

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125277

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date: December 1, 2009

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Subject: Division Director Summary Review

BLA Number: 125277

Applicant Name: Dyax Corp.

Date of Submission: September 23, 2008 (original BLA)
May 31, 2009 (Complete Response to previous action)

PDUFA Goal Date: December 1, 2009

Proprietary Name: Kalbitor

Established Name: Ecallantide

Dosage form: Injection

Strength: 30 mg

Proposed Indications: Hereditary angioedema (HAE)

Action: Approval

1. Introduction

Dyax Corp submitted a complete response on May 31, 2009, to the previous action on the original biologics license application (BLA) 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 was not approved in the previous review cycle because efficacy and safety was not demonstrated for the proposed age range, particularly ages 10 years to 18 years, and the requirements for a Risk Evaluation and Mitigation Strategy (REMS) to mitigate the risk of anaphylaxis had not been agreed upon. In addition, there were outstanding product quality related issues. This summary review will provide an overview of the original application and complete response, with an expanded discussion on the clinical efficacy and safety studies, and REMS to mitigate the risk of anaphylaxis.

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 attacks¹. Until recently, androgenic steroids were 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 the label indication “prevention of attacks of angioedema.” The drug is also used for chronic long-term therapy^{1,2}. 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^{1,2}. 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 kininogens¹.

Until recently, there were no drugs approved in the US for treatment of acute attacks of HAE. On October 9, 2009, Berinert, a human plasma derived C1 esterase inhibitor was approved for the treatment of acute abdominal or facial attacks of HAE in adults and adolescent patients.

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

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

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

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 with the TOS as a key secondary 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 acid protein containing three intra-molecular disulfide bonds, 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 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. Each vial contains a slight overfill. 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 were several CMC deficiencies identified in the previous review cycle. The deficiencies were in the areas of (b) (4), (b) (4) specifications, (b) (4) testing of drug substance after receipt at the contracture manufacturer for (b) (4), acceptance criteria for reference standard qualification, and acceptance specification for purification process in manufacturing. The applicant has addressed these deficiencies in the complete response.

Immunogenicity is a concern with ecallantide because the product is a protein produced in a 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 fully address the potential for ecallantide antibodies to cross react with TFPI, which could have clinical implications and could interfere with the immunoassays. These deficiencies were noted in the previous action letter. Dyax has addressed these deficiencies in the complete response. Some outstanding issues will be addressed as post-marketing requirements.

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. Dyax has agreed to conduct a carcinogenicity study in rats as a post-marketing required study and has submitted acceptable timelines for conduct of the study.

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. During the previous review cycle, the results were deemed not reliable because the validation information of the bio-analytical assay used in these studies for detection of ecallantide was not complete. In the previous action letter, Dyax was asked to provide validation of the bio-analytical assay. In the complete response, Dyax has submitted additional information that addresses this deficiency.

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 EDEMA4 do not suggest QT prolongation or other cardiac rhythm abnormalities.

6. Clinical Microbiology

The manufacturing process of ecallantide consists of various steps that include

(b) (4)
then (b) (4) of the drug substance i (b) (4)s 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) stopper and an aluminum seal with a flip-off cap. There were microbiology deficiencies that were noted in the previous action letter. The deficiencies were 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). Dyax has addressed these deficiencies in the complete response.

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 ² IV E 10 mg/m ² IV E 20 mg/m ² IV E 40 mg/m ² IV Placebo	49	2004	US, Israel, Belgium
EDEMA2	Phase 2, open label	Multi dose	10 - 78	E 5 mg/m ² IV E 10 mg/m ² IV E 20 mg/m ² IV E 30 mg SC Placebo	77	2006	USA, Canada, Europe
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	12-77	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
DX-88/19 (EDEMA4 OLE)	Phase 3, open-label	Multi dose	9 - 72	E 30 mg SC	95	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 EDEMA3.

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,³ 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 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 is reduced with more conservative analysis, the trends of the results remain the same. 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.

³ 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>.

c. Efficacy findings and conclusions

Dyax was originally 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 were not supportive of the efficacy of ecallantide as proposed. The main problem was the proposed age range because most of the patients enrolled in the studies were 18 years of age and older. In the complete response, Dyax proposed 16 years as the lower age bound for the indication. This is acceptable for reasons discussed later in the section.

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 ²	Ecallantide 10 mg/m ²	Ecallantide 20 mg/m ²	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).

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 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)			

The results shown for EDEMA3 are the pre-specified analysis results with imputation. [Note: The MSCS and TOS results from EDEMA 3 reported in the product label are the results without imputation for symptom complexes or medical intervention.]

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 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 (<0.001)
TOS at 4 hrs (mean)	43.3	19.2	24.1 (0.24)	67.1	-5.3	72.4 (0.006)

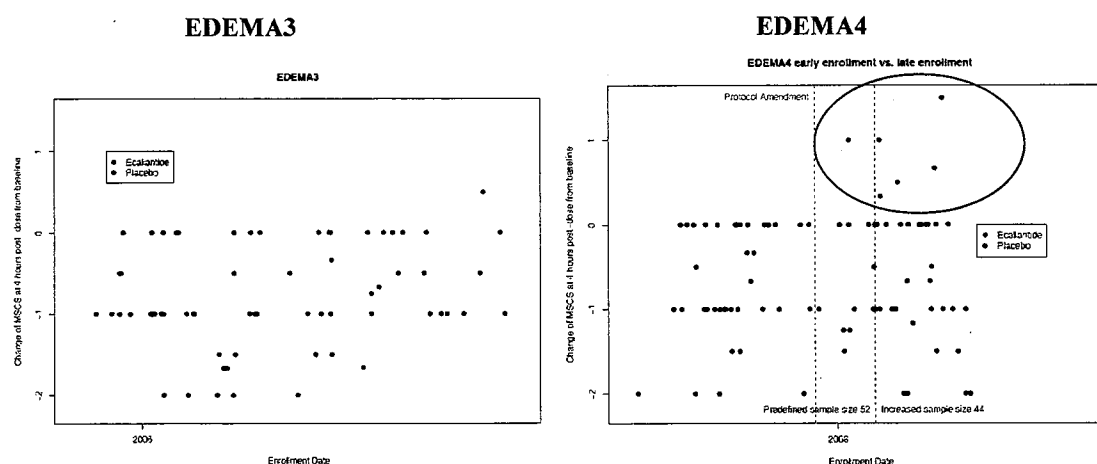


Figure 1. Individual patient data for change from baseline in MSCS.

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.

The total number of patients below 18 years of age who received any formulation of ecallantide in the whole development program was 28, of which a total of 18 received the ecallantide 30 mg SC dose. 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. Dyax acknowledges the lack of exposure data in younger patients. In the complete response, Dyax proposed 16 years of age as the lower age bound. The lower age bound was supported by exposure of 6 patients 17 years of age and 6 patients 16 years of age to ecallantide 30 mg SC dose in 11 and 30 HAE attacks, respectively, and validation of the PK data to support use of the proposed dose. The revised lower age bound of 16 years is acceptable. This is consistent with the Division's expectation that exposure in a reasonable number of patients (such as 6 per year of age) with supporting PK data and favorable numerical efficacy trends and safety findings could support approval to lower ages.

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 trends 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 255 unique HAE patients in the ecallantide program, and in these patients a total of 916 doses of ecallantide were administered to these patients. A total of 187 unique patients have received ecallantide 30 mg SC. In EDEMA3 and EDEMA4 studies, there were 168 patients (84 randomized to ecallantide and 84 randomized to placebo). The safety population consisted of 100 patients who were treated with ecallantide (84 randomized to ecallantide minus 6 patients who received ecallantide in both studies, plus 22 placebo patients who received an open-label dose of ecallantide), and 81 patients who were treated with placebo (84 randomized to placebo minus 3 patients who received placebo in both studies). A total of 143 patients in EDEMA3 and EDEMA4 studies were unique – 100 treated with ecallantide and 43 treated with placebo, since 25 patients had been in both studies. In the controlled portion of EDEMA3 and EDEMA4 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 28, of which 18 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,⁴ there were a total of 10 cases of anaphylaxis in the controlled HAE studies giving a frequency of 3.9% of patients. There were other adverse event reports suggestive of Type I hypersensitivity, including reports of rash (n=8), pruritus (n=13), and urticaria (n=5) following treatment with ecallantide. 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. The proposal was essentially a Risk Evaluation and Mitigation Strategy (REMS) that included restricted distribution through pre-identified pharmacies and a mandatory registry that

⁴ 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.

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 REMS were submitted to the Agency by Dyax on February 27, 2009. There was not enough time in the first review cycle to review and agree on the REMS; therefore, one of the deficiencies in the previous action letter was an agreed upon REMS.

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 7% of patients (18 out of 242) treated with any dose of ecallantide tested positive for anti-ecallantide antibodies. The probability of seroconversion increased with the number of treated episodes. The rate was approximately 27% in patients treated with ecallantide for 9 HAE attacks (frequency from the safety update). The long term consequence of this seroconversion is not known and will need to be studied post-marketing.

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

In the Complete Response, Dyax submitted REMS with the following elements: Medication Guide, Communication Plan, and Elements to Assure Safe Use (ETASU). The ETASU included a restricted distribution program that included a single specialty pharmacy distributor, certification of healthcare prescribers, mandatory patient registry, and distribution only to enrolled healthcare providers and enrolled pharmacies. During review, the Division and OSE determined that the ETASU that included a restricted distribution program were not necessary to ensure the safe use of ecallantide. The risk of hypersensitivity reactions is not unique to ecallantide and is an adverse event for many drug and biologic products, particularly a foreign protein-derived biologic product. Other drug products with risks of anaphylaxis do not have a restricted distribution program with elements to assure safe use, and there is no evidence to suggest that the anaphylaxis associated with ecallantide differs from more well-known drug-related anaphylaxis. In addition, it was unclear that the proposed elements to assure safe use would actually mitigate the risk of anaphylaxis and there was concern the proposed elements could hinder patient access. On October 16, 2009, the Agency requested that Dyax submit a revised REMS that included a Medication Guide and Communication Plan to communicate important information to patients and providers about the unique characteristic of anaphylaxis that may overlap with symptoms of HAE. On October 26, 2009, Dyax submitted a revised REMS consisting of a Medication Guide and Communication Plan to communicate the risk of anaphylaxis and that the signs and

symptoms of anaphylaxis and HAE attacks may overlap. The Communication Plan includes the product labeling and a Dear Healthcare Professional Letter (DHCP). Dyax plans to distribute the DHCP at the product launch and yearly thereafter for 2 years via direct mail to allergy/immunology providers and emergency medicine providers. Dyax representatives will also provide the DHCP letter and product labeling to potential prescribers during the first year of product availability. The information will also be available on the product website. Assessment of the REMS will include patients' and HCPs' understanding of the serious risks of ecallantide. The REMS was reviewed by DPAP and OSE and found to be acceptable.

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 EDEMA3 and EDEMA4 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 16 years of age included in the whole program is limited (see discussion in 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. The lower age bound of this approval will be 16 years because not enough patients below the age of 16 years have been studied. It is expected that exposure in a reasonable number of patients (such as 6 per year of age) with supporting PK data and favorable numerical efficacy trend and safety findings could support approval to lower ages.

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, DRISK, 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.

b. Physician Labeling

Dyax submitted a label in the Physician's Labeling Rule format that contained information generally supported by the submitted data. The labeling contains a Boxed Warning for anaphylaxis and a Medication guide. The label was reviewed by various disciplines of this Division, DRISK, DMEPA, SEALD, and by DDMAC. Various changes to different sections of the label were done to reflect the data accurately and better communicate the findings to health care providers. The Division and Dyax have agreed on the final labeling language.

c. Carton and Immediate Container Labels

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

One issue regarding carton and container labeling that is worth mentioning is the issue of overfill or overage. DMEPA raised concerns regarding the potential for medication errors with overfill as each vial of Kalbitor contains (b) mL overage. Overfill is not an issue unique to Kalbitor. Overfill is necessary and thus allowed in injection preparations to allow for the appropriate volume to be withdrawn. According to the USP, for the labeled size of 1.0 mL, the recommended overfill for a mobile liquid is 0.10 mL and 0.15 mL for a viscous liquid. DMEPA was concerned that for a dose of 30 mg, a patient could receive up to (b) mg of ecallantide instead of the recommended 30 mg if all of the overfill were administered. From a clinical standpoint, there are no significant safety concerns with this small amount of excess dosing. However, to minimize administration errors, DMEPA recommended language on the carton and container labeling that acknowledged the (b) mL of overfill. The Office of Biotechnology Products (OBP) and members of the Labeling and Nomenclature Committee (LNC) raised concern that this would set a new precedent for labeling of solutions for injections. After further discussion, a consensus was reached between DMEPA and members of the LNC as well as OBP that the carton and container labeling would contain the following statement "Each vial contains a slight overfill."

d. Patient Labeling and Medication Guide

A Medication Guide was required as discussed in section 8c above.

13. Action and Risk Benefit Assessment

a. Regulatory Action

Dyax has submitted adequate data to support approval of ecallantide at a dose of 30 mg SC for the treatment of acute attacks of HAE in patients 16 years of age and older. The recommended action on this application is Approval.

b. Risk Benefit Assessment

The overall risk and benefit assessment of ecallantide for the treatment of acute attacks of HAE supports its approval. Acute attacks of HAE are serious, debilitating, and potentially life threatening. Until the October 9, 2009, approval of Berinert, a human plasma derived C1 esterase inhibitor, there was no approved treatment for acute attacks

of HAE. The efficacy data submitted by Dyax to support approval of ecallantide is limited, which is understandable due to the small number of patients afflicted with the disease. Nevertheless, the submitted data has shown consistent efficacy that supports the proposed use. The primary safety concern with ecallantide is anaphylaxis. Given the lack of treatment options for acute attacks of HAE, which may itself be fatal in some patients, anaphylaxis of the reported frequency is an acceptable risk. With the REMS that has a Medication Guide and Communication Plan (discussed in section 8c above) in place for the safety risk of anaphylaxis, the overall risk-benefit assessment of ecallantide for the treatment of acute attack of HAE is favorable.

c. Post-marketing Risk Management Activities

Discussed in section 8c above.

d. Post-marketing Study Commitments

There are several outstanding safety and immunogenicity related issues that Dyax has agreed to conduct as post-marketing required studies. The studies are outlined below.

1. Conduct a long-term safety study with Kalbitor (Ecallantide) in patients with HAE to evaluate immunogenicity and hypersensitivity. The study will include the following objectives: 1) identify predictive risk factors and develop effective screening tools to mitigate the risk of anaphylaxis; 2) correlate antibody levels with adverse events and lack of efficacy; and 3) evaluate the risk of hypercoagulability and hypocoagulability.
2. Establish the sensitivity and cutpoint for the anti-ecallantide neutralizing antibody assay, using immunoaffinity purified ecallantide-specific human IgG.
3. To 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.
4. 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.
5. Conduct a study in rats to evaluate the carcinogenic potential of ecallantide. The 6-month subcutaneous toxicology study with rats could serve as the basis of dose selection.

In addition, there are two CMC related post-marketing commitments that Dyax has agreed to.

1. 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.
2. 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.