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*APPLICATION NUMBER:*

BLA 125277

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

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Reviewer Name(s) Susan Limb, MD  
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*ASL* 10/22/09  
*SLM* 10/22/09

Established Name Ecallantide  
(Proposed) Trade Name Kalbitor  
Therapeutic Class Kallikrein inhibitor  
Applicant Dyax

Formulation(s) Solution for injection  
Dosing Regimen 30 mg SC; up to 2 injections in  
24-hour period  
Indication(s) Treatment of acute attacks of  
hereditary angioedema (HAE)  
Intended Population(s) Patients 16 years and older

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## 1 Recommendations/Risk Benefit Assessment

The clinical recommendation for this application is Approval. The Applicant's proposed indication for ecallantide is "the treatment of acute attacks of hereditary angioedema (HAE) in patients 16 years of age and older." The proposed dose is 30 mg SC, which may be repeated once in a 24-hr period for a single HAE attack. The application contains sufficient evidence of efficacy to support this indication in patients ages 16 years of age and older. The application includes an adequate Risk Evaluation and Mitigation Strategy (REMS) to balance the risk of anaphylaxis.

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.

The initial application was previously submitted on September 23, 2008, and was a Priority review. The Division issued a Complete Response letter on March 25, 2009. The CR letter addressed two major clinical deficiencies, specifically, the lack of an appropriate Risk Evaluation and Mitigation Strategies (REMS) program and a lack of efficacy and safety data to support the proposed indication in pediatric patients ages 10 to 17 years. The letter also outlined three clinical postmarketing requirements to study the long-term safety and efficacy of ecallantide, with particular focus on hypersensitivity reactions, immunogenicity, and hypercoagulability.

For the Complete Response, the Applicant adjusted the proposed age range from 10 years of age and older to 16 years of age and older and included a summary of the clinical data available for patients 16 to <18 years of age. The resubmission also included validated PK data to support the population PK analysis, which does not show body weight, gender, or age to be significant factors in systemic ecallantide exposure. The available efficacy and safety data in patients 16 and 17 years of age, combined with the population PK analysis, provides adequate support for the use of ecallantide 30 mg SC for the new proposed age range of 16 years and older. For patients (b) (4) years of age, the Applicant has proposed a Phase 4, open-label study to obtain additional safety, efficacy, and PK information for this (b) (4). The proposed (b) (4) addresses the need for additional information in (b) (4). Overall, the information provided in the Complete Response addresses the first clinical deficiency outlined in the Complete Response letter dated March 25, 2009.

To address the second major deficiency, the Complete Response included the details for a REMS program, which initially included specific labeling, a Medication Guide, communication plan, and a plan for restricted distribution with mandatory patient registration and verification prior to each dose administration. Review of the proposed REMS raised several concerns, including the risk of hampering patient access as well as concerns about the effectiveness of the program in mitigating the risk of hypersensitivity. After further internal discussion between DPAP and OSE as well as discussions with the Applicant, the REMS was revised to include only specific labeling, a Medication Guide, and a communication plan. The revised REMS addresses the second major clinical deficiency outlined in the Complete Response letter dated March 25, 2009.

A Pulmonary and Allergy Drugs Advisory Committee (PADAC) meeting was previously held on February 4, 2009, during the review cycle for the original BLA. Briefly, 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. The committee also noted the relative paucity of data in pediatric patients to support the proposed age range of 10 years and older. These issues have been satisfactorily addressed in the Complete Response as described above. No new issues were identified during the review of the Complete Response to warrant another PADAC meeting, so no PADAC meeting was convened to discuss the Complete Response submission.

In summary, the Complete Response dated May 31, 2009, adequately addresses the major deficiencies outlined in the Complete Response letter dated March 25, 2009. The clinical review finds the submitted safety and efficacy data sufficient to support use of ecallantide for the proposed indication of treatment of acute HAE attacks in patients 16 years of age and older. Therefore, the clinical review recommends a regulatory action of Approval for this BLA.

## **1.1 Recommendation on Regulatory Action**

The recommended regulatory action is Approval.

The Division issued a Complete Response letter during the first review cycle for BLA 125277 on March 25, 2009. The CR letter addressed two major clinical deficiencies, namely the lack of an appropriate REMS program and a lack of efficacy and safety data to support the proposed indication in pediatric patients ages 10 to 17 years. These deficiencies are described as below:

1. *The results of the submitted clinical studies do not support the efficacy and safety of Kalbitor (ecallantide) at a dose of 30 mg SC for the treatment of acute attacks of hereditary angioedema (HAE) in patients 10 years of age and older. Particularly, the number of patients below 18 years of age exposed to Kalbitor (ecallantide) is limited and not adequate to assess efficacy or safety in this age group. To support efficacy and safety of Kalbitor (ecallantide) for treatment of acute attacks of HAE in patients 10 years of age and older, provide the following: 1. Efficacy and safety data from controlled clinical studies or open label clinical studies in a reasonable number of patients below 18 years of age and covering each year age group. Also, provide validation of the ecallantide bio-analytical assay, and comparative ecallantide exposure data in adults and pediatric patients to support the recommended pediatric dose.*
2. *Requirement for proposed Risk Evaluation and Mitigation Strategy (REMS). For the reasons described below, a REMS will be required as part of your approval.*

The Applicant has adjusted the proposed age range to patients 16 years and older, which is supported by the submitted efficacy and safety data as well as population PK analysis. A separate, Phase 4, open-label observational study will be conducted in patients 10 to 15 years of age to obtain additional clinical information on the younger age group. The pediatric information provided in the Complete Response adequately addresses the first major clinical deficiency.

The Applicant has also provided an adequate REMS program to balance the risk of hypersensitivity reactions. Following discussion with the Agency and revision during the review period, the REMS program will include specific labeling, a Medication Guide, a communication plan, and a timetable of assessments. Both DPAP and OSE have reviewed the proposed REMS and have deemed it acceptable. Therefore, the REMS program proposed in the Complete Response and subsequently revised during the review period adequately addresses the second major clinical deficiency.

No other major clinical deficiencies were identified during the review period of the Complete Response. Therefore, the clinical review recommends Approval.

## **1.2 Risk Benefit Assessment**

The application includes an adequate risk evaluation and mitigations strategies (REMS) program to balance the significant risk of anaphylaxis. Anaphylaxis and hypersensitivity reactions are the most serious potential adverse event associated with use of ecallantide and are estimated to have occurred in approximately 4% (10 of 255 unique patients) of the ecallantide HAE population. 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 are balanced by the potential efficacy benefit of ecallantide and the unmet medical need for this serious, potentially life-threatening condition when used in an appropriate medical setting and with education of both healthcare providers and patients.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

At the time of this review, review of the REMS is ongoing and finalization of the REMS is pending.

The clinical review recommends a boxed warning in labeling that discusses the risk of hypersensitivity reactions, including anaphylaxis, that is associated with the use of ecallantide. The package insert will contain specific language that advises administration of ecallantide only in medically supported settings and will caution healthcare providers and patients to monitor closely for hypersensitivity reactions, which can overlap the signs and symptoms of an acute HAE attack.

The clinical review also recommends a Medication Guide, a communication plan, and a timetable of assessments as elements of the REMS. The purpose of the REMS will be to educate healthcare providers and patients about the significant risk of hypersensitivity reactions and to promote appropriate use of the drug in clinical settings equipped to diagnose and manage hypersensitivity reactions.

### **1.4 Recommendations for Postmarket Requirements and Commitments**

The Complete Response letter dated March 25, 2009, outlined the following clinical postmarketing requirements under 505(o):

- 1. Conduct a study with Kalbitor (ecallantide) in patients with hereditary angioedema to evaluate anaphylaxis and type I hypersensitivity. The study should include objectives to identify predictive risk factors and develop effective screening tools to mitigate the risk of hypersensitivity and anaphylaxis.*
- 2. Conduct a study with Kalbitor (ecallantide) in patients with hereditary angioedema to evaluate immunogenicity. The study should include objectives to correlate antibody levels with adverse events and lack of efficacy.*

3. *Conduct a study with Kalbitor (ecallantide) in patients with hereditary angioedema to evaluate the effects on coagulation parameters.*

Regarding the third post-marketing requirement, the Applicant presented the existing clinical data to date at the pre-resubmission meeting on May 14, 2009, and requested reconsideration of the requirement for a formal clinical study of coagulation parameters. The Division concurred with the Applicant's proposal and recommended continued clinical surveillance for adverse associated with disordered coagulation. The Applicant also intends to complete *in vitro* cross-reactivity studies for antibodies against ecallantide and TFPI to assess further the potential of hypercoagulability. Based on these prior discussions, the clinical review recommends revising the third postmarketing requirement as follows:

3. *Conduct a study with Kalbitor (ecallantide) in patients with hereditary angioedema to evaluate the risk of hypercoagulability and hypocoagulability.*

The Applicant proposes a 1-year, long-term safety trial in 200 HAE patients to address these outstanding safety issues. The trial is intended to further assess the risk of hypersensitivity, immunogenicity, and disordered coagulation with repeat, intermittent use of ecallantide. A preliminary protocol was included in the Complete Response submission. The clinical review finds the proposed study design acceptable, and specific details and comments on the protocol are presented in Section 7. The Applicant anticipates initiating the trial coincident with the start of commercial marketing. A timeline for submission of the final protocol and complete study report is pending at the time of this review.

No other clinical postmarketing requirements or commitments are recommended. As an orphan indication, BLA 125277 does not trigger PREA, so no pediatric studies are required. However, the Applicant proposes a Phase 4 open-label study in patients 10 to 15 years to obtain additional safety and efficacy information for this younger age group. The details of this plan are discussed in Section 7.6.3 Pediatrics and Assessment of Effects on Growth.

In addition to the clinical postmarketing requirements, the CMC review team recommends several postmarketing requirements for the further refinement of the ecallantide immunoassays, and the Pharmacology/Toxicology review team recommends a carcinogenicity study. These other postmarketing requirements are described in Section 4.

## **2 Introduction and Regulatory Background**

## 2.1 Product Information

The established name of the 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 16 years of age and older. The proposed dosing regimen is 30 mg SC, administered as 3 separate 1 ml 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

Up until recently, no drugs have been approved for the treatment of acute HAE attacks. The standard of care for acute attacks has been supportive therapies, e.g. opiates for pain management, anti-emetics for nausea, and intubation for airway obstruction. Since angioedema is common to 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.

More recently, plasma-purified C1 inhibitor replacement product (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. On October 9, 2009, another plasma-purified C1 inhibitor replacement (Berinert™) was approved by CBER for the treatment of acute abdominal or facial HAE attacks in adult and adolescent patients

### **2.3 Availability of Proposed Active Ingredient in the United States**

Ecaltantide 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**

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
  - Long-term safety
- 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.

- 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.
- 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.
- June 13, 2007 – EDEMA3 study results and proposed BLA submission without EDEMA4. Preliminary review of the EDEMA3 results indicated that EDEMA3 alone would not be sufficient support for drug approval.
- 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.
- February 4, 2009 – Pulmonary and Allergy Drugs Advisory Committee (PADAC) Meeting (proceedings summarized in Section 9)
- March 25, 2009 – Complete Response letter issued (see summary in Section 2.6)
- May 14, 2009 – Resubmission planning meeting

- The Division advised Dyax to adjust the proposed age range to include only adults while continuing to obtain safety and efficacy data from pediatric patients under the IND. Data could be obtained from an open-label study with reasonable representation of each year age included in the proposed pediatric age range. The pediatric data could later be submitted as an efficacy supplement.
- Complete, fully detailed REMS package expected to facilitate timely review.
- May 31, 2009 – Complete Response submission

## 2.6 Other Relevant Background Information

The Division issued a Complete Response letter during the first review cycle for BLA 125277 on March 25, 2009. The CR letter addressed two major clinical deficiencies, namely the lack of an appropriate REMS program and a lack of efficacy and safety data to support the proposed indication in pediatric patients ages 10 to 17 years. These deficiencies are described as below:

- *The results of the submitted clinical studies do not support the efficacy and safety of Kalbitor (ecallantide) at a dose of 30 mg SC for the treatment of acute attacks of hereditary angioedema (HAE) in patients 10 years of age and older. Particularly, the number of patients below 18 years of age exposed to Kalbitor (ecallantide) is limited and not adequate to assess efficacy or safety in this age group. To support efficacy and safety of Kalbitor (ecallantide) for treatment of acute attacks of HAE in patients 10 years of age and older, provide the following: 1. Efficacy and safety data from controlled clinical studies or open label clinical studies in a reasonable number of patients below 18 years of age and covering each year age group. Also provide validation of the ecallantide bio-analytical assay, and comparative ecallantide exposure data in adults and pediatric patients to support the recommended pediatric dose.*
- *Requirement for proposed Risk Evaluation and Mitigation Strategy (REMS). For the reasons described below, a REMS will be required as part of your approval.*

The CR letter also outlined the following clinical postmarketing requirements under 505(o):

1. *Conduct a study with Kalbitor (ecallantide) in patients with hereditary angioedema to evaluate anaphylaxis and type I hypersensitivity. The study should include objectives to identify predictive risk factors and develop effective screening tools to mitigate the risk of hypersensitivity and anaphylaxis.*

2. *Conduct a study with Kalbitor (ecallantide) in patients with hereditary angioedema to evaluate immunogenicity. The study should include objectives to correlate antibody levels with adverse events and lack of efficacy.*
3. *Conduct a study with Kalbitor (ecallantide) in patients with hereditary angioedema to evaluate the effects on coagulation parameters.*

### **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. The BLA includes updated safety information from the ongoing open-label extension trial (DX-88/19), updated longitudinal patient profiles for individual patients, a pediatric plan and a summary of pediatric data, and a proposed REMS program.

#### **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 during the first review cycle 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. No additional audits were requested for the Complete Response review.

#### **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 review remains pending at the time of this review, but preliminary recommendations are for approval of the application with further refinement of the immunoassays as postmarketing requirements.

The Complete Response letter dated March 25, 2009, initially required a clinical study to address potential safety concerns about disordered coagulation. At the pre-resubmission meeting on May 14, 2009, the Applicant presented the existing clinical data to date and requested reconsideration of the requirement for a formal clinical trial. The Agency concurred with the Applicant's proposal and recommended continued clinical surveillance as well as in vitro cross-reactivity studies for antibodies against ecallantide and TFPI to assess further the potential of hypercoagulability.

In response, Dyax conducted an in vitro study to evaluate potential cross-reactivity between ecallantide and TFPI using a commercially available 2-stage chromogenic substrate assay (Actichrome TFPI Acitivity Assay, American Diagnostica, Greenwich, CT). Anti-ecallantide neutralizing antibodies obtained from 4 individual patients who had tested positive for neutralizing antibodies were used in the assay, along with normal control serum and plasma. According to the study report, there was no reduction in TFPI activity in the presence of neutralizing antibodies. The Applicant has also conducted additional experiments demonstrating that ecallantide does not inhibit the activation of Factor X by lipidated tissue factor/Factor VIIa complex, unlike TFPI.

The CMC review has concluded that the characterization of potential cross-reactivity between anti-ecallantide antibodies and TFPI is incomplete. The CMC review has also noted deficiencies with the existing anti-ecallantide neutralizing antibody assays and the IgE antibody assays. Specifically, the CMC review recommends the following investigations as post-marketing requirements:

- *Cross-reactivity of anti-ecallantide antibodies with TFPI*  
The CMC review concludes that the sponsor's demonstration that anti-ecallantide neutralizing Ab (Nab) does not inhibit the enzymatic activity of the endogenous protease inhibitor TFPI is not sufficient to exclude cross-reactivity of anti-ecallantide Nab with TFPI. The CMC reviewer recommends that the Applicant conduct additional in vitro studies to determine if hu anti-ecallantide antibodies bind TFPI and to perform epitope mapping of the human anti-ecallantide antibody response.
- *Anti-ecallantide and anti-*P. pastoris* IgE antibody assays*

Clinical Review  
Susan Limb, MD  
BLA 125277

Kalbitor® (ecallantide 30 mg) for subcutaneous injection

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The CMC reviewer recommends that the Applicant develop and validate new IgE detection assays using a more sensitive platform such ECL.

- *Neutralizing antibody assay*

The CMC reviewer recommends that the Applicant establish the clinically relevant LLOQ, ULOQ, LOD, and Cutpoint for this assay using immunoaffinity purified ecallantide-specific human IgG.

## 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 preliminarily stated that clinical microbiology standards generally appear adequate.

## 4.3 Preclinical Pharmacology/Toxicology

No new preclinical pharmacology/toxicology information was included in the Complete Response. The Preclinical Pharmacology/Toxicology Review team recommends approval of this Complete Response.

The Complete Response letter dated recommended that the Applicant conduct a carcinogenicity study in rats. In the resubmission, the Applicant has stated that a full protocol for this study will be submitted to the Agency for review pending approval of the BLA, with plans to initiate the study within 12 months of approval. The Applicant has proposed a 2-year carcinogenicity study in male and female rats administered 25 mg/kg (10-fold safety margin on mg/m<sup>2</sup> basis) every 7 days.

## 4.4 Clinical Pharmacology

The Applicant submitted a complete clinical pharmacology package in the original BLA, which was reviewed in detail in the Clinical Pharmacology review dated February 13, 2009. Additional validation data to support population pharmacokinetic analysis was submitted in the Complete Response. A brief summary of the submitted information is included below. At the time of this review, the final recommendations of the Clinical Pharmacology Review are pending, but the preliminary recommendation is for approval.

### 4.4.1 Mechanism of Action

Ecaltantide 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

No new clinical pharmacodynamic data was included in the Complete Response. Prior studies did not show an 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. As discussed in the Medical Officer Review dated February 28, 2009, several patients were noted to have transient aPTT prolongation after receipt of ecallantide. In general, the degree of aPTT prolongation was not clinically significant and was not associated with bleeding adverse events.

#### 4.4.3 Pharmacokinetics

The Complete Response letter dated March 25, 2009, requested that the Applicant submit performance data to validate the pharmacokinetic assays used in the Phase 2 ecallantide development program (Dyax trials DX-88/5, DX-88/13, and DX-88/15). The Complete Response included amended bioanalytic reports containing the requested performance data from [REDACTED] (b) (4). The Clinical Pharmacology reviewer has concluded that the bioanalytical results from these trials are acceptable and can be used in the population PK analysis. The population PK analysis indicates that body weight, age, and gender were not found to significantly affect ecallantide exposure, noting however, the limited number of patients (n=3) in the older age range >65 years. The results of the population PK analysis support the selection of the 30 mg dose for patients 16 years of age and older.

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

For the original submission, the Applicant conducted 10 clinical trials with ecallantide, two of which were ongoing during the first review cycle. These trials included 4 trials in healthy volunteers, 5 trials in patients with HAE, and 1 trial in patients undergoing cardiothoracic surgery (CTS). Data from 243 HAE patients treated with 846 doses of ecallantide comprised the original application.

The Complete Response references the efficacy and safety data included in the original submission, as well as updated safety information and specific responses to cited deficiencies. An additional 26 ecallantide-naïve patients have been treated with ecallantide in the EDEMA4 OLE (DX-88/19). Updated safety data from the ongoing

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Susan Limb, MD  
BLA 125277  
Kalbitor® (ecallantide 30 mg) for subcutaneous injection

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OLE are provided. As of May 1, 2009, a total of 255 unique HAE patients have received 916 ecallantide doses. Of these, 187 patients have received the 30 mg SC dose. The HAE development program is summarized in the table below.

<b>Table 1 Ecallantide clinical development program for HAE</b>							
Trial	Patients	Patients treated*	#Doses	Design	Duration/ Dosing interval	Dose	Endpoints
<b>Phase 1</b>							
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 <sup>2</sup> 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
<b>Phase 2</b>							
DX-88/2 EDEMA0	HAE/ AAE (≥18yo)	9	9	OL, SD	SD	10 mg IV 40 80	<ul style="list-style-type: none"> <li>Proportion with resolution of attack by 4h post-dose</li> <li>Safety</li> </ul>
DX-88/4 EDEMA1	HAE (≥10yo)	41	41	DB, SD	SD	5 mg/m <sup>2</sup> IV 10 20 40 Placebo	<ul style="list-style-type: none"> <li>Proportion with significant improvement by 4hr</li> <li>Safety</li> </ul>
DX-88/5 EDEMA2	HAE	77	273	OL, MD	≥7 days between attacks	5 mg/m <sup>2</sup> IV 10 20 30 mg SC	<ul style="list-style-type: none"> <li>Safety</li> <li>Proportion of successful outcomes</li> </ul>
<b>Phase 3</b>							
DX-88/14 EDEMA3-DB	HAE	37	39	DB, R, PC, with OLE	SD	30 mg SC Placebo	<ul style="list-style-type: none"> <li>Treatment outcome score (TOS)</li> <li>Safety</li> </ul>
EDEMA3-RD (open-label extension)	HAE	67	161	OL, repeat-dose	≥72h between attacks	30 mg SC	<ul style="list-style-type: none"> <li>TOS at 4h</li> <li>Safety</li> </ul>
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"> <li>Change in Mean Symptom Complex Score (MSCS) at 4h</li> <li>Safety</li> </ul>
DX-88/19 (OLE) (ongoing)	HAE	95 as of May 2009	278 as of May 2009	OL, RD	≥72h between attacks	30 mg SC	<ul style="list-style-type: none"> <li>Change in Mean Symptom Complex Score (MSCS) at 4h</li> <li>Safety</li> </ul>

\*Patients randomized to receive ecallantide. Patients could enroll in sequential trials.

## 5.2 Review Strategy

No new clinical trials were conducted for the Complete Response submission. The Applicant included updated Longitudinal Patient Profiles, re-validated PK measurements, and a summary of data obtained from pediatric patients. As the Medical Officer Review dated February 28, 2009, of the original BLA concluded that there was sufficient efficacy and safety data to support the indication in patients 18 years and older, this review focuses primarily on the summary of efficacy and safety data for patients 16 and 17 years of age as well as the additional safety data obtained from the ongoing DX-88/19 (EDEMA4 OLE).

## 5.3 Discussion of Individual Studies/Clinical Trials

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 should be noted: 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. 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.

Detailed discussion of the study design and major efficacy results of the individual clinical trials can be located in the Medical Officer Review, dated February 28, 2009.

## 6 Review of Efficacy

### **Efficacy Summary**

The application supports the proposed indication of ecallantide for the treatment of acute HAE attacks in patients 16 years of age and older. The primary efficacy support for ecallantide comes from two small, randomized, placebo-controlled Phase 3 trials, EDEMA3 and EDEMA4, which were previously reviewed in detail in the Medical Officer review dated February 28, 2009. Briefly, both trials 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 trials relied on two novel patient-reported outcome measures, the Treatment Outcome Score (TOS) and the Mean Symptom Complex Score (MSCS). The TOS at 4 hours was the designated primary efficacy endpoint for EDEMA3 and the change from baseline MSCS at 4 hours was a key secondary efficacy endpoint. In EDEMA4, the change from baseline MSCS at 4 hours was the primary efficacy endpoint while the TOS at 4 hours was a key secondary endpoint.

The results of both trials supported the efficacy of ecallantide for the proposed indication. Based on the as-treated patient population, EDEMA3 show a statistically significant difference for ecallantide over placebo for the primary efficacy endpoint, TOS at 4 hours (50 vs. 19;  $p=0.04$ ). Similarly supportive results were seen for the key secondary efficacy endpoint, Change from Baseline MSCS at 4 hours (-0.9 vs. 0.5;  $p=0.04$ ). Likewise, 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. In both trials, clinically relevant secondary endpoints such as medical intervention patterns and patients' own global assessments were evaluated. These other endpoints generally supported the efficacy of ecallantide in acute HAE attacks.

Data in pediatric patients was limited, but there is sufficient support for the inclusion of patients 16 and 17 years of age in the proposed age range. A total of 28 patients between the ages of 10 to 17 years have been treated for 137 acute attacks of HAE. Eighty-four of the 137 attacks and 18 of the 28 patients were treated with the ecallantide 30 mg SC dose. The remainder was treated with varying intravenous doses of ecallantide in earlier Phase 2 trials. Of the 28 pediatric patients, 6 patients were 16 years of age and 6 other patients were 17 years of age at their first exposure to ecallantide. As the pediatric population is limited in sample size, formal statistical analysis of efficacy results was not performed. Instead, the clinical review relied on the case narratives of the 28 individual pediatric patients, as well as comparing pediatric efficacy data to the mean efficacy results obtained for the ecallantide HAE population as a whole.

For patients 16 and 17 years, who are included in the proposed age range for this application, the MSCS and TOS scores were supportive of efficacy.

As a crude measure, the mean TOS at 4 hours and the mean change in MSCS at 4 hours for this group (both double-blind and open-label assessments) were 61 and -1.1, respectively. These values are comparable to results obtained for the population as a whole in EDEMA3 and EDEMA4. Efficacy of ecallantide in patients 16 and 17 years of age is further supported by population PK analysis, which indicates that age does not significantly impact systemic exposure to ecallantide and supports the 30 mg SC dose for 16-year-old and 17-year-old HAE patients. Based on the submitted clinical and clinical pharmacology data, the Complete Response contains adequate evidence to support the proposed age range of 16 years of age and older.

The unpredictable and highly variable nature of acute HAE attacks makes prospective trials for this condition difficult. Acute HAE attacks are potentially life-threatening and there are currently no drug products approved for treatment of acute attacks. Given these considerations, the clinical development program for ecallantide is small but provides an adequate demonstration of efficacy in acute HAE attacks in adults. When taken all together, the totality of data presented in the application supports ecallantide's efficacy for the proposed indication in patients 16 years of age and older.

## **6.1 Indication**

The proposed indication for ecallantide is "the treatment of acute attacks of HAE" in patients age 16 years and older.

### **6.1.1 Methods**

The review of efficacy relies primarily on the findings of the two pivotal, randomized, placebo-controlled efficacy and safety studies, EDEMA3 and EDEMA4. The design and conduct of these two studies are summarized in Section 5.3 and described in detail in the Medical Officer Review dated February 28, 2009. Additional evidence of support for repeat dosing is provided by EDEMA2, a Phase 2 study that involved extended, repeat open-label dosing. Anecdotal support provided by the compassionate use narratives and preliminary efficacy data from EDEMA0 and EDEMA1 were also considered in the assessment of efficacy. Based on the information provided in the original application, the clinical review previously concluded that there was sufficient evidence of efficacy to support the proposed indication in the adult patients 18 years of age and older (Medical Officer Review dated February 28, 2009). For this reason, Section 6 focuses on the efficacy data for patients <18 years of age with particular focus on patients 16 and 17 years old, since the proposed indication has been revised to patients 16 years and older. Due to the small numbers represented, formal statistical tests of efficacy in this age subgroup were not performed. The information presented in the following subsections refers to patients <18 years of age, with reference to the adult data where relevant.

### 6.1.2 Demographics

For the purposes of this review, pediatric patients are defined as patients under the age of 18 years at the time of first exposure to ecallantide. A total of 28 patients have been treated for 137 acute attacks of HAE. Eighty-four of the 137 attacks and 18 of the 28 patients were treated with the ecallantide 30 mg SC dose.

Age (years)	Number treated	# attacks treated
9	1	1
10	1	1
11	-	-
12	1	1
13	3	3
14	-	-
15	1	1
16	6	11
17	6	30

Source: DX88-107 Pediatric Data Report, Appendix 1

Patients may have received more 1 treatment for each age category and may have been included in more than 1 age category.

**Table 3 Patients <18 years of age treated with ecallantide**

ID	Gender	Age at first dose	Total # attacks	Total # doses	Cumulative dose (mg)	Received 30 mg SC
<b>Patients &lt;16 years old</b>						
8819427102	F	9	1	1	30.0	X
8805003088	M	10	1	2	60.0	X
8804017015	F	11	2	2	27.9	
8805024099	M	11	5	7	80.2	
8804023001	M	12	19	25	477.4	
8814372004	M	12	1	1	30.0	X
8814303004	F	13	1	1	30.0	X
8805003099	F	13	1	1	31.5	
8804017001	F	13	8	9	139.1	X
8814302001	F	13	1	1	30.0	X
8814302002	F	13	1	1	30.0	X
8804013006	F	14	1	1	8.5	
8805019001	F	14	1	1 (3*)	15.2 (18.7*)	
8805013094	F	15	12	12	329.5	X
8805015006	F	15	1	1	12.2	
8805022008	M	15	3	3	75.2	X
8814372001	F	15	1	1	30.0	X
<b>Patients 16 and 17 years old</b>						
8805003004	F	16	3	4	106.2	X
8814326005	M	16	3	3	90.0	X
8804018002	F	16	1	1	16.7	
8805027001	F	16	1	2	34.8	
8805054099	M	16	34	34 (37*)	983.9 (1044.4)	X
8820454001	F	16	2	2	60.0	X
8819453103	F	16	3	3	90.0	X
8804018004	M	17	4	5	156.2	
8814301010	M	17	11	12	360.0	X
8820404011	F	17	13	14	420.0	X
8819456102	F	17	2	3	90/0	X

\* Cumulative doses including doses received as part of a (b) (4).

Source: Module 1, responses-to-clinical-items.pdf and Longitudinal Patient Profiles

Nineteen (68%) of pediatric patients were female and 9 (32%) were male. The majority (89%) were White, 7% (n=2) were Black, and 1 patients reported race as biracial. The primary anatomic attack site was abdominal in 78 attacks (57%), peripheral in 38 attacks (28%), and laryngeal in 19 attacks (14%). Two attacks had missing data for attack location. In 16 attacks, a second dose of ecallantide (Dose B) was administered for failure to improve or worsening of symptoms. No patients received a second dose for severe upper airway compromise (SUAC).

#### 6.1.4 Analysis of Primary Endpoint(s)

##### **Primary endpoint selection and validation: The TOS and MSCS**

The Applicant developed two symptom scoring systems with the intent of capturing the full range of signs and symptoms of an HAE attack, the TOS and the MSCS. The TOS includes the MSCS in its calculation along with multipliers for temporal assessment, so

the two efficacy variables are related. A brief description of each of these endpoints is provided below. For a detailed discussion of the endpoint selection and the validation information provided in support of these scoring systems, refer to the Medical Officer Review dated February 28, 2009.

- **Treatment Outcome Score (TOS)**

The Treatment Outcome Score (TOS) at 4 hours 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 4). “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.

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

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. A larger negative value for the change from baseline corresponds with greater improvement from baseline. 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

**Table 5** and **Table 6** display the results for the TOS and MSCS primary efficacy assessments where available for the individual pediatric patients who received ecallantide 30 mg SC. The TOS and MSCS were not routinely assessed in the earlier stages of the clinical development program, so for participants of EDEMA1 and most of the participants in EDEMA2, TOS and MSCS measures are not available and the corresponding portions of the tables are left blank. Furthermore, only 4 pediatric patients participated in the double-blind phase of the two pivotal trials, EDEMA3 and EDEMA4, so the majority of the TOS and MSCS scores reported were obtained from unblinded, open-label assessments in the extension trials. Five of the 28 patients received their initial dose prior to the age of 18 years and then continued to receive additional doses after turning 18; the tables below display data only for those doses administered prior to the patients' 18<sup>th</sup> birthdays.

Based on the MSCS and TOS values reported at 4 and 24 hours, there is some evidence of efficacy. However, the limited number of patients under the age of 16 years makes it difficult to draw conclusions about efficacy.

<b>Table 5 MSCS and TOS efficacy results: Patients &lt;16 years of age</b>						
ID	Trial	TOS		ΔMSCS		Med intervention
		4h	24h	4h	24h	
8819427102	EDEMA4 OLE	50.0	100.0	-2.0	-3.0	N
8805003088	EDEMA2	25.0		0.0		N
	EDEMA2					N
8814372004	EDEMA3 OLE	50.0	50.0	-1.0	-1.0	N
8814303004	EDEMA3 OLE	100.0	100.0	-3.0	-2.0	N
8804017001	EDEMA2	-50.0	-50.0	0.0	0.0	Y
8814302001	EDEMA3 OLE	100.0	100.0	-3.0	-3.0	N
8814302002	EDEMA3 OLE	50.0	100.0	-2.0	-2.0	N
8805013094	EDEMA2	80.0	100.0	-2.0	-2.0	N
	EDEMA2	100.0	100.0	-3.0	-3.0	N
	EDEMA2	100.0	100.0	-2.0	-3.0	N
	EDEMA3 OLE	75.0	100.0	-1.5	-2.0	N
	EDEMA3 OLE	100.0	100.0	-2.0	-3.0	N
	EDEMA3 OLE	100.0	100.0	-2.0	-3.0	N
	EDEMA3 OLE	100.0		-2.0		N
8805022008	EDEMA3	100.0	100.0	-1.0	-2.0	N
	EDEMA3 OLE	-100.0	-100.0	0.50	0.5	Y
8814372001	EDEMA3 OLE	50.0	50.0	-1.0	-2.0	N

<b>Table 6 MSCS and TOS efficacy results: Patients 16 and 17 years of age</b>						
ID	Trial	TOS		ΔMSCS		Medical intervention
		4h	24h	4h	24h	
8805003004	EDEMA2	50.0	100.0	0.0	-1.0	N
	EDEMA2					N
	EDEMA2	100.0	100.0	-1.0	-2.0	N
8814326005	EDEMA3 OLE	100.0		-3.0		N
	EDEMA3 OLE	100.0		-3.0		N
	EDEMA3 OLE	80.0	100.0	-2.0	-2.5	N
8805054099	EDEMA2	100.0	100.0	-2.0	-2.0	N
	EDEMA2	100.0	50.0	-2.0	-2.0	N
	EDEMA3	50.0	-50.0	-1.0	0.0	N
	EDEMA3 OLE	-100.0	-100.0	0.0	0.0	Y
8820424001	EDEMA4	100.0	100.0	-1.0	-2.0	N
	EDEMA4 OLE	100.0	100.0	-2.0	-2.0	N
8819453103	EDEMA4 OLE	50.0	50.0	0.0	-1.0	N
	EDEMA4 OLE	100.0	100.0	-2.0	-2.0	N
	EDEMA4 OLE	50.0	50.0	0.0	-1.0	N
8814301010	EDEMA3	100.0	100.0	-1.0	-2.0	N
	EDEMA3 OLE	25.0	100.0	0.0	-1.0	N
8820404011	EDEMA4	100.0	100.0	-1.3	-2.0	N
	EDEMA4 OLE	100.0		-2.0		N
	EDEMA4 OLE	-50.0		0.0		N
	EDEMA4 OLE	50.0		-2.0		N
	EDEMA4 OLE	50.0	100.0	-1.5	-1.5	N
	EDEMA4 OLE	0.0	50.0	-1.0	-2.0	N
	EDEMA4 OLE	100.0	100.0	-1.0	-2.0	N
	EDEMA4 OLE	50.0		-2.0		N
8819456102	EDEMA4 OLE	50.0	0.0	0.0	0.0	N
	EDEMA4 OLE*	0.0		0.0		N
	EDEMA4 OLE*	100.0	100.0	0.0	0.0	N

For patients 16 and 17 years, who are included in the proposed age range for this application, the MSCS and TOS scores are generally supportive of efficacy although the numbers represented are small and formal statistical testing of efficacy has not been performed.

As a crude measure, the mean TOS at 4 hours and the mean change in MSCS at 4 hours for this group of 16- and 17-year-olds (both double-blind and open-label assessments) were 61 and -1.1, respectively. These values are comparable to results obtained for the study populations as a whole in EDEMA3 and EDEMA4, which are shown for reference in Table 7. For the study population as a whole in EDEMA3 (as-treated population), the mean TOS at 4 hours in the ecallantide group vs. placebo was 50 vs. 19 (p=0.04). The mean change in MSCS at 4 hours was -0.9 vs. -0.5 (p=0.04). In EDEMA4 the mean TOS at 4 hours in the ecallantide group compared to placebo was 53 vs. 8 (p<0.001). The mean changes in MSCS at 4 hours were -0.8 vs. -0.4 (p=0.01), respectively.

**Table 7 Primary efficacy results from EDEMA3 and EDEMA4: Complete patient population (16 years and older)**

	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) <i>ITT as randomized</i>	47	21	26 (0.10)	53	8	45 ( <b>&lt;0.001</b> )
TOS at 4 hrs (mean) <i>ITT as treated*</i>	50	19	31 (0.04)			
<b>MSCS</b> <b>Mean Δ from baseline 4h</b> <i>ITT as randomized</i> [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)
<b>MSCS</b> <b>Mean Δ from baseline 4h</b> <i>ITT as treated*</i> [baseline]	-0.9 [2.2]	-0.5 [2.2]	-0.4 (0.04)			

\* Population based on treatments as received. Two patients mistakenly received the wrong study drug in EDEMA3: 1 placebo patient received ecallantide and 1 ecallantide patient received placebo.

### 6.1.5 Analysis of Secondary Endpoints(s)

Other secondary endpoints to consider include the TOS and MSCS at 24 hours as a measure of durability of response, 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 for the proposed age range down to 16 years. These results are discussed in further detail below. The number of patients represented under 16 years of age is too small to permit a conclusion of efficacy in the younger age group. Results for the patients <16 years of age are displayed in the tables but are not discussed due to the small numbers represented and since the proposed indication is for patients 16 years of age and older. The discussion below for key secondary endpoints refers to patients 16 and 17 years of age only.

- **MSCS and TOS at 24 hours**

Analysis of MSCS and TOS at 24 hours suggests durability in the ecallantide response. As a crude measure, the mean TOS at 24 hours for patients 16 and 17 years of age (both double-blind and open-label assessments) was 68 and the mean change in MSCS at 24 hours was -1.4. These values are comparable to results obtained for the full age range, ITT populations in EDEMA3 and EDEMA4. For comparison, 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 (ITT population) 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.

- ***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, and is shown in Table 8 and Table 9. Where reported, the time to significant improvement was similar to the median time reported in EDEMA3, 165 minutes for ecallantide, compared to 240 minutes in the placebo group ( $p=0.14$ ). However, a large number of pediatric patients reported that significant improvement was not achieved during the initial 4-hour observation period, so a median time cannot be calculated for the pediatric patients. While this result does not support robust efficacy, these results are similar to those that were observed for the ITT population in EDEMA4. 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%) ( $p=0.05$ ).

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**Table 8 Time to beginning improvement and significant improvement (minutes): Patients <16 years**

ID	Trial	Time to beginning improvement (min)	Time to significant improvement (min)
8819427102	EDEMA4 OLE	30	225
8805003088	EDEMA2 EDEMA2	26 Not achieved	Not achieved Not achieved
8814372004	EDEMA3 OLE	30	234
8814303004	EDEMA3 OLE	22	37
8804017001	EDEMA2 EDEMA2 EDEMA2 EDEMA3 OLE EDEMA3 OLE EDEMA3 OLE EDEMA3 OLE	30 45 30 5 15 45 Not achieved	Not achieved Not achieved 182 40 Not achieved 215 Not achieved
8814302001	EDEMA3	37	62
8814302002	EDEMA3	22	67
8805013094	EDEMA2 EDEMA2 EDEMA2 EDEMA2 EDEMA2 EDEMA3 EDEMA3 OLE EDEMA3 OLE EDEMA3 OLE	28 20 12 25 24 22 22 37 22	30 30 42 60 59 52 52 82 52
8805022008	EDEMA2 EDEMA3 EDEMA3 OLE	Not achieved 22 Not achieved	Not achieved 142 Not achieved
8814372001	EDEMA3	Not achieved	Not achieved

Source: Module 5, Longitudinal patient profiles

**Table 9 Time to beginning improvement and significant improvement (minutes): Patients 16 and 17 years of age**

ID	Trial	Time to beginning improvement (min)	Time to significant improvement (min)
8805003004	EDEMA2	Not achieved	Not achieved
8814326005	EDEMA3 OLE	24	37
	EDEMA3 OLE	23	39
	EDEMA3 OLE	7	37
8805054099	EDEMA2	30	60
	EDEMA2	42	52
	EDEMA2	20	40
	EDEMA2	57	127
	EDEMA2	60	120
	EDEMA2	Not achieved	Not achieved
	EDEMA2	30	120
	EDEMA2	120	180
	EDEMA3	53	Not achieved
	EDEMA3 OLE	135	Not achieved
8820424001	EDEMA4	67	83
	EDEMA4 OLE	68	113
8819453103	EDEMA4 OLE	98	Not achieved
	EDEMA4 OLE	38	98
	EDEMA4 OLE	98	Not achieved
8814301010	EDEMA3	67	166
	EDEMA3 OLE	37	Not achieved
8820404011	EDEMA4	112	195
	EDEMA4 OLE	181	181
	EDEMA4 OLE	Not achieved	Not achieved
	EDEMA4 OLE	195	Not achieved
	EDEMA4 OLE	210	Not achieved
	EDEMA4 OLE	Not achieved	Not achieved
	EDEMA4 OLE	224	224
	EDEMA4 OLE	195	Not achieved
8819456102	EDEMA4 OLE	113	Not achieved
	EDEMA4 OLE*	Not achieved	Not achieved
	EDEMA4 OLE*	35	225

\* Single attack treated with a second dose of ecallantide for failure to improve.

Source: Module 5, Longitudinal patient profiles

• **Medical interventions**

Medical intervention patterns are of special interest as a quasi-objective marker of efficacy that is independent of any symptom scoring. The medical intervention patterns supported ecallantide's efficacy in patients ages 16 and 17 years. Out of 28 HAE attacks treated with ecallantide 30 mg SC in this age group, only 1 attack (3%) required medical intervention.

For comparison, in EDEMA3, 5 patients (14%) in the ecallantide group compared to 13 (36%) of placebo patients received medical intervention. In EDEMA4, 16 patients (33%) in the ecallantide group received medical intervention compared to 24 patients (50%) in placebo. 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.

#### 6.1.9 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 Section 7. Given the sporadic, intermittent dosing of the drug and short half-life, more persistent effects or other tolerance issues are not anticipated.

#### 6.1.10 Additional Efficacy Issues/Analyses

None.

## 7 Review of Safety

### Safety Summary

The safety of ecallantide at the proposed 30 mg SC dose in patients 16 years of age and older is supported by the clinical trial data in conjunction with the proposed risk management program. 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. Ten anaphylactic events were identified using anaphylaxis diagnostic criteria outlined by the 2006 Joint NIAID/FAAN Second Symposium on anaphylaxis. Based on a population of 255 unique HAE patients and 916 ecallantide doses administered, the anaphylaxis rate is estimated at 3.9% of HAE patients or 1.1% of doses. An additional anaphylactic event was identified in the cardiothoracic surgery trial, 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 68% after 9 doses (rate calculated based on all positive test results without censoring of titers <5). 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 fully evaluated. 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.

Given the relative lack of long-term safety data, the clinical review recommends a Phase 4 long-term safety trial to further evaluate the risk of hypersensitivity, immunogenicity, and disordered coagulation as a post-marketing requirement. The Complete Response included a proposal for a 1-year, long-term, open-label safety trial in 200 HAE patients (DX-88/24). Both ecallantide-naïve and non-naïve patients will be

enrolled. The study will include periodic assessment of laboratory parameters and antibody status. Patients who experience hypersensitivity reactions will be eligible to participate in a separate skin test and graded challenge protocol, which will further assess these clinical procedures as potential screening tools to mitigate the risk of hypersensitivity. Further refinement of the immunoassays will also be specified as post-marketing requirements, in the interest of developing in vitro screening tools to mitigate the risk of hypersensitivity and other adverse events.

Although safety data, particularly long-term follow-up, is limited, the clinical review believes that the safety profile for the proposed dose is 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 initially proposed a REMS program which included specific labeling, a Medication Guide, communication plan, and a (b) (4)

Review of the proposed REMS raised several concerns, including the risk of hampering patient access as well as concerns about the effectiveness of the program in mitigating the risk of hypersensitivity. After further internal discussion between DPAP and OSE as well as discussions with the Applicant, the REMS was revised to include specific labeling, a Medication Guide, and a communication plan. Although the REMS is currently under review, the revised REMS appears to balance the significant risk of hypersensitivity reactions including anaphylaxis associated with ecallantide.

The prior review of the original BLA submission supported the safety of ecallantide with appropriate safeguards in patients 18 years and older but regarded the data in patients under the age of 18 years to be insufficient to make an assessment in patients under the age of 18 years. In response to the Complete Response letter issued on March 25, 2009, the Applicant amended the proposed age range from 10 years and older to 16 years and older. Focused review indicates that the safety profile in patients 16 and 17 years does not differ from the safety profile reported for the clinical program as a whole. Based on the submitted information, the Complete Response supports the safety of ecallantide with the aforementioned safeguards for the entire proposed age range of 16 years and older.

In summary, the application supports the safety of ecallantide for the proposed indication in conjunction with appropriate labeling and a REMS program. A Phase 4 study to evaluate the safety of long-term use of ecallantide, particularly in regards to the risk of hypersensitivity, immunogenicity, and disordered coagulation, is recommended as a post-marketing requirement. Further refinement of immunoassays for anti-ecallantide antibodies are also recommended as post-marketing requirements in the

interest of developing potential screening tools to mitigate the risk of hypersensitivity reactions and other adverse events.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety database for ecallantide was previously reviewed in the Medical Officer review dated February 28, 2009. As part of the Complete Response, the application included updated exposure and unaudited safety data from the ongoing open-label extension trial, DX-88/19. This review focuses on the safety update included in the Complete Response from the ongoing open-label trial.

### 7.1.2 Categorization of Adverse Events

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.

The clinical review relied primarily on the provided preferred terms. For certain adverse events, particularly those related to drug hypersensitivity, related preferred terms were grouped together for the purpose of capturing relevant events and with the intent of providing a more complete listing of common AEs. For example, in the assessment of injection site reactions, the following related preferred terms were categorized together: injection site reaction, injection site pain, injection site irritation, injection site erythema, injection site urticaria, injection bruising. Additional details of the grouping of these terms is provided in Section 7.4.1

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The original BLA included several pooled datasets:

- 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

The safety update in the Complete Response includes an Analysis Population 1.1, which integrates the additional 36 ecallantide-naïve patients from DX-88/19 in the

Analysis Population 1 dataset. The safety data from the 36 patients and the updated, integrated data from Analysis Population 1.1 are the focus for this review.

## 7.2 Adequacy of Safety Assessments

Detailed description of the safety assessments can be found in the Medical Officer review dated February 28, 2009. Overall, the safety assessments performed for the ecallantide development program and the size of the safety database were appropriate, given the nature of the drug product, the proposed orphan indication, and the limited patient population.

Since the original BLA submission, an additional 36 ecallantide-naïve patients have been treated with ecallantide 30 mg SC. In total, 255 unique HAE patients have received 916 ecallantide doses (excludes 3 patients and 30 doses that were administered as part of compassionate use or as part of a rechallenge protocol). Of these 255 patients, 187 patients have been treated with the 30 mg SC dose. The others were treated with earlier IV formulations. The majority of patients (n=102; 40%) have received a single dose. Ninety-two patients (36%) have received 2 to 4 doses, and 39 patients (15%) have received 5 to 9 doses. Twenty-two patients (9%) have received more than 9 doses of ecallantide over a period spanning from 3 months up to 68 months.

The demographic characteristics of the 36 additional patients are similar to the previously enrolled population. Overall, the mean age for the ecallantide safety database is 35 years (range 9 to 78 years), and the population is 66% female (n=168) and 86% Caucasian (n=212), 5% Black (n=13), 6% Hispanic (n=14), 1% Asian (n=3), and 2% reported as other (n=4). As discussed in Section 6, there is limited safety information on patients below the age of 16 years.

## 7.3 Major Safety Results

### 7.3.1 Deaths

As discussed in the Medical Officer Review dated February 28, 2009, two deaths were reported in the ecallantide program, which do not appear to have been related to ecallantide based on the nature and timing of the deaths. No additional deaths were reported in the Complete Response safety update.

### 7.3.2 Nonfatal Serious Adverse Events

In the original BLA, 33 patients reported an SAE. An additional 10 SAEs in 8 of the 36 patients have been reported. These SAEs included the following: HAE (n=6), anxiety attack (n=1), flushing (n=1), chest discomfort (n=1), and pancreatitis (n=1).

Of these reported SAEs, one is a notable case meeting diagnostic criteria for anaphylaxis, which is described in further detail in Section 7.3.4.

### 7.3.3 Dropouts and/or Discontinuations

Of the additional 36 patients included in the safety update, none have discontinued early. One patient, 8820414001, has been put on hold due to a drug hypersensitivity reaction pending a skin testing/rechallenge procedure.

### 7.3.4 Significant Adverse Events

The adverse events described in the safety update included in the Complete Response were consistent with those described in the BLA. Drug hypersensitivity reactions, including anaphylaxis, remain the most prominent safety concern identified for ecallantide. In general, a higher proportion of patients seropositive for ecallantide antibodies (all classes) experienced hypersensitivity-related AEs in comparison to seronegative patients (see Section 7.4.6 Immunogenicity). However, anti-ecallantide antibodies were not predictive of hypersensitivity in the sense that many seropositive patients did not experience a significant hypersensitivity AE. An integrated summary of hypersensitivity reactions is included in this section of the review.

#### **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.

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*

In the original BLA, the Applicant identified 3 cases of anaphylaxis and 1 case of anaphylactoid reaction in the ecallantide program. The clinical review identified 5 additional cases of suspected anaphylaxis using the criteria outlined above. Details of the 9 cases can be found in the Medical Officer review dated February 28, 2009. One additional case of chest tightness and flushing reported as a potential drug hypersensitivity reaction was reported in the safety update for the Complete Response and is described below.

- Patient 8820414001, a 32-year-old white female, reported both chest tightness and flushing approximately 30 minutes after receipt of 15<sup>th</sup> dose of ecallantide 30 mg SC. She was treated with corticosteroids, diphenhydramine, and albuterol, and her symptoms resolved within a half hour. The SAE narrative describes the event as a potential hypersensitivity reaction, and the investigator has determined that the patient should not receive additional doses until a skin testing/rechallenge procedure has been completed. To date, the patient has tested negative for IgE against ecallantide or *P. pastoris* but positive for other antibodies against ecallantide. The patient has tested negative for neutralizing antibodies.

In total, 10 cases of anaphylaxis have been identified in the ecallantide HAE population:

- 8805051099 – EDEMA3 OLE

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- 8820401009 - EDEMA4 OLE (DX-88/19)
- 8805024097 – EDEMA2
- 8802003005 – EDEMA0
- 8804013011 – EDEMA1
- 8804013003 – EDEMA1
- 8805019001 – EDEMA2
- 8805050097 – EDEMA2
- 8814304010 – DX-88/19
- 8820414001 – DX-88/19

Based on these cases, the estimated frequency of anaphylaxis is 4% (10 out of 255 patients) for the total HAE population treated with ecallantide. This denominator excludes patients who received the drug through compassionate use (n=3) and does not include events that occurred during a rechallenge protocol. 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. The rate calculation also excludes anaphylaxis reactions in other patient populations, including one case (Patient 262) in the ecallantide cardiothoracic program.

#### **Other hypersensitivity reactions**

There were other adverse event reports suggestive of clinical hypersensitivity, including reports of rash, pruritus, and urticaria following injection, although the time course in relation to dose administration was not clearly documented in the majority of these cases. In general, while not all cases may have been attributable to ecallantide, the overall impression of these adverse events is consistent with the risk of Type I hypersensitivity associated with ecallantide. Due to the multiplicity of preferred terms, related preferred terms were grouped together to form a more accurate estimate of hypersensitivity-type reactions. These term groups and estimated frequencies are briefly described here.

#### ***Rash***

Eight patients (3%) reported any of the following related preferred terms: rash, rash macular, rash generalized, and rash erythematous. Additional details of the adverse events, if available from the longitudinal patient profiles, are provided in parentheses.

- 8804009001 (rash on chest; EDEMA2)
- 8804017003 (rash pruritic; EDEMA2)
- 8804017010 (rash, rash/red bumps on buttock; EDEMA2)
- 8805050098 (rash on right thigh; EDEMA3 OLE)
- 8805050099 (rash macular, blotchiness left upper chest and arms; EDEMA2)
- 8814301007 (rash on left forearm and antecubital area; EDEMA3 OLE)
- 8814304010 (rash on arms and chest; DX-88/19)
- 8814311013 (erythematous rash on right side of neck; EDEMA4)

One patient also experienced a rash during the rechallenge procedure:

- 8805051099 (generalized rash; Rechallenge protocol)

### ***Pruritus***

Thirteen patients (5%) reported any of the following related preferred terms: pruritus, pruritus allergic, eye or ear pruritus, and pruritus generalized. Injection site pruritus was not included in this group but was included under injection site reactions. Additional details of the adverse events, if available from the longitudinal patient profiles, are provided in parentheses.

- 8804003005 (scalp itching; EDEMA1)
- 8804009001 (abdominal itching; EDEMA3 OLE)
- 8804017003 (generalized pruritus; EDEMA2)
- 8805051099 (pruritus; EDEMA3 OLE)
- 8804017013 (pruritus on forearm; DX-88/19)
- 8805003004 (itching; EDEMA2)
- 8805017099 (bilateral pruritus of arms for 10 minutes post-infusion; EDEMA2)
- 8805028097 (intermittent swollen itchy patches; EDEMA2)
- 8805050098 (itchy red papules right groin – EDEMA3; intermittent itching similar to allergies – EDEMA3 OLE)
- 8805051099 (pruritus; EDEMA3 OLE)
- 8814301007 (generalized pruritus; EDEMA3 OLE)
- 8814310006 (itchy, watery eyes; EDEMA3)
- 8814326002 (systemic itching; EDEMA3 OLE)

### ***Urticaria***

Five patients (2%) reported any of the following 2 preferred terms after receipt of ecallantide compared to 1 patient in placebo (8814301007): urticaria, urticaria localized.

- 8804017003 (urticaria on left wrist; EDEMA2)
- 8805017018 (urticaria; EDEMA3 OLE)
- 8805019001 (urticaria on back and face; EDEMA2)
- 8820417014 (urticaria; DX-88/19)
- 8820452001 (hives – suspected allergic reaction to study drug; DX-88/19)

### **Injection site reactions**

In the pooled analysis of the two pivotal placebo-controlled trials, EDEMA3 and EDEMA4, local injection site reactions were reported in 3 (3%) patients in the ecallantide group compared to 1 (1%) in the placebo group. 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.

In the full ecallantide HAE study population, 19 patients (7%) reported any of the following related preferred terms: injection site reaction, injection site pain, injection site irritation, injection site erythema, injection site urticaria, injection bruising. The injection site reactions were not predictive of systemic hypersensitivity, nor did they appear to be predictive of other adverse events. The following patients reported some kind of injection reactions:

- 8804017010 (injection site pain; EDEMA2)
- 8804024001 (injection site irritation and paresthesia, fixed drug reaction with redness and irritation – EDEMA3 and EDEMA3 OLE)
- 8805009099 (injection site redness – EDEMA3 OLE)
- 8805024097 (injection site pruritus, local injection site reaction; EDEMA2)
- 8805028097 (injection site irritation, pain, pruritus; EDEMA2)
- 8805059099 (injection site pain, burning at infusion site; EDEMA2)
- 8814301007 (injection site erythema; EDEMA3 OLE)
- 8814301011 (injection site erythema; EDEMA2)
- 8814304005 (injection site edema; EDEMA2)
- 8814304010 (injection site erythema, 6cm area of redness; DX-88/19)
- 8814310006 (injection site pain, burning at site; EDEMA3)
- 8814326002 (injection site pruritus; EDEMA3 OLE)
- 8814337001 (injection site urticaria; EDEMA3 OLE)
- 8820417014 (injection site reaction; EDEMA4)
- 8820420001 (injection site irritation, reaction, and pain; DX-88/19)
- 8820452001 (injection site reaction, redness and swelling; DX-88/19)
- 8820452004 (injection site bruising; DX-88/19)
- 8820453002 (injection site erythema; DX-88/19)
- 8820456001 (injection site reaction, swelling and redness; DX-88/19)

One additional patient reported an injected site reaction during the rechallenge procedure:

- 8805051099 (injection site reaction; Rechallenge procedure)

### 7.3.5 Submission Specific Primary Safety Concerns

#### **Mode of administration**

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. 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.

**REMS**

At the time of this review, the REMS program remains under review and the final composition of the REMS is pending, but will include a Medication Guide and a Communication Plan.

In the resubmission, the Applicant submitted a Risk Evaluation and Management Strategies (REMS) program, the Kalbitor Safe Use Program, to promote informed risk-benefit decisions before initiating treatment with ecallantide and to establish the safe use of ecallantide in settings appropriate for managing hypersensitivity reactions and preventing HAE patients with known hypersensitivity from receiving further treatment. The basic elements proposed in the resubmission were consistent with discussions held with the Applicant in the post-review and pre-resubmission meetings. The proposed program included the following elements:

- Medication Guide

(b) (4)

(b) (4)

DRISK/OSE was consulted for review of the proposed REMS. During the review process, feedback from DRISK and ongoing internal discussions identified potential feasibility issues with the restricted access proposed under the ETASU. It was unclear how the

(b) (4)

Most importantly, it was not clear that this type of (b) (4) would mitigate the risk of hypersensitivity reactions. In addition, DPAP and OSE noted that other drugs with comparable risk of anaphylaxis do not employ restricted access as a means of mitigating the risk of hypersensitivity reactions. There was no evidence to suggest that the nature of hypersensitivity reactions associated with ecallantide differs from more well-known drug-induced hypersensitivity reactions. While there remains

some concern that the clinical signs and symptoms of hereditary angioedema (HAE) may overlap with the signs of drug hypersensitivity and cause confusion for healthcare providers and patients, ecallantide is recommended to be administered in a setting that is equipped to treat both acute conditions. Given the orphan status of the disease indication, most HAE patients are under the care of specialists who are trained in allergy and immunology, and patients tend to seek emergency treatment from the same specialized centers, which may alleviate some of the potential confusion. Both DPAP and OSE expressed concerns that the elements to assure safe use could hinder patient access, which is a significant issue since HAE patients have no alternative treatment options aside from supportive care.

After internal evaluation and discussion, DPAP and OSF made the determination that the elements to (b) (4) were not needed. Instead, the Agency recommended that the revised REMS be comprised of specific labeling in the package insert, a Medication Guide, a communication plan, and a timetable of assessments. A formal letter retracting the requirements for elements to assure safe use was issued on October 16, 2009. At the time of this review, discussions regarding the structure of the final REMS program are ongoing.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

#### **Pooled, placebo-controlled trial data (Analysis Population II)**

In the pooled analysis of the placebo-controlled Phase 3 trials, the most common AEs associated with ecallantide were 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 10. 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 10 Adverse events occurring in >1 patient and at a greater frequency in the ecallantide group vs. placebo**

Preferred term	EcCallantide N=100 (n,%)	Placebo N=81 (n,%)
<b>Patients with ≥1 AE</b>	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 reaction <sup>a</sup>	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

<sup>a</sup> Includes all patients reporting one or more of the following related preferred terms: injection site reaction, injection site pain, injection site irritation, injection site erythema, injection site urticaria, injection bruising

**Pooled, ecallantide HAE population data (Analysis Population 1.1)**

The safety data for the total HAE database (Analysis Population 1.1) was similar to the pooled analysis for the placebo-controlled trials (Analysis Population II), with the exception of a more detailed review of drug hypersensitivity events, as described in Section 7.2. The addition of 36 ecallantide-naïve patients in the safety update does not change this safety profile. An updated table of reported frequencies for the most common adverse events is shown below (Table 11). The frequencies reported for rash, pruritus, injection site reactions, and anaphylaxis, are based on the grouping of preferred terms as described in Section 7.3. Percentages were based on the number of unique patients (n=255) and specific AEs per patient were only counted once.

**Table 11 Adverse events reported in >3% of HAE patients treated with ecallantide**

Preferred term	Ecallantide N=255 <sup>a</sup> (n, %)
<b>Patients with ≥1 AE</b>	174 (68)
Headache	41 (16)
Nausea	33 (13)
Fatigue	30 (12)
Diarrhea	27 (11)
HAE	23 (9)
Upper respiratory tract infection	21 (8)
Injection site reactions <sup>b</sup>	19 (7)
Nasopharyngitis	15 (6)
Vomiting	14 (6)
Upper abdominal pain	13 (5)
Pruritus <sup>c</sup>	13 (5)
Pyrexia	12 (5)
Cough	11 (4)
Sinusitis	11 (4)
Anaphylaxis <sup>d</sup>	10 (4)
Dizziness	10 (4)
Prolonged activated partial thromboplastin time (aPTT)	10 (4)
Nasal congestion	9 (4)
Pharyngolaryngeal pain	9 (4)
Rash <sup>e</sup>	8 (3)
Dehydration	8 (3)

<sup>a</sup> 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.

<sup>b</sup> Includes all patients reporting one or more of the following related preferred terms: injection site reaction, injection site pain, injection site irritation, injection site erythema, injection site urticaria, injection bruising

<sup>c</sup> Includes all patients reporting one or more of the following related preferred terms: pruritus, pruritus allergic, eye or ear pruritus, and pruritus generalized

<sup>d</sup> Includes all patients meeting diagnostic criteria for anaphylaxis as outlined by the 2006 NIAID/FAAN Second Joint Symposium on Anaphylaxis

<sup>e</sup> Includes all patients reporting one or more of the following related preferred terms: rash, rash macular, rash generalized, and rash erythematous

#### 7.4.2 Laboratory Findings

Routine clinical laboratory testing (CBC with differential, chemistry panel, coagulation parameters, and urinalysis) was 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 and a discussion of results are provided in the Medical Officer Review dated February 28, 2009.

Overall, no clinically relevant changes in laboratory parameters were observed in Analysis Population 1, and the addition of the 36 patients in the safety update (Analysis Population 1.1), did not alter this assessment.

### **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, nor in the ecallantide HAE safety population as a whole (Analysis Population 1.1). In terms of adverse events, there was no apparent safety signal to indicate an increased bleeding risk. One patient (8804022005) was reported to have hematochezia 22 days after dosing and a second patient (8814316002) was reported to have ecchymosis 14 days after dosing. The delayed timing of these events after dosing argues against ecallantide as the inciting factor.

Conversely, there is an additional theoretical concern about hypercoagulability. Ecallantide is 88% homologous with endogenous 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 in the original BLA was notable for one patient with a pulmonary embolus. However, this patient was seronegative and the case was further confounded by a diagnosis of lupus, which is a known hypercoagulable state. No additional thromboembolic events were reported in the Complete Response safety update. The clinical review concludes that hypercoagulability remains a theoretical risk at this time and recommends ongoing clinical monitoring to assess for adverse events associated with derangements in coagulation parameters.

The Complete Response letter dated March 25, 2009, initially required a clinical study to address potential coagulopathies associated with ecallantide. At the pre-resubmission meeting on May 14, 2009, the Applicant presented the existing clinical data to date and requested reconsideration of the requirement for a formal clinical trial. The Division concurred with the Applicant's proposal and recommended continued clinical surveillance as well as in vitro cross-reactivity studies for antibodies against ecallantide and TFPI to assess further the potential of hypercoagulability. As part of the Complete Response, the Applicant conducted a cross-reactivity TFPI study, and the results of the in vitro study are discussed in further detail in Section 4.1. The Applicant has included monitoring for coagulopathic AEs in the proposed long-term safety study, which is consistent with the clinical review's recommendations regarding this potential safety concern.

### 7.4.3 Vital Signs

Routine vital sign assessment was performed at baseline and at appropriate intervals through each study. A detailed schedule of vital sign assessment timepoints and results for each study is provided in the Medical Officer Review dated February 28, 2009. Overall, there were no clinically significant changes in blood pressure or pulse associated with 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 the 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. In terms of changes in body temperature, pyrexia was one of the more commonly reported AEs in the safety database. These cases appear to have been self-limited. No additional safety signals were identified in review of the additional 36 patients in the safety update.

### 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). Based on these results that were included in the initial BLA submission, the clinical review concludes that 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/Clinical Trials

#### **Skin testing and graded challenge**

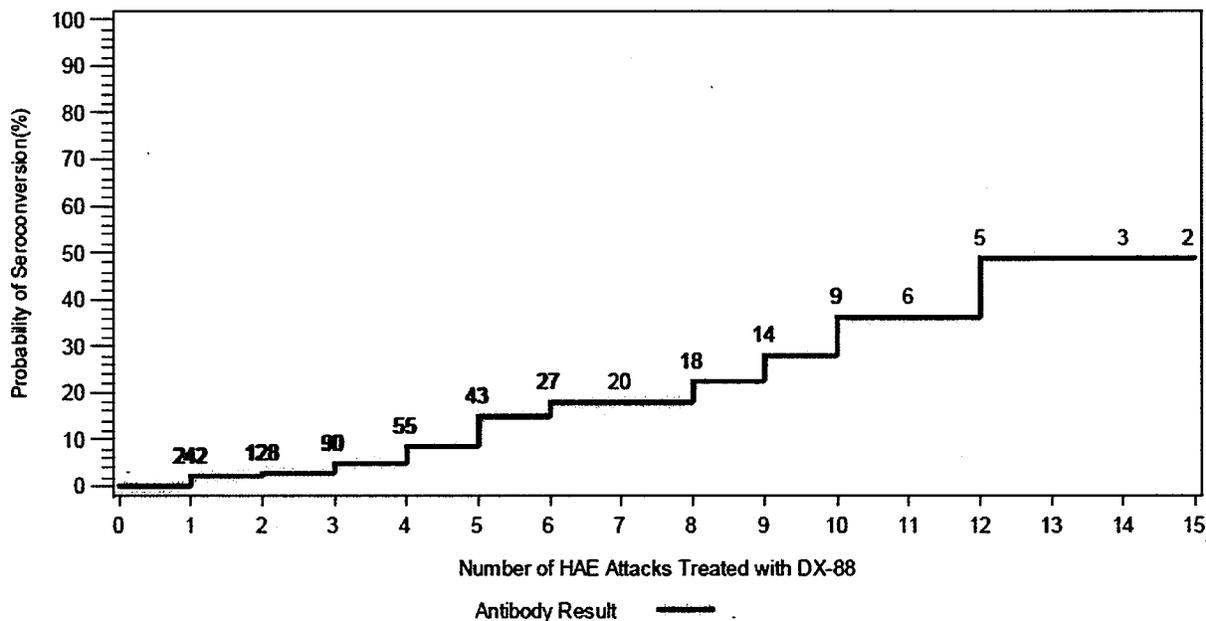
As part of the development program, the Applicant has evaluated patients with hypersensitivity reactions to ecallantide in an elective, formal skin testing and graded challenge procedure. The details of the skin testing and graded challenge protocol and results are described in the Medical Officer review dated February 28, 2009. Based on the small sample size (n=9) studied, the skin testing and graded challenge procedures appear to have a reasonable negative predictive value, in the sense that all patients with negative challenges have since gone on to receive additional doses of ecallantide without further incident. No additional patients have undergone formal skin testing and rechallenge.

(b) (4)

### 7.4.6 Immunogenicity

Prior review of anti-ecallantide antibody (all antibody classes) seroconversion (see Medical Officer Review dated February 28, 2009) noted that the probability of seroconversion increased with the number of treated episodes. Updated seroconversion for anti-ecallantide antibodies (all classes) data were provided in the Complete Response. In Analysis Population 1.1, 18 of 242 (7%) patients, for whom pre- and post-dose antibody results were available, had seroconverted. Based on the curve, the probability of seroconversion after 9 HAE attacks is estimated to be approximately 27% (Figure 1).

**Figure 1 Seroconversion to anti-ecallantide antibodies (all classes) in Analysis Population 1.1 (estimated rate with censoring of antibody levels  $\leq 5$ )**

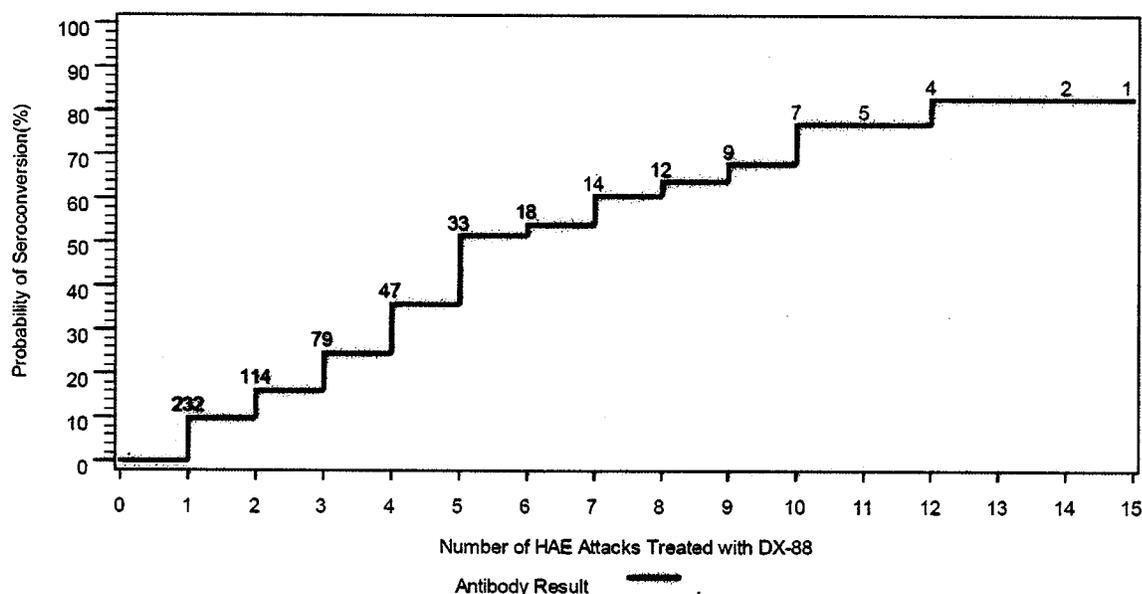


Source: Module 2, safety-update.pdf, Section 2.4.5, Figure 1

The rate of seroconversion reported in the safety update is less than the values presented in the original BLA and in the December 19, 2008, safety update. In the

December 19, 2008, safety update, 53 of 243 (22%) patients were antibody positive and the estimated rate of seroconversion was nearly 40% after 4 attacks. The Applicant accounts for this discrepancy by noting that a medical adjudication process was applied to censor antibody assay results with a titer of  $\leq 5$ . **This censoring was not used in the original BLA submission.** Without censoring, 57 of 255 (24%) in the safety update are reported to test positive for anti-ecallantide antibodies and the seroconversion rate is estimated to be approximately 68% after 9 attacks (Figure 2).

**Figure 2 Seroconversion to anti-ecallantide antibodies (all classes) in Analysis Population 1.1 (estimated rate without censoring of antibody levels  $\leq 5$ )**



Source: Module 2, safety-update.pdf, Figure 1.4

Despite the marked differences in seroconversion rates with censoring of antibody levels 5 or less, the trend of increased sensitization with increase exposure remains consistent. The long-term clinical consequences of seroconversion remain unknown at this time.

Data specific for anti-ecallantide or anti-*P. pastoris* IgE were not included in the update. The original BLA submission indicated a rate of seroconversions of 1% for anti-ecallantide IgE and 5% for anti-*P. pastoris* IgE, respectively.

Of the 21 patients reported to be positive for anti-ecallantide antibodies in the safety update, 18 (86%) reported an AE during the treatment period in comparison to 153 of 228 (67%) antibody-negative patients. Aside from hypersensitivity-related AEs, differences were noted for individual AEs but their disparate nature made 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: prolonged APTT (19 vs. 3%); diarrhea (24 v. 9%); fatigue (19 vs. 11%)| HAE (24% vs. 8%); headache (29 vs. 15%), injection site reactions (19 vs. 1%); nasopharyngitis (14 vs. 5%); nausea (29 vs. 12%); rash (14 vs. 5%), sinusitis (14 vs. 4%); upper respiratory tract infection (24 vs. 7%), nausea (17 vs. 11%), and urticaria (14 vs. 2%).

## **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. 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.

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 AE. 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=28), 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**

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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 Evaluations

### 7.6.1 Human Carcinogenicity

No carcinogenicity studies were performed for ecallantide. The Pharmacology/Toxicology review team recommends a carcinogenicity study in rats as a post-marketing requirement (Section 4).

### 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 3<sup>rd</sup> pregnancy was reported for DX-88/19 (EDEMA4 OLE) but the patient received only placebo and never received ecallantide. The pregnancy resulted in the delivery of another healthy full-term infant. No other information on ecallantide use in pregnancy or lactation in humans is available.

### 7.6.3 Pediatrics and Assessment of Effects 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, only 28 pediatric patients were studied in the clinical development program, as discussed in Section 6. In general, the nature and number of AEs observed in children appeared comparable to the adult population but the low number of patients below the age of 16 years limits conclusions about safety in this subpopulation.

#### **Common AEs in pediatric patients**

AEs were reported in 19 of 28 (68%) pediatric patients 10 to 17 years of age treated with IV or SC ecallantide, which is comparable to the proportion of adult patients 18 years and older also reporting at least one AE (155 of 227; 68%). The most common AEs occurring in more than 1 pediatric patient included the following: acute sinusitis and

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sinusitis NOS (n=4), upper respiratory tract infection (n=2), bronchitis (n=2), influenza (n=2), gastroenteritis (n=2), headache (n=5), diarrhea (n=4), pyrexia (n=3), fatigue (n=3), HAE (n=2), rhinorrhea (n=3), cough (n=2), nasal congestion (n=2), pharyngolaryngeal pain (n=2), blood CPK increased (n=4), APTT increased (n=3), and thrombin time prolonged (n=3).

**Anaphylaxis and other SAEs in pediatric patients**

In addition, anaphylaxis was identified in 2 patients, one 14-year-old (8805019001) and one 17-year-old (8805054099). In terms of other SAEs, 4 pediatric patients reported a total of 8 other SAEs, which included reports of HAE (n=3), abdominal pain diagnosed as pancreatitis (n=1), jaw fracture (noted at visit prior to dosing; n=1), and concussion, contusion, and skin laceration following a car accident (n=1). Similar to the SAEs reported for the adult patients, the disparate nature of these events makes it difficult to determine causality, although certain specific events, such as the jaw fracture and injuries sustained after a car accident appear to have occurred independent of dosing and are not likely to be attributable to ecallantide.

**Immunogenicity in pediatric patients**

Four of 28 pediatric patients (14%) have developed non-IgE antibodies to ecallantide. Two of 28 patients have had intermittently positive test results for IgE antibodies. Of these two patients, one patient experienced an anaphylactic event and also had positive IgE antibodies to *P. pastoris* following the 7<sup>th</sup> exposure of 34 doses total received. Although the rate of seroconversion does not appear to be higher in pediatric patients, given the young age and potential long duration of use over a lifetime, it is expected that most, if not all patients, will seroconvert with continued use of ecallantide. As stated in Section 7.5, the long-term implications of seroconversion are not known.

**Proposed Phase 4 pediatric study:** (b) (4)

(b) (4)

#### 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 / Safety Issues

#### Proposed long-term safety trial: DX-88/24

In the interest of obtaining additional safety information on chronic use of ecallantide, the Complete Response letter requested a long-term safety study as a post-marketing requirement. The goals of the trial will be to better assess the risk of hypersensitivity reactions, immunogenicity, and possible effects on coagulation. In the resubmission, Dyax proposed a long-term, open-label, observational trial (DX-88/24) that will evaluate immunogenicity and hypersensitivity to be conducted under BBIND 10,426.

- Trial title: A Phase 4, long-term observational safety study to evaluate immunogenicity and hypersensitivity with exposure to Kalbitor (ecallantide) for the treatment of acute attacks of HAE
- Study number: DX-88/24
- Objectives
  - Determine the rate of anaphylaxis and Type I hypersensitivity reactions upon exposure to Kalbitor
  - Determine the rate of seroconversion to anti-ecallantide antibodies upon exposure to Kalbitor
  - Determine the relationship of seroconversion to AEs
  - Determine the relationship of seroconversion to efficacy response
  - Investigate potential predictive factors for anaphylaxis and Type I hypersensitivity reactions
- Outcomes
  - Anaphylaxis and other AEs suggestive of hypersensitivity
  - Seroconversion rates based on antibody levels
  - AEs and seroconversion over time

- Overall Patient Response Assessment and seroconversion over time
- Skin test procedure results
- Study design: multi-center, open-label, non-comparator, longitudinal study
- Patients
  - N=200 (150 naïve to Kalbitor; 50 non-naïve)
  - 16 years and older

### ***Study conduct***

The proposed trial will enroll approximately 200 HAE patients 16 years and older. An estimated 150 patients will be naïve to ecallantide while the remaining 50 patients will be patients with prior exposure. Enrollment is expected to occur in a period of 3 years and each patient will be followed for approximately 1 year. Patients enrolled in the study will receive a 30 mg dose of ecallantide administered via 3 SC injections. If an attack persists, an additional 30 mg dose may be administered per the discretion of the treating physician. Patients will undergo physical exams, skin testing, and anti-ecallantide antibody testing at baseline and at 6 months after the last ecallantide exposure or after every 4 HAE treatments, whichever occurs sooner, up to 1 year.

Patients with antibody responses will be evaluated for neutralizing antibody. Anti-ecallantide IgE will be assessed in patients with clinical symptoms suggestive of hypersensitivity. Patients with signs of hypersensitivity will be given the option of undergoing follow-up skin testing and graded challenge as was performed during the clinical development program (see next section). Adverse events will be collected throughout the duration of the study. Specifically, suspected cases of anaphylaxis will be adjudicated based on NIAID/FAAN criteria for anaphylaxis. Efficacy will be assessed by an Overall Patient Response Assessment (Figure 3).

### ***Assessments***

- Efficacy - Overall Patient Response Assessment (OPRA) at 4 hours and 24 hours (Figure 3)
  - Completed every 15 minutes for the first hour
  - Follow-up phone call by study coordinator will assess the OPRA at 4 and 24 hours

### **Figure 3 Proposed trial DX-8824: Overall Patient Response Assessment**

(b) (4)

- Safety
  - AEs
  - Physical exam
  - Skin testing
  - Drug challenge – only in patients with hypersensitivity reactions
  - Antibodies

***Inclusion/exclusion criteria***

- Inclusion criteria
  - Enrolled in Kalbitor CASE program and registry
  - 16 years and older
  - Confirmed diagnosis of HAE (type I or II) by physician
  - Patient or guardian able to understand and sign informed consent form
- Exclusion criteria
  - Patients who experience a prior anaphylaxis or moderate to severe hypersensitivity reaction to Kalbitor and who have not undergone a successful rechallenge
  - Pregnancy or active breastfeeding
  - Other conditions which may interfere with safety or compliance per Investigator discretion

***Clinical review summary***

The general outline of the proposed long-term trial, DX-88/24, appears acceptable.

(b) (4)

In addition, the protocol for the Phase 4 trial should specify analysis of AEs related to disordered coagulation, given the theoretical concerns for both increased bleeding and/or clotting with ecallantide.

The following comments were conveyed to the Applicant on October 16, 2009:

- *Specify a separate analysis for adverse events related to disordered coagulation, both hypocoagulability and hypercoagulability.*
- *Revise the protocol to include a detailed description of the skin testing and graded challenge procedures that will be used in patients with evidence of clinical hypersensitivity who consent to undergo these procedures.*
- *We recommend follow-up skin testing and baseline and follow-up IgE testing in a subset of patients without evidence of clinical hypersensitivity to provide further information on the positive and negative predictive values of these tests.*

The Applicant was also requested to provide a timeline for the trial, including submission of the final protocol and the complete study report. The timeline has not yet been finalized at the time of this review.

## **8 Postmarket Experience**

Ecallantide is currently not approved or marketed elsewhere and there is no postmarketing experience available.

## 9 Appendices

### 9.1 Literature Review/References

The Applicant previously 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 16 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)”

Labeling discussions are in progress at the time of this review. The clinical review recommends a boxed warning in labeling that discusses the risk of hypersensitivity reactions, including anaphylaxis, that is associated with the use of ecallantide. The package insert should also contain specific language that advises administration of ecallantide only in medically supported settings and will caution healthcare providers and patients to monitor closely for hypersensitivity reactions, which can overlap the signs and symptoms of an acute HAE attack. In addition, a Medication Guide is required as one of the elements of the REMS.

The following are comments on the proposed label communicated to the Applicant on October 16, 2009:

- *Highlights section:*
  - (b) (4)
  - (b) (4)
  - *The indications statement has been simplified and revised to include the recommended age range.*
  - *The dosage and administration instructions regarding a second dose within a 24-hour period have been clarified. Recommendations regarding the administration by a healthcare professional in an appropriate setting have also been added.*
  - *A statement cautioning users about the similarity between certain acute HAE symptoms and hypersensitivity has been added.*
- *Section 2.2, Dosage and Administration, Administration Instructions*

- *Provide the recommended needle size for subcutaneous injection.*
- *Provide more detail on the selection of an appropriate injection site and the need for site rotation, if any.*
- *Describe the administration of a second dose, including selection of an appropriate administration site.*
- *Section 5.1, Warnings and Precautions, Hypersensitivity Reactions Including Anaphylaxis*

- [Redacted text block] (b) (4)

- *Section 6.1, Adverse Reactions, Clinical Trials Experience:*

[Large redacted text block] (b) (4)

- *Sections (b) (4) 11, and 16*

- *Alert healthcare professionals to the vial overfill amount. Provide instructions for appropriate administration of a 30 mg dose.*
- *Section 14, Clinical Studies*
  - *Provide demographic information for the pooled EDEMA3 and EDEMA4 trials.*
  - *Revise Table 2 to show the mean value of MSCS and TOS with 95% CI and p-values. Simplify the reported MSCS data values to one decimal place. Round the TOS values to the nearest whole number and do not include any decimal placed. Remove the Median, IQR, and SD. Include a footnote defining the abbreviations for MSCS and TOS.*
  - *Information on medical intervention patterns has been included. Data from other secondary efficacy variables have been removed.*

### **9.3 Advisory Committee Meeting**

A Pulmonary and Allergy Drug Products Advisory Committee meeting was previously held on February 4, 2009, to discuss ecallantide. Details of the meeting's proceedings are provided in the Medical Officer review dated February 28, 2009. Briefly, 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. The Applicant's presentation at the PADAC meeting indicated plans for a mandatory registry of 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.

No PADAC meeting was convened for the Complete Response submission.

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

<b>APPLICATION:</b> BLA 125277	<b>TRADE NAME:</b> Kalbitor
<b>APPLICANT/SPONSOR:</b> Dyax	<b>USAN NAME:</b> Ecallantide
<b>MEDICAL OFFICER:</b> Susan Limb, MD	
<b>TEAM LEADER:</b> Sally Seymour, MD	<b>CATEGORY:</b> Kallikrein inhibitor
<b>DATE:</b> June 16, 2009	<b>ROUTE:</b> Subcutaneous injection

**SUBMISSIONS REVIEWED IN THIS DOCUMENT**

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
May 31, 2009	May 31, 2009	BLA 125277	BLA electronic submission, Complete Response

**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 Complete Response for BLA 125277 for ecallantide, a recombinant human plasma kallikrein inhibitor intended for the treatment of acute attacks of hereditary angioedema (HAE) in patients 16 years of age and older. The proposed dose is 30 mg SC, which may be repeated once in a 24-hr period for a single HAE attack. 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 was previously granted Orphan Drug and Fast Track status, and the application was reviewed under Priority review. The Division issued a Complete Response letter on March 25, 2009. The CR letter addressed two major clinical deficiencies, namely the lack of an appropriate Risk Evaluation and Mitigation Strategies (REMS) program and a lack of efficacy and safety data to support the proposed indication in pediatric patients ages 10 to 17 years. The letter outlined three clinical postmarketing commitments to study the long-term safety and efficacy of ecallantide, with particular regard to hypersensitivity reactions, immunogenicity, and hypercoagulability.

In support of the application, the Applicant has adjusted the proposed age range from 10 years of age and older to 16 years of age and older. The Complete Response also includes the details for a REMS program. In addition, the resubmission includes a draft product label, updated safety information from ongoing open-label study DX-88/19 (EDEMA4 OLE), validated PK data to support population PK analysis, and updated CMC information.

From a clinical standpoint, the response is complete and is adequate to allow clinical review.

**OUTSTANDING ISSUES:** None.

## 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). (b) (4)

(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 original BLA was the subject of an Advisory Committee meeting, given that ecallantide is an NME with a novel indication. The AC voting was split for the approval of ecallantide in adults with the stipulation of safeguards implemented to minimize the risk of hypersensitivity reactions. The AC panel members requested further information in pediatric patients to establish safety and effectiveness.

The Division issued a Complete Response letter on March 25, 2009. The CR letter addressed two major clinical deficiencies, namely the lack of an appropriate REMS program and a lack of efficacy and safety data to support the proposed indication in pediatric patients ages 10 to 17 years.

1. *The results of the submitted clinical studies do not support the efficacy and safety of Kalbitor (ecallantide) at a dose of 30 mg SC for the treatment of acute attacks of hereditary angioedema (HAE) in patients 10 years of age and older. Particularly, the number of patients below 18 years of age exposed to Kalbitor (ecallantide) is limited and not adequate to assess efficacy or safety in this age group. To support efficacy and safety of Kalbitor (ecallantide) for treatment of acute attacks of HAE in patients 10 years of age and older, provide the following:*
  1. *Efficacy and safety data from controlled clinical studies or open label clinical studies in a reasonable number of patients below 18 years of age and covering each year age group. Also provide validation of the ecallantide bio-analytical assay, and comparative ecallantide exposure data in adults and pediatric patients to support the recommended pediatric dose.*
2. *Requirement for proposed Risk Evaluation and Mitigation Strategy (REMS). For the reasons described below, a REMS will be required as part of your approval.*

The CR letter also outlined the following clinical postmarketing requirements under 505(o):

1. *Conduct a study with Kalbitor (ecallantide) in patients with hereditary angioedema to evaluate anaphylaxis and type I hypersensitivity. The study should include objectives to identify predictive risk factors and develop effective screening tools to mitigate the risk of hypersensitivity and anaphylaxis.*
2. *Conduct a study with Kalbitor (ecallantide) in patients with hereditary angioedema to evaluate immunogenicity. The study should include objectives to correlate antibody levels with adverse events and lack of efficacy.*
3. *Conduct a study with Kalbitor (ecallantide) in patients with hereditary angioedema to evaluate the effects on coagulation parameters.*

## **2. CLINICAL DEVELOPMENT PROGRAM**

For the original submission, the Applicant 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 the Complete Response submission, one study remains ongoing, DX-88/19 (EDEMA4 OLE). To support the efficacy and safety of ecallantide for the proposed indication, the Applicant relies primarily on the completed HAE studies. Safety data from the ongoing OLE as of May 1, 2009 are also provided. To date, a total of 255 unique HAE patients have received 916 ecallantide doses. Of these, 187 patients have received the 30 mg SC dose. 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
<b>Phase 1</b>							
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 <sup>2</sup> 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
<b>Phase 2</b>							
DX-88/2 EDEMA0	HAE/ AAE (≥18yo)	9	9	OL, SD	SD	10 mg IV 40 80	<ul style="list-style-type: none"> <li>Proportion with resolution of attack by 4h post-dose</li> <li>Safety</li> </ul>
DX-88/4 EDEMA1	HAE (≥10yo)	41	41	DB, SD	SD	5 mg/m <sup>2</sup> IV 10 20 40 Placebo	<ul style="list-style-type: none"> <li>Proportion with significant improvement by 4hr</li> <li>Safety</li> </ul>
DX-88/5 EDEMA2	HAE	77	273	OL, MD	≥7 days between attacks	5 mg/m <sup>2</sup> IV 10 20 30 mg SC	<ul style="list-style-type: none"> <li>Safety</li> <li>Proportion of successful outcomes</li> </ul>
<b>Phase 3</b>							
DX-88/14 EDEMA3-DB	HAE	37	39	DB, R, PC, with OLE	SD	30 mg SC Placebo	<ul style="list-style-type: none"> <li>Treatment outcome score (TOS)</li> <li>Safety</li> </ul>
EDEMA3-RD (open-label extension)	HAE	67	161	OL, repeat-dose	≥72h between attacks	30 mg SC	<ul style="list-style-type: none"> <li>TOS at 4h</li> <li>Safety</li> </ul>
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"> <li>Change in Mean Symptom Complex Score (MSCS) at 4h</li> <li>Safety</li> </ul>
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"> <li>Change in Mean Symptom Complex Score (MSCS) at 4h</li> <li>Safety</li> </ul>

\*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
  - Long-term safety
- 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.
  - 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.
- 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.
- June 13, 2007 – EDEMA3 study results and proposed BLA submission without EDEMA4. Preliminary review of the EDEMA3 results indicated that EDEMA3 would not be sufficient support for drug approval. Division advised that all data

to support the efficacy and safety of ecallantide should be included in the original BLA submission.

- 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.
- February 4, 2009 – DPAP Advisory Committee Meeting
- March 25, 2009 – Complete Response letter (see summary in Section 1 of this review)
- May 14, 2009 – Resubmission planning meeting
  - The Division advised Dyax to adjust the proposed age range to include only adults while continuing to obtain safety and efficacy data from pediatric patients under the IND. Data could be obtained from an open-label study with reasonable representation of each year age included in the proposed pediatric age range. The pediatric data could later be submitted as an efficacy supplement.
  - Complete, fully detailed REMS package expected to facilitate timely review.

## **5. CLINICAL STUDIES**

Efficacy data was previously reviewed as part of the original BLA. The Complete Response submission includes updated safety information from the ongoing study, DX-88/19 and a separate summary of pediatric data. No new efficacy or safety trials were conducted for the Complete Response.

## **6. RISK MANAGEMENT**

The Applicant proposes a REMS program, the Kalbitor Safe Use Program, to promote informed risk-benefit decisions before initiating treatment with ecallantide and to establish the safe use of ecallantide in settings appropriate for managing hypersensitivity

reactions and preventing HAE patients with known hypersensitivity from receiving further treatment. The proposed program includes the following elements:

(b) (4)

*Reviewer's comment: DRISK/OSE has been consulted for review of the proposed REMS. The basic elements proposed in the resubmission are consistent with discussions held with the Applicant in the post-review and pre-resubmission meetings.*

## 7. POST-MARKETING REQUIREMENTS

### Hypersensitivity and immunogenicity

The Complete Response letter specified clinical studies to assess further the risk of anaphylaxis and other hypersensitivity reactions, immunogenicity, and possible effects on coagulation. Dyax proposed a long-term, open-label, observational study (DX-88/24) that will evaluate immunogenicity and hypersensitivity. The proposed study will enroll approximately 200 HAE patients 16 years and older. An estimated 150 patients will be naïve to ecallantide while the remaining 50 patients will be patients with prior exposure. Enrollment is expected to occur in a period of 3 years and each patient will be followed for approximately 1 year. Patients enrolled in the study will undergo physical exams, skin testing, and anti-ecallantide antibody testing at baseline and every 6 months or after 4 HAE treatments, whichever occurs sooner. Anti-ecallantide IgE will be assessed in patients with clinical symptoms suggestive of hypersensitivity. Patients with signs of hypersensitivity will be given the option of undergoing follow-up skin testing and graded challenge as was performed during the clinical development program. Adverse events will be collected throughout the duration of the study.

### Disordered coagulation

In the pre-resubmission meeting, the Division agreed that a formal clinical study of coagulation parameters would not be required. The Applicant agreed to evaluate potential cross-reactivity with TFPI, which may theoretically predispose to

hypercoaguability and to continue monitoring for AEs related to disorders in coagulability in Study DX-88/24. In the Complete Response, the Applicant has included results of in vitro studies indicating that anti-ecallantide neutralizing antibodies do not appear to reduce TFPI activity and that ecallantide does not inhibit activation of Factor X like TFPI. The resubmission also includes a final summary report of the existing data on coagulation parameters in patients.

*Reviewer's comment: The general outline of the proposed long-term study appears acceptable. Follow-up skin testing and IgE testing in a subset of patients without evidence of hypersensitivity are recommended to provide further information on the positive and negative predictive values of these tests. The synopsis does not specify whether P. pastoris antibodies will also be tested; these are recommended even though*

(b) (4)

*In addition, the protocol for the Phase 4 study should specify analysis of AEs related to disordered coagulation.*

## 8. 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 additional descriptive statement that Kalbitor eliminates or reduces HAE attack symptoms should also be removed.
2. Section 2.1, Recommended Dosing, The recommended dosing does not specify the interval for repeat administration.

(b) (4)

4. Section 14, Clinical Studies, should clearly indicate that general

(b) (4)

5. 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. Reference to a MCID for the MSCS and TOS are problematic, as there is limited experience with these PRO instruments in clinical trials for HAE and there are no gold standards for measuring efficacy in HAE trials. The presentation of results should be limited to separate results from EDEMA3 and EDEMA4 and should not include a pooled analysis. Efficacy data based on

responder analysis and medical intervention patterns should be excluded. Efficacy statements based on open-label treatment and post-hoc subgroup analyses should also be excluded.

6. The label and patient information sections do not address self-administration.
7. The proposed labeling does not include a patient package insert but refers to the proposed Medication Guide, which seems acceptable given the intended mode of administration via the REMS program.

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

(b) (4)

## **9. 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. DSI audits were previously conducted as part of the original BLA review and no data integrity issues were identified.

## **10. PEDIATRIC PROGRAM**

Ecaltantide was previously granted Orphan Drug status (February 4, 2003, Designation 02-1608) so the application qualifies for pediatric exemption. However, the Applicant intends to pursue a pediatric indication. The original BLA proposed an age range of 10 years and older. The Complete Response proposes an age range of 16 years and older. To support the use in patients 16 to <18 years, the submission includes a separate Pediatric Data Report that summarizes the data collected to date for the pediatric population, primarily in the open-label extension studies. The Sponsor has also provided PK validation data for population PK analysis to support the projected exposure in the

pediatric age range. The following table shows the extent of exposure to 30 mg SC ecallantide by year of age:

**Table 1: Number of Patients and Attacks Treated with 30 mg SC Kalbitor by Age**

Age (years)	Number of Patients Treated <sup>a</sup>	Number of Attacks Treated <sup>b</sup>
9	1	1
10	1	1
11	-	-
12	1	1
13	3	3
14	-	-
15	1	1
16	6	11
17	6	30

Source: DX88-107 Pediatric Data Report, Appendix 1

a. Patients may be included in more than 1 age category

b. Patients may have received more than 1 treatment for each age category

The submission also includes a synopsis for a proposed open-label pediatric study in patients 10 to 15 years of age to obtain efficacy and safety data in this age range. A minimum of 6 patients per age cohort will be enrolled. Patients will receive open-label 30 mg ecallantide for an acute HAE attack with the option of a second dose for inadequate response or relapse. In addition to routine lab chemistry parameters, pharmacokinetic sampling, coagulation parameters, and antibody sampling at baseline and 28 days following each dose will also be obtained. Efficacy will be based on global report at 4 hours. The data for the 10 to 15 year age group will be submitted separately as an efficacy supplement pending completion of the study.

*Reviewer's comment: The proposed pediatric study is consistent with discussions from the pre-resubmission meeting.*

## 11. SUMMARY

This is a 45-day filing and planning review of a Complete Response for BLA 125277 for ecallantide, a recombinant human plasma kallikrein inhibitor intended for the treatment of acute attacks of hereditary angioedema (HAE) in patients 16 years of age and older. The proposed dose is 30 mg SC, which may be repeated once in a 24-hr period for a single HAE attack. 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 was previously granted Orphan Drug and Fast Track status, and the application was reviewed under Priority review. The Division issued a Complete Response letter on March 25, 2009. The CR letter addressed two major clinical deficiencies, namely the lack of an appropriate Risk Evaluation and Mitigation Strategies (REMS) program and a lack of

efficacy and safety data to support the proposed indication in pediatric patients ages 10 to 17 years. The letter outlined three clinical postmarketing commitments to study the long-term safety and efficacy of ecallantide, with particular regard to hypersensitivity reactions, immunogenicity, and hypercoagulability.

In support of the application, the Applicant has adjusted the proposed age range from 10 years of age and older to 16 years of age and older. The Complete Response also includes the details for a REMS program. In addition, the resubmission includes a draft product label, updated safety information from ongoing open-label study DX-88/19 (EDEMA4 OLE), validated PK data to support population PK analysis, and updated CMC information.

From a clinical standpoint, the submission is adequate to allow clinical review.

## 9. COMMENTS TO THE APPLICANT

The following comments are to be communicated to the Applicant:

- [REDACTED] (b) (4)
- In the proposed Phase 4 study, DX-88/24, we recommend follow-up skin testing and baseline and follow-up IgE testing in a subset of patients without evidence of hypersensitivity to provide further information on the positive and negative predictive values of these tests. We also recommend that the protocol for the study specify a separate analysis for adverse events related to disordered coagulation.

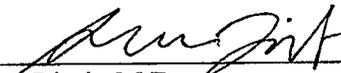
## 10. TIME LINE FOR REVIEW

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
Mid-cycle review meeting	8/26/2009
Internal labeling meeting	9/30/2009
Wrap-up meeting	10/14/2009
Primary reviews due date	10/23/2009
Labeling teleconference	10/20/2009
PDUFA due date, 6 months	12/1/2009

Reviewed by:

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

  
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Sally Seymour, M.D.  
Medical Team Leader, Division of Pulmonary and Allergy Products

## Summary Basis for Regulatory Action

<b>Date</b>	March 25, 2009
<b>From</b>	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II <span style="float: right;">CJR 3/25/09</span>
<b>Subject</b>	Summary Review
<b>NDA/BLA #</b>	N 125277
<b>Supp #</b>	
<b>Applicant Name</b>	Dyax Corporation
<b>Proprietary / Established (USAN) Names</b>	Kalbitor ecallantide <span style="float: right;">MAR 25 2009</span>
<b>Dosage Forms / Strength</b>	Solution 10 mg/mL
<b>Proposed Indication(s)</b>	Treatment of acute attacks of hereditary angioedema (HAE)
<b>Action:</b>	<i>Complete Response</i>

### 1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding ecallantide and the reader should refer to the reviews in the action package for a more detailed discussion. Hereditary angioedema (HAE) is a disease that is characterized by intermittent, unpredictable attacks of subcutaneous or submucosal edema that can be life threatening occurring in the face, gastrointestinal tract, limbs, genitalia and most concerning, in the larynx. The edema demonstrated in HAE is felt to be the result of excess bradykinin and leukotrienes. Bradykinins are formed as a result of the enzymatic activity of kallikrein which is itself mediated or controlled by C1-esterase inhibitor (C1-INH) activity. C1-INH is decreased in HAE patients, therefore, HAE patients, lacking C1-INH are unable to control the enzymatic activity of kallikrein, which in turn leads to excess bradykinin and swelling. Ecallantide is a recombinant human plasma kallikrein inhibitor (produced in yeast *Pichia pastoris*). Hence, if ecallantide inactivates kallikrein, there in theory would be decreased formation of bradykinin and less or no angioedema. HAE itself is rare, autosomal dominant, affecting 1 in 10,000 to 50,000 individuals. There are three forms, two of which are the principal types. Type 1 (80-85% of cases) is caused by decreased production of C1-INH, type 2 (most of the remaining cases) has formation of normal amounts of C1-INH, but it is functionally deficient and type 3, a very rare form that may be X-linked. Currently, there are not any products approved for treatment of the acute attack of HAE. Because HAE is a rare disease, ecallantide was granted Orphan Drug Status in February 2003 and an expedited review was performed for this cycle.

As is nicely outlined in Dr. Limb and Seymour's reviews, treatment for HAE is thought of in three ways including chronic long-term, short-term prophylactic and acute attack therapy. In the US, Cinryze, a plasma-derived C1 inhibitor replacement therapy has been recently approved for routine prophylaxis and androgenic steroids (Danazol-marketed, stanazol and oxymetholone-not marketed) are approved for "prevention of attacks of angioedema". In other

countries, epsilon aminocaproic acid (EACA) and tranexamic acid (TA) are approved as chronic long-term therapy.

Due to the rarity of the disease, the number of subjects that could be enrolled in clinical trials is limited and therefore the results have limited robustness. However, the clinical team and I are convinced that the totality of the data from Dyax has demonstrated that ecallantide has demonstrated efficacy in the acute treatment of HAE in patients 18 years of age and older. Dr. Chowdhury's review nicely documents the thinking regarding younger age groups which is that, while we don't expect the drug to behave differently in adolescent patients, we do not have data to confirm this notion and validation of the bioanalytical assay comparing adult and pediatric exposure is lacking.

Despite the thinking that efficacy has been demonstrated, ecallantide has also demonstrated a significant safety issue of anaphylaxis (definition criteria in 2006 NIAID/FAAN Second Symposium on Anaphylaxis<sup>1</sup>). I believe that the risk and benefit considerations would not allow marketing of ecallantide if it were to be available without restrictions placed on its distribution. As such, I believe a substantial REMS is required to assure that the use is limited to centers with expertise. The REMS and some product manufacturing issues as outlined in Drs. Seymour and Chowdhury's reviews will result in a Complete Response action during this cycle and I will expand upon these comments below.

#### Efficacy

This has been thoroughly covered in Drs. Liu, Limb, Seymour and Chowdhury's reviews. I note here, as the other reviews highlight, there is little exposure in pediatric subjects. The evaluation for efficacy is rather complicated and is based mainly on two studies, EDEMA3 and EDEMA4 using a patient reported outcomes (PRO) instrument developed by the sponsor. Complicating this evaluation, as is common in drug development, is that there is not a recognized 'gold standard' to evaluate the efficacy of therapy and a limited population upon which to perform the studies required to validate a PRO. However, since HAE attacks are highly variable in terms of symptoms and location, and it would be difficult if not impossible to define objective measures to monitor as a primary efficacy endpoint, the sponsor did attempt to develop a PRO and used their instrument for the clinical trials. As such, this evaluation tool has all of the caveats that one must keep in mind when trying to determine the validity of the results.

The sponsor utilized two measures: The Mean Symptom Complex Severity (MSCS) and the Treatment Outcome Score (TOS). These are discussed in great detail in Drs. Liu, Limb and Seymour's reviews and I will not repeat here except to say that the TOS is very complicated and is not intuitive in its conceptual framework, although it appears to me that its value is in magnifying the demonstrated effects, be they favorable or unfavorable. I also believe it would be difficult to understand the clinical significance of the magnitude of change demonstrated by a TOS result. I think it is also important to realize that the MSCS is on a 0-3 scale, so in reality, it does not have an expanded scale such that small changes, either worsening or improvement, may be difficult to capture. This may tend to underestimate an effect (good or

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<sup>1</sup> Sampson HA et al. J Allergy Clin Immunol 2006; 117:391-7

bad), such that if one is seen, it is probably noteworthy. In any event, I have used the MSCS as the main guide to my deliberations regarding ecallantide's demonstration of efficacy. I have placed in the appendix an excellent summary of the two different PRO approaches from Dr. Seymour's review for reference.

In EDEMA3 the primary endpoint was TOS and the primary endpoint for EDEMA4 was MSCS (which was conducted under a SPA). The table below, taken from Dr. Seymour's review, demonstrates the results.

Table 1 Efficacy Results from EDEMA3 and EDEMA4						
	EDEMA3			EDEMA4		
	Ecallantide 30 mg N=36	Placebo N=36	Diff from Pbo (p value)	Ecallantide 30 mg N=48	Placebo N=48	Diff from Pbo (p value)
TOS at 4 hrs (mean) <i>ITT as randomized</i>	46.8	21.3	25.5 (0.100)	53.4	8.1	45.3 (0.003)
TOS at 4 hrs (mean) <i>ITT as treated</i>	49.5	18.5	31.0 (0.037)			
MSCS – mean Δ from baseline 4 hrs <i>ITT as randomized</i> [baseline]	-0.88 [2.15]	-0.51 [2.26]	-0.37 (0.094)	-0.81 [2.18]	-0.37 [2.02]	-0.44 (0.01)
MSCS – mean Δ from baseline 4 hrs <i>ITT as treated</i> [baseline]	-0.91 [2.17]	-0.48 [2.24]	-0.43 (0.044)			

It is important to note that there are two different analyses for each PRO, ITT as randomized and ITT as treated. This is because in EDEMA3, one patient in each arm received the incorrect study medication. As such, when those subjects are placed in the group corresponding with the actual medication they received, we see that the p-value goes from >0.05 to < 0.05. This could represent that the data are not very robust, but is also a demonstration of the small size of the studies that can be associated with studying medications for orphan indications. EDEMA4 did not have a medication administration error and has p-values that are less than 0.05. This table also demonstrates that the TOS does exaggerate the results noted from the MSCS, whether positive or negative and does serve in some capacity to expand the limited scale that I noted with the MSCS.

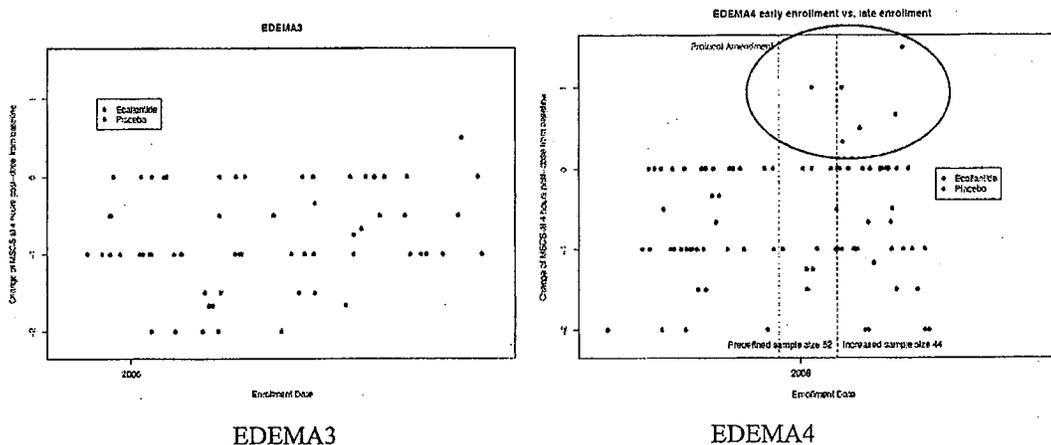
However, EDEMA4 is not without controversy. When the sponsors received the outcome of EDEMA3, they realized that EDEMA4 was underpowered when using MSCS as the outcome measure. As such, they included a protocol amendment to increase the sample size during the trial. We approved the amendment, but specified that we were concerned that the patient demographics and baseline disease characteristics not change with the increase in sample size and that we planned on doing sensitivity analysis to assure ourselves of such. As demonstrated below, analyses pre and post protocol amendment give different, perplexing, results (table from Dr. Seymour's review).

Table 2 Efficacy Results from EDEMA4 Pre and Post Sample Size Adjustment		
	EDEMA4 Pre sample size adjustment (52 patients)	EDEMA4 Post sample size adjustment (44 patients)

	Ecallantide 30 mg N=28	Placebo N=24	Diff from Pbo (p value)	Ecallantide 30 mg N=20	Placebo N=23	Diff from Pbo (p value)
<b>Mean Symptom Complex Score (MSCS)</b>						
MSCS – mean Δ from baseline 4 hrs [baseline]	-0.71 [2.27]	-0.62 [2.12]	-0.09 (0.826)	-0.94 [2.06]	-0.06 [1.92]	-0.88 ( <i>&lt;0.001</i> )
<b>Treatment Outcome Score (TOS)</b>						
TOS at 4 hrs (mean)	43.3	19.2	24.1 (0.24)	67.1	-5.3	72.4 (0.006)

As noted above, the additional 44 subjects appear to be driving the results of the study. To help understand this discrepancy, a look at the individual subject data is presented below (from Dr. Seymour's review).

Figure 1 Individual Patient Data for Change from Baseline MSCS



It would appear from this table that five subjects in the placebo group enrolled after the amendment had actual worsening of their symptoms compared to their presentation symptoms and that is driving the results. Although it is noted that there was one placebo subject that had a worsening of symptoms before the amendment, this was an unusual occurrence as can be seen from the remaining data of EDEMA4 and also from the EDEMA3 study. In order to try to explain these results, the review team has thoroughly reviewed these findings and there is no evidence of differences in demographics, baseline HAE history, attack presentation, or duration of attack prior to presentation for therapy, which would distinguish the outlier subjects (who were from four different sites which had enrolled other subjects). Also, there is not any evidence to suggest that the study conduct or subject recruitment was altered. It is interesting to also look at the ecallantide and placebo group response as presented in the table below.

**Efficacy Results from EDEMA3 and EDEMA4**

		MCSC(mean Δ from baseline 4 hrs)		Difference
		Ecallantide 30 mg	Placebo	
<b>EDEMA 3</b>		0.9	0.5	0.4
<b>EDEMA 4</b>	Overall	0.8	0.4	0.4

	Original subjects (n=52)	0.7	0.6	0.1
	Additional subjects (n=44)	0.9	0.1	0.8

The effect size for ecallantide is relatively consistent between the EDEMA3 and EDEMA4 studies and also within the original and additional subject groups of the EDEMA4 study, while the placebo response varies greatly within the EDEMA4 study dependant upon study period. The overall results between EDEMA3 and EDEMA4 are very similar. While the periodicity finding in EDEMA4 is perplexing, without evidence that the data should not be trusted, the end results do demonstrate efficacy for ecallantide. This also demonstrates that ecallantide was effective for the subjects in the second half of EDEMA4.

The sponsor also monitored some key secondary efficacy variables listed below

1. Responder analysis
2. Durability of response at 24 hours
3. Proportion of patients receiving medical intervention
4. Time to significant improvement (based on subject global self-assessment independent of MSCS or TOS)

For the most part, all of the secondary endpoints demonstrated numerical differences favoring ecallantide, in some cases with p-values  $\leq 0.05$ . These included, as Dr. Limb points out, the endpoints that did not use MSCS or TOS as an evaluation tool: subjects receiving medical intervention or time to significant improvement.

I believe that the totality of the data do demonstrate that ecallantide has efficacy in the treatment of HAE, but I do make that conclusion with some reservations, most of which were also noted by the other reviewers and also the panel members of the advisory committee (to be discussed later). Ecallantide's demonstration of efficacy is very tenuous and probably would represent the bare minimum demonstration of robustness that I would accept, which in turn is influenced by the rarity of disease, difficulty conducting these trials and lack of effective therapies. I also note that Dr. Liu's review recommends an alternative analysis that would utilize area under the curve (AUC) using MSCS. I found her recommendations interesting and feel that this might also provide us with a different way of looking at this type of data and another sensitivity evaluation (bearing in mind that EDEMA4 was conducted under a SPA and therefore we have agreed that specified primary analysis should be used as the determining factor for regulatory decisions if supported by secondary endpoints). The statistical team feels that the recommendation for MSCS AUC is in a conceptual phase, and did not recommend that it should be used at this point as something upon which to make a regulatory decision. Also, the sponsor did not collect the MSCS at the time points necessary to conduct an AUC evaluation. While the AUC may be data analysis in the category of 'good to know', I do not believe it is 'have to know' to determine efficacy.

## Safety

The safety exposure is reviewed in Dr. Seymour and Limb's reviews and I again note that there has been very limited exposure in pediatric subjects. For the most part AEs of minimal clinical consequence were similar in the ecallantide and placebo groups. However, ecallantide is a therapeutic protein and has clearly demonstrated that it can cause hypersensitivity and immunogenicity with anaphylaxis. Considering the nature and clinical presentation of HAE, identifying that someone is actually having an anaphylactic reaction to the medication instead of the clinical course of HAE could be very challenging to an inexperienced clinician. Dr. Seymour's review notes that the anaphylaxis rate in subjects was 3.7%, which translated to 1.1% of given doses. She also notes that 13% of subjects treated with ecallantide seroconvert to anti-ecallantide antibodies (any class) with an estimate seroconversion rate of 50% after 7 doses, although positive antibody status did not appear to increase the frequency of AEs.

The sponsors did conduct rechallenge of subjects with hypersensitivity reactions. The study included a skin prick and intradermal phase, which if negative, allowed a test-dose phase. Of the nine subjects undergoing rechallenge testing procedures, six successfully completed the test-dose phase and four were able to continue therapy with ecallantide without additional hypersensitivity reactions. In three subjects that were not able to continue due to hypersensitivity reactions, all had IgE antibodies to *P. pastoris* although not necessarily at the time of the hypersensitivity reactions. However, positivity to *P. pastoris* was not predictive as there were subjects with IgE antibody positivity that did not have hypersensitivity reactions. I also note there is some question as to the quality of the antibody testing.

Also Dr. Limb and Ragheb's reviews noted that ecallantide shares 88% homology with human tissue factor pathway inhibitor (TFPI) and as such there is a potential for antibodies to ecallantide to cross-react with TFPI. In knock-out mouse models, TFPI deficiency caused hypercoagulability. As such, if cross-reactivity were to occur this could predispose patients to thrombotic events. Although there was no evidence of this in the database, the reviewers feel this has not been adequately addressed.

### Advisory Committee Meeting

I agree with Dr. Seymour's review of the Advisory Committee Meeting (AC). The committee members recognized the limitations of the efficacy and safety data, and also noted this in context to the expectations of the difficulty obtaining data in the population being studied. Panel members noted the high immunogenicity of ecallantide and were concerned with the hypersensitivity and anaphylaxis data. They also noted that there was very little exposure in pediatric patients.

The panel voted the following:

Efficacy data sufficient in patients:	yes	no	abstain
Less than 18 years of age	3	10	

18 years of age and older	8	4	1
Safety established:			
Less than 18 years of age	2	11	
18 years of age and older	5	8	
Should be approved:			
	6	5	2

Some panel members that voted against approval noted that if the indication were limited to adults and with some type of restricted distribution program and an appropriate REMS, they would favor approval. Most of the safety comments were targeted toward developing methods to predict those that may be at risk for anaphylaxis and post-marketing study of potential coagulation concerns. In my view, the panel discussion, even those voting for approval, was such that, they felt ecallantide could only be approved with an appropriate risk management strategy in place that would include some type of restricted distribution.

### **Conclusions and Recommendations**

HAE can be a devastating disease as was clearly described by the numerous patients that presented the challenges of their lives during the open public session at the AC. Frustrating their lives is that at present we do not have an approved therapy for the treatment of acute attacks and these attacks can be very debilitating and life-threatening. Ecallantide has offered the promise of a possible therapy, but at a significant price of potential hypersensitivity/anaphylaxis reactions. It is ironic that the symptoms of HAE in some sufferers may be similar to those of the potential severe adverse effect of ecallantide.

The demonstration of efficacy relies on two pivotal trials, each with findings that cause concern about the evaluation and robustness of efficacy demonstrations. On the other hand, this drug is being developed for a limited population, which presents its own obstacles for reasonable trial design.

I believe the preponderance of data demonstrates that ecallantide has efficacy, but would limit the indication to those 18 years of age and greater, as there is not enough data in younger age groups, either for safety or efficacy, upon which to draw conclusions. I also believe that the safety of this drug dictates that it can only be used with an adequate REMS in place that would include a restricted distribution component as well as many of the other components outlined in Dr. Seymour's review.

The action for this cycle should be a Complete Response. The sponsor will need to submit an adequate REMS, appropriate labeling and resolve the remaining CMC issues. To expand the indication below the age of 18 years will require data as outlined in Dr. Chowdhury's review.

Appendix (PRO description from Dr. Seymour's review)

The PRO developed by Dyax utilizes two measures: the Mean Symptom Complex Severity (MSCS) and the Treatment Outcome Score (TOS). The MSCS assesses symptom severity at a point in time. The TOS evaluates symptom response to therapy. These measures attempt to address the variability of an HAE attack and symptoms. The conceptual frameworks for both measures are shown in the figure below.

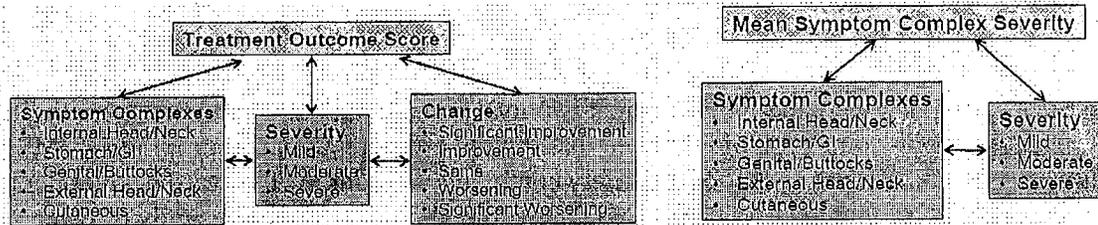


Figure 2 Conceptual Frameworks for TOS and MSCS

Upon presentation, patients identified HAE symptoms grouped by a symptom complex, i.e. Internal Head/Neck, Stomach/GI, Genital/Buttocks, External Head/Neck, or Cutaneous. The patient ranked each symptom complex severity as normal (0), Mild (1), Moderate (2), or Severe (3). Following study medication, patients assessed response as follows: Significant Improvement (a lot better), Improvement (a little better), Same (unchanged), Worsening (a little worse), or Significant Worsening (a lot worse), scored as 100, 50, 0, -50, -100, respectively. The information regarding symptom severity and response was recorded by the patient in the electronic diary at pre-specified time intervals.

Using the information recorded in the patient diaries, the TOS at 4 hours was calculated to weight the response for each complex based upon the severity of each symptom complex at baseline. In the determination of the TOS, the symptom complex score is the response to treatment (score of -100 to 100) and the complex weight is the severity (0 to 3).

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

Thus a patient with moderate (2 severity score) GI symptoms and severe (3 severity score) cutaneous symptoms at baseline who at 4 hours had the same GI symptoms (0 response score) and improvement of cutaneous symptoms (50 response score) would have the following TOS:

$$4 \text{ hour TOS} = \frac{(2 \times 0) + (3 \times 50)}{5} = 30$$

## Memorandum

To: BLA# 125277, Kalbitor (ecallantide)

From: Sally Seymour, MD  
Deputy Director for Safety  
Division of Pulmonary and Allergy Products

Regarding: Post-marketing Requirements and Commitment Templates

Date: December 1, 2009

Biologics Licensing Application (BLA) #125277 is for ecallantide for the treatment of acute attacks of hereditary angioedema (HAE) in patients 16 years of age and older. The trade name is Kalbitor. HAE is a rare, autosomal dominant disorder estimated to affect 1 in 10,000 to 50,000 individuals. HAE is a condition characterized by intermittent, unpredictable attacks of pain and subcutaneous or submucosal edema of the face, larynx, gastrointestinal tract, limbs, and/or genitalia. Attacks can be life-threatening, particularly those attacks involving the airway. Because of the rarity of HAE, ecallantide has Orphan Drug Status. Ecallantide is immunogenic and anaphylaxis is the primary safety signal of concern. Because of the risk of anaphylaxis, a REMS was required, which includes a Medication Guide and Communication Plan. The REMS will help convey the serious risk of anaphylaxis, the need for ecallantide to be administered by a healthcare professional with support to manage anaphylaxis, and the overlapping symptoms of HAE attacks and anaphylaxis.

There are 5 post-marketing-requirements and two post-marketing commitments for ecallantide. Since ecallantide is an orphan product, PREA is not triggered. This document provides the templates for the post-marketing requirements and commitments.

## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

---

PMR/PMC Description: A long-term, observational safety study with Kalbitor (ecallantide) in patients with hereditary angioedema to evaluate hypersensitivity, immunogenicity, and coagulation disorders. The study should include the following objectives: 1) identify predictive risk factors and develop effective screening tools to mitigate the risk of hypersensitivity and anaphylaxis; 2) correlate antibody levels with adverse events and lack of efficacy; and 3) evaluate the risk of hypercoagulability and hypocoagulability.

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PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>12/31/2009</u>
	Study/Clinical trial Completion Date:	<u>02/28/2014</u>
	Final Report Submission Date:	<u>08/31/2014</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The clinical review of the ecallantide development program noted a significant risk of hypersensitivity reactions, including anaphylaxis. There are also theoretical concerns about adverse events related to immunogenicity and disordered coagulation. Given the orphan status and life-threatening potential of the disease indication, hereditary angioedema (HAE), the premarketing safety profile for ecallantide is acceptable for drug approval. Additional postmarketing assessment of adverse events associated with disordered coagulation, immunogenicity, and hypersensitivity reactions including anaphylaxis will be required to provide long-term safety information as well as to explore potential ways to mitigate these risks.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the long-term safety trial is to assess further the risk of hypersensitivity reactions including anaphylaxis, immunogenicity, and disordered coagulation with wider, chronic, intermittent use of the ecallantide. While the size of the safety database for ecallantide was appropriate given the orphan status of the disease indication, hereditary angioedema (HAE), additional postmarketing assessment of these adverse events is warranted:

1) Hypersensitivity reactions including anaphylaxis: In clinical trials, ecallantide was associated with a rate of anaphylaxis of approximately 4% as well as other hypersensitivity reactions. Further evaluation of the rate of anaphylaxis and hypersensitivity reactions with chronic, intermittent use of ecallantide is recommended. Development of potential predictive screening tests, including anti-drug antibody titers, allergy skin testing, and graded challenge, is recommended in the interest of mitigating the risk of hypersensitivity reactions.

2) Immunogenicity: In clinical trials, ecallantide was noted to be significantly immunogenic. The long-term consequences of seroconversion are unknown. Further evaluation of adverse events and potential loss of efficacy correlated to antibody status is recommended.

3) Disordered coagulation: Ecallantide is known to prolong aPTT. Minor, transient prolongations of aPTT have been observed in clinical trials but have not been associated with bleeding adverse events. Conversely, ecallantide is structurally similar to human tissue factor protein inhibitor (TFPI), raising the concern that anti-drug antibodies may be cross-reactive to TFPI. In animal models, TFPI knockout is an embryonic lethal due to hypercoagulability. However, adverse events associated with increased clotting have not been observed. Further surveillance and evaluation for the theoretic risks of hypercoagulability and/or hypocoagulability are recommended.

3. If the study/clinical trial is a PMR, check the applicable regulation.  
*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk*

Analysis using pharmacovigilance system?

*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The Applicant has agreed to conduct a long-term, observational study (DX-88/24) that will assess adverse events associated with disordered coagulation, immunogenicity, and hypersensitivity reactions including anaphylaxis. The study will include 200 patients (n=150 drug-naïve patients) with hereditary angioedema who will be followed for 1 year. Patients will be dosed as needed for the treatment of hereditary angioedema attacks, which are sporadic and unpredictable. In addition to adverse events, anti-drug antibodies and allergy skin testing will be assessed at pre-specified intervals. Patients who experience clinical hypersensitivity reactions will be eligible to undergo more extensive allergy skin testing and a graded challenge procedure with successive concentrations of ecallantide.

Required

Observational pharmacoepidemiologic study

Registry studies

*Continuation of Question 4*

Primary safety study or clinical trial

Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety

Thorough Q-T clinical trial

Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

Pharmacokinetic studies or clinical trials

Drug interaction or bioavailability studies or clinical trials

Dosing trials

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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PMR/PMC Description: Establish the sensitivity and cutpoint for the anti-ecallantide neutralizing antibody assay, using immunoaffinity purified ecallantide-specific human IgG

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PMR/PMC Schedule Milestones: Final protocol Submission Date: MM/DD/YYYY  
Study/Clinical trial Completion Date: MM/DD/YYYY  
Final Report Submission Date: 03/30/2010  
Other: \_\_\_\_\_ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The clinical review of the ecallantide development program noted a significant risk of hypersensitivity reactions, including anaphylaxis. Ecallantide was also shown to be immunogenic in the clinical program. Given the orphan status and life-threatening potential of the disease indication, hereditary angioedema (HAE), the premarketing safety profile for ecallantide is acceptable for drug approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Neutralizing antibodies to protein therapeutics can diminish the efficacy and impact the safety of a product. The sensitivity of immunogenicity assays to detect such antibodies is initially established using surrogate positive controls. Once true positive controls become available, it is important to re-establish the sensitivity and cutpoint of the assay to ensure that the assay is truly performing in a clinically meaningful way.

3. If the study/clinical trial is a PMR, check the applicable regulation.  
*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Establish the sensitivity and cutpoint for the anti-ecallantide neutralizing antibody assay, using immunoaffinity purified ecallantide-specific human IgG

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

---

**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

---

(signature line for BLAs)

## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

---

PMR/PMC Description: Evaluate for cross-reactivity of anti-ecallantide antibodies with TFPI, perform studies to determine if human anti-ecallantide antibodies bind TFPI and perform suitability studies and epitope mapping of the human anti-ecallantide antibody response if binding is observed.

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PMR/PMC Schedule Milestones: Final protocol Submission Date: MM/DD/YYYY  
Study/Clinical trial Completion Date: MM/DD/YYYY  
Final Report Submission Date: 08/31/2010  
Other: \_\_\_\_\_ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The clinical review of the ecallantide development program noted a significant risk of hypersensitivity reactions, including anaphylaxis. Ecallantide was also shown to be immunogenic in the clinical program. Given the orphan status and life-threatening potential of the disease indication, hereditary angioedema (HAE), the premarketing safety profile for ecallantide is acceptable for drug approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Anti-drug antibodies to protein therapeutics derived from native human proteins can impact safety if they cross-react with the endogenous protein, in this case TFPI. By neutralizing or altering the bioavailability of TFPI, it is inferred from the literature that such antibodies could induce hypercoagulable states in treated patients. Evaluating for such cross-reactivity will permit for a better risk assessment of this product.

3. If the study/clinical trial is a PMR, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

To evaluate for cross-reactivity of anti- ecallantide antibodies with TFPI, perform studies to determine if human anti- ecallantide antibodies bind TFPI and perform validation studies and epitope mapping of the human anti- ecallantide antibody response if binding is observed.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)  
Cross reactivity of anti-ecallantide antibodies to TFPI
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

---

**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

---

(signature line for BLAs)

## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

---

PMR/PMC Description: Develop and validate anti - ecallantide and anti - P. pastoris specific human IgE detection assays using a sensitive platform such as ECL. Such assays should be free from interference by anti- ecallantide IgG antibodies.

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PMR/PMC Schedule Milestones:

Final protocol Submission Date:	<u>MM/DD/YYYY</u>
Study/Clinical trial Completion Date:	<u>MM/DD/YYYY</u>
Final Report Submission Date:	<u>09/30/2010</u>
Other: Submit Method Development Reports for FDA Review	<u>04/30/2010</u>

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1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The clinical review of the ecallantide development program noted a significant risk of hypersensitivity reactions, including anaphylaxis. Ecallantide was also shown to be immunogenic in the clinical program. Given the orphan status and life-threatening potential of the disease indication, hereditary angioedema (HAE), the premarketing safety profile for ecallantide is acceptable for drug approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

This protein therapeutic is associated with clinical hypersensitivity reactions to both the drug itself (ecallantide) and proteins from the host cell (P. pastoris) from which the drug was derived. Such reactions are often associated with the development of antigen specific IgE antibodies. The sponsor had developed assays to detect such antibodies, but these assays were found to be inadequate. In order to support the post-marketing long-term safety study, a highly specific and sensitive assay to detect such IgE antibodies will need to be developed and validated.

3. If the study/clinical trial is a PMR, check the applicable regulation.  
*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Develop and validate anti - ecallantide and anti - P. pastoris specific human IgE detection assays using a sensitive platform such as ECL.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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PMR/PMC Description: Carcinogenicity Study

PMR/PMC Schedule Milestones: Final protocol Submission Date: 06/30/2010  
Study/Clinical trial Completion Date: 09/30/2012  
Final Report Submission Date: 09/30/2013  
Other: \_\_\_\_\_

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The clinical review of the ecallantide development program noted a significant risk of hypersensitivity reactions, including anaphylaxis. Ecallantide was also shown to be immunogenic in the clinical program. Given the orphan status and life-threatening potential of the disease indication, hereditary angioedema (HAE), the premarketing safety profile for ecallantide is acceptable for drug approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

This study will assess the carcinogenic risk to hereditary angioedema patients receiving chronic intermittent dosing of ecallantide.

3. If the study/clinical trial is a PMR, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Dyax is proposing a 2-year carcinogenicity study design which would administer 25 mg/kg ecallantide to male and female rats at a seven day dose interval. A draft protocol will be submitted to the Division in Feb 2010 for review and ECAC concurrence. The protocol will be finalized in June 2010. The study will be started in September 2010. It is projected that the in-life phase will be completed in September 2012. A final report should be available in September 2013.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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PMR/PMC Description: The submission, as a pre-approval supplement, of an updated stability protocol for drug product that will add an accelerated or stress stability condition as part of the annual stability program. The data accumulated from this protocol will be submitted to the BLA on an annual basis.

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PMR/PMC Schedule Milestones: Final protocol Submission Date: 01/31/2010  
Study/Clinical trial Completion Date: MM/DD/YYYY  
Final Report Submission Date: MM/DD/YYYY  
Other: \_\_\_\_\_ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Because this requirement involves the design of a study to be implemented post approval as part of the annual stability program, the issue can be resolved with a submission following approval with absolutely no consequences to patients.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The purpose of an annual stability study is not to reevaluate the dating period but rather confirm that all the process changes (including personnel) made during the last year had no impact on product quality. Since a stability study performed at 5°C is expected to have limited ability to detect significant changes that might affect product quality; the sponsor should include an accelerated or stress stability study that would be more sensitive to small but significant changes in product quality.

3. If the study/clinical trial is a PMR, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor proposes to submit an updated annual stability protocol that includes accelerated storage conditions that would be more sensitive to detecting changes to product stability. Once the PMC has been accepted by the FDA, the protocol will be implemented for the first annual stability study and the resulting data submitted to the BLA in the AR.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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PMR/PMC Description: To evaluate the minimum fill volume required to provide appropriate dosage withdrawal and whether an adjustment to the fill volume for the drug product is necessary to reduce the likelihood that a patient will be overdosed with any excess drug product. The final study report including identification of a new fill volume, if found to be necessary, will be provided. Should the fill volume need to be changed, this report will include a proposed execution plan.

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PMR/PMC Schedule Milestones: Final protocol Submission Date: 04/30/2010  
Study/Clinical trial Completion Date: MM/DD/YYYY  
Final Report Submission Date: MM/DD/YYYY  
Other: \_\_\_\_\_ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Some liquid (~ (b) (4) mL) remains in the vial after withdrawal of the recommended volume. Therefore, it is likely that occasionally health care providers will administer the excess volume to patients even though the PI gives detailed instructions on administration. While there have been no reports of overdose with Kalbitor and HAE patients have received single doses up to (b) mg intravenously without evidence of dose-related toxicity, it is prudent to limit any potential overdose. There is also a risk for pooling containers and compromising the sterility of the product that excess volumes might increase. Given that the actual amount of overage is relatively low and the use of the product in a clinical setting (i.e., the temptation to pool is very low) the risk to patient safety is also low. Thus, excessive overfill is not an approvability issue because of the low theoretical risks associated with this issue.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Excess overfills could be delivered to the patient resulting in an overdose or might tempt health care providers to pool single use vials for use in other patients. Storing pooled product provides an opportunity for entry and potentially propagation of microorganisms which would compromise patient safety. The goal is to perform studies design to the minimal fill volume required for adequate product recovery thus preventing any significant amounts of left over product.

3. If the study/clinical trial is a PMR, check the applicable regulation.  
*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor proposes to include perform a study to assess the minimum volume in the vial to deliver a full dose of DP, 1 mL per vial at 10 mg/mL (3 vials used to get full dose, 30 mg). The sponsor will provide the data and a risk analysis for the need for new fill volume.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
  - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
  - Thorough Q-T clinical trial
  - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
  - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## SUMMARY REVIEW OF REGULATORY ACTION

MAR 25 2009

Date: March 25, 2009

From: Badrul A. Chowdhury, MD, PhD *Badrul A. Chowdhury*  
Director, Division of Pulmonary and Allergy Products,  
CDER, FDA

Subject: Division Director Summary Review

BLA Number: 125277

Applicant Name: Dyax Corp.

Date of Submission: September 23, 2008

PDUFA Goal Date: March 25, 2009

Proprietary Name: Kalbitor

Established Name: Ecallantide

Dosage form: Injection

Strength: 30 mg

Proposed Indications: Hereditary angioedema (HAE)

Action: Complete Response

### 1. Introduction

Dyax Corp submitted this biologics license application for use of ecallantide for the treatment of acute attacks of hereditary angioedema (HAE) in patients 10 years of age and older. The proposed dose is 30 mg by subcutaneous (SC) injection. The application is based on clinical efficacy and safety studies. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies.

### 2. Background

HAE is a rare autosomal dominant inherited disease characterized by intermittent and unpredictable attacks of angioedema involving various organs, particularly the skin, intestine, and upper airway. HAE is estimated to affect 1 in 10,000 to 50,000 individuals worldwide and is categorized as an orphan disease in the US. There are two major types of HAE, called type I and type II, and a minor type called type III. Type I (80-85% of all HAE patients) is caused by decreased production of C1-INH, and type II (most of the remaining cases) is caused by functional deficiency of C1-INH. Type III is a very rare form that seems to be X-linked.

HAE attacks are potentially life-threatening, particularly cases that involve the upper airway. The treatment options for HAE are usually divided into three categories – chronic long-term prophylaxis, short-term prophylaxis to prevent attacks, and treatment of acute attacks<sup>1</sup>. Androgenic steroids are the only drug class approved for use in patients with HAE in the United States (US). Danazol is approved and marketed in the US with

<sup>1</sup> MM Frank. Hereditary angioedema: The clinical syndrome and its management in the United States. Immunol Allergy Clin N Am 2006; 26:653-668.

the label indication "prevention of attacks of angioedema." The drug is also used for chronic long-term therapy<sup>1,2</sup>. Stanazolol and oxymetholone are also approved with similar indications, but are no longer marketed in the US. In 2008, Cinryze, a human plasma derived C1 inhibitor was approved for routine prophylaxis of HAE attacks. Elsewhere in the world, epsilon aminocaproic acid (EACA) and tranexamic acid (TA) are approved for use in HAE patients. EACA and TA are used as chronic long-term therapy in HAE, but these are not thought to be effective in acute attacks<sup>1,2</sup>. Fresh frozen plasma is often used for short-term prophylaxis to prevent acute attacks and for treatment of acute attacks, but the use of fresh frozen plasma in HAE is controversial as it can worsen an attack by providing more substrate that can be acted on to release additional mediators such as high molecular weight kininogens<sup>1</sup>.

At present there are no drugs approved in the US for treatment of acute attacks of HAE. Ecallantide is a new molecular entity proposed for the treatment of acute attacks of HAE. Ecallantide is a recombinant 60 amino acid protein identified by phage display technology from a library of human tissue factor pathway inhibitor (TFPI). The putative mechanism of action of ecallantide is inhibition of human plasma kallikrein. The kallikrein-bradykinin pathway is not directly responsible etiologically for HAE, but is thought to play an important role in causing the symptoms of HAE once activated. Activity of plasma kallikrein is regulated by C1-INH and in the absence of adequate C1-INH the activation of plasma kallikrein is largely unopposed. Plasma kallikrein cleaves high molecular weight kininogen (HMWK) with the release of bradykinin. Bradykinin acts on the vasculature to increase capillary permeability. The trigger for the initial activation of plasma kallikrein in HAE patients is not known.

The Agency and Dyax had various interactions dating back to 2002 when the applicant first came to the Agency for regulatory guidance. This product was initially regulated in CBER and was later transferred to CDER and assigned to this Division. When the product was transferred from CBER to CDER, the first of two phase 3 studies was already underway. The major issue discussed with the applicant at various meetings was the primary efficacy variable. The first phase 3 study used Treatment Outcome Score (TOS) as the primary efficacy variable. The TOS score is a composite score that measures baseline severity for different anatomic symptom complexes and the corresponding response to treatment for each symptom complex. This Division questioned the appropriateness of TOS, so the Division suggested that the second phase 3 study use the Mean Symptom Complex Score (MSCS) as the primary efficacy variable. The MSCS and TOS are based on the same symptom complexes, and the MSCS score was already a key secondary endpoint in the first phase 3 study.

### **3. Chemistry, Manufacturing, and Controls**

The drug substance, ecallantide, is a plasma kallikrein inhibitor initially identified through iterative selection and screening of phage display libraries of the first Kunitz domain of human tissue factor pathway inhibitor (TFPI). The molecule is a 60 amino

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<sup>2</sup> MM Frank, Jiang H. New therapies for hereditary angioedema: Disease outlook changes dramatically. *J Allergy Clin Immunol* 2008; 121:272-280.

acid protein containing (b) (4) and shares 88% identity with TFPI. For commercial marketing, ecallantide is produced by recombinant DNA technology by expression in the yeast, *Pichia pastoris*. The recombinant ecallantide protein is secreted into the fermentation medium and recovered and purified by chromatography. Biologic activity is determined by an in vitro activity assay (affinity to human plasma kallikrein). Ecallantide reversibly binds human kallikrein. Glycosylation, oxidation, and N-terminal truncation can occur forming ecallantide related variants. The product related variants have been characterized and are biologically active.

The drug product, with the proposed trade name Kalbitor, is supplied as a 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 pH of the solution is 7.0. The proposed expiry period is 36 months for drug product stored at -20°C. Based on CMC review, the submitted stability data support this expiry period.

The drug substance is manufactured by Avencia Biologics at a facility in Billingham, United Kingdom. The drug product is manufactured by Hollister-Stier Laboratories, Spokane, Washington, United States. All manufacturing and testing sites related to the product have acceptable inspection status.

There are several major CMC deficiencies that the applicant will need to address before the product can be approved. The deficiencies are in the areas of cell bank characterization, release and stability specifications, identity testing of drug substance that will be shipped to contracture manufacturer for filling, acceptance criteria for reference standard qualification, and acceptance specification for purification process in manufacturing.

Immunogenicity is a concern with ecallantide because the product is a protein produced in biological system. To evaluate immunogenicity, ideally screening begins with a sensitive immunoassay and if the results are positive, a confirmatory assay is performed. If positive, titers are determined. Immunogenicity assays were developed by Dyax to detect the following antibodies in serum: 1) antibodies of all types to ecallantide, 2) neutralizing antibodies to ecallantide, 3) IgE antibody to ecallantide, and 4) IgE antibody to *Pichia pastoris* yeast. Dyax developed an electrochemiluminescent assay for non-IgE antibodies to ecallantide, and a (b) (4) enzyme-linked immunoabsorbent assays (ELISA) for IgE antibody to ecallantide and IgE antibody to *Pichia pastoris*. The immunoassays are adequately validated, but there are deficiencies with the sensitivity and specificity of the assays. In addition, Dyax did not address the potential for ecallantide antibodies to cross react with TFPI, which could have clinical implications and could interfere with the immunoassays.

#### **4. Nonclinical Pharmacology and Toxicology**

Dyax submitted a complete pharmacology and toxicology program to support chronic intermittent use of ecallantide. The program included six-month repeat subcutaneous general toxicology studies mainly in rats and monkeys, and reproductive and developmental toxicology studies in rats and rabbits.

In the general toxicology studies the findings of note were injection site reactions in rats and monkeys, a small number of deaths in rats with no cause that could be causally related to ecallantide, and transient prolongation of aPTT in rats and monkeys with no evidence of gross bleeding. In both rats and monkeys, anti-ecallantide antibodies were seen in all treated groups in a generally dose-dependent fashion. With the development of anti-ecallantide antibodies, exposure to ecallantide was increased and clearance was reduced, but there was no increase in toxicity, and activity of ecallantide seemed to be maintained as evidenced by elevated aPTT in these animals. Reproductive toxicology studies did not show any adverse effects on male and female fertility and reproductive functions. The embryo-fetal development study with intravenous administration in rats showed increased numbers of early resorptions and percentages of resorbed conceptuses per litter in the presence of mild maternal toxicity at a dose approximately 13 times maximum recommended human dose on a mg/kg basis. These findings will be reported in the labeling and Pregnancy Category C is recommended. Carcinogenicity studies have not been conducted. Dyax was informed that evaluation of carcinogenicity potential was required given that the intended use of the drug was judged to be chronic intermittent and the lifetime consequences of inhibiting kallikrein or other off-target effects were not known. This is acceptable as a post-marketing commitment given the indication. Dyax will be asked to conduct a carcinogenicity study in rats at a later time, if such a study is feasible given the immunogenicity of ecallantide in animals.

#### **5. Clinical Pharmacology and Biopharmaceutics**

The pharmacokinetics of ecallantide was evaluated following intravenous and subcutaneous administration. The absolute bioavailability of ecallantide following subcutaneous administration is approximately 90%, and maximum plasma concentrations are observed approximately 2 to 3 hours after dosing. The elimination half-life is approximately 2.0 hours. No clinical or preclinical studies were conducted to assess mass balance, route of excretion, or metabolism of the drug. Such studies are usually not required for biologics. Being a small polypeptide, ecallantide is expected to be eliminated by metabolic catabolism and renal elimination.

Population PK analysis was conducted with all the PK data obtained from clinical studies. The results are not reliable because the validation information of the bio-analytical assay used in these studies for detection of ecallantide is not complete. The applicant has been asked to provide validation of the bio-analytical assay, and the PK data may need to be analyzed based on the new information requested. The complete response letter will include this deficiency for Dyax to address.

Drug-drug interaction and studies in impaired renal or impaired hepatic patients were not performed. This is acceptable for this biologic product in this orphan population. A thorough QT study was deemed not warranted because of the negative results from preclinical studies, the results from the early clinical studies, the expected manner of use (intermittent) and the potential life-saving indication for a serious disease. ECG monitoring in EDEMA4 study was accepted as an alternative. ECG data in EDEMA 4 did not suggest QT prolongation or other cardiac rhythm abnormalities.

## 6. Clinical Microbiology

The manufacturing process of ecallantide consists of various steps that include preparation of the inoculum, fermentation, chromatographic steps, filtration steps, and then filling of the drug substance in sterile (irradiated) bottles of various sizes. The final product for commercial use is supplied in sterile, preservative-free isotonic solution with an ecallantide concentration of 10 mg/ml in a 2 ml glass vial as single dose. The vial is sealed with (b) (4) stopped and an aluminum seal with a flip-off cap. There are microbiology deficiencies that the applicant will need to address before the product can be approved. The deficiencies are in the area of depyrogenation of the 2 mL glass vials, validation studies for stopper sterilization, sensitivity of the dye ingress container-closure integrity test, and waiver request for (b) (4) test.

## 7. Clinical and Statistical – Efficacy

### a. Overview of the clinical program

The clinical program submitted with this application consists of multiple studies, including two phase 3 studies. The clinical program included both HAE type I and type II patients. The scope of the clinical program and the size of the studies are reasonable for this orphan indication. Some characteristics of the relevant studies are shown in Table 1. Because of the limited number of HAE patients, the applicant allowed patients to participate in more than one study. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

Table 1. Clinical studies

ID	Study type	Study duration	Patient Age, yr	Treatment groups*	N (ITT)	Study Year#	Countries
EDEMA0	Phase 2, open label	Single dose	31 - 67	E 10 mg IV E 40 mg IV E 80 mg IV	9	2003	Germany, UK, Italy, Spain
EDEMA1	Phase 2, double-blind	Single dose	11 - 62	E 5 mg/m <sup>2</sup> IV E 10 mg/m <sup>2</sup> IV E 20 mg/m <sup>2</sup> IV E 40 mg/m <sup>2</sup> IV Placebo	49	2004	US, Israel, Belgium
EDEMA2	Phase 2, open label	Multi dose	10 - 78	E 5 mg/m <sup>2</sup> IV E 10 mg/m <sup>2</sup> IV E 20 mg/m <sup>2</sup> IV E 30 mg SC	77	2006	USA, Canada, Europe

ID	Study type	Study duration	Patient Age, yr	Treatment groups*	N (ITT)	Study Year#	Countries
				Placebo			
EDEMA3	Phase 3, double-blind	Multi dose	11 - 77	E 30 mg SC Placebo	72	2007	USA, Canada, EU, Israel
EDEMA3 OLE	Phase 3, open-label	Multi dose		E 30 mg SC	67	2007	USA, Canada, EU, Israel
EDEMA4	Phase 3, double-blind	Multi dose	13 - 72	E 30 mg SC Placebo	96	2008	USA, Canada
EDEMA4 OLE	Phase 3, open-label	Multi dose		E 30 mg SC	77	Not ended	USA, Canada
* E = Ecallantide, Studies EDEMA3 and EDEMA4 had open label extension (OLE)							
# Year study subject enrollment ended							

b. Design and conduct of the studies

The clinical studies of importance are the dose-ranging study EDEMA2, and the two phase 3 studies, EDEMA3 and EDEMA4. Study EDEMA4 was conducted under a Special Protocol Agreement (SPA) with the Agency. These studies are described further below. Other studies are relatively small and of limited value and are not discussed further in this document.

EDEMA2 was an open-label, multi-dose, dose-ranging study conducted in HAE patients in a physician supervised setting during acute attacks. Patients presenting within 4 hours of onset of an acute attack of at least moderate severity were treated with a single dose of ecallantide. If no improvement was noted within 4 hours, a second dose could be administered. Primary efficacy variables in the study were the proportion of patients with a successful outcome (defined as attack resolution within 4 hour after a single dose that was maintained for greater than 24 hours) and the proportion of patients with partial response (defined as an initial response to dosing followed by relapse 4 to 24 hours after dosing). Safety assessment included recording of adverse events, vital signs, clinical laboratory measures, ECG, physical examination, and development of antibodies to ecallantide or *Pichia pastoris*. Although the study was not blinded, it provides information to support the dose selection for the subsequent phase 3 studies.

EDEMA3 was a randomized, double-blind, placebo-controlled study conducted in HAE patients in a physician supervised setting during acute attacks. Patients presenting within 8 hours of onset of an acute moderate to severe attack were randomized to receive a single dose of ecallantide 30 mg SC or placebo. Patients were stratified by anatomic attack location (laryngeal vs. other) and by prior enrollment in other ecallantide studies. Patients were eligible to receive an additional dose of ecallantide for severe upper airway compromise at the investigators' discretion. Patients were observed in a clinic setting for at least 4 hours after dosing and up to 3 follow-up visits were scheduled on discharge. The primary efficacy endpoint was the treatment outcome score (TOS) at 4 hours (described further below). An important secondary efficacy endpoint was the change in Mean Symptom Complex Severity score (MSCS) from baseline at 4 hours (described further below). Safety assessments included the recording of adverse events, vital signs, clinical laboratory measures, ECG, physical examination, and monitoring for the development of antibodies to ecallantide or *Pichia pastoris*. Patients treated in the

double-blind phase were given the option to continue into the open-label extension phase. During the open-label extension phase, patients with new acute attacks were required to present to the study site within 8 hours of onset of an acute attack as in the double-blind phase, and qualified patients were treated with ecallantide 30 mg SC. If patients had an incomplete response to treatment, a second, randomized blinded dose of ecallantide or placebo could be administered. Efficacy assessment was the same as those in the double-blind phase.

EDEMA4 was designed and conducted similarly to EDEMA3. One major difference from EDEMA3 was that the primary efficacy endpoint was changed to the MSCS, and the TOS was a secondary endpoint (described further below). The primary efficacy endpoint was changed on this Division's recommendation. This study also had an open label extension phase similar to EDEMA 3.

Some design and study conduct elements of EDEMA3 and EDEMA4 are expanded upon further below. An understanding of these will help interpret the efficacy results described in the subsequent section.

#### Primary efficacy variables

As mentioned above, efficacy variables in the phase 3 studies were the Mean Symptom Complex Severity score (MSCS) and the Treatment Outcome Score (TOS).

MSCS is based on symptom severity at a point in time. The MSCS is the arithmetic mean calculated from patients' recording of HAE symptom severity on a 0-3 scale (0=normal, 1=mild, 2=moderate, and 3=severe) of individual symptom complexes from different body locations (i.e., internal head and neck, stomach and gastrointestinal, genital and buttock, external head and neck, or cutaneous). MSCS data are available for baseline (hour 0), and for post-dosing hours 4 and 24.

TOS is based on the baseline symptom severity score and response to therapy. Patients recorded a global response to therapy on a -100 to +100 scale (-100=significant worsening, -50=worsening, 0=unchanged, +50=improvement, +100=significant improvement). To calculate the TOS, each symptom complex score was graded on the 0-3 severity scale then multiplied by a response to treatment factor. TOS data are available for post-dosing hours 1, 2, 3, 4 and 24.

There are no patient reported outcome instruments for acute attacks of HAE that can be considered as standard. Dyax developed the MSCS and TOS to assess HAE symptoms and response to treatment. The development of these instruments partly predates the Agency Guidance on this topic,<sup>3</sup> but in general follows the framework outlined in the Guidance. The main issue with the TOS is that it is somewhat removed from actual patient report of symptom scores, and because of the factors of severity scale rating and response to treatment built into the score, the final TOS score is difficult to interpret. The

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<sup>3</sup> Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Draft Guidance. Issued on February 2006. Available at: <http://www.fda.gov/CDER.guidance/5460dft.pdf>.

response multiplier may exaggerate small differences. The MSCS score is more straightforward and easy to interpret. The Division discussed this issue about TOS with Dyax, and on the Division's suggestion the primary endpoint of EDEMA4 was changed to MSCS. However, for both EDEMA3 and EDEMA4 studies, both MSCS and TOS scores were available.

#### Treatment error in EDEMA3

Two patients received wrong study drug: one patient randomized to receive active treatment was given placebo, and another patients randomized to receive placebo was given active treatment. The results and conclusions of EDEMA3 study are affected by these two patients (discussed further below in efficacy findings and conclusion section).

#### Sample size change in EDEMA4

During the conduct of the EDEMA4 study, Dyax increased the sample size from 52 to 96 patients to accommodate for the change of the primary endpoint from TOS to MSCS. The results and conclusions of the EDEMA4 study are affected by this sample size change (discussed further below in efficacy findings and conclusion section).

#### Imputation of missing data

Study EDEMA3 had a pre-specified analyses plan with imputation of missing data, whereas study EDEMA4 had no imputation of missing data. EDEMA3 employed imputations for emerging symptom complexes and medical intervention after dosing and within 4 hours of dosing. There were more emerging symptom complexes and medical interventions in the placebo group, and therefore, more data were imputed in the placebo arm that increased the effect size of the treatment difference. This data imputation method used by Dyax was not conservative, and sensitivity analyses were performed by the Agency's statistical team using other models of imputations to test robustness. While the magnitude of effect sizes changes with more conservative analysis, the trends of the results do not. Also, there is no definite way to conclude what model is appropriate. In this document results based on the models used by Dyax are presented.

#### **c. Efficacy findings and conclusions**

Dyax is seeking marketing approval for ecallantide at a dose of 30 mg SC for the treatment of acute attacks of HAE in patients 10 years of age and older. The results of the submitted clinical studies do not support efficacy of ecallantide as proposed. The main problem is the proposed age range. Demonstration of efficacy could be concluded for patients 18 years of age and older, but not for patients below 18 years of age because of the limited number of pediatric patients studied. Efficacy in general was not robust, which is possibly due to the limitation of sample size for this rare disease. The existing data needs to be further analyzed to provide more complete efficacy information for the purpose of describing the clinical trials in the product label.

Dose and dosing frequency selection in HAE patients is challenging due to the limited patients available to study during acute attacks. Dyax performed three phase 2 studies, EDEMA0, EDEMA1, and EDEMA2, which provide some dose ranging information. These studies support selection of the single ecallantide 30 mg SC dose administered on

presentation to patients with acute attacks of HAE. Results of EDEMA2 are shown in Table 2. Ecallantide 30 mg SC provided numerically the most favorable response.

**Table 2. Efficacy results from EDEMA 2**

	Ecallantide 5 mg/m <sup>2</sup>	Ecallantide 10 mg/m <sup>2</sup>	Ecallantide 20 mg/m <sup>2</sup>	Ecallantide 30 mg SC
Number of patients *	18	55	9	31
Number of attacks treated	24	141	15	60
Proportion of patients with successful outcome †	46%	68%	60%	82%
Proportion of patients with partial response ‡	33%	16%	27%	12%

\* The number of patients exceeds 77 because patients could receive different doses of ecallantide  
† Successful outcome defined as onset of resolution within 4 hours of dosing and continuing for 24 hours following a single dose  
‡ Partial response defined as response to dosing followed by a relapse within 24 hours

In the two phase 3 studies a total of 168 patients were included in the randomized placebo-controlled portion of the studies. The most common symptom complexes were stomach/gastrointestinal and cutaneous. Only two patients were lost in the single dose portion of the study; one patient was lost to follow up after the first visit, and another patient left the treatment facility against medical advice.

Results of the TOS and MSCS for the two studies are shown in Table 3. In EDEMA3, the difference between ecallantide and placebo is statistically significant when the ITT is defined as treated, but not statistically significant when the ITT is defined as randomized. On review of the study conduct, it was concluded that the treatment error was a mix up of drug and placebo during treatment, and, therefore, defining ITT defined as treated is reasonable. In EDEMA4, the difference between ecallantide and placebo is not statistically significant for the original 52 patients, while the difference between ecallantide and placebo are statistically significant for the additional 44 patients and the total 96 patients (Table 4). The change in efficacy for the additional 44 patients is driven by placebo patients responding appreciably worse compared to the original 52 patients in EDEMA4 and also when compared to the EDEMA3 patients (Figure 1). On review of the study conduct, no explanation was found for this appreciably worse response to placebo for the additional 44 patients, and, therefore, it is reasonable to accept the results of the ITT defined as the total 96 patients. The efficacy results overall are not robust, but are consistent enough for these small sample size studies, to conclude that ecallantide has efficacy in treating acute attacks of HAE. The secondary endpoints results mostly trended in the direction favoring ecallantide (data not shown in this review). The main deficiency from an efficacy standpoint is the inadequate data in patients below 18 years of age.

Of the various anatomical attack sites, laryngeal involvement is the most serious and is often associated with mortality. In the EDEMA3 and EDEMA4 studies, there were a total of 18 events of laryngeal involvement, of which 12 were treated with ecallantide and 6 were treated with placebo. The numbers are too small for formal statistical testing. For both MSCS and TOS, the ecallantide treated group had a better response compared to the placebo treated group, and for TOS the difference was statistically significantly different.

Table 3. Efficacy results from EDEMA3 and EDEMA4

	EDEMA3			EDEMA4		
	Ecallantide 30 mg SC N=36	Placebo N=36	Diff from Pbo (p value)	Ecallantide 30 mg SC N=48	Placebo N=48	Diff from Pbo (p value)
TOS at 4 hrs (mean) <i>ITT as randomized</i>	46.8	21.3	25.5 (0.100)	53.4	8.1	45.3 (0.003)
TOS at 4 hrs (mean) <i>ITT as treated</i>	49.5	18.5	31.0 (0.037)			
MSCS – mean $\Delta$ from baseline 4 hrs <i>ITT as randomized</i> [baseline]	-0.88 [2.15]	-0.51 [2.26]	-0.37 (0.094)	-0.81 [2.18]	-0.37 [2.02]	-0.44 (0.01)
MSCS – mean $\Delta$ from baseline 4 hrs <i>ITT as treated</i> [baseline]	-0.91 [2.17]	-0.48 [2.24]	-0.43 (0.044)			

Table 4. Efficacy results from EDEMA4, pre- and post-sample size adjustment

	EDEMA4 Pre sample size adjustment (52 patients)			EDEMA4 Post sample size adjustment (44 patients)		
	Ecallantide 30 mg SC N=28	Placebo N=24	Diff from Pbo (p value)	Ecallantide 30 mg SC N=20	Placebo N=23	Diff from Pbo (p value)
MSCS – mean $\Delta$ from baseline 4 hrs [baseline]	-0.71 [2.27]	-0.62 [2.12]	-0.09 (0.826)	-0.94 [2.06]	-0.06 [1.92]	-0.88 ( $<0.001$ )
TOS at 4 hrs (mean)	43.3	19.2	24.1 (0.24)	67.1	-5.3	72.4 (0.006)

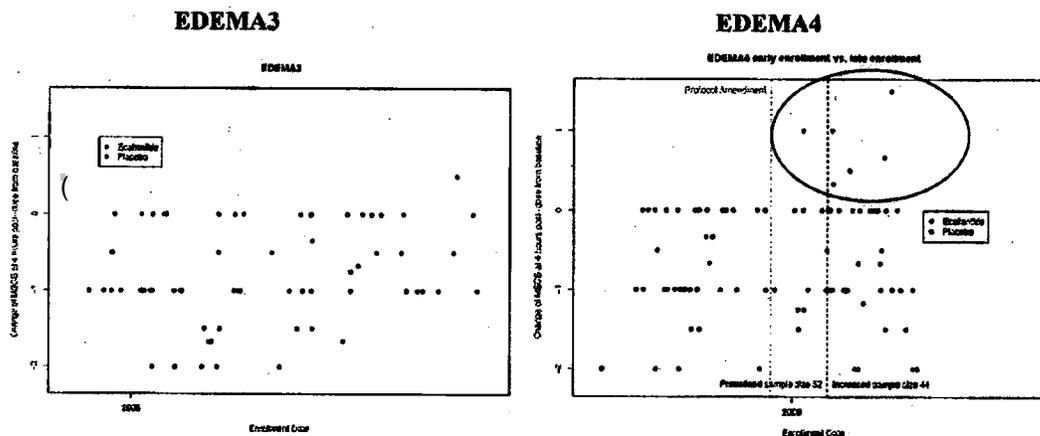


Figure 1. Individual patient data for change from baseline in MSCS.

The total number of patients below 18 years of age who received any formulation of ecallantide in the whole development program was 25, of which a total of 15 received the ecallantide 30 mg SC dose. In the phase 3 studies, only 4 patients below 18 years of age received ecallantide 30 mcg SC in the double-blind portion of the studies: two 16 year old patients and two 17 year old patients. Although HAE is an autosomal dominant

disease, the disease typically does not manifest until late childhood or early adulthood, raising the possibility that human development may influence the vasoactive mediator cascades responsible for HAE symptoms, one of which is the target for ecallantide. The existing data do not suggest that ecallantide would behave differently in pediatric patients compared to adult patients, but data to confirm this notion is lacking. To support efficacy in patients below 18 years of age, Dyax will need to conduct at least one open-label study in a reasonable number of patients (such as 6 per year of age groups) and show favorable numerical efficacy trends. Dyax will also need to provide validation of the ecallantide bio-analytical assay that can allow comparison of adult and pediatric ecallantide exposure data (see Section 5 above).

The primary efficacy endpoints of the phase 3 studies, MSCS and TOS, provide changes from baseline at 4 hours post-dose. Since the results of the primary efficacy endpoints are not robust, assessments of MSCS and TOS at time points between dosing and 4 hour post-dose will provide additional useful efficacy information, particularly for describing the clinical trials in the product label. Dyax will be asked to conduct such analyses and submit the results to the Agency. This can be done during review of the complete response.

Data regarding repeat dosing of ecallantide for recurrent attacks of HAE in the same patient is limited and comes primarily from the open label extension of the phase 3 studies. The limited data show numerically favorable trend to support repeat dosing. Furthermore, from a mechanistic standpoint there is no reason to believe that ecallantide will not be effective on repeat dosing.

## **8. Safety**

### **a. Safety database**

The safety database for ecallantide 30 mg is based primarily on the five studies in HAE patients (Table 1). There were a total of 243 unique HAE patients in the ecallantide program, and in these patients a total of 846 doses of ecallantide were administered to these patients. In the controlled portion of the phase 3 studies, a total of 100 patients received 125 doses of ecallantide 30 mg SC. Additional safety data is obtained from the open-label portions of the phase 3 studies that included patients rolled over from the controlled portions and some new patients enrolled. Most of the patients exposed to ecallantide were 18 years of age and older. As discussed above (Section 7), the total number of patients below 18 years of age who received any formulation of ecallantide was 25, of which 15 received ecallantide 30 mg SC dose. The database is limited, but adequate for this orphan disease and the limited scope of treatment of acute attacks of HAE for patients 18 years of age and older, but not for patients below 18 years of age.

### **b. Safety findings and conclusion**

There were no deaths in the phase 3 studies. There was one death in the EDEMA1 study in a patient with a history of kidney transplant. The patient died of chronic renal failure. The major safety finding of concern from the clinical program was anaphylaxis and type I hypersensitivity. Other safety concerns are a high frequency of seroconversion after

exposure to ecallantide and the possible effect of ecallantide on the coagulation system. These are further expanded below.

Anaphylaxis was a common finding in the ecallantide studies. Using generally accepted diagnostic criteria of anaphylaxis,<sup>4</sup> there were a total of 8 cases of anaphylaxis in the controlled HAE studies giving a frequency of 3.7% of patients (8 out of 219 patients), and 1.3% of doses (8 out of 609 doses). There was one additional case of anaphylaxis in the EDEMA4 open-label-extension, which was not factored in the frequency calculation above. There were 7 other cases suggestive of type I hypersensitivity reactions (not anaphylaxis) and 5 cases of pruritus following injection in the controlled ecallantide studies. Most of these cases occurred after repeat dosing of ecallantide. Some of these patients had IgE to ecallantide detected (note that the antibody assay for ecallantide lacks sensitivity). To further assess these cases, Dyax conducted a formal rechallenge study (DX88-102) where 9 patients were subjected to rechallenge with graded skin-testing and an IV test dose. Three of the 9 patients had positive rechallenges. This is a high frequency of positive rechallenge because it is generally known that over time antibody titer wanes and patients lose sensitivity.

A high frequency of anaphylaxis and type I hypersensitivity to ecallantide is not surprising because ecallantide is a therapeutic protein, the protein is produced in non-human cells, and ecallantide was shown to be immunogenic in animals. The risk of anaphylaxis itself will not preclude approval of ecallantide, because the proposed benefit is on a life threatening aspect of HAE, and acute attacks of HAE are generally treated in a health care setting by health care providers who are knowledgeable and equipped to treat anaphylaxis.

Because of the risk of anaphylaxis, Dyax presented a safe use strategy at the Advisory Committee meeting held on February 4, 2009, where this application was discussed. Dyax proposed a safe use strategy that includes restricted distribution through pre-identified pharmacies and a mandatory registry that will include tracking of anaphylaxis and hypersensitivity reactions, antibody status of patients, and follow-up on rechallenge and desensitization procedures for patients with anaphylaxis. This proposal as presented at the advisory committee meeting is more conservative than the relatively unrestricted distribution and access that Dyax had originally proposed in the application submitted to the Agency. The details of the safe use strategy was submitted by Dyax on February 27, 2009, but have not been reviewed by the Agency. Without Agency review and agreement of the safe use strategy, this application cannot be approved.

Other than anaphylaxis and type I hypersensitivity discussed above, another immunological finding of concern is the high frequency of seroconversion in patients exposed to ecallantide. Approximately 13% of patients (26 out of 202) treated with any dose of ecallantide tested positive for anti-ecallantide antibodies. The probability of

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<sup>4</sup> Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Bock SA, Branum A, Brown SG, Camargo CA, et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy Anaphylaxis Network Symposium. *J Allergy Clin Immunol* 2006; 117:391-7.

seroconversion increased with the number of treated episodes. The rate was approximately 50% in patients who received 8 doses of ecallantide (frequency from the safety update). The long term consequence of this seroconversion is not known and will need to be studied post-marketing. The seroconversion data at this time is imprecise, and may be an underestimate, because the immunogenicity assay lacks sensitivity.

Another safety issue of concern is potential cross-reactivity with human tissue factor pathway inhibitor (TFPI) that may increase coagulability of blood. In the phase 3 studies there were no events of thrombosis or bleeding in patients treated with ecallantide. There were no changes in the mean coagulation parameters, and no substantial changes in shift tables. There were 3 patients in the ecallantide group who had elevated thrombin time and none in the placebo group.

**c. REMS/RiskMAP**

REMS will be necessary for this drug because of the safety findings described above in section 8. As discussed above, at the Advisory Committee meeting, Dyax proposed a safe use strategy for use of ecallantide. The details of the safe use strategy was submitted by Dyax on February 27, 2009, but have not been reviewed by the Agency.

**9. Advisory Committee Meeting**

A Pulmonary Allergy Drugs Advisory Committee was held on February 4, 2009, to discuss this application for ecallantide. Important discussion items included anaphylaxis and hypersensitivity, adequacy of the efficacy and safety data, and the adequacy of the pediatric data.

The panel members noted that ecallantide was highly immunogenic and that the data on anaphylaxis may underestimate the actual risk. But the panel members acknowledged that given the lack of any treatment of acute attacks of HAE, which may itself be fatal in some patients, anaphylaxis of this frequency can be an acceptable risk, provided the risk is managed reasonably. The panel members made such comments acknowledging the safe use strategy that includes restricted distribution and mandatory registry that was outlined by Dyax at the meeting. The panel members also made some suggestions on future studies to understand the mechanism of anaphylaxis and strategies for testing patients to predict anaphylaxis. The panel members noted that such studies may be challenging and may not yield definitive results.

On discussing efficacy and safety, the panel members noted the limitations of the efficacy and safety data, but noted the limitations of treatment options for HAE patients. The voting favored that the efficacy data for ecallantide was sufficient in patients 18 years of age and older (8 Yes, 4 No, 1 Abstain), but not in patients less than 18 years of age (3 Yes, 10 No). The committee voted that the safety of ecallantide was not adequately established in all age groups (5 Yes, 8 No (adults) and 2 Yes, 11 No (pediatrics)) and further information is necessary. With regards to recommendation for approval, the committee was split (6 Yes, 5 No, 2 Abstain), but some panel members noted that if limited to adults only, they would recommend approval. Generally, the committee was

more in favor of approval in adults, but not in patients less than 18 years of age. The panel recommended risk management strategies for anaphylaxis.

The panel members suggested some additional efficacy analyses to supplement the analyses presented at the meeting. The major suggestions included data analysis for EDEMA with and without imputation for severe upper airway compromise, analysis to test whether patients with historical low C1-INH level or low historical C4 levels have different (better) efficacy, analysis with three symptom complexes rather than the five where the three external complexes (external head and neck, genital and buttock, and cutaneous) are grouped together as one so that the skin type manifestations are counted once, and analysis of primary efficacy variables calculated as area under the curve. The Agency will conduct these additional analyses and has or will contact Dyax for additional data sets as necessary.

#### **10. Pediatric**

The Pediatric Research Equity Act is not triggered because of the orphan status of the application. The total number of patients below 18 years of age included in the whole program is limited and not sufficient to conclude efficacy and safety in pediatric patients (see expanded discussion sections 7 and 8 above). Although HAE is an autosomal dominant disease, the disease typically does not manifest until late childhood or early adulthood, raising the possibility that human development may influence the vasoactive mediator cascades responsible for HAE symptoms, one of which is the target for ecallantide. The existing data do not suggest that ecallantide would behave differently in pediatric patients compared to adult patients. To support efficacy and safety of ecallantide in pediatric patients, Dyax will need to provide data from at least one open-label study in a reasonable number of patients (such as 6 per year of age groups) and show favorable numerical efficacy trends and an adequate safety profile. Dyax will also need to provide validation of the ecallantide bio-analytical assay that can allow comparison of adult and pediatric ecallantide exposure data (see Section 5 above).

#### **11. Other Relevant Regulatory Issues**

##### **a. DSI Audits**

DSI audited one site in Atlanta, Georgia, recommended by the clinical review team. This site enrolled the largest number of patients in both the pivotal phase 3 studies. Audit of the site did not show any major deficiency. Review of the application did not identify any irregularities that would raise concerns regarding data integrity. No ethical issues were present. All studies were conducted in accordance with accepted ethical standards.

##### **b. Financial Disclosure**

The applicant submitted acceptable financial disclosure statements. The applicant certified that no investigator entered into any financial arrangements that could affect the outcome of the study.

**c. Others**

There are no outstanding issues with consults received from DDMAC, DMEPA, or from other groups in CDER.

**12. Labeling**

**a. Proprietary Name**

The proposed proprietary name Kalbitor was reviewed by DMEPA and found to be acceptable. However, DMEPA raised concerns with the established name, ecallantide, regarding potential for confusion with another established name (exenatide, which is the established name for Byetta). The recommendation is for Dyax to discuss this issue with USAN/INN and petition for a new established name.

**b. Physician Labeling**

The labeling was not reviewed in detail during review of this application because the application cannot be approved based on the submitted data. The applicant will need to submit data to support approval below 18 years of age, or restrict the labeling to 18 years of age and older. Additional analysis of the efficacy data may also be necessary to better understand the efficacy of the product in patients 18 years of age and older. The safe use strategy that included restricted distribution and mandatory registry as proposed by Dyax at the Advisory Committee meeting is likely to impact the final labeling language. The details of the safe use strategy was submitted by Dyax on February 27, 2009, but have not been reviewed by the Agency. It will be more useful to do a comprehensive label review and discuss with the applicant with a label that is expected to be final or close to final.

**c. Carton and Immediate Container Labels**

These were reviewed by various disciplines of this Division, and DMEPA, and found to be generally acceptable.

**d. Patient Labeling and Medication Guide**

There is not patient labeling for this product as it is proposed to be administered by a health care provider. A Medication Guide will be required as part of a REMA to inform patients of the risk of ecallantide.

**13. Action and Risk Benefit Assessment**

**a. Regulatory Action**

Dyax is seeking marketing approval for ecallantide at a dose of 30 mg SC for the treatment of acute attacks of HAE in patients 10 years of age and older. There are outstanding efficacy and safety issues and CMC issues that need to be addressed before this application can be approved. The recommended action on this application is complete response. The outstanding issues are expanded below.

The results of the submitted clinical studies do not support efficacy and safety of ecallantide at a dose of 30 mcg SC for the treatment of acute attacks of HAE in patients 10 years of age and older. Particularly, the number of patients below 18 years of age

exposed to ecallantide is limited and is not adequate to assess efficacy or safety in this age group. To support the efficacy and safety of ecallantide for treatment of acute attacks of HAE in patients below 18 years of age, Dyax will need to provide efficacy and safety data from controlled clinical studies or open label clinical studies in a reasonable number of patients below 18 years of age and covering each year age group. Dyax will also need to provide validation of the ecallantide bio-analytical assay, and comparative ecallantide exposure data in adults and pediatric patients to support the recommended pediatric dose. As an alternative, Dyax may seek approval for patients 18 years of age and older based on efficacy and safety data from the existing two phase 3 studies. Dyax will be asked to provide further analyses of available efficacy variable data, particularly the TOS data, at time points between dosing of ecallantide and before 4 hours post-dose from EDEMA3 and EDEMA4 studies. This will provide additional useful efficacy information that may supplement the already submitted efficacy analysis for these studies.

The outstanding safety issues, particularly anaphylaxis and type I hypersensitivity reaction, is a substantial safety risk that will need to be managed by appropriate safe use strategy. The application lacks an adequate Risk Evaluation and Mitigation Strategy (REMS) to address the safety risk of anaphylaxis. The REMS will likely include a medication guide, communication plan, and elements to assure safe use of the product. At the Advisory Committee meeting held on February 4, 2009, where this application was discussed, Dyax proposed a safe use strategy that includes restricted distribution and mandatory registry. The details of the safe use strategy was submitted by Dyax on February 27, 2009, but have not been reviewed by the Agency. Agency review and agreement of the safe use strategy is necessary before this application can be approved.

There are several CMC and microbiology deficiencies that will also need to be addressed before this application can be approved. The deficiencies are outlined in sections 3 and 6 of this document.

**b. Risk Benefit Assessment**

The overall risk and benefit assessment of ecallantide for the treatment of acute attacks of HAE as submitted by Dyax does not support its approval for reasons discussed above in section 13a. It is likely that the application can be approved if the indication is limited to 18 years of age and older, an appropriate safe use strategy including restricted distribution and mandatory registry is in place, and the outstanding CMC deficiencies are addressed.

**c. Post-marketing Risk Management Activities**

Not relevant because the application will not be approved. When approved, this product will require post-marketing risk management activities as outlined in section 13a above.

**d. Post-marketing Study Commitments**

Not relevant during this review cycle because the application will not be approved.

There are three outstanding clinical safety issues that will need to be addressed either as specific studies or under the registry proposed by Dyax. The outstanding safety issues

are anaphylaxis and type I hypersensitivity, high frequency of seroconversion in patients exposed to ecallantide, and exploring the effect of ecallantide on the coagulation system. These are further expanded below.

1. For anaphylaxis and type I hypersensitivity, Dyax will need to track all events of interest under the mandatory registry with the goal of identifying predictive risk factors and developing effective screening tools to mitigate the risk. A prespecified number of patients, or all patients for a prespecified duration, treated with ecallantide should be monitored for anaphylaxis, and tested for specific IgE antibody at a reasonable time (possibly 6 weeks) after dosing. An attempt should be made to develop tests, such as serum specific IgE or skin test, that can predict anaphylaxis risk.
2. For immunogenicity, a prespecified number of patients, or all patients for a prespecified duration, treated with ecallantide should be serially tested as prespecified time, for specific IgM and IgG antibodies. An attempt should be made to correlate the antibody levels to immune complex type or antibody mediated type adverse events, and also for lack of efficacy. The existing antibody assay will need to be refined to acceptable levels of sensitivity and specificity.
3. For possible effect on coagulation, a prespecified number of patients, or all patients for a prespecified duration, treated with ecallantide should have coagulation parameters tested at an appropriate time after dosing. Patients should also be monitored for possible adverse events of thrombosis or bleeding.

Animal carcinogenicity study has not been conducted with ecallantide. Dyax will be asked to conduct carcinogenicity study at a later time, if such a study is feasible given the immunogenicity of ecallantide in animals.

Clinical deficiencies for action letter:

1. The results of the submitted clinical studies do not support efficacy and safety of ecallantide at a dose of 30 mcg SC for the treatment of acute attacks of HAE in patients 10 years of age and older. Particularly, the number of patients below 18 years of age exposed to ecallantide is limited and not adequate to assess efficacy or safety in this age group. To support efficacy and safety of ecallantide for treatment of acute attacks of HAE in patients 10 years of age and older, provide the following: 1. Efficacy and safety data from controlled clinical studies or open label clinical studies in a reasonable number of patients below 18 years of age and covering each year age group. Also provide validation of the ecallantide bio-analytical assay, and comparative ecallantide exposure data in adults and pediatric patients to support the recommended pediatric dose. 2. Analyses of available efficacy variable data at time points between dosing of ecallantide and before 4 hours post-dose for all evaluable patients from EDEMA3 and EDEMA4 studies.

This will provide additional useful efficacy information that may supplement the already submitted efficacy analysis for these studies.

2. Anaphylaxis and type I hypersensitivity reactions are substantial safety risks and will need to be managed by appropriate safe use strategy. The application lacks an adequate Risk Evaluation and Mitigation Strategy (REMS) to address this safety risk. The REMS will likely include a medication guide, communication plan, and elements to assure safe use of the product, including, but not necessarily limited to, restricted distribution and a mandatory registry as proposed by you at the Advisory Committee meeting held on February 4, 2009, where this application was discussed. Submit details of the safe use strategy for Agency review and agreement.