pharmacovigilance registry to track hypersensitivity adverse events, antibody status, and any rechallenge/desensitization procedures that are performed.*
- *Patient and healthcare provider education materials regarding the risk of hypersensitivity reactions and appropriate management of anaphylaxis.*

1.4 Recommendations for other Post Marketing Study Commitments

No formal recommendations for other post-marketing study commitments are made at this time due the recommendation for a Complete Response.

Reviewer's comment: Although a Complete Response is recommended at this time, the clinical review recommends the following for further study in the ecallantide development program:

- *Anaphylaxis and hypersensitivity*
The clinical review recommends formal study of anaphylaxis and hypersensitivity events with the goal of identifying predictive risk factors and developing effective screening tools to mitigate the risk of reaction. The study should include clinical monitoring of events, serial antibody testing, and refinement of rechallenge procedures, (b) (4) Given the significant risk of anaphylaxis and the highly immunogenic nature of ecallantide observed to date, the clinical review does not foresee self-administration as a viable mode of drug administration. Therefore, a formal study of the safety and efficacy patient self-administration is not recommended at this time.
- *Immunogenicity*
Based on the data presented in the BLA submission, ecallantide appears to be highly immunogenic. The long-term consequences of seroconversion are not known. The clinical review recommends the following for further evaluation of ecallantide's immunogenicity:
 - *Long-term serial antibody testing of patients who receive ecallantide to determine if antibody levels correlate with adverse events or decreases in efficacy.*
 - *Refinement of in vitro assays for all classes of antibody directed against ecallantide and *Pichia pastoris*.*
 - *Evaluation of the cross-reactivity potential between ecallantide and human TFPI. In knock-out mouse models, TFPI deficiency is an embryonic lethal due to hypercoagulability. Based on this literature, TFPI cross-reactivity may theoretically predispose to thrombotic events in humans.*

- **Pediatric use**
As ecallantide qualifies as an Orphan Drug Product, it is exempt from PREA and pediatric studies are not required. However, as the Applicant originally sought a pediatric indication down to the age of 10 years and there is much clinical interest in making this product available to the pediatric population, the clinical review recommends a pediatric registry conducted under the auspice of a compassionate use program. In this way, pediatric HAE patients may continue to have access to ecallantide while permitting the collection of additional efficacy and safety information in this patient population for inclusion in a future efficacy and safety supplement.
- **Use in pregnancy**
The Applicant has proposed monitoring of pregnancy outcomes. Given that HAE is a lifelong condition, a pregnancy registry to track maternal and fetal outcomes is recommended by the clinical review.
- **Carcinogenicity**
As ecallantide use is expected to be used on a chronic, intermittent basis, the clinical review recommends a preclinical carcinogenicity study in rats.

2 Introduction and Regulatory Background

2.1 Product Information

The established name of the subject product of this application is ecallantide and the proposed tradename is Kalbitor™. The established name will be used in this review to refer to the product. Ecallantide is supplied as a colorless, sterile, preservative-free isotonic solution with an ecallantide concentration of 10 mg/ml in a 2 ml glass vial. Each vial contains 10 mg ecallantide, 8.0 mg sodium chloride, 0.76 mg disodium hydrogen orthophosphate (dihydrate), 0.2 mg monopotassium phosphate, and 0.2 mg potassium chloride in water for injection, USP. The active ingredient, ecallantide, is a new molecular entity and a novel recombinant inhibitor of human plasma kallikrein. It is a 60-amino-acid protein produced in *Pichia pastoris* yeast cells by recombinant DNA technology. Ecallantide was identified through iterative selection and screening of phage display libraries of the first Kunitz domain of human tissue factor pathway inhibitor (TFPI) and shares 88% homology with endogenous TFPI.

The proposed indication for ecallantide is the treatment of acute attacks of HAE in patients 10 years of age and older. The proposed dosing regimen is 30 mg SC, administered as 3 separate injections. In cases of insufficient relief or recurrence of symptoms, an additional 30 mg dose may be administered within a 24-hour period.

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently, there are no drug products approved for the treatment of acute attacks of HAE in the US. The standard of care for acute attacks remains supportive therapies, e.g. opiates for pain management, anti-emetics for nausea, and intubation for airway obstruction. Since angioedema

is common the both HAE and anaphylaxis, epinephrine is sometimes used in the treatment of acute HAE attacks but its efficacy for this indication is limited.

Several drug products are available for prophylaxis, although their effectiveness in preventing acute attacks is limited or not established. Danazol (NDA 74-582) is approved for the prevention of attacks of hereditary angioedema of all types (cutaneous, abdominal, and laryngeal). Oxymetholone (NDA 22-965) and stanozolol (NDA 12-885) had similar indications but are no longer marketed in the US. Another androgen, oxandrolone, is used off-label in the US as an alternative to danazol. The androgens are associated with several adverse effects that limit their use. For example, they are associated with hepatotoxicity and hepatocellular adenomas. Their masculinizing effects further limit their use in children and women. Although not approved in the US for an HAE indication, antifibrinolytic agents are also used for prophylaxis. These drugs are associated with muscle cramps, increased creatinine kinase levels, and an increased risk of thrombosis. Fresh frozen plasma is used as short-term prophylaxis, but the literature suggests that its use in an acute attack may actually exacerbate attacks. Most recently, plasma-purified C1 inhibitor (Cinryze™) administered intravenously was approved for routine prophylaxis of HAE attacks in adults and adolescents, but its efficacy in acute attacks has not been established.

2.3 Availability of Proposed Active Ingredient in the United States

Ecallantide is currently not marketed in the US.

2.4 Important Safety Issues With Consideration to Related Drugs

No other members of the pharmacologic class are currently marketed.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

BBIND 10426 was originally opened in April 2002 in CBER prior to transfer to CDER (DPAP) in October 2005. The following is a timeline of pertinent regulatory proceedings:

- April 30, 2002 – BBIND 10426 (CBER) opened.
- February 4, 2003 – Orphan Drug designation granted.
- June 26, 2003 – initial application for Fast Track designation submitted and denied by CBER on the grounds that the application did not focus on severe, life-threatening aspects of HAE attacks nor addressed unmet medical needs.
- October 2005 – BBIND 10426 transferred to CDER (DPAP).
- April 5, 2006 – Meeting with sponsor. Following deficiencies in the clinical development program were identified:
 - Inadequate support for 30 mg SQ dose selection; lower doses may be efficacious. Advised to conduct additional dose-ranging studies with SQ doses of 10, 40, and 80 mg doses with clinically meaningful endpoints.
 - Need for validation of PRO instrument used in primary efficacy endpoint for Phase 3 study

- Long-term safety data needed
- Inconsistency between indication claims and Fast Track designation objectives
- August 29, 2006 – End-of-Phase-2 meeting with sponsor. The following issues were addressed:
 - Agreement that Treatment Outcome Score (TOS) and the Mean Symptom Complex Score (MSCS) are appropriate efficacy endpoints for use in pivotal studies if validated. The Division advised the sponsor to submit a cognitive debriefing protocol for review.
 - The Division advised the sponsor to add a placebo arm to confirmatory study for comparison to 30 mg dose. Planned 5 mg dose unnecessary.
 - The Division advised that the unit of observation should be at patient level, not number of individual attacks, which may introduce bias into the efficacy analysis.
 - The Division advised a long-term, open-label safety study with a sample size larger than the proposed 30 patients and with a defined study duration. Antibody testing should be performed throughout treatment.
 - Sponsor plans to submit new application for Fast Track designation based on endpoints from the pivotal protocols.
 - Sponsor proposed a BLA submission containing a total of 11 clinical studies with 3 main clinical trials:
 - **EDEMA1** – a single ascending dose, DB, PC trial in 49 HAE patients in the US and Belgium. The sponsor concluded that the treatment was well tolerated, and patients receiving DX-88 achieved significant improvement compared to the placebo group by 4h post-dose (72 vs. 25%; p=0.0169).
 - **EDEMA3** – an ongoing, R, DB, PC trial in the US, Europe, and Canada to assess safety and efficacy of 30mg SC DX-88. Patients are treated for a single acute attack in the double-blind portion of the study and are invited to enter the open-label portion of study to assess the effect of repeat 30 mg doses for subsequent attacks (maximum 20 attacks). Efficacy in the study is measured by TOS; secondary endpoints included a change in MSCS and time to onset of improvement.
 - **EDEMA4** – proposed, R, DB, PC trial to assess safety and efficacy of 30mg SC DX-88 versus placebo in treatment of moderate-to-severe acute HAE attacks.
- September 26, 2006 – cognitive debriefing protocol and SAP for TOS/MSCS validation in EDEMA3 submitted for review. PRO consult obtained and comments communicated to the Sponsor.
- October 6, 2006 – protocol submitted for long-term, open-label extension study
- October 13, 2006 – request for Special Protocol Assessment for EDEMA4. Comments were communicated to the Sponsor, including a discussion of the proposed efficacy endpoints. The Division recommended that the Mean Symptom Complex Score (MSCS) be designated as the primary efficacy variable and the Treatment Outcome Score (TOS) be a secondary efficacy variable, in contrast to the EDEMA3 study design, due to difficulties with the interpretation of a compound score like the TOS. Other issues were the management of severe upper airway compromise in the study and the need for validation of the PRO instruments. The Sponsor agreed to the Division's

recommendations but did not re-submit a revised protocol with a request for SPA to reach a formal agreement. The Sponsor subsequently submitted a revised protocol March 22, 2007, containing changes consistent with discussions with the Division. These were later reviewed and later deemed to constitute an SPA agreement on EDEMA4.

- June 13, 2007 – EDEMA3 study results and proposed BLA submission without EDEMA4. The Division informed the Sponsor that determinations regarding filing would be made at the time of BLA submission. However, the Division informed the Sponsor that preliminary review of the EDEMA3 results indicated that EDEMA3 would not be sufficient support for drug approval, and that all data to support the efficacy and safety of ecallantide should be included in the original BLA submission.
 - EDEMA3 efficacy results were encouraging but not statistically robust. Two patients accidentally did not receive the randomized study drug, i.e. a placebo patient received ecallantide and an ecallantide patient received placebo. The primary efficacy endpoint, Treatment Outcome Score, did not meet statistical significance ($p=0.1$) when based on the ITT population. Using a modified ITT (patients as treated), the p-value improved to 0.037.
- November 17, 2006 – Fast Track designation granted
- August 23, 2007 – Proposed change to EDEMA4 protocol analysis (imputation for missing values). The Division informed the Sponsor that analysis should be performed without imputation. Proposed imputations could be included as additional sensitivity analyses.
- August 24, 2007 – Proposed assessment of QT prolongation request. Given the largely negative results from the preclinical studies, the lack of effect observed in the clinical studies, and the expected manner of use and indication for the proposed drug product, a thorough QT study for ecallantide did not appear warranted. More intensive ECG monitoring in the Phase 3 program beyond the proposed ECG monitoring for EDEMA4 was unlikely to provide much additional information given the small numbers of patients enrolled, the intermittent dosing, and in consideration of the life-threatening potential of HAE attacks. See Medical Officer review dated September 26, 2007 for further discussion.
- October 30, 2007 – Meeting to discuss BLA submission format, including presentation of safety data.
- January 15, 2008 – Rolling review granted.

2.6 Other Relevant Background Information

EcCallantide has not yet been approved for marketing for any indication.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The BLA is an electronic submission and is adequately organized to permit clinical review. In addition to information provided in the original submission, information requests for follow-up safety data for DX-88/19 (the EDEMA4 open-label extension study) and longitudinal patient profiles were communicated to the Applicant during the review cycle. Longitudinal patient profiles were submitted on December 16, 2008. A safety update of the ongoing EDEMA4 OLE (DX-88/19) and the completed cardiac surgery study (DX-88/16) were submitted on December 19, 2008; an additional submission with updated adverse event tables and immunogenicity information was submitted on February 12, 2009.

In addition, DPAP requested that the Applicant address the issue of patient self-administration in the 60-day filing letter dated November 21, 2008. The Applicant provided a proposal for addressing self-administration in the December 19, 2008, submission, but on December 24, 2008, submitted a new proposal for restricting ecallantide use to administration by a healthcare professional pending further formal study of the risks and benefits of self-administration.

3.2 Compliance with Good Clinical Practices

The Applicant states that no debarred investigators participated in the study, and all studies were conducted under Good Clinical Practices.

The Division requested an audit by the Division of Scientific Investigations (DSI) for this NDA since ecallantide is a new molecular entity proposed for a novel indication and the data for efficacy and safety is based on small sample sizes due to the rarity of HAE. A single investigator, Dr. Robyn Levy, MD (Atlanta, GA), was responsible for a relatively large number of patients enrolled in both pivotal studies (n=8 in EDEMA8 and n=15 in EDEMA4), so her site was recommended for audit in addition to a sponsor inspection. The Clinical Inspection Summary dated February 6, 2009, reported that the respective inspections support the validity of the submitted data and confirm adherence to Good Clinical Practices.

3.3 Financial Disclosures

The Applicant certifies that no financial arrangements were made with the clinical investigators requiring disclosure.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC/Office of Therapeutic Proteins (OTP) reviewers' recommended action on this application at the time of this review is pending. A site inspection was conducted in January 2009. The CMC reviewers have not identified any approvability issues. The CMC review has noted that glycosylation, oxidation, and N-terminal truncation can occur and lead to formation of ecallantide-related variants. The product-related variants have been characterized and are biologically active.

In addition, the CMC reviewers have stated that both the assays for neutralizing antibodies and IgE antibodies lack sensitivity, which may lead to an underestimation of patients who have seroconverted upon exposure to ecallantide. The assays for non-IgE antibody to ecallantide appear adequate. The CMC reviewers have also noted that the Applicant has not made an assessment of potential cross-reactivity with endogenous tissue factor pathway inhibitor (TFPI). Ecallantide shares 88% homology with TFPI. In knock-out mouse models, TFPI deficiency is an embryonic lethal due to hypercoagulability. Based on this literature, TFPI cross-reactivity may theoretically predispose to thrombotic events in humans.

Reviewer's comment: In a submission dated January 29, 2009, the Applicant informed the Division that in vitro assays to assess cross-reactivity between antibodies against ecallantide and TFPI will be performed. Details can be found in the CMC/OTP team's review.

4.2 Clinical Microbiology

The Clinical Microbiology/Office of Compliance reviewers' recommended action on this application at the time of this review is pending. The review team has stated that clinical microbiology standards generally appear adequate but there is one potential approvability issue.

(b) (4)

(b) (4) At the time of this review, an update on this issue is pending.

4.3 Preclinical Pharmacology/Toxicology

Dyax submitted a complete pharmacology/toxicology package for this BLA. The Preclinical Pharmacology/Toxicology review of this application and final recommendations are pending at the time of this review. The program included 6 month, repeat dose, subcutaneous toxicology studies in rats and monkeys and other short term toxicology studies. Reproductive toxicology assessment included a rat fertility study and teratology studies in rats and rabbits. The most prominent toxicity observed in both species was severe injection site reactions. Similar reactions have not been observed in clinical studies to date; only mild, self-limited injection site reactions have been reported in humans. In rats, transaminitis was also noted. In the rat study, deaths were

noted in female rats in the high dose groups, but the causes of death were not determined although histological changes in the heart of a couple of animals suggested a possible cardiac etiology. No deaths occurred in male rats or in any of the monkeys. Ecallantide also caused a dose-dependent, reversible prolongation of aPTT, presumably due to inhibition of the kallikrein-mediated activation of Factor XII to XIIa in the intrinsic coagulation cascade. The aPTT elevations were not associated with any bleeding.

In terms of immunogenicity, ecallantide antibodies were noted in both rats and monkeys. Clearance of ecallantide was reduced and systemic exposure was increased following the development of ecallantide antibodies. No increase in toxicity was noted with the higher exposure.

A carcinogenicity study was not submitted with this BLA; however, this is acceptable given the proposed indication and patient population. The animal data indicates that a carcinogenicity study in 1 species would be feasible. If the BLA is approved, a carcinogenicity study may be performed post-marketing.

4.4 Clinical Pharmacology

The Applicant submitted a complete clinical pharmacology package for this BLA. The clinical pharmacology and final recommendations are pending at the time of this review, but a brief summary of the submitted information is included below.

4.4.1 Mechanism of Action

Ecallantide binds plasma kallikrein with high affinity and high specificity, blocking the action of plasma kallikrein. Ordinarily, kallikrein activity is regulated by C1-esterase inhibitor (C1 INH). In HAE patients with low or absent levels of functional C1-INH, kallikrein activity goes unchecked and is thought to lead to widespread release of bradykinin. In turn, bradykinin increases vascular permeability which leads to the swelling characteristic of acute HAE attacks.

4.4.2 Pharmacodynamics

Pharmacodynamic and pharmacokinetic data are reviewed in greater detail in the Clinical Pharmacology reviewer's assessment. Limited dose-ranging was performed in the clinical program. Briefly, a dose response based on patient-reported symptomatology was demonstrated in EDEMA2 between 5 mg/m² to 20 mg/m² IV, however, the efficacy measures used in this study were not validated. The 30 mg SC dose corresponds approximately to a 15 mg/m² IV dose. Exposure was dose-proportional in this dose range. No exposure-response relationships for ecallantide to components of the complement pathway or kallikrein-kinin pathway have been established. In vitro, ecallantide causes a dose-dependent, reversible prolongation of activated partial thromboplastin time (aPTT). The transient prolongation in aPTT is due to inhibition of the kallikrein-mediated activation of Factor XII to XIIa in the intrinsic coagulation cascade.

Reviewer's comment: A rigorous comparison of different dose levels for efficacy was not performed and only EDEMA2 included the 30 mg SC dose used for the phase 3 program. The primary efficacy endpoints used in EDEMA2 were the following: 1) proportion of successful

outcomes (i.e. attack resolution begun by 4 hours after a single dose and maintained for greater than 24 hours after a single dose) and 2) the proportion of patients who have a partial response (i.e. an initial response to dosing followed by a relapse 4 to 24 hours after the dosing). These endpoints were gross patient-reported measures and were not validated endpoints.

4.4.3 Pharmacokinetics

Following administration of a single 30 mg ecallantide dose in healthy subjects, a mean maximum plasma concentration of 586 ± 106 ng/ml was observed 2 to 3 hours after dosing. Plasma levels declined rapidly with a mean elimination half-life of 2.0 ± 0.5 hours. Plasma clearance was 153 ± 20 ml/min and the V_d was 26.4 ± 7.8 L. The maximum ecallantide concentration expected in HAE patients receiving the 30 mg SC dose is 0.6 mcg/ml or 85 nM. Ecallantide is a small protein (7054 Da) and it is presumed that it undergoes renal elimination. According to the application, population PK analysis demonstrated that no dose adjustment is needed for age, gender, or race, assuming normal renal and hepatic function. Studies in renal and hepatic impairment have not been conducted. The plasma concentrations at 1, 2, and 4 hours post dosing for ecallantide administered intravenously (5, 10, and 20 mg/m²) and subcutaneously (30 mg) is shown in the table below.

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Table 1 EDEMA2: Plasma ecallantide concentrations (ng/ml) at 1, 2, and 4 hours post-dose by dosage level (FP population)			
Dosage level	1 hour	2 hours	4 hours
5 mg/m² IV			
<i>N</i>	23	23	24
<i>Mean (SD)</i>	192.5 (109.6)	135.1 (234.0)	23.0 (22.4)
<i>Median</i>	191.4	84.3	19.1
<i>Range</i>	30.0-402.1	12.1-1165.7	0-66.9
10 mg/m² IV			
<i>N</i>	138	138	139
<i>Mean (SD)</i>	602.8 (778.1)	265.2 (217.8)	86.1 (65.8)
<i>Median</i>	415.4	222.0	71.2
<i>Range</i>	0-5438.2	0-1768.5	0-447.8
20 mg/m² IV			
<i>N</i>	11	14	14
<i>Mean (SD)</i>	1235.1 (1205.6)	276.2 (121.3)	170.4 (186.1)
<i>Median</i>	729.0	265.7	104.4
<i>Range</i>	594.7-4613.3	104.3-609.3	24.2-672.8
30 mg SC			
<i>N</i>	70	68	70
<i>Mean (SD)</i>	509.7 (281.2)	627.5 (326.7)	473.8 (208.5)
<i>Median</i>	488.2	586.7	477.0
<i>Range</i>	66.1-1323.9	78.5-1623.6	0-1016.5

Source: dx-88-5-csr-body.pdf, Section 11.4.2, Table 26

Reviewer's comment: EDEMA2 is the primary source of PK data for HAE patients, including children. Only 3 patients over the age of 65 years were enrolled, so estimates on geriatric exposure cannot be made. In addition, the validity of the raw PK data has not been confirmed as of the time of this review. Samples from EDEMA2 were sent to 3 different contract research organizations for analysis: (b) (4). Of these 3, only data from (b) (4) has been validated. As population PK analysis relies on the EDEMA2 PK values, the current estimates on pediatric exposure and even adult exposure may not be valid. An update from the Applicant on this issue is pending at the time of this review.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

The Applicant conducted 11 clinical studies with ecallantide in the HAE program, two of which are ongoing. These studies include 4 trials in healthy volunteers and 7 studies in HAE. The Applicant also conducted a rechallenge study in patients with hypersensitivity reactions to ecallantide and a study in cardiothoracic surgery (CTS). At the time of BLA submission, two studies remained ongoing: 1 open-label HAE study (DX-88/19, EDEMA4 OLE) and the CTS study. To support the efficacy and safety of ecallantide for the proposed indication, the Applicant relied primarily on the completed HAE studies. Safety data from rechallenges, compassionate use, and SAEs from the two ongoing studies (as of July 31, 2008) were also provided. Comprehensive efficacy and safety data from the EDEMA4 OLE were not provided

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in the submission; only limited report of hypersensitivity reactions and a safety update through November 10, 2008 (BLA amendment dated December 18, 2008) were provided. Safety update information is integrated into the body of the safety review. As of November 10, 2008, 243 HAE patients have received 846 ecallantide doses.

Table 2 Ecallantide clinical development program for HAE

Study	Patients	Patients treated*	#Doses	Design	Duration/ Dosing Interval	Dose	Endpoints
Phase 1							
DX-88/1	Healthy	12	12	DB, SD	SD	10 mg IV 20 40 80 placebo	tolerability
DX-88/6	Healthy	8	29	OL, MD	4 weeks (weekly dose)	20 mg/m ² IV	Safety and PK
DX-88/13	Healthy	18	51	OL, MD, X- over	(weekly dose)	30 mg IV 10mg SC 30 mg SC	Safety, PK
DX-88/15	Healthy	24	47	DB, R, X-over	SD	30 mg liquid SC 30 mg lyophil SC Placebo	PK
Phase 2							
DX-88/2 EDEMA0	HAE/ AAE (≥18yo)	9	9	OL, SD	SD	10 mg IV 40 80	<ul style="list-style-type: none"> • Proportion with resolution of attack by 4h post-dose • Safety
DX-88/4 EDEMA1	HAE (≥10yo)	41	41	DB, SD	SD	5 mg/m ² IV 10 20 40 Placebo	<ul style="list-style-type: none"> • Proportion with significant improvement by 4hr • Safety
DX-88/5 EDEMA2	HAE	77	273	OL, MD	≥7 days between attacks	5 mg/m ² IV 10 20 30 mg SC	<ul style="list-style-type: none"> • Safety • Proportion of successful outcomes
Phase 3							
DX-88/14 EDEMA3- DB	HAE	37	39	DB, R, PC, with OLE	SD	30 mg SC Placebo	<ul style="list-style-type: none"> • Treatment outcome score (TOS) • Safety
EDEMA3- RD (open- label extension)	HAE	67	161	OL, repeat- dose	≥72h between attacks	30 mg SC	<ul style="list-style-type: none"> • TOS at 4h • Safety
DX-88/20 EDEMA4	HAE	70	86	DB, R, PC with OLE	SD, extra OL dose for airway compromise or incomplete response/ relapse	30 mg SC Placebo	<ul style="list-style-type: none"> • Change in Mean Symptom Complex Score (MSCS) at 4h • Safety
DX-88/19 (OLE) (ongoing)	HAE	75 as of Nov08	237 as of Nov08	OL, RD	≥72h between attacks	30 mg SC	<ul style="list-style-type: none"> • Change in Mean Symptom Complex Score (MSCS) at 4h • Safety

*Patients randomized to receive ecallantide. Patients could enroll in sequential studies.

5.2 Review Strategy

The two Phase 3 studies (EDEMA3 and EDEMA4), the open-label dose-ranging repeat dose study (EDEMA2), and the two other Phase 2 studies (EDEMA0 and EDEMA1) in Table 1 were reviewed, with the greatest emphasis placed on the pivotal Phase 3 efficacy and safety studies. Efficacy and safety data from the EDEMA3 OLE and partial safety data from the EDEMA4 OLE were also included in the review. EDEMA3 and EDEMA4 are presented and discussed in Section 5.3 below; more detailed review of these two studies and the other studies are located in the Individual Study Reviews found in Section 10. EDEMA2 was reviewed to assess the extent of dose-ranging performed in the clinical development program and for additional safety and information on repeat doses, given the small number of patients exposed in the overall clinical development program. Additional studies not shown in Table 2 that were also reviewed include PRO validation studies intended to support the primary and secondary efficacy variables used in the Phase 3 studies and a rechallenge study in patients with hypersensitivity reactions to ecallantide. Data from the Phase 1 program, compassionate use, and Study DX-88/16 (cardiothoracic surgery study) were also evaluated for additional safety information.

Reviews of the studies are based primarily on the Dyax study reports, original protocols, and statistical analysis plans. The Applicant's summary data tables were reviewed in detail. Appendix tables were also reviewed in varying amounts of detail, depending upon the endpoint and review issue. Case report forms (CRFs) were also reviewed.

The Applicant provided bibliographies within the study reports and expert opinion reports in the application. These references in addition to the results of a literature search conducted by the reviewer were reviewed to the extent of their relevance to the review.

5.3 Discussion of Individual Studies

This section presents an overview of efficacy data from the two pivotal studies; more detailed discussion of these studies and the other clinical studies can be found in Section 6 and in the Individual Study Summaries located in Section 10. A detailed discussion of safety data is presented separately in Section 7.

The clinical development program included two randomized, placebo-controlled Phase 3 studies, EDEMA3 and EDEMA4. The design and conduct of the studies were similar. Each study consisted of a double-blind phase and an optional, open-label phase. During the double-blind phase, patients presenting within 8 hours of onset of symptoms of a moderate to severe, acute HAE attack were randomized to receive a single 30 mg dose of ecallantide or placebo. In EDEMA3, patients were eligible to receive an additional unblinded 30 mg ecallantide dose (Dose B) for severe upper airway compromise (SUAC); in EDEMA4, patients were eligible for Dose B for SUAC *or* recurrent, persistent symptoms. During the OLE phase of both studies, patients presented with new acute HAE attacks and received ecallantide 30 mg SC. In the EDEMA3 OLE, the initial dose could be followed by a second, blinded dose (Dose B; randomized 1:1 ecallantide:placebo) for persistent or worsening symptoms. In EDEMA4, Dose B was open-label ecallantide.

Although EDEMA3 and EDEMA4 were similar in design, two major differences between the studies make an individual presentation of each study useful: 1) different primary efficacy endpoints and 2) differing pre-specified statistical analyses with imputation for missing data (EDEMA3) in contrast to no imputation (EDEMA4). EDEMA3 used the TOS at 4 hours as the primary efficacy endpoint; change in MSCS from baseline at 4 hours was a secondary endpoint. During the SPA discussion of EDEMA4, the Division raised concerns about the transparency of the TOS and recommended switching the two endpoints. As a result, EDEMA4 was conducted under SPA using the MSCS as the pre-specified primary efficacy variable and the TOS as a key secondary efficacy variable. A more detailed description of these endpoints and the validation studies conducted to support these PRO instruments is included below and in Section 6 of this review. In terms of data imputation, EDEMA3 employed imputations for emerging symptom complexes and medical interventions. In both studies, sensitivity analyses were performed using imputations for emerging symptoms and medical interventions to test the robustness of the study conclusions.

The clinical program did not include a placebo-controlled evaluation of repeat exposures. The OLE efficacy results from EDEMA3 and EDEMA4 are described in this section, as clinical data to support chronic, repeat use of ecallantide is derived primarily from the OLE phase of EDEMA3. Additional support is provided by open-label data obtained from the Phase 2 study, EDEMA2. The inclusion/exclusion criteria and efficacy assessments performed in EDEMA2 were not as rigorous as those performed in the Phase 3 program, so the EDEMA2 results are considered as secondary support. The design and results of EDEMA2 are presented here and in further detail in the Individual Study Summaries located in Section 10. OLE efficacy and safety data from EDEMA4 were not included in the original submission and were not submitted in time for inclusion in this briefing document.

5.3.1 EDEMA3

Study design and conduct

EDEMA3 was a 2-part Phase 3 study conducted in the US, Canada, and Europe. The first phase was a randomized, double-blind, placebo-controlled, single-dose phase (97 days duration for DB phase) followed by an open-label extension phase where patients could receive treatment for additional acute HAE attacks. Patients with symptoms of a moderate to severe HAE attack presenting within 8 hours of symptom onset were eligible for treatment with a single dose of 30 mg ecallantide SC. The main efficacy variables are briefly described below; further detail about these variables and the supporting validation data is found in Section 6.1.5.

- *Treatment Outcome Score (TOS)*

The primary efficacy endpoint was the Treatment Outcome Score (TOS) at 4 hours. The TOS is a composite, weighted symptom complex score intended to assess global symptom response to treatment. The following symptom complexes were assessed: 1) internal head/neck, 2) stomach/GI, 3) genital/buttocks, 4) external head/neck, and 5) cutaneous. Each individual symptom complex score is based on a severity rating for that particular group of symptoms

multiplied by a “response-to-treatment” factor, so that the outcome is incorporated into the final TOS value.

$$\text{TOS} = \frac{\sum(\text{Baseline severity assessment} \times \text{Response to treatment})}{\sum \text{Baseline severity assessment}}$$

In this equation, “baseline severity” is scored on a scale of 0 to 3, with 3 being the most severe (see definitions of severity ratings in Table 3). “Response to treatment” is scored as -100, -50, 0, 50, or 100, with -100 representing significant worsening and a score of 100 representing significant improvement. A response score of 0 corresponds to no change. The maximum and minimum possible TOS values are +100 and -100, respectively, with a higher value corresponding to greater improvement. A TOS of 0 signifies no change.

Reviewer’s comment: The primary efficacy variable, TOS, is a complicated score that is difficult to interpret, due in part to the response and severity multipliers used. Overall, a higher number corresponds to a better response to study drug, although the magnitude of response for a given TOS value is not intuitively clear. The response multiplier may exaggerate small differences, which may or may not be clinically meaningful, or potentially obscure important changes. Since the TOS is a composite score, individual symptom complexes can potentially cancel one another out. For example, if a patient experiences significant improvement of cutaneous symptoms but significant worsening of laryngeal symptoms, the respective changes will cancel one another out so that the final TOS is 0 = no change.

- **Mean Symptom Complex Score (MSCS)**

The secondary efficacy endpoint was the change from baseline Mean Symptom Complex Score (MSCS) at 4 hours. The MSCS is an arithmetic mean of individual symptom complexes. Unlike the TOS, there is no inherent time/outcome element in the MSCS; hence, response to treatment is assessed as “the change from baseline MSCS.” The maximum possible calculated MSCS value is 3.0 and the minimum possible value is 0; accordingly, the greatest possible change from baseline is ±3.0. The table below shows the scoring for severity assessment used in the MSCS calculation.

Severity Assessment	Score	Definition
Severe	3	treatment or intervention required due to inability to perform activities of daily living (e.g. throat swollen/difficulty breathing, lips swollen/cannot eat, feet swollen/cannot walk)
Moderate	2	treatment or intervention highly desirable and symptoms impact activities of daily living (e.g. hands swollen/cannot button shirt, feet swollen/discomfort wearing shoes)
Mild	1	noticeable symptoms but do not impact activities of daily living
Normal	0	patient’s state absent of an acute HAE attack

Study results

A total of 36 patients received one 30 mg dose of ecallantide. Two of these 36 received a second 30 mg dose for SUAC. One placebo patient also received an open-label 30 mg dose for SUAC. The disposition of the patients and the demographic information are summarized in Table 4 and Table 5.

	Ecallantide N=36 N(%)	Placebo N=36 N(%)	Total N=72 N(%)
Intent to treat population ^a	36 (100)	36 (100)	72 (100)
Per protocol population ^b	35 (97)	36 (100)	71 (99)
Safety population ^c	36 (100)	36 (100)	72 (100)
Patients completing double-blind phase	35 (97)	36 (100)	71 (99)
Patients rolling over to continuation study ^d	21 (58))	27 (75)	48 (67)
Patients withdrawing from study	1 (3)	0	1 (1)
Adverse event	0	0	0
Noncompliance or protocol violation	0	0	0
Withdrawal of consent	0	0	0
Lost to follow-up	1 (3)	0	1 (1)
Investigator discretion	0	0	0
Left study site against medical advice	0	0	0

^a Patients who received any amount of study drug and completed the 4-hour follow-up

^b Patients who received a complete dose of study drug with no major protocol violations and completed the 4-hour follow-up

^c Patients who received any amount of study drug

^d All patients were eligible to enroll in the open-label extension study.

Source: dx-88-14b-csr-body.pdf, Section 10.1, Table 3

	Ecallantide N=36	Placebo N=36	Total N=72
Age			
Mean (SD)	39 (15)	32 (14)	35 (15)
Range	18-77	11-57	11-77
Sex (N,%)			
Male	12 (33)	13 (36)	25 (35)
Female	24 (67)	23 (64)	47 (65)
Race (N,%)			
White	33 (92)	32 (89)	65 (90)
Black	1 (3)	4 (11)	5 (7)
Hispanic	2 (6)	0	2 (3)
Prior use of ecallantide	8 (22)	11 (31)	19 (26)

Source: dx-88-14db-csr-body.pdf, Section 11.2.1, Table 4

Details regarding the patients' HAE history and concomitant medications can be found in the individual study review located in Section 10. In EDEMA3, the most commonly reported symptom complexes of at least moderate to severe severity in the ecallantide group were evenly divided between cutaneous (n=21, 58%) and stomach/GI (n=20, 56%) locations. In the placebo group, 14 (39%) patients reported cutaneous symptoms and 21 (58%) reported stomach/GI symptoms. Laryngeal attacks were reported in 9 (25%) ecallantide patients and 4 (11%) placebo patients. Results of the main efficacy analyses for both EDEMA3 and EDEMA4 (discussed in the next section) are presented below.

Table 6 Primary efficacy results from EDEMA3 and EDEMA4						
	EDEMA3			EDEMA4		
	Ecallantide N=36	Placebo N=36	Treatment difference (p value)	Ecallantide N=48	Placebo N=48	Treatment difference (p value)
TOS at 4 hrs (mean) ITT as randomized	47	21	26 (0.10)	53	8	45 (<0.001)
TOS at 4 hrs (mean) ITT as treated	50	19	31 (0.04)			
MSCS Mean Δ from baseline 4h ITT as randomized [baseline]	-0.9 [2.2]	-0.5 [2.3]	-0.4 (0.09)	-0.8 [2.2]	-0.4 [2.0]	-0.4 (0.01)
MSCS Mean Δ from baseline 4h ITT as treated* [baseline]	-0.9 [2.2]	-0.5 [2.2]	-0.4 (0.04)			

* Population based on treatments as received

Reviewer's comment: Two patients mistakenly received the wrong study drug in EDEMA3: 1 placebo patient received ecallantide and 1 ecallantide patient received placebo. When the efficacy endpoints are recalculated using a dataset corrected for these protocol violations, the differences between the ecallantide and placebo arms are statistically significant. These results suggest that ecallantide has some efficacy, although the results do not appear to be robust and the limitations of a small sample size are apparent.

A formal subgroup analysis for EDEMA3 was not provided by the Applicant; post hoc analyses performed by the Division's statistical reviewer did not show any clear differences in efficacy based on anatomical attack site, gender, or history of prior exposure to ecallantide. Subgroup analysis by age or race is limited by the small sample size.

Other secondary efficacy endpoints assessed were numerically supportive if not statistically significant when based on the ITT population. **Time to significant improvement** was based on patients' global response assessments, which was independent of the TOS and MSCS calculations. The median time to significant improvement was 165.0 minutes for ecallantide. The estimated median for placebo was not reached by 240 minutes, but the difference was not statistically significant (p=0.14). The results were not altered using the as-treated dataset, but were statistically significant in favor of ecallantide when based on the per protocol dataset (p=0.05). This efficacy variable gives some assurance that the TOS and MSCS did not obscure important clinical changes, e.g. laryngeal worsening cancelled out by cutaneous improvement. A **responder analysis** was also performed. Using a cutoff value of 70 for TOS at 4 hours, 15 patients (42%) in the ecallantide group qualified as having a successful response assessment in comparison to 12 (33%) patients in the placebo group (p=0.47). No statistically significant differences were observed when adjusted for attack location or prior use of ecallantide. TOS values at the 24-hour timepoint were collected to assess the **durability of response**. The median TOS at 24 hours was 75 for the ecallantide group compared to 0 in the placebo group (p=0.04). **Rescue medication use** patterns also favored the ecallantide arm over placebo; 5 (14%) in the ecallantide arm required medical intervention in comparison to 13 (36%) in the placebo arm. The most commonly administered interventions were emergency medications such as opioids for

pain control and anti-emetics. No patients required intubation or urgent surgical decompression. In both treatment groups, fewer patients with peripheral attacks required intervention than patients with a laryngeal attack (p=0.01).

Reviewer's comment: The secondary efficacy endpoints are generally supportive of ecallantide's effectiveness for the proposed indication. Although not statistically significant, the findings suggest durability of response and a reasonable response rate for the drug. Time to significant improvement and rescue medication are of special interest as these measures are independent of the TOS and MSCS and support the efficacy of ecallantide over placebo

Extension, repeat-dose phase

Following the double-blind, placebo-controlled phase of EDEMA3, patients were eligible to continue in the repeat-dose, open-label extension for up to 20 separate HAE attacks. New patients who did not participate in the double-blind phase were also eligible to enroll in the repeat-dose phase. A new attack was defined as an HAE attack that presented after a return to normal state following a previous acute attack. Patients were treated with a single, 30 mg dose of ecallantide. If symptoms did not resolve completely, patients could be given a second blinded dose of 30 mg ecallantide or placebo within 4 to 24 hours of the initial single dose.

From the double-blind phase, 22 ecallantide and 26 placebo patients received at least 1 dose of ecallantide in the OLE phase. Another 19 new patients also joined the study, for a total of 67 patients in the safety population. A total of 160 attacks were treated during the OLE. The majority of patients were treated for 1 attack during the OLE; 1 patient was treated for 13 attacks. Sixty-five of 153 treated attacks in the ITT population involved multiple symptom complexes. Thirty-three attacks had laryngeal involvement. The Applicant reported heterogeneity in individual patients, both in attack site and in severity, from one attack to the next, which is consistent with the natural history of HAE described in the literature.

The TOS at 4 hours and the change in MSCS from baseline at 4 hours varied somewhat by treatment episode, but results were generally consistent over time. The first treatment episode only includes new patients who did not participate in the double-blind phase. The following table summarizes these results.

Table 7 EDEMA3 OLE repeat dose efficacy results			
Treatment episode	N	Mean TOS at 4h	Mean Δ MSCS at 4h
DB dose ITT as treated	36	50	-0.9
1	18	71	-1.2
2	51	73	-1.1
3	30	82	-1.3
4	21	81	-1.4
5	11	49	-0.9
6	9	60	-0.9

Based on subgroup analysis provided by DPAP's statistical reviewer, there were no major efficacy differences between ecallantide-naïve patients and patients with a history of prior exposure. Only 3 patients received Dose B, limiting analysis. Of the 2 patients who received placebo as Dose B, both patients reported symptoms to be "a lot better or resolved" at the 4- and 24-hour assessments. The third patient who received ecallantide as Dose B reported symptoms to be the "same" and did not receive further treatment in the study.

Reviewer's comment: The TOS values suggest efficacy over repeated doses, although the number of patients upon which the TOS is based decreases with each episode. This may be a function of the underlying rate of attacks; alternatively, these results could be due to self-selection of responders vs. non-responders, meaning that patients with incomplete or unsatisfactory responses may have chosen not to present for treatment of future attacks. The MSCS scores appear consistent with the TOS, which is expected as the MSCS is a component of the TOS calculation. In the absence of a control, these results are difficult to interpret as the natural course of an HAE attack is gradual improvement. Numerically, the magnitude of the MSCS results appears comparable to those observed for the ecallantide arm in the double-blind phase.

Conclusions

EDEMA3 is generally supportive of ecallantide's efficacy in the treatment of acute HAE attacks but the study did not demonstrate a statistically significant difference between ecallantide and placebo for the ITT population as randomized. The Applicant attributes the non-significant results to the accidental administration of placebo to 1 patient assigned to ecallantide and ecallantide to 1 patient assigned to placebo. When the data was reanalyzed using an as-treated dataset to correct for this error, the results were found to be statistically significant. While this post hoc analysis along with secondary and tertiary endpoints suggest efficacy, these results are not robust and confirmatory results from the second placebo-controlled trial, EDEMA4, are needed.

5.3.2 EDEMA4

Study design and conduct

EDEMA4 was the second pivotal Phase 3 study conducted in the US and Canada and similar in design to EDEMA3. Patients presenting within 8 hours of onset of moderate to severe HAE symptoms were randomized to treatment with 30 mg ecallantide SC or placebo. Patients were stratified by location of attack (laryngeal vs. other sites). Patients with evidence of upper airway compromise within 4 hours of dosing were eligible for an open-label dose of ecallantide. Similarly, patients with symptom relapse/recurrence at least 4 hours after dosing and within 24 hours of dosing were also eligible for open-label treatment with a single dose. Unlike EDEMA3, change from baseline MSCS at 4 hours post-dose was the designated primary efficacy endpoint for EDEMA4; the TOS was a key secondary efficacy endpoint. As noted above, the MSCS is the arithmetic mean of the severity grade of the individual symptom complexes, where each symptom complex is assessed a severity grade of severe to normal. A decrease from baseline MSCS corresponds to a reduction in severity. The same anatomic symptom complexes as in EDEMA3 were assessed.

No imputations were made for the primary analysis. Sensitivity analyses performed to assess the effects of emerging symptom complexes and medical interventions were performed using the following imputations: Emerging symptom complexes were included in the MSCS calculation if present at the 4-hour and 24-hour MSCS assessment timepoints. If medical interventions were performed during an attack, the affected symptom complex(es) were assigned a severity of "severe" at 4 and/or 24 hours.

Efficacy results

Ninety-six patients were enrolled; 48 in the ecallantide arm and 48 in the placebo arm. The disposition of the patients and baseline demographics are shown in Table 8 and Table 9.

	Ecallantide N=48 N (%)	Placebo N=48 N (%)	Total N=96 N (%)
Intent to treat population ^a	48 (100)	48 (100)	96 (100)
Per protocol population ^b	47 (98)	48 (100)	95 (99)
Safety population ^c	48 (100)	48 (100)	96 (100)
Patients rolling over to continuation study ^d	47 (98)	46 (96)	93 (97)
Patients withdrawing from study			
Adverse event	0	1 (2)	1 (1)
Noncompliance or protocol violation	0	0	0
Withdrawal of consent	0	0	0
Lost to follow-up	0	0	0
Investigator discretion	0	0	0
Left study site against medical advice	0	1 (2)	1 (1)

^a Patients who received any amount of study drug

^b Patients who received a complete dose of study drug with no major protocol violations

^c Patients who received any amount of study drug

^d All patients were intended to roll over to the open-label extension study (DX-88/19) for follow-up safety assessments. A total of 2 patients (1 in the ecallantide arm and 1 in the placebo arm) declined further participation. An additional patient in the placebo arm left the study site against medical advice and was not enrolled in the follow up study.

Source: dx-88-20-csr-body.pdf, Section 10.1, Table 2

	Ecallantide N=48	Placebo N=48	Total N=96
Age			
Mean (SD)	37 (13)	38 (12)	38 (13)
Range	15-72	13-72	13-72
Sex (N,%)			
Male	11 (23)	20 (42)	31 (32)
Female	37 (77)	28 (58)	65 (68)
Race (N,%)			
White	39 (81)	43 (90)	82 (85)
Black	3 (6)	3 (6)	6 (6)
Asian	1 (2)	1 (2)	2 (2)
Hispanic	4 (8)	1 (2)	5 (5)
Other	1 (2)	0	1 (1)
Prior use of ecallantide (N,%)	17 (35)	19 (40)	36 (38)

Source: dx-88-csr-body.pdf, Section 11.2.1, Table 4

In the ITT population, a total of 36 patients had previously participated in another ecallantide study. Details regarding the patients' HAE history and concomitant medications can be found in the individual study review located in Section 10. In EDEMA4, the most commonly reported moderate-severe symptom complex in the ecallantide group was cutaneous, with 22 (46%) patients reporting cutaneous symptoms of moderate-severe severity compared to 17 (35%) patients in the placebo arm. The placebo arm had a larger number of patients reporting moderate-severe GI symptoms compared to the ecallantide arm: 26 (54%) vs. 13 (27%), respectively. Laryngeal symptoms of moderate-severe severity were reported with similar frequency in the treatment groups: 8 (17%) patients in the ecallantide group and 7 (15%) patients in the placebo group.

Reviewer comment: The distribution of attack sites is not equal, with cutaneous attacks predominating in the ecallantide group versus stomach/GI attacks in the placebo group. This uneven distribution could impact efficacy findings, if ecallantide works better on cutaneous symptoms, for example, or if the PRO instruments do not assess different attack site symptoms similarly. However, the literature and the PRO validation studies actually suggest that GI symptoms, primarily pain, tend to be considered more significant in HAE attacks and perhaps more easily assessed by PRO measures.

Results from the primary efficacy analysis are shown in Table 6. The treatment arms had comparable baseline MSCS scores. A statistically significant greater decrease in MSCS from baseline was observed in the ecallantide group compared to the placebo arm (-0.8 vs. -0.4; $p=0.01$; Table 6). Similar results were observed for the per-protocol population analysis as well ($p=0.01$). For the mean TOS at 4 hours, a statistically significant difference between the ecallantide group and the placebo group (50 vs. 8, $p=0.003$). Similar TOS results were also reported for the PP population. Imputations for emerging symptom complexes and medical interventions were also performed. These results are displayed in Table 10.

Table 10 EDEMA4: Primary efficacy endpoint sensitivity analyses			
	Mean change from baseline MSCS at 4 hours		P
	Ecallantide (N=47)	Placebo (N=48)	
Imputation for emerging symptoms	-0.8 (0.6)	-0.2 (0.9)	<0.001
Imputation for emerging symptoms and medical intervention	-0.8 (0.7)	-0.1 (0.9)	<0.001

Source: dx-88-20-csr.pdf, Summary tables 14.2.3.2.1 and 14.2.3.2.2

Other secondary efficacy endpoints were also generally supportive of ecallantide's efficacy in terms of numerical trends, if not statistically significant. The exception was the mean time to significant improvement for ecallantide, which was 184.3 minutes compared to 154.3 minutes for the placebo group ($p=0.12$); a median time to improvement was not reached within the 4 hour period for either group. However, a greater proportion of patients reported significant improvement during the initial 4-hour post-dosing period for ecallantide ($n=22$, 45%) compared to placebo ($n=12$, 26%) ($p=0.05$). Durability of response was supported by statistically significant differences in MSCS scores (-1.5 vs. -1.1; $p=0.04$) and the TOS (89 vs. 55; $p=0.03$) at

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Kalbitor™ (ecallantide)

available. In October 2006 the Applicant submitted an SPA for the EDEMA4 study. During the SPA review, the Division raised concerns about the complex nature of the TOS. Given the complexity of the scoring system with its severity multipliers and the inclusion of a temporal assessment of response into the score, the Division raised concerns that the TOS was not intuitive and hard to interpret. Due to the response multipliers, small differences of uncertain clinical relevance could be exaggerated. The Division felt that defining a clinically meaningful difference would prove difficult. Conversely, as a composite score, the TOS could potentially obscure important changes. For example, a patient with significant improvement in cutaneous symptoms but significant worsening in laryngeal symptoms would have a TOS of 0, equivalent to no change. In addition, the Division was concerned that the TOS would be difficult to represent accurately in a product label and cause confusion for clinical practitioners. As a result, the Division recommended that the Applicant use the MSCS as the primary efficacy variable for EDEMA4 and include the TOS as a key secondary endpoint to facilitate cross-study comparisons between the two pivotal studies. The MSCS is a more straightforward global symptom score that captures symptom severity at a point in time. To support both PRO instruments, the Applicant submitted validation reports as well as the results of cognitive debriefing interviews with patients and proxy respondents.

Reviewer's comment: There are no previously validated PRO instruments available for use in HAE. The complex nature of an HAE attack – the various anatomic sites of attack and different symptom manifestations at these locations – makes objective measurement of drug responses in this condition difficult. Usually, an anatomic site will predominate but other sites are frequently involved and an attack may continue to evolve over time. Even for a given individual, attacks can vary from one to the next and affect the intra-individual retest reliability of a PRO instrument.

- ***Cognitive debriefing interviews***

Cognitive debriefing interviews were conducted in 21 subjects: 15 patients with angioedema (including 2 children) and 6 proxy respondents (1 husband of a patient, 1 mother of a child patient, 3 clinical site coordinators, and 1 physician). On average, the patients reported an attack frequency of 1 attack every 3.5 months that typically lasted in duration from 10 hours to 3 days. When asked about the most recent attack, patients reported symptom complexes consistent with those specified for the MSCS and TOS calculations. Severity was described in terms of effects on daily activities which appeared to be consistent with the severity definitions used in the Phase 3 trials. In addition, patients noted that the most severe symptom within a complex determined their rating of severity. Of note, patients reported a hierarchy in anatomic sites, noting that GI symptoms and laryngeal symptoms were more severe than cutaneous symptoms due to the pain associated with GI swelling and life-threatening nature of laryngeal swelling. Based on the interview comments, it appeared that a moderate GI attack was considered inherently more severe than a moderate cutaneous attack. Overall, participants appeared to understand the terms used in the MSCS and TOS, with the exception of the term “cutaneous” and the distinction between “internal” versus “external” head and neck symptoms. Based on this feedback, the investigators recommended that patients be presented with all the symptom complexes and their definitions prior to

completion of the e-diaries in the study. These recommendations were implemented in EDEMA4 but were made after the completion of EDEMA3.

• **PRO validation (Study DX88-103)**

Study DX88-103 was intended to assess the psychometric properties of the TOS and MSCS, using data collected from EDEMA3. The study demonstrated moderate test-retest reliability (TOS intra-class correlation coefficient [ICC] = 0.52; MSCS ICC = 0.62) by comparing TOS and MSCS scores to a global improvement measure in a subset of patients who had reported no change or “same” at the 4 hour timepoint on the global improvement measure. The TOS and MSCS correlated with the global improvement score at 4 hours, suggesting construct validity. The TOS and MSCS also discriminated between the global improvement groups at 4 hours, indicating discriminant validity. Using a triangulation approach and comparison to the global improvement measurement scores, a minimum clinically important difference (MCID) for both the TOS and MSCS was estimated: TOS MCID = 30 points and MSCS MCID 0.30 points.

Reviewer’s comment: The treatment differences that were observed in EDEMA4 for the change in MSCS (treatment difference = -0.4) and the TOS at 4 hours (treatment difference -45) exceed the proposed MCID. To put the estimated MCID values in another context, a difference of 42 was found in the mean TOS values for patients reporting no change and those reporting improvement at 4 hours on the global improvement measure. For the MSCS, a difference of 0.5 was found in the change in MSCS values for patients reporting no change versus those reporting improvement at 4 hours. Based on these data, clinical review finds the proposed MCID values for both the MSCS and the TOS to be reasonable.

The Applicant has followed the guidelines set forth in the PRO Guidance for Industry to validate the two instruments, TOS and MSCS. Both symptom scores appear to capture patients’ HAE symptoms with some degree of test-retest reliability and differences in the scores appear to correlate statistically with patient-reported clinical changes. In addition to the validation data provided by the Applicant, individual line listings of patients’ efficacy TOS, MSCS, and global improvement item scores in both EDEMA3 and EDEMA4 were reviewed and generally appear to corroborate the study’s findings. That being said, the TOS remains difficult to interpret and represent and concern remains that the response outcome multipliers may exaggerate differences of questionable clinical relevance or obscure important changes.

Another issue is the relative weight of anatomic sites in both composite scores; since cutaneous, external head/neck, and genital/buttocks are all peripheral attack sites, peripheral symptoms may impact the score more than laryngeal or GI/abdominal attacks. To explore this issue further, the Division requested that the Applicant perform exploratory reanalysis of the MSCS endpoint using only 3 symptom complexes – peripheral, GI/abdominal, and laryngeal (Information Request dated February 10, 2009). Based on this modified MSCS score, the change from baseline MSCS in the ecallantide group vs. placebo was -1.1 vs. -0.7 ($p < 0.001$) in EDEMA3 and -1.1 vs. -0.6 ($p < 0.001$) in EDEMA4. Since earlier subgroup analysis suggested that GI/abdominal attacks tend to show greater treatment differences than peripheral attacks (Table 16), these results are as expected and do not alter the clinical review’s conclusions on efficacy.

Efficacy findings

The two Phase 3 studies, EDEMA3 and EDEMA4, provide the primary efficacy support for the proposed indication, the treatment of acute HAE attacks. Both EDEMA3 and EDEMA4 studies were randomized and placebo-controlled and used appropriate inclusion/exclusion criteria and efficacy endpoints. The patients enrolled and their presentations were consistent with typical HAE attacks described in the literature.

The primary results of the two studies are summarized in Table 6. EDEMA4 had robust results with a change from baseline MSCS at 4 hours for the ecallantide group of -0.8 versus -0.4 in the placebo group ($p=0.01$). The treatment difference of -0.4 is greater than the MCID estimated in the PRO validation studies. Looking at additional sensitivity analyses that include imputation for emerging symptoms and medical interventions, the difference between ecallantide and placebo is further accentuated (Table 10). Statistically significant findings for the TOS at 4 hours were also reported in EDEMA4 (53 vs. 8; $p=0.003$). However, additional analysis of the results pre- and post-sample size change indicated that the treatment difference was not consistent across the duration of the study. The statistically significant results were driven by 6 outlier patients in the placebo group who performed notably worse than the rest of the cohort. Review of the 6 individual patients did not show any clear distinguishing factors in terms of demographics, HAE history, or attack presentation, including the anatomic attack site. The patients were also enrolled from 6 different US study sites that had previously participated in other EDEMA studies, arguing against a site-specific procedural change. The discrepancy in results pre- and post-amendment may be a reflection of the inherent variability of the disease. There is no other evidence to suggest that study conduct or patient recruitment were altered by the sample size change. Nevertheless, since the cause of the discrepancy remains unknown, the clinical review relied more heavily on additional secondary efficacy endpoints, in particular the medical intervention patterns and self-global assessments, to confirm the primary efficacy findings.

EDEMA3 did not have robust results. As described in Section 5.3, 2 patients mistakenly received the wrong study drug. When the efficacy endpoints were recalculated using a dataset based on the ITT as treated population, the differences between the ecallantide and placebo arms were found to be statistically significant. These results support ecallantide's efficacy, although the results do not appear to be robust and the limitations of a small sample size are apparent. In terms of the TOS, EDEMA3 results (ecallantide vs. placebo, 47 vs. 21; $p=0.100$) were generally comparable to the EDEMA4 results, although the placebo group appears to have done relatively worse in EDEMA4 when compared to EDEMA3. However, the baseline values and the magnitude of change in MSCS reported for EDEMA3 were similar to the overall findings in EDEMA4 (-0.9 vs. -0.5; $p=0.09$). The MSCS scores suggest that the placebo groups overall (minus the 6 outlier patients in EDEMA4) performed similarly across studies and indicate that the sample size of EDEMA3 may have contributed to the non-significant findings. The MSCS scores also highlight the difficulty in TOS interpretation, since the TOS does not permit a comparison of baseline status and the subsequent change from baseline.

With regards to repeat dosing, the clinical program did not include a placebo-controlled evaluation of chronic, intermittent dosing. The support for repeat dosing is based primarily on information obtained from the open-label experience in EDEMA3, EDEMA4, and EDEMA2 in

conjunction with extrapolation from the single-dose experience. In the whole clinical program, 108 patients (50%) had only a single exposure. Eighty patients (37%) had 2 to 4 doses and 19 patients had 5 to 9 doses. One patient in EDEMA3 had a total of 14 doses. Overall, the MSCS and TOS in the open label period appeared to be consistent with the single dose data, suggesting that the effects of ecallantide do not diminish with repeat doses. However, these results could be due to self-selection of responders vs. non-responders, meaning that patients with incomplete or unsatisfactory responses may have chosen not to present for treatment of future attacks. Given the underlying pathophysiology and the fact that HAE attacks are generally unique events, it is reasonable to assume that ecallantide would be equally efficacious for future attacks. The exception would be in the case of neutralizing antibodies which could theoretically inhibit drug action at a sufficient titer. Based on the data presented, however, there does not appear to be any negative or positive correlation between the development of non-IgE antibodies to ecallantide and efficacy, with the caveat that the total number of patients represented is quite small. The issue of immunogenicity is addressed in further detail in Section 7. In general, the number of treatment episodes was not associated with any decrease in efficacy, although it cannot be ruled out that patients with less favorable responses may have declined to present for treatment of further episodes, resulting in self-selection of responders for the higher number of doses.

Although there are limitations with the repeat dose data – lack of placebo control and potential for selection bias – the uncontrolled, repeat dose data combined with extrapolation of the single-dose data supports the efficacy of ecallantide with repeat dosing.

6.1.6 Analysis of Secondary Endpoints(s)

Both the TOS and MSCS are discussed above, as these were used as primary and key secondary efficacy variables, respectively, in EDEMA3, and vice versa in EDEMA4. Other secondary endpoints to consider include the TOS and MSCS at 24 hours as a measure of durability of response, responder analysis, time to significant improvement, and medical interventions as a different measure of efficacy. Overall, the secondary efficacy endpoints provide confirmatory evidence of ecallantide's efficacy. Several of the secondary efficacy variables are discussed below.

- ***MSCS and TOS at 24 hours***

Analysis of MSCS and TOS at 24 hours suggests durability in the ecallantide response. In EDEMA3 the mean TOS at 24 hours in the ecallantide group vs. placebo was 44 vs. -1 (p=0.04). The mean change in MSCS at 24 hours was -0.9 vs. -0.5 (p=0.14). In EDEMA4 the mean TOS at 24 hours in the ecallantide group compared to placebo was 89 vs. 55 (p=0.03). The mean changes in MSCS at 24 hours were -1.5 vs. -1.1 (p=0.04), respectively.

- ***Responder analysis (TOS \geq 70)***

Based on the PRO validation studies, a TOS value of 30 was deemed the MCID. The Applicant performed responder analysis using a range of cutoff values for the TOS at intervals approximately based on this MCID: ≥ 30 , ≥ 50 , ≥ 70 , and 100. A similar proportion of patients in each of the phase 3 studies qualified as “responders” based on these cutoff values. For example, in EDEMA3 15 patients (42%) in the ecallantide group compared to 12

(33%) in the placebo group had a TOS \geq 70 at 4 hours (p=0.47). In EDEMA4 more ecallantide patients (22 of 48, 46%) qualified as responders compared to the placebo arm (9 of 47, 19%) [p=0.01]. No statistically significant differences were observed when stratified by attack location or prior use of ecallantide.

- ***Time to significant improvement***

Time to significant improvement was based on patients' global self-assessment scores, which were independent of the MSCS and TOS calculations. In EDEMA3, the median time to significant improvement was 165 minutes for ecallantide, compared to 240 minutes in the placebo group (p=0.14). In EDEMA4, the reported mean time for ecallantide was actually higher than in the placebo group (184.3 vs. 154.3 minutes, p=0.12); a median time to improvement was not reached within the 4 hour period for either group. However, a greater proportion of patients reported significant improvement during the initial 4-hour post-dosing period for ecallantide (n=22, 45%) compared to placebo (n=12, 26%) (p=0.05).

- ***Medical interventions***

The medical intervention patterns supported ecallantide's efficacy, as more placebo patients required additional intervention during an attack. In EDEMA3, 5 patients (14%) in the ecallantide group compared to 13 (36%) of placebo patients received medical intervention. Similarly, in EDEMA4, fewer patients in the ecallantide group (n=16, 33%) received medical intervention than in the placebo group (n=24, 50%). The most commonly administered interventions were emergency medications such as opioids for pain control and anti-emetics. No patients required intubation or urgent surgical decompression. Medical intervention patterns are of special interest as quasi-objective marker of efficacy that is independent of any symptom scoring.

6.1.7 Other Endpoints

Several patients in both studies received additional open-label dosing for severe upper airway compromise (SUAC) or for incomplete response/relapse (Dose B). On the basis of the data provided, there was no apparent decrease in efficacy with repeat dosing within a 24-hour period. However, as these were unblinded, uncontrolled assessments, conclusions about efficacy are limited.

6.1.8 Subpopulations

Pediatrics

A limited number of pediatric patients were evaluated in the clinical program (Table 15). There were 25 pediatric patients in the development program who received any formulation of ecallantide; a total of 15 patients 10 to 17 years received the to-be-marketed 30 mg SC dose. Of these 15, only 4 received ecallantide as part of a double-blind study, two 16-year-old patients and two 17-year-old patients. Younger patients were studied during the open-label dosing. Although the available data do not suggest that ecallantide would behave differently in a pediatric patient, extrapolation of adult data to children is problematic. Although HAE is an autosomal dominant disease and the symptomatic manifestations of HAE are the same across age groups, the disease

typically does not manifest until late childhood or early adolescence. The delay in symptomatic disease suggests that human development may influence the vasoactive mediator cascades responsible for HAE symptoms. Furthermore, at the time of this review, the validity of the pharmacokinetic exposure data in children for ecallantide remains in question. Without validated estimates of drug exposure in children, extrapolation of adult data to children is not possible. From the clinical review's perspective, there is inadequate experience with ecallantide in adolescents and children less than 18 years of age to draw conclusions about efficacy in this age group.

Study	Number of patients <18 years of age [†]
EDEMA4	2 (ages 16 and 17 years)
EDEMA3	2 (ages 16 and 17 years)
EDEMA3 OLE	10 (ages 13 to 17 years)
EDEMA2	14 (ages 10 to 17 years)
EDEMA1	6 (ages 11 to 17 years)

[†] Patients were eligible to participate in more than one study

[‡] Includes patients who received the IV formulation. A total of 15 patients <18 years have received the 30 mg SC dose.

Anatomic attack site

For both studies, subgroup analysis on the basis of anatomic attack site was complicated by the fact that patients frequently presented with multiple symptoms and the symptom scores collected were composite symptom scores. In general, there were no clear differences in efficacy on the basis of predominant attack location, although the Applicant's pooled post-hoc analyses showed that the greatest treatment differences were observed for abdominal attacks and these attacks tended to respond more quickly to ecallantide (Table 16). Other post-hoc analyses presented by the Applicant at the PADAC meeting indicated that a shorter time interval between onset of symptoms and ecallantide administration was generally associated with greater treatment responses.

Primary attack site	Ecallantide (N=70)	Placebo (N=73)	P
Abdominal			
N	23	39	
Mean change in MSCS	-1.4	-0.5	0.001
TOS	62	27	0.03
Laryngeal			
N	12	6	
Mean change in MSCS	-1.0	-0.6	0.34
TOS	74	13	0.04
Peripheral			
N	32	22	
Mean change in MSCS	-0.7	-0.4	0.11
TOS	44	13	0.04

Source: summary-clin-efficacy-acute-attacks-of-hereditary-angioedema.pdf, Tables 2.7.3.5.1 and 2.7.3.5.2

Prior ecallantide exposure

Since patients were permitted to enroll in multiple sequential ecallantide studies, there is concern that self-selection of responders may have occurred and impacted efficacy results, particularly for repeat-dosing. To address this issue, the Applicant stratified the control portions of EDEMA3 and EDEMA4 for history of prior participation in an ecallantide study. The Applicant also submitted a subgroup analysis on the pooled Phase 3 population for naïve vs. non-naïve patients. Based on this analysis, patients with prior ecallantide exposure responded similarly to ecallantide compared to their drug-naïve counterparts.

Table 17 Mean change in MSCS and TOS at 4 hours by history of prior exposure to ecallantide: Pooled Phase 3 population from EDEMA3 (ITT-as-treated population) and EDEMA4

Primary attack site	EcCallantide (N=70)	Placebo (N=73)	P
Naïve			
N	57	49	
Mean change in MSCS	-1.0	-0.5	0.01
TOS	56	15	<0.001
Non-naïve			
N	10	18	
Mean change in MSCS	-1.1	-0.3	0.04
TOS	52	33	0.04

Source: summary-clin-efficacy-acute-attacks-of-hereditary-angioedema.pdf, Table 2.7.3.48 and 2.7.3.49

Gender

Subgroup analysis by gender on the pooled Phase 3 population shows similar efficacy between males (n=21) and females (n=49). In the male subgroup, the mean change in MSCS for ecallantide compared to placebo was -1.0 vs. -0.4 (p=0.04). For females, the MSCS results were -1.0 vs. -0.5, respectively (p=0.01). Similar results were observed for the TOS. The mean TOS at 4 hours for ecallantide compared to placebo in males was 47 vs. 7 (p=0.01) and in females was 59 vs. 28 (p=0.02).

Other subgroups

Other subpopulation analyses were limited by the small sample size. Based on the information provided, there does not appear to be any differential efficacy by race or in patients older than 65 years of age. Patients with renal or hepatic impairment were not specifically evaluated.

6.1.9 Analysis of Clinical Information Relevant to Dosing Recommendations

The total amount of circulating pre-kallikrein is estimated to be 500 nM. With the intent of achieving stoichiometric equivalence, an 18 mg dose of ecallantide was estimated to achieve a plasma concentration of 500nM. The clinical program was intended to assess a range of doses around this projected plasma concentration, and included both IV formulations (5 to 80 mg/m² IV) in EDEMA0 and EDEMA1 as well as the 30 mg SC dose in EDEMA2. However, the evaluable dose-ranging data collected in the clinical program was limited. EDEMA0 and EDEMA1 were not designed or powered in such a way as to permit any conclusions to be made about the comparative efficacy among the different dose levels. Details of these two studies are located in the respective Individual Study Reviews in Section 10. On the basis of EDEMA2, the 30 mg SC was the dose selected for study in the Phase 3 program. The SC dose had

administration advantages over the intravenous form of the study studied in the earlier dosing cohorts of EDEMA2 and appeared to provide more consistent plasma levels over the initial 4 hour dosing period. Based on the provided information, the proposed 30 mg SC dose is reasonable.

6.1.10 Discussion of Persistence of Efficacy and/or Tolerance Effects

Durability of response over an initial 24 hour period and potential tolerance effects secondary to the development of neutralizing antibodies are discussed above in Sections 6.1.5 and 6.1.6. Given the sporadic, intermittent dosing of the drug and short half-life, more persistent effects or other tolerance issues are not anticipated.

6.1.11 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

The safety of ecallantide at the proposed 30 mg SC dose in patients 18 years of age and older is supported in part by the submitted clinical study data, but an adequate risk management program to balance the safety concerns was not included in the application. Safety data showed that ecallantide is most commonly associated with headache, nausea, diarrhea, pyrexia, and injection site reactions. The most concerning adverse events were anaphylaxis and other hypersensitivity reactions. Nine anaphylactic events were identified using anaphylaxis diagnostic criteria outlined by the 2006 Joint NIAID/FAAN Second Symposium on anaphylaxis. Based on a population of 243 unique HAE patients and 846 ecallantide doses administered, the anaphylaxis rate is estimated at 3.7% of HAE patients or 1.1% of doses. An additional anaphylactic event was identified in the cardiothoracic surgery study, but given confounding comorbidities and other differences between the surgical patients and the HAE population, the cardiothoracic patients were excluded from the anaphylaxis rate calculation. As a more general concern, ecallantide appears to be highly immunogenic with an estimated seroconversion rate of 30% after 8 doses. The long-term consequences of seroconversion are not known at this time. Also, potential cross-reactivity with human tissue factor pathway inhibitor (TFPI) has not yet been studied. In knock-out mouse models, TFPI deficiency is an embryonic lethal due to hypercoagulability. Based on this literature, TFPI cross-reactivity may theoretically predispose to thrombotic events in humans.

Although safety data, particularly long-term follow-up, is limited, the clinical review believes that the safety profile for the proposed dose would be acceptable with appropriate risk evaluation and management strategies (REMS). Anaphylaxis reactions are unpredictable and life-threatening events. However, HAE is also unpredictable and life-threatening and there are currently no approved therapies for use in acute attacks. Medical care facilities equipped to treat manifestations of acute HAE attacks such as laryngeal edema are an appropriate setting for

administering ecallantide and monitoring for anaphylaxis. In addition, HAE patients, given the nature of their disease and the rarity of the condition, tend to be a relatively sophisticated patient population that would be receptive to patient education about anaphylaxis and drug hypersensitivity. The Applicant has submitted general plans for a mandatory registry of healthcare providers and patients with restricted distribution via a central pharmacy, but detailed plans for their REMS were not submitted for review in the application. As a result, the clinical review cannot make a recommendation for Approval at this time.

As mentioned in Section 6, few patients under the age of 18 years have been treated with the to-be-marketed 30 mg SC ecallantide dose. While there is no evidence from the available data that the pediatric safety profile differs from that in adults, the application lacks sufficient data to make an assessment in patients under the age of 18 years for the proposed indication. Extrapolation of adult safety data to children is problematic. Although HAE is an autosomal dominant disease and the symptomatic manifestations of HAE are the same across age groups, the disease typically does not manifest until late childhood or early adolescence. The delay in symptomatic disease suggests that human development may influence the mediator cascades responsible for HAE symptoms. Furthermore, at the time of this review, the validity of the pharmacokinetic exposure data in children for ecallantide remains in question. Without validated estimates of drug exposure in children, extrapolation of adult data to children is not possible.

In summary, the data indicate a safety signal of anaphylaxis with ecallantide. Detailed and appropriate risk management strategies are necessary to balance the significant risk of anaphylaxis and other hypersensitivity reactions associated with ecallantide. While some data in pediatric patients is available, the data are not sufficient to draw conclusions about safety in this population.

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

The clinical review focused on the studies that used the to-be-marketed SC formulation in HAE patients: EDEMA2, EDEMA3, and EDEMA4. Additional safety information was obtained from the Phase 1 studies, the cardiothoracic study, the rechallenge study, and the compassionate use case narratives. General information on the study design and patient numbers is presented in Table 2, while more detailed information is provided in Section 5.3 and in the individual study reviews located in Section 10.

7.1.2 Adequacy of Data

The data submitted in support for ecallantide for the proposed indication was adequate for the adult population. The doses and durations of exposure were generally appropriate given the constraints of conducting studies for an orphan disease, as were the safety evaluations performed during the development program. The Applicant provided patient data listings that were appropriately indexed for review, as well as CRFs for all SAEs. Investigators used NCI CTC criteria for grading AE severity. AE coding was performed using the MedDRA coding

dictionary (Version 6.0). In review of SAE case narratives, SAE verbatim terms, and the SAE preferred terms, coding was performed appropriately.

Minimal safety data was provided for the pediatric age range as noted in Section 6.1.2.8. As a result, the clinical review does not recommend approval of this application for the 10 to 17 years age range.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

The Applicant provided several pooled datasets for the Integrated Summary of Safety:

- Analysis Population I: All HAE patients treated with ecallantide in EDEMA studies, excluding the EDEMA4 OLE (Study DX-88/19), the compassionate use, or rechallenge study.
- Analysis Population II: Patients from controlled phase of EDEMA3 and EDEMA4
- Analysis Population III: EDEMA3 OLE patients
- Analysis Population IV : Healthy volunteers in ecallantide studies

Limited safety information on an additional 24 patients from the EDEMA4 OLE up to November 10, 2008, was submitted in a safety update (December 19, 2008) and a response to an information request (February 12, 2009). The clinical safety review relied on Analysis Population II to estimate and compare the incidence of various AEs to placebo. This population was representative of the clinical program and appears representative of the general HAE population. Patients were permitted to participate sequentially in multiple ecallantide studies, so 16 patients from EDEMA3 also enrolled in EDEMA4. The Division previously raised concern about the handling of these patients in the safety analysis, so the Applicant has provided longitudinal patient profiles for all patients that include a unique identification number. The Analysis Population II represents 100 unique patients who have received 125 doses of ecallantide. If a patient received placebo in one study and ecallantide in the next, safety data collected during exposure to placebo was attributed to placebo and the same for ecallantide. Also, any EDEMA4 placebo patient who received a Dose B for airway compromise or incomplete response/relapse was analyzed as a placebo-treated patient up to the time of the open-label dose and as an ecallantide-treated patient from the time of ecallantide to the study conclusion.

As noted in Section 6, the clinical program does not include placebo-controlled data on repeat dosing. For evidence of safety in repeat dosing, the clinical review relied on the pooled analysis of all HAE patients treated with ecallantide in EDEMA studies (Analysis Population I plus the patients from the safety updates), excluding the compassionate use and rechallenge studies. Analysis Population I represented 219 patients who received 609 doses of ecallantide. This population included all AEs reported by patients. While Analysis Population I is of interest due to the greater numbers represented, it includes patients who received the IV formulation of ecallantide in a range of other doses. The generalizability of the Analysis Population I findings to the to-be-marketed SC formulation is uncertain. For example, the IV formulation may not be as immunogenic as the SC formulation, as SC drug administration may be associated with increased sensitization. As a results, Analysis Population I could potentially underestimate the

rate of hypersensitivity reactions. Limited safety information for 24 unique EDEMA4 OLE patients was included in the December 19, 2008, safety update and the February 12, 2009, response to information request. The clinical review included these 24 patients in the calculation of adverse event frequencies for the total HAE population (n=243)

Data from healthy volunteers (Analysis Population IV) and the CTS study patients were reviewed in terms of specific AEs, namely hypersensitivity and anaphylaxis reactions.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

HAE is an orphan disease with life-threatening potential so the guidelines put forth in the current ICH guidance (*ICH E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-life-threatening Conditions*) and the *Guidance for Industry: Pre-marketing Risk Assessment* (March 2005) on extent and duration of exposure are limited in their applicability. Given the limitations of this rare condition and previous discussions with the Division during the end-of-phase-2 and pre-BLA interactions, including the SPA agreement for EDEMA4, the clinical program includes adequate exposure information at the appropriate dose for an adult HAE population. The design of the studies, both open-label and placebo-controlled, was adequate to make a safety assessment.

Total human exposure to ecallantide in the development program (Analysis Population I) is shown below.

Table 18 Total ecallantide exposure for all HAE patients (Analysis Population I)			
Ecallantide (N=219)			
Number of patients with:	N (%)	Min - Max Total cumulative dose (mg)	Min - Max duration
1 dose	108 (49)	8.5 - 89.6	1 day
2 to 4 doses	80 (37)	27.9 - 153.2	1 day - 51 months, 15 days
5 to 9 doses	19 (9)	80.2 - 310.8	1 month, 27 days - 59 months, 5 days
>9 doses	12 (6)	169.2 - 623.9	13 months, 26 days - 44 months, 13 days

Source : summary-clin-safety.pdf, Table 2.7.4.5

The demographic information for the Phase 1 healthy volunteer studies, the pooled Phase 2-3 studies (Analysis Population I), and the pooled Phase 3 studies (Analysis Population II) are presented in Table 19. The demographics across the clinical program were comparable, with the exception of the healthy volunteer pool being younger on average.

Table 19 Demographics of Phase 1, Phase 2, and Phase 3 ecallantide studies				
	Phase 1	Pooled Phase 2-3	Phase 3	
	Analysis Population IV (Healthy subjects)	Analysis Population I	Analysis Population II	
	Ecallantide N=62	Ecallantide N=219	Ecallantide N=100	Placebo N=81
Age (yrs)				
N	62	219	100	81
Mean (SD)	28.5 (8.9)	34.6 (13.7)	36.5 (12.7)	35.4 (13.4)
Range	18-55	10-78	15-77	10-72
Gender (n, %)				
Female	34 (54.8)	144 (64.8)	66 (66.0)	50 (61.7)
Male	28 (45.2)	75 (34.2)	34 (34.0)	31 (38.3)
Race (n, %)				
Asian	3 (4.8)	3 (1.4)	2 (2.0)	1 (1.2)
Black	6 (9.7)	13 (6.2)	6 (6.0)	6 (7.4)
Caucasian	52 (83.9)	178 (84.8)	4 (84.0)	73 (90.1)
Hispanic	0	13 (6.2)	7 (7.0)	1 (1.2)
Other	1 (1.6)	3 (1.4)	1 (1.0)	-

Source: summary-clin-safety.pdf, Table 2.7.4.8 and iss.pdf, Appendix 4, Table 2.3

Exposure data in pediatric patients is far more limited (Table 15) and the generalizability of the safety findings from the adult population to pediatric patients remains in question. Of 25 patients under the age of 18 years, only 15 have received the to-be-marketed 30 mg SC dose. Only 4 pediatric patients (two 16-year-olds and two 17-year-olds) received ecallantide during the double-blind phase of a controlled study. As previously discussed, extrapolation of adult data to children is problematic. Although HAE is an autosomal dominant disease and the symptomatic manifestations of HAE are the same across age groups, the disease typically does not manifest until late childhood or early adolescence. The delay in symptomatic disease suggests that human development may influence the mediator cascades responsible for HAE symptoms and potentially affect ecallantide response.

Certain other subpopulations, such as patients over 75 years and people with renal or hepatic impairment, were not studied in significant numbers. However, given the rarity of HAE and its life-threatening potential, extensive pre-marketing safety assessment in these subpopulations is not expected.

7.2.2 Explorations for Dose Response

Both Phase 3 studies were conducted using a single 30 mg SC dose (~15 mg/m² IV). Intravenous doses ranging from 5 to 80 mg/m² IV were studied in the Phase 1 and 2 programs. The total dose and duration for all HAE patients in the clinical program is summarized in Table 18. In general, there were no evident correlations between AEs and dose, and the types of AEs reported across dose groups were similar. The most serious AE, anaphylaxis, was found to occur at all dose levels, which is consistent with an antibody-mediated hypersensitivity reaction.

7.2.3 Special Animal and/or In Vitro Testing

At the time of this review, the Pharmacology/Toxicology review is ongoing. Upon preliminary review, the preclinical testing was adequate. Two major concerns were raised by the preclinical data: injection site reactions in animals and impaired coagulation in in vitro studies. These issues are addressed later in this review and in further detail in the Pharmacology/Toxicology team's review.

7.2.4 Routine Clinical Testing

Routine clinical testing included the following: CBC with differential, routine serum chemistry, coagulations tests, and urinalysis. Reference ranges were based on ranges published in the "Laboratory Handbook of Reference Intervals – Massachusetts General Hospital Clinical Laboratories" (February 2007) and "Laboratory Reference Values" as reported in the New England Journal of Medicine (Kratz et al., 2004). Laboratory data was collected at baseline and at appropriate intervals following dosing and at follow-up.

7.2.5 Metabolic, Clearance, and Interaction Workup

The pharmacokinetics of ecallantide are described briefly in Section 4.4 and in detail in the Clinical Pharmacology team's review. No formal drug-drug interaction studies were included in this program. Ecallantide is a biologic product and not expected to interact with the CYP450 enzymes or p-glycoproteins.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Ecallantide is a biologic, immunogenic product and sensitization with hypersensitivity reactions including anaphylaxis is expected. In addition to screening for adverse events of this nature, the Applicant conducted serial antibody samples to evaluate for development of non-IgE antibodies to ecallantide and IgE antibodies to ecallantide and *P. pastoris*. The Applicant also conducted a rechallenge study to assess the risks and benefits of rechallenge in patients with ecallantide hypersensitivity reactions. These results are presented in more detail in Sections 7.3 and 7.4.

7.3 Major Safety Results

7.3.1 Deaths

Two deaths were reported in the ecallantide program. Patient 8804022001 (EDEMA1) had a history of dual nephrectomy and kidney transplant 1 year prior to enrollment. The patient was reported to have chronic rejection of the transplant and died of chronic renal failure 29 days after administration of ecallantide. Patient 101 (DX88/16, CTS study) died of perioperative myocardial infarction and multi-organ system failure. The treatment assignment for this patient has not yet been unblinded.

Reviewer's comment: Based on the nature and timing of the deaths, neither case appears to be related to the administration of ecallantide.

7.3.2 Nonfatal Serious Adverse Events

Of 243 patients in all HAE studies (Analysis Population I + safety update patients from EDEMA4 OLE), 33 (14%) experienced a SAE. Twenty-one patients (9% of total HAE population) reported an HAE attack as an SAE. Other SAEs reported included a wide range of events: abdominal pain (n=1), colitis (n=1), pancreatitis (n=1), infectious diarrhea and hematochezia (n=1), concussion and contusion due to car accident (n=1), jaw fracture (n=1), skin laceration (n=1), ECG signs of myocardial ischemia (n=1), chronic renal failure (n=1), hip contusion (n=1), and syncope (n=1). One case of pulmonary embolism was reported in a 42-year-old female patient (Patient 415103) during the EDEMA4 OLE 13 days after treatment with a single dose of ecallantide. The patient's medical history is notable for lupus and tobacco use, which are significant risk factors for hypercoagulability. The same patient was also diagnosed with transient elevated LFTs reported as an SAE which resolved after discontinuation of simvastatin, which is commonly associated with transaminitis.

In addition, 3 cases of anaphylaxis and 1 anaphylactoid reaction were reported. These SAEs and other hypersensitivity-related reactions are discussed separately in Section 7.3.4 under Significant Adverse Events.

Reviewer's comment: Although an exacerbating effect cannot be ruled out, most likely the reports of HAE as an SAE reflect the underlying condition. In the Phase 3 studies, the reports of HAE attack as an AE in the placebo group exceeded the number reported in the ecallantide group.

There is concern for thromboembolic events given the theoretical possibility of cross-reactivity between antibodies against ecallantide and endogenous TFPI. In the case of Patient 41503 with a pulmonary embolism, the pulmonary embolus was diagnosed approximately 3 weeks after her first exposure to ecallantide and 2 weeks after her 2nd dose. The patient tested positive with a titer <5 for antibodies to ecallantide on a single occasion prior to her first exposure to ecallantide and subsequently tested negative on 2 other occasions for any antibodies, suggesting that the one-time positive result was a false positive. The patient's known hypercoagulable state at baseline (lupus and tobacco use) combined with the antibody data makes a causal association with ecallantide more difficult to establish but the possibility cannot be ruled out.

7.3.3 Dropouts and/or Discontinuations

Two patients withdrew due to AEs. Patient 8804024001 withdrew 6 weeks after receipt of 10th dose of ecallantide following a new diagnosis of B-cell lymphoproliferative disease and Patient 8805051099 (discussed in Section 7.3.4) withdrew following anaphylaxis.

Reviewer's comment: On the basis of one case report, a causal relationship between the B-cell disorder and drug cannot be made. In contrast, the anaphylactic event is most likely secondary to drug administration.

7.3.4 Significant Adverse Events

Anaphylaxis

As a protein therapeutic, hypersensitivity reactions to ecallantide are expected. In an attempt to capture these events, the Applicant performed a search using the following MedDRA preferred terms: adverse drug reaction, anaphylactic reaction, anaphylactoid reaction, erythema, flushing, pharyngeal edema, pruritus, pruritus generalized, rash erythematous, rhinitis allergic, throat irritation, urticaria, urticaria localized, and wheezing. For the purposes of the BLA submission, the Applicant defined anaphylaxis as "a severe systemic immunologic reaction, rapid in onset, presumably caused by antibody-mediated release of vasoactive mediators from tissue mast cells and peripheral blood basophils." Anaphylactoid reaction was defined as "an immediate, non-immunologic, systemic reaction that mimics anaphylaxis but is caused by non-antibody-mediated release of mediators from mast cells and basophils."

Reviewer's comment: For the purpose of this review, any AEs defined as anaphylaxis or anaphylactoid were accepted as such. In review of other AEs suggestive of anaphylaxis or other hypersensitivity reactions, the clinical review relied on the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis (Sampson HA et al. J Allergy Clin Immunol 2006). The criteria do not make a distinction based on underlying mechanism. These criteria are summarized as follows:

1. *Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula), and at least one of the following:*
 - a. *Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)*
 - b. *Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)*
2. *Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):*
 - a. *Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)*
 - b. *Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)*
 - c. *Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)*
 - d. *Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)*
3. *Reduced BP after exposure to known allergen for that patient (minutes to several hours):*
 - a. *Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
 - b. *Adults: systolic BP of less*

As noted in Section 7.3.2, the Applicant identified 3 cases of anaphylaxis and 1 case of anaphylactoid reaction in the ecallantide program:

- Patient 8805051099 (EDEMA3) experienced anaphylaxis twice – the first time after her 17th dose of ecallantide and the second during a rechallenge procedure. Her first event was characterized by generalized erythema, pruritus, and decreased blood pressure (82/50 mmHg) with an oxygen saturation of 90% on room air. She received epinephrine, diphenhydramine, and supplement oxygen and her blood pressure increased to 110.80 mmHg. Serum tryptase taken 4 hours after the event was 10.4 mcg/L (normal range: 1.9-13.5 mcg/L). The second event was characterized by dyspnea, generalized rash, anxiety, pharyngeal edema, vomiting, diarrhea, urinary incontinence, hypotension and hypoxia following rechallenge with a partial 1mg SC dose. The patient was noted to have tested intermittently positive to IgE against *P. pastoris* up to 2 years before the first event as well as non-IgE to ecallantide.
- Patient 8820401009 (EDEMA4 OLE, DX-88/19) developed anaphylaxis after her 4th dose of ecallantide, consisting of erythema, generalized pruritus, tingling of the tongue, lethargy, change in mental state, and vomiting. She was treated with 2 doses of 0.3 mg epinephrine, hydroxyzine, solumedrol, and IV fluids. A serum tryptase taken 6 hours after the event was 30 ng/ml (normal range L 2-10 ng/ml). The patient had intermittently tested positive for non-IgE and IgE antibodies to ecallantide since her 2nd dose and 3rd doses, respectively, although she tested negative for IgE to ecallantide immediately prior to the event.
- Patient 8805024097 (EDEMA2) developed anaphylaxis 10 minutes after her 6th dose. She experienced nausea, diaphoresis, dizziness, and a feeling of faintness before receiving treatment with epinephrine, hydrocortisone, cetirizine and ranitidine. Serum tryptase taken 4 hours and 12 minutes after the event was within normal range (2.7 ng/ml). The patient tested positive for non-IgE antibodies to ecallantide after the 5th dose and positive for IgE 7 days after the anaphylaxis. The patient went on to complete a successful rechallenge procedure and received 11 additional doses of ecallantide.
- Patient 8802003005 (EDEMA0) was identified was having an anaphylactoid reaction consisting of dysphagia, pruritus, urticaria, edema, dyspnea, abdominal pain, and enteritis 5 minutes after her first dose of ecallantide (40 mg/m² IV). She was treated with epinephrine, polaramine, and hydrocortisone. She test positive for ecallantide antibodies per the investigator's own immunoblot, but subsequently negative on the Applicant's ELISA assays. No rechallenge procedure was attempted.

Using the diagnostic criteria for anaphylaxis outlined above, the clinical review identified 5 additional potential case of anaphylaxis:

- Patient 8804013011 (EDEMA1) reported 3 separate episodes of sneezing, throat itchiness, congestion, rhinorrhea, and shortness of breath following the 1st, 2nd, and 4th doses of 20 mg/m² ecallantide IV. The time to onset is not recorded and patient's medical history if confounded by a history of asthma and allergic rhinitis. The patient has not tested positive for antibody formation to ecallantide or *P. pastoris*.
- Patient 8804013003 (EDEMA1) developed rhinitis, itchy throat, and shortness of breath following receipt of her 1st dose of ecallantide 20 mg/m² IV. The patient was treated with

epinephrine, antihistamines, and corticosteroids. The patient underwent a rechallenge procedure and developed rhinitis symptoms 42 minutes after the start of the test dose infusion. The patient has not tested positive for antibody formation to *P. pastoris*.

- Patient 8805019001 (EDEMA2) experienced symptoms suggestive of anaphylaxis during a rechallenge procedure. Her initial reaction consisted of worsening allergic rhinitis symptoms, conjunctival erythema, eye swelling, and urticaria 2 minutes after the start of the 1st ecallantide dose (10 mg/m² IV). The patient tested positive for IgE antibodies to *P. pastoris* 1 year prior to the reaction but had tested negative in subsequent assays. On rechallenge 18 months later, she developed sneezing, nasal congestion, throat itchiness, and cough.
- Patient 8805050097 (EDEMA2) developed abdominal pain, nausea, vomiting, throat itchiness, and nasal congestion following receipt of the 1st dose of ecallantide for treatment of an external head/neck HAE attack. Study drug infusion was stopped. No antibodies were detected and the patient did not undergo a rechallenge procedure.
- Patient 8814304010 (EDEMA4 OLE, DX-88/19, Patient 404103) had rash, injection site erythema, dyspnea, and laryngeal edema after her 6th dose of ecallantide. This patient had previously been enrolled in EDEMA3 (304010) and the double-blind phase of EDEMA4 (404004). The patient tested positive for non-IgE antibodies to ecallantide and neutralizing antibodies to ecallantide. She has not received additional doses but is expected to undergo a rechallenge protocol.

Anaphylaxis reactions in other patient populations

The Applicant also submitted safety data from the cardiothoracic surgery patients. Although the perioperative conditions and surgical/medical comorbidities limit comparisons of this patient population to the HAE population, there was one notable case of anaphylaxis (Patient 262) in a patient who received low-dose ecallantide. Four and a half hours after the start of the ecallantide infusion and 30 minutes and 5 minutes into transfusions of packed red blood cells and fresh frozen plasma, respectively, the patient had life-threatening hypotension (SBP of 60 mmHg on 40 mcg/min norepinephrine) requiring chest compressions, decreased oxygen saturation, and bronchoconstriction associated with high peak inspiratory pressure on mechanical ventilation. Ecallantide infusion was stopped. Shortly after receiving diphenhydramine and ranitidine, the patient SBP recovered to 150 mmHg had norepinephrine was withdrawn. A serum tryptase level taken 45 minutes after the event was elevated at 31 mcg/ml, consistent with mediator release that is characteristic of anaphylaxis.

No anaphylaxis was reported in healthy volunteers.

Reviewer's comment: Per the Applicant's submission and December 18, 2008, safety update, 243 HAE patients received 846 doses of ecallantide in the ecallantide HAE studies (Analysis Population I plus the safety update DX-88/19 patients up through November 10, 2008). These numbers excludes compassionate use [n=8] and rechallenge protocols [n=9]). Based on the HAE patients who have received at least 1 dose of ecallantide, an anaphylaxis rate of 3.7% patients (9 cases of 243 HAE patients) or 1.1% doses (9 of 846 doses) is observed. Patient 8805051099 had 2 anaphylactic episodes: the first time in EDEMA3 and then again during the

rechallenge procedure. Since the rechallenge study is not included in the anaphylaxis rate calculation, only the patient's first event is included.

Other hypersensitivity reactions

In addition to these anaphylactic events, several cases suggestive of a Type I hypersensitivity reaction were also identified.

- Patient 8804013007 (EDEMA1) reported sneezing after the 1st dose of 40 mg/m² IV ecallantide, relieved by antihistamine. The patient experienced nasal stuffiness a rechallenge procedure and has not received any further doses of ecallantide. No antibodies to ecallantide or *P. pastoris* were reported for this patient.
- Patient 8805017018 (EDEMA3) developed urticaria 3½ hours following ecallantide 30 mg SC for a laryngeal HAE attack. Non-IgE antibodies to ecallantide were demonstrated at the 28-day follow-up and IgE antibodies to *P. pastoris* at the 57-day follow-up. The patient has not attempted a rechallenge procedure.
- Patient 8805054099 (EDEMA2) reported headache, blurred vision, flushing, urticaria, pruritus, conjunctival injection, increased heart rate (120 → 172 bpm) and increased blood pressure (122/73 → 152/100 bpm) within 1 minute of completing the 6th dose infusion of 10 mg/m² IV ecallantide. The patient tested positive for non-IgE antibodies to ecallantide and later neutralizing antibodies in EDEMA3. The patient also tested positive for IgE to *P. pastoris* on two separate occasions. The patient underwent a successful rechallenge and went on to receive 16 additional doses of ecallantide.
- Patient 8814326002 (EDEMA3) reported pruritus and nausea 12 minutes after receipt of a 4th dose of ecallantide. The patient tested positive for non-IgE antibodies to ecallantide and IgE to *P. pastoris*. The patient had a positive wheal and flare response during the skin testing phase of rechallenge and has not received additional doses.
- Patient 8814302002 (EDEMA3-RD) experienced increased heart rate and blood pressure and flushing 10 minutes after receipt of a 2nd dose of 30 mg ecallantide SC. The patient tested positive for non-IgE antibodies to ecallantide on ECL bridging assay and negative by ELISA. The patient received 1 additional dose of ecallantide and reported chest tightness and flu-like symptoms following the dose. The time to onset was not reported.
- Patient 8805024099 reported itchy throat after the 2nd and 3rd of 6 ecallantide doses.
- Patient 8804017010 reported an erythematous rash on the buttocks the day following the 11th IV dose and again after the 12th SC dose. The second rash was also accompanied by injection site pain.

Urticaria was reported in 9 of 243 (3.7%) patients following injection and 6 (2.5%) other patients reported pruritus or generalized pruritus following injection, although the time course in relation to dose administration is not clearly documented in the majority of cases.

Injection site reactions

In Analysis Population II, local injection site reactions were reported in 3 (3%) patients in the ecallantide group compared to 1 (1%) in the placebo group. All three of the patients were seronegative for antibody to ecallantide and *P. pastoris*. In the total HAE population (Analysis Population I + the EDEMA4 OLE safety update patients), injection site reactions were reported

in 15 of 243 (6%) of patients. The reactions were characterized primarily by pain, pruritus and erythema. Two cases of local urticaria were reported. The reactions were all transient and resolved without intervention, differing from the severe local reactions observed in preclinical studies.

Reviewer's comment: The injection site reactions were not predictive of systemic hypersensitivity reactions.

7.3.5 Submission Specific Primary Safety Concerns

As mentioned in Section 1.3, the clinical review recommends that ecallantide be administered by a healthcare professional in an appropriately monitored setting given the risk for anaphylaxis and hypersensitivity reactions. Although self-administration may offer certain benefits in terms of patient convenience and potentially greater efficacy, the safety and feasibility of self-administration have not been evaluated in the clinical development program to date. In the BLA submission, the Applicant initially included patient self-administration as an option at the discretion of the healthcare provider and the patient. The Division communicated concern about self-administration given the absence of supportive data in the 60-day filing letter. In response, the Applicant informed the Division in a letter dated December 24, 2008, that the self-administration issue would be deferred. The Applicant stated that post-marketing information on anaphylaxis reactions and a separate clinical study to assess self-administration would be used to inform future decisions on commercial self-administration options.

Given the significant risk of anaphylaxis, the clinical review does not foresee self-administration as a viable mode of drug administration in the future, unless the Applicant is able to develop effective screening methods that mitigate the risk. As off-label self-administration remains a possibility pending approval, the clinical review recommends that post-marketing risk management strategies include mandatory registration of healthcare providers and patients as well as extensive education materials for both regarding the risk of hypersensitivity events.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common AEs associated with ecallantide are headache, nausea, diarrhea, pyrexia, and nasopharyngitis. AEs occurring in >1 patient and at a frequency greater in the ecallantide group than placebo are shown in Table 20. Of note, HAE attack was reported in 3 (3%) ecallantide patients versus 4 (5%) placebo patients. Prolonged prothrombin time was reported in no ecallantide patients compared to 2 in placebo.

Table 20 Adverse events occurring in >1 patient and at a greater frequency in the ecallantide group vs. placebo (Analysis Population II)

Preferred term	Ecaltantide N=100 (n,%)	Placebo N=81 (n,%)
Patients with ≥1 AE	36 (36)	28 (35)
Headache	8 (8)	6 (7)
Nausea	5 (5)	1 (1)
Diarrhea	4 (4)	3 (4)
Pyrexia	4 (4)	-
Nasopharyngitis	3 (3)	-
Injection site pain or reaction	3 (3)	1 (1)
Dizziness	2 (2)	1 (1)
Erythematous rash	2 (2)	-
Fatigue	2 (2)	-
Pharyngolaryngeal pain	2 (2)	-
Upper abdominal pain	2 (2)	-

Source: summary-clin-safety.pdf, Table 2.7.4.11

The most common AEs identified appear to be consistent in the pooled Phase 3 program (Analysis Population II) when compared to safety data for the total HAE database (Analysis Population I + patients in safety update from EDEMA4 OLE). In the total HAE safety database of 243 patients, the most common AEs reported were headache, fatigue, nausea, diarrhea, upper respiratory infections, injection site reactions, nasopharyngitis, pruritus, pyrexia, nausea, vomiting, and upper abdominal pain. HAE as an AE was also reported in 18 patients (8%). Anaphylaxis is calculated at a rate of 4% (9 of 243 patients).

Table 21 Adverse events reported in >3% of HAE patients treated with ecallantide

Preferred term	Ecallantide N=243* (n, %)
Patients with ≥1 AE	162 (67)
Headache	39 (16)
Fatigue	29 (12)
Nausea	29 (12)
Diarhea	27 (11)
HAE	18 (7)
Upper respiratory tract infection	19 (8)
Injection site reactions	15 (6)
Nasopharyngitis	15 (6)
Pruritus	14 (6)
Upper abdominal pain	13 (5)
Vomiting	13 (5)
Urticaria	12 (5)
Dizziness	10 (4)
Prolonged activated partial thromboplastin time (aPTT)	10 (4)
Pyrexia	11 (5)
Rash	11 (5)
Sinusitis	10 (4)
Anaphylaxis	9 (4)
Cough	9 (4)
Dehydration	9 (4)
Nasal congestion	9 (4)
Pharyngolaryngeal pain	8 (3)
Dyspepsia	7 (3)
Prolonged creatine phosphokinase	7 (3)
Prolonged thrombin time	7 (3)

* Percentages based on number of unique patients. Patients reporting more than 1 event with the same preferred term or SOC were counted only once for that preferred term or SOC.

Source: response-to-questions-clinpharm-clinstat.pdf, Table 5.1.4 (February 12, 2009 submission) and clinical review's assessment of anaphylaxis cases

Reviewer's comment: The numbers shown in Table 21 are based on the clinical review's integration of the December 19, 2008, safety update into the adverse event frequencies reported in the initial BLA and updated adverse event tables submitted on February 12, 2008. Percentages were based on the number of unique patients (n=243) and specific adverse events per patient were only counted once.

7.4.2 Laboratory Findings

Overview of laboratory testing and selection of studies for drug-control comparisons

As presented in Section 7.2.4, routine clinical laboratory testing (CBC with differential, chemistry panel, coagulation parameters, and urinalysis) were performed at baseline and at appropriate intervals through each study. Serum sampling for antibody formation to ecallantide and *P. pastoris* was also obtained at baseline and at follow-up visits. A detailed schedule of collection timepoints for each study is provided in the Individual Study Reviews located in Section 10.

Measures of central tendency, outliers, and marked outliers were reviewed for each lab parameter. Baseline is defined as the closest observation prior to dosing. Laboratory changes were not performed by study visit because of the variety of time points used for laboratory assessments across studies. Instead, the most abnormal value from all follow-up visits was selected for analysis. For comparison to placebo control, the review focuses on the Analysis Population II, consisting of the pooled Phase III data. The entire HAE population (Analysis Population I) is also reviewed, particularly in terms of repeat dose data and outliers.

Hematology

Mean changes in hematology parameters

No clear differences in hematocrit, total white cell count and differential, or platelet number were observed between baseline and post-baseline ecallantide and placebo-treated groups in the pooled Phase 3 analysis (Analysis Population II) (Table 22). Similar mean values were observed in the pooled Phase 2 and Phase 3 analysis (Analysis Population I),

Table 22 Mean change in hematology parameters (Analysis Population II)

Indices	Ecallantide N=100			Placebo N=81		
	Baseline	Post-baseline		Baseline	Post-baseline	
		Lowest	Highest		Lowest	Highest
Hematocrit (%)						
N	97	97	97	74	74	74
Mean (SD)	43.7 (4.2)	40.7 (3.9)	43.8 (4.0)	43.5 (4.9)	41.1 (5.0)	43.9 (4.7)
Median	43.0	40.0	44.0	43.5	41.0	44.0
(Min, Max)	(33, 51)	(31, 50)	(35, 54)	(34, 54)	(32, 52)	(33, 54)
WBC (x10³/mcl)						
N	97	97	97	74	74	74
Mean (SD)	8.2 (2.6)	6.7 (1.9)	8.9 (2.6)	8.4 (2.6)	7.2 (2.5)	9.2 (2.2)
Median	7.9	6.7	8.7	8.4	6.8	9.0
(Min, Max)	(3.8, 20.6)	(3.5, 16.2)	(3.9, 20.2)	(2.9, 15)	(3.3, 14.3)	(4.5, 15.8)
Basophils (%)						
N	97	97	97	74	74	74
Mean (SD)	0.7 (0.4)	0.5 (0.3)	0.9 (0.5)	0.8 (0.5)	0.6 (0.4)	1.0 (0.5)
Median	0.7	0.5	0.8	0.7	0.5	0.9
(Min, Max)	(0, 2.1)	(0, 1.8)	(0, 2.9)	(0, 2.2)	(0, 2.2)	(0.3, 2.2)
Eosinophils (%)						
N	97	97	97	74	74	74
Mean (SD)	1.6 (1.1)	1.5 (1.3)	2.5 (1.7)	1.8 (1.2)	1.5 (1.0)	2.6 (2.4)
Median	1.3	1.3	2.0	1.3	1.2	2.1
(Min, Max)	(0.1, 6)	(0, 9)	(0.2, 9)	(0, 5.3)	(0, 4.7)	(0.4, 19)
Lymphocytes (%)						
N	97	97	97	74	74	74
Mean (SD)	25.6 (9.2)	25.0 (8.5)	32.4 (8.4)	26.6 (9.8)	25.8 (10.5)	33.3 (9.8)
Median	24.5	24.6	32.4	25.5	26.3	32.9
(Min, Max)	(3.4, 48.2)	(3.9, 45)	(12.9, 54.5)	(4.6, 54)	(5.3, 55)	(5.6, 57.8)
Monocytes (%)						
N	97	97	97	74	74	74
Mean (SD)	5.2 (1.7)	4.6 (1.4)	5.8 (1.6)	5.4 (2.0)	4.8 (1.8)	6.2 (2.0)
Median	4.9	4.4	5.5	5.2	4.6	6.4
(Min, Max)	(1.9, 13)	(1.5, 10)	(3.2, 10.8)	(1, 12.2)	(1.7, 10.1)	(1.7, 12)
Neutrophils (%)						
N	97	97	97	74	74	74
Mean (SD)	66.8 (10.0)	59.1 (9.0)	67.7 (9.6)	65.4 (11.3)	57.9 (10.7)	66.6 (12.0)
Median	67.9	58.6	68.0	65.6	57.7	65.8
(Min, Max)	(45.9, 93)	(38, 81.1)	(48.4, 92.1)	(34.5, 93.1)	(33.2, 90.6)	(38.3, 90.7)
Platelets (x10³/mcl)						
N	97	97	97	72	72	72
Mean (SD)	273.4 (59.5)	261.1 (61.2)	293.2 (67.1)	281.0 (59.8)	267.7 (62.6)	299.5 (56.8)
Median	266.0	253.0	284.0	273.0	266.5	287.0
(Min, Max)	(163, 461)	(126, 456)	(171, 494)	(156, 458)	(133, 403)	(195, 465)

Source: iss.pdf, Appendix 4, Table 7.1.1.2

Outliers and marked outliers in hematology parameters

No patients discontinued from the study or were reported as an AE secondary to a change in a hematology parameter. The following table summarizes the number of patients with a shift from normal to abnormal (or a post-baseline value worse than baseline if the baseline value exceeded the cutoff range for normal) in both the pooled Phase 2/3 analysis (I) and the pooled Phase 3 analysis (II).

Table 23 Outliers for hematology parameters in Analysis Populations I and II

Laboratory test	Cutoff	Population I		Population II			
		Ecallantide (N=219)		Ecallantide (N=100)		Placebo (N=81)	
		N ^a	N (%) ^b	N ^a	N (%) ^b	N ^a	N (%) ^b
Hemoglobin	≤10 g/dL	215	3 (1)	97	-	74	1 (1)
WBC	<3.0 x 10 ⁹ /L	215	-	97	-	74	-
WBC	>ULN	215	55 (26)	97	13 (13)	74	10 (14)
Neutrophils	<30%	206	2 (1)	97	-	74	-
Lymphocytes	<5%	206	9 (4)	97	1 (1)	74	-
Platelets	<75.0 x 10 ⁹ /L	214	1 (0.4)	97	-	72	-

^a Number of patients with both a baseline and post-baseline value

^b Number of patients with a normal → abnormal or worsened value exceeding the normal range

ULN = upper limit of normal

Source: summary-clin-safety.pdf, Table 2.7.4.37

Coagulation parameters

Mean changes in coagulation parameters

In vitro studies demonstrated that ecallantide could prolong activated clotting time (ACT) and aPTT, potentially leading to an anti-hemostatic effect. As a result, aPTT, prothrombin time (PT), and thrombin time (TT) were routinely monitored in the clinical studies. Overall, there were no clinically relevant mean changes in coagulation parameters in the ecallantide group versus the placebo group (Table 24).

Table 24 Mean change in coagulation parameters (Analysis Population II)

Indices	Ecallantide N=100			Placebo N=81		
	Baseline	Post-baseline		Baseline	Post-baseline	
		Lowest	Highest		Lowest	Highest
aPTT (sec)						
N	96	96	96	74	74	74
Mean (SD)	21.3 (4.9)	20.4 (2.0)	23.0 (4.4)	21.5 (5.3)	20.1 (1.6)	22.9 (8.6)
Median	20.6	20.2	22.1	20.7	20.2	21.6
(Min, Max)	(16.2, 54.9)	(15.1, 25.9)	(17.3, 47.2)	(16, 58.7)	(14.7, 23.4)	(15.5, 91.2)
PT (sec)						
N	96	96	96	75	75	75
Mean (SD)	11.2 (1.6)	10.8 (1.0)	11.6 (1.5)	11.4 (1.8)	11.0 (1.0)	12.7 (7.0)
Median	11.0	10.6	11.5	11.4	11.0	11.9
(Min, Max)	(9.4, 20.5)	(9.4, 13.3)	(9.7, 18.9)	(9.4, 21.3)	(9.8, 13.2)	(9.5, 60)
Thrombin time (sec)						
N	95	95	95	73	73	73
Mean (SD)	16.4 (2.2)	15.7 (1.1)	17.5 (4.7)	16.2 (1.3)	15.7 (1.0)	16.9 (2.1)
Median	15.9	15.5	16.5	16.2	15.6	16.4
(Min, Max)	(14, 28.3)	(13.7, 20.3)	(14.3, 52.9)	(13.4, 21.3)	(13, 20.3)	(13.5, 26.4)

Source: iss.pdf, Appendix 4, Table 7.3.1.2

Reviewer's comment: The clinical data do not suggest an increased risk of bleeding associated with ecallantide. The in vitro studies were conducted with ecallantide concentrations of 2 mcg/ml or greater, whereas the maximum observed ecallantide plasma concentration following the 30 mg SC dose is ~0.6 mcg/ml (3-fold lower). At the to-be-marketed dose, ecallantide is

expected to inhibit plasma activity by 10% and any effects on coagulation parameters would likely be transient given the short-half life.

Outliers and marked outliers in coagulation parameters

Data on outliers for coagulation parameters are reported in Table 25. No discontinuations from an HAE study secondary to coagulation abnormalities were reported. No bleeding events were reported for any of these patients. The aPTT elevations as high as 140.8 sec was reported; all aPTT elevations were observed in the IV formulation dosing groups. Seven of the 9 returned to baseline at follow-up. In the remaining 2, follow-up values were not reported. Similarly, in patients with PT elevations, all returned to within normal range at follow-up with the exception of 3 with missing follow-up PT values.

Of the 3 patients in the Analysis Population II reported with elevations in thrombin time, 2 had abnormal results (35.3 and 33.7 sec, respectively) at Follow-up Visit 1 (7 days post-dose) but normal TT at the 4-hour post-dose time point (17.1 and 21.7 sec, respectively) and at a later follow-up (Visit 2).

Table 25 Outliers for coagulation parameters in Analysis Populations I and II

Laboratory test	Cutoff	Population I		Population II			
		Ecallantide (N=219)		Ecallantide (N=100)		Placebo (N=81)	
		N ^a	N (%) ^b	N ^a	N (%) ^b	N ^a	N (%) ^b
aPTT	>1.5 x ULN	213	9 (4)	96	-	74	1 (1)
PT	>1.5 x ULN	201	7 (4)	96	-	75	2 (3)
Thrombin time	>30 sec	186	19 (10)	95	3 (3)	73	-

^a Number of patients with both a baseline and post-baseline value

^b Number of patients with a normal → abnormal or worsened value exceeding the normal range

ULN = upper limit of normal

Source: summary-clin-safety.pdf, Table 2.7.4.37

Reviewer's comment: Based on the outlier data, observed changes in coagulation parameters do not appear to correlate with an increased bleeding risk. Although in vitro studies have raised the concern about possible anti-hemostatic effects, there is an additional theoretical concern about hypercoagulability. Ecallantide is highly homologous with Tissue Factor Protein Inhibitor (TFPI). TFPI knockout is a lethal mutation in mouse models due to increased coagulation. Theoretically, neutralizing antibodies against ecallantide could bind endogenous TFPI and lead to hypercoagulability. The clinical safety database is notable for one patient with a pulmonary embolus. However, this patient was seronegative and the case is further confounded by a diagnosis of lupus, which is a known hypercoagulable state. In addition to ongoing clinical surveillance, the issue could be further explored by cross-reactivity studies for antibodies against ecallantide and TFPI.

Clinical chemistry

Mean changes in clinical chemistry parameters

Overall, there were no clinically significant mean changes from baseline when comparing clinical chemistry parameters in the ecallantide group to placebo (Table 26).

Table 26 Mean change in clinical chemistry parameters (Analysis Population II)						
Indices	Ecaltantide (N=100)			Placebo (N=81)		
	Baseline	Post-baseline		Baseline	Post-baseline	
		Lowest	Highest		Lowest	Highest
AST/SGPT (U/L)						
N	98	98	98	75	76	76
Mean (SD)	27.4 (27.0)	24.5 (32.1)	33.4 (43.0)	25.8 (17.0)	23.9 (18.0)	31.5 (25.4)
Median	19.0	16.0	21.5	22.0	20.5	24.5
(Min, Max)	(7, 183)	(7, 297)	(10, 297)	(7, 134)	(7, 124)	(10, 162)
AST/SGOT (U/L)						
N	98	98	98	75	75	75
Mean (SD)	29.6 (69.9)	20.6 (12.3)	4.7 (97.1)	21.8 (7.2)	20.3 (6.9)	25.1 (10.7)
Median	20.0	18.0	21.0	19.0	19.0	23.0
(Min, Max)	(11, 706)	(9, 116)	(12, 975)	(10, 55)	(10, 52)	(13, 85)
Alk phos (U/L)						
N	98	98	98	77	77	77
Mean (SD)	72.0 (19.7)	67.7 (20.6)	74.2 (20.5)	77.6 (31.4)	72.0 (28.3)	80.1 (32.8)
Median	69.0	64.5	2.5	69.0	66.0	72.0
(Min, Max)	(40, 161)	(34, 175)	(40, 175)	(35, 267)	(33, 220)	(34, 258)
Total billi (mg/dl)						
N	98	98	98	76	76	76
Mean (SD)	0.4 (0.2)	0.3 (0.2)	0.5 (0.2)	0.4 (0.2)	0.4 (0.2)	0.5 (0.2)
Median	0.4	0.3	0.5	0.4	0.3	0.4
(Min, Max)	(0.2, 1.4)	(0.2, 0.8)	(0.2, 1.5)	(0.2, 1.4)	(0.2, 1.1)	(0.2, 1.1)
BUN (mg/dl)						
N	98	98	98	77	77	77
Mean (SD)	12.8 (3.7)	10.8 (3.1)	13.9 (3.7)	13.8 (4.6)	12.0 (3.9)	14.6 (4.5)
Median	13.0	10.5	14.0	13.0	12.0	14.0
(Min, Max)	(5, 22)	(5, 21)	(8, 25)	(5, 29)	(5, 26)	(5, 29)
Creatinine (mg/dl)						
N	98	98	98	77	77	77
Mean (SD)	0.9 (0.2)	0.8 (0.2)	0.9 (0.2)	0.9 (0.2)	0.8 (0.1)	0.9 (0.2)
Median	0.9	0.8	0.9	0.8	0.8	0.9
(Min, Max)	(0.5, 1.2)	(0.4, 1.2)	(0.5, 1.3)	(0.5, 1.3)	(0.6, 1.2)	(0.6, 1.3)
Cr kinase (U/L)						
N	98	98	98	76	76	76
Mean (SD)	413.7 (2888)	87.4 (70.2)	527.2 (3867)	106.4 (67.0)	85.9 (48.9)	134.6 (100.3)
Median	91.5	64.5	96.5	85.0	73.5	101.0
(Min, Max)	(26, 29K)	(25, 569)	(42, 38K)	(24, 275)	(24, 275)	(36, 540)
GGT (U/L)						
N	98	98	98	77	77	77
Mean (SD)	23.3 (18.6)	21.1 (17.5)	25.2 (20.1)	25.1 (20.8)	23.1 (19.4)	27.2 (22.7)
Median	17.5	16.0	19.0	19.0	16.0	18.0
(Min, Max)	(8, 123)	(5, 118)	(8, 134)	(5, 104)	(4, 107)	(6, 107)
Glucose (mg/dl)						
N	98	98	98	76	76	76
Mean (SD)	93.9 (18.9)	85.4 (16.2)	110.1 (26.9)	102.0 (34.7)	92.4 (19.2)	111.4 (31.7)
Median	90.5	85.0	106.0	90.5	91.0	103.0
(Min, Max)	(62, 178)	(26, 146)	(71, 269)	(62, 294)	(50, 162)	(75, 260)
LDH (U/L)						
N	97	97	97	76	76	76
Mean (SD)	180.8 (221.7)	145.3 (27.6)	186.1 (233.2)	161.2 (25.1)	147.9 (26.0)	163.3 (28.3)
Median	156.0	144.0	159.0	157.5	144.5	159.5
(Min, Max)	(83, 2323)	(70, 217)	(70, 2435)	(91, 222)	(89, 211)	(89, 222)
Total protein (g/dl)						
N	98	98	98	77	77	77
Mean (SD)	7.1 (0.4)	6.8 (0.5)	7.2 (0.4)	7.1 (0.5)	6.8 (0.5)	7.2 (0.5)
Median	7.1	6.8	7.3	7.1	6.8	7.2
(Min, Max)	(6.1, 8.1)	(5.8, 7.9)	(6.3, 8.3)	(6, 9)	(5.3, 8.8)	(5.7, 9.2)

Source: iss.pdf, Appendix 4, Table 7.2.1.2

Outliers and marked outliers in clinical chemistry parameters

No patients discontinued secondary to abnormal laboratory values. No patients met criteria for Hy's law. The most notable individual abnormalities were observed for creatinine kinase. Both ecallantide and placebo-treated patients appeared to have CK elevations, which may be related to the severity of tissue swelling associated with an HAE attack. In general, values returned to within reference range or near baseline at later follow-up or were normal post-dose but then noted to be elevated at later follow-up 1 week or more later; the time course of these latter cases make it difficult to attribute the lab abnormalities to ecallantide given the drug's short half life. The following cases did not resolve during the specified follow-up period:

- Patient 8814317011 had a total bilirubin of 1.6 mg/dl and had a documented history of Gilbert's syndrome.
- Patient 8805013099 had a total bilirubin of 1.3 mg/dl pre-dose, 1.8 mg/dl at Day 7 and 1.2 at Week 4.
- Patient 8804022001 had an elevated creatinine of 6.2 mg/dl on Day 7 and an LDH of 1145 U/L at Follow-up Visit 2. The patient was a kidney transplant patient with chronic renal failure who died during the study. This death is described in Section 7.3.1.
- Patient 8004009001 had an LDH of 618 U/L at Follow-up Visit 1 which remained elevated at 617 at the 4-week blood draw. Pre-dose value was 403 U/L. Further follow-up is not provided.
- Patient 8804022004 had an LDH of 769 U/L at Follow-up Visit 1 which remained elevated at 507 at the 4-week blood draw. Pre-dose value was 403 U/L. Further follow-up is not provided.
- Patient 8805051099 had an LDH of 816 U/L at Follow-up Visit 1. Baseline level was 608 U/L. Further follow-up is not provided.
- Patient 8805059099 had an LDH of 707 U/L at baseline and 1134 U/L at 4 hours post-dose. Further follow-up is not provided.
- Patient 8820426020 had several lab abnormalities on admission, most notably a CK of 28,650 U/L (negative MB fraction). At follow-up visit 1, the CK was 569 U/L.
- Patient 8804032001 had a pre-dose glucose of 248.8 mg/dl and 429 mg/dl at discharge. The patient was a known diabetic.

Table 27 Outliers for clinical chemistry parameters in Analysis Populations I and II

Laboratory test	Cutoff value	Population I		Population II			
		Ecallantide (N=219)		Ecallantide (N=100)		Placebo (N=81)	
		N ^a	N (%) ^b	N ^a	N (%) ^b	N ^a	N (%) ^b
ALT/SGPT	>2.5 x ULN	217	18 (8)	98	4 (4)	76	2 (3)
AST/SGOT	>2.5 x ULN	217	9 (4)	98	2 (2)	75	-
Alk phos	>2.5 x ULN	217	1 (0.5)	98	-	77	-
Total bili	>1.5 x ULN	217	4 (2)	98	-	76	-
GGT	>2.5 X ULN	213	8 (4)	98	1 (1)	77	2 (3)
LDH	>2.5 x ULN	205	9 (4)	97	1 (1)	76	-
Creatinine	>1.5 x ULN	217	1 (0.5)	98	-	77	-
BUN	>35 mg/dl	217	1 (0.5)	98	-	77	-
Cr kinase	>ULN	207	39 (19)	98	10 (10)	76	7 (9)
Glucose	<55 mg/dl	217	9 (4)	98	2 (2)	76	1 (1)
Glucose	>210 mg/dl	217	7 (3)	98	1 (1)	76	1 (1)

^a Number of patients with both a baseline and post-baseline value

^b Number of patients with a normal → abnormal or worsened value exceeding the normal range

ULN = upper limit of normal

Source: summary-clin-safety.pdf, Table 2.7.4.39

Reviewer's comment: Ecallantide does not appear to have any clear effects on routine chemistry parameters. Creatinine kinase was noted to be elevated in both the ecallantide and placebo populations, perhaps as a nonspecific result of soft tissue swelling from acute HAE attacks.

7.4.3 Vital Signs

Overview of vital sign assessment and selection of studies for drug-control comparisons

Routine vital sign assessment was performed at baseline and at appropriate intervals through each study. The review focuses on the initial 24 hours following dosing given the pharmacokinetics of ecallantide. A detailed schedule of vital sign assessment timepoints for each study is provided in the Individual Study Reviews located in Section 10.

Measures of central tendency, outliers, and marked outliers were reviewed for each vital sign. Baseline is defined as the closest observation prior to dosing. Vital sign changes were not performed by study visit because of the variety of time points used for laboratory assessments across studies. Instead, the most abnormal value from all follow-up visits was selected for analysis. For comparison to placebo control, the review focuses on the Analysis Population II, consisting of the pooled Phase III data. The entire HAE population (Analysis Population I) is also reviewed, particularly in terms of repeat dose data and outliers.

Mean change in vital signs

No clinically meaningful differences in mean change in vital signs were reported between the ecallantide and placebo treatment groups in the Phase 3 program. Although pyrexia was one of the more common AEs reported for ecallantide, mean values for body temperature did not reflect this AE. The changes are summarized in Table 28.

Table 28 Mean change in vital signs (Analysis Population II)

Indices	Ecallantide (N=100)			Placebo (N=81)		
	Baseline	Post-baseline		Baseline	Post-baseline	
		Lowest	Highest		Lowest	Highest
Temperature (°C)						
N	100	100	100	77	77	77
Mean (SD)	36.6 (0.5)	36.4 (0.3)	36.9 (0.5)	36.6 (0.4)	36.4 (0.3)	36.9 (0.3)
Median	36.6	36.4	36.9	36.6	36.4	36.9
(Min, Max)	(35.5, 38.5)	(35.6, 37.1)	(36.1, 39.3)	(35.6, 38.2)	(35.3, 37.1)	(36.2, 37.8)
Pulse (bpm)						
N	100	100	100	77	77	77
Mean (SD)	80.1 (14.2)	67.2 (10.3)	81.2 (12.4)	80.0 (13.5)	70.5 (10.1)	83.5 (10.3)
Median	80.0	67.0	80.0	79.0	70.0	84.0
(Min, Max)	(51, 123)	(47, 117)	(52, 121)	(54, 114)	(41, 92)	(59, 115)
Systolic BP (mmHg)						
N	100	100	100	77	77	77
Mean (SD)	121.6 (14.7)	113.4 (11.6)	126.5 (12.6)	119.0 (14.9)	111.5 (12.8)	123.1 (13.3)
Median	121.0	115.5	126.0	118.0	110.0	120.0
(Min, Max)	(95, 175)	(87, 139)	(93, 168)	(78, 160)	(87, 140)	(95, 164)
Diastolic BP (mmHg)						
N	100	100	100	77	77	77
Mean (SD)	78.4 (9.2)	70.5 (10.0)	81.9 (8.6)	75.7 (10.8)	69.9 (9.7)	78.8 (10.2)
Median	80.0	70.0	82.0	76.0	70.0	78.0
(Min, Max)	(58, 102)	(48, 95)	(55, 105)	(45, 100)	(45, 92)	(53, 112)

Source: iss.pdf, Appendix 4, Table 8.1.2

Outliers and marked outliers in vital signs

No patients were discontinued from the study secondary to vital sign abnormalities. The total number of patients with shifts from normal → abnormal are shown in Table 29. Review of outliers is consistent with the commonly reported AE of pyrexia, with 4 patients reporting temperatures >38°C after receipt of ecallantide in the Phase 3 program. More patients with transient decreases in blood pressure and pulse were also reported in the ecallantide group compared to placebo. One patient (Patient 8805051099) experienced hypotension in the setting of an anaphylactic reaction to ecallantide, described in Section 7.3.4.

Table 29 Outliers for vital signs in Analysis Populations I and II

Laboratory test	Cutoff value	Population I		Population II			
		Ecallantide (N=219)		Ecallantide (N=100)		Placebo (N=81)	
		N ^a	N (%) ^b	N ^a	N (%) ^b	N ^a	N (%) ^b
Temperature	≥38°C	219	10 (5)	100	4 (4)	77	-
SBP	≥150 mmHg	219	29 (13)	100	2 (2)	77	2 (3)
SBP	>20% decrease	219	50 (23)	100	11 (11)	77	3 (4)
DBP	>20mmHg increase	219	33 (15)	100	1 (1)	77	3 (4)
Pulse	<60bpm	219	76 (34)	100	18 (18)	77	10 (13)
Pulse	>120 bpm	219	9 (4)	100	-	77	-

^a Number of patients with both a baseline and post-baseline value

^b Number of patients with a normal → abnormal or worsened value exceeding the normal range

ULN = upper limit of normal

Reviewer's comment: There do not appear to be any clear vital sign shifts due to ecallantide. Review of the individual narratives suggest that the observed decrease in blood pressure and pulse in the majority of these cases may have been related to resolution of pain and the acuity of the initial attack, as these vital sign changes appeared to correlate to some extent with patient reports of improvement. The exception would be in cases of anaphylaxis, where decreased blood pressure and tachycardia were recorded as would be consistent with anaphylactic cardiovascular changes.

7.4.4 Electrocardiograms (ECGs)

No formal QT studies were conducted in the ecallantide program. Given the absence of a preclinical effect and the expected mode and setting of administration, ECG monitoring in EDEMA4 in lieu of a separate formal thorough QT study was performed as discussed with the Division (August 24, 2007 submission). Twelve-lead ECGs were obtained at screening, pre-dose, between 2 and 4 hours to correspond to the Cmax window, and at Follow-up Visit 1. All ECGs were interpreted by a central reader.

No mean shifts from normal → abnormal were recorded. None of the ecallantide or placebo patients reached a threshold QTc interval of >500msec post-dose in Analysis Population II. The longest QTc interval recorded was 469 msec in an ecallantide patient and 521 msec at baseline in a placebo patient. One ecallantide patient had a >65msec change from baseline noted only at Follow-up Visit 1, making correlation to the drug less likely.

Reviewer's comment: Based on these results, ecallantide does not appear to have an effect on the QTc interval. Aside from transient supraventricular tachycardia and asymptomatic bradycardia, no arrhythmias were reported as AEs.

7.4.5 Special Safety Studies

Study DX88-102, Rechallenge study

In order to further define hypersensitivity reactions to ecallantide, patients with a history of a hypersensitivity reaction in EDEMA1, EDEMA2, or EDEMA3 were invited to enroll in a rechallenge study. The study consisted of 2 phases: a skin-testing phase and a test-dose phase. For the skin-test phase, escalating doses of ecallantide were administered by skin-prick and intradermal injection and compared to histamine and saline controls. A skin test was considered positive if the difference in the observed erythema or edema was >3mm from the saline control. For the test-dose phase, escalating doses were administered via intravenous infusion. The escalating dose procedure was not intended as a drug desensitization protocol. If any test was positive, the patient could proceed to the next test only with the approval of the Sponsor and the investigator. At the investigator's discretion, patients could also undergo a separate desensitization protocol. Details of the dosing for each phase of rechallenge are found in the Individual Study Summary, Section 10.6.1.

Nine patients underwent the rechallenge testing procedures. Six of the 9 patients successfully completed the test-dosing phase. Four of the 6 patients have since gone on to participate in other

ecallantide studies and have not experienced additional hypersensitivity reactions. Three patients had positive test results:

- Patient 8805019001 was a prior participant in EDEMA2. After the initial dose of 20 mg/m² IV, the patient developed eye erythema, eye swelling, urticaria of the back and face, nasal congestion, rhinorrhea and sneezing. She tested positive for specific IgE to *P. pastoris* 3 weeks prior to ever receiving study drug. During the rechallenge, she successfully completed the skin testing phase. However, approximately 8 minutes after the start of the 3 mg IV infusion, she developed sneezing, rhinorrhea, nasal congestion, cough, and throat itchiness. She received Benadryl and her symptoms resolved.
- Patient 8805051099 participated in EDEMA2 and received 13 doses of ecallantide without reaction. The patient subsequently enrolled in EDEMA3 and received 7 doses over a 5-month period. After the 7th dose, she developed pruritus and anaphylaxis (hypoxia and hypotension). The patient had positive IgE antibodies to *P. pastoris*. During the rechallenge, the patient developed a positive skin reaction on ID testing at the 1:100,000 dose. The investigator requested permission to administer a 1 mg SC dose. Seven minutes after dosing, the patient developed dyspnea, rash, anxiety, pharyngeal edema, vomiting, diarrhea, urinary incontinence, and hypoxia, consistent with anaphylaxis. The patient was treated with epinephrine and conveyed to the hospital for further observation prior to being discharged home. The patient has not participated in further studies.
- Patient 8814326002 was a participant in EDEMA 3 and received 4 doses of ecallantide. After the 4th injection, the patient experience nausea, pruritus, and injection site pruritus. The patient tested positive for IgE antibodies to *P. pastoris* and non-IgE antibodies to ecallantide. During rechallenge, the patient had a positive ID test at 1:10,000 dilution. The patient did not participate in further studies.

Reviewer's comment: Overall, the rechallenge procedure successfully identified patients who could receive additional ecallantide. None of the patients who had a successful rechallenge who then went on to further dosing have had new AEs suggestive of hypersensitivity. The safety of the rechallenge procedure, performed in the appropriate setting, appears comparable to similar graded challenge procedures for other drug allergies. However, the total number of patients studied was limited, so the generalizability of these results is uncertain.

A negative rechallenge result does not mean that the original reaction was not due to hypersensitivity. Negative rechallenges may be due to loss of sensitization over time or the absence of other co-factors that were present at the time of the original reaction. While direct comparison of rechallenge studies for other drugs is difficult due to differences in rechallenge protocols, the range of drugs tested, and individual patient factors, it is worth noting that the positive rechallenge rate of approximately 33% for ecallantide is higher than rates reported in the literature for several other drugs known to cause anaphylaxis.

*Notably, antibody status was not predictive. While all 3 patients who failed rechallenge and the patient with the most severe reaction, Patient 8805051099, did have positive IgE antibodies to *P. pastoris*, the application includes information on other patients with positive antibodies who did not have any hypersensitivity reactions, suggesting that the positive predictive value may be limited. The negative predictive value may be higher but this issue has not been systematically addressed.*

7.4.6 Immunogenicity

Antibody screening and methodology

Screening for formation of non-IgE and IgE antibodies to ecallantide and IgE antibodies to *P. pastoris* were performed throughout the clinical program. The schedule for antibody testing in each study is provided in the Individual Study Reviews located in Section 10. An ELISA assay was used in EDEMA3 and a more sensitive ECL assay was used for EDEMA4. Serum samples obtained from EDEMA3 were retested retroactively using the new ECL assay where sample quantity was sufficient. Retesting of sera from older studies (EDEMA0, EDEMA1, and EDEMA2) was not performed because the stability of the older samples was uncertain. Neutralizing antibody assays were performed on samples confirmed positive by ECL assay. Serum samples negative for anti-ecallantide antibodies were presumed to be negative for neutralizing antibodies and were not assayed.

Overall, ELISA and ECL assay results correlated closely per the Applicant. For the purposes of safety analysis, the antibody status of subjects was based on the combined results of both assays. If a sample tested positive to either assay, the sample was considered positive.

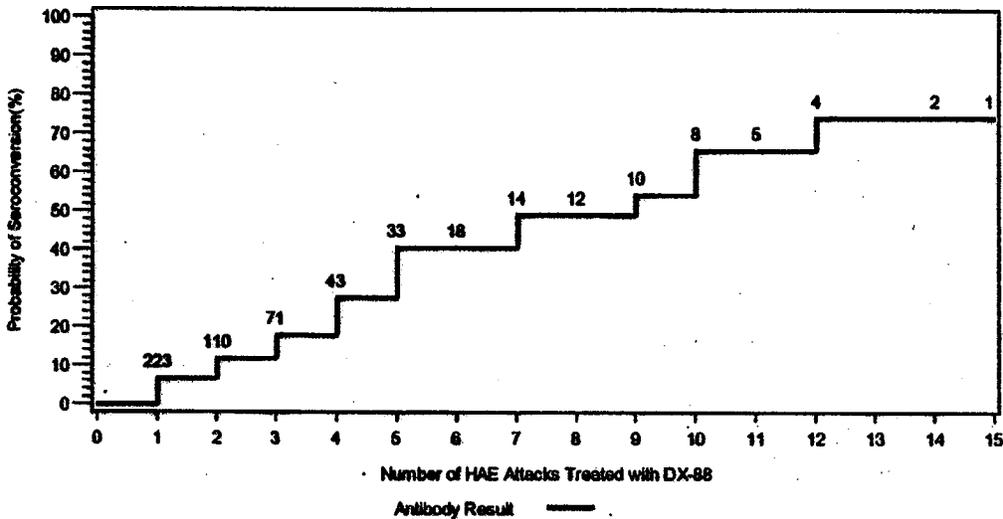
Reviewer's comment: The Agency's final review of the immunogenicity assays is pending at the time of this review; however, the review suggests that the IgE assays and neutralizing antibody assays are limited in sensitivity, likely resulting in an underestimate of seroconversion. The non-IgE antibody assays appear adequate.

Antibody seroconversion

The number of patients at risk to seroconvert was based on patients with at least 1 post-baseline evaluation. Patients with a missing pre-treatment evaluation were considered negative at baseline; patients who were positive at pre-treatment were excluded. Therefore, the number of seroconversions represents those patients with a negative or missing pre-treatment evaluation and a positive post-treatment evaluation. Based on these criteria, 26 of 202 (13%) patients in Analysis Population I seroconverted to anti-ecallantide antibodies (any class). As of the December 19, 2008, safety update, 53 of 243 patients (22%) were antibody positive and 183 patients (75%) were antibody negative. In Analysis Population I, 4 of 195 (2%) seroconverted to anti-ecallantide IgE, and 14 of 175 (8%) seroconverted to anti-*P. pastoris* IgE. Four patients with neutralizing antibodies were identified in the Analysis Population I. An additional 6 patients included in the December 19, 2008, safety update from the EDEMA4 OLE were reported to have neutralizing antibodies.

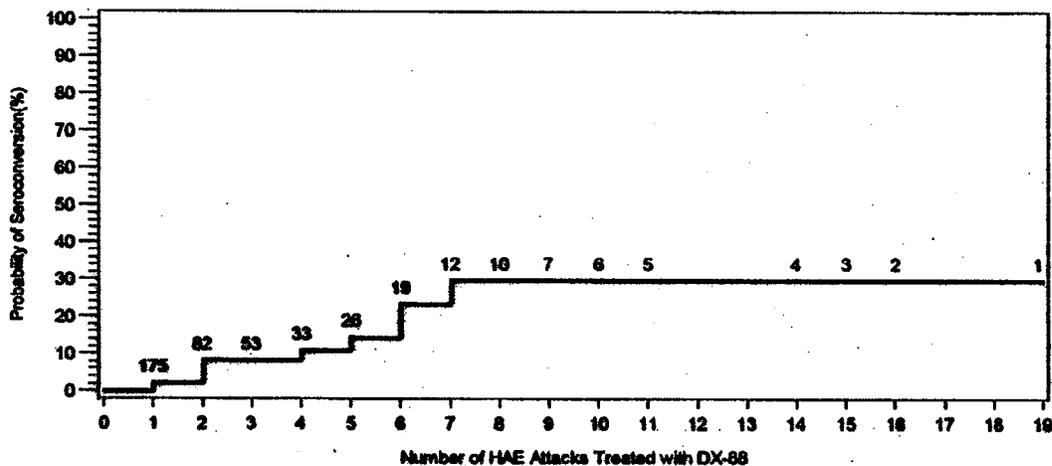
The probability of seroconversion increased with the number of treated episodes. There are few patients treated for more than 10 HAE attacks, so extrapolation beyond this point is not possible. Figure 2 displays a Kaplan-Meier analysis of the probability of seroconversion for both IgE and non-IgE antibodies to ecallantide over the number of treated HAE episode. Based on this analysis the estimated rate of seroconversion for all antibodies to ecallantide is approximately 40% after 5 attacks. Seroconversion to IgE anti-ecallantide was not observed until the 4th exposure to ecallantide and the probability of seroconversion after 8 attacks is estimated to be 12%.

Figure 2 Number of ecallantide-treated HAE attacks to seroconversion of IgE and non-IgE antibodies to ecallantide (Analysis Population I + safety update patients)



For *P. pastoris* IgE antibodies, there was an increase in the probability of seroconversion up through the 7th episode and then the rate was estimated at 30% after 7 attacks. These results are summarized in Figure 3.

Figure 3 Number of ecallantide-treated HAE attacks to seroconversion of IgE antibodies to *P. pastoris* (Analysis Population I)



Adverse events by antibody status

Anaphylaxis and other hypersensitivity reactions are discussed separately in Section 7.3.4. In terms of other AEs, there was no apparent differences in the overall frequency of AEs reported in patient seronegative versus seropositive for IgE and non-IgE to ecallantide and anti-*P. pastoris* IgE for Analysis Population I. Aside from hypersensitivity-related AEs, differences were noted for individual AEs but their disparate nature makes it difficult to draw conclusions. AEs that

were noted to occur more commonly in anti-ecallantide positive (any class) patients compared to seronegative patients included the following: headache (23 v. 15%), upper respiratory tract infection (17 v. 6%), nausea (17 v. 11%), diarrhea (13 vs. 10%), nasopharyngitis (13 v 4%), and prolonged aPTT (9 v. 3%), lymphadenopathy (4 vs. 1%), and injection site reaction (8 vs. 1%).

Of the 4 patients in Analysis Population I who tested positive for neutralizing antibodies, 3 reported an adverse drug reaction. Patients 8805054099, 8805024907, and 8814326002 reported reactions suggestive of drug hypersensitivity. However, the time course between development of neutralizing antibodies and the reactions were not closely correlated, with the two events separated in each of the cases by months to years.

Cross-reactivity with Tissue Factor Protein Inhibitor (TFPI)

As noted in Section 4.1, the Applicant has not made an assessment of potential cross-reactivity with endogenous tissue factor pathway inhibitor (TFPI). Ecallantide shares 88% homology with TFPI. In knock-out mouse models, TFPI deficiency is an embryonic lethal due to hypercoagulability. Based on this literature, TFPI cross-reactivity may theoretically predispose to thrombotic events in humans.

Reviewer's comment: The clinical safety database is notable for one patient with a pulmonary embolus. However, this patient was seronegative and the case is further confounded by a diagnosis of lupus, which is a known hypercoagulable state. In addition to ongoing clinical surveillance, the issue could be further explored by cross-reactivity studies for antibodies against ecallantide and TFPI.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There was no apparent dose dependency for AEs but as noted, limited dose-ranging was performed in the clinical development program. In terms of number of doses, the percentage of patients reporting at least one or more adverse events increased with number of exposures. Fifty-two of 108 (48%) who received a single dose reported at least one AE compared to 60 of 80 (75%) who received 2-4 doses and 18 of 19 (95%) who received 5 to 9 doses. All 12 patients who received >9 doses reported at least 1 AE. The nature of the AEs reported did not appear to change, with the exception of hypersensitivity reactions. Although hypersensitivity reactions, including 1 case of anaphylaxis, were observed in patients upon first exposure, the other cases of anaphylaxis occurred in patients who had had multiple exposures to ecallantide.

Reviewer's comment: The increase in percentage of patients reporting an AE with increasing dose exposure is not unexpected, as patients who have had more HAE attacks and treatments have had more opportunities to experience an HAE. Likewise, the occurrence of anaphylaxis with multiple exposures is expected as well.

7.5.2 Time Dependency for Adverse Events

The majority of AEs were reported within the first 24 hours of dosing. There were no AEs consistently associated with a delayed time to onset.

7.5.3 Drug-Demographic Interactions

In general, subgroup analysis was limited by small sample sizes. The percentage of ecallantide-treated patients reporting AEs was similar between male (67%) and female (64%) patients in the whole HAE population (Analysis Population I). There were no apparent differences in the nature of AEs, with the exception of anaphylaxis, which all occurred in female patients with the exception of 1 case. The number of pediatric patients was small (n=25), but the available data do not suggest an increased rate of adverse events or a different pattern of adverse events. The number of geriatric patients (n=4) was too small to draw conclusions about safety, as was the case with racial subgroups.

7.5.4 Drug-Disease Interactions

The AEs frequency or profile did not appear to be associated with presenting attack severity, anatomic attack sites, or with the subtype of HAE (Type I vs. Type II).

7.5.5 Drug-Drug Interactions

No formal drug-drug interaction studies were conducted. Ecallantide is a small protein and is not expected to interact with CYP450 enzymes or p-glycoproteins.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

No carcinogenicity studies were performed for ecallantide. One patient discontinued from study due to a new diagnosis of B-cell lymphoproliferative disorder.

Reviewer's comment: The Pharmacology/Toxicology reviewer has concluded that a formal carcinogenicity study in rats is feasible and would be an appropriate post-marketing commitment if approved. A detailed review of the topic is found in the Pharmacology/Toxicology team's review.

7.6.2 Human Reproduction and Pregnancy Data

Although appropriate contraception was specified in all the protocols, two patients were exposed to ecallantide with conception estimated to have occurred within 6 days of the last ecallantide dose for 1 patient and within 28 days of the first dose and 15 days prior to the second dose. Both patients were reported to have normal pregnancies with delivery of healthy, full-term infants. An

additional ongoing 3rd pregnancy is reported for DX-88/19 (EDEMA4 OLE). No other information on ecallantide use in pregnancy or lactation in humans is available.

7.6.3 Pediatrics and Effect on Growth

No formal studies in pediatrics or effect on growth were conducted for ecallantide. Although the inclusion criteria for EDEMA2, EDEMA3, and EDEMA4 included patients down to the age of 10 years, few pediatric patients were studied in the clinical development program. The nature and number of AEs observed in children appeared comparable to the adult population but the low number of patients limits conclusions about safety in this subpopulation. The limitations of the safety database in regards to the pediatric population numbers are discussed more fully in Section 7.2.1.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No data is presented on overdose, drug abuse potential, withdrawal and rebound. In the CTS studies, ecallantide doses of up to 100.8 mg IV have been administered to patients without evidence of added toxicity per the Applicant. Given the expected mode of administration through a healthcare provider and intermittent use for HAE, combined with the short half-life of the drug, overdose, drug abuse, and withdrawal are not anticipated.

7.7 Additional Submissions

The Applicant submitted a safety update on December 19, 2008. The update contained information on Study DX-88/19, the ongoing OLE for EDEMA4, and Study DX-88/16, the cardiac surgery study.

Study DX-88/19 (EDEMA4 OLE)

The BLA submission originally contained 219 unique HAE patients who had been treated with ecallantide. The update included an additional 22 ecallantide-naïve patients treated with ecallantide in the EDEMA4 OLE. Of these 22 patients, 11 are new patients who were not enrolled in the double-blind phase of EDEMA4. As of November 10, 2008, a total of 237 doses have been administered to treat 219 acute HAE attacks in the EDEMA4 OLE. No deaths were reported and no patients discontinued prematurely from the study due to an adverse event. Adverse event data from the safety update, including information on new cases of hypersensitivity, are included in the SAE descriptions and adverse event frequency calculations in Sections 7.3 and 7.4. Limited clinical laboratory parameter data from the safety update appeared consistent with the data presented for the placebo-controlled population (Analysis Population II) and the general ecallantide HAE population (Analysis Population I), so these data are not presented in detail in this review. Updated adverse event frequencies for the patients included in the December 19, 2009 submission were included in the response to information request dated February 12, 2009.

Study DX-88/16 (CTS study)

DX-88/16 was a Phase 2 randomized, double-blind, placebo-controlled trial of ecallantide in patients undergoing cardiopulmonary bypass for coronary artery bypass grafting, single valve repair, or single valve-replacement. Patients were randomized to received intravenous low-dose (maximum 15.6 mg dose), high-dose (maximum 91.0 mg dose), or placebo. A total of 69 patients were treated in the study. The safety update for the recently completed CTS study did not show any new hypersensitivity reactions aside from the case of anaphylaxis reported in the BLA submission.

8 Postmarketing Experience

EcCallantide is currently not marketed for any indication.

9 Appendices

9.1 Literature Review/References

The Applicant provided 37 literature references with electronic copies regarding hereditary angioedema, the role of kallikrein in HAE, and anaphylaxis. In addition, the reviewer performed an electronic PubMed search [search term: ecallantide] that yielded 13 literature reports, two of which overlapped with the references provided by the Applicant. These reports were reviewed briefly and did not suggest additional safety concerns.

9.2 Labeling Recommendations

Proposed package labeling has been included in this submission [1.14]. The sponsor seeks an indication for the "treatment of acute attacks of hereditary angioedema (HAE). (b) (4)" As the clinical review's recommended action is a Complete Response, a line-by-line labeling review is not included. The following are more general comments on the proposed label:

1. The label should include a Boxed Warning about anaphylaxis and provide strict recommendations on use in supervised medical setting with appropriate monitoring for hypersensitivity reactions.
2. Section 1, Indications and Usage, does not specify the intended age range. The recommendations of the clinical review are to limit usage in adults pending further evaluation in a pediatric population. The additional descriptive statement that Kalbitor eliminates or reduces HAE attack symptoms should also be removed.
3. Section 2.1, Recommended Dosing, The recommended dosing does not specify the interval for repeat administration. In the clinical studies, 1 to 2 doses within a 24-hour period for a single HAE attack were administered.
4. Section 4, Contraindications, states that ecallantide should not be administered to patients who have a known hypersensitivity (b) (4)

A similar statement is made (

(b) (4)

(b) (4)

6. Section 6.1, Clinical Trials Experience, should clearly indicate that several patients were enrolled in both EDEMA3 and EDEMA4.
7. Section 14, Clinical Studies, includes a detailed description of the MSCS and TOS endpoints and presents data from the two pivotal studies, EDEMA4 and EDEMA3, as well as composite data from the efficacy studies. The p-values presented for EDEMA3 are based on the ITT-as-treated population with data imputation. Given the difficulty with interpretation of the TOS efficacy variable and EDEMA3's failure to win on its prespecified primary endpoint (TOS), the description of TOS and presentation of data from EDEMA3 in the clinical studies section may be problematic. A general statement stating that EDEMA3 was of similar design to EDEMA4 and supportive of safety and efficacy may be less likely to cause confusion. If included, the analysis should be based on ITT population, not the ITT-as-treated population. Furthermore, efficacy statements based on pooled analyses, open-label treatment, and post-hoc subgroup analyses should not be included.

Reviewer's comments: The proposed label follows the new content and format requirements.

9.3 Advisory Committee Meeting

A Pulmonary and Allergy Drug Advisory Committee (PADAC) Meeting was held on February 4, 2009, to discuss the efficacy and safety results with a panel of 13 outside experts in a public forum. In addition to formal presentations from the Applicant and the Division's clinical reviewer and statistical reviewer, the meeting included personal testimonies from HAE patients and patient advocates that highlighted the paucity of treatments for this life-threatening and often debilitating condition. The 5 questions posed to the Committee and a tabulation of votes are shown below:

Table 30 Questions and voting results for February 4, 2009 Pulmonary and Allergy Drug Advisory Committee Meeting on ecallantide			
Questions	Votes		
	Yes	No	Abstain
Q1. Discuss the hypersensitivity and anaphylaxis data and provide recommendations for further evaluation, if necessary.	Non-voting question		
Q2. Does the data provide substantial and convincing evidence that ecallantide provides a clinically meaningful beneficial effect on acute attacks of hereditary angioedema?			
a. In patients 18 years of age and older <i>If not, what further efficacy data should be obtained?</i>	8	4	1
b. In patients 10 to 17 years of age <i>If not, what further efficacy data should be obtained?</i>	3	10	0
Q3. Has the safety of ecallantide been adequately assessed for the treatment of acute attacks of hereditary angioedema?			
a. In patients 18 years of age and older <i>If not, what further safety data should be obtained?</i>	5	8	0
b. In patients 10 to 17 years of age <i>If not, what further safety data should be obtained?</i>	2	11	0
Q4. Do the safety and efficacy data provide substantial and convincing evidence to support the approval of ecallantide for the treatment of acute attacks of hereditary angioedema?	6	5	2
<i>If not, what additional information is necessary to support approval?</i>			
Q5. Does the committee have recommendations regarding the following:	Non-voting question		
a. Labeling			
b. Risk mitigation strategies for hypersensitivity and anaphylaxis reactions			
c. Potential for self-administration			
d. Other			

In general, the committee acknowledged the limitations of the efficacy and safety data, particularly in children. The vote on Question 4 regarding approval of ecallantide for the proposed indication was split (Yes 6, No 5, Abstain 2). However, the comments from the PADAC suggested that given the difficulty in conducting prospective trials in HAE and the unmet medical need, the Committee felt that there was enough information to support approval in adult HAE patients with the caveat of close monitoring and the Applicant's safe use plan. The Applicant's presentation at the PADAC meeting indicated plans for a mandatory registry patients and restricted distribution via a central pharmacy to help insure appropriate supervision of dosing and to limit off-label use. The Committee also stressed the importance of obtaining long-term immunogenicity data, assessing potential cross-reactivity with endogenous TFPI, and refining anti-drug antibody assays with the goal of developing effective screening methods for patients at risk for hypersensitivity reactions.

The clinical review agrees with the recommendations of the Committee, noting that the safety profile for the proposed dose would be acceptable with appropriate risk management strategies for hypersensitivity reactions. However, the Applicant did not provide a detailed risk management program in the application, and there was insufficient time during the Priority

Clinical Review
Susan Limb, MD
BLA 125277, N0002
Kalbitor™ (ecallantide)

Review period to accommodate a later submission with review and approval of the plan from the Agency. A risk management strategy involving a registry and restricted distribution, as proposed by Dyax, is quite complex and will take time for the Agency and Dyax to come to agreement. Therefore, the clinical review recommends a Complete Response action at this time.

10 Individual Study Reviews

10.1 Individual Study Report: EDEMA0

10.1.1 Study Protocol: DX88/2 (EDEMA0)

10.1.1.1 Administrative information

- Title: Open-label, single ascending IV dose study to assess the tolerability and efficacy of DX88 administered following the onset of peripheral and/or facial edema or abdominal symptoms in patients with angioedema
- Study dates: March 27, 2001 to April 9, 2003
- Study sites: 4 sites (Germany, Italy, Spain)
- Study report date: June 7, 2007

10.1.1.2 Objectives/Rationale

- Assess the tolerability and efficacy of ascending single doses of ecallantide in HAE
- Determine the PK profile of ascending single doses of ecallantide in HAE/AAE patients

10.1.1.3 Study design overview

EDEMA0 was an open-label, single ascending dose study of ecallantide in patients with acute HAE and acquired angioedema (AAE) attacks. Three patients were enrolled at each dose level (10, 40, and 80 mg administered intravenously over 10 minutes) within 10 hours of onset of an HAE/AAE attack. The dose level was increased serially after the safety and efficacy data for the lower preceding dose level had been reviewed. A total of 9 patients (3 per dose group) were enrolled among the dose groups.

10.1.1.4 Study population

Adult patients with HAE or AAE.

Inclusion criteria

- Age 18 years or older
- Previously confirmed diagnosis and history of HAE OR
- AAE defined as acquired function C1 INH deficiency with
 - A history of recurrent angioedema
 - Functional deficiency of C1 INH (<50% normal value)
 - Normal or low level of C1q
 - No evidence of genetic disease
- Presentation within 10 hours of onset of attack

Exclusion criteria

- Life-threatening episode of angioedema
- Use of prophylactic aspirin
- Pregnancy or breastfeeding

- Serum creatinine >200mcM/L

10.1.1.5 Study treatments

Single 10-minute IV infusion of 10, 40, or 80 mg ecallantide.

Reviewer's comment: Dose selection was based on PK sampling from Phase 1 data. An 18 mg dose was estimated to achieve a plasma concentration of 500nm, the same concentration estimated for the total amount of circulating pre-kallikrein.

10.1.1.6 Study procedures

The following table summarizes the schedule of procedures and assessments.

Table 31 EDEMA0: Schedule of assessments											
	Screen	Pre-dose Day 0	Treatment visit	Post-treatment day*					Post-treatment		
			24-hf post-treatment period	2	3	4	5	6	Wk 1	Wks 4-6	
Pregnancy test	X	X								X	
History	X										
Physical exam	X		24 hr							X	
Temperature	X	X	15, 30 min and 1, 2, 4, 8, 12, 24 hr							X	
BP and HR	X	X	15, 30, 45 min and 1, 2, 4, 8, 12, 24 hr							X	
ECG	X	X	2x during first 8 hr then at 24 hr							X	X
Previous and concomitant medications	X	X		X	X	X	X	X	X	X	X
Angioedema sx assessment	X	X	5, 10, 15, 30 min and 1, 2, 4, 6, 8, 12, 16, 20, 24 hr								
Digital photographs ¹		X	30 min then hourly until attack regression, then hourly for 3 hrs							X	
Investigator pain assessment	X	X	Q15min for first 4 hrs								
McGill Pain Questionnaire ²	X	X	24 hr								
Abdominal ultrasound ²	X	X	Once during 24 hr	X						X	
Waist measurement ²	X	X	Once during 24 hr							X	
PK sampling	X	X	5, 10, 15, 30 min, 1, 2, 4, 6, 8, 12, 24 hr								
Coagulation labs	X	X	1, 4, 24 hr							X	
Special labs ³	X	X	1, 4, 8, 24 hr	X						X	
Routine labs ⁴	X	X	24 hr							X	
Patient diary No.1	Dispense	Collect									
Patient diary No.2		X	Dispense after 24 hr							Collect	
AEs	X	X	X	X	X	X	X	X	X	X	X

* By telephone or if logistically feasible by visit day

¹ At dosing for all patients, but at follow-up only in cases of peripheral or facial attack

² At screening for all patients, but at follow-up only in cases of abdominal attack

³ C1-INH, C4, kallikrein

⁴ Routine chemistry, hematology, and urinalysis

Source: dx-88-2-csr-body.pdf, Table 9-2

10.1.1.7 Efficacy parameters

- Attack classification and symptom assessment by the investigator and verified against the patient diary
- Digital photography in cases of peripheral or facial attacks
- Visual Analog Scale (VAS) for pain by investigator
- McGill Pain Questionnaire (GI attacks)
- Abdominal ultrasound (GI attacks)
- Waist circumference (GI attacks)
- Patient diaries
 - Attack site
 - Pain, difficulty in motion, appetite, sleep, general function, and global satisfaction (on VAS)

10.1.1.8 Safety parameters

- AEs
- ECG
- Routine clinical laboratory tests (glucose, urea, creatinine, total bilirubin, AST, ALT, GGT, alkaline phosphatase, creatinine kinase, total protein, CBC with differential, urinalysis)
- Pregnancy test
- Special labs: C1 INH (antigenic and functional), C4, kallikrein and consumption of high molecular weight kininogen (HMWK; surrogate marker)
- Anti-ecallantide non-IgE antibody

10.1.1.9 PK parameters

- C_{max}
- T_{max}
- $T_{1/2}$
- Terminal elimination rate constant
- AUC

10.1.1.10 Dose Review

A dose review group consisting of the sponsor, its agent (b) (4), and the investigators was to review the safety and efficacy data at each dose level. The original protocol stated that the group would generate a written report for each discussion, but the Applicant states that these reports have not been recovered despite due diligence.

10.1.2 Results

10.1.2.1 Study patients

A total of 48 patients were screened. Treatment was restricted to the first 9 patients who returned for treatment of an acute attack, 3 per dose level. No patients discontinued from the study. Four male and 5 female patients enrolled; 7 had a diagnosis of HAE and 2 patients treated with the 80 mg dose had a diagnosis of AAE. The mean age was 51.8 years (range 31 to 67 years). Three patients presented with facial HAE attacks, 2 patients reported abdominal

symptoms predominantly, 2 patients reported peripheral symptoms, and 1 patient reported a mix of peripheral and abdominal involvement.

10.1.2.2 Efficacy endpoint outcomes

The primary efficacy endpoint was the proportion of patients who reported beginning of resolution of attack symptoms by 4 hours post-dose. The beginning or resolution was the time at which the first sign and/or symptom present at dosing was no longer present. Using this definition, 2 patients in the 10 mg reported beginning of attack resolution by 4 hours, compared to 1 patient in the 40 mg group and 1 patient in the 80 mg group.

Reviewer's comment: Given the small numbers of patients and lack of a control, no conclusions can be made about efficacy or relative dose response.

10.1.2.3 Safety outcomes

No deaths were reported in the study. A total of 18 AEs were reported by 4 patients: 4 AEs among 2 patients in the 10 mg group and 14 AEs among 2 patients in the 40 mg group. One AE, cough, was recorded in 2 patients. The other AEs included a range of organ systems: hypertension NOS, injection site reaction, nasopharyngitis, dry mouth, sleep apnea, iron deficiency anemia, pyrexia, hemoglobin decreased, asthenia, breast mass NOS, breast pain, irregular menstruation, and rhinitis NOS.

One SAE, anaphylactoid reaction, was reported in Patient 305 after receipt of the 40 mg dose. The patient initially presented for treatment of acute genital edema. Within 5 minutes of the start of the infusion, she reported pruritus, which rapidly progressed to urticaria, edema, dysphagia, dyspnea, enteritis, and acute abdominal pain with an urge to defecate. She was treated with epinephrine, polaramine IV, and hydrocortisone IV. She was hospitalized overnight for observation prior to discharge without further sequelae. The investigator independently performed immunoblotting and detected both IgE and non-IgE antibodies to ecallantide. A separate ELISA assay performed by the applicant was negative for ecallantide or *P. pastoris* antibodies. No rechallenge procedure was attempted.

10.1.3 Study summary and conclusions

EDEMA0 demonstrated that IV doses of ecallantide up to 80 mg were tolerated in a sample of 9 adult patients without major toxicity with the exception of anaphylaxis. Anaphylaxis was observed to occur even upon initial exposure. No conclusions regarding efficacy could be made given the small number of participants and lack of a control arm.

10.2 Individual Study Report: EDEMA1

10.2.1 Study Protocol: Study DX88/4 (EDEMA1)

10.2.1.1 Administrative information

- Title: An ascending four dose placebo controlled study to assess the efficacy and tolerability of DX-88 (ecallantide) administered following onset of acute attacks of HAE
- Study Dates: October 22, 2002 to May 4, 2004

- Study sites: 29 sites in the US, 1 site in Belgium, 1 site in Israel
- Study report date: June 20, 2004

10.2.1.2 Objectives/Rationale

- Determine an effective dose of ecallantide in patients experience acute HAE attacks

10.2.1.3 Study design overview

EDEMA1 was a randomized, placebo-controlled, double-blind ascending dose-ranging study of ecallantide in patients ≥ 10 years of age with acute HAE attacks. The study evaluated 4 dose groups (5, 10, 20, and 40 mg/m² IV) of ecallantide compared to placebo. Twelve patients per dose level were treated; 2 assigned to placebo and 10 to ecallantide. Patients received a single dose and were asked to assess their symptoms during a resident period and 2-6 days post dose, with additional follow-up visits at 1, 2, and 4 weeks.

10.2.1.4 Study population

Patients 10 years of age or older presenting within 4 hours of onset of HAE symptoms of at least moderate severity.

Inclusion criteria

- 10 years of age or older
- Confirmed diagnosis of HAE with at least 1 clinical and 1 laboratory criterion:
 - Clinical criteria
 - Recurrent, self-limited, non-inflammatory angioedema lasting more than 12 hours without urticaria
 - Recurrent abdominal pain lasting more than 6 hours without organic disease
 - Recurrent laryngeal edema
 - Familial history
 - Laboratory criteria
 - C1-INH functional level <50% normal
 - Historical documentation of C1-INH mutation

Exclusion criteria

- Serious intercurrent illness or active infection
- Serum creatinine >10% ULN or LFT >2x ULN
- AAE
- Receipt of investigational drug or device within 30 days
- Pregnancy or breastfeeding
- Patients previously treated with ecallantide

10.2.1.5 Study treatments

Single 10 minute infusion of ecallantide (5, 10, 20, or 40 mg/m²; maximum dose of 100 mg) or placebo.

10.2.1.6 Study procedures

The table below summarizes the schedule of procedures:

	Screen	Pre-dose	Post-treatment evaluation												
			0-1h	1-24 hours post-dose								Day 2-6 ¹	Day 7	Wk 2	Wk 4
				1	2	4	6	8	12	24					
Pregnancy test	X	X													
Medical history	X														
Physical exam	X										X		X	X	X
Waist measurement	X		X												
Vital signs	X	X	X	X	X	X	X	X	X	X	X		X	X	X
ECG	X	X				X									
Symptom record		X	X	X	X	X	X	X	X						
Diary	Issue	review													
Study drug			X												
Photograph ²		X	X	X	X	X	X	X	X						
VAS ³		X	X	X	X	X									
McGill Pain Questionnaire ³		X		X		X									
Urinalysis	X	X	X												
Concomitant meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK sampling		X	X	X	X	X	X	X	X	X					
Routine labs	X	X							X						
Special labs ⁴	X	X		X		X		X		X					
Coagulation labs	X	X		X		X		X		X		X	X	X	
Antibody test ⁵	X	X												X	X

¹ Phone evaluation

² Peripheral attacks only

³ abdominal attacks only

⁴ Special labs: C1-INH, C4, kallikrein, HMWK

⁵ Anti-ecallantide non-IgE antibodies

Source: dx-88-4-csr-body.pdf, Table 9-1

10.2.1.7 Efficacy parameters

- Percentage of patients reporting significant improvement at the primary attack location within 4 hours after drug infusion.

10.2.1.8 Safety parameters

- AEs
- ECG
- Routine clinical laboratory tests (glucose, urea, creatinine, total bilirubin, AST, ALT, GGT, alkaline phosphatase, creatinine kinase, total protein, CBC with differential, urinalysis)
- Pregnancy test

- Special labs: C1 INH (antigenic and functional), C4, kallikrein and consumption of high molecular weight kininogen (HMWK; surrogate marker)
- Anti-ecallantide non-IgE antibody

10.2.1.9 PK parameters

- C_{max}
- T_{max}
- $T_{1/2}$
- Terminal elimination rate constant
- AUC

10.2.1.10 Data safety monitoring board

An independent DSMB consisting of 3 clinical pharmacologist and/or HAE experts plus a 4th independent member was organized. A blinded DSMB determined whether to proceed to the next dose level at the end of each dose cohort. A decision to terminate the study for reasons of lack of safety and efficacy was part of the review.

10.2.2 Results

10.2.2.1 Study patients

Patient disposition

A total of 140 patients were screened and the first 48 patients returning for treatment of an acute HAE attack were enrolled. The 48th and 49th patients presented at approximately the same time so a total of 49 patients were treated. Forty-three patients completed the full 4 weeks of the study, while 6 patients discontinued early. Of the 6, 3 were lost to follow-up and 2 refused to return for follow-up and were coded as non-compliant. The final patient, Patient 2201 died due to renal failure. The patient was a renal transplant patient who suffered from chronic rejection of the transplant prior to enrollment in the study.

Demographics

Thirty-eight (77.6%) patients were female. The majority (n=43, 87.8%) were Caucasian, 4 (8.2%) were Hispanic, 1 (2.0%) was black, and 1 (2.0%) was categorized as other. The mean age was 32.5 years (range 11-62 years). On average, patients presented within 134 minutes of onset of symptoms. Primary attack locations were reported as follows: n=23 (47%) abdominal, n=22 (45%) peripheral, and n=4 (8%) laryngeal. The various locations were evenly distributed in the ecallantide and placebo treatment groups. Nine patients reported HAE symptoms in other locations in addition to the designated primary attack site.

10.2.2.2 Efficacy endpoint outcomes

The proportion of patients reporting a significant improvement (“successful outcome”) for the primary attack location at 4 hours post-dose was the primary efficacy outcome assessed. Overall, in the ecallantide group, 29 of 40 (72.5%) reported significant improvement compared to 2 of 8 patients (25.0%) in the placebo group (p=0.0169). The proportion of successful outcomes by dose level is shown in

Table 33 EDEMA1: Proportion of successful outcomes by dose cohort

Dose level	Ecaltantide	Placebo	P
5 mg/m ²	8/10 (80%)	1/2 (50%)	0.454
10 mg/m ²	5/10 (50%)	0/2	0.470
20 mg/m ²	7/10 (70%)	0/2	0.152
40 mg/m ²	9/10 (90%)	1/2	0.318

Source: dx-88-4-csr-body.pdf

Reviewer's comment: The comparison of the pooled ecaltantide and placebo groups support the efficacy of ecaltantide. The comparisons by dose cohort however are limited by the small sample sizes and do not permit a controlled evaluation of dose response.

10.2.2.3 Safety outcomes

A total of 124 AEs were reported. Thirty-nine of 49 patients (79.6%) reported at least 1 AE. In the ecaltantide arm, 32 of 41 (78.1%) reported at least 1 AE compared to 7 of 8 (87.5%) in the placebo group. The most commonly reported AE was headache, reported by 6 patients (14.6%) of the ecaltantide group. Other AEs reported in at least patients included the following: diarrhea NOS, vomiting NOS, abdominal pain NOS, nausea NOS, upper respiratory tract infection, cough, and allergic rhinitis.

A total of 5 SAEs were reported for 5 ecaltantide patients.

- Patient 1303 (20 mg/m²) had allergic rhinitis (sneezing, itchy throat, congestion, nasal drainage, and shortness of breath) with throat edema within 3 minutes of start of infusion. The patient was treated with 2 doses of epinephrine and cetirizine. The patient was discharged 8 hours later without further sequelae.
- Patient 501 (10 mg/m²) was hospitalized for an HAE attack 21 days after treatment with ecaltantide.
- Patient 2205 (5 mg/m²) was treated with ecaltantide for an abdominal attack. Twenty-three days later, the patient was hospitalized for swelling of the chest and difficulty breathing. Two days after admission, the patient had seizure. The patient was discharged 2 days after the event without sequelae.
- Patient 2510 (20 mg/m²) was treated with ecaltantide for an abdominal attack. Twenty-seven days later, the patient presented for follow-up and was noted to have an ECG suggestive of ischemic changes. Echocardiogram, angiogram, and repeat ECG showed no sign of cardiac ischemia.
- Patient 2201 was a study death and is described in detail below.

One death was reported. Patient 8804022001 had a history of dual nephrectomy and kidney transplant 1 year prior to enrollment. The patient was reported to have chronic rejection of the transplant and died of chronic renal failure 29 days after administration of ecaltantide.

Reviewer's comment: Patient 1303's case description meets diagnostic criteria for anaphylaxis.

10.2.3 Study summary and conclusions

EDEMA1 demonstrated that IV doses of ecallantide up to 40 mg/m² were tolerated without major toxicity, with the exception of anaphylaxis. The risk of anaphylaxis was present even upon initial exposure. In a pooled analysis of ecallantide versus placebo, ecallantide appears to have efficacy. There was no clear dose response among the 4 doses tested.

10.3 Individual Study Report: EDEMA2

10.3.1 Study Protocol: EDEMA2/DX-88/5

10.3.1.1 Administrative information

- Title: Study DX-88/5: EDEMA2: Evaluation of DX-88's effects in mitigating angioedema – An open-label study to assess the efficacy and tolerability of repeated doses of DX-88 (recombinant plasma kallikrein inhibitor) in patients with HAE
- Dates: November 13, 2003 to January 24, 2003
- Multicenter: US, Europe, and Canada
- Study report date: July 2, 2008

10.3.1.2 Objectives/Rationale

- Assess the safety and efficacy of repeated dosing of DX-88 (ecallantide) in HAE acute attacks

10.3.1.3 Study design overview

EDEMA2 was an open-label repeat dose study of ecallantide for the treatment of acute HAE attacks. Qualified patients presenting within 4 hours of the onset of an acute attack of at least moderate severity were treated with a single dose of ecallantide (Dose A). If no improvement was noted within 4 hours, a second dose (Dose B) could be administered. Patients could receive a maximum of 20 doses for separate attacks.

10.3.1.4 Study population

The study was based on planned treatment of 240 attacks, which consisted of 77 patients.

Inclusion criteria

- Age 10 years or older
- Confirmed physician diagnosis of HAE
- Presentation within 4 hours of onset of symptoms
- HAE attack of at least moderate severity

Exclusion criteria

- Serious intercurrent illness or active infection
- Serum creatinine >110% ULN and/or not <50% of calculated Cr clearance or liver transaminases >2x ULN
- Receipt of an investigational drug or device other than ecallantide within 30 days prior
- Pregnancy or active breastfeeding
- Acquired angioedema

- Patients who had not completed their Day 8 follow-up procedures for a previously treated attack

Reviewer's comment: The diagnostic criteria for HAE and exclusion of AAE are not as rigorous as those specified for the Phase 3 program. For a Phase 2 study focused primarily on safety of repeated doses, these diagnostic criteria are acceptable; however, the extent to which EDEMA2 results can be used to support the efficacy of repeated doses is limited.

10.3.1.5 Study treatments

Escalating IV doses (5 mg/m², 10 mg/m², or 20 mg/m²) were administered by sequential dose cohorts. The transition from each dosage cohort to the next was based on the review of safety and efficacy in the EDEMA1 study by the DSMB. For example, once the DSMB had determined the 10 mg/m² dose level safe in EDEMA1, patients enrolled in EDEMA2 were then given 10 mg/m². Patients were not restricted to a particular dose cohort and could receive repeated doses of ecallantide at a different dose level from the one received previously. From July 2005 to study conclusion, IV infusions were changed to ecallantide 30 mg SC fixed dose. Patients who had an incomplete response were eligible for Dose B.

10.3.1.6 Study procedures

The following table outlines the schedule of procedures.

EDEMA2	Screen	Enroll	Post-dosing evaluation			Follow-up day		
			Post-dosing (hr)			Days 2-6 (phone)	Day 7	4 wks
			0-1	2	4			
Informed consent	X							
Urine pregnancy test		X						
History, demographics	X							
Physical exam	X				X		X	X
Vital signs	X	X	X	X	X		X	X
ECG	X	X			X		X	X
Urinanalysis	X	X						
Dosing			X					
Digital photograph		X	X	X	X			
VAS		X	X	X	X			
McGill Pain Questionnaire		X						
Concomitant meds	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X
Blood samples								
• Chemistry	X	X					X	X
• CBC/diff	X	X			X		X	X
• Coag panel	X	X			X		X	X
• Antibody levels	X	X	X		X			
• PK test		X	X	X	X		X	X

Source: dx-88-5-csr-body.pdf, Table 4

10.3.1.7 Efficacy parameters

Primary efficacy endpoints

- Proportion of successful outcomes (i.e. attack resolution begun by 4 hours after a single dose and maintained for greater than 24 hours after a single dose)
- Proportion of patients who have a partial response (i.e. an initial response to dosing followed by a relapse 4 to 24 hours after the dosing)

Secondary efficacy endpoints

- The proportion of patients who respond to a second dose of ecallantide after an initial partial response
- Time to resolution onset of each acute attack as determined by patient report
- Time to resolution onset of each acute attack as determined by digital photography (optional) or pain scores in abdominal attacks
- Development of ecallantide antibodies
- Relationship between PK and clinical effect

10.3.1.8 Safety parameters

- Adverse events
- Laboratory assessments
- Vital signs
- ECG
- Physical examination
- Development of antibodies to ecallantide or *P. pastoris*

10.3.1.9 Statistical plan

Descriptive statistics were used to summarize patient demographic data and other baseline characteristics. Efficacy analyses were based on the patients' first attack in EDEMA2, in the interest of keeping efficacy comparisons among dose groups independent of one another. The unit of analyses for most endpoints was by treatment episode, not by individual patient.

10.3.2 Results

10.3.2.1 Protocol deviations

A number of protocol deviations were reported. The most common deviation was the administration of study drug outside the protocol window. In 4 cases, dosing assignment was not obtained prior to dose. Patient 1804 received 10mg/m² ecallantide as prophylaxis prior to jaw surgery as compassionate use.

In addition, 7 patients were granted exception of inclusion criteria in presenting more than 4 hours after onset of HAE attack. Two patients became pregnant during the study: Patient 6299 had her last dose of ecallantide on April 8, 2005 and gave birth to a healthy male infant on (b) (6). Patient 6299 received ecallantide on November 2, 2005 but soon after found out she was pregnant despite a negative pregnancy test at screening, with an estimated date of conception in (b) (6). She delivered a healthy male infant on (b) (6).

Reviewer's comment: The deviations are not likely to significantly impact the results of the study.

10.3.2.2 Datasets analyzed

The ITT and safety analysis are based on all study-treated attacks. The PP population consists of all study-treated attacks with no major protocol violation. The difference between these 2 populations is 1 episode.

10.3.2.3 Study patients

A total of 77 patients from 26 study sites were enrolled and treated for 240 HAE attacks. This population constitutes the ITT population. Twenty of the 77 (26.%) had had prior exposure to ecallantide.

Baseline demographics

Table 35 EDEMA2: Patient demographics					
	5 mg/m ² N=14	10 mg/m ² N=40	20 mg/m ² N=9	30 mg N=14	Overall N=77
Age					
Mean (SD)	34.6 (13.6)	31.7 (15.2)	28.7 (12.4)	38.0 (11.8)	33.0 (14.1)
Range	11-53	13-78	12-52	10-55	10-78
Sex (N,%)					
Male	6 (42.9%)	11 (27.5%)	4 (44.4%)	8 (57.1%)	50 (64.9%)
Female	8 (57.1%)	29 (72.5%)	5 (55.6%)	6 (42.9%)	27 (35.1%)
Race (N,%)					
White	10 (71.4%)	38 (95.0%)	8 (88.9%)	11 (78.6%)	67 (87.0%)
Black	3 (21.4%)	2 (5.0%)	0	0	5 (6.5%)
Hispanic	1 (7.1%)	0	1 (11.1%)	2 (14.3%)	4 (5.2%)
Asian	0	0	0	1 (7.1%)	1 (1.3%)

Source: dx-88-5-csr-body.pdf, Section 11.2.1, Table 7

HAE history

The 77 patients enrolled in EDEMA2 ranged in age from 10 to 78 years. Of the 77, 68 (88%) had a diagnosis of Type I HAE, 8 (10.4%) had Type II HAE, and 1 patient was reported as unknown due to the absence of diagnostic or confirmatory laboratory testing. The 77 patients experienced a mean attack frequency of 2.5 attacks/month. The mean duration of the most recent HAE attack was 47.9 hours (SD 37.9). The most common locations of HAE attack by history was abdominal (48.1%), followed by peripheral (32.5%). One patient reported laryngeal attack as the most common site of attack. Fourteen patients (18.2%) reported that a combination of attack sites was the most common presentation.

The most common concomitant treatments for HAE reported by the patients included attenuated androgens oxandrolone (n=6) and stanozolol (n=4), hydrocodone (n=6), oxycodone (n=2), aminocaproic acid (n=2), and fresh frozen plasma (n=2).

HAE presentation

Peripheral HAE attacks were reported as the first study-treated attacks for 35 (45.5%) patients. Abdominal attacks were reported for 32 (41.6%) patients. Ten (13.0%) patients presented with laryngeal attacks for their first study-treated attack. The total number of study-treated HAE attacks at each dose level and location is shown below.

Table 36 EDEMA2: Attack site of 240 study-treated HAE attacks

Primary location	Intravenous			Subcutaneous	Overall N=77
	5 mg/m ² N=14	10 mg/m ² N=40	20 mg/m ² N=9	30 mg N=14	
Peripheral	14 (58.3%)	57 (40.4%)	5 (33.3%)	17 (28.3%)	93 (38.8%)
Abdominal	10 (41.7%)	65 (46.1%)	5 (33.3%)	33 (55.0%)	113 (47.1%)
Laryngeal	0	19 (13.5%)	5 (33.3%)	10 (16.7%)	34 (14.2%)

Source: dx-88-4-csr-body.pdf, Section 11.2.5.1, Table 13

10.3.2.4 Efficacy endpoint outcomes

Primary efficacy endpoint: Successful and partial outcomes

Successful outcome

A successful outcome was defined as onset of resolution within 4 hours of dosing and continuing for 24 hours of dosing. Of the 240 treated attacks, 165 attacks (68.9%) were reported to have a successful outcome. Among the 4 dosage levels, the 30 mg SC dose had the highest proportion of successful outcomes (49 of 60 attacks, 81.7%), followed by the 10 mg/m² IV and 20 mg/m² IV doses (68.1% and 60.0%, respectively). The 5 mg/m² IV dose had 11 of 24 attacks (45.8%) with successful outcomes.

Reviewer's comment: Based on EDEMA3, the 30 mg SC dose is the most appropriate for study in the Phase 3 program. The 30 mg SC dose corresponds approximately to a 15 mg/m² dose in an average-sized adult.

Partial response

Another 41 of 240 attacks (17.1%) were reported as having a partial response, meaning a response to dosing for at least 1 symptom at the primary attack site within 4 hours of treatment followed by a relapse within 24 hours or receipt of Dose B. A partial response was reported for 11.7% of the SC dose-treated attacks, 26.7% for the 20 mg/m² IV-treated attacks, 15.6% of the 10 mg/m² IV-treated attacks, and 33.3% of the 5 mg/m² IV-treated attacks. By attack site, peripheral attacks were reported to have a 23.7% (22 of 93 attacks) partial response rate, followed by 13.3% (15 of 113 attacks) for abdominal attacks, and 11.8% (4 of 34 attacks) for laryngeal attacks.

Secondary efficacy endpoints

Dose B

Of 31 evaluable attacks treated with Dose B, 22 were reported to have a positive response at 4 hours. Data at 24 hours was not collected systematically for Dose B.

Time to beginning of attack resolution by patient report

Time to beginning of attack resolution was defined as the time within 4 hours of the end of ecallantide treatment when the patient first reported relief of symptoms at the primary attack site. Patients receiving emergency intervention were censored at the time of therapy. Overall, the median time to beginning of attack resolution was 43.0 minutes for Attack 1, 38.0 minutes for

Attack 2, 37.5 minutes for Attack 3. Attacks treated with the 30 mg SC dose had a median time of 37.5 minutes for Attack 1 and 18 minutes for Attack 3.

Reviewer's comment: The time to beginning of attack resolution does not show a clear dose response among the different dose groups, although the 30 mg SC dose appears to have performed the most consistently. There does not appear to be a decrease in efficacy from the first attack to the 3rd attack, although the number of treated attacks also decreased from 14 to 6, making the comparison less certain. It may be that efficacy is consistent over multiple treatments; alternatively, there may be a core group of responders to drug whereas patients with less pronounced responses may elect not to receive additional doses.

Abdominal attack responses

A number of different instruments were used to assess response to abdominal attacks, including a Visual Analog Scale (VAS) for pain, the McGill Pain Questionnaire, and change in waist girth. According to VAS measurements, pain was reduced by 83.2%, 79.5%, and 66.8% at 4 hours post-dosing for Attacks 1, 2, and 3, respectively. These results corresponded with an average reduction of 2 scale points (total of 0 to 5) on the McGill Pain questionnaire at 4 hours. For Attacks 1 and 2, an average 2 to 4% reduction in waist circumference was measured at 4 hours; for Attack 3, the decrease in average waist circumference was negligible.

Reviewer's comment: These measures of various aspects of abdominal attacks are generally supportive. It is worth noting, however, that neither the VAS nor the McGill Pain Questionnaire are PRO instruments validated for use in HAE, nor is waist circumference a routinely utilized clinical measure.

Plasma ecallantide concentrations at 1, 2, and 4 hours

Plasma concentrations at several timepoints for the different doses are shown in the table below.

Table 37 EDEMA2: Plasma ecallantide concentrations (ng/ml) at 1, 2, and 4 hours post-dose by dosage level (PP population)

Dosage level	1 hour	2 hours	4 hours
5 mg/m² IV			
N	23	23	24
Mean (SD)	192.5 (109.6)	135.1 (234.0)	23.0 (22.4)
Median	191.4	84.3	19.1
Range	30.0-402.1	12.1-1165.7	0-66.9
10 mg/m² IV			
N	138	138	139
Mean (SD)	602.8 (778.1)	265.2 (217.8)	86.1 (65.8)
Median	415.4	222.0	71.2
Range	0-5438.2	0-1768.5	0-447.8
20 mg/m² IV			
N	11	14	14
Mean (SD)	1235.1 (1205.6)	276.2 (121.3)	170.4 (186.1)
Median	729.0	265.7	104.4
Range	594.7-4613.3	104.3-609.3	24.2-672.8
30 mg SC			
N	70	68	70
Mean (SD)	509.7 (281.2)	627.5 (326.7)	473.8 (208.5)
Median	488.2	586.7	477.0
Range	66.1-1323.9	78.5-1623.6	0-1016.5

Source: dx-88-5-csr-body.pdf, Section 11.4.2, Table 26

Reviewer's comment: The pharmacokinetic parameters assessed in EDEMA2 are reviewed in detail in the Clinical Pharmacology Team's review. Based on the findings here, there appears to be a fair amount of variability in plasma concentration levels, which could potentially result in different degrees of efficacy among individuals. When comparing the different dosage levels, the 30 mg SC dose appears to have the most constant levels over the initial 4 hour period post-dose.

EDEMA2 is the primary source of PK data for HAE patients, including children. Only 3 patients over the age of 65 years were enrolled, so estimates on geriatric exposure cannot be made. In addition, the validity of the raw PK data has not been confirmed as of the time of this review. Samples from EDEMA2 were sent to 3 different contract research organizations for analysis: (b) (4). Of these 3, only data from (b) (4) has been validated. As population PK analysis relies on the EDEMA2 PK values, the current extrapolations on pediatric exposure and even adult exposure may not be valid. An update from the Applicant on this issue is pending at the time of this review.

10.3.2.5 Safety outcomes

Drug exposure

As previously mentioned, 20 patients had had prior exposure to ecallantide in a previous study. During EDEMA3, 33 patients were treated for 1 attack while another 13 patients were treated for 2 attacks. Twenty-one patients were treated for 3-7 attacks, and 6 patients were treated for 8-12 attacks. A single patient was treated for 13, 14, 15, 16, 17, or 18 attacks each. By dose level, 18 patients were treated with 5 mg/m² IV, 55 with 10 mg/m² IV, 9 with 20 mg/m² IV, and 31 with 30 mg SC. Correspondingly, 24 attacks were treated with 5 mg/m² IV, 141 with 10 mg/m² IV, 15 with 20 mg/m² IV, and 60 with 30 mg SC.

Adverse events

SAEs and deaths

No deaths occurred during the study. Nine patients reported HAE as an SAE. Other SAEs that were reported include the following: ovarian necrosis with abdominal adhesions (Day 25), pancreatitis (onset Day 2), and jaw fracture (Day 1 prior to attack). In addition, 2 patients with hypersensitivity drug reactions were reported as SAEs.

- Patient 2497 had pruritus, tingling, popular rash, flushing, nausea, dizziness, diaphoresis, and faintness during Treatment Episode 6 within 10 minutes of injection with ecallantide 30 mg SC. She was treated with diphenhydramine, IM epinephrine, IV hydrocortisone, cetirizine, and ranitidine. During the episode, her blood pressure decreased from a pre-dose baseline of 102/67 → 87/60 mmHg at 30 minutes post-dose. A serum tryptase level taken at 2 hours post-event was 2.7 ng/ml. The patient did not receive additional doses of ecallantide after the event.
- Patient 5499 developed flushing, hives, and conjunctival redness with tearing with 1 minute of 10mg/m² IV infusion for Treatment Episode 6. His heart rate increased from 120 → 172 bpm and blood pressure increased from 122/73 → 152/100 mmHg. The infusion was stopped prior to completion and patient was treated with diphenhydramine. The case narrative notes that serum tryptase levels were drawn but results are not reported. The patient subsequently received 2 additional doses of 30 mg SC in EDEMA2.

Reviewer's comment: Patient 2497's case qualifies as an anaphylactic event. Patient 5499's event is evocative of an allergic reaction but does not meet full criteria for anaphylaxis. The SAEs of HAE reported are likely a reflection of the underlying disease. Based on other efficacy data provided, it does not appear that ecallantide makes an acute attack worse although this possibility cannot be fully excluded. Of the other SAEs, the time courses reported make them less likely to be related to study drug with the exception of the case of pancreatitis. The case of pancreatitis occurred in a 16 year-old female patient with a comorbid diagnosis of lupus. This patient went on to receive 3 additional doses of SC ecallantide without incident.

Discontinuations due to AEs

There were no discontinuations due to AEs.

Common adverse events

A wide range of AEs were reported. The most frequently reported AEs included the following: GI disorders (nausea, diarrhea, abdominal pain, dyspepsia), fatigue, upper respiratory tract infection, and headache. Given the small sample sizes and the varying number of patients in each dosage levels, it is difficult to draw conclusions about specific AEs for particular dosage levels. For the same reason, it is also difficult to draw conclusions about possible dose relationships. Overall, the 30 mg SC dose appears comparable to the 10 mg/m² and 20 mg/m² IV doses in terms of proportion of patients reporting at least 1 AE (52%, 51%, and 44%, respectively). The 5 mg/m² IV dose group appeared to have the smallest proportion (27.8%) of patients reporting at least 1 AE.

Administration site reactions

Eight patients reported local administration site reactions: 2 patients receiving ecallantide 10 mg/m² IV and 6 patients who received ecallantide 30 mg SC. The reactions were characterized by local pain/soreness and burning. One patient who received a SC dose reported local pruritus as well.

Other allergic drug reactions

In addition to the 2 SAEs described above, a number of other AEs were reported by patients that were suggestive of a potential allergic drug reaction.

- Patient 0701 (2nd dose) reported pruritus and rash. Seronegative for antibodies to ecallantide and *P. pastoris*.
- Patient 1703 (2nd and 4th doses) reported generalized pruritus after the 2nd dose and localized urticaria on the left wrist after the 4th dose. The patient has since received 6 additional doses. Seronegative for antibodies to ecallantide and *P. pastoris*.
- Patient 1901 (13th dose) pruritus 7 hours after treatment. Patient has received multiple doses since the reported reaction.

10.3.3 Study summary and conclusions

The EDEMA2 data support the selection of the 30 mg SC dose for study in the Phase 3 program. EDEMA2 is generally supportive of ecallantide's efficacy for acute attacks of HAE. The strength of the findings are limited by two main factors: 1) the inclusion criteria (specifically, the HAE diagnostic criteria) were not as rigorous as those specified in the Phase 3 program and could have potentially resulted in the inclusion of acquired angioedema (AAE) patients; and 2) the efficacy measurements were based on unvalidated symptom scores that were unrelated to the MSCS and TOS, limiting cross-study comparisons. As a result, although EDEMA2's results are positive and reinforce the findings of EDEMA3 and EDEMA4, EDEMA2 remains a secondary study in terms of efficacy support. In terms of safety, the primary safety concern is anaphylaxis and other hypersensitivity reactions. Antibody status does not appear to be predictive of these reactions. Reactions on both repeat and first exposure were observed.

One outstanding issue which has not been resolved at the time of this review is the validity of the pharmacokinetic measurements performed in EDEMA2. EDEMA2 is the primary source of PK data for HAE patients, including children, in the ecallantide program. The validity of the raw PK data had not been confirmed as of the time of this review. Samples from EDEMA2 were sent to 3 different contract research organizations for analysis: [REDACTED] (b) (4) and [REDACTED]. Of these [REDACTED] only data from [REDACTED] (b) [REDACTED] has been validated. As population PK analysis relies on the EDEMA2 PK values, the current estimates of pediatric exposure and geriatric exposure may not be valid, potentially limiting the extrapolation of efficacy and safety data to patients in the extreme ranges of age.

10.4 Individual Study Report: EDEMA3

10.4.1 Study Protocol: EDEMA3

10.4.1.1 Administrative information

- Title: EDEMA3, Evaluation of DX-88's effects in mitigating angioedema: A double-blind, placebo-controlled study followed by a repeat dosing phase to assess the efficacy and safety of DX-88 (recombinant plasma kallikrein inhibitor) for the treatment of acute attacks of HAE
- Study sites: Multicenter – 25 sites in the US, Canada, Europe, and Israel
- Study dates: December 8, 2005 to February 10, 2007
- Study report date: May 23, 2008

10.4.1.2 Objectives/Rationale

- To assess the efficacy and safety of DX-88 (ecallantide) in the treatment of acute attacks of HAE

10.4.1.3 Study design overview

The study was a Phase 3, randomized, double-blind, placebo-controlled multicenter study. Patients 10 years of age and older presenting within 8 hours of onset of a moderate to severe HAE attack were randomized to receive a single dose of 30 mg SC ecallantide or placebo. Patients were stratified by anatomic attack location (laryngeal vs. other) or by prior enrollment in other ecallantide studies.

Patients were eligible to receive an additional open-label dose of ecallantide if the patient was at risk of *severe upper airway compromise* (SUAC) and the Investigator judged that additional treatment was warranted. Risk of SUAC was defined as the presence of ≥ 3 of the following 7 findings: appearance or worsening of dyspnea, appearance or worsening of stridor, increased respiratory effort, change or loss of voice, cyanosis, decreased oxygen saturation, or increased PaCO₂ and/ or decreased PaO₂.

Patients were observed for a minimum of 4 hours after dosing prior to discharge and up to 3 follow-up visits were scheduled. Total study duration was up to 97 days including screening, enrollment, and the follow-up visits. Alternatively, patients could roll over to the open-label extension (OLE) phase of the study after a minimum of 1 follow-up visit for treatment of new, separate HAE attacks. Once 72 patient treatments were completed in the double-blind part, the repeat dosing OLE was open to all patients regardless of prior participation in the double-blind part. The OLE repeat-dose phase is described separately in Section 10.4.3.

10.4.1.4 Study population

Patients 10 years or older with documented diagnosis of Type I or II HAE were eligible.

Inclusion criteria

- 10 years of age or older
- Documented diagnosis of Type I or II HAE:
 - Clinical history consistent with HAE (SC or mucosal nonpruritic swelling without accompanying urticaria)

- Function or antigenic C1-INH level below the lower limit of the normal range or up to 15% above the lower limit of the normal range as defined by the reference laboratory
- C4 level below the lower limit of the normal range or up to 15% above the lower limit of the normal range as defined by the reference laboratory
- Age of reported onset ≤ 25 years or documented complement component C1q level at or above the lower limit of the normal range
- Enrollment visit: presentation at the site within 8 hours of patient recognition of an acute HAE attack with at least one moderate to severe symptom complex (patient and investigator must agree that at least one symptom complex is moderate or severe):
 - Normal – patient's state absent of an acute HAE attack
 - Mild – noticeable symptoms but do not impact activities of daily living
 - Moderate – treatment or intervention highly desirable and symptoms impact activities of daily living
 - Severe – treatment or intervention required due to inability to perform activities of daily living
- Sexually active and fertile patients required to use at least 2 methods of contraception for the duration of the study

Exclusion criteria

- Receipt of an investigational drug or device other than ecallantide within 30 days prior to study treatment
- Patients who received ecallantide within 7 days of presentation for dosing in the double-blind part of EDEMA3
- Treatment with non-investigational C1-INH concentrate for angioedema within 7 days prior to enrollment
- Acquired angioedema, estrogen-dependent angioedema, and/or drug-induced angioedema
- Pregnancy or breastfeeding
- Any other condition that may compromise safety or compliance at the discretion of the investigator

Patients could withdraw from the study at any time at their own request or could be withdrawn at the discretion of the investigator or sponsor. Reasons for early withdrawal included adverse event, noncompliance or protocol violation, withdrawn consent, or termination of the study.

10.4.1.5 Study treatments

Treatments administered

- Initial dose
 - Single 30 mg ecallantide administered via 3 x 1cc SC injections to the upper arm, thigh, and abdomen. In the event that an injection site coincided with an attack site, multiple injections could be administered to the same site as long as the injections were separated by a minimum of 5cm.
 - Placebo
- Additional dosing

- Open-label 30 mg ecallantide
- Standard of care

Blinding

Ecallantide and placebo are both clear colorless liquids and are indistinguishable by appearance. Vials were labeled with assigned codes corresponding to the randomization codes. A single statistician was unblinded to assigned study treatment; all other study personnel and patients remained blinded.

Randomization

Patients were randomized 1:1 to ecallantide or placebo. The randomization was stratified by anatomic location of the attack (laryngeal vs. others) as determined by the investigator and by prior participation in an ecallantide clinical study (patients may or may not have received ecallantide in the previous study). A third-party vendor provided a centralized web-based or telephone-based system for generation the randomization assignments to individual patients as they presented at the time of their attacks.

Prior and concomitant therapy

Receipt of certain medications was reason for exclusion, as noted above. The CRF was used to record any additional concomitant medications and emergency treatments administered, if any. Emergency treatments included opioid/pain medication, anti-emetics (5-HT3 receptor antagonists), and HAE alternative therapies, listed as follows:

- Aminocaproic acid
- C1-INH
- Fresh frozen plasma
- Tranexamic acid
- Methylprednisolone
- Oxandrolone
- Danazol
- Prednisone
- Stanozolol
- Dexamethasone
- Dehydroepiandrosterone
- Methyltestosterone

Treatment compliance

All study drugs were administered in clinic. Study drug accountability was verified during on-site monitoring visits conducted by the Sponsor.

10.4.1.6 Study procedures

Table 38 EDEMA3: Schedule of procedures

EDEMA3	Screen	Enroll	Post-dosing evaluation						Follow-up day		
			Post-dosing (hr)				Discharge	Day 2*	Visit 1 6-10	Visit 2 23-37	Visit 3 83-87
			0-1.5	2	3	4					
Informed consent	X										
Urine pregnancy test	X	X									
History, demographics	X										
Physical exam	X	X					X		X	X	
Vital signs	X	X					X		X	X	
ECG	X	X							X	X	
Urinalysis	X	X		X					X	X	
eDiary completion		X	X	X	X	X	X	X	X		
Symptom complex identification		X	X	X	X	X		X			
Assessment of overall response			X	X	X	X		X			
Symptom complex assessment*			X	X	X	X		X			
Severity assessment*		X				X					
Dosing		X									
Open-label DX-88 for incomplete response or relapse						X					
Dosing for severe upper respiratory compromise*			X	X	X	X					
Clinical observations			X	X	X	X	X				
Concomitant meds	X	X	X	X	X	X	X				
Adverse events	X	X	X	X	X	X	X	X	X	X	
Blood samples											
• Chemistry	X	X					X		X	X	
• CBC/diff	X	X					X		X	X	
• Coag panel	X	X					X		X	X	
• C1-INH level (if not done)	X								X	X	
• C4 (if not done before)	X										
• Antibody levels	X	X							X	X	X

* Phone call

Source: dx-88-14db-csr-body.pdf, Section 9.1, Table 2

10.4.1.7 Efficacy parameters

Primary efficacy endpoint: Treatment Outcome Score (TOS) at 4 hours

The primary efficacy endpoint was the Treatment Outcome Score (TOS) at 4 hours. The TOS is a composite, weighted symptom complex score intended to assess global symptom response to treatment. The following symptom complexes were assessed: 1) internal head/neck, 2) stomach/GI, 3) genital/buttocks, 4) external head/neck, and 5) cutaneous. Each individual symptom complex score is based on a severity rating for that particular group of symptoms multiplied by a "response-to-treatment" factor, so that the outcome is incorporated into the final TOS value.

$$TOS = \frac{\sum(\text{Baseline severity assessment} \times \text{Response to treatment})}{\sum \text{Baseline severity assessment}}$$

In this equation, “baseline severity” is scored on a scale of 0 to 3, with 3 being the most severe (see definitions of severity ratings in Table 39). “Response to treatment” is scored as -100, -50, 0, 50, or 100, with -100 representing significant worsening and a score of 100 representing significant improvement. The maximum and minimum possible TOS values are +100 and -100, respectively, with a higher value corresponding to greater improvement. A TOS of 0 signifies no change.

A higher TOS value corresponded to a greater response. Emerging symptom complexes were weighted according to their peak severity assessment and if still present at 4 and/or 24 hours were assigned a response assessment of “significant worsening” (i.e. -100). Emerging symptom complexes that were no longer present at 4 and/or 24 hours were assigned an assessment of “same.” Medical interventions that were clearly directed to a specific symptom complex only affected that particular symptom complex response (e.g. anti-nausea medications would be regarded as “significant worsening” for the GI/abdominal complex but would not affect the Cutaneous response assessment). Medical interventions that were not clearly directed to a specific symptom complex affected all symptom complexes. A sensitivity analysis was performed setting the symptom complex weights to “1” to assess the robustness of the baseline weighting of the severity symptoms used for calculating TOS

Reviewer’s comment: The primary efficacy variable, TOS, is a complicated score that is difficult to interpret, due in part to the response and severity multipliers used. Overall, a higher number corresponds to a better response to study drug, although the magnitude of response for a given TOS value is not intuitively clear. The response multiplier may exaggerate small differences, which may or may not be clinically meaningful, or potentially obscure important changes. Since the TOS is a composite score, individual symptom complexes can potentially cancel one another out. For example, if a patient experiencing significant improvement of cutaneous symptoms but significant worsening of laryngeal symptoms, the respective changes may cancel one another out so that the final TOS is 0 = no change.

Secondary efficacy endpoints

- **Change in Mean Symptom Complex Severity (MSCS) from baseline at 4 hours**
 - The MSCS is the arithmetic mean of the severity grade of the individual symptom complexes, where each symptom complex is assessed a severity grade of severe to normal. A decrease from baseline MSCS corresponds to a reduction in severity.
 - A baseline severity assessment for emerging symptom complexes were considered “normal.”
 - Medical interventions resulted in an automatic severity assessment of “severe” at 4 and 24 hours. Medical interventions that were clearly directed to a specific symptom complex only affected that particular symptom complex response. Medical interventions that were not clearly directed to a specific symptom complex affected all symptom complexes.
 - The use of open-label ecallantide for SUAC resulted in a severity assessment of “severe” at 4 and 24 hours.

Table 39 Severity assessment for MSCS calculation		
Severity Assessment	Score	Definition
Severe	3	treatment or intervention required due to inability to perform activities of daily living (e.g. throat swollen/difficulty breathing, lips swollen/cannot eat, feet swollen/cannot walk)
Moderate	2	treatment or intervention highly desirable and symptoms impact activities of daily living (e.g. hands swollen/cannot button shirt, feet swollen/discomfort wearing shoes)
Mild	1	noticeable symptoms but do not impact activities of daily living
Normal	0	patient's state absent of an acute HAE attack

- **Time to onset of significant improvement in overall response**
 - Based on “overall response” assessment
 - “Significant improvement” defined as an overall response assessment of “a lot better or resolved”
 - Patients who did not report significant improvement through 4 hours post-dosing were censored at 240 minutes
 - Patients that received additional therapy were censored at the time of medical intervention

Tertiary efficacy endpoints

- Durability of response/TOS at 24 hours post-dosing
- TOS at 4 hours as determined by the investigator
- Proportion of responders at 4 hours
 - TOS ≥ 70
- Time to onset of sustained improvement
 - Sustained response defined as any positive overall response assessment for a continuous duration ≥ 45 minutes
- Proportion of patients receiving medical intervention
- Assessment of open-label treatment with ecallantide for SUAC
- Change in clinical laboratory measures

10.4.1.8 Safety parameters

Adverse events

All AEs were reported from enrollment (Study day 1) through the conclusion of follow-up visit 2. Any AEs that were suspected to be related to study procedures were reported from time of informed consent through enrollment and from follow-up visit 2 to 3. Investigators used NCI CTC criteria for grading AE severity. AE coding was performed using the MedDRA coding dictionary (Version 6.0).

Physical exam

Routine exams were conducted at screening and/or enrollment prior to dosing, study discharge, follow-up visits 1 and 2.

Vital signs

Body temperature, heart rate, blood pressure, and weight were recorded at screening and/or enrollment prior to dosing, study discharge, follow-up visits 1 and 2.

Electrocardiogram

A 12-lead ECG was obtained for each patient at screening, enrollment prior to dosing, 2 hours post-dose, follow-up visits 1 and 2. In situations where an ECG could not be taken immediately due to the severity of the patient's attack site, the ECG screening from baseline was used as the baseline.

Clinical laboratory parameters

A CBC with differential and platelet count, serum chemistries, and coagulation tests were obtained at screening and/or enrollment prior to dosing, study discharge, follow-up visits 1 and 2. A routine urinalysis was obtained at screening and/or enrollment prior to dosing, study discharge, and follow-up visit 1. A urine pregnancy test was performed at screening and at enrollment.

Antibody testing

Samples for serum antibody testing were collected at screening and/or enrollment prior to dosing, follow-up visits 1 (Study day 6 to 10), 2 (Study day 23 to 37), and 3 (Study day 83 to 97). Antibody testing was performed for detection of development of IgE and non-IgE antibodies to ecallantide and IgE antibodies to *P pastoris*.

10.4.1.9 Statistical plan

The sample size of 62 was calculated to provide 85% power, based on the assumption that 72.5% of ecallantide patients would have significant improvement by 4 hours compared to 25% of placebo. The sample size was later increase to 72 to ensure a sufficient number of patients used the eDiary to aid the validation of the PRO measures.

All analyses were based on the intent-to-treat population. Additional analyses based on the per-protocol population and as-treated populations were also performed for comparison. The as-treated population analysis was performed because after conclusion of the study, the Applicant discovered that 2 patients were randomized on the same day at the same study center and received incorrect treatment. One patient randomized to receive ecallantide received placebo instead and the second patient assigned to placebo received ecallantide.

The primary and secondary efficacy analyses on TOS at 4 hours and change from baseline MSCS were performed using a Wilcoxon Rank Sum Test, assuming a non-normal distribution of results. Imputations were used for emerging symptom complexes and medical interventions in the primary analysis. Demographic data and safety data were presented using descriptive statistics.

Reviewer's comment: The imputation rules were intended for a conservative measure of the TOS and MSCS. The statistical reviewer has noted that the imputations favor study drug if there are

more emerging symptom complexes or medical interventions in the placebo arm, exaggerating the treatment difference. While the clinical review notes that these type of data imputations may not be entirely conservative, emerging symptom complexes and medical interventions in the placebo arm are clinically relevant markers of efficacy and provide a clinical context for the MSCS and TOS scores, which are novel PRO instruments.

10.4.2 Results

10.4.1.1 Protocol amendments

- Amendment 1, September 26, 2006 – increased the sample size from 62 to 72 patients to facilitate PRO validation and changed the statistical analysis of the primary efficacy endpoint to a more conservative test, the Wilcoxon Signed Rank test.
- Amendments 1.1 (June 18, 2007) and 1.2 (July 17, 2007) – updated administrative information (personnel and address changes).

10.4.2.2 Study patient disposition

Seventy-two patients were randomized; 36 in the ecallantide arm and 36 in the placebo arm. Patient 361004 was not included in the per-protocol population due to an eDiary malfunction that prevented completion of the baseline and 4-hour post-dose assessment. The disposition of the patients is shown in Error! Reference source not found..

	EcCallantide N=36 N(%)	Placebo N=36 N(%)	Total N=72 N(%)
Intent to treat population ^a	36 (100.0)	36 (100.0)	72 (100.0)
Per protocol population ^b	35 (97.2)	36 (100.0)	71 (98.6)
Safety population ^c	36 (100.0)	36 (100.0)	72 (100.0)
Patients completing double-blind phase	35 (97.2)	36 (100.0)	71 (98.6)
Patients rolling over to continuation study ^d	21 (58.3)	27 (75.0)	48 (66.7)
Patients withdrawing from study	1 (2.8)	0	1 (1.4)
Adverse event	0	0	0
Noncompliance or protocol violation	0	0	0
Withdrawal of consent	0	0	0
Lost to follow-up	1 (2.8)	0	1 (1.4)
Investigator discretion	0	0	0
Left study site against medical advice	0	0	0

^a Patients who received any amount of study drug and completed the 4-hour follow-up

^b Patients who received a complete dose of study drug with no major protocol violations and completed the 4-hour follow-up

^c Patients who received any amount of study drug

^d All patients were eligible to enroll in the open-label extension study.

Source: dx-88-14b-csr-body.pdf, Section 10.1, Table 3

10.4.2.3 Protocol deviations

A complete listing is provided in Appendix 16.2.2.1.0 of the full study report. The major protocol deviation was the administration of incorrect study medication to two patients, as described in Section 10.4.1.9. There were also deviations related to study entry criteria: 1 patient failed to have a pregnancy test at screening and 2 patients had C1-INH levels verified post-dose

rather than prior to treatment. Other protocol deviations related to the use of a paper diary rather than eDiary was reported for 8 patients.

Reviewer's comment: The incorrect administration of study treatment appears to have impacted the study results. The Applicant has provided an alternative as-treated analysis to demonstrate that statistically significant results would be achieved if these two patients were included in the analysis under the received rather than assigned treatment group. The other protocol violations do not seem likely to have impacted the overall results, although given the small sample size, such effects cannot be ruled out.

10.4.2.4 Treatment compliance

All study drug was administered subcutaneously by study personnel.

10.4.2.5 Datasets analyzed

As described in the Statistical Analysis section, 3 populations were analyzed: ITT-as-randomized, ITT-as-treated, and Per Protocol.

10.4.2.6 Demographics and baseline characteristics

Patient demographics

The demographics at baseline are shown in Table 5. A higher proportion of patients in the placebo group (11 of 36, 31%) had received prior treatment with ecallantide in previous studies compared to the ecallantide group (8 of 36 22%). The majority of patients with prior exposure were treated in EDEMA2 with open-label ecallantide.

Table 41 EDEMA3: Patient demographics			
	Ecallantide N=36	Placebo N=36	Total N=72
Age			
Mean (SD)	38.5 (14.6)	32.2 (13.8)	35.4 (14.5)
Range	18-77	11-57	13-77
Sex (N,%)			
Male	12 (33.3)	13 (36.1)	25 (34.7)
Female	24 (66.7)	23 (63.9)	47 (65.3)
Race (N,%)			
White	33 (91.7)	32 (88.9)	65 (90.3)
Black	1 (2.8)	4 (11.1)	5 (6.9)
Hispanic	2 (5.6)	0	2 (2.8)

Source: dx-88-14db-csr-body.pdf, Section 11.2.1, Table 4

Reviewer's comment: The treatment groups appear comparable in terms of age and racial distribution, but the ecallantide group has a higher number of female patients compared to the placebo arm. The significance of this gender imbalance is uncertain as HAE occurs in males and females at the same rate. There is some evidence in the literature to suggest that HAE is exacerbated by hormonal fluctuations and thus women may have more frequent or severe attacks. The difference in prior exposure to ecallantide is not likely to have weighted the

treatment group with more responders, since a greater number of patients in the placebo group had a history of ecallantide exposure.

Patient HAE history

Table 42 EDEMA3: HAE attack history		
	Ecallantide N=36	Placebo N=36
Age at first HAE symptom onset		
Mean (SD)	12.1 (6.5)	10.3 (6.9)
Range	1-32	1-25
Lowest historical functional C1-INH		
Mean % (SD)	18.7 (20.4)	22.8 (24.8)
Range	0-59	0-97
Lowest historical antigenic C1-INH, mg/dl		
Mean (SD)	22.4 (24.0)	18.4 (21.8)
Range	3-79	0-80
Lowest historical C4, mg/dl		
Mean (SD)	10.6 (12.9)	9.9 (13.5)
Range	0-55	0-56
Most common prior HAE symptom complex (N,%)		
Laryngeal	3 (8.3)	2 (5.6)
Stomach/GI	22 (61.1)	21 (58.3)
Genital/buttocks	4 (11.1)	1 (2.8)
External head and neck	3 (8.3)	0
Cutaneous	20 (55.6)	17 (4.2)

Source: dx-14db-csr-body.pdf, Section 11.2.3 Table 6 and 7

Reviewer's comment: The treatment groups appear fairly comparable in terms of age of onset, historical laboratory values, and prior attack site history. In terms of historical function C1-INH levels, the range in the placebo group is as high as 97%, which would be within normal range. However, upon review of individual line listings, patients with a functional level within the normal range appeared to have documented levels below normal, which are consistent with inclusion criteria. The range of normal for antigenic levels varies by reference laboratory. For most labs, the upper cutoff for normal antigenic level is ~40-50 mg/dl.

Previous and concomitant medications

The majority of patients had taken androgens as prior prophylactic therapy for HAE: danazol and stanozolol in 58.3% and 47.2% in the ecallantide group compared to 38.9% and 33.3%, respectively, in the placebo group. Aminocaproic acid, fresh frozen plasma, diphenhydramine, C1-inhibitor replacement, prednisone, and hydroxyzine were also reported by several patients as commonly used acute treatments in the past.

At screening, all patients reported taking concomitant medications. The most commonly listed medication was danazol (11 of 36 in the ecallantide arm, 5 of 36 in the placebo arm). Other commonly used medications included stanozolol, systemic antihistamines, acetaminophen, levothyroxine, lorazepam, and ibuprofen.

Reviewer's comment: There appears to have been an imbalance in the number of patients taking danazol between the two treatment arms. The impact of this discrepancy is unclear, although the severity of presenting attacks appears comparable between the two groups.

Presenting symptom complex severity

Each randomized patient presented with at least one symptom complex that was moderate to severe. Patients could report multiple symptom complexes. The most commonly reported symptom complexes in the ecallantide group were cutaneous (n=21) and stomach/GI (n=20). In the placebo group, 14 patients reported cutaneous symptoms and 21 reported stomach/GI symptoms. Laryngeal attacks were reported in 9 ecallantide patients and 4 placebo patients. The patient-reported severity of the symptom complexes is displayed below.

Table 43 EDEMA3: Severity of symptom complexes at baseline		
	Ecallantide N=36 N, %	Placebo N=36 N, %
Internal head/neck symptoms (including laryngeal)		
Mild	1 (2.8)	1 (2.8)
Moderate	7 (19.4)	1 (2.8)
Severe	1 (2.8)	2 (5.6)
Stomach/GI		
Mild	1 (2.8)	1 (2.8)
Moderate	14 (38.9)	13 (36.1)
Severe	5 (13.9)	7 (19.4)
Genital/buttocks		
Mild	0	0
Moderate	1 (2.8)	3 (8.3)
Severe	1 (2.8)	1 (2.8)
External head/neck		
Mild	2 (5.6)	3 (8.3)
Moderate	1 (2.8)	3 (8.3)
Severe	1 (2.8)	3 (8.3)
Cutaneous		
Mild	4 (11.1)	1 (2.8)
Moderate	13 (36.1)	11 (30.6)
Severe	4 (11.1)	2 (5.6)

Source: dc-88-14db-csr-body.pdf, Section 11.2.5, Table 13

Reviewer's comment: The distribution of symptom complexes and severity at baseline appears comparable between the two treatment arms.

10.4.2.7 Efficacy endpoint outcomes

Primary efficacy endpoint: TOS at 4 hours

Based on the pre-specified analysis, the study failed to demonstrate a statistically significant difference between ecallantide and placebo. Numerically, the results favored ecallantide over placebo. When re-analyzed used the as-treated population, the results show a statistically significant benefit for ecallantide over placebo. The Per Protocol results confirm the As-Treated results.

Table 44 EDEMA3: TOS at 4 hours						
Statistic	ITT-as-randomized			ITT-as-treated		
	Ecallantide N=36	Placebo N=36	P	Ecallantide N=36	Placebo N=36	P
Mean	46.8	21.3	0.100	49.5	18.5	0.037
Median	50.0	0		50.0	0	
Std Dev	59.3	69.0		59.4	67.8	
Min, Max	(-100, 100)	(-100, 100)		(-100, 100)	(-100, 100)	
25 th , 75 th	(0, 100)	(0, 100)		(0, 100)	(0, 100)	

Source: dx-88-14db-csr-body.pdf, Section 11.4.1, Table 14

Reviewer's comment: The success of the study is altered by the dosing mistake described in Section 103.4.2.3, Protocol Deviations, where two patients erroneously received the wrong medication. These results suggest that ecallantide has some efficacy, although the results do not appear to be robust and the limitations of a small sample size are apparent. Also, the standard deviations appear to be quite large, suggesting a fair amount of variability in the dataset. For reference, the proposed MCID for the TOS is 30 points. The treatment difference for the ITT-as-randomized is 26 points; for the ITT-as-treated, the treatment difference is 31 points.

Secondary efficacy endpoints

Change in MSCS from Baseline

Although numerically favorable, the study did not show a statistically significant benefit based on the ITT-as-randomized analysis for the key secondary efficacy endpoint, change in MSCS from baseline at 4 hours. When reanalyzed using the as-treated population, the results are statistically significant (-0.9 vs. -0.5; p=0.044).

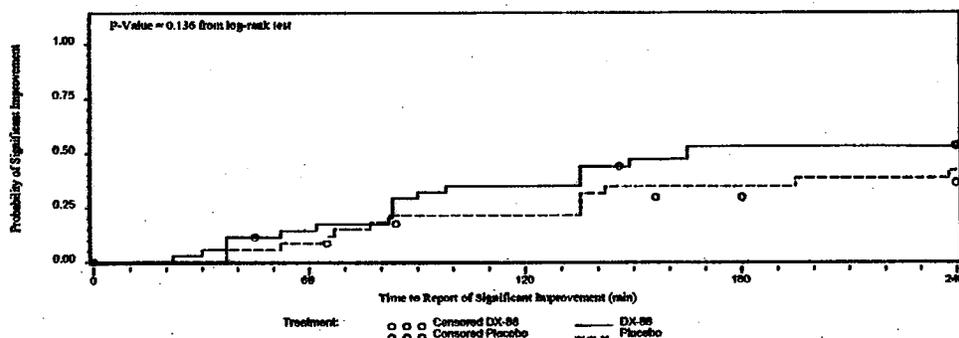
Table 45 EDEMA3: Primary efficacy endpoint, Change from baseline MSCS at 4 hours post-dose			
	Baseline MSCS	Change from baseline at 4h	P
Ecallantide (N=36)	2.2 (0.5)	-0.9 (1.1)	0.09
Placebo (N=36)	2.3 (1.0)	-0.5 (0.7)	

Reviewer's comment: Although not statistically significant, the treatment difference is -0.4, which exceeds the proposed MCID of 0.3 points. These results are similar to those observed in EDEMA4.

Time to Significant Improvement

Based on patients' global response assessments, which was independent of the TOS and MSCS calculations, the median time to significant improvement was 165.0 minutes for ecallantide. The estimated median for placebo was not reached by 240 minutes, but the difference was not statistically significant (p=0.136). The results were not altered using the as-treated dataset, but were statistically significant in favor of ecallantide when based on the per protocol dataset (p=0.045). The time to significant improvement for the two treatment arms is shown in Figure 4.

Figure 4 EDEMA3: Time to patient report of significant improvement in overall response (ITT-as-randomized)



Best Possible Copy

Reviewer's comment: Time to patient report of significant improvement in overall response confirms the efficacy findings and provides a patient-based global assessment that is independent of the TOS and MSCS. This efficacy variable gives some assurance that the TOS and MSCS did not obscure important clinical changes, e.g. laryngeal worsening cancelled out by cutaneous improvement.

Tertiary efficacy endpoints

TOS at 24 hours post-dosing

The median (IQR) TOS at 24 hours postdose was 75.0 (0, 100) in the ecallantide group compared to 0 (-100,100) in the placebo group ($p=0.044$).

Reviewer's comment: The TOS at 24 hours supports a durable improvement in symptoms.

Change in MSCS from baseline at 24 hours

The mean change in MSCS at 24 hours was -0.87 (SD 1.0) in the ecallantide group and -0.46 (SD 1.1) in the placebo group ($p=0.142$). Similar results were obtained for the as-treated population analysis.

Reviewer's comment: These results are comparable with the change from MSCS observed at 4 hours post-dose. While numerically favorable, the results are not statistically significant.

Time to onset of sustained improvement in overall response

The mean time to onset of sustained improvement was 79 minutes in the ecallantide group and 113 minutes in the placebo group ($p=0.075$). When assessed using the as-treated population, the mean times are 77 and 116 minutes, respectively ($p=0.023$).

Proportion of successful response assessment at 4 hours post-dosing ($TOS \geq 70$)

Fifteen patients (42%) in the ecallantide group compared to 12 (33.3%) in the placebo group had a $TOS \geq 70$ at 4 hours ($p=0.47$). No statistically significant differences were observed when adjusted for attack location or prior use of ecallantide.

Proportion of patients receiving medical intervention

Five patients (14%) in the ecallantide group compared to 13 (36%) of placebo received medical intervention. The most commonly administered interventions were emergency medications such as opioids for pain control and anti-emetics. No patients required intubation or urgent surgical decompression. In both treatment groups, fewer patients with peripheral attacks required intervention than patients with a laryngeal attack ($p=0.014$).

Open-label experience due to SUAC (Dose B)

One patient (311016) in the placebo group and 2 patients (326012 and 361004) in the ecallantide group received open-label ecallantide for SUAC that occurred soon after dosing with the randomized study drug.

- Patient 311016 initially presented with laryngeal edema and reported worsening dyspnea, increased respiration, and change/loss voice almost immediately after receipt of placebo. Within 15 minutes of receipt of open-label ecallantide, she reported symptoms as “a little better.” Her symptom assessment remained “a little better” up to 4 hours post-dose. At 24 hours, she reported symptoms as “a lot better or resolved” along with self-administration of diphenhydramine and epinephrine SC for the attack.
- Patient 326012 presented with mild external head/neck symptoms and moderate internal head/neck symptoms. She did not report any symptom improvement 45 minutes after the initial dose and subsequently developed appearance or worsening of stridor, change/loss of voice, and increased respiratory effort. Thirty minutes after the second, open-label SUAC dose, the patient reported symptoms as “a lot better or resolved.” No other medical interventions were recorded.
- Patient 361004 presented with laryngeal edema. At 1 hour 45 minutes after the initial ecallantide dose, the patient reported symptoms as “a little worse.” Thirty minutes after receipt of a second, open-label dose, the symptoms were reported as “a little better.” An updated overall response assessment at 24 hours was not recorded for this patient but per the case narrative, the patient had recovered without sequelae by that time.

10.4.2.8 Safety outcomes

Extent of exposure

A total of 36 patients received one 30 mg dose of ecallantide. Two of these 36 received a second 30 mg dose for SUAC. One placebo patient also received an open-label 30 mg dose for SUAC.

Adverse events

Deaths and serious adverse events (SAE)

No deaths were reported in the study. Three cases of HAE in the ecallantide arm and 2 cases in placebo were reported as SAEs.

- Patient 322002 (ecallantide) was hospitalized for an acute HAE attack of peripheral edema 4 days after treatment with ecallantide for a separate abdominal HAE attack. The patient was discharged without sequelae.

- Patient 334001 (ecallantide) initially presented with laryngeal edema and was treated with ecallantide before being hospitalized later that same day for a GI HAE attack. The patient was discharged without sequelae.
- Patient 361004 (ecallantide) was treated at 9:40 am for laryngeal edema. The patient was later hospitalized that same day for SUAC and treated with a second ecallantide dose at 12:06pm. The patient was discharged the next day and recovered without sequelae.
- Patient 304004 (placebo) was hospitalized for an acute peripheral HAE attack of the right hand 6 days after receipt of placebo for an acute external head/neck HAE attack. The patient was discharged the next day without sequelae.
- Patient 326003 (placebo) was hospitalized with an acute stomach/GI HAE attack 1 day after treatment with placebo for an acute stomach/GI attack. The patient was treated with normal saline, ketorolac, and ondansetron and recovered without sequelae.

Study discontinuation due to AE

No early discontinuations from the study due to an AE were reported.

Common adverse events

The most common adverse events are shown in Table 46. HAE was reported as an AE in 3 patients in the ecallantide arm and 4 patients in the placebo arm. Local injection site reactions were reported in 1 patient in the ecallantide group and 1 patient in the placebo group.

Table 46 EDEMA3: Adverse events occurring in ≥2 patients in the ecallantide group and greater than in the placebo group		
Adverse event	Ecallantide N=36 N,%	Placebo N=36 N,%
Patients with 1 or more AEs	20 (55.6)	12 (33.3)
Patients with no AEs	16 (44.4)	24 (66.7)
Headache	4 (11.1)	2 (5.6)
Diarhea	3 (8.3)	0
Pyrexia	3 (8.3)	0
Nasopharyngitis	2 (5.6)	1 (2.8)
Nasal congestion	2 (5.6)	0
Tachycardia NOS	2 (5.6)	1 (2.8)

Reviewer's comment: The overall AE event profile appears consistent with AEs reported in previous trials and in EDEMA4.

Laboratory evaluations

No clinically significant alterations in mean routine laboratory tests, including coagulation parameters, were reported for either treatment group. Two patients in the ecallantide group had a transient rise in thrombin time at 4 hours. One ecallantide patient also experienced anemia 3 days after dosing but was reported as recovered 1 week later. Another ecallantide patient was reported as having a blood glucose level of 26 mg/dl (normal 70 -115 mg/dl) at 4 hours post-dose. The hypoglycemia resolved and values within normal range were reported at follow-up visits.

Antibody testing

No IgE antibodies to ecallantide were detected. Two patients with prior exposure to ecallantide tested positive for non-IgE ecallantide antibodies prior to dosing in EDEMA 3 and also at Follow-up Visit 1. Both patients were reported as having improved symptoms as measured by the TOS at 4 hours. Seven ecallantide patients and 4 placebo patients tested positive for IgE antibodies to *P. pastoris*. No hypersensitivity reactions were reported in these 11 patients.

Reviewer's comment: The study duration for the double-blind phase of EDEMA3 was up to 97 days in duration if patients completed all follow-up visits. Additional antibody information was collected from patients who rolled over to the open-label extension phase, so not all patient data is represented from the double-blind phase alone.

Vital signs

No clinically significant alterations in mean vital signs were observed in either treatment group. Tachycardia NOS was noted in two patients in the ecallantide group. Patient 301008 had a baseline heart rate of 124 bpm → 110 bpm at 2 hours post-dose → 76 bpm at the first follow-up visit. Patient 313003 had a baseline heart rate of 101 bpm → 105 bpm at 2 hours post-dose → 60 bpm at first follow-up. Three patients were recorded as having pyrexia. Patient 305001 reported a fever 1 day after ecallantide that resolved with a 325 mg dose of aspirin. Patient 317002 also reported a fever 1 day after ecallantide that resolved with 650 mg acetaminophen and acetaminophen/codeine. Patient 318002 was recorded as being febrile 2 hours after ecallantide. The patient recovered after 1000mg acetaminophen. The patient also reported an influenza-like illness and fatigue.

Reviewer's comment: The tachycardia does not appear to be treatment-related, given the documentation prior to ecallantide administration. Fever may potentially be related given the time course and absence of other evident fever sources.

Physical exams

The majority of physical exam findings reported were signs and symptoms related to the presenting HAE attack. No notable abnormalities were otherwise reported.

ECGs

No mean changes in ECG parameters were recorded for either treatment group. Both tachycardia and bradycardia were observed in several individuals. Patient 315003 was noted to have sinus bradycardia at screening of 54 bpm → 47 bpm at 2 hours post-dose. No follow-up information is available on this patient.

Reviewer's comment: Overall, the safety profile for ecallantide in EDEMA3 appears acceptable. No SAEs were recorded besides HAE, which most likely reflects the underlying condition since more patients in the placebo group were noted to have this HAE. Hypersensitivity reactions remain a concern for this biologic product, although the rate of events would be expected to be quite low in a single-dose study. The open-label phase with repeat doses is more likely to yield information on antibody responses and hypersensitivity reactions.

10.4.3 EDEMA3 Open-label extension study

10.4.3.1 Administrative information

- Study period: December 28, 2005 (first patient began treatment in repeat-dose phase) to September 21, 2007 (last patient completed)
- Study report date: August 6, 2008
- Study sites: multicenter, 24 sites in the US, Canada, Belgium, Italy, and Israel

10.4.3.2 Study design and conduct

Patients previously enrolled in the double-blind phase of EDEMA3 could enroll in the open-label phase once the Follow-up Visit 1 had been completed. Once the double-blind phase was closed, all patients who had qualified were eligible for participating in the repeat-dosing open-label phase. Patients 10 years and older with new attacks were eligible for repeat doses in this phase. A new attack was defined as an HAE attack that presented after a return to normal state following a previous acute attack. Patients were required to present to the study site within 8 hours of onset of an acute attack with the same symptom complexes outlined in the double-blind phase. Qualified patients received 30 mg ecallantide SC. If patients had an incomplete response to treatment, Dose B of study drug could be given anytime from 4 hours through 24 hours post-dosing. Dose B consisted of randomized study drug (1:1 ecallantide:placebo). Incomplete response was defined as a reoccurrence of an attack between 4 and 24 hours after initial improvement after dosing or as not achieving "significant improvement" within 4 hours following some improvement after dosing. Patients who showed no response to the initial dose of ecallantide were not eligible for Dose B treatment with study drug. After administration of study drug, patients were discharged at 4 hours post-dose with 1 follow-up phone call and up to 3 planned follow-up visits at Days 6-10, 23-47, and 83-97 after treatment. Patients could be treated for a maximum of 20 attacks at an interval of 8 days or more.

The TOS and MSCS were recorded as efficacy variables. Safety was assessed through AEs, laboratory test evaluations, physical exams, ECGs, antibodies to ecallantide and *P. pastoris*, and vital signs. Antibody testing was performed at screening if not done during the double-blind phase, enrollment, and at each follow-up visit.

10.4.3.3 Results

Patient disposition

From the double-blind phase, 22 ecallantide and 26 placebo patients received at least 1 dose of ecallantide in the OLE phase. Another 19 new patients also joined the study, for a total of 67 patients in the safety population. One new patient (365004) was excluded from the ITT dataset due to missing data at the 4-hour post-dose assessment. Three patients (4.5%) had an incomplete response and received blinded Dose B. Of the 3, 1 patient received ecallantide and 2 patients received placebo. Patient 301002 withdrew due to an AE of lymphoproliferative disorder. Another patient, Patient 305001 experienced an anaphylactic reaction during Treatment Episode 7 and did not receive further medication but was not formally withdrawn from the study.

	Ecallantide N=22 N (%)	Placebo N=26 N (%)	New patients N=19 N (%)	Total N=72 N (%)
Intent to treat population ^a	22 (100.0)	26 (100.0)	18 (94.7)	66 (98.5)
Per protocol population ^b	21 (95.5)	26 (100.0)	18 (94.7)	65 (97.0)
Safety population ^c	22 (100.0)	26 (100.0)	19 (100.0)	67 (100.0)
Patients receiving Dose B	1 (4.5)	1 (3.8)	1 (5.4)	3 (4.5)
Patients withdrawing from study	4 (18.2)	1 (3.8)	5 (26.3)	10 (14.9)
Adverse event	1 (4.5)	0	0	1 (1.5)
Lost to follow-up	2 (9.1)	0	2 (10.5)	4 (6.0)
Voluntary withdrawal	0	1 (3.8)	1 (5.3)	2 (3.0)
Other*	1 (4.5)	0	2 (10.5)	3 (5)

Source: dx-88-14rd-csr-body.pdf, Section 10.1, Table 3

^a Patients who received any amount of study drug

^b Patients who received a complete dose of study drug with no major protocol violations

^c Patients who received any amount of study drug

* 1 patient enrolled in EDEMA4; 2 other patients withdrawn due to Sponsor's decision to discontinue the study.

Patient exposure

In addition to 22 patients from the ecallantide arm in the double-blind phase and 1 patient in the placebo arm that received ecallantide for SUAC, 17 patients (25.8%) had had prior exposure to ecallantide as part of EDEMA1 (n=4) and EDEMA2 (n=15). A total of 160 attacks were treated during the OLE. The majority of patients were treated for 1 attack during the OLE; 1 patient was treated for 13 attacks. The exposure is summarized in Table 48.

HAE attack number	Ecallantide N=22 N (%)	Placebo N=26 N (%)	New patients N=19 N (%)	Total N=67 N (%)
1*	0	0	18 (100.0)	18 (27.3)
2	22 (100.0)	26 (100.0)	3 (16.7)	51 (77.3)
3	13 (59.1)	17 (65.4)	0	30 (45.5)
4	6 (27.3)	15 (57.7)	0	21 (31.8)
5	5 (22.7)	6 (23.1)	0	11 (16.7)
6	4 (18.2)	5 (19.2)	0	9 (13.6)
7	2 (9.1)	1 (3.8)	0	3 (4.5)
8	1 (4.5)	0	0	1 (1.5)
9	2 (9.1)	1 (3.8)	0	3 (4.5)
10	0	1 (3.8)	0	1 (1.5)
11	1 (4.5)	1 (3.8)	0	2 (3.0)
12	1 (4.5)	0	0	1 (1.5)
13	1 (4.5)	0	0	1 (1.5)
14	1 (4.5)	0	0	1 (1.5)

* Includes attack treated during the double-blind phase

Source: dx-88-14rd-csr-body.pdf, Section 10.1, Table 4

Sixty-five of 153 treated attacks in the ITT population involved multiple symptom complexes. Thirty-three attacks had laryngeal involvement. The Applicant reports heterogeneity in individual patients, both in attack site and in severity, from one attack to the next.

Reviewer's comment: The repeat exposure data is limited, given that the number of patients who received more than 2 doses total is so few. The OLE was almost 2 years in duration. While enrollment was ongoing and not all patients were in the study for the entire duration, it is still somewhat surprising that the patients did not present for treatment more frequently. Moderate-to-severe qualifying attacks may have been relatively infrequent. Alternatively, patients may have sought treatment elsewhere for subsequent attacks. The observation of heterogeneity in attack site and severity is consistent with other reports in the literature.

Demographics

The participants in the OLE phase were comparable in terms of age, gender, ethnicity, and HAE history to those patients in the double-blind phase. The OLE included 11 patients who were ≤18 years of age and 7 patients ≤16 years of age.

Efficacy results

The TOS at 4 hours and the change in MSCS from baseline at 4 hours varied by treatment episode. The first treatment episode only includes new patients who did not participate in the double-blind phase. The following tables summarize these results.

Table 49 EDEMA3 OLE: TOS at 4 hours by treatment episode

Treatment episode	N	Median (IQR)	Mean (SD)
1	18	68.8 (50, 100)	71.3 (28.9)
2	51	100 (50, 100)	73.3 (44.9)
3	30	100 (70, 100)	81.9 (28.5)
4	21	100 (38, 100)	81.2 (24.5)
5	11	100 (0, 100)	48.5 (68.5)
6	9	60 (50, 100)	60.4 (49.3)

Source: dx-88-14rd-csr-body.pdf, Section 11.4.1.1, Table 15

Change in MSCS at 4 hours

Table 50 EDEMA3 OLE: Mean change in MSCS at 4 hours by treatment episode

Treatment episode	N	Median (IQR)	Mean (SD)
1	17	-1.0 (-1.5, -1.0)	-1.2 (0.9)
2	51	-1.0 (-1.8, -0.5)	-1.1 (0.9)
3	30	-1.0 (-2.0, -1.0)	-1.3 (0.9)
4	21	-2.0 (-2.0, -1.0)	-1.4 (0.8)
5	11	-1.0 (-1.3, 0)	-0.9 (0.7)
6	9	-1.0 (-1.0, -0.3)	-0.9 (0.8)

Source: dx-88-14rd-csr-body.pdf, Section 11.4.1.1, Table 16

Only 3 patients received Dose B, limiting analysis. Of the 2 patients who received placebo as Dose B, both patients reported symptoms to be “a lot better or resolved” at the 4- and 24-hour assessments. The third patient who received ecallantide as Dose B reported symptoms to be the “same” and did not receive further treatment in the study.

Reviewer's comment: The TOS values suggest efficacy over repeated doses, although the number of patients upon which the TOS is based decreases with each episode. This may be a function of the underlying rate of attacks; alternatively, these results could be due to self-selection of responders vs. non-responders. The MSCS scores appear consistent with the TOS, which is expected as the MSCS is included in the calculation of the TOS. In the absence of a control, these results are difficult to interpret as the natural course of an HAE attack is gradual improvement. Numerically, the results appear comparable to those observed for the ecallantide arm in the double-blind phase and do not indicate any decline in efficacy with repeated use.

Safety endpoints

Common adverse events

Overall, 40 patients (59.7%) reported at least 1 AE during the OLE. Similar AEs as those observed during the double-blind phase were reported. The most common events included headache (n=10), nausea (n=6), HAE (n=6), URI NOS (n=6), and nasopharyngitis (n=5). There was no clear correlation with the nature or frequency of these events by treatment episode. The majority of AEs were reported by 1 patient each.

SAEs

Seven patients reported a total of 18 SAEs, including Patient 305001 who reported a total of 9 SAEs and subsequently withdrew from the treatment episode and did not receive further treatment in the study.

- Patient 305001 experienced anaphylaxis during her 7th treatment episode. Following the event, the patient skin tested positive to ecallantide. She underwent a rechallenge procedure with 1 mg ecallantide SC and developed pharyngeal edema, hypoxia, dyspnea, generalized rash, urinary incontinence, vomiting, anxiety/sense of impending doom, and diarrhea. The patient received 2 doses of epinephrine and was observed in a hospital emergency room for an additional 5 hours prior to discharge home. The patient tested positive for non-IgE antibodies to ecallantide and IgE antibodies to *P. pastoris*. Patient 305001 was previously enrolled in EDEMA2 and had received 13 injections of ecallantide for 12 separate HAE attacks.
- Patient 301002 discontinued from the study due to a diagnosis of lymphoproliferative disease made 16 days after the second follow-up visit for the 11th treatment episode.
- The other SAEs included concussion and laceration sustained during a motor vehicle accident, infectious diarrhea with hematochezia, colitis NOS, and 2 hospitalizations due to HAE.

Laboratory and vital sign evaluations

No consistent patterns or persistent changes in laboratory parameters were observed, both in terms of individual values or mean values. Similarly, no consistent changes in vital sign parameters were observed.

Antibody testing and hypersensitivity reactions

Fifteen of 67 patients (22.4%) had at least 1 serum sample test positive for antibodies to *P. pastoris* or ecallantide. Two patients had positive samples for non-IgE antibodies to ecallantide

and IgE to *P. pastoris*. Four patients (6.0%) tested positive for non-IgE antibodies to ecallantide. Nine (13.4%) tested positive for IgE to *P. pastoris*. One patient tested positive for IgE to ecallantide (Patient 326002) at the first follow-up visit for treatment episode #4, but tested negative on subsequent follow-up visits. No hypersensitivity reaction is reported for the patient, but on the 4th treatment episode, the patient reported generalized pruritus and nausea occurring approximately 10 minutes after injection that last for 25 minutes, followed by injection site pruritus 6.5 hours after injection.

Of the 11 patients with positive IgE to *P. pastoris*, 1 patient had an anaphylactic event and positive rechallenge (Patient 305001, described above) and 1 patient had generalized pruritus and nausea (Patient 326002, described above). A third patient, Patient 317005, developed urticaria approximately 2 hours after receipt of ecallantide. The other nine patients do not have any AEs reported to suggest an allergic reaction (search terms: urticaria, pruritus, rash, wheezing, bronchospasm, syncope, dizziness, lightheadedness, diaphoresis, injection site reaction, drug reaction, and allergy).

In addition to patients with positive serologies, 1 patient reported abdominal itching 4.5 hours after receipt of ecallantide while another patient reported itching "similar to allergies" although the time-course is not specified in this case. Several cases of rash are reported but the time-courses are not specified. Six patients reported some type of injection site reaction, including Patient 326002 described above with the suspected hypersensitivity reaction.

The individual efficacy results over time do not suggest a potential neutralizing effect from non-IgE antibodies to ecallantide, but the data is limited to 6 patients.

Reviewer's comment: Hypersensitivity reactions, including anaphylaxis, appear to be the most serious of the adverse events recorded and the most clearly related to drug administration. A frequency is difficult to calculate give the unequal exposures to the drug among individual patients.

10.4.4 Study summary and conclusions

EDEMA3 is generally supportive of ecallantide's efficacy in the treatment of acute HAE attacks but the study did not demonstrate a statistically significant difference between ecallantide and placebo. The Applicant attributes the non-significant results to the accidental administration of placebo to 1 patient assigned to ecallantide and ecallantide to 1 patient assigned to placebo. When the data is analyzed using an as-treated dataset to correct for this error, the results are statistically significant. While this sensitivity analysis along with secondary and tertiary endpoints suggest efficacy, these results are not robust and confirmatory results from the second placebo-controlled trial, EDEMA4, are needed.

10.5 Individual Study Report: EDEMA4

10.5.1 Study Protocol: EDEMA4 (DX-88/20)

10.5.1.1 Administrative information

- Title: EDEMA4, A randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of DX-88 (ecallantide) for the treatment of acute attacks of HAE
- Study sites: Multicenter, US and Canada
- Study dates: April 16, 2007 to June 26, 2008
- Study report date: September 1, 2008

10.5.1.2 Objectives/Rationale

- Assess the efficacy and safety of 30 mg SC ecallantide vs. placebo in the treatment of moderate to severe acute HAE attacks

10.5.1.3 Study design overview

The study was a Phase 3, randomized, double-blind, placebo-controlled multicenter study conducted under SPA. Patients presenting within 8 hours of onset of a moderate to severe HAE attack were randomized to receive a single dose of 30 mg SC ecallantide or placebo. Patients were stratified by anatomic attack location (laryngeal vs. other).

Patients were eligible to receive an additional open-label dose of ecallantide if the patient was at risk of *severe upper airway compromise (SUAC)* within 4 hours after dosing. Risk of SUAC was defined as the presence of ≥ 3 of the following 7 findings: appearance or worsening of dyspnea, appearance or worsening of stridor, increased respiratory effort, change or loss of voice, cyanosis, decreased oxygen saturation, or increased PaCO₂ and/ or decreased PaO₂. A single additional dose could also be administered if symptoms had failed to resolve or if an attack relapsed from 4 to 24 hours post-first-dose. *Failure to respond* was defined as not achieving "beginning of improvement" within 4 hours post-initial-dose. *Incomplete response* was defined as not achieving "significant improvement" within 4 hours post-dose. Relapse was defined as a reoccurrence of an attack between 4 and 24 hours post-dose.

After treatment, patients were rolled over to an extension study for treatment with open-label ecallantide for new, separate HAE attacks (Study DX-88/19). A study report for DX-88/19 was not included in the BLA.

10.5.1.4 Study population

Patients 10 years or older with documented diagnosis of Type I or II HAE were eligible.

Inclusion criteria

- 10 years of age or older
- Documented diagnosis of Type I or II HAE:
 - Clinical history consistent with HAE (SC or mucosal nonpruritic swelling without accompanying urticaria)
 - Function or antigenic C1-INH level below the lower limit of the normal range or up to 15% above the lower limit of the normal range as defined by the reference laboratory

- C4 level below the lower limit of the normal range or up to 15% above the lower limit of the normal range as defined by the reference laboratory
- Age of reported onset ≤ 25 years or documented complement component C1q level at or above the lower limit of the normal range
- Enrollment visit: presentation at the site within 8 hours of patient recognition of an acute HAE attack with at least one moderate to severe symptom complex (patient and investigator must agree that at least one symptom complex is moderate or severe):
 - **Normal** – patient's state absent of an acute HAE attack
 - **Mild** – noticeable symptoms but do not impact activities of daily living
 - **Moderate** – treatment or intervention highly desirable and symptoms impact activities of daily living
 - **Severe** – treatment or intervention required due to inability to perform activities of daily living
- Sexually active and fertile patients required to use at least 2 methods of contraception for the duration of the study

Exclusion criteria

- Receipt of an investigational drug or device within 30 days prior to study treatment with the exception of:
 - C1-INH concentrate for angioedema within 7 days
 - Ecallantide within 3 days
- Acquired angioedema, estrogen-dependent angioedema, and/or drug-induced angioedema
- Pregnancy or breastfeeding
- Any other condition that may compromise safety or compliance at the discretion of the investigator

Patients could withdraw from the study at any time at their own request or could be withdrawn at the discretion of the investigator or sponsor. Reasons for early withdrawal included adverse event, noncompliance or protocol violation, withdrawn consent, or termination of the study.

10.5.1.5 Study treatments

Treatments administered

- Initial dose
 - Single 30 mg ecallantide administered via 3 x 1cc SC injections to the upper arm, thigh, and abdomen. In the event that an injection site coincided with an attack site, multiple injections could be administered to the same site as long as the injections were separated by a minimum of 5cm.
 - Placebo
- Additional dosing
 - Open-label 30 mg ecallantide
 - Standard of care

Blinding

Ecallantide and placebo are both clear colorless liquids and are indistinguishable by appearance. Vials were labeled with assigned codes corresponding to the randomization codes. A single statistician was unblinded to assigned study treatment; all other study personnel and patients remained blinded.

Randomization

Patients were randomized 1:1 to ecallantide or placebo. The randomization was stratified by anatomic location of the attack (laryngeal vs. others) as determined by the investigator and by prior participation in an ecallantide clinical study (patients may or may not have received ecallantide in the previous study). A third-party vendor provided a centralized web-based or telephone-based system for generation the randomization assignments to individual patients as they presented at the time of their attacks.

Prior and concomitant therapy

Receipt of certain medications was reason for exclusion, as noted above. The CRF was used to record any additional concomitant medications and emergency treatments administered, if any. Emergency treatments included opioid/pain medication, anti-emetics (5-HT3 receptor antagonists), and HAE alternative therapies, listed as follows:

- Aminocaproic acid
- C1-INH
- Fresh frozen plasma
- Tranexamic acid
- Methylprednisolone
- Oxandrolone
- Danazol
- Prednisone
- Stanozolol
- Dexamethasone
- Dehydroepiandrosterone
- Methyltestosterone

Treatment compliance

All study drugs were administered in clinic. Study drug accountability was verified during on-site monitoring visits conducted by the Sponsor.

10.5.1.6 Study procedures

Table 51 EDEMA4: Schedule of procedures									
EDEMA4	Screen	Enroll	Post-dosing evaluation						
			0-4 hrs				Discharge (if ≥5 hrs post-dose)	Day 2	FU Visit 1 Day 7
			0-1	2	3	4			
Informed consent	X							X†	
Urine pregnancy test	X	X							
History, demographics	X								
Physical exam	X	X				X	X	X	
Vital signs	X	X				X	X	X	
ECG	X	X		X		X	X	X	
Urinalysis	X	X						X	
eDiary training	X					X			
eDiary completion		X	X	X	X	X		X	
Symptom complex categorization*		X	X	X	X	X			
Assessment of overall well-being*			X	X	X	X			
Symptom complex assessment*			X	X	X	X			
Severity assessment*		X				X			
Dosing		X							
Open-label DX-88 for incomplete response or relapse						X			
Dosing for severe upper respiratory compromise°			X	X	X	X			
Clinical observations			X	X	X	X	X		
Concomitant meds	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	
Blood samples									
• Chemistry	X	X				X		X	
• CBC/diff	X	X				X		X	
• Coag panel	X	X				X		X	
• C1-INH level (if not done)	X								
• C4 (if not done before)	X								
• Antibody levels									
Phone F/U		X					X	x	

† For DX-88/19 (open-label extension study)

* via eDiary

° Can occur at any time

10.5.1.7 Efficacy parameters

Primary efficacy endpoint: Change from baseline in MSCS

The primary efficacy endpoint was the change from baseline in Mean Symptom Complex Score (MSCS) at 4 hours post-dosing. The MSCS is the arithmetic mean of the severity grade of the individual symptom complexes, where each symptom complex is assessed a severity grade of severe to normal (Table 3).

A decrease from baseline MSCS corresponds to a reduction in severity. The minimum and maximum possible change in MSCS is ±3.0. The following symptom complexes were assessed:

- internal head/neck
- stomach/GI
- genital/buttocks
- external head/neck
- cutaneous

No imputations were made for the primary analysis. Sensitivity analyses performed to assess the effects of emerging symptom complexes and medical interventions were performed using the following imputations. Emerging symptom complexes were included in the MSCS calculation if present at the 4-hour and 24-hour MSCS assessment timepoints. If medical interventions were performed during an attack, the affected symptom complex(es) were assigned a severity of "severe" at 4 and/or 24 hours.

Secondary efficacy endpoints

- **Treatment Outcome Score (TOS) at 4 hours post-dose.** The TOS is a composite global symptom response score:

$$\text{TOS} = \frac{\sum(\text{Baseline severity assessment} \times \text{Response to treatment})}{\sum \text{Baseline severity assessment}}$$

- Symptom complex identification (same complexes assessed for the MSCS)
- Severity assessment of each symptom complex at baseline
 - Severe = 3
 - Moderate = 2
 - Mild = 1
 - Normal = 0
- Response assessment of each symptom complex post-dose ("symptom complex score")
 - Significant improvement = 100, "a lot better or resolved"
 - Improvement = 50, "a little better"
 - Same = 0,
 - Worsening = -50, "a little worse"
 - Significant worsening = -100, "a lot worse"
- The maximum and minimum possible TOS values are +100 and -100, respectively, with a higher value corresponding to greater improvement. A TOS of 0 signifies no change.
- Imputations for sensitivity analyses:
 - Emerging symptom complexes were weighted at the peak severity assessment. If the emerging complex was still present at 4 hours and/or 24 hours, an assignment of "significant worsening" was made. If not present at those timepoints, an assignment of "same" was made.
 - If medical intervention during an attack was performed, a response assessment of "significant worsening" and a severity assessment of "severe" were given at 4 and/or 24 hours.
- **Time to "significant improvement" in Overall Response Assessment, based on period of 15 minutes post-dose to 4 hours post-dose**
 - Global symptom assessment by patient; not based on MSCS or TOS
 - Significant improvement = 100, "a lot better or resolved"
 - Improvement = 50, "a little better"
 - Same = 0,

- Worsening = -50, “a little worse”
- Significant worsening = -100, “a lot worse”
 - Assessed at 15, 30, 45, 60, 75, 90, and 105 minutes, 2, 2.5, 3, 2.5, and 4 hours
- **Proportion of patients maintaining a significant improvement (“a lot better or resolved”)** in overall response continuously during the 24-period after dosing
- **Proportion of responders at 4 hours post-dose**
 - Improvement in existing laryngeal symptoms (not based on changes in individual symptom complex scores but on the overall MSCS)
 - Stabilization of existing peripheral/stomach/GI symptom complexes (4-hour score no worse than baseline)
 - Decrease in MSCS in 4 hours

Tertiary efficacy endpoints

- Durability of response at 24 hours post dose based on MSCS
- Durability of response at 24 hours post-dose based on TOS
- Proportion of responders at 4 hours post-dose based on $TOS \geq 70$
- Proportion of responders at 4 hours post-dose based on $TOS \geq 50$
- Time to onset of sustained improvement in overall response assessment
- Proportion of patients receiving medical intervention
- Assessment of response to open-label dosing for failed or incomplete response or for relapse baseline on the change from baseline MSCS at 4 hours post Dose B
- Assessment of response to open-label dosing for SUAC based on change from baseline MSCS to 4 hours post-SUAC dose

10.5.1.8 Safety parameters

Adverse events

AEs were recorded at enrollment (Study Day 1) through to the follow-up Visit 1 (Study day 7). AE severity was graded using the NCI CTCAE Version 3.0 criteria. Coding of AEs was done using MedDRA Version 10.0 and tabulated by SOC, HLT, and PT. A new and different HAE symptom was recorded as an emerging symptom but was not to be reported as an AE.

Reviewer’s comment: The applicability of these severity grading criteria, which were developed for use in cancer patients, to HAE patients is undetermined.

Physical examination

Physical exams were conducted at screening, enrollment (predose), 4 hours post-dosing, and at Follow-up Visit 1 (Study day 7). If discharge was delayed by 1 hour or more, an exam was repeated.

Vital signs

Body temperature, heart rate, respiratory rate, and sitting blood pressure were assessed at screening, enrollment (predose), 2 hours post-dose, 4 hours post-dose, and at Follow-up Visit 1 (Study day 7). If discharge was delayed by 1 hour or more, vital signs were repeated.

ECG

A 12-lead ECG was performed at screening, enrollment (predose), 2 hours post-dose, 4 hours post-dose, and at Follow-up. If discharge was delayed by 1 hour or more, an ECG was repeated. In cases where an ECG could not be performed immediately due to the severity of the attack, the ECG taken at screening was utilized as baseline. All ECGs were read by a central reading facility (b) (4) that was blinded to patient treatment assignment.

Reviewer's comment: In previous discussions, the Division agreed to the Applicant's proposal for intensive ECG monitoring in EDEMA4 in lieu of a designated thorough QT study.

Clinical laboratory evaluations

Samples for lab evaluations were collected at screening, enrollment (predose), 4 hours post-dose, and at follow-up visit. Lab evaluations included the following: CBC with differential, routine serum chemistry, and coagulations tests. Urinalysis was performed at screening, enrollment, and at Follow-up Visit 1.

Antibody testing

Testing for all classes of antibodies to ecallantide and IgE antibodies to *P pastoris* were performed at enrollment and Follow-up Visit 1 (Study Day 7).

10.5.1.9 Statistical plan

The primary efficacy analysis was conducted on the ITT population, using the Wilcoxon rank sum test blocked by the stratification used for randomization (attack location and prior enrollment in an ecallantide study). No data imputation was performed. Additional sensitivity analyses were performed to assess the effects of emerging symptoms and medical interventions, as described above in 10.5.1.7.

Safety analysis was based on all patients who received any amount of drug. Tabulations and descriptive statistics were used to represent the safety data.

A sample size of 96 patients was calculated to give the study 80% power to detect a probability of 66.6% that an observation in the placebo treated group was less than an observation in the ecallantide treated group using a Wilcoxon rank sum test with a 0.05 two-sided significance level, assuming a 43% effect size. The effect size was approximated from EDEMA3 results, which showed a change in MSCS at 4 hours in the ecallantide arm was -1.10 and -0.63 for placebo.

10.5.2 Results

10.5.2.1 Protocol amendments

- Protocol Amendment 0.1, February 21, 2007 – updated administrative information
- Protocol Amendment 2, December 3, 2007 – increased study size from 52 to 96 patients. Allowed option of paper diary in instances where an eDiary could not be administered. Additional discussion regarding the impact of Protocol Amendment 2 on the primary efficacy findings is found in Section 10.5.2.7.

10.5.2.2 Study patients

Patient disposition

Ninety-six patients were enrolled; 48 in the ecallantide arm and 48 in the placebo arm. The disposition of the patients is shown in Table 8. In the ITT population, a total of 36 patients (17 in the ecallantide arm and 19 in the placebo arm) had previously participated in another ecallantide study. In the ecallantide group, 16 patients participated in EDEMA3, 3 patients in EDEMA1, and 4 patients in EDEMA4. In the placebo group, 15 patients were in EDEMA3, 2 patients in EDEMA1, and 8 patients in EDEMA2.

	Ecallantide N=48 N(%)	Placebo N=48 N(%)	Total N=96 N(%)
Intent to treat population ^a	48 (100.0)	48 (100.0)	96 (100.0)
Per protocol population ^b	47 (97.9)	48 (100.0)	95 (99.0)
Safety population ^c	48 (100.0)	48 (100.0)	96 (100.0)
Patients rolling over to continuation study ^d	47 (97.9)	46 (95.8)	93 (96.9)
Patients withdrawing from study		1 (2.1)	1 (1.0)
Adverse event	0	0	0
Noncompliance or protocol violation	0	0	0
Withdrawal of consent	0	0	0
Lost to follow-up	0	0	0
Investigator discretion	0	0	0
Left study site against medical advice	0	1 (2.1)	1 (1.0)

^a Patients who received any amount of study drug

^b Patients who received a complete dose of study drug with no major protocol violations

^c Patients who received any amount of study drug

^d All patients were intended to roll over to the open-label extension study (DX-88/19) for follow-up safety assessments. A total of 2 patients (1 in the ecallantide arm and 1 in the placebo arm) declined further participation. An additional patient in the placebo arm left the study site against medical advice and was not enrolled in the follow up study.

Source: dx-88-20-csr-body.pdf, Section 10.1, Table 2

10.5.2.3 Protocol deviations

Protocol violations and deviations are summarized in Section 10.2 of the applicant's study report and in Appendix 16.2.2. The majority of violations were due to incomplete e-Diary assessments. In addition, several protocol violated related to patient inclusion criteria were recorded.

- Patient 403019 did not have a documented low C4.
- Patient 407003 did not have historical laboratory levels for C1-INH and C1. Blood samples were taken later.
- Patient 443002 had onset of HAE symptoms at >25 years and did not have a documented C1q level. A blood sample taken prior to dosing later showed a low C1q, which would be more consistent with acquired angioedema (AAE).

10.5.2.4 Treatment compliance

All patients received one 30 mg (3 vials) of study drug. In addition, 3 patients in the placebo group and 1 patient in the ecallantide group received open-label ecallantide for SUAC, and 14 patients in the ecallantide group and 20 patients in the placebo group received 30 mg ecallantide as Dose B.

10.5.2.5 Datasets analyzed

Analyses were based on the intention-to-treat (ITT) population unless otherwise specified. Additional analyses with the per-protocol (PP) population were also performed.

10.5.2.6 Demographics and baseline characteristics

Patient demographics

	Ecallantide N=48	Placebo N=48	Total N=96
Age			
Mean (SD)	37.0 (13.1)	38.0 (12.2)	37.5 (12.6)
Range	15-72	13-72	13-72
Sex (N,%)			
Male	11 (22.9)	20 (41.7)	31 (32.3)
Female	37 (77.1)	28 (58.3)	65 (67.7)
Race (N,%)			
White	39 (81.3)	43 (89.6)	82 (85.4)
Black	3 (6.3)	3 (6.3)	6 (6.3)
Asian	1 (2.1)	1 (2.1)	2 (2.1)
Hispanic	4 (8.3)	1 (2.1)	5 (5.2)
Other	1 (2.1)	0	1 (1.0)

Source: dx-88-csr-body.pdf, Section 11.2.1, Table 4

Reviewer's comment: The treatment groups appear comparable in terms of age and racial distribution, but the ecallantide group has a higher number of female patients compared to the placebo arm. The significance of this gender imbalance is uncertain.

Patient HAE history

Table 54 EDEMA4: Patient HAE history			
	Ecallantide N=48	Placebo N=48	Total N=96
Age at first HAE symptom onset Mean (SD) Range	13.4 (7.4) 0-44	13.0 (9.5) 1-59	13.2 (8.5) 0-59
Lowest historical functional C1-INH Mean % (SD) Range	31.8 (20.1) 0.1-78.0	22.7 (19.6) 0-61.0	27.3 (20.2) 0-78.0
Lowest historical antigenic C1-INH, mg/dl Mean (SD) Range	10.2 (17.1) 0-80.0	12.7 (23.2) 2.4-90.0	11.6 (20.5) 0-90.0
Lowest historical C4, mg/dl Mean (SD) Range	8.8 (13.2) 0-59.0	10.0 (10.9) 1.3-60.0	9.4 (12.0) 0-60.0
Most common prior HAE symptom complex (N,%)			
Laryngeal	3 (6.3)	2 (4.2)	5 (5.2)
Stomach/GI	21 (43.8)	26 (54.2)	47 (49.0)
Genital/buttocks	2 (4.2)	2 (4.2)	4 (4.2)
External head and neck	2 (4.2)	2 (4.2)	4 (4.2)
Cutaneous	26 (54.2)	23 (47.9)	49 (51.0)

Source: dx-88-csr-body.pdf, Section 11.2.3 Table 6 and 7

Reviewer's comment: The treatment groups appear comparable in terms of age of onset, historical laboratory values, and prior attack site history.

Concomitant medications

The majority of patients, 83 of 96, reported taking concomitant medications at screening (42 in the ecallantide arm, 41 in placebo arm). The most common medications used were sex hormones, taken in similar proportions by both treatment arms. Notable differences between the treatment groups were the following:

- Antihistamines: 18.8% ecallantide vs. 35.4% placebo
- Medications for obstructive airway disease: 4.2% ecallantide vs. 18.8% placebo
- Psychoanaleptics: 29.2% ecallantide vs. 8.5% placebo

Reviewer's comment: The significance of these differences in concomitant medications is unclear. These particular medications are not known to have a specific efficacious or exacerbating effect in HAE, although both antihistamines and psychoanaleptics are occasionally used to treat urticaria and non-hereditary angioedema.

Presenting symptom complex severity

Each randomized patient presented with at least one symptom complex that was moderate to severe. Patients could report multiple symptom complexes. In the ecallantide group, the most commonly reported moderate-severe symptom complex was cutaneous. The placebo arm had a larger number of patients reporting moderate-severe GI symptoms in comparison.

Table 55 EDEMA4: Patient-reported symptom complex severity at baseline

	Ecallantide N=48 N, %	Placebo N=48 N, %	Total N=96 N, %
Number of symptom complexes at baseline	80	75	155
Internal head/neck symptoms (including laryngeal)			
Mild	0	6 (12.8)	6 (6.3)
Moderate	6 (12.5)	6 (12.8)	12 (12.6)
Severe	2 (4.2)	1 (2.1)	3 (3.2)
Stomach/GI			
Mild	5 (10.4)	1 (2.1)	6 (6.3)
Moderate	9 (18.8)	20 (42.6)	29 (30.5)
Severe	4 (8.3)	6 (12.8)	10 (10.5)
Genital/buttocks			
Mild	0	1 (2.1)	1 (1.1)
Moderate	4 (8.3)	3 (6.4)	7 (7.4)
Severe	2 (4.2)	1 (2.1)	3 (3.2)
External head/neck			
Mild	4 (8.3)	0	4 (4.2)
Moderate	8 (16.7)	9 (19.1)	17 (17.9)
Severe	2 (4.2)	0	2 (2.1)
Cutaneous			
Mild	2 (4.2)	4 (8.5)	6 (6.3)
Moderate	23 (47.9)	17 (36.2)	40 (42.1)
Severe	9 (18.8)	0	9 (9.5)

Source: dx-88-20-csr.pdf, Section 11.2.5, Table 11

Reviewer comment: The distribution of attack sites is not equal, with cutaneous attacks predominating in the ecallantide group versus stomach/GI attacks in the placebo group. This uneven distribution could impact efficacy findings, if ecallantide works better on cutaneous symptoms, for example, or if the PRO instruments do not assess different attack site symptoms similarly. However, the literature and the PRO validation studies actually suggest the opposite relationship – GI symptoms, primarily pain, tend to resolve more rapidly than peripheral symptoms in most HAE attacks and show larger responses on the TOS. In terms of laryngeal involvement, the groups are comparable.

10.5.2.7 Efficacy endpoint outcomes

Primary efficacy endpoint: Change from baseline MSCS at 4 hours

Results from the primary efficacy analysis are shown below. The treatment arms had comparable baseline MSCS scores. A statistically significant greater decrease in MSCS from baseline was observed in the ecallantide group compared to the placebo arm. Similar results were observed for the per-protocol population analysis as well (p=0.011).

Table 56 EDEMA4: Primary efficacy endpoint, Change from baseline MSCS at 4 hours post-dose

	Baseline MSCS	Change from baseline at 4h	P
Ecallantide	2.2 (0.5)	-0.8 (0.6)	0.01
Placebo	2.0 (0.4)	-0.4 (0.8)	

Source: dx-88-20-csr.pdf, Section 11.4.1.1, Table 14

Imputations for emerging symptom complexes and medical interventions were also performed. These results are displayed in Table 10 EDEMA4: Primary efficacy endpoint sensitivity analyses.

	Mean change from baseline MSCS at 4 hours		
	Ecallantide (N=47)	Placebo (N=48)	P
Imputation for emerging symptoms	-0.8 (0.6)	-0.2 (0.9)	<0.001
Imputation for emerging symptoms and medical intervention	-0.8 (0.7)	-0.1 (0.9)	<0.001

Source: dx-88-20-csr.pdf, Summary tables 14.2.3.2.1 and 14.2.3.2.2

Reviewer's comment: The primary efficacy results support the efficacy of ecallantide. The treatment difference of -0.4 exceeds the proposed MCID of 0.3, which the clinical review accepts as clinically relevant. Additional sensitivity analyses performed for emerging symptoms and medical interventions also support ecallantide's efficacy.

Secondary efficacy endpoints

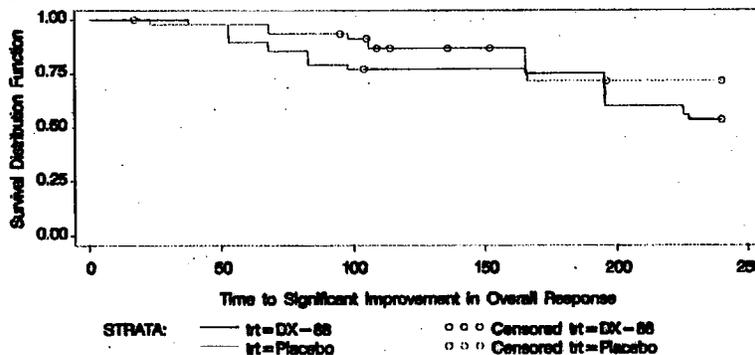
TOS at 4 hours

The TOS at 4 hours was the primary efficacy endpoint in the other pivotal Phase 3 trial, EDEMA3. A statistically significant difference between the ecallantide group (mean TOS 53.4, SD 49.7) and the placebo group (mean TOS 8.1, SD 63.2) was observed (p=0.003). Similar results were reported for the PP population. A positive TOS represents symptom improvement.

Time to significant improvement in overall response

Although a greater proportion of ecallantide patients reported significant improvement than placebo (22 vs. 12 patients, p=0.05), no statistically significant differences were noted in the time to significant improvement in overall response between ecallantide and placebo (184.3 vs. 154.3 minutes; p=0.117). Results were censored at 4 hours (Figure 5).

Figure 5 EDEMA4: Time to significant improvement in overall response (Source: dx-88-csr-body.pdf, Figure 3)



Proportion of patients with a successful response at 4 hours based on MSCS

A “successful response” was defined as improvement in an existing laryngeal symptom complex, stabilization of an existing peripheral symptom complex, or a decrease in MSCS of at least -1.0. Using this definition, 45 of 48 (93.8%) of ecallantide patients were responders versus 28 of 47 (59.6%) of placebo patients ($p<0.001$). When assessed by logistic regression models, anatomic site of attack was also predictive of a successful response, meaning the odds of having a successful response within 4 hours was 8.49 times higher for non-laryngeal attack patients compared to laryngeal attacks ($p=0.022$). Prior exposure to ecallantide was not a predictor of successful response.

Maintenance of significant improvement in overall response

“Maintenance” was defined as achieving and maintaining an assessment of “a lot better or resolved” through 24 hours after dosing. Twenty-one of 48 (43.8%) ecallantide patients compared to 10 of 47 (21.3%) placebo patients reported maintenance ($p=0.022$). Attack site location and prior exposure to ecallantide were not determinants of response.

Tertiary efficacy endpoints

Durability of response at 24 hours post-dosing based on MSCS and TOS

Both the change in MSCS and TOS at 24 hours were statistically significant in favor of ecallantide (Table 58). Sensitivity analyses performed for emerging symptoms and medical intervention were consistent with a more durable response in the ecallantide arm versus placebo ($p=0.019$ and 0.041).

Table 58 EDEMA4: Mean change from baseline MSCS and TOS at 24 hours

	Baseline MSCS	Δ MSCS at 24 hours	P	TOS at 24 hours	P
Ecallantide	2.2 (0.5)	-1.5 (0.6)	0.039	88.8	0.019
Placebo	2.0 (0.4)	-1.1 (0.8)		55.1	

Source: dx-88-20-csr.pdf, Section 11.4.3.1, Tables 24 and 27

Proportion of responders at 4 hours based on TOS \geq 70 and TOS \geq 50

Using a TOS cutoff of 70, more ecallantide patients (22 of 48, 45.8%) qualified as responders compared to the placebo arm (9 of 47, 19.1%) [$p=0.011$]. When a similar analysis is performed using a TOS cutoff of 50, similar results are obtained (68.8% vs. 27.7%, respectively; $p<0.001$). Attack location and prior exposure to ecallantide were not significant predictors for either cutoff point.

Patients receiving medical intervention during attack

Fewer patients in the ecallantide group (16 of 48, 33.3%) received medical intervention than in the placebo group (24 of 48, 50.0%) [$p=0.106$]. There were no statistically significant differences in medical intervention patterns by prior use of ecallantide or attack location. No patients required urgent surgical decompression or intubation. The most common medical interventions administered were emergency medications, consisting of 5-HT3 receptor antagonists, opioids, anti-emetics. One placebo patient also received C1-INH replacement therapy.

Open-label ecallantide administered for SUAC or incomplete response/relapse was considered a medical intervention. Of the 48 ecallantide patients, 14 (29.2%) received a Dose B of ecallantide for incomplete response or relapse, and 1 received Dose B for SUAC. The

majority (n=11) received a Dose B within 6 hours of the first dose of ecallantide. In the placebo group, 20 (41.7%) received a Dose B for incomplete response or relapse, and 3 (6.3%) patients received Dose B for SUAC. The mean change in MSCS for patients receiving a Dose B for incomplete response or relapse was -0.8; for SUAC patients, the mean change in MSCS was -0.1. Dose B was unblinded, so there is no control for comparison.

Reviewer's comment: In general, the secondary and tertiary endpoints are numerically supportive, if not statistically significant, in favor of ecallantide over placebo. The efficacy variables which are independent of the MSCS and TOS calculation – patients' self global-assessments, medical interventions, and emerging symptoms – help confirm the MSCS and TOS scores.

EDEMA4 efficacy results pre- and post-sample size change

However, exploratory analysis of the EDEMA4 results performed by the statistical review team raised questions about the robustness of these findings. The Applicant amended the protocol once the study had been initiated to increase the sample size from 52 to 96 patients. At the time, the Division had agreed to the amendment provided that it was not based upon an unblinded assessment of EDEMA4 collected up until that time point. In addition, the Division had stated that patient selection and study conduct should not change. Table 11 shows the efficacy results pre-and post-sample size adjustment.

	EDEMA4 pre-sample size change N=52			EDEMA4 post-sample size change N=44		
	Ecaltantide N=28	Placebo N=24	Treatment difference (p value)	Ecaltantide N=20	Placebo N=24	Treatment difference (p value)
MSCS						
Mean Δ from baseline 4h [baseline]	-0.7 [2.3]	-0.6 [2.1]	-0.1 (0.83)	-0.9 [2.1]	-0.1 [1.9]	-0.8 (<0.001)
TOS at 4 hrs (mean)	43	19	24 (0.24)	67	-5	72 (0.006)

The results for the original 52 patients planned for EDEMA4 were not significant, while the results for the additional 44 patients were statistically significant. The 44 patients added after the protocol amendment drive the statistically significant results. In particular, the placebo group performed appreciably worse than in the latter part of the study. When comparing the patients enrolled before and after the sample size change (Table 12), no clear differences in demographics or baseline HAE history emerge to explain the discrepancy.

Table 60 EDEMA4 demographics and HAE history pre- and post-sample size change				
	Pre-sample size Δ		Post-sample size Δ	
	Ecallantide N=28	Placebo N=24	Ecallantide N=20	Placebo N=24
Mean age	38	36	36	40
Female, n (%)	20 (71)	12 (50)	17 (85)	16 (67)
Caucasian, n (%)	25 (89)	22 (92)	14 (70)	21 (88)
Mean age at first HAE symptom onset	14	11	13	15
Mean % lowest historical functional C1-INH	30	29	5	13
Mean lowest historical antigenic C1-INH, mg/dl	8	15	15	11
Mean lowest historical C4, mg/dl	6	10	13	10
Primary attack location, n(%)				
Abdominal	6 (21)	15 (63)	4 (20)	10 (44)
Laryngeal	3 (11)	2 (8)	5 (25)	5 (22)
Peripheral	19 (68)	7 (29)	11 (55)	8 (35)
Severity				
Moderate	16 (57)	19 (79)	16 (80)	21 (91)
Severe	12 (43)	5 (21)	4 (20)	2 (9)

More patients in the earlier part of the study appear to have participated in other ecallantide studies, which is not surprising. In terms of presentation, there appear to be more severe attacks in general before the sample size adjustment compared to afterwards as well as fewer laryngeal attacks. Both before and sample size adjustment, more patients in the ecallantide group had severe attacks compared to placebo. Conceivably, more severe attacks may be less likely to respond to ecallantide, although this pattern was not been consistently observed in the efficacy data as a whole. When comparing the results pre- and post-amendment, the performance of the ecallantide group is not that different despite differences in starting severity.

Reviewer's comment: The mean lowest historical functional C1-INH levels appear to be lower in the post-sample size change group. C1-INH levels do not predict frequency or severity of attacks, but it is conceivable that there may be some correlation between C1-INH levels and response to therapy. Further exploratory analysis of this issue is pending at the time of this review. However, it is unlikely that this discrepancy explains the contrasting results pre- and post-sample size change since it is the placebo group which appears to perform poorly in the second half of the study.

The Applicant proposed that relative differences in the primary anatomic site of attack may have impacted these results. According to the Applicant's experience, abdominal attacks tend to resolve more quickly and have larger responses at 4 hours in comparison to peripheral attacks. There were proportionately more placebo patients with peripheral attacks following the sample size change compared to before, although in both parts of the study, there were still more ecallantide patients with peripheral attacks. In addition, there is no predominant attack site among the most extreme patients who drive the primary results. The following figure illustrates how 6 placebo patients treated after the study amendment performed appreciably worse than the rest of the cohort (circled in green).

Figure 6 EDEMA4: Placebo outlier patients

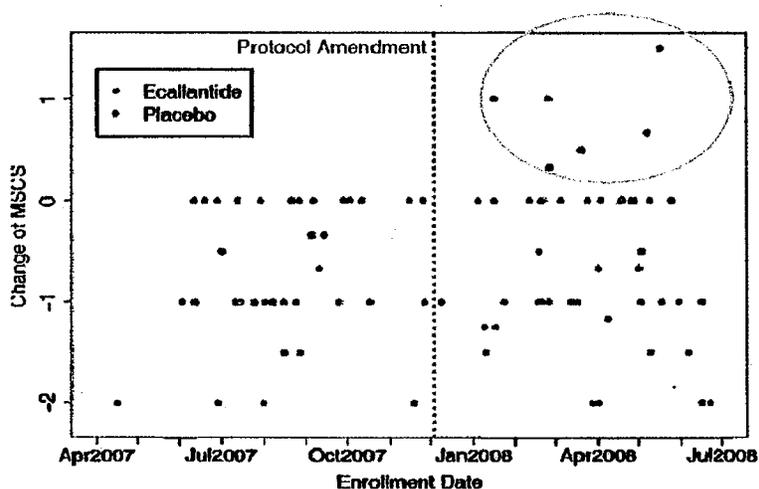


Table 13 summarizes the demographics and efficacy results for the 6 identified outlier patients. Both male and female patients were represented and the age was close to the mean age for the total population. The patients were each recruited at a different US study site. No single anatomic attack site predominated. All of the patients required a Dose B for persistence or worsening of symptoms. Some patients appeared to improve after administration of Dose B while 1 patient reported no improvement and a second worsened considerably and required hospitalization for a worsening abdominal attack. There were no clear characteristics that distinguished these 6 patients from the rest of the study population.

Patient	Age	Δ MSCS [baseline]	TOS	Global self-assessment	Other interventions	Attack site
413003	39y WF	1.0 [2.0]	-100	Lot worse	Dose B (MSCS -2.0)	Abd
417002	39y WF	1.0 [1.5]	-33.3	Little worse	Dose B (MSCS -0.5) Ibuprofen Day2	Periph
438004	37y WM	1.0 [2.0]	0	same	Dose B (MSCS 0)	Periph
438005	30y WM	0.3 [1.7]	-70.0	Little worse	Dose B (MSCS 0.33)	Abd
439006	27y WF	1.5 [1.5]	-100	Lot worse	Dose B (MSCS 1.5) ondansetron morphine oxycodone/acetaminophen Hospitalized for worsening attack	Abd
459001	32y HM	0.7 [2.0]	-66.7	Lot worse	Dose B (MSCS -1.0)	Larynx

10.5.2.8 Safety outcomes

Extent of exposure

Forty-eight patients received double-blinded ecallantide; an equal number received double-blinded placebo. In addition to the double-blinded dose, 1 patient (2.1%) in the ecallantide arm

and 3 patients in the placebo arm received an open-label ecallantide dose for SUAC. Another 14 of 48 patients (29.2%) in the ecallantide group and 20 of 48 (41.7%) in the placebo group received open-label ecallantide as Dose B for failure to resolve to relapsing symptoms. One of the 3 patients in the placebo group who received an SUAC dose also received a Dose B of ecallantide (2 doses of 30 mg ecallantide total in addition to the double-blinded placebo dose). Overall, 70 of 96 patients (72.9%) received at least 1 dose of 30 mg ecallantide and 16 patients received 2 doses of 30 mg ecallantide during the study.

Reviewer's comment: The use of open-label dosing for SUAC and Dose B complicates the safety assessment, since only 10 patients received placebo alone.

Adverse events

Deaths and Serious Adverse Events (SAE)

No deaths or life-threatening AEs were reported during the double-blind treatment portion. A total of 3 SAEs were reported. During the double-blind portion, 2 patients in the placebo arm reported an SAE of HAE. No patients in the ecallantide arm reported an SAE during the double-blind portion. For patients who received open-label ecallantide for SUAC or Dose B, 1 patient reported an SAE of worsening HAE requiring hospitalization.

Discontinuations due to AEs

No discontinuations due to AEs were reported, although 1 patient in the ecallantide arm and 2 patients in the placebo arm declined to enroll in the subsequent open-label extension study (DX-88/19).

Common adverse events

Table 62 displays AEs occurring in 2 or more patients during double-blind treatment.

Table 62 EDEMA4: Adverse events occurring in 2 or more patients		
Adverse event	Ecallantide N=48 N (%)	Placebo N=48 N (%)
Headache	2 (4.2)	5 (10.4)
Nausea	3 (6.3)	1 (2.1)
Dizziness	2 (4.2)	1 (2.1)
Vomiting	0	3 (6.3)
Diarrhea	0	3 (6.3)
Abdominal pain	1 (2.1)	2 (4.2)
HAE	0	3 (6.3)

Source: dx-88-20-csr-body.pdf, Section 12.2.1

Among patients who received open-label ecallantide for SUAC or Dose B, 2 of 37 patients (5.4%) reported a local injection site reaction. These reactions were described as transient and were characterized by local erythema and swelling. These reactions were not accompanied by pruritus, urticaria, or other symptoms suggestive of hypersensitivity. Local injection site reaction

was reported in 1 placebo patient in the double-blind portion of the study. No other AEs were reported in more than 1 patient during the open-label portion.

Reviewer's comment: Given the low sample size, the assessment of common adverse events is limited. The most commonly reported symptoms in the ecallantide group could also be attributed to HAE. Of note, the overall reporting rate for HAE as an AE is much lower in this study than the rate reported in EDEMA3. In both studies, HAE was not to be reported as an AE but the Applicant reports that this guideline may not have been followed in EDEMA3.

Laboratory testing

No clinically significant alterations in mean routine laboratory tests, including coagulation parameters, were reported. In individual patients, 9 of 44 ecallantide patients (20.5%) had a shift from euglycemia to hyperglycemia at the 4 hour mark.

In terms of antibody testing, one patient (403019) developed new anti-ecallantide antibodies during the study after a single dose. Three patients in the ecallantide arm tested positive at the lower limit of detection (titer of 5 or less) at study entry (438001, 417002, and 452004); 2 of these 4 had no prior exposure to ecallantide. A 4th patient (404004) had titers well above 5 and had previously participated in EDEMA3 and had received 2 doses of ecallantide. This patient also tested positive during EDEMA3. In the placebo group, 2 patients tested positive at screening and follow-up, while 2 more were negative at study entry before seroconverting at follow-up. No patients developed IgE antibodies to ecallantide to *P pastoris* within the 7 day follow-up period.

Reviewer's comment: The antibody testing was extended to 28 day follow-up as part of the open-label extension study, DX-88/19. Those results are not included in the submission.

Vital signs

No clinically significant mean changes in vital sign parameters were reported. One patient (428004) in the ecallantide group reported pyrexia on Day 3 of double-blind treatment accompanied by pharyngolaryngeal pain that resolved by the next day without treatment.

Physical examinations

The majority of physical exam findings reported were signs and symptoms related to the presenting HAE attack. No notable abnormalities were otherwise reported.

Electrocardiograms

In the ecallantide group, the mean change in QTc interval from baseline was 2.5, 3.5, and -6.2 msec at 2 hours, 4 hours, and 7 days post-dose, respectively. In the placebo group for the same time points, the mean changes were -0.3, 2.0, and -8.3 msec, respectively. No patients in either treatment group had a QTc value >500 msec during double-blind treatment. No significant individual shifts from normal to abnormal were reported. Similarly, no clinically relevant mean changes were observed for the ST segment, PR or QRS intervals.

Reviewer's comment: In lieu of a formal QT study, the Applicant performed more intensive ECG monitoring during EDEMA4 to address any potential QTc effects. The intervals selected for ECG monitoring were previously discussed with the Division.

10.5.4 Study summary and conclusions

EDEMA4 provides efficacy and safety support for ecallantide as a treatment of acute HAE attacks. The study used a related but different endpoint for the primary efficacy analysis and was also approximately double in sample size compared to EDEMA3, which may explain in part the different statistical outcomes in the two studies. In terms of effect sizes and treatment differences, the MSCS results from EDEMA4 and EDEMA3 were similar, which suggests that EDEMA3's non-significant findings may be due in part to the smaller sample size. The EDEMA4 primary efficacy results appear robust but additional analysis of the results pre- and post-sample size change indicate that the results are driven largely by several outlier patients in the placebo group who performed worse than the placebo patients in the first half of the study. This inconsistency in the results may be a reflection of the inherent variability of the disease. As the reason for this discrepancy remains uncertain, the clinical review relies on additional evidence of support from the secondary endpoints, particularly the global self-assessment and the medical intervention patterns, which were two efficacy measures that were independent of the MSCS and TOS calculations. When considered in its entirety and given the unmet medical need, the results of EDEMA4 are supportive of the proposed indication in patients 18 years of age and older. Conclusions about efficacy in the pediatric population cannot be made, as only 2 patients under the age of 18 years (ages 16 and 17 years) received ecallantide during the double-blind phase of the study.

10.6 Individual Study Report: Rechallenge study

10.6.1 Study Protocol: Study DX88-102

10.6.1.1 Administrative information

- Title: DX88-102, Clinical report of the DX-88 (ecallantide) rechallenge testing procedures
- Study report date: July 30, 2008

10.6.1.2 Objectives/Rationale

- Evaluate the sensitivity to ecallantide in patients with prior hypersensitivity reactions in EDEMA1, EDEMA2, or EDEMA3 clinical studies

10.6.1.3 Study design overview

In order to further define hypersensitivity reactions to ecallantide, patients with a history of a reaction in EDEMA1, EDEMA2, or EDEMA3 were invited to enroll in a rechallenge study. The study consisted of 2 phases: a skin-testing phase and a test-dose phase. For the skin-test phase, escalating doses of ecallantide were administered by skin-prick and intradermal injection and compared to histamine and saline controls. A skin test was considered positive if the difference in the observed erythema or edema was >3mm from the saline control. For the test-dose phase, escalating doses were administered via intravenous infusion. No subcutaneous injections were

administered and the escalating dose procedure was not intended as a drug desensitization protocol.

If any test was positive, the patient could proceed to the next test only with the approval of the Sponsor and the investigator. At the investigator's discretion, patients could also undergo a separate desensitization protocol.

10.6.1.4 Study population

Patients with a history of prior hypersensitivity reaction to ecallantide during EDEMA1, EDEMA2, and EDEMA3 were eligible to participate. The reaction had to be assessed as moderate or severe in intensity by the investigator or medical monitor and have characteristics of an immune-mediated, acute hypersensitivity reaction (e.g. bronchospasm, hypotension, urticaria, etc.).

Inclusion criteria

- >10 years of age
- 2 barrier methods of contraception for the duration of the rechallenge up through 28 days after the last dose of ecallantide if sexually active and fertile

Exclusion criteria

- Undocumented, ongoing acute allergic symptoms
- Pregnancy or breastfeeding
- Antihistamine use 48 hours prior to skin testing
- Current alcohol or drug abuse
- Receipt of an investigational drug or device other than ecallantide within 30 days prior to rechallenge dosing
- Other conditions which may compromise safety or compliance per the investigator

10.6.1.5 Study treatments and procedures

Rechallenge phase

Skin-testing phase

- Skin prick testing
 - Low host-cell-protein (HCP, <5ng/ml) ecallantide
 - 1:100
 - 1:10
 - Full strength (10mg/ml)
 - High HCP (23.5 ng/ml) ecallantide
 - 1:100
 - 1:10
 - Full strength (10mg/ml)
 - Saline negative control
 - Histamine positive control
- Intradermal testing
 - Both low and high HCP
 - 1:100,000
 - 1:10,000
 - 1:1,000
 - 1:100
 - 1:10
 - Full-strength (10 mg/ml)
 - Histamine
 - Saline

Test-dose phase

If all skin testing was negative, patients could enter the test dose phase.

- Stage 1 (low HCP; all doses administered over 3 minutes via IV at an interval of 30 minutes)
 - 3 mg
 - 4.5 mg
 - 7.5 mg
 - 15 mg
- Stage 2 (no sooner than 72 hours after Stage 1)
 - 30 mg ecallantide (20 ml over 30 minutes)

If Stage 2 completed successfully, patient could re-enroll in regular study.

Desensitization

If positive results observed during skin testing or test-dosing, the investigator could design a unique desensitization procedure for the patient pending approval by the Sponsor. In the end, no desensitizations were performed.

10.6.1.6 Efficacy parameters

No formal efficacy assessments were made.

10.6.1.7 Safety parameters

Routine safety assessments included the following:

- Adverse events
- Vital signs

- Physical exams
- Tryptase levels at screening, prior to skin testing and test dosing, and following each test dose

The schedule of procedures is shown below.

Procedure	Screening for Rechallenge Procedures	Visit 1	Visit 2
Informed Consent Form	X		
Vital Signs ^a	X	X	X
Physical Exam	X	X	X
Medical History	X		
Concomitant Medications ^b	X		
PST		X	
Intradermal Skin Test		X	
Intravenous Testing Phase 1		X	
Intravenous Testing Phase 2			X
Adverse Events		X	X
Tryptase Levels ^c	X	X	X
Antibody Collection ^c	X	X	X

^a Heart rate, blood pressure, temperature.

^b Concomitant medications were reviewed prior to skin testing.

^c Not consistently collected.

10.6.1.8 Statistical plan

No formal statistical analysis was planned.

10.6.2 Results

10.6.2.1 Study patients

Nine patients underwent the rechallenge testing procedures. Two of the 9 had had a hypersensitivity reaction in EDEMA1, 5 patients were from EDEMA2, and 2 patients were from the repeat-dosing phase of EDEMA3. Six of the 9 patients were female and all were Caucasian. The mean age was 30 years.

10.6.2.2 Outcomes

The following table summarizes the outcome of rechallenge for all 9 patients. Six of the 9 patients successfully completed the test-dosing phase. Four of the 6 patients have since gone on to participate in other ecallantide studies and have not experienced additional hypersensitivity reactions. Three patients had positive test results:

- Patient 8805019001 was a prior participant in EDEMA2. After the initial dose of 20 mg/m² IV, the patient developed eye erythema, eye swelling, urticaria of the back and face, nasal congestion, rhinorrhea and sneezing. She tested positive for specific IgE to *P. pastoris* 3 weeks prior to ever receiving study drug. During the rechallenge, she successfully completed the skin testing phase. However, approximately 8 minutes after the start of the 3 mg IV infusion, she developed sneezing, rhinorrhea, nasal congestion, cough, and throat itchiness. She received Benadryl and her symptoms resolved.

- Patient 8805051099 participated in EDEMA2 and received 13 doses of ecallantide without reaction. The patient subsequently enrolled in EDEMA3 and received 7 doses over a 5-month period. After the 7th dose, she developed pruritus and anaphylaxis (hypoxia and hypotension). The patient had positive IgE antibodies to *P. pastoris*. During the rechallenge, the patient developed a positive skin reaction on ID testing at the 1:100,000 dose. The investigator requested permission to administer a 1 mg SC dose. Seven minutes after dosing, the patient developed dyspnea, rash, anxiety, pharyngeal edema, vomiting, diarrhea, urinary incontinence, and hypoxia, consistent with anaphylaxis. The patient was treated with epinephrine and conveyed to the hospital for further observation prior to being discharged home. The patient has not participated in further studies.
- Patient 8814326002 was a participant in EDEMA 3 and received 4 doses of ecallantide. After the 4th injection, the patient experience nausea, pruritus, and injection site pruritus. The patient tested positive for IgE antibodies to *P. pastoris* and non-IgE antibodies to ecallantide. During rechallenge, the patient had a positive ID test at 1:10,000 dilution. The patient did not participate in further studies.

Results of the rechallenge procedure for all 9 patients is summarized below.

Patient	Skin-Testing Phase		Test-Dosing Phase		Eligible for Future Treatment with Ecallantide
	PST	ID	Stage 1	Stage 2	
8804013002	Completed	Completed	Completed	Completed	Yes
8804013003	Completed	Completed	Completed	Completed	Yes
8804013007	Completed	Completed	Completed	Completed	Yes
8804013011	Completed	Completed	Completed	Completed	Yes
8805019001	Complete	Complete	Received 3 mg dose prior to hypersensitivity AEs	Not done	No
8805024097	Completed	Completed	Completed	Completed	Yes
8805054099	Completed	Completed	Completed	Completed	Yes
8805051099	Completed	Received 1:100,000 dilution prior to hypersensitivity AEs	Not done*	Not done	No
8814326002	Completed	Received: up to 1:1000 dilution prior to positive skin reaction	Not done	Not done	No

* Patient 8805051099 did not advance to the Test-Dosing phase of the rechallenge, but instead received an additional 1 mg SC rechallenge dose of ecallantide.

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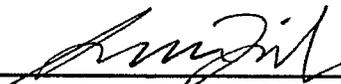
10.6.4 Study summary and conclusions

Overall, the rechallenge procedure successfully identified patients who could receive additional ecallantide. None of the patients who had a successful rechallenge who then went on to further dosing have had new AEs suggestive of hypersensitivity. The safety of the rechallenge procedure, performed in the appropriate setting, appears comparable to similar graded challenge procedures for other drug allergies. However, the total number of patients studied is limited, so the generalizability of these results is uncertain.

Notably, it is not possible to predict on the basis of the case narratives of the original hypersensitivity reactions which patients may fail or pass a graded challenge. The case narratives are similar enough that history alone would be insufficient to make this prediction. Antibody status also is not clearly predictive. While all 3 patients who failed rechallenge and the patient with the most severe reaction, Patient 8805051099, did have positive IgE antibodies to *P. pastoris*, the application includes information on other patients with positive antibodies who did not have any hypersensitivity reactions, suggesting that the positive predictive value may be limited. The negative predictive value may be higher but this issue has not been systematically addressed.

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Signatures:

Reviewer Signature:  Date: 2/13/09
Susan Limb, M.D.

Team Leader Signature:  Date: 2/13/09
Sally Seymour, M.D

Concurrence Yes No

MEDICAL OFFICER REVIEW
Division Of Pulmonary and Allergy Products (HFD-570)

APPLICATION: BLA 125277	TRADE NAME: Kalbitor
APPLICANT/SPONSOR: Dyax	USAN NAME: Ecallantide
MEDICAL OFFICER: Susan Limb, MD	
TEAM LEADER: Sally Seymour, MD	CATEGORY: Kallikrein inhibitor
DATE: November 12, 2008	ROUTE: Subcutaneous injection

SUBMISSIONS REVIEWED IN THIS DOCUMENT

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
September 23, 2008	September 23, 2008	BLA 125277, N0002	BLA electronic submission

RELATED APPLICATIONS

<u>Document Date</u>	<u>Application Type</u>	<u>Comments</u>
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REVIEW SUMMARY:

This is a 45-day filing and planning review of a BLA for ecallantide, a recombinant human plasma kallikrein inhibitor intended for the treatment of acute attacks of hereditary angioedema (HAE) in patients 10 years of age and older. HAE is a rare, autosomal dominant disorder estimated to affect 1 in 10,000 to 50,000 individuals. The disease is characterized by sporadic, unpredictable attacks of angioedema and mucosal swelling. Attacks can be life-threatening, particularly those attacks involving the airway. Currently, no products are approved for the treatment of acute attacks. The drug has been granted Orphan Drug and Fast Track status, and the application will be reviewed under Priority review.

In support of the application, the Applicant has submitted results of five clinical studies in HAE, including two pivotal, placebo-controlled trials, EDEMA3 (DX-88/14) and EDEMA4 (DX-88/20). EDEMA4 was conducted under an SPA. Additional safety and efficacy data obtained from the ongoing open-label extension of EDEMA3 is also submitted; data from the EDEMA4 extension has not been included in this initial submission. These study reports are appropriately indexed and organized to allow review. The sponsor has provided an Integrated Summary of Efficacy, Integrated Summary of Safety, Integrated Summary of Benefits and Risks, copies of proposed labeling, and appropriate case report forms.

From a clinical standpoint, the submission is adequate to allow clinical review and qualifies for Priority review. The submission is fileable.

OUTSTANDING ISSUES: None.

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS: X	FILEABLE	NOT FILEABLE
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1. GENERAL INFORMATION AND BACKGROUND

DX-88 (ecallantide) is a kallikrein inhibitor intended to treat symptoms of hereditary angioedema (HAE). HAE is a rare, autosomal dominant disorder estimated to affect 1 in 10,000 to 50,000 individuals. HAE patients have low concentration (Type 1) or low functional activity (Type 2) of C1 esterase inhibitor (C1 INH). Major symptoms include angioedema and edema affecting the airway and GI tract. Anabolic androgens, antifibrinolytic agents, and replacement therapies are used for prophylaxis. In the US, treatment for acute attacks is limited to supportive care; no drug products are currently approved the treatment of acute attacks of HAE.

The text from the proposed INDICATIONS AND USAGE section of the label follows: "Kalbitor is a plasma kallikrein inhibitor indicated for treatment of acute attacks of hereditary angioedema (HAE). [REDACTED] (b) (4)

[REDACTED] In the Integrated Summary of Risks and Benefits, the BLA states that Kalbitor is "intended for use under the guidance and supervision of a healthcare professional for the treatment of acute attacks by SC administration."

[REDACTED] (b) (4)

The 505(b)(1) BLA application is an electronic submission. The BLA qualifies for a priority review on the basis that acute HAE attacks have life-threatening potential for which there does not exist an approved, efficacious therapy. The BLA will be the subject of an Advisory Committee meeting, given that ecallantide is an NME with a novel indication.

2. CLINICAL DEVELOPMENT PROGRAM

The Applicant has conducted 10 clinical studies with ecallantide, two of which are ongoing. These studies include 4 trials in healthy volunteers, 5 studies in HAE, and 1 study in cardiothoracic surgery (CTS). At the time of BLA submission, two studies remain ongoing: 1 open-label HAE study and the CTS study. To support the efficacy and safety of ecallantide for the proposed indication, the Applicant relies primarily on the completed HAE studies. Safety data from rechallenges, compassionate use, and SAEs from the two ongoing studies (as of July 31, 2008) are also provided. To date, a total of 222 HAE patients have received 638 ecallantide doses. Of these 222 patients, 108 patients received a single dose, 80 patients received 2 to 4 doses, 19 patients received 5 to 9 doses, and 12 patients received >9 doses. The HAE development program is summarized in the table below.

Table 1 Ecallantide clinical development program for HAE							
Study	Patients	Patients treated*	#Doses	Design	Duration/ Dosing interval	Dose	Endpoints
Phase 1							
DX-88/1	Healthy	12	12	DB, SD	SD	10 mg IV 20 40 80 placebo	tolerability
DX-88/6	Healthy	8	29	OL, MD	4 weeks (weekly dose)	20 mg/m ² IV	Safety and PK
DX-88/13	Healthy	18	51	OL, MD, X-over	(weekly dose)	30 mg IV 10mg SC 30 mg SC	Safety, PK
DX-88/15	Healthy	24	47	DB, R, X-over	SD	30 mg liquid SC 30 mg lyophil SC Placebo	PK
Phase 2							
DX-88/2 EDEMA0	HAE/ AAE (≥18yo)	9	9	OL, SD	SD	10 mg IV 40 80	<ul style="list-style-type: none"> Proportion with resolution of attack by 4h post-dose Safety
DX-88/4 EDEMA1	HAE (≥10yo)	41	41	DB, SD	SD	5 mg/m ² IV 10 20 40 Placebo	<ul style="list-style-type: none"> Proportion with significant improvement by 4hr Safety
DX-88/5 EDEMA2	HAE	77	273	OL, MD	≥7 days between attacks	5 mg/m ² IV 10 20 30 mg SC	<ul style="list-style-type: none"> Safety Proportion of successful outcomes
Phase 3							
DX-88/14 EDEMA3-DB	HAE	37	39	DB, R, PC, with OLE	SD	30 mg SC Placebo	<ul style="list-style-type: none"> Treatment outcome score (TOS) Safety
EDEMA3-RD (open-label extension)	HAE	67	161	OL, repeat-dose	≥72h between attacks	30 mg SC	<ul style="list-style-type: none"> TOS at 4h Safety
DX-88/20 EDEMA4	HAE	70	86	DB, R, PC with OLE	SD, extra OL dose for airway compromise or incomplete response/relapse	30 mg SC Placebo	<ul style="list-style-type: none"> Change in Mean Symptom Complex Score (MSCS) at 4h Safety
DX-88/19 (OLE) (ongoing)	HAE	77 as of 31-Jul-08	?	OL, RD	≥72h between attacks	30 mg SC	<ul style="list-style-type: none"> Change in Mean Symptom Complex Score (MSCS) at 4h Safety

*Patients randomized to receive ecallantide. Patients could enroll in sequential studies.

3. FOREIGN MARKETING AND REGULATORY HISTORY

No application for approval for marketing of ecallantide has been made in any foreign country.

The following is a timeline of regulatory proceedings:

- April 30, 2002 – BBIND 10426 (CBER) opened.
- February 4, 2003 – Orphan Drug designation granted.
- June 26, 2003 – initial application for Fast Track designation submitted and denied by CBER on the grounds that the application did not focus on severe, life-threatening aspects of HAE attacks nor addressed unmet medical needs.
- October 2005 – BBIND 10426 transferred to CDER (DPAP).
- April 5, 2006 – Meeting with sponsor. Following deficiencies in the clinical development program were identified:
 - Inadequate support for 30 mg SQ dose selection; lower doses may be efficacious. Advised to conduct additional dose-ranging studies with SQ doses of 10, 40, and 80 mg doses with clinically meaningful endpoints.
 - Need for validation of PRO instrument used in primary efficacy endpoint for Phase 3 study
 - Long-term safety
 - Inconsistency between indication claims and Fast Track designation objectives
- August 29, 2006 – End-of-Phase-2 meeting with sponsor. The following issues were addressed:
 - Agreement that Treatment Outcome Score (TOS) and the Mean Symptom Complex Score (MSCS) are appropriate efficacy endpoints for use in pivotal studies if validated. The Division advised the sponsor to submit a cognitive debriefing protocol for review.
 - The Division advised the sponsor to add a placebo arm to confirmatory study for comparison to 30 mg dose. Planned 5 mg dose unnecessary.
 - The Division advised that the unit of observation should be at patient level, not number of individual attacks, which may introduce bias into the efficacy analysis.
 - The Division advised a long-term, open-label safety study with a sample size larger than the proposed 30 patients and with a defined study duration. Antibody testing should be performed throughout treatment.
 - Sponsor plans to submit new application for Fast Track designation based on endpoints from the pivotal protocols.
 - Sponsor proposed a BLA submission containing a total of 11 clinical studies with 3 main clinical trials:
 - **EDEMA1** – a single ascending dose, DB, PC trial in 49 HAE patients in the US and Belgium. The sponsor concluded that the treatment was well tolerated, and patients receiving DX-88 achieved significant improvement compared to the placebo group by 4h post-dose (72 vs. 25%; p=0.0169).
 - **EDEMA3** – an ongoing, R, DB, PC trial in the US, Europe, and Canada to assess safety and efficacy of 30mg SC DX-88. Patients are treated for a single acute attack in the double-blind portion of the study and are invited to enter the open-label portion of study to assess the effect of repeat 30 mg doses for subsequent attacks (maximum 20 attacks). Efficacy in the study is measured by TOS;

secondary endpoints included a change in MSCS and time to onset of improvement.

- **EDEMA4** – proposed, R, DB, PC trial to assess safety and efficacy of 30mg SC DX-88 versus placebo in treatment of moderate-to-severe acute HAE attacks.
- September 26, 2006 – cognitive debriefing protocol and SAP for TOS/MSCS validation in EDEMA3 submitted for review. PRO consult obtained and comments communicated to the Sponsor.
- October 6, 2006 – protocol submitted for long-term, open-label extension study
- October 13, 2006 – request for Special Protocol Assessment for EDEMA4. Comments were communicated to the Sponsor, including a discussion of the proposed efficacy endpoints. The Division recommended that the Mean Symptom Complex Score (MSCS) be designated as the primary efficacy variable and the Treatment Outcome Score (TOS) be a secondary efficacy variable, in contrast to the EDEMA3 study design, due to difficulties with the interpretation of a compound score like the TOS. Other issues were the management of severe upper airway compromise in the study and the need for validation of the PRO instruments. The Sponsor agreed to the Division's recommendations but did not re-submit a revised protocol with a request for SPA to reach a formal agreement. The Sponsor subsequently submitted a revised protocol March 22, 2007, containing changes consistent with discussions with the Division. These were later reviewed and later deemed to constitute an SPA agreement on EDEMA4.
- June 13, 2007 – EDEMA3 study results and proposed BLA submission without EDEMA4. The Division informed the Sponsor that determinations regarding filing would be made at the time of BLA submission. However, the Division informed the Sponsor that preliminary review of the EDEMA3 results indicated that EDEMA3 would not be sufficient support for drug approval, and that all data to support the efficacy and safety of ecallantide should be included in the original BLA submission.
 - EDEMA3 efficacy results were encouraging but not statistically robust. Two patients accidentally did not receive the randomized study drug, i.e. a placebo patient received ecallantide and an ecallantide patient received placebo. The primary efficacy endpoint, Treatment Outcome Score, did not meet statistical significance ($p=0.1$) when based on the ITT population. Using a modified ITT (patients as treated), the p-value improved to 0.037.
- November 17, 2006 – Fast Track designation granted
- August 23, 2007 – Proposed change to EDEMA4 protocol analysis (imputation for missing values). The Division informed the Sponsor that analysis should be performed without imputation. Proposed imputations could be included as additional sensitivity analyses.
- August 24, 2007 – Proposed assessment of QT prolongation request. Given the largely negative results from the preclinical studies, the lack of effect observed to date in the clinical studies, and the expected manner of use and indication for the proposed drug product, a thorough QT study for ecallantide does not appear warranted. More intensive ECG monitoring in the Phase 3 program beyond the

- proposed ECG monitoring for EDEMA4 is unlikely to provide much additional information given the small numbers of patients enrolled, the intermittent dosing, and in consideration of the life-threatening potential of HAE attacks. See Medical Officer review dated September 26, 2007 for further discussion.
- October 30, 2007 – Meeting to discuss BLA submission format, including presentation of safety data.
- January 15, 2008 – Rolling review granted.

4. ITEMS REQUIRED FOR FILING AND REVIEWER COMMENTS (21 CFR 314.50)

See attached filing checklist.

5. CLINICAL STUDIES

The submission refers to 5 completed studies in HAE patients, including 2 pivotal, double-blind, placebo-controlled studies in HAE patients, EDEMA3-DB (DX-88/4) and EDEMA4 (DX-88/20). Efficacy and safety data obtained from the open-label extension phase of EDEMA3, EDEMA3-RD (DX-88/14), is also submitted for review. Limited data from the extension of EDEMA4 is provided as enrollment is ongoing. A total of 219 unique HAE patients have received ecallantide, including 24 pediatric patients ages 10 to 17 years. One-hundred-eight of the 219 (49%) have received 1 dose; 12 patients have received over 9 doses (2 patients have received 25 treatments in EDEMA3 OLE).

The clinical review of efficacy and safety of the proposed product will focus on the two Phase 3 trials, EDEMA3 and EDEMA4, and the extensions phases of each trial. A brief overview of the pivotal studies is provided below. Additional data from the open-label Phase 2 studies in HAE patients, as well as general safety data from studies in other patient populations, will also be reviewed. The study reports and synopses are appropriately indexed to allow review; however, no study report for the extension phase of EDEMA4 is included in this submission.

In addition to clinical trial reports, the submission includes the results of cognitive debriefing interviews (UBC A2-4272 Report), psychometric analysis reports, and expert panel opinions to support the PRO instruments used to define the primary efficacy variables in the two pivotal studies, EDEMA3 and EDEMA4. The submission also includes a summary of compassionate use and results of a rechallenge procedure used in several cases of suspected hypersensitivity to ecallantide.

5.1 EDEMA3 (Study DX-88/14)

Study design

EDEMA3 was a 2-part Phase 3 study conducted in the US, Canada, and Europe. The first phase was a randomized, double-blind, placebo-controlled, single-dose phase followed by an open-label extension phase where patients could receive treatment for additional acute HAE attacks. Patients with symptoms of a moderate to severe HAE attack presenting within 8 hours of symptom onset were eligible for treatment with a

single dose of 30 mg ecallantide SC. The primary efficacy endpoint was the Treatment Outcome Score (TOS) at 4 hours. The TOS is a composite, weighted symptom complex outcome score. Each individual symptom complex score is based on a severity rating for that particular group of symptoms multiplied by a “response-to-treatment” factor, so that the outcome is incorporated into the final TOS value.

$$TOS = \frac{\sum \text{symptom complex score} \times \text{symptom complex weight}}{\sum \text{symptom complex weight}}$$

where “symptom complex score” = (severity of individual symptom complex)(response-to-treatment multiplier). Severity is scored on a scale of 0 to 3, with 3 being the most severe. Response assessment is scored as -100, -50, 0, 50, or 100, with -100 representing significant worsening and a score of 100 representing significant improvement.

The secondary efficacy endpoint was the change from baseline Mean Symptom Complex Score (MSCS) at 4 hours. The MSCS is the arithmetic mean of individual symptom complexes. Unlike the TOS, there is no inherent time/outcome element in the MSCS; hence, response to treatment is assessed as “the change from baseline MSCS.”

Reviewer’s comment: The primary efficacy variable, TOS, is a complicated score that is difficult to interpret, due in part to the response and severity multipliers used. Overall, a higher number corresponds to a better response to study drug, although the magnitude of response for a given TOS value is not intuitively clear. For this reason, in the EDEMA4 SPA, the Division recommended that the applicant use the change from baseline MSCS as the primary endpoint with the TOS as a supportive secondary endpoint. The MSCS was felt to be more transparent and more similar to symptom scoring used for other conditions.

Study results

Results of the main efficacy analyses are presented below.

Table 2 - EDEMA3 Efficacy analyses						
Endpoint	ITT			ITT as treated*		
	Ecallantide N=36	Placebo N=36	P	Ecallantide N=36	Placebo N=36	P
Mean TOS at 4h (SD)	46.8 (59.34)	21.3 (69.04)	0.100	49.5 (59.43)	18.5 (67.78)	0.037
Change from baseline MSCS at 4h (SD)	-0.88 (1.11)	-0.51 (0.68)	0.094	-0.91 (1.10)	-0.48 (0.68)	0.044

* Population based on treatments as received

Reviewer’s comment: Two patients mistakenly received the wrong study drug: 1 placebo patient received ecallantide and 1 ecallantide patient received placebo. When the efficacy endpoints are recalculated using a dataset corrected for these protocol

violations, the differences between the ecallantide and placebo arms are statistically significant.

A total of 20 of 36 patients (55.6%) in the ecallantide group reported an AE, compared to 12 of 36 (33.3%) in the placebo arm. The most common adverse events reported were HAE, headache, and pyrexia. No cases of anaphylaxis were reported and all serum samples tested negative for anti-ecallantide IgE antibodies. Seven patients in the ecallantide group and 4 patients in the placebo arm tested positive for anti-*P pastoris* IgE.

Reviewer's comment: The analysis of common adverse events for a study with such a small sample size is problematic. A more detailed review of individual patient data will be performed for the primary clinical review.

Extension, repeat-dose phase

Following the double-blind, placebo-controlled phase of EDEMA3, patients were eligible to continue in the repeat-dose, open-label extension for up to 20 separate HAE attacks. New patients who did not participate in the double-blind phase were also eligible to enroll in the repeat-dose phase. Patients were treated with a single, 30 mg dose of ecallantide. If symptoms did not resolve completely, patients could be given a second blinded dose of 30 mg ecallantide or placebo within 4 to 24 hours of the initial single dose.

During this phase of the study, 1 patient experienced an AE suggestive of anaphylaxis. Upon rechallenge, the patient developed anaphylaxis again. The patient tested positive to IgE for *P pastoris* and non-IgE antibodies to ecallantide. Ten other patients also tested positive to IgE for *P pastoris* but without clinical evidence of hypersensitivity.

Conclusions

Based on a preliminary review, EDEMA3 failed to meet its prespecified primary endpoint. The results are generally supportive of efficacy and safety for the proposed indication but do not provide conclusive evidence on their own.

5.2 EDEMA4 (Study DX-88/20)

Study design

EDEMA4 was the second pivotal Phase 3 study conducted in the US and Canada and similar in design to EDEMA3. Patients presenting within 8 hours of onset of moderate to severe HAE symptoms were randomized to treatment with 30 mg ecallantide SC or placebo. Patients were stratified by location of attack (laryngeal vs. other sites). Patients with evidence of upper airway compromise within 4 hours of dosing were eligible for an open-label dose of ecallantide. Similarly, patients with symptom relapse/recurrence at least 4 hours after dosing and within 24 hours of dosing were also eligible for open-label treatment with a single dose. Unlike EDEMA3, change from baseline MSCS at 4 hours post-dose was the designated primary efficacy endpoint for EDEMA4; the TOS was a key secondary efficacy endpoint.

Study results

The main results of EDEMA4 are summarized in the table below.

Table 3 EDEMA4 Efficacy analyses			
Endpoint	ITT		
	Ecallantide N=48	Placebo N=48	P
Mean change from baseline MSCS at 4h (SD)	-0.8 (0.63)	-0.4 (0.82)	0.01
Mean TOS at 4 h (SD)	53.4 (49.70)	8.1 (63.18)	0.003

Reviewer's comment: Based on the analyses presented by the Applicant, EDEMA4 won on both endpoints. The result values are overall similar to those results seen in EDEMA3, with the exception of the placebo TOS score in EDEMA4. In comparison to EDEMA3, it appears that the placebo group in EDEMA4 had poorer responses overall or were more severe.

According to the BLA, 8 of 48 (16.7%) ecallantide patients experienced an AE compared to 19 of 48 (39.6%) in the placebo group. The most common AEs included nausea, headache, and dizziness. Four patients tested positive for anti-ecallantide IgE at study entry; no patients who were tested developed new ecallantide antibodies or anti-*P. pastoris* IgE antibodies during the course of the study. Per the Applicant, no hypersensitivity reactions were observed during the course of the double-blind portion of EDEMA4.

Reviewer's comment: HAE was not reported as a common AE, in contrast to EDEMA3, which suggests different ascertainment or reporting criteria between the two studies. It seems unlikely that the severity or frequency of HAE attacks would vary that much between the two studies.

Open-label, repeat-dose extension phase

Following the double-blind, placebo-controlled phase of EDEMA4, patients are eligible to continue in the repeat-dose, open-label extension for up to 20 separate HAE attacks. New patients who did not participate in the double-blind phase are also eligible to enroll in the repeat-dose phase. Patients were treated with a single, 30 mg dose of ecallantide. If symptoms did not resolve completely, patients could be given a second 30 mg ecallantide dose within 4 to 24 hours of the initial single dose. Each attack episode had to be separated by an interval of at least 72 hours.

The study remains ongoing and a study report has not been submitted with the application.

Reviewer's comment: Although the omission of a study report for the extension of EDEMA4 is not a filing issue, this omission may prove to be major review issue as the patient numbers and overall data to support repeated administration are quite limited.

Conclusions

Based on preliminary review, EDEMA4 appears to support the efficacy and safety of ecallantide for the proposed indication, although the extent of support for repeated, chronic administration may be a review issue in the absence of data from the extension phase of the study.

5.3 Proposed risk management

The Applicant proposes a risk management program for the following 3 objectives:

- Surveillance for hypersensitivity to assess further the frequency and potential risk factors
- Assessment of the effectiveness of a rechallenge procedure to minimize subsequent risk of severe hypersensitivity reactions
- Monitoring pregnancy outcomes

The plan is based several tools and data-collection strategies: 1) development and distribution of education materials; 2) an exclusive distribution channel (single specialty pharmacy and central intake hub); 3) a pharmacovigilance system to monitor and follow up on AEs of special interest, namely, hypersensitivity reactions, including anaphylaxis; and 4) a hypersensitivity registry. The hypersensitivity registry remains in planning stages at the time of submission, but will be intended to capture demographic and outcome information as well as preventing administration of additional doses from the centralized pharmacy until causality is resolved.

Reviewer's comment: The details of the risk management plan are not provided in the submission. Also, the plan does not address the risk of hypersensitivity reactions and other AEs during self-administration of ecallantide. As the clinical program did not specifically evaluate the feasibility, safety, or efficacy of self-administration, this mode of drug administration is a safety concern and will be a review issue.

6. BRIEF REVIEW OF PROPOSED LABELING

Proposed package labeling has been included in this submission [1.14]. The sponsor seeks an indication for the "treatment of acute attacks of hereditary angioedema (HAE).

(b) (4)

1. Section 1. Indications and Usage, does not specify the intended age range. The (b) (4)
2. Section 2.1, Recommended Dosing, The recommended dosing does not specify the interval for repeat administration.
3. Section 4, Contraindications, states that ecallantide should not be administered to patients who have a known hypersensitivity (b) (4)

(b) (4)

(b) (4)

5. Section 6.1, Clinical Trials Experience, should clearly indicate that several patients were enrolled in both EDEMA3 and EDEMA4.
6. Section 14, Clinical Studies, includes a detailed description of the MSCS and TOS endpoints and presents data from the two pivotal studies, EDEMA4 and EDEMA3, as well as composite data from the efficacy studies. The p-values presented for EDEMA3 are based on the ITT-as-treated population without data imputation. Given the difficulty with interpretation of the TOS efficacy variable and EDEMA3's failure to win on its prespecified primary endpoint (TOS), the description of TOS and presentation of data from EDEMA3 in the clinical studies section may be problematic. A general statement stating that EDEMA3 was of similar design to EDEMA4 and supportive of safety and efficacy may be less likely to cause confusion. If included, the analysis should be based on ITT population, not the ITT-as-treated population. The section will also need to address the several patients who participated in both EDEMA 4 and EDEMA3. Furthermore, efficacy statements based on open-label treatment and post-hoc subgroup analyses should not be included.
7. (b) (4)

Reviewer's comments: The proposed label follows the new content and format requirements. A more extensive review of the product label is to follow.

7. DSI REVIEW/AUDIT

The Applicant certifies that no debarred persons participated in the conduct of the studies for ecallantide and that no financial arrangements were made with the clinical investigators requiring disclosure. Dr. Robyn Levy, MD (Atlanta, GA) enrolled the most patients for both pivotal studies (n=8 in EDEMA3 and n=15 in EDEMA4). This investigator's study site is recommended for DSI audit, given that ecallantide is a new molecular entity proposed for a novel indication and the data for efficacy and safety is based on small sample sizes due to the rarity of HAE.

7. PEDIATRIC WAIVER REQUEST

Ecallantide was previously granted Orphan Drug status (February 4, 2003, Designation 02-1608) so the application qualifies for pediatric exemption.

8. SUMMARY

This is a 45-day filing and planning review of a BLA for ecallantide, a recombinant human plasma kallikrein inhibitor intended for the treatment of acute attacks of hereditary angioedema (HAE) in patients 10 years of age and older. HAE is a rare, autosomal dominant disorder estimated to affect 1 in 10,000 to 50,000 individuals. The disease is characterized by sporadic, unpredictable attacks of angioedema and mucosal

swelling. Attacks can be life-threatening, particularly those attacks involving the airway. Currently, no products are approved for the treatment of acute attacks. The drug has been granted Orphan Drug and Fast Track status, and the application will be reviewed under Priority review.

In support of the application, the Applicant has submitted results of five clinical studies in HAE, including two pivotal, placebo-controlled trials, EDEMA3 (DX-88/14) and EDEMA4 (DX-88/20). EDEMA4 was conducted under an SPA. Additional safety and efficacy data obtained from the ongoing open-label extension of EDEMA3 is also submitted; data from the EDEMA4 extension has not been included in this initial submission. These study reports are appropriately indexed and organized to allow review. The sponsor has provided an Integrated Summary of Efficacy, Integrated Summary of Safety, Integrated Summary of Benefits and Risks, copies of proposed labeling, and appropriate case report forms.

From a clinical standpoint, the submission is adequate to allow clinical review and qualifies for Priority review. The submission is fileable.

9. COMMENTS TO THE SPONSOR

The following comments will be submitted to the Applicant:

-  (b) (4)
- Provide a safety update of Study DX-88/19 (EDEMA4 open-label extension study) by December 22, 2009.

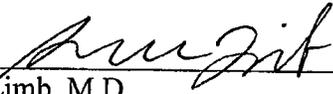
10. TIME LINE FOR REVIEW

The timeline for review and processing of the BLA is as follows:

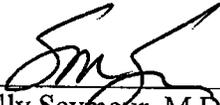
Table 2. Proposed schedule for review of BLA 125277

Milestone	Target Date for Completion
60-day filing letter	11/21/2008
Mid-cycle review meeting	12/16/2008
Internal labeling meeting	1/21/2009
PADAC meeting	02/04/2009
Wrap-up meeting	02/09/2009
Primary reviews due date	2/16/2009
Labeling teleconference	2/11/2009
PDUFA due date, 10 months	3/23/2009

Reviewed by:



Susan Limb, M.D.
Medical Officer, Division of Pulmonary and Allergy Products



Sally Seymour, M.D.
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