Advisory Committee Briefing Document

Kalbitor® (ecallantide)

For Acute Attacks of Hereditary Angioedema

(BLA 125277)

Pulmonary-Allergy Drugs Advisory Committee

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Dyax Corp.

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Abbreviation	Definition
5-HT3	serotonin receptor subtype 3
AAR	administration-associated reaction
AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
aPTT	activated partial thromboplastin time
AUC	area under the curve
BB-IND	Biologic Investigational New Drug
BLA	Biologics License Application
BUN	blood urea nitrogen
C1-INH	component-1 esterase inhibitor
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CTC	common toxicity criteria
CTS	cardio-thoracic surgery
DB	double-blind
ECG	electrocardiogram
ECL	electrochemiluminescence
EDEMA	Evaluation of DX-88's Effect in Mitigating Angioedema
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
GI	gastrointestinal
HAE	hereditary angioedema
HMWK	high molecular weight kininogen
ID	identification
IgE	immunoglobulin E
IM	intramuscular
INa	inward sodium current
IQR	interquartile range
ITT	intent-to-treat
IV	intravenous
LACI	lipoprotein-associated coagulation inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimally important difference
MSCS	Mean Symptom Complex Severity
NIAID	National Institute of Allergy and Infectious Disease
NOEL	No observable effect level
P pastoris	Pichia pastoris
PRO	patient reported outcome
PT	prothrombin time
RD	repeat-dose
SAE	serious adverse event

Abbreviation	Definition
SC	subcutaneous
SD	standard deviation
SOC	system organ class
SPA	Special Protocol Assessment
SUAC	severe upper airway compromise
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TFPI	tissue factor pathway inhibitor
TOS	Treatment Outcome Score
TT	thrombin time
ULN	upper limit of normal
US	United States
VAS	visual analog scale

EXECUTIVE SUMMARY

Hereditary angioedema (HAE) is a rare[1], severely debilitating and life-threatening disease, manifested by intermittent, chronic, acute attacks of pain and edema. HAE is caused by genetic mutations affecting the complement component-1 esterase inhibitor (C1-INH) gene. In the absence of sufficient C1-INH, the normal regulation of human plasma kallikrein is altered, leading to excess plasma kallikrein and release of bradykinin (see Section 2.2). Attacks occur when elevated levels of bradykinin lead to increased vascular permeability and extravasation of fluids, thereby producing the symptoms of pain and edema. Attacks and the associated symptom patterns and severity are episodic, unpredictable, and highly variable, often striking multiple anatomic locations (laryngeal, abdominal, or peripheral) simultaneously and with varying degrees of severity. Untreated attacks typically last from 2 to 5 days and may continue to progress at an unpredictable rate, becoming more severe or spreading to involve other anatomic locations. [3, 4]

Acute and chronic burden of illness stems from attacks at all locations including peripheral, abdominal, and laryngeal. However, attacks occurring in the laryngeal or abdominal areas are of most clinical concern as they are severely debilitating and life-threatening.

- *Acute laryngeal edema is the major cause of angioedema-related mortality.* Even among properly diagnosed and informed patients, these attacks can be fatal. Death due to airway obstruction occurred in 4 of 59 (7%) patients with HAE in a collected experience over 20 years.[18] Patients with no previous history of upper airway involvement during acute HAE exacerbations still run a risk of asphyxia. In a recent study [19, 20], 5 of 6 individuals who asphyxiated during an acute HAE attack had never experienced upper airway involvement during previous attacks. The threat of death by asphyxiation can have profoundly adverse psychological effects on all patients with HAE. [10]

- *Abdominal attacks can cause severe abdominal pain, nausea, and vomiting. Some patients undergo unnecessary abdominal surgery*, including appendectomy, because bowel sounds are often diminished or silent, and guarding and rebound tenderness may be present on physical examination. [3] Additionally, a shift of fluids into the interstitium or peritoneal cavity during abdominal attacks can cause clinically significant hypotension.[13]

- *Peripheral attacks cause significant pain, physical disability, and disfigurement.* Control of the attack as soon as possible after it starts can stop its progression, decrease the likelihood of spreading to other anatomic locations and decrease symptom severity.

HAE patients also suffer a reduced quality of life as many patients spend 20 to 100 days per year unable to engage in normal activities,[6, 10, 14] with up to 100 lost days of school or work per year.[15] Each HAE attack has a profound impact on patients, including physical deformity, restricted mobility, incapacitating pain, risk of asphyxiation, risk of unnecessary

[1] The prevalence of HAE is estimated at 1 in 10,000 to 1 in 50,000 in the general population, representing between 6,000 to 30,000 individuals in the United States (US).[5]

surgery, and frequent hospitalization and there is currently no available effective treatment.[10, 13]

There are no drugs approved in the US for the treatment of acute attacks of HAE. Non-specific treatments such as antihistamines, corticosteroids, and epinephrine are sometimes administered in an attempt to ameliorate individual symptoms of the attack. However, HAE attacks generally do not respond because these treatments target mast-cell mediated sequelae (ie, histamine release) as opposed to kallikrein-mediated bradykinin formation that occurs during HAE attacks. Other commonly used treatments such as fresh-frozen plasma, hydration, and narcotics may provide symptomatic relief but lack evidence of effectiveness to treat attack symptoms and many have associated risks.[7, 8] Thus, there is a strong need for patients who suffer HAE attacks to receive a treatment with evidence supporting its use.

Prophylactic treatments for HAE have been employed and are approved for use. Notably, in October 2008, C1 Inhibitor (Human) (Lev Pharmaceuticals, Inc.) was approved for prophylaxis against HAE attacks. Prophylactic use treatments involve chronic, routine administration over the course of a lifetime and do not entirely eliminate acute attacks of HAE (see Section 1.4). Hence, there continues to be an unmet need for treatment of acute attacks, and particularly a therapy with a unique, targeted mechanism of action against the pathway of an attack.

Kalbitor (ecallantide) is a plasma kallikrein inhibitor designed to address the progression of an HAE attack by acting at a critical point in the mechanistic pathway of the HAE attack. The product is intended to be given acutely to treat an attack.

Kalbitor (ecallantide) 30 mg SC has been proven safe and effective for the treatment of acute attacks of HAE through the conduct of 10 clinical studies, including two similarly designed multicenter, double-blind, placebo-controlled studies (EDEMA4 and EDEMA3-DB). A total of 317 subjects have received over 800 doses of ecallantide (342 IV doses and 468 SC doses), including those treated for the blood loss in the cardiothoracic surgery (CTS) program. Among those treated with ecallantide are 219 unique HAE patients receiving over 600 doses, representing a substantive database for an orphan indication.

- Studies enrolled patients who are representative of the overall HAE population [1, 3, 4, 8, 12], including all anatomical locations of HAE attacks. Each study enrolled a substantial number of ecallantide-naïve patients as well as previously-treated patients (see Section 2.3.4). The eligibility of a patient to participate in more than one trial, though not concurrently, was considered acceptable by Dyax and regulatory agencies for the development program in this rare population.

- Efficacy was measured using two validated patient-reported outcomes (PRO) (see Section 2.3.2.4) both evaluating comprehensive multi-site attack location and severity. One, the MSCS score, provides a comprehensive point in time measure of symptom severity; and the other, the TOS, provides a comprehensive measure of response to therapy. Measurements were performed at 4 hours and 24 hours post-dose.

- Efficacy of single doses of ecallantide in producing rapid, reliable, durable and consistent attack resolution was established through evaluation in 2 placebo-controlled studies.
    - Patients were randomized 1:1 to active:placebo with 96 patients in EDEMA4 and 72 patients in EDEMA3
    - A statistically-significant difference in change from baseline in MSCS score at 4 hours post-dose was observed in EDEMA4 (P=0.010) and in EDEMA3-DB (P=0.044). (see Section 3.1.1)
    - A statistically-significant difference in TOS at 4 hours was observed in EDEMA4 (P=0.003) and EDEMA3-DB (P=0.037). (see Section 3.1.2)
    - A statistically-significant different in change from baseline in MSCS score at 24 hours post-dose (P=0.039) was observed in EDEMA4. The results for this analysis were not statistically significant in EDEMA3, which had fewer patients than EDEMA4. However, results of the TOS at 24 hours post-dose were statistically significant in both the EDEMA4 and EDEMA3 studies. Durability of response to ecallantide, defined as maintenance of response from 4 to 24 hours, was also demonstrated using pooled data from EDEMA4 and EDEMA3-DB. Taken together, these findings support the sustainability of response following treatment. (see Section 3.3)
    - 72.9% of patients treated with ecallantide (versus 57.5% placebo) reported beginning of improvement in overall response within 4 hours; 68.6% of patients treated with ecallantide (versus 41.1% placebo) achieved onset of sustained improvement in overall response by 4 hours. (see Section 3.2)
    - Placebo-controlled studies included patients experiencing laryngeal, abdominal, and peripheral attacks. The studies demonstrate that ecallantide is effective at treating symptoms of attacks at all anatomic locations (see Sections 3.4.1 and 3.4.2).

- Efficacy of treatment of subsequent attacks with ecallantide was established through evaluation in 2 open-label repeat-dose studies (EDEMA3-RD and DX-88/19 [a currently ongoing study]) as well as across studies for patients participating multiple times (pooled data) (see Section 3.5)
    - In EDEMA3-RD, 66 patients were treated for 153 HAE attacks. Of these patients, 51 experienced 2 or more attacks.
    - In EDEMA3-RD, the clinical effect of ecallantide was maintained across subsequent attacks.
    - Approximately half of the patients in the total program (108 of 219, 49.3%) received 1 dose of ecallantide and 12 (5.5%) patients have received over 9 doses. The maximum number of treatments administered to date is 25 (2 patients).

- Overall, treatment-emergent adverse events (TEAEs) occurred at a low rate and were manageable. The most common adverse events (≥5%) were headache, nausea, fatigue, diarrhea, upper respiratory tract infection, HAE, nasopharyngitis, vomiting, upper abdominal pain, and pyrexia; most were mild or moderate in severity. There were 2 deaths across all 317 treated subjects ever exposed to ecallantide; both were unrelated to study drug and are described in detail in Section 4.1.4.

- The most clinically-relevant TEAEs were hypersensitivity reactions to ecallantide, including anaphylaxis and/or anaphylactoid reactions which were observed in the clinical program. Overall, 13 patients experienced symptoms of possible hypersensitivity and all recovered without sequelae. Of these 13 patients, 4 demonstrated symptoms and clinical courses suggestive of anaphylaxis syndrome (anaphylactoid or anaphylactic reactions). These 4 cases are presented detail in Section 4.1.3.3.
    - In the clinical program, these reactions occurred within 15 minutes after dosing and included pruritus, urticaria, allergic rhinitis, throat irritation, pharyngeal edema, flushing, wheezing, rhinorrhea, and occasionally, hypotension. All patients who experienced these reactions recovered with treatment (e.g., antihistamines, epinephrine).
    - In clinical practice, administration of ecallantide is recommended for use only under the guidance and supervision of a healthcare professional where there is also the capacity to recognize and manage any potential anaphylaxis reaction.
    - Post-marketing, Dyax-sponsored, risk management activities will be implemented to ensure that physicians and patients are aware of the proper use of ecallantide, including possible risks and to continue collection of safety information to further quantify risks (see Section 5.2).

- Antibody status did not appear to correlate with the occurrence of AEs. Immunogenicity was assessed using validated enzyme-linked immunosorbent assay (ELISA) and bridging electrochemiluminescence (ECL) assay formats. For all antibodies, including anti-ecallantide (all classes and immunoglobulin E [IgE]) and IgE against host cell proteins (P pastoris), the incidence of seroconversion seemed to increase with increasing exposure to drug; however, patient numbers were too low to make a definitive assessment. (see Section 4.2.4)

- Repeat doses were well tolerated. Of 219 patients in the program, 19 patients (8.7%) received 5 to 9 doses of ecallantide (cumulatively ranging from 80.2 to 310.8 mg) administered over a minimum of 1 month and 27 days and a maximum of 59 months and 5 days. Further, 12 patients (5.5%) received more than 9 doses of ecallantide (cumulatively ranging from 169.2 to 623.9 mg) administered over a minimum of 13 months and 26 days and a maximum of 44 months and 13 days.

In summary, ecallantide has been demonstrated to be safe and effective for patients suffering from acute attacks of HAE, a severely debilitating and life-threatening disease. The potential adverse events associated with ecallantide use can be managed. Safety information will continue to be collected in the post-marketing setting to further quantify adverse events. Ecallantide acts quickly at all symptom sites to mitigate the attack and reduce symptom severity by 4 hours, provides sustained and durable relief at 24 hours, and reduces the need for other medical intervention.

This briefing document provides an orientation to ecallantide for the members of the Pulmonary-Allergy Drugs Advisory Committee. The contents follow a conventional arrangement providing in sequence, general information about the disease and the drug, details of the efficacy and safety data, summaries of key findings and concluding with an

overall benefit-risk statement and proposed risk management activities. Additional information is provided in appendix format in order to clarify background detail.

1 HEREDITARY ANGIOEDEMA

1.1 Disease Epidemiology and Biology

Hereditary Angioedema (HAE) is a rare disease, with the prevalence estimated at 1 in 10,000 to 1 in 50,000 in the general population, representing between 6,000 and 30,000 individuals in the US.[5] The condition typically presents after puberty and by age 30, but diagnosis is often delayed.[7] Delayed diagnosis may result in part from low disease-awareness within the general medical community. While affecting both genders, HAE attacks occur more frequently in females; this gender difference, in conjunction with the increased occurrence after puberty and diminution after menopause, suggests a hormone-influenced mechanism.[4,11]

HAE is caused by genetic mutations affecting the C1 Esterase inhibitor (C1-INH) gene located on chromosome 11q, and is inherited as an autosomal dominant trait, with up to 25% of newly diagnosed cases representing new spontaneous mutations.[2, 10] Normally, C1-INH functions to regulate vasodilatation by inhibiting the ability of plasma kallikrein to cleave and activate the potent vasodilator bradykinin.[12] During an HAE attack, mutated C1-INH fails to appropriately regulate kallikrein, resulting in endogenous release of bradykinin. As the level of circulating bradykinin increases, vasodilatation and progressive swelling (edema) occur at variable anatomical locations.

1.2 Disease Description

The disease of HAE is manifested by episodic attacks that produce edema in various anatomical locations. Most HAE patients can identify one or more possible triggers of some of their attacks; known stimuli that induce HAE attacks include stress, surgical procedures, and hormonal changes.[12] Nonetheless, many attacks occur without a known precipitating factor, which adds to the overall complexity of the disease.[13] The frequency of HAE attacks ranges from less than 1 per year to more than 100 per year and attacks typically last 2 to 5 days.[3, 4]

In the early stages of an attack, many patients feel a tingling sensation in the affected body area. [13] As vascular permeability increases, swelling begins to worsen and generally continues to increase for the first 24 hours. Symptoms of HAE attacks gradually subside 48 to 72 hours after swelling reaches its peak.[13]. However there may be longer term sequelae that lead to a generalized burden of illness.

If swelling occurs in the hands, feet, arms or legs, face or external genitalia it is referred to as a “peripheral attack” and produces disfigurement that is often painful and can make normal activities difficult or impossible. Edema of the gastrointestinal system and abdomen is referred to as an “abdominal attack” and is a significant health threat, since the edema can result in severe abdominal pain, nausea, and vomiting. Laryngeal edema or swelling of the internal components of the head and neck is referred to as a “laryngeal attack” and is life-threatening and may result in death by asphyxiation.

Although the edema is referred to as an “attack”and a specific site may be mentioned to describe the attack, in fact each attack comprises highly variable symptom patterns and symptom severity.[1, 2] For example, the edema may begin, worsen, and end in one anatomical location, or it may begin in one location and emerge in another location, or it may occur in many locations simultaneously. Further, the severity of each attack is variable and each anatomical site will have its own severity and consequences. For example, during an HAE attack, edema may present first in a foot and later in the face of a patient, and the severity of the edema in the foot may be considered mild while the severity in the face may be considered severe.

Thus, an HAE attack may include one or all of the above-mentioned attack sites, or may begin in one site and emerge in another. Fatal episodes have occurred in patients who previously have experienced only mild or benign attacks.[7] The number of events per year does not predict the severity of the next attack or whether the next attack will be an airway event.[8] Further, it is not possible to predict which patients will have laryngeal attacks or which attacks might progress to laryngeal attacks.[10] In undiagnosed patients, mortality has been reported in up to 30% to 50% of patients, primarily due to asphyxiation.[16, 17]

1.3 Medical Need

The disease of HAE represents a continuing and unmet medical need, since there is no treatment approved for acute attacks of HAE in the US. HAE attacks do not respond to traditional treatments for angioedema or hypersensitivity reactions (ie, antihistamines, epinephrine, and corticosteroids) because these treatments target mast-cell mediated sequelae (ie, histamine release) as opposed to kallikrein-mediated bradykinin formation that occurs during HAE attacks. In the US, current treatment for acute attacks of HAE is directed at palliative and symptomatic care but does not alter the course of an HAE attack. These treatments generally are fresh-frozen plasma, hydration, and narcotics.

HAE attacks can strike at any anatomical location, generally categorized into 3 primary areas, laryngeal, abdominal, and peripheral. Attacks occuring in the laryngeal and abdominal areas are of most clinical concern as they are life-threatening and severely debilitating.

Acute laryngeal edema is the major cause of angioedema-related mortality. Proper diagnosis, patient education, and management have led to a decrease in the number of patient deaths due to laryngeal edema. However, even among properly diagnosed and informed patients, HAE attacks can be fatal. Death due to airway obstruction occurred in 4 of 59 (7%) patients with HAE in a collected experience over 20 years. [18] Patients with no previous history of upper airway involvement during acute HAE attacks still run a risk of asphyxiating; in a recent study, 5 of 6 individuals who asphyxiated during an acute attack of HAE had never experienced upper airway involvement during previous attacks. [19, 20] Current management of laryngeal attacks may require intubation or tracheostomy.

Abdominal attacks can cause severe abdominal pain, nausea, and vomiting. Assessment and treatment of these attacks is complicated since they are often misdiagnosed. Bowel sounds are often diminished or silent, and guarding and rebound tenderness may be present on physical examination, leading in some cases to unnecessary abdominal surgery including

appendectomy. [3] A shift of fluids into the interstitium or peritoneal cavity during abdominal attacks can cause clinically significant hypotension. [13]

HAE that manifests in a peripheral attack can cause severe pain, physical disability, and disfigurement. A peripheral attack that is untreated can progress to a different site at any time. Thus, for example, a peripheral attack can progress to a severe laryngeal attack at an unpredictable rate and without warning. Therefore, treatment of a peripheral attack is medically necessary in order to provide relief to the patient and to prevent the attack from worsening. [5]

In summary, there is a medical need for a treatment that can be administered soon after symptom onset and alter or stop the course of the HAE attack providing rapid, reliable, and consistent symptom relief to patients.

1.4 Currently Available Therapy for HAE

There is no approved treatment for acute attacks of HAE in the US. Treatment is symptomatic and palliative in nature. Currently available prophylactic treatments, desribed below, do not entirely prevent HAE attacks and any attack that occurs carries a significant risk to the patient due to the unpredictable nature of HAE.

A C1 Inhibitor (Human) is currently approved in the US for prophylaxis against hereditary angioedema attacks. During clinical trials conducted with this product, patients treated prophylactically for 12 weeks experienced a mean of 6.3±5.5 attacks (approximately 1 attack every 2 weeks) over the course of the 12 week study period. [21] This presents a reduction in approximately 52% of attack frequency. This therapy has prophylactic benefit to HAE patients and the risks associated with this product include those known for plasma-derived products, as well as the inconvenience of intravenous administration.

Other prophylactic therapies for HAE include attenuated androgens and antifibrinolytic agents, which have been shown to reduce the frequency and severity of HAE attacks. In addition to the efficacy seen in HAE patients taking androgens, these drugs can have significant side effects and are contraindicated in children. Androgens are an undesirable option for women of child-bearing potential due to virization, liver effects, and potential adverse effects on fetal growth and development;[3] conversely, women of child-bearing potential constitute a significant proportion of the population seeking treatment for HAE. Patients with HAE taking androgens also report a lower health-related quality of life than patients not receiving androgens and report a greater incidence of side effects compared with patients on other treatments for HAE.[22] Notwithstanding the side effects [7, 22], patients with HAE continue these therapies due to the overall burden of illness associated with HAE attacks.

1.5 Overall Burden of Illness

Patients with HAE not only suffer the short-term effects of each individual attack, but they also suffer from a chronic burden of illness and reduced quality of life.

Part of the profound impact of HAE on patients results not just from the attack itself but also from the time away from normal activities. An acute attack typically lasts from 2-5 days and occurs from 1 time to 100 times per year. During attacks, patients often miss school or work; many patients spend 20 to 100 days per year unable to engage in normal activities [15], with up to 100 lost days of school or work per year.[3, 4] Social and financial burdens for a patient are further complicated when they are unable to participate in normal activities, resulting in decrements in mental and physical health and missed opportunities in education and work.[6, 10, 14]

During each attack lasting 2 to 5 days, patients suffer pain, physical disfigurement, and the threat of mortality from laryngeal edema. The unpredictable nature of the attacks that occur without warning and at undeterminable intervals causes a patient to worriedly anticipate when the next attack might occur, how long will last, and how severe it will be, contributing to anxiety, depression, and feelings of isolation[12]. The threat of death by asphyxiation can have profoundly adverse psychological effects on all patients with HAE.[10] All told, HAE creates a social and emotional burden on patients and their caregivers.

In summary, HAE is a burdensome, life-threatening, severely debilitating, and life-altering disease.[1, 2] Physicians and patients need a treatment that can be administered at symptom onset, precisely target the mechanistic pathway of the HAE attack, and quickly, reliably, and consistently alleviate the complex symptoms of an HAE attack allowing patients to confidently conduct their normal daily lives.

2 DEVELOPMENT PROGRAM

2.1 Kalbitor (ecallantide)

Ecallantide (company code DX-88) is a novel, potent and specific plasma kallikrein inhibitor (Ki=25pM) identified using phage display technology and a library consisting of rationally designed variants of the first Kunitz domain of human lipoprotein-associated coagulation inhibitor (LACI), also known as tissue factor pathway inhibitor (TFPI).[23, 24] The primary sequences of ecallantide and LACI are highly homologous and differ by 7 amino acids. Ecallantide is a 60 amino-acid protein produced by expression in the yeast Pichia pastoris, and has a high affinity and high specificity for human plasma kallikrein, a serine protease that is active in the intrinsic coagulation, pain, and inflammation pathways [25]. Ecallantide is a “first-in-class” inhibitor of plasma kallikrein.

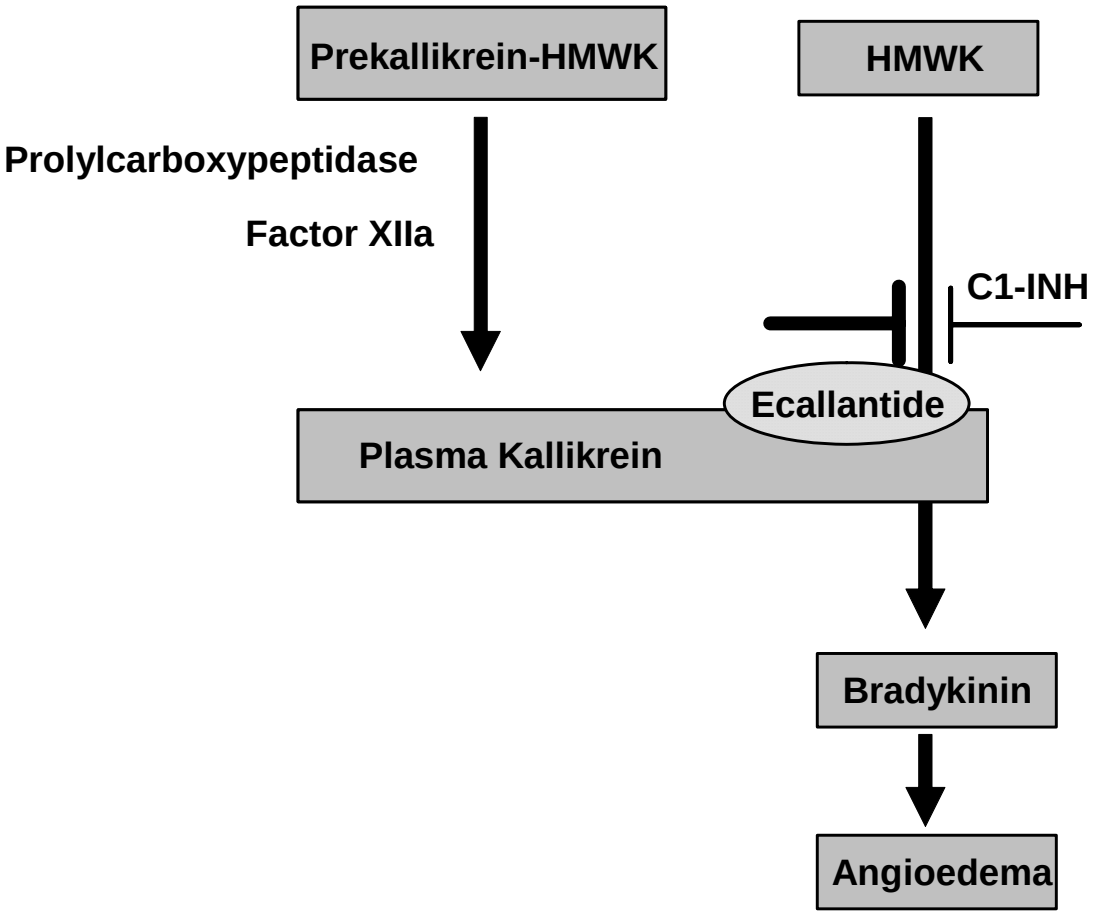
Ecallantide is formulated as a 10 mg/mL clear and colorless, sterile, preservative-free and nonpyrogenic solution in phosphate buffered saline, pH 7.0. Each vial contains 10 mg ecallantide. Ecallantide should be stored at refrigerated temperatures and protected from light. The recommended dose of ecallantide is 30 mg (3.0 mL), administered subcutaneously (SC) as divided 10 mg doses and injection sites should be distant from the location of angioedema.

2.2 Mechanism of Action

Acute attacks of HAE are produced by a disregulated kallikrein-kinin (contact activation) system with resultant endogenous bradykinin overdrive. The central role of plasma kallikrein in the pathogenesis of the signs and symptoms of acute HAE attacks has been well established in the scientific literature.[1, 2, 26] The activity of human plasma kallikrein is normally regulated by C1-INH; however, HAE is characterized by either C1-INH deficiency (Type I HAE) or dysfunctional C1-INH (Type II HAE). In the absence of adequate C1-INH activity, the activation of plasma kallikrein is largely unopposed. This leads to the characteristic acute HAE attack.

The mechanistic trigger for the initial activation of plasma kallikrein in patients is unknown at present, but the end result is cleavage of high molecular weight kininogen (HMWK) by plasma kallikrein with the release of bradykinin. Bradykinin acts on the vasculature to increase capillary and endothelial permeability, resulting in extravasation of fluids producing the characteristic pathognomonic signs and symptoms of HAE attacks. Acting upon upstream elements in the kinin pathway, ecallantide has the ability to produce rapid, specific, complete, and reversible blockade of plasma kallikrein, thereby reducing excess endogenous bradykinin and offering a promising treatment for acute attacks of HAE (Figure 1). A comprehensive development program was therefore undertaken to evaluate utility of the product for treating attacks of HAE.

Figure 1. Ecallantide Activity in the C1-INH Inhibition Pathway



HMWK=high molecular weight kininogen, C1-INH=complement component-1 esterase inhibitor

2.3 Overview of Development Program

Development of ecallantide was conducted under a US Biologic Investigational New Drug application (BB-IND), originally filed to the Center for Biologics Evaluation and Research (CBER) in May 2002. In October 2003, the BB-IND was transferred to the Center for Drug Evaluation and Research (CDER). Ecallantide has Orphan Drug Designation for treatment of angioedema and Fast Track Designation for treatment of acute attacks of HAE. The Biologics License Application (BLA) has been classified as priority review.

2.3.1 Overview of Nonclinical Program

In support of the safe clinical use of ecallantide, a comprehensive nonclinical program was conducted to establish the safety and tolerability profile of ecallantide, including pharmacokinetic and pharmacodynamic studies, safety pharmacology studies, intravenous (IV) and SC single- and repeat-dose toxicology studies in the rat, monkey, and minipig, reproductive toxicology studies in rats and rabbits, prenatal and postnatal development studies in rats, and local tolerance studies in rats. Altogether, effects of ecallantide were evaluated in 25 in vivo toxicology studies and 4 in vitro test systems.

Rats and cynomolgus monkeys were chosen as the primary rodent and non-rodent animal models for the evaluation of ecallantide toxicity. Both species were pharmacologically responsive to ecallantide both in vitro and in vivo. During nonclinical development, ecallantide was administered by both SC and intravenous (IV) routes. Pharmacokinetic assessments to define the in vivo disposition were conducted throughout the nonclinical development program. Toxicokinetic assessments were incorporated into the multiple dose and reproductive safety studies to determine exposure and corresponding safety factors.

Since ecallantide may be administered numerous times over the course of a patient's lifetime, chronic 6-month safety studies were conducted in both rats and cynomolgus monkeys. Ecallantide may be used by women of childbearing potential; therefore, a comprehensive reproductive safety program was completed. Rats were used for the assessment of fertility, teratogenicity, and developmental effects, while the rabbit was used as the second species for the teratogenicity assessment. Minipigs were utilized in the local tolerance studies, since pigs, having vascularized skin with a true SC layer, are an accepted model for human skin.

Overall, no systemic toxicities were observed in the repeat-dose toxicology studies and exposure was maintained throughout the dosing phase at levels that provide an adequate safety margin. Clinical safety margins, for the to-be-marketed dose, were calculated based on both administered dose (mg/kg) and exposure (C_{max} and AUC) at the no-observable-effect level (NOEL) from the multiple-dose and reproductive toxicology studies. Since ecallantide has been shown not to accumulate upon repeated dosing, and exposure is increased in the presence of anti-ecallantide antibodies in animals, first-dose C_{max} and AUC values were used in the calculation of the safety margins. Comparative clinical exposures for the calculation of the safety factors were derived from clinical Study DX-88/13, in which subjects were administered the 30 mg dose (or 0.4 mg/kg dose based on a 70 kg subject) of ecallantide by the SC route, and the range of exposure (AUC) safety margins was between 4 and 58 across the species tested (Table 1).

Table 1. Ecallantide Clinical Safety Margins as a Function of SC Exposure in Repeat-Dose Toxicology Studies

Study	Species	Study Description	NOEL (mg/kg)	C_{max} (µg/mL)	AUC_{inf} (µg*min/mL)	Safety Margin	
						C_{max}	AUC_{inf}
WIL-446021	Rat	6-month Toxicity	25 (males)	5	1791[a]	8	10
			10 (females)	2	760[a]	3	4
WIL-446010	Cynomolgus Monkey	3-Month Toxicity	25	38[b]	10458[b]	63	58
WIL-446020	Cynomolgus Monkey	6-Month Toxicity	25	22[b]	5126[b]	37	28
BXA00012	Rat	Teratology	20[c]	2.5	856	4	5
BXA00031	Rabbit	Teratology	20[c,d]	40	9492	67	52
DX-88/13	Human	Single 30 mg dose	—	0.6	181	—	—

Source: Nonclinical Overview, Table 2.4.9

[a] AUC_{0-24} not AUC_{inf}

[b] Male and female data combined

[c] Based on developmental NOEL, not maternal NOEL or NOAEL

[d] Dose range finding study

Following SC administration to male and female rats and cynomolgus monkeys at doses up to 25 mg/kg every 3 days for 6 months, ecallantide-related findings were limited to reversible irritation at injection sites and transient prolongation of activated partial thromboplastin time (aPTT). No abnormal bleeding patterns were observed in any animal, suggesting that the extent of aPTT prolongation did not have apparent physiologic consequences.

Mortality was observed following IV administration of ecallantide to female rats at doses in excess of 20 mg/kg IV and to female rabbits at doses of at least 5 mg/kg IV. However, no deaths occurred in rats or monkeys given ecallantide SC at doses up to 25 mg/kg.

In rats, IV bolus administration of ecallantide at doses in excess of 20 mg/kg was associated with deaths in approximately 20 of 376 (5%) main study and toxicokinetic rats. It occurred in female animals only and was not observed in male animals. No gross findings were observed that indicate a potential cause of death in these animals. Implications for a possible cardiac etiology in these deaths came from a limited number of animals in 2 in vivo studies. Study WIL-446006 led to the conclusion that right-sided cardiac compromise was a likely factor in the cause of death in the 5 of 88 (6%) female rats that died following the IV administration of 25 and 50 mg/kg ecallantide. Sub-gross evaluation of the hearts from these animals revealed moderate to marked dilation of the right atria and/or ventricles. However, there were no associated histologic findings in the heart and similar sub-gross findings in other affected animals have not been observed. Results from Study BXA00001 showed intraventricular conduction disturbances in 3 of 6 (50%) rats following the IV injection of 25 and 50 mg/kg ecallantide.

Taken together, this electrocardiogram (ECG) data and findings of dilated atria and ventricles raised the possibility that a general cardiac etiology was responsible for the deaths. A battery of in vitro/ex vivo studies demonstrated no potential for ecallantide to affect individual ion channels involved in cardiac conduction or general cardiac function at concentrations in excess of those resulting in mortality in the in vivo toxicity studies. In addition, there were no ecallantide-related clinical observations and no dose-dependent or biologically significant changes in heart rate, blood pressure, core body temperature, or electrocardiograms in cynomolgus monkeys administered single doses of ecallantide at SC doses up to 25 mg/kg (Study BXA00010) or IV doses up to 23 mg/kg (Study ITR 3131).

Brief commentary on the potential that the findings described above reflect an anaphylactic reaction in rodents is warranted. The clinical observations in Study WIL-446006 are inconsistent with literature-reported observations and histologic findings from relevant mouse anaphylaxis models.[31, 32] While some of the clinical findings with ecallantide (respiratory depression with attendant hypoactivity and cyanosis) may be consistent with anaphylaxis in rodents, the histologic features suggestive of anaphylaxis were not observed. In the anaphylaxis models, airway constriction with alveolar wall thickening, pulmonary edema and evidence of general congestion, and infiltration of inflammatory mediator cells is noted. The findings in WIL-446006 encompassed dilation of the atria and ventricles, hepatic congestion, and vacuolation of the renal tubular epithelium, which taken together, as noted earlier, are more suggestive of a cardiac etiology.

The apparent gender-specificity of the mortality following IV dosing was investigated using surgically-manipulated animals. Ovariectomized female rats did appear to have a reduced sensitivity to these effects, suggesting that female hormones may contribute to ecallantide-mediated toxicity. These findings were limited to female rats and were not observed in female non-human primates when administered IV. In human studies, no cardiac-related events were reported and, as described later in this document, there was no apparent effect on QTc, nor any apparent gender bias. Thus, it is unlikely that these findings observed in rats are likely to impact human safety.

In developmental toxicology studies, ecallantide administered SC at 20 mg/kg showed no effects representing a 50-fold margin of safety over the relevant human dose. When given IV to pregnant rats at 15 and 20 mg/kg, adverse effects on the fetus were observed (Study 2204-001). The NOEL for IV administration was established at 10 mg/kg, representing a 25-fold margin of safety. While only observed following IV dosing, which is not the intended clinical route for treatment of HAE, a pregnancy Category C label for ecallantide is felt to be an appropriately conservative approach due to the fetal effects that were observed in Study 2204-001, which included vertebral/rib malformations and dilation of the lateral ventricles. There are no animal or human studies to assess the carcinogenic or mutagenic potential of ecallantide. To date, 3 human pregnancies in the clinical development program have been noted; none of the conceptions were concurrent with systemic exposure to ecallantide; of the 2 known outcomes, both were healthy infants. One pregnancy is currently ongoing.

The immunogenicity of ecallantide and the effect of anti-ecallantide antibodies on ecallantide exposure were assessed in both rats and cynomolgus monkeys. Ecallantide was shown to be immunogenic following repeat SC dosing in rats and cynomolgus monkeys. Anti-ecallantide antibodies were detected in animals from all dose groups with a greater percentage of animals being antibody-positive in the higher dose groups. Exposure was also noted to be increased in anti-ecallantide antibody-positive animals. The increased exposure did not result in a differential toxicity profile and ecallantide was tolerated similarly in both antibody-positive and antibody-negative animals.

Overall, the scope and findings of the nonclinical development program supports the safety of ecallantide and provides an assessment of the potential clinical risks associated with intermittent chronic administration. No systemic toxicities were observed in the repeat-dose toxicology studies and exposure was maintained throughout the dosing phase at levels that provide an adequate safety margin (between 4 and 58 across species tested, as a function of SC exposure). The nonclinical safety profile suggests that ecallantide should be well tolerated in the clinic and the risk for unexpected systemic toxicity should be low.

2.3.2 Overview of Clinical Program

The HAE clinical development program was designed to establish the safety and efficacy of ecallantide in attenuating the signs and symptoms of acute attacks of HAE. As shown in Table 2, the overall HAE development program consists of 10 clinical studies.

- 4 Phase 1 pharmacokinetic studies in healthy subjects: DX-88/1, DX-88/6, DX-88/13, and DX-88/15
- 3 Phase 2 studies in patients with HAE: EDEMA0℠, EDEMA1® and EDEMA2®
- 2 Phase 3 studies in patients with HAE: EDEMA3®, and EDEMA4® (EDEMA3 was conducted in two parts, the placebo-controlled double-blind part [EDEMA3-DB®] and an open-label continuation part [EDEMA3-RD®])
- 1 ongoing open-label continuation study in HAE patients: DX-88/19

In addition to these studies, patients also received varying doses of ecallantide in the following settings: compassionate use, skin test and rechallenge procedure, and in 2 Phase 2 studies for another indication (cardiothoracic surgery).

In the completed studies at the time of BLA, a total of 317 subjects have received over 800 doses of ecallantide (342 IV doses and 468 SC doses). Among those treated with ecallantide are 219 unique HAE patients receiving over 600 doses, representing a substantive database for an orphan indication.

Key aspects of the ecallantide development program were discussed with the FDA, including dose selection, development and validation of the efficacy assessment instruments and the size of the clinical safety database.

Table 2. Clinical Studies in Patients with HAE

Study Number	Design	Dose	N
	Phase 2 Early Development Studies		
EDEMA0	Open-label, escalating, single dose in patients with HAE attacks	Ecallantide 10 mg IV Ecallantide 40 mg IV Ecallantide 80 mg IV	3 3 3
EDEMA1	Double-blind, placebo-controlled, escalating, single dose	Placebo IV Ecallantide 5 mg/m^2 IV Ecallantide 10 mg/m^2 IV Ecallantide 20 mg/m^2 IV Ecallantide 40 mg/m^2 IV	8 10 10 10 11
EDEMA2	Open-label, ascending, repeat-dose	Ecallantide 5 mg/m^2 IV Ecallantide 10 mg/m^2 IV Ecallantide 20 mg/m^2 IV Ecallantide 30 mg SC	18[a] 55[a] 9[a] 31[a]
	Phase 3 Double-blind Studies		
EDEMA4	Double-blind, placebo-controlled, single dose followed by possible open-label dose for severe upper airway compromise, incomplete response, or relapse	Placebo SC Ecallantide 30 mg SC	48 48
EDEMA3-DB	Double-blind, placebo-controlled, single-dose followed by possible open-label dose for severe upper airway compromise	Placebo SC Ecallantide 30 mg SC	36 36
	Multiple Attack Repeat-Treatment Studies		
EDEMA3-RD	Open-label, repeat-dose (≥72 hours apart per episode treated)	Ecallantide 30 mg SC	67
DX-88/19	Open-label, repeat-dose (≥72 hours apart per episode treated), continuation study	Ecallantide 30 mg SC	Ongoing

HAE=hereditary angioedema, IV=intravenous, SC=subcutaneous, RD=repeat-dose, DB=double-blind a Seventy-seven patients were enrolled in EDEMA2. Any individual patient may have been treated at more than 1 dose level and may have been treated for more than 1 attack at each dose level.

2.3.2.1 Total Exposure and Duration of Exposure (HAE Patients)

Table 3 summarizes HAE patient exposure in the entire program. Data are available for 219 unique HAE patients; including 24 pediatric patients aged 10 through 17 years.

Table 3. HAE Patient Exposure

Phase	Study Number (Name)	Patients Newly Exposed to Ecallantide	Patients Re-Exposed to Ecallantide	Total Number of Patients Who Received Ecallantide
Phase 2	DX-88/2 (EDEMA0)	9	0	9
Phase 2	DX-88/4 (EDEMA1)	41	0	41
Phase 2	DX-88/5 (EDEMA2)	58	19	77
Phase 3	DX-88/14 (EDEMA3) DB	29	8	37
Phase 3	DX-88/14 (EDEMA3) RD	35	32	67
Phase 3	DX-88/20 (EDEMA4)	47	23	70
Total Number of Unique Patients Exposed to Ecallantide		**219**		

Source: ISS Summary Listing 1.1 HAE=hereditary angioedema; DB=double-blind; RD=repeat dosing; SC=subcutaneous

Table 4 provides total ecallantide cumulative dose exposure and exposure duration for all ecallantide-treated patients in all HAE studies. The number of times a patient received ecallantide (via either IV infusions or SC injections, including SUAC and Dose B) was further categorized as follows:

- 1 dose
- 2 to 4 doses
- 5 to 9 doses
- more than 9 doses

Table 4. Total Ecallantide Exposure for All HAE Patients

	Ecallantide (N=219)			
	n	(%)	Min; Max Total Cumulative Dose (mg)	Min; Max Duration of Exposure
Number of patients with [a]:				
1 dose	108	(49.3)	8.5; 89.6	1 day
2 to 4 doses	80	(36.5)	27.9; 153.2	1 day; 51 months, 15 days
5 to 9 doses	19	(8.7)	80.2; 310.8	1 month, 27 days; 59 months, 5 days
>9 doses	12	(5.5)	169.2; 623.9	13 months, 26 days; 44 months, 13 days

Source: ISS Summary Table 3.1, ISS Summary Listing 1.1, Longitudinal Patient Profiles
HAE=hereditary angioedema
[a] Exposure is defined as the cumulative number of doses across all studies in this analysis population; categories are mutually exclusive. Only ecallantide exposure (including ecallantide doses for SUAC and as Dose B) for patients who received both ecallantide and placebo is included.

In the group of patients receiving more than 1 dose, 80 patients (36.5%) received 2 to 4 doses of ecallantide administered over a minimum of 1 day and a maximum of 51 months and 15 days. Nineteen patients (8.7%) received 5 to 9 doses of ecallantide administered over a minimum of 1 month and 27 days and a maximum of 59 months and 5 days. Finally, 12 patients (5.5%) received more than 9 doses of ecallantide administered over a minimum of 13 months and 26 days and a maximum of 44 months and 13 days.

2.3.2.2 Clinical Pharmacology

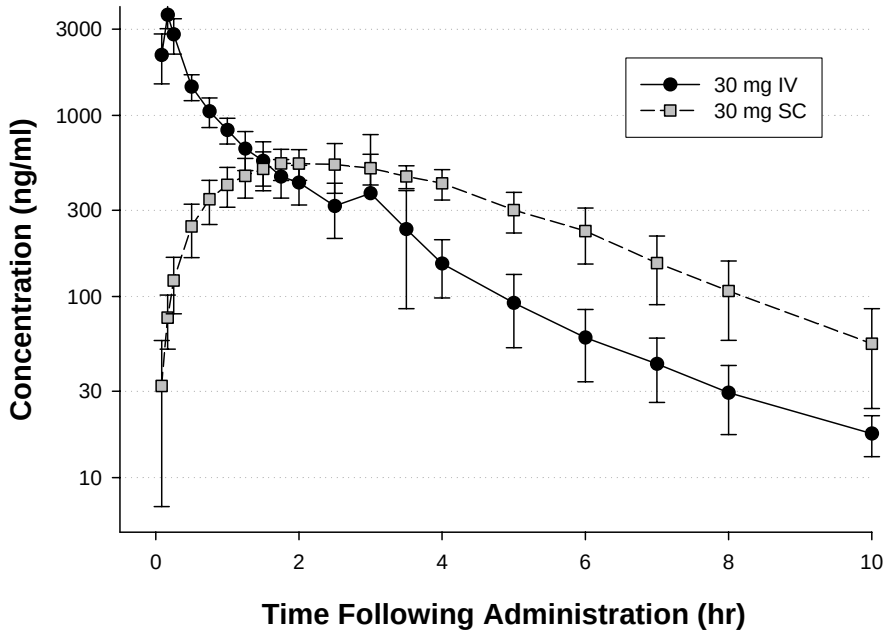
The early clinical development program determined the tolerability and pharmacokinetic profile of IV- and SC-administrated ecallantide. Pharmacokinetic data have been collected in 7 completed studies to date. Four studies (DX-88/1, DX-88/6, DX-88/13, and DX-88/15) were performed in healthy subjects and 3 studies (EDEMA0, EDEMA1, and EDEMA2) were performed in HAE patients during acute attacks.

Ecallantide showed linear pharmacokinetics and was dose-proportional up to 96 mg IV. Peak concentrations occurred 2 to 3 hours after SC administration, although drug absorption was slightly slower in heavier patients. Although no clinical drug-drug interaction studies have been conducted to date, given the protein nature of the drug, it is expected that ecallantide will not affect the pharmacokinetics of drugs metabolized by the cytochrome p450 system or drugs that are enzyme inducers or inhibitors of cytochrome p450 will not affect the pharmacokinetics of ecallantide.

Following the administration of a single 30 mg SC dose of ecallantide to healthy subjects, a mean (±standard deviation [SD]) maximum plasma concentration of 586 ± 106 ng/mL was observed approximately 2 to 3 hours post-dose. The mean area under the concentration (AUC)-time curve was 3017 ± 402 ng*hr/mL. Following administration, plasma concentration declined with a mean elimination half-life of 2.0 ± 0.5 hours. Plasma clearance was 153 ± 20 mL/min and the volume of distribution was 26.4 ± 7.8 L. Ecallantide is a small protein (7054 Da) and renal elimination in the urine of treated subjects has been demonstrated.

Mean concentration versus time curves for IV and SC administration of the 30 mg dose obtained in study DX-88/13 are shown in Figure 2. Maximum plasma concentrations of ecallantide were observed later (mean t_{max} values were delayed approximately 2 hours) and were reduced over 6-fold following SC administration as compared to IV administration. Although the plasma concentration-time profiles appeared to differ, the overall exposure, as measured by $AUC_{0\text{-}inf}$, was similar between routes, with an absolute bioavailability of 91% following SC administration. The clearance and elimination $t_{1/2}$ was similar (approximately 2 hours) following both routes of administration and there was evidence of dose proportionality. In patients and in healthy subjects, ecallantide was shown to rapidly distribute throughout the vascular compartment following either IV or SC administration. This rapid distribution was consistent with the goal of plasma kallikrein inhibition.

Figure 2. Mean Ecallantide Concentration Following IV and SC Administration



IV=intravenous, SC-subcutaneous

The population pharmacokinetics of ecallantide has been investigated in 35 patients with HAE (24 female and 11 male) and 62 healthy subjects, (34 female and 28 male) 11 to 68 years of age. There was no noted difference in the pharmacokinetics between these 2 groups. The clearance of ecallantide was 7.56 L/h with a volume of distribution at steady-state of 15.1 L. Between-subject variability was 38% for clearance. Ecallantide was rapidly cleared with an effective half-life of 0.8 to 4.5 hours. Given the short half-life, once-daily repeated-dose administration did not result in accumulation, and repeated-dose pharmacokinetics was similar to single-dose. Patient age, sex, and baseline creatinine clearance had no impact on ecallantide pharmacokinetics.

2.3.2.3 Proof of Concept and Dose Selection in Patients

The early clinical development program in patients demonstrated clinically relevant activity as a result of inhibiting the kallikrein pathway. The Phase 2 program, described below, also provided information for appropriate dose selection, efficacy assessment timepoint, and the basis for creation and refinement of tools for comprehensively assessing meaningful clinical impact to be used in the subsequent Phase 3 studies.

EDEMA0 (Evaluation of DX-88's Effects in Mitigating Angioedema), the first clinical trial of the development program in patients, was an open-label, Phase 2, single escalating-dose study designed to assess the tolerability and efficacy of ecallantide administered via IV infusion over 10 minutes for patients experiencing acute attacks of HAE. A total of 9 adult patients were enrolled within 10 hours of onset of an attack, 3 at each ecallantide dose level (10, 40, and 80 mg). Several efficacy endpoints were explored using symptom assessment tools of pain intensity (VAS and McGill Pain Questionnaire), abdominal ultrasound, waist circumference, and digital photographs. Results from EDEMA0 revealed signs of efficacy

with ecallantide: all patients showed a response within 4 hours after dosing. No apparent dose response was observed, and ecallantide appeared to be well-tolerated.

EDEMA1, the first placebo-controlled trial of the development program, was a randomized, double-blind, Phase 2, escalating dose-ranging study designed to evaluate the safety and efficacy of ecallantide in patients at least 10 years of age experiencing acute attacks of HAE, considered at least moderately severe. A total of 49 patients were treated with a single IV dose of ecallantide at 5, 10, 20, or 40 mg/m^2 or placebo. Efficacy assessments continued to be explored in EDEMA1 using patient reports of improvement in symptoms. A significantly greater proportion of patients treated with ecallantide compared to placebo achieved significant improvement by 4 hours after dosing (P=0.017). Similar efficacy results were observed at all ecallantide doses. Ecallantide demonstrated clinical activity against acute attacks of HAE at all anatomic locations studied (abdominal, peripheral, and laryngeal).

The use of a 4-hour time point to assess efficacy was established based on several components: a discussion with an expert panel of investigators with clinical experience treating HAE patients, previous experience with C1-INH, and a sensitivity analysis of the EDEMA1 primary endpoint, as outlined below:

- The expert panel of investigators with clinical experience treating HAE confirmed that, since an untreated acute attack of HAE usually lasts between 2 and 5 days [3, 4], any improvement within 4 hours after treatment represents a clinically important response.
- In a placebo-controlled trial examining the efficacy and safety of C1-INH concentrate in patients with HAE carried out at the NIH in the 1990's [28], 95% of C1-INH treated patients and 12% of placebo treated patients reported the beginning of symptom resolution by 4 hours post-infusion, representing a discriminant signal to noise ratio at this time point.
- A sensitivity analysis of the EDEMA1 primary analysis, time to significant improvement, conducted at 30-minute intervals up to 5 hours post-infusion showed that the early placebo response, occurring within 60 minutes, remained constant until the end of the 4-hour assessment period. The ratio ecallantide: placebo response (ie, signal to noise) peaked at 4 hours and remained stable through 5 hours.

Thus, the primary endpoints for future studies were evaluated at 4 hours post-treatment.

EDEMA2 was designed as an open-label, repeated-dose (dosing for subsequent attacks) study of ecallantide in patients experiencing acute attacks of HAE. Upon presentation to the clinic with a moderate to severe HAE attack, patients at least 10 years of age were treated with a single dose of ecallantide; treatment of up to 20 attacks per patient was permitted. Significant improvement in symptoms was based on patient reports and through standard pain VAS and McGill questionnaire. Treatments were initially administered by IV infusion at different doses (5, 10, or 20 mg/m^2 IV). However, after extensive discussions with physicians and patients, in addition to growing knowledge of the clinical patterns of HAE attacks, SC dosing was introduced into EDEMA2. As discussed in greater detail below, a dose of 30 mg SC was selected, based on the available pharmacokinetic data and the increasing adverse events observed at doses of 40 mg IV and higher.

Early clinical studies in HAE patients demonstrated that a range of IV dose levels were safe and effective. Study DX-88/13 established comparability in fundamental pharmacokinetic parameters, including clearance, elimination half-life, and volume of distribution, between IV and SC routes of administration. As a result, the IV dose-ranging studies support the therapeutic window (tolerability and efficacy) for ecallantide when administered SC.

Data from 77 patients treated for 240 attacks attacks showed clinical response at all dose levels with similar time to onset of response across doses. The achieved peak concentration, which is higher following IV dosing, did not appear to be a critical factor in the onset of response or the time to onset of response; the initial concentrations achieved with 30 mg SC administration appeared sufficient for rapid onset of symptom relief. Successful outcome based on improvement of response at 4 hours and maintained at 24 hours (the primary endpoint evaluation) was achieved following treatment with 30 mg SC in 49 of 60 (81.7%) attacks treated, as compared to 11 of 24 (45.8%) attacks treated at 5 mg/m^2, 96 of 141 (68.1%) at 10 mg/m^2, and 9 of 15 (60.0%) at 20 mg/m^2. Time to onset of response was similar across doses. Thus, based upon data that ecallantide administered at a fixed 30 mg SC dose showed superior efficacy and comparable or better safety compared to 5, 10, and 20 mg/m^2 IV dose levels and offers rapid less burdensome use for health care professionals, this dose was selected for Phase 3 studies.

EDEMA2 also evaluated early versions of HAE-specific patient-reported outcome (PRO) instruments, the Treatment Outcome Score (TOS) and Mean Symptom Complex Severity (MSCS) score, using a preliminary psychometric analysis. The use of these early versions of the instruments in EDEMA2 provided key information to refine and validate the final PRO instruments that were used in the Phase 3 studies, as discussed in the next section.

2.3.2.4 Clinical Assessment Tools

Measuring symptom severity and response to treatment in HAE is challenging due to the complexity of HAE attacks and therefore the development of disease-specific assessment instruments was deemed necessary to fully assess response to treatment in the Phase 3 studies. Following are details on the rationale, description, development, and validation of the patient-reported outcome (PRO) instruments developed for use in the Phase 3 confirmatory studies.

NEED FOR DEVELOPMENT OF AN HAE DISEASE-SPECIFIC PRO

As described in Section 1.1, HAE attacks are characterized by a highly variable constellation of symptoms within any given attack that may include any combination of swelling and pain of the face, larynx, gastrointestinal (GI) tract, extremities, and/or genitals.[4, 14] Furthermore, in any given acute attack, patients might experience swelling patterns on various combinations of body sites with new symptoms emerging and other symptoms subsiding relatively rapidly within a single attack.[13] Other symptoms, including nausea, malaise, anxiety, dizziness, and overall discomfort, are frequently present and the severity of these symptoms can only be fully evaluated by the patient. Clinical measures considered and used as endpoints in the early phases of the EDEMA program included:

- digital photographs of the affected areas of patients experiencing peripheral edema;
- waist measurements in subjects with abdominal edema or extremity measurements in subjects with peripheral edema;
- visual analog scale (VAS) and McGill Questionnaire to assess pain in subjects with abdominal edema; and
- respiration rate in subjects with laryngeal edema

Despite the usefulness of each of these clinical measures, the above do address a specific symptom of the attack (ie, pain, swelling, etc.) but none provide an overall comprehensive assessment of the patient that includes all the presenting symptoms with varying degrees of clinical impact. Indeed, no known clinical measure existed that had the ability to accurately and comprehensively assess all of the relevant characteristics of an acute attack of HAE.

A PRO measure was determined to be the optimal way to comprehensively capture all relevant symptoms and to quantify severity and improvement of symptoms during an attack, for the following reasons:

- no objective clinical measure existed for quantifying the severity of an acute attack of HAE;
- symptom manifestation is both complex and variable; and
- some signs and symptoms are known only to the patient (such as internal swelling, cramping, and pain)

Therefore, Dyax developed and validated comprehensive PRO instruments that could evaluate all signs and symptoms of an acute attack of HAE at any anatomical site, as well as capture severity of each symptom across anatomical sites, to obtain a comprehensive assessment of attack severity and response to treatment for the full constellation of symptoms. Following is a description of these PRO instruments and their development and validation.

DESCRIPTION OF THE MSCS SCORE AND TOS

The PRO instruments used to assess efficacy in the Phase 3 studies are the Mean Symptom Complex Severity (MSCS) score and the Treatment Outcome Score (TOS). The PRO instruments are designed to comprehensively assess symptom severity and response to treatment and were developed with input from external psychometric experts, practicing clinicians, HAE patients, and guidance from the FDA. Both PROs evaluate symptoms that occur at any anatomic location, identified by 5 symptom complexes that relate to the 3 common terms used to describe HAE attacks:

- laryngeal (internal head/neck)
- abdominal (GI/abdominal)
- peripheral (genital/buttocks, external head/neck, and cutaneous).

A schematic describing the categorization of attack symptoms into corresponding symptom complexes is provided in Appendix A as well as the formulas used to calculate the MSCS score and TOS.

The MSCS score is a comprehensive point-in-time measure of symptom severity. At baseline, patients identified all active symptom complexes and rated severity (1=mild, 2=moderate, 3=severe). At 4 and 24 hours post-dose, patients rated the severity of all symptom complexes identified at baseline on a categorical scale (0=normal, 1=mild, 2=moderate, 3=severe). New (emerging) symptom complexes were identified as they arose and severity was assigned as described above. Definitions of mild, moderate, and severe are provided in Appendix A, along with an example of each severity category. Severity ratings were averaged to obtain the MSCS score. A decrease in MSCS score reflects improvement in symptoms.

The TOS is a comprehensive measure of response to therapy. At 1, 2, 3, 4, and 24 hours post-dose, patient's assessment of response as compared to baseline was collected and recorded on a categorical scale (significant improvement [100], improvement [50], same [0], worsening [-50], significant worsening [-100]) for each symptom complex. The response to each symptom complex was weighted by the baseline severity and then averaged for the TOS. A schematic of the response assessment is provided in Appendix A. An increase in TOS reflects improvement in symptoms.

DEVELOPMENT AND VALIDATION OF THE PROS

Development of the MSCS score and TOS began with a retrospective modeling of data from an early clinical study (EDEMA1) and early versions of these instruments were used prospectively in EDEMA2. In EDEMA2, both PROs demonstrated responsiveness to treatment and discrimination between subjects who rated their overall symptom improvement differently. The MSCS score and TOS were also highly and significantly correlated with the McGill Pain Questionnaire scores among those participants experiencing abdominal attacks, providing evidence of concurrent validity. These measures were then established and validated using cognitive debriefing interviews and analysis of their psychometric properties in EDEMA3. The PRO validation methods were discussed and agreed with the FDA and follow FDA guidelines as well as commonly accepted published guidelines for validation [9].

Cognitive interviews with 15 patients (including 2 pediatric patients), and 6 proxy respondents were undertaken to evaluate the content validity of the MSCS score and TOS assessments. Instructions, items, and the electronic data capture mode were tested for readability, comprehension, interpretability, navigability, and usability. Special efforts were made to recruit children and adolescents and proxy respondents to ensure the MSCS score and the TOS are equally valid for these special populations. Results of the debriefing interviews were supportive of the content validity and usability of the MSCS score and the TOS items. Participants were able to understand the concepts of the measures, the symptom complex concepts were reported to be comprehensive, and participants were able to use and fill out the electronic diary. The MSCS score and the TOS items capture well the diverse and variable symptomatology for patients with HAE.

Results from the EDEMA3 analyses were supportive of robust measurement properties, including reliability and validity, of the TOS and MSCS score. Demonstrating reproducibility of the TOS and MSCS score is challenging given the rapid changes in symptoms characteristic of HAE attacks and the relatively small sample sizes included in the

analysis. However, intraclass correlation coefficients from the test-retest reliability assessment suggested that the TOS demonstrated moderate agreement and change in the MSCS score demonstrated substantial agreement according to criteria presented by Landis and Koch.[27] Moderate to large correlations between the TOS and change in the MSCS score as well as between the TOS and change in the MSCS score and the assessment of overall response at 4 hours demonstrated construct validity and responsiveness to change. The TOS and change in MSCS score significantly discriminated between overall improvement categories, demonstrating good discriminant validity of the instruments despite measurement challenges, including small sample sizes in the worsening categories.

EDEMA3 also evaluated the minimally important difference (MID) of the TOS and change in the MSCS score, which refers to the smallest difference in a score that is considered to be meaningful or important. Two methods were used (anchor and distribution methods) and results of these analyses provide estimates of the MID for TOS and MSCS score are 30 and -0.30, respectively. A clinically-meaningful improvement may actually be represented by a larger value than that suggested by the MID. For context, a 1 point change on the MSCS scale represents 1 category of severity shift which is a very strong clincial response. These interpretation guidelines can be used to help define responders to treatment in a clinical trial setting. The versions of the MSCS score and TOS used in EDEMA3 were not changed after validation activities and were considered final; these versions were utilized in EDEMA4.

UTILIZATION OF THE PROS

In the Phase 3 studies, the MSCS score and TOS were obtained through the use of an electronic diary format. The electronic diary is a hand-held device that generates questions for the subject to answer. While the formulas that determine the MSCS score and TOS are appropriately comprehensive and complex to match the complexity of the severity and symptoms of an acute attack of HAE, the questions asked of the subjects in the electronic diary are in fact simple and straightforward. Training for completing the electronic diary was provided to subjects at screening, prior to the subject presenting at the site with symptoms of an acute attack of HAE.

When a subject presented to an investigational site during an acute attack, the subject received the electronic diary that asked simple questions. Subjects were asked about symptom location, symptom severity, and response to treatment. The responses to these questions generated the MSCS score and TOS. Subjects were also asked to rate how they felt overall compared with how they felt prior to receiving study drug every 15 minutes for the first 2 hours, then every 30 minutes for the third and fourth hour, and again at 25 hours post-dose. From this overall assessment measurement, the efficacy endpoints of time to significant improvement in overall response and time to sustained improvement in overall response were determined. The overall assessment was captured at the same post-dose time points as described for symptom complex identification. Scoring was based on a 5-point scale: a lot better or resolved, a little better, same, a little worse, or a lot worse.

In both Phase 3 confirmatory studies, the change from baseline in MSCS score at 4 hours and TOS at 4 hours were the primary or secondary measures. These assessments were also completed at 24 hours post-dose.

2.3.2.5 Confirmatory Studies

Following selection of dose and development of the PRO instruments, the Phase 3 program was initiated with 2 randomized, placebo-controlled clinical studies, EDEMA3-DB and EDEMA4, to confirm the safety and efficacy of Kalbitor in the treatment of acute attacks of HAE. Both studies, described in more detail below, were largely similar in design and both met pre-specified, primary, secondary, and tertiary endpoints. Additionally, EDEMA4 was conducted under special protocol assessment (SPA) agreement with the FDA. Key features of both of these studies included the following:

- use of disease-specific PRO instruments to assess efficacy;
- inclusion of patients with symptoms at any attack location, which allowed for the assessment of treatment effect for all types of HAE attacks;
- enrollment of males and females between 10 and 78 years, which reflects the demographics of the broader HAE population seeking treatment for acute attacks [7], and
- a systematic program of antibody testing

EDEMA4 was a randomized, double-blind, placebo-controlled study conducted in the US and Canada to evaluate the efficacy and safety of 30 mg SC dose of ecallantide versus placebo in the treatment of moderate to severe acute attacks of HAE. A total of 96 patients ≥10 years of age were randomized 1:1 to receive treatment with either ecallantide 30 mg SC (N=48) or placebo (N=48). Randomization was stratified based upon anatomic location of the HAE attack (laryngeal versus all other locations) and by prior exposure to ecallantide. A second dose of open-label ecallantide 30 mg SC could be administered within the first 4 hours if the patient was at risk for severe upper airway compromise (referred to as SUAC dose), or between the 4-hour and 24-hour assessments if a patient had an incomplete or no response, or had a relapse following the initial dose of study drug (referred to as Dose B).

EDEMA4 was conducted under SPA agreement. Key points of the SPA agreement included the use of the validated PRO for change from baseline in the MSCS score as the primary endpoint, the analysis methods for EDEMA4 key endpoint analyses, allowance for HAE patients to participate in more than 1 clinical study (albeit not concurrently). In addition, it was agreed with the FDA that per-protocol ECG monitoring in EDEMA4 was an acceptable alternative to a thorough QT study (see Section 4.2.1).

EDEMA3-DB was a randomized, double-blind study conducted in the US, Canada, Europe and Israel to evaluate the efficacy and safety of 30 mg SC dose of ecallantide versus placebo in the treatment of moderate to severe acute attacks of HAE. The study also served to validate the PRO measures (see Section 2.3.2.4). A total of 72 patients ≥10 years of age were randomized 1:1 to receive treatment with either ecallantide 30 mg SC (N=36) or placebo (N=36). Randomization was stratified based upon anatomic location of the HAE attack (laryngeal, abdominal, or peripheral) and by prior exposure to ecallantide. If the patient demonstrated worsening respiratory distress, a single dose of open-label ecallantide 30 mg SC (SUAC dose) could have been administered within 4 hours of the initial dose.

2.3.3 Statistical Considerations

All studies conducted as part of the clinical development program were analyzed using appropriate and accepted statistical methods. TOS and change from baseline for the MSCS score were analyzed using the nonparametric Wilcoxon rank sum test because it was assumed that the data would not have a normal distribution. The median and interquartile (IQR) range are the primary descriptive statistics used for reporting the results since the Wilcoxon rank sum test is based on ranked data. Means and standard deviations are also presented to further characterize the distributions of the data. The time-to-event endpoints were analyzed using Kaplan-Meier methodology. In the time-to-event analyses, patients were evaluated for their response to therapy at regular intervals through 4 hours and were therefore censored at 4 hours if the endpoint had not been reached. Patients who received medical intervention within 4 hours of dosing were censored at the time of the intervention.

For the primary analysis methods in EDEMA4, data imputation was not utilized for key endpoints per FDA recommendation. Only those patients with non-missing endpoint response assessments were included in the calculations for the change from baseline in the MSCS score and for the TOS. Therefore, for efficacy analyses, including intent-to-treat (ITT), only those patients with non-missing or partially missing severity and response assessments were included in the MSCS change and TOS calculation. In EDEMA3-DB, imputation for emerging symptom complexes and medical intervention was predefined for the analyses involving TOS and change in MSCS score (Appendix A).

To take into account data from patients who received SUAC or Dose B doses as well as other medical interventions that could have affected the endpoint, sensitivity analyses were performed in which MSCS score and TOS data from EDEMA4 were also analyzed at 24 hours with the imputation methodologies utilized in EDEMA3-DB. For other efficacy endpoints, patients who received a second dose for SUAC or Dose B were considered non-responders for the responder analyses.

The intent-to-treat (ITT) population was the primary analysis population for the 2 studies. In EDEMA3-DB, 2 patients who were randomized at approximately the same time at the same study center were inadvertently each given the treatment intended for the other. The ITT-as-treated analysis corrects the treatment error by analyzing these 2 patients according to the treatment that they actually received. ITT-as-randomized analyses were also performed and are provided for completeness in Appendix C.

EDEMA4 and EDEMA3-DB had similar populations and endpoints and were well-matched at baseline, allowing for an appropriate pooling into an integrated analysis to assess treatment effects in a larger patient group and to evaluate subgroups that could not be analyzed in the individual studies due to sample size constraints. Seventy patients treated with ecallantide 30 mg SC and 73 patients treated with placebo were included in the integrated analyses. The key endpoints (change in MSCS score and TOS at 4 hours) were analyzed without data imputations. For other efficacy endpoints, imputations were used for emerging symptoms and medical intervention.

2.3.4 Patient Populations Enrolled

Studies enrolled subjects representative of the overall HAE population. All anatomical sites of HAE attack locations were represented in a pattern similar to the expected frequency. Although patients were eligible to participate in more than 1 ecallantide clinical study, the development program did not result in enrichment of responders; the majority of patients enrolled in each study were naive to ecallantide (Table 3). Unique patients have therefore been identified and accounted for in all analyses. In particular, the number of unique patients is used as the denominator for integrated safety analyses and is supported by analyses based on exposure (treatment episode).

In both phase 3 studies, eligible patients were male or female, ≥10 years of age, and with a confirmed diagnosis of HAE. To be eligible for randomization, patients were to report to the site within 8 hours after recognition of at least 1 moderate or severe symptom complex. Previous treatment with ecallantide was permitted; however, patients who received ecallantide within 3 days prior to study treatment were excluded from EDEMA4, and patients who received ecallantide within 7 days of presentation for dosing were excluded from EDEMA3-DB.

2.3.4.1 EDEMA4 Study Population

In EDEMA4, with the exception of gender, the demographic and baseline characteristics were similar in the ecallantide and placebo groups. A higher proportion of females (77.1%) were in the ecallantide group than in the placebo group (58.3%), although the overall proportion of females in the study was representative of the overall HAE population that seeks treatment. [1, 3, 4, 8, 12] Patients were predominantly Caucasian (85.4%), and the mean age was 38 years. A majority of patients (33 of 48 patients [68.8%] in the ecallantide group and 29 of 48 patients [60.4%] in the placebo group) were naïve to ecallantide.

All major attack locations were represented and Table 5 summarizes severity by primary attack location. A majority of patients in the ecallantide treatment group had peripheral as their primary attack location (30 of 48 patients, 62.5%). Of the patients in the ecallantide treatment group, 41.7% had moderate peripheral symptoms and 20.8% had severe peripheral symptoms. In comparison, a majority of patients in the placebo treatment group had abdominal as their primary attack location (25 of 47 patients, 53.2%). Of the patients in the placebo treatment group, 40.4% had moderate abdominal symptoms and 12.8% had severe abdominal symptoms.

Table 5. Primary Attack Location Severity at Baseline in EDEMA4

	Ecallantide (N=48)		Placebo (N=48)[a]	
Primary Attack Location	**Moderate**	**Severe**	**Moderate**	**Severe**
Abdominal	6 (12.5%)	4 (8.3%)	19 (40.4%)	6 (12.8%)
Laryngeal	6 (12.5%)	2 (4.2%)	6 (12.8%)	1 (2.1%)
Peripheral	20 (41.7%)	10 (20.8%)	15 (31.9%)	0 (0.0%)

[a] Patient 413001 mistakenly used a test Logpad and had no patient diary data available, including identification of symptom complexes present at baseline. Therefore percentages are calculated based on N=47.

2.3.4.2 EDEMA3-DB Study Population

In EDEMA3-DB, demographic and baseline characteristics were similar in the ecallantide and placebo groups. The majority of patients were female (65.3%) and most were Caucasian (90.3%). The mean age was 35 years. A majority of patients (28 of 36 patients [77.8%] in the ecallantide group and 25 of 36 patients [69.4%] in the placebo group) were naïve to ecallantide.

All major attack locations were represented and Table 6 summarizes severity by primary attack location. The most common primary attack location for patients in the ecallantide treatment group was abdominal (18 of 36 patients, 50.0%). Of the patients in the ecallantide treatment group, 36.1% had moderate abdominal symptoms and 13.9% had severe abdominal symptoms. Similarly, the most common primary attack location for patients in the placebo treatment group was abdominal (21 of 36 patients, 58.3%). Of the patients in the placebo treatment group, 38.9% had moderate abdominal symptoms and 19.4% had severe abdominal symptoms. A higher percentage of patients had laryngeal edema as their primary attack location in the ecallantide treatment group (8 of 36, 22.2%) than in the placebo treatment group (3 of 36, 8.3%).

Table 6. Primary Attack Location Severity at Baseline in EDEMA3-DB

	Ecallantide (N=36)		**Placebo (N=36)**	
Primary Attack Location	**Moderate**	**Severe**	**Moderate**	**Severe**
Abdominal	13 (36.1%)	5 (13.9%)	14 (38.9%)	7 (19.4%)
Laryngeal	7 (19.4%)	1 (2.8%)	1 (2.8%)	2 (5.6%)
Peripheral	6 (16.7%)	4 (11.1%)	10 (27.8%)	2 (5.6%)

3 EVIDENCE OF EFFECT

Evidence of effect for ecallantide was achieved through conduct of two confirmatory studies (EDEMA4 and EDEMA3-DB) designed to evaluate the amelioration of signs and symptoms of acute attacks of HAE by ecallantide, measured by response at 4 hours, time to symptom relief, and durability of response, as well as other relevant measures of clinical impact.

This section presents the results from the pre-specified primary and secondary endpoints (change in MSCS and TOS at 4 hours) for EDEMA4, EDEMA3 and pooled analyses. As noted in Section 3.2, results from the pre-specified secondary endpoint, time to significant improvement, is presented only for the Integrated Phase 3 Analysis. In addition, other study endpoints and post-hoc analyses are presented, when informative.

3.1 Treatment Effect at 4 Hours

3.1.1 Change from Baseline in MSCS Score at 4 Hours Post-Dose

The MSCS score is the arithmetic mean of the severity grades of the individual symptom complexes (Appendix A). A decrease from baseline in the MSCS score represents an improvement in symptom severity.

Change from baseline in MSCS score at 4 hours post-dose was compared between the ecallantide and placebo treatment groups to assess change in symptom severity. In EDEMA4, the difference between the treatments was statistically significant, in favor of ecallantide treatment (P=0.010) (Table 7). The median (IQR) change from baseline in the MSCS score at 4 hours for the ecallantide group was -1.0 (-1.0, 0.0) compared with 0.0 (-1.0, 0.0) in the placebo group. The mean (±SD) change from baseline in the MSCS score at 4 hours for the ecallantide group was -0.81 (±0.63) compared with -0.37 (±0.82) in the placebo group. Most patients achieved a 1 point or 1 category improvement in symptom severity.

As shown in Table 7, the finding of a statistically-significant and clinically-relevant resolution of symptoms (change in MSCS score) at 4 hours is confirmed by similar findings in EDEMA3-DB and the integrated analysis.

Table 7. Change from Baseline in MSCS Score at 4 Hours Post-Dose

Statistics	Baseline		4 Hours		Change		P-Value
	Ecallantide	Placebo	Ecallantide	Placebo	Ecallantide	Placebo	
EDEMA4							
N	48	48	48	48	48	48	
n	47	42	47	42	47	42	
Median	2.0	2.0	1.0	2.0	-1.0	0.0	0.010[a]
IQR	2.0, 2.5	2.0, 2.0	1.0, 2.0	1.0, 2.0	-1.0, 0.0	-1.0, 0.0	
Mean	2.18	1.99	1.38	1.62	-0.81	-0.37	
SD	0.50	0.35	0.75	0.77	0.63	0.82	
EDEMA3-DB (imputed for emerging symptoms and medical intervention)							
N	36	36	36	36	36	36	
n	36	36	36	36	36	36	
Median	2.0	2.0	1.0	2.0	-1.0	-0.4	0.044[b]
IQR	2.0, 2.5	2.0, 3.0	0.5, 2.0	1.0, 2.5	-1.5, -0.3	-1.0, 0.0	
Mean	2.17	2.24	1.26	1.75	-0.91	-0.48	
SD	0.51	0.55	0.96	0.90	1.10	0.68	
Integrated Phase 3 Analysis							
N	70	73	70	73	70	73	
n	70	73	67	67	67	67	
Median	2.00	2.00	1.00	2.00	-1.00	-0.33	0.001[b]
IQR	2.00, 2.50	2.00, 2.00	1.00, 2.00	1.00, 2.00	-1.50, -0.50	-1.00, 0.00	
Mean	2.17	2.13	1.22	1.63	-0.97	-0.47	
SD	0.49	0.47	0.77	0.78	0.78	0.71	

Source: SCE Table 2.7.3.10 and 2.7.3.26
IQR=interquartile range, MSCS=Mean Symptom Complex Severity, SD=standard deviation, DB=double-blind
[a] Blocked Wilcoxon rank sum test
[b] Wilcoxon rank sum test

3.1.2 TOS at 4 Hours Post-Dose

TOS is a composite of symptom complex severity and response compared to baseline, as described (Appendix A). A positive score for TOS represents symptom improvement.

TOS at 4 hours post-dose was compared between the ecallantide and placebo treatment groups to assess symptom improvement. In EDEMA4, at 4 hours post-dose, the difference in TOS between the ecallantide and placebo treatment groups was statistically significant, in favor of the ecallantide treatment group (P=0.003) (Table 8). The median (IQR) for the ecallantide group was 50.0 (0.0, 100.0) compared to 0.0 (-50.0, 50.0) for the placebo group. The mean (±SD) for the ecallantide group was 53.4 (±49.7) compared to 8.1 (±63.2) for the placebo group. Most patients achieved a 50 point or 1 category improvement in response to treatment.

As shown in Table 8, improvement in symptoms in EDEMA4 is confirmed by similar findings in TOS at 4 hours in the EDEMA3-DB and the Integrated Phase 3 analysis, and supports the findings for the MSCS score.

Table 8. TOS at 4 Hours Post-Dose

Statistics	Ecallantide	Placebo	P-Value
EDEMA4			
N	48	48	
n	47	42	
Median	50.0	0.0	0.003[a]
IQR	0.0, 100.0	-50.0, 50.0	
Mean	53.4	8.1	
SD	49.70	63.18	
EDEMA3-DB (imputed for emerging symptoms and medical intervention)			
N	36	36	
n	36	36	
Median	50.0	0.0	0.037[b]
IQR	0.0, 100.0	0.0, 100.0	
Mean	49.5	18.5	
SD	59.43	67.78	
Integrated Phase 3 Analysis			
N	70	73	
n	67	67	
Median	50.0	0.0	0.001[b]
IQR	16.7, 100.0	0.0, 66.7	
Mean	55.5	20.0	
SD	46.49	58.94	

Source: SCE Table 2.7.3.14 and Table 2.7.3.29
IQR=interquartile range, SD=standard deviation, TOS=Treatment Outcome Score, DB=double-blind
[a] Blocked Wilcoxon rank sum test
[b] Wilcoxon rank sum test

3.1.3 Responder Analysis at 4 Hours Post-Dose

Analysis of the proportion of patients who respond is important to help understand anticipated clinical response from a therapy. Therefore, post hoc analyses were completed to examine the proportion of responders at various thresholds for change in MSCS score and TOS in the Integrated Phase 3 dataset and are presented below.

3.1.3.1 Responder Analysis by Threshold Levels for Change in MSCS Score at 4 Hours Post-Dose: Integrated Phase 3 Analysis

The threshold levels examined for change in MSCS score at 4 hours post-dose were ≤ -0.3, ≤ -0.5, ≤ -0.7 and ≤-1.0, and were anchored by the MID established during PRO validation for the change in MSCS score (-0.30, see Section 2.3.2.4). Patients who received a SUAC dose within 4 hours post-dose were considered non-responders. Data are summarized in Table 9.

At 4 hours, a significantly-larger proportion of patients in the ecallantide group were responders compared to the placebo group at each threshold level, including the highest threshold of ≤-1.0 (P=0.012). At the MID (-0.3), 74.3% of patients in the ecallantide group experienced an improvement in severity of symptoms from baseline to 4 hours compared

with 49.3% of patients in the placebo group (P=0.003), thus supporting superiority and clinical utility for ecallantide.

Table 9. Proportion of Responders at 4 Hours Based on Varying Threshold Levels for Change in the MSCS Score: Integrated Phase 3 Analysis

	Ecallantide (N=70)		Placebo (N=73)		
	n	(%)	n	(%)	P-Value[a]
Number evaluable	70		71		
Threshold level					
≤ -0.3	52	74.3	35	49.3	0.003
≤ -0.5	52	74.3	32	45.1	0.001
≤ -0.7	43	61.4	27	38.0	0.007
≤ -1.0	42	60.0	27	38.0	0.012

Source: SCE Tables 2.7.3.34 and 2.7.3.35
DB=double-blind, MSCS=Mean Symptom Complex Severity
[a] Fisher's exact test
[b] No imputations for medical intervention or symptom complexes that emerged after treatment. Patients who received a SUAC dose within 4 hours were considered non-responders.

3.1.3.2 Responder Analysis by Threshold Levels for TOS at 4 Hours Post-Dose: Integrated Phase 3 Analysis

The threshold levels examinded for TOS at 4 hours post-dose were ≥ 30, ≥ 50, ≥ 70 and ≥ 100 and were anchored by the MID was established during the PRO validation (30, see Section 2.3.2.4). Patients who received a SUAC dose within 4 hours post-dose were considered non-responders. Data are summarized in Table 10.

A significantly-larger proportion of patients in the ecallantide group were responders compared to the placebo group at each threshold level, including the highest threshold of ≥100 (P=0.042). At the MID (30), 70.0% of patients in the ecallantide group experienced an improvement at 4 hours compared with 38.0% of patients in the placebo group (P<0.001), superiority that supports the findings with the MSCS score and hence clinical utility for ecallantide.

Table 10. Proportion of Responders at 4 Hours Based on Varying Threshold Levels for TOS: Integrated Phase 3 Analysis

	Ecallantide (N=70)		Placebo (N=73)		P-Value[a]
	n	(%)	n	(%)	
4 hours[b]					
Number evaluable	70		71		
Threshold level					
≥30	49	70.0	27	38.0	<0.001
≥50	49	70.0	27	38.0	<0.001
≥70	30	42.9	16	22.5	0.012
≥100	26	37.1	15	21.1	0.042

Source: SCE Tables 2.7.3.36 and 2.7.3.37
DB=double-blind, TOS=Treatment Outcome Score
[a] Fisher's exact test
[b] No imputations for medical intervention or symptom complexes that emerged post-treatment. Patients who received a SUAC dose within 4 hours were considered non-responders.

3.2 Response Time

How quickly a drug works particularly in an acute setting is also extremely important information for a patient and physician. Time to event, as prespecified by a number of definitions, was examined throughout the EDEMA clinical development program. In particular, and as a result of the larger number of patients included, the Integrated Phase 3 dataset allows for additional analyses and provides more consolidated information than analysis of either Phase 3 study, independently and are presented in this section. Table 11 provides the definitions of the time-to event endpoints used for these analyses.

Table 11. Definitions of Time-to-Event Endpoints

Efficacy Endpoint	Definition
Time to beginning of improvement in overall response	Beginning of improvement in overall response was defined as achieving a response of "a little better" or "a lot better or resolved" in overall response within 4 hours after dosing. Time to beginning of improvement in overall response was the first time after dosing that the patient reported such a response.
Time to onset of sustained improvement in overall response	Sustained improvement in overall response was defined as a response of "a little better" or "a lot better or resolved" in overall response for a continuous duration of at least 45 minutes. Time to onset of sustained improvement in overall response was the first time after dosing that the patient reported such a response.
Time to significant improvement in overall response	Significant improvement in overall response was defined as achieving a response of "a lot better or resolved" in overall response. This is comparable to achieving a complete or near complete resolution of symptoms. Time to significant improvement in overall response was the first time after dosing that the patient reported such a response.

However it should be noted that patients were evaluated for their response to therapy at regular intervals through 4 hours, and then not again until 24 hours, and hence median time estimates for the placebo group may not be available.

In the early clinical development program, these definitions were developed and tested and data generated as follows. Onset of relief is a measure that reflects the earliest part of response to interventions. Data from EDEMA0, EDEMA1, and EDEMA2 were very consistent, providing a range of median time to onset of relief of 24 to 50 minutes with medians clustering around 30 minutes post treatment. This is generally consistent with the known pharmacokinetic profile of ecallantide with 100% inhibition of plasma kallikrein expected to be attained by concentrations at less than the mean Cmax peak expected from 30 mg SC which occurs around 2 hours.

Time to onset of sustained improvement in overall response and time to significant improvement in overall response both reflect an extent of response over time and both relate to the further establishment of response. Estimates across the early EDEMA trials are consistent, with medians ranging from 38 to 105 minutes with a cluster around 1 hour post treatment for time to onset of sustained improvement in overall response. These estimates are also consistent with median time to maximum concentration observed with the clinical dose of 30 mg SC. Similar patterns are seen for time to significant improvement in overall response.

Time to complete resolution was examined in EDEMA0 and EDEMA1, providing estimates of 1470 and 1050 minutes, or 1.02 and 0.72 days, respectively,which compare favorably with the natural history for untreated attack resolution (typically from 2 to 5 days) [7].

The following sections detail the time to event information obtained from the confirmatory Phase 3 program.

3.2.1 Time to Beginning of Improvement in Overall Response

Given the importance of time-to-event data, a post hoc analysis of time to beginning of improvement was performed using integrated Phase 3 data (Table 12).

A total of 72.9% of patients (51 of 70) in the ecallantide group and 57.5% of patients (42 of 73) in the placebo group began to achieve improvement in overall response within 4 hours after study drug administration. While more ecallantide-treated patients began to achieve improvement by 4 hours, the differences in distributions for time to beginning of improvement in overall response did not reach statistical significance between the ecallantide and placebo groups (P=0.154 for Wilcoxon test, P=0.085 for log-rank test). The median (IQR) time to beginning of improvement in overall response was 67.0 (37.0, 225.0) for the ecallantide group and was 105.0 (37.0, not reached) for the placebo group.

Table 12. Time to Beginning of Improvement in Overall Response: Integrated Phase 3 Analysis

Endpoint	Ecallantide (N=70) n (%)	Placebo (N=73) n (%)	P-Value	P-Value
Proportion of patients beginning to improve by 4 hours[a], n (%)				
	51 (72.9)	42 (57.5)	0.079[b]	
Time to beginning of improvement by 4 hours[a] (estimated median [IQR]), minutes				
	67.0 (37.0, 225.0)	105.0 (37.0, --)	0.154[c]	0.085[d]

Source: Supplemental Efficacy Analysis Table E66-4 -- indicates not reached
[a] Patients who did not begin to improve within 4 hours were censored at the time of their last assessment through 4 hours. Patients who received medical intervention that could have affected their response to treatment were censored at the time of the medical intervention.
[b] Fisher's exact test c Wilcoxon test (Kaplan-Meier) d Log-rank test (Kaplan-Meier)

3.2.2 Time to Onset of Sustained Improvement in Overall Response

A total of 68.6% of patients (48 of 70) in the ecallantide group and 41.1% of patients (30 of 73) in the placebo group achieved onset of sustained improvement in overall response within 4 hours after study drug administration. The distributions for time to onset of sustained improvement in overall response for the ecallantide group and the placebo group were statistically-significantly different (P=0.030 for Wilcoxon test, P=0.005 for log-rank test). The median time to onset of sustained improvement in overall response was 98.0 minutes for the ecallantide group and was not reached for the placebo group by 4 hours.

3.2.3 Time to Significant Improvement in Overall Response

A total of 41.7% of patients (33 of 70) in the ecallantide group and 26.0% of patients (19 of 73) in the placebo group achieved significant improvement in overall response within 4 hours after study drug administration. The distributions for the time to significant improvement in overall response in the ecallantide group and the placebo group were statistically-significantly different (P=0.018 for Wilcoxon test, P=0.015 for log-rank test). The median time to significant improvement in overall response was not reached for either treatment group by 4 hours. Although medians were not reached, the difference between ecallantide

and placebo was present in both early and later time periods, as demonstrated by the statistically-significant Wilcoxon and log-rank tests.

In contrast, no statistically-significant treatment effect on time to significant improvement in overall response was observed in the individual studies, EDEMA4 and EDEMA3-DB, likely related to the smaller sample size for these studies compared to the Integrated Phase 3 analysis.

Taken together, results from the HAE clinical trial program indicate that ecallantide achieves rapid and extensive relief of symptoms associated with acute HAE attacks, consistent with the known pharmacokinetics of ecallantide and consequent target plasma kallikrein enzyme inhibition. In terms of medical utility, physicians and patients alike can expect the beginning of symptom amelioration around 30 minutes post-dose, establishment of response around 2 hours (concordant with t_{max}) and in general, complete resolution within 24 hours.

3.3 Durability of Response at 24 Hours Post-Dose

Given the propensity for an untreated HAE attack to continue to worsen over 24 hours and take 2 to 5 days to resolve, durability of response at 24 hours was examined as a clinically-relevant endpoint. Durability of the response to ecallantide was examined by 2 methods. The first method was the protocol-specified method of analysis of change in MSCS score and TOS at 24 hours post-dose. The second method was an analysis of the individual patient outcomes comparing the responses at 4 and 24 hours (proportion of patients with durable response).

3.3.1 Change From Baseline in MSCS Score at 24 Hours Post-Dose

Change from baseline in MSCS score at 24 hours post-dose was compared between the ecallantide and placebo treatment groups to evaluate change in symptom severity and provide an assessment of the durability of the treatment effect. In EDEMA4, at 24 hours post-dose, the change from baseline in MSCS score was significantly greater in the ecallantide group than in the placebo group (P=0.039) (Table 13). The median (IQR) change was -1.6 (-2.0, -1.0) for the ecallantide group and -1.0 (-2.0, -0.6) for the placebo group (N=32 and N=24, respectively). The mean (±SD) change was -1.5 (±0.63) for the ecallantide group and -1.1 (±0.84) for the placebo group.The finding of a larger change from baseline in MSCS score at 24 hours in the ecallantide group than in the placebo group, supports the more complete clinical resolution of symptoms by 24 hours.

As shown in Table 13, this confirmed by similar findings in EDEMA3-DB (strong trend but not statistically significant) and the Integrated Phase 3 analysis.

Table 13. Change from Baseline in MSCS Score at 24 Hours Post-Dose

Statistics	Baseline		24 Hours		Change		P Value
	Ecallantide	Placebo	Ecallantide	Placebo	Ecallantide	Placebo	
EDEMA4							
N	48	48	48	48	48	48	
n	32	24	32	24	32	24	
Median	2.0	2.0	0.3	1.0	-1.6	-1.0	0.039[a]
IQR	2.0, 2.0	2.0, 2.0	0.0, 1.0	0.0, 1.8	-2.0, -1.0	-2.0, -0.6	
Mean	2.1	2.1	0.6	1.0	-1.5	-1.1	
SD	0.45	0.41	0.66	0.89	0.63	0.84	
EDEMA3-DB (imputed for emerging symptoms and medical intervention)							
N	33	34	33	34	33	34	
n	33	33	33	33	33	33	
Median	2.0	2.0	1.0	1.3	-1.0	-0.50	0.142[b]
IQR	2.0, 2.3	2.0, 3.0	0.5, 2.0	1.0, 3.0	-2.0, 0.0	-1.0, 0.0	
Mean	2.1	2.2	1.2	1.7	-0.87	-0.46	
SD	0.52	0.57	1.00	1.05	1.14	1.07	
Integrated Phase 3 Analysis							
N	70	73	70	73	70	73	
n	70	73	51	49	51	49	
Median	2.00	2.0	1.0	1.0	-1.5	-1.0	
IQR	2.0, 2.5	2.0, 2.0	0.0, 1.0	0.5, 2.0	-2.0, -1.0	-1.7, -0.5	0.028[b]
Mean	2.2	2.1	0.8	1.1	-1.4	-1.0	
SD	0.49	0.75	0.47	0.82	0.78	0.73	

Source: SCE Table 2.7.3.12 and Supplemental Efficacy Analysis Table E4-1
IQR = interquartile range; SD = standard deviation

[a] Blocked Wilcoxon rank sum test

[b] Wilcoxon rank sum test

3.3.2 TOS at 24 Hours Post-Dose

TOS at 24 hours post-dose was compared between the ecallantide and placebo treatment groups to evaluate symptom improvement and provide an assessment of the durability of the treatment effect (Table 14). In EDEMA4, at 24 hours post-dose, TOS was significantly higher for patients treated with ecallantide than for patients treated with placebo (P=0.029). Although the medians for both groups were the same (100.0), the IQR for the ecallantide group was (100.0, 100.0) compared with (7.1, 100.0) for the placebo group (N=32 and N=24, respectively). The mean (±SD) TOS for the ecallantide group was 88.8 (±28.14) compared to 55.1 (±58.33) for the placebo group.

As shown in Table 14, the TOS improvement at 24 hours in EDEMA4 is confirmed by similar findings in EDEMA3-DB and the Integrated Phase 3 analysis. Together with the MSCS score improvements, these data support the more complete clinical resolution of attack symptoms by ecallantide at 24 hours compared with placebo.

Table 14. TOS at 24 Hours Post-Dose

Statistics	Ecallantide	Placebo	P Value
EDEMA4			
N	48	48	
n	32	24	0.029[a]
Median	100.0	100.0	
IQR	100.0, 100.0	7.1, 100.0	
Mean	88.8	55.1	
SD	28.14	58.33	
EDEMA3-DB (imputed for emerging symptoms and medical intervention)			
N	33	34	
n	33	34	0.044[b]
Median	75.0	0.0	
IQR	0.0, 100.0	-100.0, 100.0	
Mean	44.3	-0.5	
SD	70.43	87.85	
Integrated Phase 3 Analysis			
N	70	73	
n	51	50	0.041[b]
Median	100	76	
IQR	50, 100	0, 100	
Mean	76	51	
SD	40.4	59.6	

Source: SCE Table 2.7.3.16 and Supplemental Efficacy Analysis Table E4-2
IQR = interquartile range; SD = standard deviation; TOS = Treatment outcome score

[a] Blocked Wilcoxon rank sum test

[b] Wilcoxon rank sum test

3.3.3 Proportion of Patients with Durable Response

The proportion of patients in EDEMA4 with a durable response (defined as an improvement in overall response at 4 hours that was either maintained or improved at 24 hours) was examined. Results of these post hoc analyses revealed a statistically-significant difference in the proportion of patients with a durable response between the ecallantide group and the placebo group (P=0.030). Twenty-four of 46 patients (52.2%) in the ecallantide group experienced a durable response, whereas 12 of 43 patients (27.9%) in the placebo group experienced a durable response.

Similiar results were observed with EDEMA3-DB (post-hoc) with 19 of 33 patients (57.6%) in the ecallantide group experienced a durable response, whereas 13 of 34 patients (38.2%) in the placebo group experienced a durable response. These proportions were not statistically-significantly different (P=0.145).

Analysis of the integrated Phase 3 data shows a statistically-significant difference in the proportion of patients with a durable response between those who received ecallantide (34 of 65, 52.3%) and those who received placebo (22 of 68, 32.4%) at 24 hours post-dose

(P=0.023). Patients who received open-label ecallantide (SUAC or Dose B) were considered treatment failures in this analysis.

The majority of ecallantide patients in this pooled data set achieved a response by 4 hours and maintained it through 24 hours post-dose from a single dose of study drug, indicating durability of response on an individual patient basis. These data support the findings in the individual phase 3 trials and for the MSCS score and TOS, such that patients on ecallantide can expect to have sustained attack symptom resolution within the first 24 hours post-dose.

3.4 Additional Measures of Clinical Impact

While the MSCS score and TOS provide global or composite measures of symptom resolution in an HAE attack, valuable information as to clinical utility can be obtained from an examination of effect of ecallantide by primary attack location. Furthermore for the each primary attack locations, time to response data provides an important guide to rapidity of attack resolution. Finally, reducing the need for other medical intervention, including drugs with significant side effect profiles or lack of efficacy is also key to understanding therapeutic benefit. Additional analyses in each of these areas are presented in the following sections.

3.4.1 Treatment Effects by Primary Attack Location

HAE attacks often occur with symptoms in multiple anatomic locations. Attack location was defined as abdominal (includes the GI/abdominal symptom complex); laryngeal (includes the internal head/neck symptom complex); or peripheral (includes the external head/neck, cutaneous, and genital/buttocks symptom complexes).

Subpopulation analyses by primary HAE attack location (abdominal, laryngeal, or peripheral) were performed for change from baseline in MSCS score at 4 hours, TOS at 4 hours, and time to significant improvement in overall response and are summarized in Table 15.

For change from baseline in MSCS score at 4 hours post-dose, there was a significant difference between the ecallantide and placebo groups for patients who had an abdominal attack (P=0.001). Similar improvement trends were seen in patients who had a peripheral attack; however, the difference between the ecallantide and placebo groups was not statistically significant (P=0.111). A similar trend toward significance with ecallantide was also noted for laryngeal attacks (P=0.335).

For TOS at 4 hours, all 3 attack locations demonstrated a significant difference between the ecallantide and placebo groups, in favor of ecallantide (P=0.026 for abdominal attacks, P=0.041 for laryngeal attacks, and P=0.035 for peripheral attacks).

Table 15. Subgroup Analysis by Primary Attack Location: Integrated Phase 3 Analysis

Efficacy Endpoint	Ecallantide (N=70)		Placebo (N=73)			
Primary attack location[a]	n		n		P-Value	P-Value
MSCS score - Change from baseline at 4 hours (median [IQR])						
Abdominal	23	-1.0 (-2.0, -1.0)	39	-0.5 (-1.0, 0.0)	0.001[b]	
Laryngeal	12	-1.0 (-1.5, -0.5)	6	-0.7 (-1.0, 0.0)	0.335[b]	
Peripheral	32	-1.0 (-1.0, 0.0)	22	0.0 (-1.0, 0.0)	0.111[b]	
TOS at 4 hours (median [IQR])						
Abdominal	23	50.0 (50.0, 100.0)	39	25.0 (0.0, 100.0)	0.026[b]	
Laryngeal	12	100.0 (66.7, 100.0)	6	-25.0 (-50.0, 60.0)	0.041[b]	
Peripheral	32	50.0 (0.0, 100.0)	22	0.0 (-33.3, 50.0)	0.035[b]	
Proportion of patients with significant improvement in overall response[c], n (%)						
Abdominal	23	15 (65.2)	41	13 (31.7)	ND	
Laryngeal	15	9 (60.0)	9	1 (11.1)	ND	
Peripheral	32	9 (28.1)	23	5 (21.7)	ND	
Time to significant improvement in overall response[c] (estimated median [IQR]), minutes						
Abdominal	23	135.0 (62.0, --)	41	-- (135.0, --)	0.011[d]	0.011[e]
Laryngeal	15	195.0 (90.0, --)	9	-- (--, --)	0.043[d]	0.033[e]
Peripheral	32	-- (225.0, --)	23	-- (--,--)	0.567[d]	0.584[e]

Source: SCE Tables 2.7.3.51, 2.7.3.52, and 2.7.3.53 DB=double-blind , IQR=interquartile range, MSCS=Mean Symptom Complex Severity, TOS=Treatment Outcome Score ND=not done, -- indicates not reached

[a] Primary attack location was determined in a hierarchial manner, first to be laryngeal if moderate/severe internal head/neck symptom complex was identified at baseline, then abdominal if moderate/severe GI/abdominal symptom complex was identified at baseline, and then peripheral if moderate/severe external head/neck, genital or cutaneous symptom complex was identified at baseline.

[b] Wilcoxon rank sum test

[c] Patients who did not experience significant improvement in overall response within 4 hours were censored at the time of their last assessment through 4 hours. Patients who received medical intervention that could have affected their response to treatment were censored at the time of the medical intervention.

[d] Wilcoxon test (Kaplan-Meier)

[e] Log-rank test (Kaplan-Meier)

The proportion of patients who had an abdominal attack that achieved significant improvement in overall response for the ecallantide group was 65.2% (15 of 23 patients) and for the placebo group was 31.7% (13 of 41 patients). The distribution of time to significant improvement in overall response for patients who had an abdominal attack in the ecallantide group was significantly different from the placebo group, in favor of ecallantide (P=0.011 for both the Wilcoxon and log-rank tests).

Similarly, the proportion of patients who had a laryngeal attack that achieved significant improvement in overall response for the ecallantide group was 60.0% (9 of 15 patients) and for the placebo group was 11.1% (1 of 9 patients). The distribution of time to significant improvement in overall response for patients who had a laryngeal attack in the ecallantide group was significantly different from the placebo group, in favor of ecallantide (P=0.043 for the Wilcoxon test and P=0.033 log-rank test).

The proportion of patients who had a peripheral attack that achieved significant improvement in overall response for the ecallantide group was 28.1% (9 of 32 patients) and for the placebo group was 21.7% (5 of 23 patients). Unlike the results seen for the 2 other attack locations,

the distribution of time to significant improvement in overall response for patients who had a peripheral attack in the ecallantide group was not significantly different from the placebo group (P=0.567 for the Wilcoxon test and P=0.584 for the log-rank test).

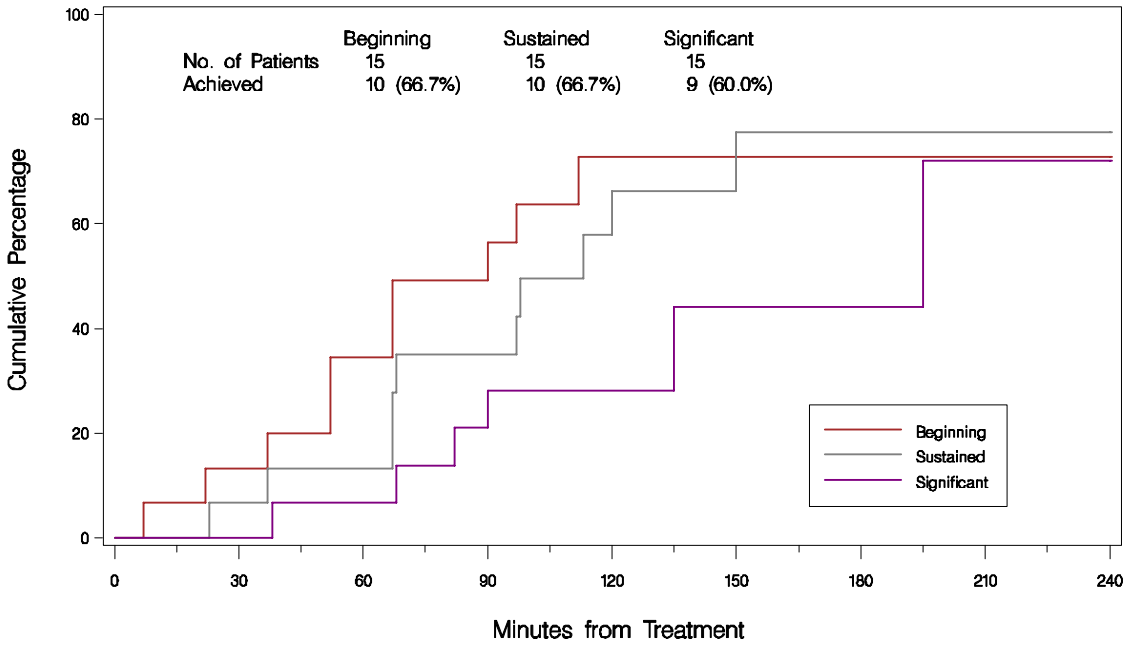
3.4.2 Time to Response by Primary Attack Location

In the analyses that follow, time to the beginning of improvement in overall response, time to the onset of sustained improvement in overall response, and time to significant improvement in overall response (see Table 11 for definitions) are show together in a single graph for each primary attack location for each treatment group. The time-to-effect thresholds defined in these analyses represent increasing levels of improvement; this is depicted by the positioning of the curves to one another in the graphs. Analyses were performed on the Integrated Phase 3 data.

TREATMENT EFFECT FOR LARYNGEAL ATTACKS

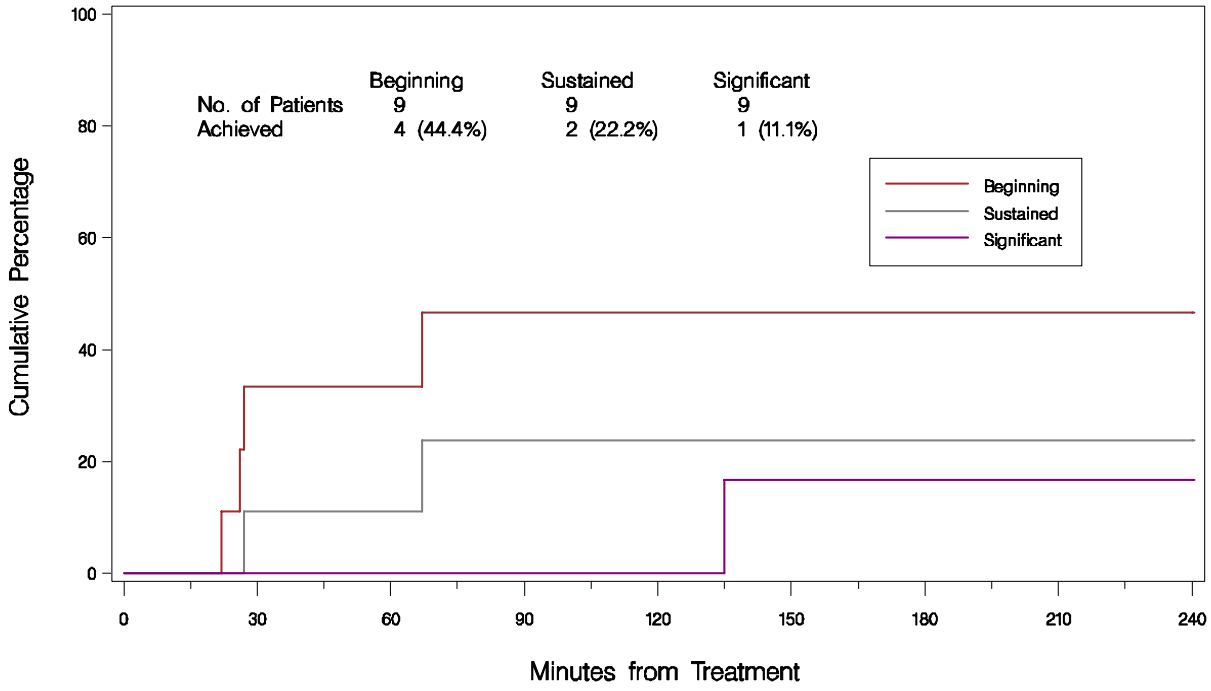
Figure 3 shows a Kaplan-Meier plot of number of patients achieving success following a timecourse after treatment with ecallantide. This graph indicates that response is seen within the first 15 minutes following treatment and is sustained and significant in almost all of the patients who respond.

Figure 3. Time to Beginning of Improvement, Onset of Sustained Improvement, and Significant Improvement in Overall Response by Laryngeal Attack Location for Ecallantide-Treated Patients



In comparison, Figure 4 shows that patients on placebo are more likely to progress with their attacks and with delayed resolution that may require additional intervention based on the time course shown below.

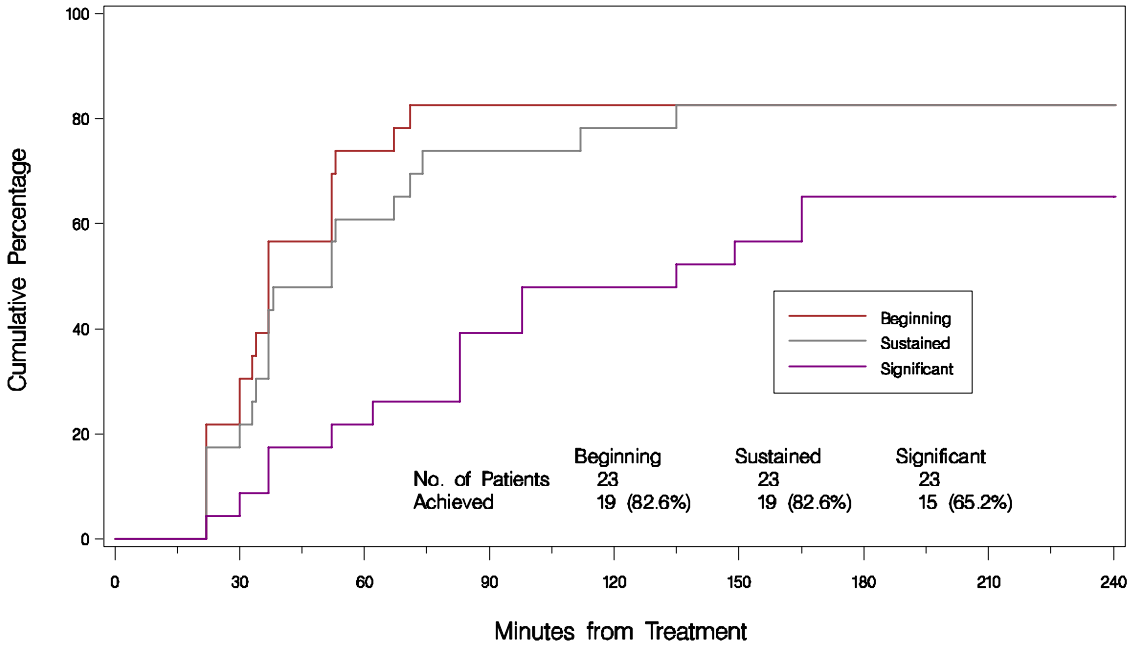
Figure 4. Time to Beginning of Improvement, Onset of Sustained Improvement, and Significant Improvement in Overall Response by Laryngeal Attack Location for Placebo-Treated Patients



TREATMENT EFFECT FOR ABDOMINAL ATTACKS

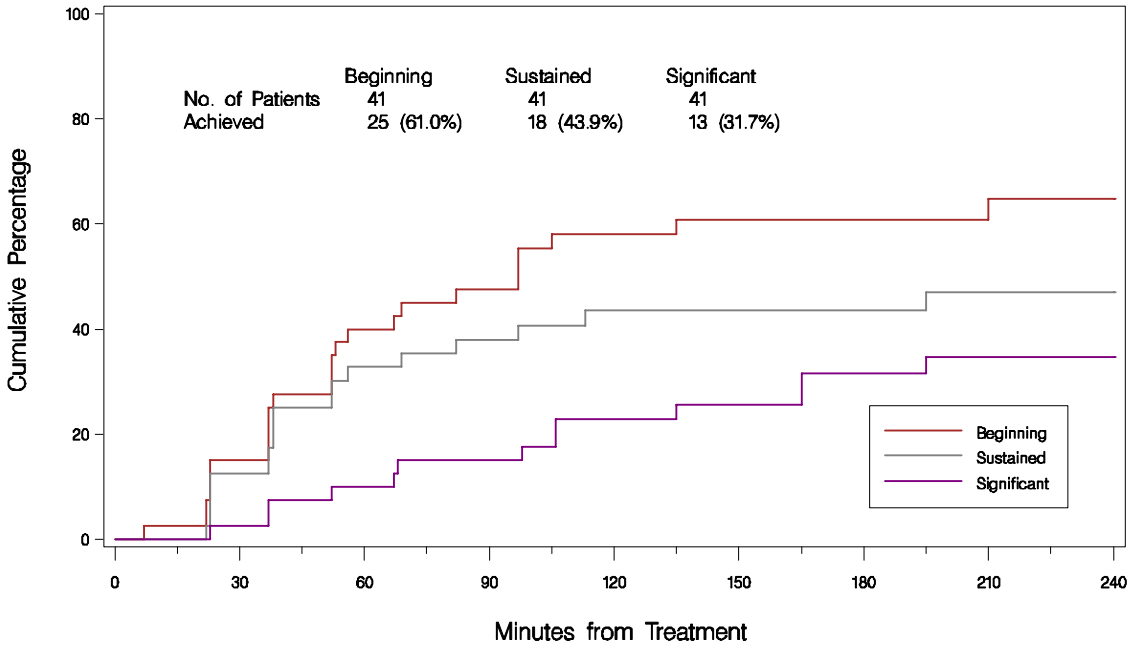
The beginning of improvement and onset of sustained improvement curves for ecallantide are nearly identical (Figure 5), indicating that improvement in abdominal symptoms is realized early and is not transient. Following an initiation of response by 30 minutes, within 75 minutes 83% of ecallantide patients had begun to improve and 74% had experienced sustained improvement.

Figure 5. Time to Beginning of Improvement, Onset of Sustained Improvement, and Significant Improvement in Overall Response by Abdominal Attack Location for Ecallantide-Treated Patients, Integrated Phase 3 Analysis



The beginning of improvement and onset of sustained improvement curves for the placebo group are overlapping immediately after treatment but then start to diverge at about 1 hour post dose (Figure 6). Within 75 minutes 45% of placebo patients had begun to improve and 35% had experienced sustained improvement. Most of the ecallantide patients who experienced the beginning of improvement within 4 hours following treatment also experienced significant improvement in this time frame compared to approximately half of the placebo patients.

Figure 6. Time to Beginning of Improvement, Onset of Sustained Improvement, and Significant Improvement in Overall Response by Abdominal Attack Location for Placebo-Treated Patients, Integrated Phase 3 Analysis



Approximately 20% of both ecallantide and placebo patients experienced an improvement for their abdominal attacks within 30 minutes of receiving treatment. However, the percentage of additional patients who experienced benefit from treatment increased rapidly to 82% by 75 minutes for ecallantide patients compared to a slower rate of increase by 75 minutes (to 45%) for placebo-treated patients.

TREATMENT EFFECT FOR PERIPHERAL ATTACKS

Similar percentages of placebo- and ecallantide-treated patients experienced the beginning of improvement and the onset of sustained improvement during the first 30 minutes following treatment (Figure 7 and Figure 8). Subsequently, these time-to-event curves rose more rapidly for the ecallantide patients than for the placebo patients. Time to significant improvement was similar for the ecallantide and placebo patients.

Figure 7. Time to Beginning of Improvement, Onset of Sustained Improvement, and Significant Improvement in Overall Response by Peripheral Attack Location for Ecallantide-Treated Patients, Integrated Phase 3 Analysis

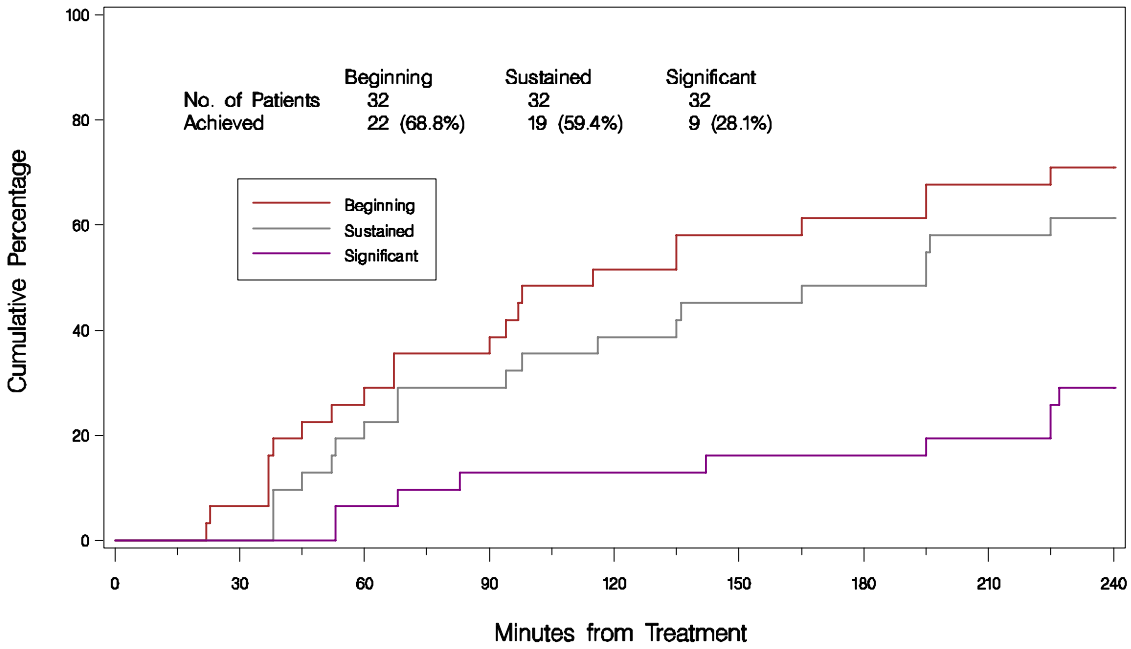
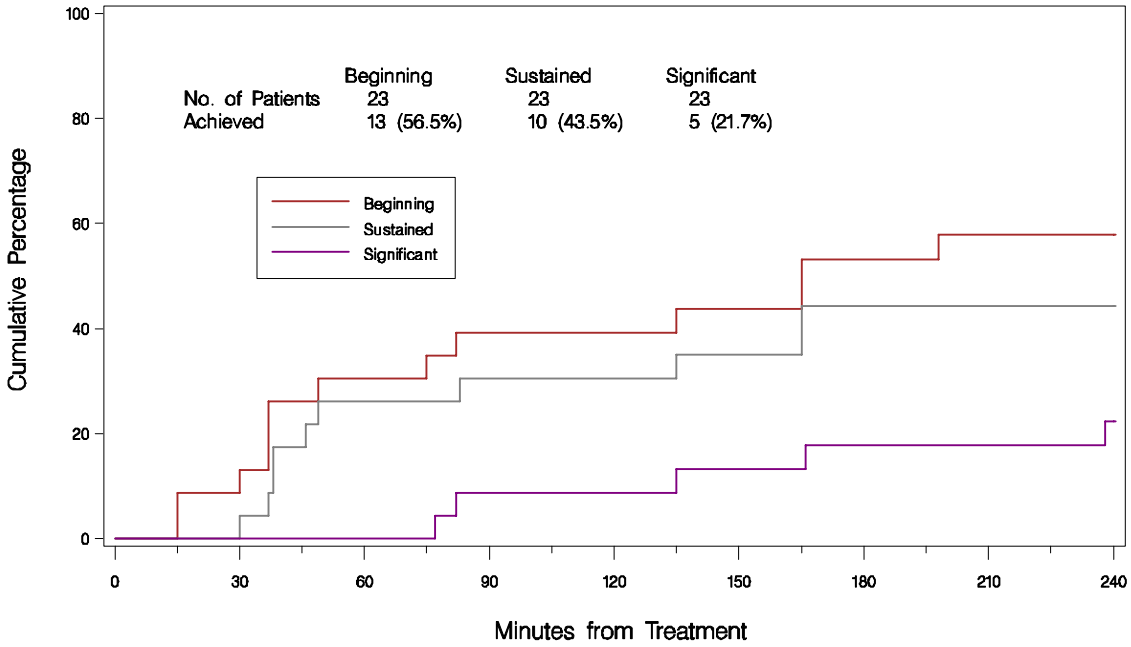


Figure 8. Time to Beginning of Improvement, Onset of Sustained Improvement, and Significant Improvement in Overall Response by Peripheral Attack Location for Placebo-Treated Patients, Integrated Phase 3 Analysis



In summary, ecallantide appears to provide early, sustained and clinically relevant treatment for symptoms of attacks at all anatomic locations.

3.4.3 Proportion of Patients who Required Medical Intervention, Including Open-Label Ecallantide

Reducing the need for medical intervention is key to providing therapeutic benefit. Patients who required medical intervention in EDEMA4 are presented in Table 16. Medical intervention was defined as emergency medications, including open-label administration of ecallantide (SUAC or as Dose B), new or increased doses of serotonin receptor subtype 3 (5-HT3) antagonists, opioids, anti-emetic medications, or C1-INH.

Fewer patients in the ecallantide group required medical intervention compared to the placebo group. For patients in the ecallantide group, 16 of 48 (33.3%) required medical intervention within 24 hours post-dose, compared with 24 of 48 patients (50.0%) in the placebo group. This difference was not statistically significant (P=0.106).

Patients who experienced severe upper airway compromise (SUAC) between 0 and 4 hours after receiving their initial dose of study drug were permitted an open-label dose of ecallantide 30 mg SC. For patients who initially received placebo, SUAC dose represented the first time they received ecallantide during the study; whereas for patients who initially

received ecallantide, SUAC dose represented the second dose of ecallantide administered for a treatment episode.

- Three of 48 patients who received placebo as their initial treatment were treated for SUAC. All SUAC doses were administered within approximately 1.75 hours after the administration of the initial dose.
- Additionally, 1 patient who received ecallantide as the initial treatment was administered a SUAC dose.

Dose B open-label treatment was permitted between 4 and 24 hours post-dose for no response, incomplete response, or relapse (Table 16).

- Of the 48 patients who received ecallantide as their initial treatment, 14 patients (29.2%) were treated with Dose B.
- Of the 48 patients who received placebo as their initial treatment, 20 patients (41.7%) were treated with Dose B. One of these 20 placebo-treated patients also received a SUAC dose. The characteristics of patients receiving Dose B are described in Table 16. Most Dose B was administered for failure to respond and was administered within the first 6 hours regardless of initial treatment assignment. Of particular however, a greater proportion of patients with laryngeal attacks treated initially with placebo required Dose B intervention. The majority of patients receiving Dose B experienced a treatment benefit as demonstrated by the change in MSCS score to better within 4 hours post-Dose B. Together these data support the need for initial treatment with ecallantide to resolve symptoms associated with an HAE attack and that a second dose may be required in in some patients, if initial response is not adequate.

Table 16. Patient Characteristics and Response to Treatment for Patients who Received a Dose B in EDEMA4

	Ecallantide (N=14) n/N (%)	**Placebo (N=20) n/N (%)**
Symptom complexes at baseline[a, b,c]		
Cutaneous	11/34 (32.4)	8/21 (38.1)
External head/neck	3/14 (21.4)	4/9 (44.4)
Genital/buttocks	2/6 (33.3)	1/5 (20.0)
Internal head/neck	1/8 (12.5)	8/13 (61.5)
GI/abdominal	4/18 (22.2)	9/27 (33.3)
Primary attack location[c]		
Abdominal	2/10 (20.0)	8/25 (32.0)
Laryngeal	1/8 (12.5)	5/7 (71.4)
Peripheral	11/30 (36.7)	6/15 (40.0)
Severity at the primary attack location[c]		
Moderate	6/32 (18.8)	17/40 (42.5)
Severe	8/16 (50.0)	2/7 (28.6)
Reason for receiving Dose B		
Incomplete response	3/14 (21.4)	5/20 (25.0)

Table 16. Patient Characteristics and Response to Treatment for Patients who Received a Dose B in EDEMA4

	Ecallantide (N=14) n/N (%)	Placebo (N=20) n/N (%)
Failure to respond	10/14 (71.4)	15/20 (75.0)
Relapse	1/14 (7.1)	0
Timing of Dose B after the initial dose		
<6 hours	11/14 (78.6)	17/20 (85.0)
6 to <12 hours	0	1/20 (5.0)
12 to <20 hours	0	1/20 (5.0)
≥ 20 hours	3/14 (21.4)	1/20 (5.0)
Change in MSCS score 4 hours after Dose B		
Better	9/14 (64.3)	10/20 (50.0)
Same	5/14 (35.7)	5/20 (25.0)
Worse	0	1/20 (5.0)
Not Evaluable	0	4[d]/20 (20.0)

[a] Patients may have had more than one symptom complex at baseline
[b] Includes symptom complexes that were mild in severity
[c] Not available for one placebo patient (413001)
[d] Includes Patient 413001 who did not have the 4-hour evaluation after the initial dose or after Dose B.

3.5 Treatment of Subsequent Attacks

As previously noted, HAE patients suffer recurrent acute attacks over prolonged time periods. Treatment for acute attacks must therefore maintain consistent effect when used to treat multiple attacks at various intervals.

The efficacy data for the use of ecallantide in treating multiple separate acute attacks of HAE comes primarily from the EDEMA3 open-label extension, EDEMA3-RD. In addition, given that patients could participate in more than one clinical study in the program, information across studies was evaluated to further understand retention of efficacy for intermitant use. An ongoing open-label extension study (DX-88/19) will provide additional data on acute, intermittent use of ecallantide.

Two methods were used to evaluate the retention of therapeutic effect after repeated use. The first was by analysis of data collected in EDEMA3-RD, and the second was evaluation of pooled data from EDEMA3-RD, EDEMA3-DB, and EDEMA4 (referred to as the Repeated-Treatment Analysis).

3.5.1 EDEMA3-RD

EDEMA3-RD was an open-label extension study to evaluate the effects of repeated ecallantide treatments in patients who experienced multiple acute HAE attacks. For each attack, patients received a 30 mg SC open-label dose of ecallantide. If the attack did not resolve completely, the patient could receive a second dose (Dose B) between 4 and 24 hours

after initial treatment as a blinded randomized (1:1) dose of either ecallantide 30 mg SC or placebo. Efficacy endpoints collected included the TOS at 4 hours post-dose, the change from baseline in MSCS score at 4 hours post-dose, and the time to significant improvement in overall response, the pre-specified primary and secondary endpoints of the study.

It should be noted that the treatment episode number presented below is based on EDEMA3 total exposure (including the double-blind part of EDEMA3) and therefore may differ from the ecallantide exposure number. The treatment episode 2 represents the first ecallantide exposure within EDEMA3 for those patients who were treated with placebo in the double-blind part of the study.

A total of 66 patients were included in the analysis population, including 48 patients who had participated in EDEMA3-DB and 18 new patients.

3.5.1.1 Summary of HAE Attacks

Efficacy results are reported for treatment episodes 1 through 6 (N ≥5 patients each). As summarized in Table 17, approximately half of the patients in this study were treated for 3 or fewer attacks (or 2 attacks in the repeat-dosing part); 1 patient was treated for a total of 14 attacks (or 13 attacks in the repeat-dosing part).

Table 17. Summary of HAE Attacks Treated in EDEMA3-RD (ITT Population)[a]

Treatment Episode	Total (N=66) n (%)
1	18 (27.3)[b]
2	51 (77.3)
3	30 (45.5)
4	21 (31.8)
5	11 (16.7)
6	9 (13.6)
7	3 (4.5)
8	1 (1.5)
9	3 (4.5)
10	1 (1.5)
11	2 (3.0)
12	1 (1.5)
13	1 (1.5)
14	1 (1.5)
Total	153[a]

Source: SCE Table 2.7.3.58
HAE=hereditary angioedema, RD=repeat-dose
[a] A total of 160 attacks were treated during the repeat-dosing part of EDEMA3; 153 attacks were included in the ITT population. Seven episodes could not be evaluated.
[b] Patients who participated in EDEMA3-DB were first counted in episode 2 of EDEMA3-RD.

3.5.1.2 Change from Baseline in MSCS Score at 4 Hours Post-Dose—EDEMA3-RD

The median and mean values for the change from baseline in MSCS score at 4 hours post-dose were consistently negative across multiple episodes, indicating an improvement in symptom burden (Table 18). As with TOS at 4 hours, fluctuations were observed in mean change in MSCS score at 4 hours, particularly in the higher episode categories.

Table 18. Change from Baseline in MSCS Score at 4 Hours Post-Dose Over Multiple Treatment Episodes: EDEMA3-RD

Treatment Episode	N	Median (IQR)	Mean (SD)
1	17	-1.0 (-1.5, -1.0)	-1.16 (0.87)
2	51	-1.0 (-1.8, -0.5)	-1.12 (0.90)
3	30	-1.0 (-2.0, -1.0)	-1.31 (0.87)
4	21	-2.0 (-2.0, -1.0)	-1.38 (0.79)
5	11	-1.0 (-1.3, 0.0)	-0.89 (0.72)
6	9	-1.0 (-1.0, -0.3)	-0.97 (0.75)

Source: SCE Table 2.7.3.60
IQR=interquartile range, MSCS=Mean Symptom Complex Severity, RD=repeat-dose, SD=standard deviation

Additional analyses were performed for the change from baseline in MSCS score at 4 hours using data from the 9 patients treated for episodes 2 through 6 in EDEMA3-RD (Table 19). Changes in MSCS score values were consistently negative across the treatment episodes.

Table 19. Change from Baseline in MSCS Score at 4 Hours Post-Dose: Patients Treated with Ecallantide for Episodes 2 Through 6 in EDEMA3-RD

Treatment Episode	N	Median (IQR)	Mean (SD)
2	9	-1.0 (-1.0, 0.0)	-0.80 (0.76)
3	9	-1.5 (-2.0, -1.0)	-1.56 (0.68)
4	9	-2.0 (-2.0, -2.0)	-1.78 (0.67)
5	9	-1.0 (-1.0, -0.5)	-0.87 (0.63)
6	9	-1.0 (-1.0, -0.3)	-0.87 (0.75)

Source: Supplemental Efficacy Analysis Table E44-7a
IQR=interquartile range, MSCS=Mean Symptom Complex Severity, RD=repeat-dose, SD=standard deviation

3.5.1.3 TOS at 4 Hours Post-Dose—EDEMA3-RD

The mean and median values for TOS at 4 hours post-dose across multiple treatment episodes are shown in Table 20. The TOS scores were consistently positive indicating the symptom improvement resulting from ecallantide treatment was maintained for at least 6 episodes. Fluctuations in individual patient responses and in group TOS from treatment episode to treatment episode occurred but were inconsistent.

Table 20. TOS at 4 Hours Post-Dose Over Multiple Treatment Episodes: EDEMA3-RD

Treatment Episode	N	Median (IQR)	Mean (SD)
1	18	68.8 (50, 100)	71.3 (28.85)
2	51	100.0 (50, 100)	73.3 (44.9)
3	30	100.0 (70, 100)	81.9 (28.52)
4	21	100.0 (38, 100)	81.2 (24.53)
5	11	100.0 (0, 100)	48.5 (68.5)
6	9	60.0 (50, 100)	60.4 (49.26)

Source: SCE Table 2.7.3.59
IQR=interquartile range, RD=repeat-dose, SD=standard deviation, TOS=Treatment Outcome Score

Nine patients were treated for 6 attacks (or for 5 attacks in the repeat-dosing part of EDEMA3). Additional TOS analyses were conducted using data from these 9 patients only. Median (IQR) and mean (SD) TOS by treatment episode in EDEMA3-RD (ie, episodes 2 though 6) are summarized in Table 21. Again TOS values were consistently positive across the treatment episodes.

Table 21. TOS at 4 Hours Post-Dose: Patients Treated with Ecallantide for Episodes 2 Through 6 in EDEMA3-RD

Treatment Episode	N	Median (IQR)	Mean (SD)
2	9	70.0 (50.0, 100.0)	54.1 (66.64)
3	9	100.0 (100.0, 100.0)	92.2 (15.64)
4	9	100.0 (100.0, 100.0)	94.4 (16.67)
5	9	100.0 (0.0, 100.0)	42.6 (74.12)
6	9	60.0 (50.0, 100.0)	60.4 (49.26)

Source: Supplemental Efficacy Analysis Table E44-7b
IQR=interquartile range, RD=repeat-dose, SD=standard deviation, TOS=Treatment Outcome Score

3.5.2 Repeated-Treatment Analysis

A Repeated-Treatment Analysis was also conducted to assess the retention of therapeutic effect after repeated use or exposure using data pooled from the EDEMA3-DB, EDEMA3-RD, and EDEMA4 studies. MSCS score and TOS were determined for patients who had data at both baseline and 4 hours by the total number of exposures to ecallantide, including episodes from EDEMA0, EDEMA1, EDEMA2, compassionate use, and rechallenge.

Retention of efficacy was summarized for patients who received ecallantide in each episode category using descriptive statistics. The Wilcoxon signed rank test was used to compare the change in MSCS score and TOS at 4 hours to zero for each category.

3.5.2.1 Study Drug Exposure: Repeated-Treatment Analysis

Exposure to ecallantide for patients in the Repeated-Treatment Analysis is summarized by number of treated episodes in Table 22. A total of 117 patients with a combined total of 244 treatment episodes were included in the Repeated-Treatment Analysis. The majority of patients (82.1%) received treatment for their first episode in EDEMA3 or EDEMA4; however, 19 patients (16.2%) received ecallantide for 5 or more treatment episodes.

Table 22. Summary of Repeat Exposure to Ecallantide: Repeated-Treatment Analysis

Patient Exposure to Ecallantide	Ecallantide (Number of Patients=117)
Number of patients	117
Number of episodes treated with ecallantide included in this analysis[a]	244
Cumulative number of episodes across all studies	
Mean (SD)	2.9 (3.73)
Median	1.0
Range	1, 23
Cumulative episode number[b], n (%)	
1	96 (82.1)
2	38 (32.5)
3	25 (21.4)
4	12 (10.3)
≥5	19 (16.2)[c]

Source: SCE Table 2.7.3.65
SD=standard deviation
[a] Summarizes the number of episodes treated with ecallantide in EDEMA4 or in EDEMA3 (double-blind or repeat-dose).
[b] Episodes with fewer than 12 patients were grouped in the analysis of repeat exposures.
[c] Represents 73 treated episodes.

3.5.2.2 Change from Baseline in MSCS Score at 4 Hours by Number of Treated Episodes—Repeated-Treatment Analysis

The median (IQR) for the actual change from baseline of the MSCS score at 4 hours ranged from -1.0 (-2.0, -1.0) to -1.0 (-1.3, 0.0) over 5 treatment episodes, and the mean (±SD) ranged from -1.30 (±0.80) to -0.86 (±0.74) (Table 23). Upon repeated treatments, for up to at least 5 treatment episodes, the actual change in MSCS score at 4 hours was consistently statistically-significantly different from zero (P≤0.008).

Table 23. Change from Baseline in MSCS Score at 4 Hours Post-Dose by Number of Treated Episodes: Repeated-Treatment Analysis

Episode Number[a]	N	Median (IQR)	Mean (SD)	P-Value[b]
1	92	-1.0 (-1.5, -0.5)	-1.05 (0.838)	<0.001
2	37	-1.0 (-1.5, -0.7)	-1.14 (0.840)	<0.001
3	25	-1.0 (-2.0, -1.0)	-1.30 (0.797)	<0.001
4	12	-1.0 (-1.3, 0.0)	-0.86 (0.741)	0.008
≥5	19	-1.0 (-1.3, 0.0)	-0.86 (0.746)	<0.001

Source: SCE Table 2.7.3.66
IQR=interquartile range, MSCS=Mean Symptom Complex Severity, SD=standard deviation
Note: No imputations were completed for symptom complexes that emerged after treatment or for medical intervention.
Note: Episodes with fewer than 12 patients were combined with subsequent episodes until the episode category contained at least 12 unique patients.
[a] The episode number accounts for ecallantide-treated episodes in EDEMA0, EDEMA1, EDEMA2, compassionate use, and rechallenge. The number of patients shown for each episode number reflects the number treated for that episode number in the EDEMA3-DB, EDEMA3-RD, and EDEMA4 studies.
[b] P-value from Wilcoxon signed rank test, comparing the raw change in MSCS score at 4 hours to 0.

3.5.2.3 TOS at 4 Hours by Number of Treated Episodes—Repeated-Treatment Analysis

The median (IQR) TOS at 4 hours ranged from 66.7 (50.0, 100.0) to 100.0 (53.1, 100.0) over 5 treatment episodes (Table 24). Upon repeated treatments, for up to at least 5 treatment episodes, the TOS at 4 hours was consistently statistically different from zero (P≤0.001). The mean (±SD) TOS at 4 hours ranged from 62.7 (±37.3) to 79.7 (±33.0) over 5 treatment episodes.

Table 24. TOS at 4 Hours Post-Dose by Number of Treated Episodes: Repeated-Treatment Analysis

	Ecallantide (Number of Treatment Episodes=244)			
Episode Number[a]	**Actual TOS**			
Episode Number[a]	N	Median (IQR)	Mean (SD)	P-Value[b]
1	93	66.7 (50.0, 100.0)	63.1 (41.08)	<0.001
2	37	100.0 (50.0, 100.0)	77.0 (31.19)	<0.001
3	25	83.3 (50.0, 100.0)	71.9 (37.72)	<0.001
4	12	100.0 (53.1, 100.0)	79.7 (32.98)	0.001
≥5	19	66.7 (50.0, 100.0)	62.7 (37.31)	<0.001

Source: SCE Table 2.7.3.67
IQR=interquartile range, MSCS=Mean Symptom Complex Severity, SD=standard deviation
Note: No imputations were completed for symptom complexes that emerged after treatment or for medical intervention.
Note: Episodes with fewer than 12 patients were combined with subsequent episodes until the episode category contained at least 12 unique patients.
[a] The episode number accounts for ecallantide-treated episodes in EDEMA0, EDEMA1, EDEMA2, compassionate use, and rechallenge. The number of patients shown for each episode number reflects the number treated for that episode number in the EDEMA3-DB, EDEMA3-RD, and EDEMA4 studies.
[b] P-value from Wilcoxon signed rank test, comparing TOS at 4 hours to 0.

3.6 Efficacy Conclusions

Results from the EDEMA clinical development program supports the conclusion that ecallantide provides rapid amelioration of symptoms of acute attacks of HAE that is durable and consistent (reproducible) across multiple attacks. These attributes address the unmet medical need in the HAE patient community.

Ecallantide is clinically superior to placebo for measures of symptom and symptom severity control and resolution by 4 hours, as assessed by the primary endpoints:

- Ecallantide demonstrated statistically-significant improvement compared to placebo in the primary endpoint of change from baseline in measures of symptom severity and burden (MSCS score and TOS) at 4 hours post-dose.
- Responder analyses by thresholds for clinically relevant change in MSCS score and TOS at 4 hours all demonstrated a significantly larger proportion of responders in the ecallantide group.
- Ecallantide provided symptom resolution for critical anatomic locations including laryngeal and abdominal attacks.

Ecallantide demonstrated a rapid onset of initial, sustained, and significant symptom relief as determined by analyses of the integrated phase 3 dataset, confirming earlier phase 2 data, including greater proportions of patients on ecallantide who experienced relief by these predetermined time to effect thresholds.

Ecallantide demonstrated durability of response through 24 hours by change in MSCS score and TOS at 24 hours, which was statistically superior to placebo, and by a larger proportion of patients in the ecallantide group who demonstrated a more durable response between 4 and 24 hours than did placebo group patients.

Ecallantide demonstrated consistent efficacy in the treatment of multiple attacks of HAE over extended time periods with sustained responses demonstrated in EDEMA3-RD study and in the Repeat Treatment Analysis.

4 EVIDENCE OF SAFETY

Safety data were pooled and analyzed according to 2 defined Analysis Populations as determined by patient group and study design (Table 25). Patient exposure, adverse events, SAEs, deaths, hypersensitivity, immunogenicity, laboratory evaluations, and vital signs are presented for both populations. Rechallenge administration, compassionate use, healthy subjects, and the CTS study data have not been integrated into these Analysis Populations.

Table 25. Analysis Populations for Safety

Analysis Population	Description	Completed Studies Included [a, b]	Treatment(s) Analyzed
All ecallantide-treated HAE patients	All patients treated with ecallantide in HAE studies (N=219). Provides an assessment of the overall safety profile of ecallantide in HAE patients. Includes open-label and double-blind treatments	EDEMA0, EDEMA1, EDEMA2, EDEMA3-DB, EDEMA3-RD, EDEMA4	Ecallantide
HAE patients treated in Phase 3 DB Studies	Patients in the 2 double-blind Phase 3 studies in the program (100 ecallantide-treated and 81 placebo-treated). Provides a direct comparison of ecallantide-treated HAE patients with those treated with placebo. Presented first throughout the document.	EDEMA3-DB, EDEMA4	Ecallantide and Placebo

DB=double-blind; HAE=hereditary angioedema; RD=repeatdose
[a] Within each Analysis Population, the TEAEs reported for patients who participated in multiple studies are only captured from the included studies.
[b] Note that rechallenge administration, compassionate use, healthy subjects, and CTS are not captured in these Populations.

The Analysis Population “All ecallantide-treated HAE patients” includes all patients treated with ecallantide in the 5 completed EDEMA studies (N=219). All TEAEs reported by a patient following any exposure to ecallantide are captured; thus, for patients who participated in multiple studies, all TEAEs reported at any time during the development program are included in the analysis.

The Analysis Population “HAE patients treated in Phase 3 DB Studies” includes patients from the 2 double-blind Phase 3 studies (EDEMA3-DB and EDEMA4) in which patients were treated for a single HAE attack with either ecallantide (N=100) or placebo (N=81), and allows for direct comparison to placebo. Patients who participated in both studies and who received placebo in one study and ecallantide in the other, or who were randomized to placebo and received open-label ecallantide in EDEMA4, are counted in both groups (Table 26). Only TEAEs reported during EDEMA3-DB or EDEMA4 were analyzed in this Analysis Population.

The "HAE patients treated in Phase 3 DB Studies" population is a subset of all ecallantide-treated HAE patients. Therefore, all AEs reported for patients who received ecallantide in the Phase 3 studies are also included in the Analysis Population “All ecallantide-treated HAE patients”. Caution should be exercised when comparing safety data from both Analysis Populations as the HAE patients treated in Phase 3 DB Studies received only 1 or 2 doses of

30 mg ecallantide SC whereas ecallantide-treated HAE patients were exposed to a variety of routes of administration, dosages, and number of exposures and included open-label exposure, which typically result in more observed AEs.

Table 26. Treatments for HAE patients in Phase 3 DB Studies

Treatments	Number of Patients
Placebo only in one or both double-blind studies	43
Ecallantide only in one or both double-blind studies	62
Placebo in one double-blind study and *ecallantide* in the other	19
Placebo in one or both double-blind studies and open-label *ecallantide* (SUAC or Dose B) in EDEMA4	19
Total Placebo [43+19+19]	**81**
Total Ecallantide [62+19+19]	**100**

4.1 Adverse Event Profile

4.1.1 Treatment-Emergent Adverse Events

This section summarizes TEAEs, defined as any event with onset date/time on or after administration of study drug in the first study in which a patient participated, through 28 days after the last dose for the last study within a given Analysis Population.

Adverse event tables display the number and percentage of patients with TEAEs organized by MedDRA preferred term. Patients reporting more than 1 TEAE with the same preferred term or SOC are counted only once for that preferred term. Analyses of TEAEs were conducted by overall incidence, Common Toxicity Criteria (CTC) grade (severity), relationship (data not shown), exposure (see Section 4.1.1.2, antibody status (see Section 4.2.4.3), and for administration-associated reactions (AARs) (see Section 4.1.3.1).

Table 27 presents the number of patients who experienced treatment-emergent adverse events (TEAEs), treatment-related TEAEs, treatment-emergent serious adverse events (TESAEs), and discontinuations due to TEAEs.

Table 27. TEAEs, TESAEs, Discontinuations Due to TEAEs, and Deaths

	All Ecallantide-Treated HAE Patients		HAE Patients Treated in Phase 3 DB Studies			
	Ecallantide (N=219)		Ecallantide (N=100)		Placebo (N=81)	
	n	(%)	n	(%)	n	(%)
One or more TEAEs	142	(64.8)	36	(36.0)	28	(34.6)
Treatment-related TEAEs [a]	78	(35.6)	15	(15.0)	11	(13.6)
One or more TESAEs	26	(11.9)	3	(3.0)	3	(3.7)
Treatment-related TESAEs [a]	7	(3.2)	0	-	0	-
Deaths	1	(0.3)	0	-	0	-
Withdrew from study due to a TEAE	2	(0.7)	0	-	0	-
Withdrew from study due to a TESAE	2	(0.7)	0	-	0	-
Withdrew from study due to a treatment-related TESAE [a]	1	(0.5)	0	-	0	-

Source: ISS Summary Tables 5.1.1, 5.1.2, 5.3.1, 5.3.2, 6.1.1, 6.1.2, 6.3.1, 6.3.2; ISS Summary Listings 1.1 and 1.2.
[a] Determined by the investigator to be possibly, probably, or definitely related to study drug, including AEs where the relationship was missing.

Among HAE patients treated in Phase 3 DB Studies, 36 ecallantide-treated patients (36.0%) experienced a TEAE, compared to 28 placebo-treated patients (34.6%). Fifteen (15.0%) and 11 (13.6%) ecallantide- and placebo-treated patients, respectively, experienced a treatment-related event. Three patients in each group experienced a TESAE. There were no treatment-related TESAEs, deaths, or withdrawals due to TEAEs in this Analysis Population.

Among all ecallantide-treated HAE patients, 142 patients (64.8%) experienced a TEAE; 78 patients (35.6%) experienced a treatment-related TEAE; 26 patients (11.9%) experienced a TESAE; and 7 patients (3.2%) experienced a treatment-related TESAE. One death occurred in a patient with pre-existing chronic renal failure. This patient began rejecting a transplanted kidney prior to treatment with ecallantide. The patient died of chronic renal failure subsequent to rejecting his renal transplant, 29 days following the last dose of ecallantide. The death was considered unrelated to study drug by the investigator (see Section 4.1.4). Two patients (0.9%) withdrew from study participation due to a TESAE; one of these 2 patients withdrew due to a treatment-related TESAE (an ecallantide-treated patient who experienced anaphylaxis).

Of note, there were 2 instances where HAE attacks were captured as adverse events:

- For the HAE attacks that were the presenting attack for treatment, the attack was captured (as an SAE) if the patient was hospitalized.
- During the follow-up period (up to 3 month post-dose), any HAE attack that the patient experienced that was not treated within the study, was captured as either an AE or an SAE

4.1.1.1 TEAEs in HAE patients Treated in Phase 3 DB Studies

COMMON TREATMENT-EMERGENT ADVERSE EVENTS

Overall, 36 of 100 ecallantide-treated patients (36.0%) and 28 of 81 placebo-treated patients (34.6%) experienced at least 1 TEAE. The most common (3%) TEAEs that occurred at a higher incidence in the ecallantide group were headache, nausea, diarrhea, pyrexia, and nasopharyngitis, as presented in Table 28.

Table 28. TEAEs in ≥3% of HAE Patients Treated in Phase 3 DB Studies

	Ecallantide (N=100)		Placebo (N=81)	
Preferred Term	**N**	**(%)**	**n**	**(%)**
Patients with ≥1 TEAE	36	(36.0)	28	(34.6)
Headache	8	(8.0)	6	(7.4)
Nausea	5	(5.0)	1	(1.2)
Diarrhea	4	(4.0)	3	(3.7)
Pyrexia	4	(4.0)	0	-
Heriditary Angioedema	3	(3.0)	4	(4.9)
Nasopharyngitis	3	(3.0)	0	-

Source: ISS Summary Table 5.1.2.
TEAE=treatment–emergent adverse event
Note: Percentages based on number of unique patients in the safety population for each treatment group.

In summary, the overall TEAE experience indicates that ecallantide is safe and well tolerated. The TEAE profile for ecallantide- and placebo-treated populations were similar, with headache, nausea, diarrhea, pyrexia, and nasopharyngitis being the most common events occurring at a slightly greater incidence in patients receiving ecallantide.

SEVERITY OF ADVERSE EVENTS

The severity of TEAEs was assessed using the CTC grading system, which ranges in grades, where 1 represents a mild TEAE, and 5 denotes death. Patients who had more than 1 level of severity for a given preferred term or SOC were counted only once in the most severe category for that preferred term or SOC.

Among HAE patients treated in Phase 3 DB studies, 20 ecallantide-treated patients (20.0%) and 14 placebo-treated patients (17.3%) experienced a TEAE that had a maximum severity of CTC Grade 1; 11 ecallantide-treated patients (11.0%) and 8 placebo-treated patients (9.9%) experienced a TEAE with a maximum CTC Grade 2 (moderate); and 5 ecallantide-treated patients (5.0%) and 6 placebo-treated patients (7.4%) experienced a TEAE with a maximum CTC Grade 3 (severe). No Grade 4 or 5 events were reported in the Phase 3 DB studies.

In summary, the majority of TEAEs were mild or moderate in severity, irrespective of whether the patient was treated with ecallantide or placebo.

ADVERSE EVENTS BY GENDER, AGE, AND RACE

Data were stratified by gender, age, and race. The numbers of pediatric, geriatric, and non-Caucasian patients were too small to make meaningful conclusions on TEAE incidences by age group or race. However, no outlier trends were observed. The data did not indicate an imbalance between male and female patients and TEAEs experienced with ecallantide use.

4.1.1.2 TEAEs in All Ecallantide-Treated HAE Patients

COMMON TEAES

Overall, 142 of 219 (64.8%) patients experienced at least 1 TEAE. The most common TEAEs were headache, nausea, fatigue, and diarrhea, as presented in Table 29.

Table 29. TEAEs in ≥3% of All Ecallantide-Treated HAE Patients

	Ecallantide (N=219)	
Preferred Term	**N**	**(%)**
Patients with ≥1 TEAE	142	(64.8)
Headache	36	(16.4)
Nausea	27	(12.3)
Fatigue	27	(12.3)
Diarrhea	24	(11.0)
Upper Respiratory Tract Infection	19	(8.7)
Hereditary Angioedema	18	(8.2)
Nasopharyngitis	13	(5.9)
Vomiting	12	(5.5)
Upper Abdominal Pain	11	(5.0)
Pyrexia	11	(5.0)
Pruritus	10	(4.6)
Rash	9	(4.1)
Sinusitis	9	(4.1)
Abdominal Pain	9	(4.1)
Prolonged Activated Partial Thromboplastin Time	9	(4.1)
Dizziness	8	(3.7)
Cough	8	(3.7)
Nasal Congestion	8	(3.7)
Pharyngolaryngeal Pain	8	(3.7)
Prolonged Thrombin Time	7	(3.2)
Dehydration	7	(3.2)
Dyspepsia	7	(3.2)

Source: ISS Summary Tables 5.1.1.
TEAE=treatment–emergent adverse event
Note: (1) Patients reporting more than 1 event with the same preferred term are counted only once for that preferred term
(2) Percentages based on number of unique patients among all ecallantide-treated HAE patients.

In summary, the overall TEAE experience among all ecallantide-treated HAE patients indicates that ecallantide is safe and well tolerated. Although the types of common adverse events are similar in both Analysis Populations, a higher incidence of common adverse

events was observed in all ecallantide-treated HAE patients, as expected due to greater number of exposures to ecallantide in this population.

SEVERITY OF ADVERSE EVENTS

Forty-seven of 219 patients (21.5%) experienced a TEAE that had a maximum severity of CTC Grade 1, 54 patients (24.7%) with a maximum CTC Grade 2, 33 patients (15.1%) with a maximum CTC Grade 3, and 7 patients (3.2%) with a maximum CTC Grade 4. One patient died, however the event was coded as life-threatening (Grade 4) with an outcome of death. No CTC Grade 5 event was reported.

Severe (Grade 3) TEAEs experienced by at least 2 patients included: HAE (8 patients, 3.7%), prolonged aPTT (3 patients, 1.4%), prolonged thrombin time (TT) (3 patients, 1.4%), abdominal pain (2 patients, 0.9%), vomiting (2 patients, 0.9%), and urticaria (2 patients, 0.9%).

Life-threatening (Grade 4) TEAEs reported by at least 1 patient included: HAE (3 patients, 1.4%), leukocytosis (1 patient, 0.5%), increased aspartate transaminase (AST) (1 patient, 0.5%), and chronic renal failure (1 patient, 0.5%). The outcome of this event was death, described in Section 4.1.4.

In addition, Patient 8805051099 experienced several events during the skin-testing and rechallenge procedure that were determined to be life-threatening (Grade 4) by the investigator (see Section 4.1.2.3). Dyax considered these events collectively as a serious, life-threatening anaphylactic reaction to ecallantide.

In summary, the majority of TEAEs were mild or moderate in severity in all ecallantide-treated HAE patients.

CUMULATIVE ADVERSE EVENTS BY EXPOSURE

Among all ecallantide-treated HAE patients, patients were categorized into exposure categories as described in Section 2.3.2.1. Each patient is represented in only one of the exposure categories. Fifty-two of 108 patients (48.1%), 60 of 80 patients (75.0%), 18 of 19 patients (94.7%), and 12 of 12 patients (100%) who were treated once, 2-4 times, 5-9 times, or >9 times, respectively, with ecallantide, experienced at least 1 TEAE.

As expected, there was an increase in the cumulative incidence of TEAEs as the number of doses given increased. That is, if a patient was treated more than 9 times with ecallantide, there was a greater chance of experiencing an event during at least 1 of the treatment episodes than for a patient treated only once with ecallantide. However, an increase in the number of doses was not associated with an increase in severity of events.

In the 12 patients who received more than 9 doses of ecallantide, the most commonly reported TEAEs were diarrhea (7 patients), nausea (6 patients), vomiting (6 patients), fatigue (5 patients), pyrexia (5 patients), headache (5 patients), and upper respiratory tract infection (4 patients). Overall, the cumulative incidence for these events increased with increasing number of doses received.

An anaphylactic reaction (considered related to study drug by the investigator) was experienced by 1 of the 12 patients (8.3%) who had received more than 9 doses of ecallantide and an anaphylactoid reaction (considered related to study drug by the investigator) was experienced by 1 of the 108 patients (0.9%) who had received 1 dose. A hypersensitivity reaction was experienced by 1 (0.9%) patient (considered unrelated to study drug by the investigator) who had received 1 dose. In addition, 2 patients (16.7%) experienced adverse drug reactions after receiving more than 9 doses of ecallantide.

In summary, a cumulative increase in TEAEs was observed as the number of doses given increased, although the adverse event profile did not alter. However this warranted further analysis to identify possible implications as outlined below.

ADVERSE EVENTS BY TREATMENT EPISODE

A post hoc analysis was completed to explore whether the percentage of patients who experienced one or more AEs in a given treatment episode increased as the number of episodes that the patients received treatment for increased. In this analysis, AEs reported by all 219 patients for the first treatment episode were collected. For subsequent episode numbers, AEs by episode were collected only for those patients who participated in all episodes up to and including a given episode number. For example, for the 90 patients who were treated for two episodes, the AEs reported for episode 1 and for episode 2 were collected separately; for the 61 patients who were treated for three episodes, the AEs reported for episode1, episode 2 and episode 3 were collected separately. This continued through the 14 patients who were treated for eight episodes. The number and percentage of patients reporting AEs by episode are presented in Table 30.

Two important observations come from this analysis. The first is that the number of patients reporting AEs in a given episode does not increase in a consistent manner across increasing episode numbers. In fact, the number of patients who experienced an AE is the greatest in the first exposure to ecallantide for patients who were treated more than once, regardless of how many more times they were treated.

The second observation is that the percentage of patients reporting an AE in the first exposure to ecallantide is the smallest when summarizing for the first exposure for the total population (N=219). Thus, more patients who went on to receive multiple treatments experienced at least one AE in their first exposure than did patients in the total population (and hence more patients who went on to receive multiple treatments experienced at least one AE than did patients who received only one treatment). This indicates that there was no selection bias against subsequent treatment based on experiencing AEs with the first treatment.

Table 30. Adverse Events by Treatment Episode

No. of Episodes Treated	N	Number (Percentage) of Patients Reporting 1 or More Adverse Events							
		Episode 1	Episode 2	Episode 3	Episode 4	Episode 5	Episode 6	Episode 7	Episode 8
1	219	122 (55.7)							
2	90	61 (67.8)	55 (61.1)						
3	61	43 (70.5)	38 (62.3)	37 (60.7)					
4	38	30 (78.9)	24 (63.2)	24 (63.2)	26 (68.4)				
5	29	25 (86.2)	18 (62.1)	20 (69.0)	22 (75.9)	14 (48.3)			
6	21	18 (85.7)	14 (66.7)	14 (66.7)	17 (81.0)	10 (47.6)	12 (57.1)		
7	16	15 (93.8)	11 (68.8)	11 (68.8)	13 (81.3)	7 (43.8)	10 (62.5)	10 (62.5)	
8	14	13 (92.9)	9 (64.3)	10 (71.4)	11 (78.6)	6 (42.9)	8 (57.1)	10 (71.4)	9 (64.3)

Source: Supplemental Safety Analysis Table 5.11.1
Note: Percentages are based on the number of unique patients treated for the respective number of episodes.

4.1.2 Serious Adverse Events

4.1.2.1 TESAEs in HAE Patients Treated in Phase 3 DB Studies

Three of 100 ecallantide-treated patients (3.0%) experienced a total of 3 TESAEs compared to 3 of 81 (3.7%) placebo-treated patients who experienced 3 TESAEs. All 3 TESAEs that occurred in the ecallantide group were HAE attacks that resulted in hospitalization, 1 of which was defined as moderate, and 2 which were defined as severe. All 3 were considered unrelated to treatment. Of the 3 TESAEs that occurred in the placebo group, 2 were HAE attacks that were defined as severe, and 1 was a hospitalization for an HAE attack of moderate severity. All 3 were considered unrelated to treatment. None of the TESAEs in HAE patients in Phase 3 DB Studies were considered life-threatening. Table 31 summarizes the incidence of TESAEs among HAE patients treated in Phase 3 DB Studies.

Table 31. TESAEs in HAE Patients Treated in Phase 3 DB Studies

	Ecallantide (N=100)		Placebo (N=81)	
Preferred Term	**n**	**(%)**	**n**	**(%)**
Patients with ≥1 TESAE	3	(3.0)	3	(3.7)
Hereditary Angioedema	3	(3.0)	2	(2.5)
Hospitalization	0	-	1	(1.2)

Source: ISS Summary Table 6.1.1 and 6.1.2. TESAE=treatment-emergent serious adverse event

4.1.2.2 TESAEs in All Ecallantide-Treated HAE Patients

Of the 219 ecallantide treated HAE patients, 26 (11.9%) experienced 1 or more TESAE. Of these 26 patients, 2 (0.9%) had TESAEs considered mild in severity, 6 (2.7%) were moderate, 13 (5.9%) were severe, and 5 (2.3%) were life-threatening. The TESAEs experienced by 7 patients were considered related to ecallantide treatment while the other 19 patients experienced unrelated TESAEs.

Fourteen of the 26 patients had an HAE attack that resulted in hospitalization and was classified as a TESAE (3 of these attacks were in ecallantide-treated patients in the double-blind studies, also accounted for in the analysis of HAE patients treated in Phase 3 DB Studies, refer to Section 4.1.2.1). One of these attacks was considered related to treatment while the other 13 were considered unrelated.

Other TESAEs that were considered related to ecallantide treatment included the following: adverse drug reaction in 2 patients, HAE attack in 1 patient, anaphylactoid reaction in 1 patient, pharyngeal edema in 1 patient, pancreatitis in 1 patient. In addition, Patient 8805051099 experienced several TESAEs, including an anaphylactic reaction during EDEMA3-RD study then several TESAEs during a rechallenge procedure (see Section 4.1.2.3 and patient narrative in Section 4.1.3.3) collectively determined to be anaphylaxis syndrome by Dyax. All of the TESAEs for this patient were CTC Grade 3 or 4 and were considered definitely related to study drug.

In summary, the most notable TESAEs were anaphylactic reaction (severe, definitely related), anaphylactoid reaction (severe, probably related), and 2 adverse drug reactions (1 severe, probably related, considered by Dyax to be a case of anaphylactic reaction; 1 moderate, definitely related, considered by Dyax to be a case of generalized hypersensitivity case). These are described and discussed further in Section 4.1.3.3 and Section 4.1.3.4.

Table 32 summarizes the incidence of TESAEs in all ecallantide-treated HAE patients.

Table 32. TESAEs in All Ecallantide-Treated HAE Patients (N=219)

Preferred Term	n	(%)
Patients with ≥1 TESAE	26	(11.9)
Hereditary Angioedema	14	(6.4)
Adverse Drug Reaction	2	(0.9)
Abdominal Pain	1	(0.5)
Colitis	1	(0.5)
Hematochezia	1	(0.5)
Pancreatitis	1	(0.5)
Anaphylactic Reaction	1	(0.5)
Anaphylactoid Reaction	1	(0.5)
Infectious Diarrhea	1	(0.5)
Concussion	1	(0.5)
Contusion	1	(0.5)
Jaw Fracture	1	(0.5)
Skin Laceration	1	(0.5)
ECG Signs of Myocardial Ischemia	1	(0.5)
Convulsion	1	(0.5)
Chronic Renal Failure	1	(0.5)

Source: ISS Summary Table 6.1.1 and 6.1.2.
ECG=electrocardiogram, TESAE=treatment-emergent serious adverse event
Note: Percentages based on number of unique patients in the safety population for each treatment group.

4.1.2.3 TESAEs in Other Populations

Serious adverse events experienced by healthy subjects, cardiothoracic surgery patients, those patients undergoing the rechallenge procedure, and patients treated under compassionate use are described below. There were no SAEs reported in healthy subject studies.

In the completed CTS Phase 2 study (patients received ≤30 mg, ≤60 mg, or ≤120 mg ecallantide, IV), 7 of 31 patients (22.6%) treated with ecallantide experienced 8 SAEs (pleural effusion, ventricular fibrillation, cerebrovascular accident, delirium tremens, ileus paralytic, skin necrosis at the site of the vein graft, and 2 patients had atrial fibrillation). One of 11 patients (9.1%) who received placebo experienced 1 SAE (hemorrhage). All of these SAEs were assessed by the investigator as not related to study drug.

Rechallenge testing was done on some patients who experienced potential hypersensitivity reactions. Therefore, only nine patients have undergone the skin test and rechallenge procedure. Two patients experienced multiple SAEs during the skin test and rechallenge procedure. For 1 patient, the 8 SAEs experienced during the skin test and rechallenge procedure were collectively determined to be anaphylaxis, while the SAEs experienced by the second patient were cough, nasal congestion, rhinnorrhea, sneezing and throat itchiness.

Qualified patients with a diagnosis of HAE who were unable to participate in an ongoing ecallantide clinical trial were eligible for compassionate use of ecallantide for treating acute attacks of HAE. Prophylactic treatment prior to scheduled surgery (eg, dental surgery) was also considered for compassionate use. Eight patients have been treated with ecallantide for compassionate use. There was 1 SAE reported, an event of abdominal pain that required hospitalization. The investigator considered the event unrelated to study drug.

4.1.3 Hypersensitivity

As hypersensitivity was reported in a few patients, Dyax performed a retrospective identification of TEAEs that might signal hypersensitivity. To capture potential hypersensitivity reactions to ecallantide, all adverse events reported during clinical development were evaluated in a systematic manner. However, it should be noted that retrospective identification of TEAEs that might signal hypersensitivity can be difficult in patients experiencing symptoms of acute attacks of HAE, since many of the symptoms (ie, swelling, rash, wheezing, laryngeal edema, hypotension) are also symptoms associated with hypersensitivity reactions.

For this evaluation the term administration-associated reaction (AAR) was used to capture all treatment-related TEAEs that occurred within 1 day of study drug administration. If the time of onset of a treatment-related TEAE was unknown, events that occurred on Study Day 2, up to 48 hours after study drug administration, were included to ensure the capture of all AARs. In addition, investigators were asked to identify and report any adverse events that they deemed to have a potential hypersensitivity component.

All AARs were reviewed and categorized as local or systemic. Local AARs included injection-site reaction, injection-site swelling, injection-site bruising, and injection-site pain; but may have also included erythema, paresthesia, pruritus, or wheal formation at the site of the SC injection. Local reactions did not extend beyond a small area of local skin or the venous access route.

Systemic AARs consisted of all treatment-related TEAEs that occurred on the day of study drug administration and were not classified as local. To ensure complete identification of all reactions potentially related to hypersensitivity, multiple preferred terms were reviewed, including 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. AARs identified by these terms are discussed individually. Records of patients who reported any events with these MedDRA preferred terms were reviewed.

For this analysis, anaphylaxis was defined as a severe, potentially serious, systemic immunologic reaction, rapid in onset, caused by antibody-mediated release (usually IgE) of vasoactive mediators from tissue mast cells and peripheral blood basophils. Prior sensitization or presence of antibodies that can cross-link on an effector cell surface are required [3]. 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.

4.1.3.1 Administration-Associated Reactions

AARs IN HAE PATIENTS TREATED IN PHASE 3 DB STUDIES

Among HAE patients treated in Phase 3 DB Studies, a total of 13 patients (13.0%) in the ecallantide group and 8 patients (9.9%) in the placebo group reported events categorized as AARs. Three patients (3.0%) in the ecallantide group and 1 patient (1.2%) in the placebo group reported local reactions. Eleven patients (11.0%) in the ecallantide group and 7 patients (8.6%) in the placebo group reported systemic reactions.

There were no reactions that were reported by the investigator as anaphylaxis, anaphylactoid reactions or adverse drug reactions. Three events (pruritus generalized, rash erythematous, and urticaria) were evaluated in this analysis as potential hypersensitivity reactions. Two of these events (generalized pruritus and urticaria) were reported in a single patient in the placebo group. The urticaria reported was a single lesion on the forehead. The third event, erythematous rash, was observed in a single patient in the ecallantide group and was not thought to be consistent with hypersensitivity.

In summary, there were no events in HAE patients treated in Phase 3 DB Studies that appeared to result from hypersensitivity to ecallantide. Milder symptoms suggestive of allergy (eg, rhinitis, pruritus, and urticaria) were not more common in ecallantide-treated patients than in placebo-treated patients. This Analysis Population was a relatively small population and is composed of patients with TEAE data collected following a small number of injections. The information is valuable however, because it allows for a direct comparison between ecallantide and placebo groups and highlights the difficulty of identifying the true relationship and small incidence of treatment-related hypersensitivity reactions in this orphan disease.

AARs IN ALL ECALLANTIDE-TREATED HAE PATIENTS

Among all ecallantide-treated HAE patients, a total of 65 patients (29.7%) reported treatment-related TEAEs within 1 day of receiving ecallantide. Those identified as potentially due to hypersensitivity are identified in Table 33.

Thirteen of 219 patients (5.9%) reported local reactions with the most common being injection-site pain (5 patients, 2.3%) followed by injection-site erythema, irritation, pruritus, and reaction, which were reported in 2 patients (0.9%) each. Most injection-site reactions were reported by patients following SC administration (10 of the 13 patients, 76.9%).

Fifty-nine patients (26.9%) reported events that could be considered as systemic AARs. Of these, 23 TEAEs were evaluated as potentially due to hypersensitivity.

Table 33. Number (%) of Patients with AARs Evaluated as Potentially Due to Hypersensitivity in All Ecallantide-Treated HAE Patients (N=219)

	n	(%)
Pruritus	5	(2.3)
Adverse Drug Reaction	2	(0.9)
Generalized Pruritus	2	(0.9)
Rhinitis Allergic	2	(0.9)
Throat Irritation	2	(0.9)
Localized Urticaria	2	(0.9)
Wheezing	2	(0.9)
Anaphylactic Reaction	1	(0.5)
Anaphylactoid Reaction	1	(0.5)
Flushing	1	(0.5)
Pharyngeal Edema	1	(0.5)
Rash Erythematous	1	(0.5)
Urticaria	1	(0.5)

Source: ISS Summary Table 5.9.1.

Upon review, many of the TEAEs reported by patients captured in Table 33 did not satisfy criteria for hypersensitivity or anaphylaxis reactions. These included 5 patients reporting pruritus or generalized pruritis, 1 patient reporting rash erythematous, 1 patient reporting 2 episodes of throat irritation, and 1 patient reporting wheezing. In addition, 1 AAR was reported with the MedDRA preferred term erythema. The lack of other simultaneous symptoms in these patients, the absence of reported changes in vital signs, and the observation that many of these patients went on to receive subsequent treatments with ecallantide without further TEAEs are strong arguments against any association with hypersensitivity.

4.1.3.2 Skin Test and Rechallenge Procedure

In order to determine causality in the occurrence of hypersensitivity reactions, a skin test and rechallenge procedure was developed to evaluate the sensitivity to ecallantide in patients who had previously experienced a hypersensitivity or hypersensitivity-like reaction in an EDEMA clinical study. A total of 9 patients participated, 8 of whom had a prior hypersensitivity reaction, and 1 who had allergic rhinitis and a family history of sensitivity to ecallantide. These procedures occurred in the absence of an HAE attack and were performed in 2 phases: a skin-testing phase and a test-dosing phase. In each phase, patients received escalating doses of ecallantide. If no reactions were observed in the skin-testing phase, patients could enter the test-dose phase. If a patient experienced a positive reaction to ecallantide at any time during the rechallenge, skin-testing and test-dosing rechallenge procedures ended.

Several of the patients with symptoms appearing to be due to hypersensitivity went through the skin test and rechallenge procedure (4 of 8 successfully; ie, not demonstrating hypersensitvity) and 2 of the 4 patients who successfully completed the skin test and rechallenge procedure received additional doses of ecallantide in clinical trials without experiencing further symptoms. This suggests that the original symptoms in these 4 patients may not have been treatment-related hypersensitivity.

Of the 4 patients who did experience a hypersensitivity reaction during the skin test and rechallenge, 1 patient (ear pruritus and rhinorrhea) was deemed eligible to participate in further clinical trials. However, when enrolled in EDEMA4 the patient was randomized to placebo treatment so no further information is available regarding further treatment with ecallantide. The remaining 3 patients who experienced a hypersensitivity reaction during the skin test and rechallenge procedure were not eligible to receive further doses of ecallantide; 1 patient experienced a reaction consistent with anaphylaxis; 1 patient experienced symptoms of cough, nasal congestion, rhinorrhea, sneezing, and throat itchiness; 1 patient experienced a positive skin reaction to intradermal injection of ecallantide. The skin test and rechallenge procedure was an effective diagnostic tool for determining causality and whether further treatment with ecallantide was suitable for patients who experience hypersensitivity reactions following dosing.

4.1.3.3 Anaphylaxis

For both anaphylactic and anaphylactoid reactions, the presenting signs and symptoms are similar and include urticaria and pruritus as well as more concerning and life-threatening manifestations of an allergic reaction, such as occurrence of hypotension and respiratory distress. However, similarities in the symptomatology of acute attacks of HAE and hypersensitivity reactions have made it difficult to differentiate between the two conditions when categorizing the data retrospectively. It should be noted that HAE symptoms are bradykinin mediated while any potential anaphylaxis reaction is histamine mediated.

After evaluation of all treatment-related TEAEs that occurred within 1 day of ecallantide administration, 13 patients were identified as having experienced symptoms of possible hypersensitivity, all of whom recovered without sequelae. Of these 13 patients, 4 were identified as having demonstrated symptoms and clinical courses suggestive of anaphylaxis syndrome (anaphylactoid or anaphylactic reactions) – see narratives below. Thus, the incidence of anaphylaxis syndrome is 4 of 317 subjects and patients (1.3%) in the ecallantide development program with over 800 doses administered. As expected with anaphylaxis, onset of symptoms occurred shortly following administration of ecallantide. For all but 1 of these patients, the initial hypersensitivity-like reaction occurred following multiple prior exposures to ecallantide. Three out of the 4 patients were confirmed positive for anti-ecallantide antibodies. There is insufficient data to determine if there is a correlation between the time of seroconversion and the reaction. Appendix B presents a tabular summary of the 4 cases of analphylaxis syndrome observed in the ecallantide program and criteria used for determining anaphylaxis.

A careful examination of predisposing factors revealed a history of allergy/atopy in most patients experiencing symptoms associated with anaphylaxis, which is a documented risk factor for anaphylaxis [29, 30]. Furthermore, while antibody positivity may be a permissive factor in determining the occurrence of a reaction, there was a lack of clear association to be found in the database, with the vast majority of antibody-positive patients not experiencing any form of reaction. Given this, a definitive clinical diagnosis of causality can only be made using a controlled rechallenge test.

The following are short narratives of the 4 patients identified as having experienced symptoms indicative of anaphylaxis syndrome. Tabular summary detail is provided in Appendix B.

Patient 8802003005 in EDEMA0 had a relevant medical history for allergies to pollen and cat dander. Five minutes following administration of the first dose of ecallantide (40 mg/m^2 IV), the patient experienced dysphagia, pruritus, urticaria, edema, dyspnea, abdominal pain, and enteritis. The patient was treated with SC adrenaline, IV polaramine, and IV hydrocortisone. She was positive for antibodies to ecallantide per the investigator (immunoblot), but negative on enzyme-linked immunosorbent assay (ELISA) for both non-IgE and IgE antibodies. The discrepancy between the antibody assay results was not reconciled. The patient did not attempt the rechallenge procedure. The SAE was coded as anaphylactoid reaction and the investigator reported the event as probably related to study drug. The event was reported by the investigator as having resolved without sequelae.

Patient 8805024097 in EDEMA2 had a relevant medical history of allergy to hornet stings. Medication history included Danazol 200 mg daily. The sixth dose of ecallantide (30 mg SC) was administered to treat an acute abdominal attack of HAE. Ten minutes post-dose, she reported itching and tingling of her palms and soles, which progressed to involve her buttock and scalp. The patient was given diphenhydramine. At that time, a few red blotches were noted on her face, along with mild erythema and a few small papules surrounding 1 of the 3 injection sites. Increased facial flushing and flushing of the neck was also noted. She experienced nausea, diaphoresis, dizziness and began feeling faint. The patient was given epinephrine, hydrocortisone, cetirizine and ranitidine. Her symptoms completely resolved within minutes of epinephrine administration. A tryptase level was obtained from a serum sample collected 4 hours and 12 minutes following the dose of ecallantide and was normal (2.7 ng/mL with the normal range <11.4 ng/mL). The patient was positive for non-IgE antibodies to ecallantide, with the first positive assay on a sample obtained immediately prior to the sixth dose; the 1 resulting in the AAR. The patient had one assay positive for IgE anti-ecallantide antibodies, the sample obtained 7 days following the AAR. Subsequently in EDEMA3, neutralizing antibodies to ecallantide were demonstrated in this patient. The patient did not demonstrate hypersensitivity in the rechallenge procedure, and went on to receive 11 additional doses of study drug with no AARs reported. The SAE was coded adverse drug reaction during study, and the investigator reported the event as probably related to study drug. Dyax categorized this event as “anaphylactic reaction” based on the clinical picture. The event was reported by the investigator as having resolved without sequelae.

Patient 8805051099 in EDEMA3-RD had a relevant medical history of asthma and allergies to penicillin, sunflower seeds, and blueberries. Following administration of the 17^{th} dose of ecallantide (30 mg SC), the patient experienced an anaphylactic reaction (pruritus, generalized erythema, and decreased blood pressure [decreased to 82/56 mmHg]). Her oxygen saturation was 90% (no baseline oxygen saturation levels were provided). The patient was treated with oral lorazepam, diphenhydramine, epinephrine, and supplemental oxygen. Within 1 hour of initial symptoms, oxygen saturation was 94%, blood pressure was 110/80 mmHg, and the pruritus had abated. Approximately 4 hours following the onset of the adverse events, the patient's tryptase level was 10.4 µg/L (normal range: 1.9-13.5 µg/L).

The patient had tested positive for IgE antibodies to *P pastoris* in assays obtained at multiple time points, the earliest was the sample obtained during the 28-day follow-up after the fourth exposure, approximately 2 years before the anaphylactic reaction. The patient did test positive for antibodies to ecallantide (non-IgE) intermittently at low titers prior to the AAR. The patient underwent the rechallenge procedure and did demonstrate hypersensitivity – positive skin test and anaphylactic reaction to partial dose following pretreatment with hydroxyzine and prednisone. She was treated with epinephrine and nebulized levalbuterol. Her tryptase levels were normal during the skin tests. The initial event was coded anaphylaxis reaction during the study, and the investigator reported the event as definitely related to study drug. Concomitant medications at the time of the event were Ativan (lorazepam), albuterol, Advair (fluticasone and salmeterol), Danocrine (danazol), Crestor (rosuvastatin), Effexor XR (venlafaxine), and Risperdal (risperidone). The individual symptoms that occurred during the rechallenge procedure were reported as individual SAEs, considered definitely related to ecallantide exposure and included: dyspnea, rash generalized, anxiety, pharyngeal edema, vomiting, diarrhea, urinary incontinence, and hypoxia. Although reported individually, Dyax considers these symptoms collectively to be one AAR of an anaphylactic reaction. The investigator reported the event resolved without sequelae.

Patient 401-103 in the Continuation Study (DX-88/19) received her fourth exposure to ecallantide (30 mg SC). Within minutes the patient reported pruritus and tingling of the tongue, followed by generalized pruritus. At this time the patient stated that she "was not feeling well." Site personnel noticed erythema on the left arm and neck of the patient, who stated that she was dizzy and nauseated. The patient received 0.3 mg epinephrine SC for a possible anaphylactic reaction. Following the epinephrine, the patient appeared confused and started vomiting. She was noted to be lethargic and positioned on her left side. A second dose of 0.3 mg epinephrine SC was administered 4 minutes after the initial dose of epinephrine along with 50 mg hydroxyzine IM. Blood pressure was 110/70 mmHg at this time. The patient was given solumedrol and IV fluids. Both symptoms of the acute event, as well as the initial cutaneous swelling improved. A tryptase level in a serum sample obtained 6 hours and 25 minutes following study drug administration was 30 ng/mL (normal range 210 ng/mL). At the time of the event, the patient was positive for both anti-ecallantide antibodies (electrochemiluminescence [ECL] assay, seroconversion noted at the 28-day follow-up for the second exposure) and for IgE anti-ecallantide antibodies (ELISA, seroconversion at the 7-day follow-up for the third exposure). The patient has not yet undergone the rechallenge procedure and has had no further exposure to ecallantide. This event has been coded as anaphylaxis and the investigator has indicated that it was definitely related to study drug.

4.1.3.4 Generalized Hypersensitivity Cases

Of the 13 patients identified as having experienced symptoms of possible hypersensitivity, 2 patients with the symptoms of pruritus and/or urticaria, suggestive of generalized hypersensitivity reactions, have been identified. Neither exhibited systemic cardiovascular, central nervous system, or respiratory symptoms suggestive of anaphylaxis, resulting in the separate classification of generalized hypersensitivity. Both patients had a history of allergies. In addition, both were positive for antibodies specific for ecallantide and *P*.

pastoris. Appendix B presents a tabular summary of the 2 cases of generalized hypersensitivity cases observed in the ecallantide program.

The following are short narratives of the 2 patients identified as having experienced symptoms indicative of generalized hypersensitivity.

Patient 8805054099 in EDEMA2 had a relevant medical history of asthma and allergic rhinitis. Medication history included danazol, venlafaxine, darvocet N, vitamin D, levothyroxine, loratadine, acetaminophen, hydroxizine, desonide cream, and clobetasol cream. Within 1 minute of completing the IV infusion of the sixth dose of ecallantide (10 mg/m^2 IV), the patient experienced headache, blurred vision, flushing, urticaria, pruritus, conjunctival injection, increased heart rate (172 bpm from his normal resting rate of approximately 120 beats per minute), and increased blood pressure (152/100 mmHg from a pre-dose 122/73 mmHg). The patient was treated with diphenhydramine for the event. The patient has consistently tested positive for non-IgE antibodies to ecallantide, with seroconversion first noted in the 7 day follow-up for the fifth exposure to ecallantide. Tryptase levels were not obtained during the AAR. Subsequent testing in EDEMA3 has demonstrated the presence of neutralizing antibodies to ecallantide. The patient had two samples test positive for IgE antibodies to *P pastoris*, the samples obtained at enrollment and the 7 day follow-up for the sixth exposure, the one resulting in the AAR. The patient did not demonstrate hypersensitivity to ecallantide in the rechallenge procedure, and went on to receive 16 additional doses with no AARs, except for a single episode of nausea following the seventh exposure to ecallantide (administered to treat an abdominal attack of HAE). The SAE was coded as adverse drug reaction during study and the investigator reported the event as definitely related to study drug. The event was reported by the investigator to be resolved without sequelae.

Patient 8814326002 in EDEMA3 had a relevant medical history of hay fever, allergies to penicillin, sulfa drugs, grapes, milk, and eggs. Twelve minutes after administration of the fourth dose of ecallantide (30 mg SC), the patient experienced pruritus and nausea (not SAEs). The symptoms resolved completely within 25 minutes without treatment. The patient also reported local site reactions following this dose of ecallantide. The patient was positive for non-IgE antibodies to ecallantide (seroconversion noted on the 7-day follow-up after the third exposure) and positive for IgE antibodies to *P pastoris* (seroconversion noted on the 7-day follow-up after the second exposure). The patient did demonstrate hypersensitivity in the rechallenge procedure; a wheal and flare following the intradermal portion of the rechallenge procedure. This patient has not received further exposure to ecallantide. The AAR was coded as pruritus generalized. The investigator reported the events as probably related to study drug.

4.1.4 Deaths

One death occurred in the HAE development program with ecallantide to date. One additional death was reported in the DX-88/16 cardiothoracic surgery study.

Patient 8804022001, a 47-year old white male with chronic renal failure, died while enrolled in EDEMA1. During this study, the patient received a single IV dose of ecallantide at 10 mg/m^2.

Concomitant medications were reported as cyclosporine (100 mg twice daily), mycophenolate mofetil (500 mg twice daily), prednisone (5 mg daily), valganciclovir HCl (450 mg 3 times/week), amlodipine besylate (5 mg daily), Glyburide (5 mg twice daily), and oxandrolone (2.5 mg twice daily).

His renal function, on enrollment in the study, showed a creatinine of 3.1 mg/dL (status post kidney transplant), and was, thus, ineligible for study entry. He also had a continued mild elevation of creatine phosphokinase that was felt secondary to the use of androgens (for HAE). The patient also had multiple other medical problems, including hyperlipidemia, surgery for hyperparathyroidism, asthma, and other conditions. After discussion between the principle investigator and Dyax, the patient was enrolled in the study.

The patient was treated for an acute peripheral (facial) attack of HAE. At the time of treatment, his creatinine had already risen to 6.2 mg/dL, and he was slowly rejecting his transplanted kidney. It was noted on an ECG that the patient had a significant amount of ventricular ectopy. This had also been noted on previous ECGs. His asthma related dyspnea was worsening and this was documented with pulmonary function tests performed on the day of admission. Chest pains or other cardiac symptoms were absent. The investigator was concerned that the patient may have developed, between the time he was screened and when he was treated for the episode of HAE, a cardiomyopathy, or, possibly a silent subendocardial myocardial infarction.

The patient died from renal failure secondary to rejecting his renal transplant 29 days after the administration of ecallantide. The event and outcome were assessed as unrelated to study medication by the investigator, who stated that the patient began rejecting the transplanted kidney prior to treatment with ecallantide.

Patient 101 died in the CTS study DX-88/16. During this study, the patient received a single IV low-dose dose of ecallantide (≤15 mg).

Concomitant medications at the time of this event were vasopressin, epinephrine, levophed, and nicardipine.

This 67-year-old male with a history of hypertension, obesity, non-insulin dependent diabetes, chronic atrial fibrillation, and recent non-Q-wave myocardial infarction was enrolled in CTS study DX-88/16 and underwent a coronary artery bypass graft. He required multiple vasopressors as well as insertion of an intra-aortic balloon pump (IABP) postoperatively; however, all vasopressors were weaned prior to his transfer to the ICU. Later that evening, vasopressin and nicardipine were briefly restarted, but were later

discontinued. The following morning (Study Day 2) the patient developed a peri-operative myocardial infarction. An attempt to wean the patient off of the IABP that morning failed, and he went into cardiogenic shock; he subsequently developed renal failure, shock liver, and respiratory failure with acidosis on the same day. Renal, pulmonary, and endocrinology consults were requested, and the patient was begun on renal dialysis (CVVHD) the following day. At the time of the initial SAE report, liver failure was continuing, he remained on CVVHD for his renal failure, was still on mechanical ventilation, and had no bowel sounds. The patient's condition subsequently worsened with persistent elevation of his white blood count and other abnormalities. He developed encephalopathy as part of the multisystem organ failure and continued to be unresponsive and to require vasopressors, mechanical ventilation, and hemodialysis. At the request of family members, all supportive measures were discontinued on Study Day 12. The patient died the same day of peri-operative myocardial infarction and multi-organ system failure, considered to be unrelated to study drug by the investigator.

4.2 Special Safety Evaluations

On the basis of nonclinical findings described in Section 2.3.1, suggestive of a cardiac etiology in rodent deaths, cardiovascular safety was comprehensively assessed in human subjects. In addition, regarding the mechanistic pathway, the potential for coagulation disorders was also extensively studied. This section summarizes the findings.

4.2.1 Cardiovascular Safety

In lieu of a thorough QTc study, it was agreed with the FDA that ECG monitoring in EDEMA4 would provide acceptable safety data for review of the effect of ecallantide on QT intervals.

As per protocol, a 12-lead ECG was performed on EDEMA4 patients at screening, enrollment (pre-dose), 2 hours post-dose, 4 hours post-dose, discharge, and at Follow-up Visit 1 (Study Day 7 [±2 days]). These timepoints cover the C_{max} window, which is 2 to 4 hours post-dose. If discharge occurred 1 hour or more after the 4-hour post-dose assessment, an ECG was to be repeated at discharge. In cases where the ECG could not be performed immediately before treatment due to severity of the patient's attack state, the ECG taken at screening was to be utilized as the baseline. ECG recordings were centrally read by readers blinded to patient treatment assignment. QRS complexes from Lead II of the ECG machine were to be used to calculate QTc, unless that lead had some artifact, whereupon one of the precordial leads was to be used. QT intervals were clinically corrected for heart rate using Bazett's formula (where $QTc = QT / \sqrt{RR}$).

The mean QTc value at baseline was 405.8 msec and 411.6 msec for ecallantide-treated (N=48) and placebo-treated patients (N=48), respectively. The mean change from baseline at 2 hours (N=46), 4 hours (N=46), and 7 days (N=33) in ecallantide-treated patients was 2.5 msec, 3.5 msec, and -6.2 msec, respectively. In placebo-treated patients, the mean change from baseline at 2 hours (N=42), 4 hours (N=40), and 7 days (N=26) was -0.3 msec, 2.0 msec, and -8.3 msec, respectively.

No patient in either treatment group had a QTc value of >500 msec during double-blind treatment, and 1 patient (placebo group, 7 days post-dose) had a QTc of 480 to 499 msec. Three patients in the ecallantide group and 4 patients in the placebo group had QTc values of 450 to 479 msec. During double-blind treatment, no patient in either group had a change in QTc value 60 msec. Two patients in the ecallantide group had changes in QTc values of 30 to 59 msec. Patients with at least one post-dose QTc value 450 msec or a change in QTc value of 30 to 59 msec are described in Appendix D.

No TEAEs related to cardiac function, QTc interval prolongation were reported nor were any ECG abnormalities. Around the Cmax window, no prolongation of QTc was observed at 2 to 4 hours post-dose in the ecallantide-treated group compared with placebo, and no outliers in QTc thresholds (>500 msec or change >60 msec) were observed. Overall, any changes in mean QTc values reflect intrinsic variability and are not clinically relevant.

Ecallantide is known to inhibit the formation of bradykinin, a potent vasodilator. Therefore, administration of ecallantide could theoretically result in an increase in blood pressure. However, mild reductions in blood pressure within the first 24 hours of dosing were observed in ecallantide-treated HAE patients that may be related to study drug. The changes were not clinically significant, and importantly, there was no clustering around a specific time point. Due to the nature of the HAE attack, many patients suffer from dehydration and extreme pain, requiring IV fluids, morphine, and other potent analgesics around the time of ecallantide administration. Together, these factors may have contributed to the reduction in blood pressure. In addition, as the severity of the HAE attack was reduced by the administration of ecallantide, patients may become less stressed, resulting in a reduction in blood pressure.

Regarding cardiovascular safety overall, mild reductions in blood pressure within the first 24 hours of dosing were observed in ecallantide-treated patients that may be related to study drug. However, the reductions were not clinically significant. No clinically-meaningful findings on ECG measurements, including the QTc interval were observed in HAE patients. Therefore, there have been no findings or observations in the clinical development program to suggest that the nonclinical findings in female rodents are applicable to humans.

4.2.2 Coagulation Safety

The effect of ecallantide on aPTT was measured because of its potential effect on the intrinsic coagulation pathway. No abnormal bleeding patterns were observed in the nonclinical safety program, suggesting that the extent of aPTT prolongation did not have apparent physiologic consequences.

A transient prolongation of aPTT of approximately 2-fold was observed in humans following IV dosing of ecallantide at doses in excess of 20 mg/m^2. No clinically significant prolongation in aPTT has been observed in healthy subjects and patients administered ecallantide SC at doses of 30 mg, and no safety signal with respect to bleeding or bruising phenomena has emerged in HAE patients.

Coagulation in the clinical setting was examined using aPTT, prothrombin time (PT), and thrombin time (TT). The threshold values for the coagulation analysis were: aPTT (>1.5 x upper limit of normal [ULN]); PT (>1.5 x ULN); and TT (>30 seconds). In HAE patients, elevations in aPTT reaching threshold were observed in 0 ecallantide-treated patients and 1 placebo-treated patient (1.4%), while elevations in TT reaching threshold were observed in 3 ecallantide-treated patients (3.2%) and 0 placebo-treated patients. On repeated dosing, there were no clinically-meaningful changes in either aPTT or PT for patients treated with ecallantide, suggesting that ecallantide has little or no inhibitory activity on plasmin, plasma factor XIIa, or plasma factor XIa at the 30 mg SC dose administered, and that this does not change with repeated exposures to ecallantide.

In summary, elevations of aPTT, PT, and TT were not associated with abnormal bleeding patterns or any signs of increased bleeding risk in clinical studies. In addition, given ecallantide's intermittent dosing for acute HAE attacks and its short half-life, any coagulation abnormalities observed are expected to be transient.

4.2.3 Hepatic and Renal Function

In nonclinical toxicology, there was no histologic evidence for liver or kidney as target organs for toxicity related to ecallantide.

In HAE patients, assessment of hepatic chemistry parameters showed elevations in alanine transaminase (ALT) reaching threshold (>2.5 x ULN) in 4 ecallantide-treated patients (4.1%) and 2 placebo-treated patients (2.6%). Elevations in AST reaching threshold (>2.5 x ULN) were observed in 2 ecallantide-treated patients (2.0%) and 0 placebo-treated patients. No elevations in total bilirubin reached threshold (>1.5 x ULN). Elevations in ALT and AST were most likely due to the severity of the HAE attack, or concomitant medication the patients were on or had taken recently, such as the anabolic steroids stanozolol or danazol. No patients reached the criteria set forth in Hy's Rule that measures a drug's capability for causing liver injury.

No elevations reaching threshold were observed for blood urea nitrogen (BUN) (>35 mg/dL) or creatinine (1.5 x ULN) in the assessment of renal chemistry parameters for HAE patients in Phase 3 DB Studies.

Together, clinical chemistries for hepatic and renal function do not reveal any clinically relevant findings.

4.2.4 Immunogenicity

As with all protein therapeutics, there is a potential for immunogenicity in humans. Immunogenicity was assessed using validated ELISA and ECL assays. The ECL assay, developed based on advice from the FDA, is considered more sensitive and quantitative than the ELISA that was initially used to assess antibody status. The EDEMA4 study exclusively utilized the ECL detection format, while all studies through EDEMA3 utilized the ELISA assay. However, EDEMA3 serum samples were retested using the ECL detection format. During retesting, the results of the ELISA and ECL correlated with one another, at both the

patient and sample levels. Data were analyzed by seroconversion status as well as by "positive at any time" status.

4.2.4.1 Antibody Seroconversion

The number of patients who seroconvert is determined as the number of patients whose pre-treatment assessment is either negative or missing, and have a positive post-treatment evaluation. In all ecallantide-treated HAE patients, 26 of 202 (12.9%) patients seroconverted to anti-ecallantide antibodies (all classes), 4 of 195 (2.1%) patients seroconverted to anti-ecallantide IgE antibodies, and 14 of 175 (8.0%) patients seroconverted to anti-*Pichia pastoris* IgE antibodies. For all antibodies, the incidence of seroconversion appears to increase with increasing exposure to ecallantide. In the clinical studies, anti-ecallantide and anti-ecallantide IgE antibody status did not correlate with the percentage of patients experiencing a TEAE, although a positive antibody response to *Pichia pastoris* may be associated with an increase in the percentage of patients that experience a TEAE (Sections 4.1.1.1 and 4.1.1.2).

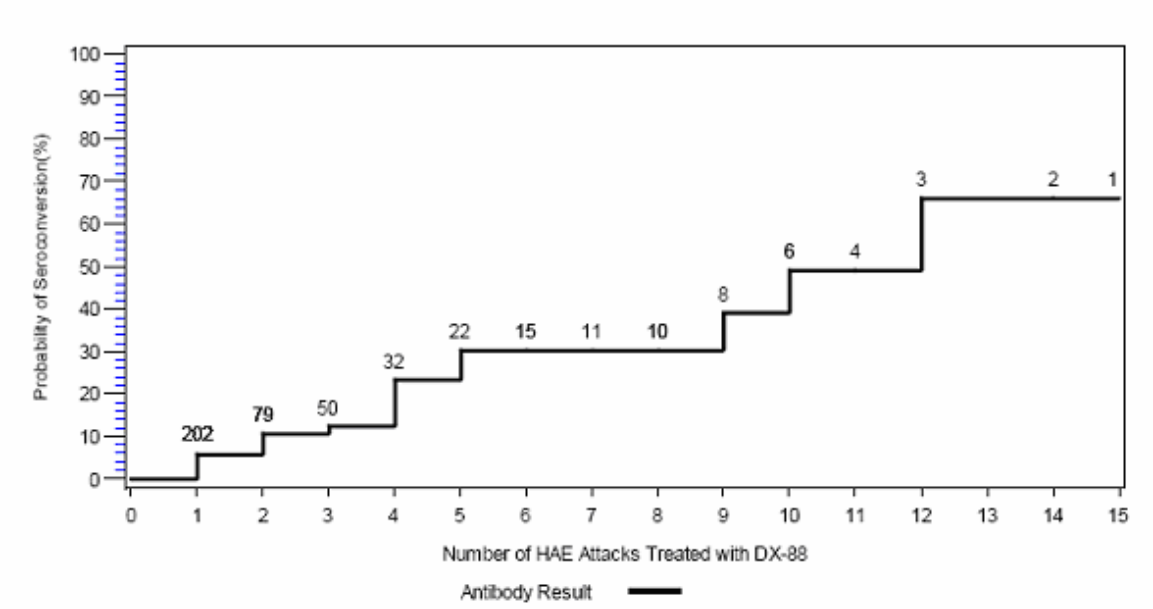
For patients treated in Phase 3 DB studies, the more sensitive and specific ECL format was utilized on 133 patients exposed to ecallantide. Of these, 119 had pre-dose and 1 or more post-dose samples analyzed, with positive detection in 10 patients yielding a seroconversion rate of 8.4%. Positive samples were assayed for neutralizing antibodies which were positive in 4 patients. In patients negative at baseline for neutralizing antibodies, 2 of 127 (1.6%) demonstrated servoconversion to neutralizing antibodies. There was no apparent correlation between safety and efficacy and presence of neutralizing antibodies.

In summary, the clinical data support the conclusion that ecallantide antibody status is generally not associated with the occurrence of adverse events, and that ecallantide is well tolerated in both antibody positive and negative patients.

4.2.4.2 Number of Attacks to Seroconversion

For anti-ecallantide (all classes) antibodies in all ecallantide-treated HAE patients, there is a steady increase in the probability of seroconversion with each treatment episode through the fifth treatment episode, with no further increases through the ninth treatment episode. Based on the curve, the probability of seroconverting to anti-ecallantide (all classes) antibodies through the eighth ecallantide-treated episode is estimated to be approximately 30% (Figure 9). There are too few patients who were treated for more than 8 HAE attacks to make any further conclusions.

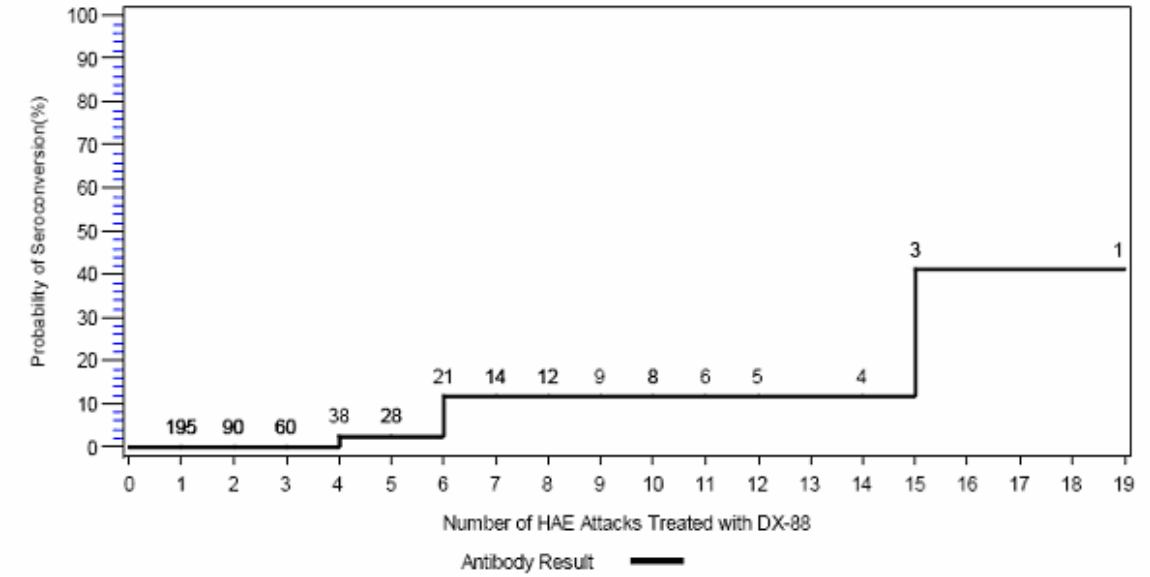
Figure 9. Number of Ecallantide-Treated HAE Attacks to Seroconversion: Anti-Ecallantide (All Classes) Antibodies in All Ecallantide-Treated HAE Patients



Note: The estimations of event probabilities are based on the Kaplan-Meier method.
The numbers provided on the curve represent the number of patients having at least the corresponding number of HAE attacks.

For anti-ecallantide IgE antibodies, there is no seroconversion observed until the fourth treatment episode. Although no further increase in the probability of seroconversion occurred from the sixth through the fourteenth treatment episodes, there are too few patients who were treated for more than 8 HAE attacks to make any further conclusions. Based on the curve, the probability of seroconverting to IgE anti-ecallantide antibodies through the 8th ecallantide-treated episode is estimated to be approximately 12% (Figure 10).

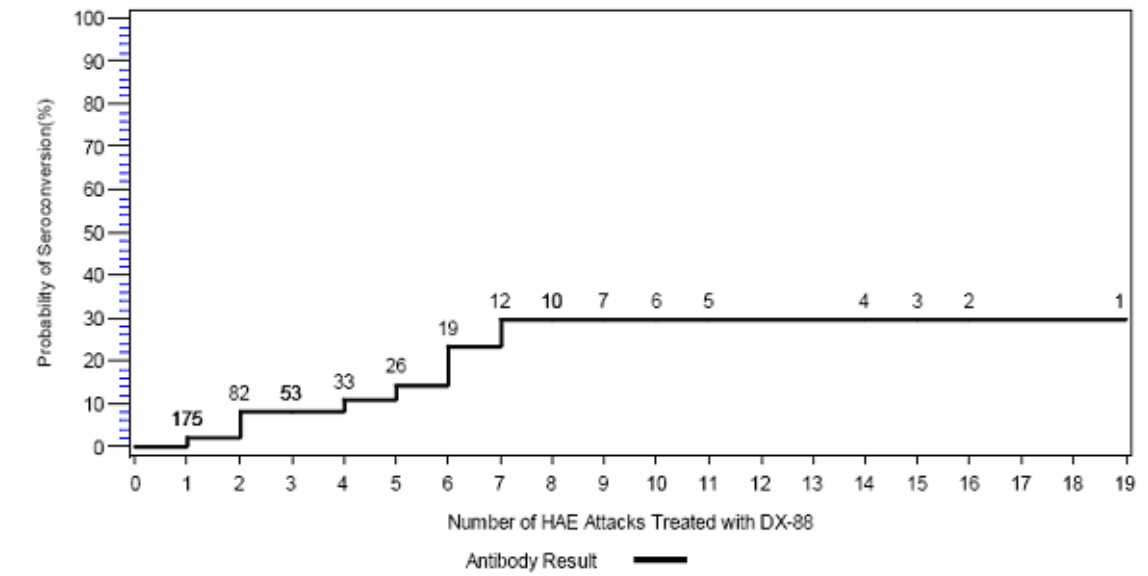
Figure 10. Number of Ecallantide-Treated HAE Attacks to Seroconversion: Anti-Ecallantide IgE Antibodies in All Ecallantide-Treated HAE Patients



Note: The estimations of event probabilities are based on the Kaplan-Meier method.
The numbers provided on the curve represent the number of patients having at least the corresponding number of HAE attacks.

For anti-*P pastoris* IgE antibodies, there is an increase in the probability of seroconversion through the seventh treatment episode. No further increase in the probability of seroconversion occurred after the seventh treatment episode. Based on the curve, the probability of seroconverting to IgE anti-*P pastoris* antibodies through the eighth ecallantide-treated episode is estimated to be approximately 30% (Figure 11). There are too few patients who were treated for more than 8 HAE attacks to make any further conclusions.

Figure 11. Number of Ecallantide-Treated HAE Attacks to Seroconversion: Anti-*P pastoris* IgE Antibodies in All Ecallantide-Treated HAE Patients



Note: The estimations of event probabilities are based on the Kaplan-Meier method.
The numbers provided on the curve represent the number of patients having at least the corresponding number of HAE attacks.

In summary, the rate of seroconversion for anti-ecallantide (all classes) antibodies, antiecallantide IgE antibodies, and anti-*P pastoris* antibodies is estimated to be approximately 30%, 12% and 30% through the eighth ecallantide-treated episode, respectively. It is difficult to estimate the rate of seroconversion after 8 HAE attacks.

4.2.4.3 Immunogenicity and Adverse Events

ADVERSE EVENTS BY ANTI-ECALLANTIDE (ALL CLASSES) ANTIBODY STATUS

Anti-ecallantide (all classes) antibody data are available on 216 patients. Thirty-six of 216 patients (16.7%) were positive for anti-ecallantide antibodies (this does not refer to seroconversion, but rather all patients that were ever positive for anti-ecallantide antibodies), while 180 of 216 (83.3%) were negative for anti-ecallantide antibodies. Of the 36 anti-ecallantide antibody-positive patients, 25 (69.4%) experienced a TEAE; of the 180 antibody-negative patients, 116 (64.4%) experienced a TEAE. Positive anti-ecallantide antibody status does not appear to increase the likelihood of patients experiencing TEAEs.

For the following TEAEs there was a difference of at least 7% between antibody positive and antibody negative patients who were treated with ecallantide: headache (positive 25.0%, negative 15.0%); upper respiratory tract infections (positive 22.2%, negative 6.1%); nausea (positive 19.4%, negative 11.1%); diarrhea (positive 16.7%, negative 9.4%); nasopharyngitis (positive 13.9%, negative 4.4%); and prolonged aPTT (positive 11.1%, negative 2.8%).

In summary, anti-ecallantide antibody positive status does not appear to increase the overall incidence of TEAEs although some TEAEs occurred in a higher percentage of antibody positive patients.

ADVERSE EVENTS BY ANTI-ECALLANTIDE IGE ANTIBODY STATUS

Patients were assessed for anti-ecallantide IgE antibody production routinely.

Anti-ecallantide IgE antibody data are available on 198 patients. Four of 198 patients (2.0%) were positive for anti-ecallantide IgE antibodies (includes all ecallantide-treated HAE patients ever positive for anti-ecallantide IgE), while 194 of 198 (98.0%) were negative for anti-ecallantide IgE antibodies. All 4 antibody-positive patients experienced a TEAE; of the 194 antibody-negative patients, 124 (63.9%) experienced a TEAE.

The following TEAEs were experienced by at least 2 anti-ecallantide IgE positive patients among all ecallantide-treated HAE patients: diarrhea (positive 100%, negative 9.3%); nausea (positive 75.0%, negative 11.9%); upper respiratory tract infections (positive 50.0%, negative 7.2%); dyspepsia (positive 50.0%, negative 2.6%); pharyngolaryngeal pain (positive 50.0%, negative 3.1%); adverse drug reaction (positive 50.0%, negative 0.0%); and injection site pruritus (positive 50.0%, negative 0.0%).

Of note, 2 patients that were anti-ecallantide IgE negative experienced anaphylactic and anphylactoid reactions (refer to Section 4.1.3.3, Patient 8802003005 and Patient 8805051099). Both events resolved without sequelae.

Although the number of anti-ecallantide IgE antibody positive patients is small in all ecallantide-treated HAE patients, a positive relationship between TEAEs referred to above and antibody status is present.

ADVERSE EVENTS BY ANTI-PICHIA PASTORIS IGE ANTIBODY STATUS

Anti-*P pastoris* IgE antibody status is available on 190 ecallantide-treated HAE patients. Twenty six (26) of 190 patients (13.7%) were positive for anti-*P pastoris* antibodies (includes all ecallantide-treated HAE patients ever positive for *P pastoris* IgE antibodies) while 164/190 (86.3%) were negative for anti-*P pastoris* antibodies. Of the 26 antibody-positive patients, 21 (80.8%) experienced a TEAE; of the 164 antibody-negative patients, 105 (64.0%) experienced a TEAE.

In summary, a positive antibody status to *P pastoris* may be associated with an increase in the percentage of patients who experience a TEAE, but no specifically related TEAEs could be defined, as the number of positive patients is too small to make a definite conclusion.

4.2.4.4 Immunogenicity and Efficacy

Subpopulation analyses by immunogenicity status were performed for change from baseline in MSCS score at 4 hours, TOS at 4 hours, and time to significant improvement in overall response using the following 4 subgroups: antibodies of any class specific to ecallantide; IgE antibodies specific to ecallantide; IgE antibodies specific to *P pastoris*, and neutralizing

antibodies to ecallantide. Immunogenicity status was considered positive if the patient ever tested positive for the specified antibody/antibodies at any point in the program. Only patients who tested positive for antibodies against ecallantide were tested for the presence of neutralizing antibodies. For the purpose of determining the percentage of patients with neutralizing antibodies, all patients who tested negative for antibodies against ecallantide were considered negative for neutralizing antibodies.

Analysis of the effects of the presence of antibodies to ecallantide or *P pastoris* within the integrated Analysis Population was difficult due to the small number of patients who tested positive: 8 ecallantide-treated patients were positive for antibodies against ecallantide, and 6 placebo-treated patients were positive. Similarly, 2 patients (ecallantide) tested positive for IgE against ecallantide, and 12 patients (7 ecallantide and 5 placebo) were positive for IgE specific for *P pastoris*. Seven patients in the ecallantide group who were positive for antibodies against ecallantide were also tested for neutralizing antibodies; 2 were positive. In general, no loss of response was observed with the presence of antibodies to ecallantide or *P pastoris*. Of special note, the 2 patients with neutralizing antibodies continued to respond to ecallantide in the time after dosing, as determined by TOS at 4 hours and by time to significant improvement in overall response in EDEMA3-RD and EDEMA4. In summary, antibody presence did not appear to affect efficacy.

4.3 Safety Conclusions

The safety of ecallantide was evaluated in a comprehensive clinical program and the results support the conclusion that ecallantide demonstrates a favorable safety profile. The most serious risks seen with ecallantide during the clinical development program were hypersensitivities and anaphylaxis, which resolved with treatment and without sequelae. The safety results represent an acceptable safety profile.

In the HAE program, 219 patients received over 600 doses, of whom approximately half (108, 49.3%) received a single dose of ecallantide. Eighty patients (36.5%) received 2 to 4 doses, 19 (8.7%) patients received 5 to 9 doses, and 12 (5.5%) patients received more than 9 doses.

For single and repeated treatment doses of 30 mg SC, ecallantide was well tolerated with the most common TEAEs for ecallantide-treated patients being headache, nausea, and fatigue. The majority of TEAEs were mild or moderate in severity and only 2 patients (0.7%) among all ecallantide-treated HAE patients withdrew because of adverse events.

Given the clincial presentation of HAE described in Section 1, key subpopulations, including age and gender, were examined for safety. No meaningful differences were seen in the TEAEs experienced between male and female patients among HAE patients treated in the Phase 3 double-blind studies. The number of pediatric, geriatric, and non-Caucasian patients among HAE patients treated in the Phase 3 double-blind studies is too small to make valid conclusions on TEAE incidences by age group or race.

The most serious reactions observed in the program were hypersensitivity and anaphylaxis and additional surveillance is warranted to determine the true incidence and potential risk factors.

- Among all ecallantide-treated HAE patients, the most notable TESAEs were anaphylactic reaction (severe, definitely related), anaphylactoid reaction (severe, probably related), and 2 adverse drug reactions (1 severe, probably related; 1 moderate, definitely related).

- After evaluation of all treatment-related TEAEs that occurred within one day of ecallantide administration, 4 patients were identified as having demonstrated symptoms and clinical courses suggestive of anaphylaxis syndrome (anaphylactoid or anaphylactic reactions). This yields an overall rate of 1.3% (4 of 317) of subjects exposed to ecallantide in the overall program with over 800 doses administered.

- The successful rechallenge and subsequent dosing suggests that some patients may be able to tolerate additional doses of ecallantide even after an apparent hypersensitivity reaction.

- Rechallenge appears to be an effective diagnostic tool for determining hypersenstitivity causality and whether further treatment with ecallantide is suitable for patients who experience hypersensitivity reactions following dosing.

As with all therapeutic proteins, there is a potential for immunogenicity in humans and the EDEMA program systematically tested for antibodies.

- For all antibodies (anti-ecallantide [all classes and IgE] and anti- *P pastoris* IgE), the incidence of seroconversion appears to increase with increasing exposure to ecallantide. However, anti-ecallantide and IgE anti-ecallantide antibody status does not appear to correlate with the occurrence of TEAEs.

- No specific treatment-related TEAEs could be defined since the number of positive patients is too small a patient population to make a definite conclusion. No apparent correlation was seen between presence and effects of neutralizing antibodies.

On the basis of preclinical findings suggestive of a cardiac etiology in rodent deaths, cardiovascular safety was comprehensively examined in human subjects. There have been no findings or observations in the clinical development program to suggest that nonclinical findings in rats are applicable to humans.

Regarding the mechanistic pathway, the potential for coagulation disorders was also extensively studied. Evaluation of coagulation parameters (aPTT, PT, and TT) revealed no clinically significant alterations at the 30 mg SC dose. In no case were there occurrences of hemorrhage or any other manifestation of bleeding.

5 BENEFIT RISK ASSESSMENT

5.1 Summary of Benefit-Risk

The treatment of HAE patients and the attacks they experience present an area of unmet medical need. Both patients and physicians seek a therapy that can quickly, reliably, consistently, and safely reverse or significantly reduce the symptoms of acute attacks of HAE. Such a therapy would minimize more severe consequences, such as severe upper airway compromise, as well as minimize the overall impact of the disease on the daily lives and functional abilities of HAE patients.

Ecallantide meets patient and physician needs and the data presented demonstrate with statistical significance and medical relevance, the effect of ecallantide in controlling presenting and emerging symptoms of an HAE attack. Administered by the SC route as a single dose, ecallantide acts quickly at all symptom sites to reduce symptom severity by 4 hours, provides sustained and durable relief through 24 hours, provides consistent relief over multiple attack intervention, and reduces the need for other medical intervention. Given that untreated HAE attacks can endure for up to 5 days, the onset of relief by 4 hours and achievement of durable relief by 24 hours reflect the clinical utility of intervention with ecallantide. In particular, the effect of ecallantide in resolving a life-threatening laryngeal attack and burdensome abdominal symptoms provides a meaningful and positive impact for a patient suffering an acute HAE attack. Medical experience suggests that early intervention in an HAE Attack may prevent progression to more serious attack manifestations.

Furthermore, through the comprehensive nonclinical and clinical development program, ecallantide has been demonstrated to be safe and well tolerated for use in HAE patients. The most notable risk is the potential for hypersensitivity, including anaphylaxis, which can be managed with standard available medical care including epinephrine, antihistamines, and corticosteroids. Predisposing factors to developing and the role, if any, of antibodies to ecallantide or to Pichia pastoris, remain to be elucidated. However, physicians have at their disposal the option of skin testing and rechallenge to confirm causality. While antibody formation is expected with a protein therapeutic, in the case of ecallantide, it appears to occur at a moderately low rate and does not seem to confer alteration in efficacy or safety risk. Ecallantide is intended for use only under the guidance and supervision of a healthcare professional for the treatment of acute attacks of HAE.

Ecallantide, a recombinant protein produced by fermentation in an albumin-free process, is not associated with risk of viral contamination. The 30 mg SC dose proposed for marketing represents an optimal selection based on toxicology, pharmacokinetics, efficacy, safety, and tolerability within the dose ranges assessed in nonclinical and clinical studies. Based on clinical data, in persistent attacks, an additional dose of 30 mg SC may be safely administered.

The benefit to HAE patients of using ecallantide outweighs the potential risks. Ecallantide is effective in ameliorating an HAE attack and in resolving symptoms, such as the life-threatening edema associated with laryngeal attacks, the pain, edema, and vomiting associated with abdominal attacks, and the pain and disability associated with a peripheral

attack. Use of ecallantide would also potentially alleviate the need for androgens and opiates. By inhibiting the kallikrein-kinin system, ecallantide provides upstream modulation of effectors involved in HAE attack symptoms and in particular works to reduce excess levels of endogenous bradykinin.

5.2 Risk Management Plan

During clinical studies, the most serious risk associated with use of ecallantide was hypersensitivity reactions, including anaphylaxis in 4 patients. These reactions occurred within 15 minutes after dosing and included pruritus, urticaria, allergic rhinitis, throat irritation, pharyngeal edema, flushing, wheezing, rhinorrhea, and occasionally, hypotension. All patients who experienced these reactions recovered spontaneously or with treatment (eg, antihistamines and epinephrine). This orphan disease is made up of a knowledgeable patient community treated by specialized physicians familiar with the disease as well as hypersensitivity reactions. The optimal use of ecallantide will be enhanced by undertaking certain risk-assessment and risk-minimization activities as part of commercial availability. Furthermore, while the safety database is recognized to be one of the largest available for this rare disease, it is still necessary to continue to collect safety information from "real-world" use of ecallantide in order to further quantify potentially serious risks.

In order to further strengthen what it considers to already be a favorable benefit / risk analysis, Dyax proposes a post-marketing risk management plan with the overall goals of, in the short term, ensuring the safe use of ecallantide and in the longer term, developing methods to identify patients susceptible to anaphylaxis. Tools employed to meet these goals will be focused on the following:

- Expanded surveillance for hypersensitivity to further assess frequency and potential risk factors; and
- Effectiveness of a skin-testing and rechallenge procedure to determine drug-related causality in minimizing subsequent risk of severe hypersensitivity reactions including anaphylaxis.

Consequently, with regard to overall risk management, a number of specific tools and data-collection approaches are intended in order to ensure safe use and minimize risk of anaphylaxis:

- Dyax will develop and provide relevant educational materials to communicate risk and safe use of the product for physicians and patients.
- Second, an exclusive distribution channel (single specialty pharmacy and central intake hub) will be employed to ensure that physicians and patients have access to treatment and educational reminders. The channel hub will also facilitate the dissemination of educational materials and the implementation of risk assessment and management tools, as well as ensure that for those patients who experience a hypersensitivity reaction after receiving ecallantide, a rechallenge procedure is available and that subsequent doses of ecallantide will not be dispensed from the centralized pharmacy until causality is resolved.

- Third, a comprehensive pharmacovigilance system will be used to monitor and report overall safety and to capture reports and follow up for the AEs of special interest (expanded surveillance), namely, hypersensitivity-type reactions including anaphylaxis.
- Fourth, a comprehensive Registry for HAE patients will be established. The specifics of Registry design are still under development, but will include capture of key demographic and outcome information such as age, race, gender, HAE history (including attack rate and severity), treatment received and outcome from such treatment (including safety and efficacy assessments), and treatment follow-up (including antibody testing, skin testing and rechallenge), when used. The data collected will be analyzed to determine the frequency of occurrence and, if possible, identify characteristics for those patients at risk of anaphylaxis following exposure to ecallantide.

6 CONCLUSIONS

HAE is a serious, life-threatening, debilitating disease for which there is no FDA-approved treatment for managing an acute attack. Treatments currently used in an attempt to manage symptoms of acute attacks are not effective.

Ecallantide is effective in ameliorating an HAE attack and in resolving symptoms such as the life-threatening edema associated with laryngeal attacks, the pain, edema, and vomiting associated with abdominal attacks, and the pain and disability associated with a peripheral attack. Use of ecallantide would also potentially alleviate the need for other interventions including androgens and opiates. The adverse events associated with the use of ecallantide are generally mild and do not require treatment. In the event of a serious hypersensitivity reaction, which will occur within the first hour, standard treatment can be administered to manage a positive outcome. A comprehensive post marketing program will be employed to facilitate safe use of the product, communicate important use and risk information and continue collection of important safety information.

More than 219 HAE patients have received over 600 doses which represents a thorough, complete, and comprehensive effort for this orphan disease population.

In summary, ecallantide is an effective and safe treatment needed by patients who suffer from acute attacks of HAE.

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8 APPENDICES

Appendix A Patient Reported Outcome Assessments

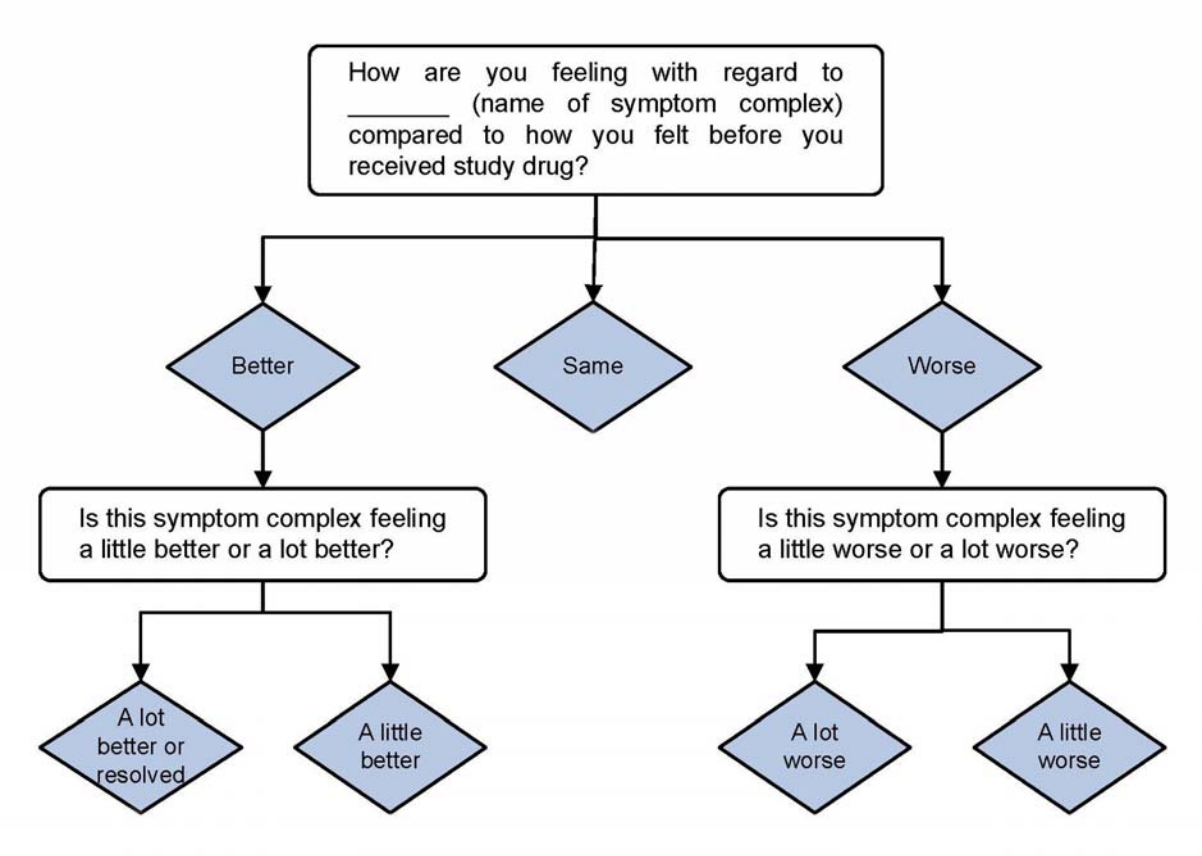
Symptom Complexes Evaluated in the TOS and MSCS Score

INTERNAL HEAD/NECK	STOMACH/ GI	GENITAL/ BUTTOCKS	EXTERNAL HEAD/NECK	CUTANEOUS
MOUTH/LIPS/ THROAT	**STOMACH**	**PUBIC AREA/ BUTTOCKS**	**FACE/NECK**	**EXTERNAL ARMS/LEGS/ BACK/CHEST**
Areas: Lip, Palate, Tongue, Mouth, Throat, Larynx	***Areas:*** Stomach, Intestines, Bowel	***Areas:*** Genitals, Buttocks, Testicles, Scrotum, Labia, Groin, Private Parts	***Areas:*** Face, Ear, Nose, Jaw, Cheek, Chin, Forehead, Eye, Neck	***Areas:*** Chest, Back, Shoulder, Arm, Hand, Finger, Hip, Leg, Ankle, Foot, Toe
Signs or Symptoms: swelling or tightening, pain, soreness, aching, choking or tingling, hoarseness, altered speech, difficulty breathing, difficulty swallowing, burning or thirst	***Signs or Symptoms:*** swelling or pressure, pain, aching, tenderness, hardness or bloating, nausea or vomiting, constipation or diarrhea, urge to use the bathroom, redness, rash, or itching	***Signs or Symptoms:*** swelling, pain, warm sensation, redness, rash, or itching	***Signs or Symptoms:*** swelling, pain, redness, rash, itching	***Signs or Symptoms:*** pain or aching, swelling or hardness, feeling of pulsation, redness, rash, itching

Severity Assessment Evaluated in the TOS and MSCS Score

Mild	Moderate	Severe
• When your symptoms are noticeable but they do not affect your activities of daily living.	• When your symptoms affect your activities of daily living. • Seeking doctor's assistance or treatment is highly desirable.	• When your symptoms prevent you from performing your activities of daily living. • Seeking doctor's assistance and treatment is required.
Example	***Example***	***Example***
Hand is swollen but you can still hold a pencil or grip a utensil.	Hands are swollen and you cannot button your shirt or your feet are swollen and wearing shoes is uncomfortable.	Your throat is swollen and you are having difficulty breathing or your lips are swollen and you cannot eat.

Response Assessment Evaluated in the TOS



Responses were rated relative to baseline (immediately prior to dosing) and were assigned the following scores:

100 = Significant improvement: Symptom complex is "a lot better or resolved" (eg, patient reports to site with severe abdominal symptoms and is then able to eat, patient reports to site with hand swelling that restricts movement and is then able to grip a pencil, or patient reports to site with severe laryngeal symptoms and is then able to eat or drink).

50 = Improvement: Symptom complex is "a little better" (eg, patient reports to site doubled over with severe abdominal discomfort and then is able to stand upright or walk, patient reports to site with hand swelling that restricts movement and is then able to bend fingers, or patient reports to site with severe laryngeal symptoms and is then able to swallow).

0 = Same: Symptom complex is unchanged (eg, patient's attack has not gotten any more or less comfortable and patient feels the symptoms are the same as when he reported to the site).

(-50) = Worsening: Symptom complex is "a little worse" (eg, patient reports to site with abdominal cramping and bloating and starts to feel nauseous or in pain, patient reports to site with hand swelling that restricts movement and then notices swelling has spread to wrist, or patient reports to site with throat tingling and tongue swelling and then experiences altered speech).

(-100) = Significant worsening: Symptom complex is "a lot worse" (eg, patient reports to the site with abdominal cramping and bloating and then begins to feel severely nauseous or vomits or is doubled over with severe discomfort and unable to stand upright, patient reports to site with hand swelling that restricts movement and then notices swelling has spread to wrist and becomes tight and very uncomfortable, or patient reports to site with throat tingling and tongue swelling and then experiences shortness of breath).

Formula for Calculating MSCS Score

The MSCS score is calculated for each patient at baseline, 4 hours, and 24 hours. The MSCS score is the arithmetic mean of the individual symptom complex severity assessments (Normal=0 [not available at baseline], Mild=1, Moderate= 2, Severe=3).

$$\text{MSCS score} = \frac{\Sigma \text{ symptom complex severity assessment}}{\text{number of symptom complexes}}$$

Imputation for Emerging Symptoms

EDEMA4 MSCS score calculation scheme
No baseline severity is available for emerging symptoms. Calculation of MSCS score at baseline will not account for emerging symptoms (ie, if only 2 symptoms at baseline, MSCS score will average the severity of only these 2 symptoms). Severity is available for emerging symptoms at 4 hours. Calculation of MSCS score at 4 hours will account for emerging symptoms (ie, if a third symptom appears after t=0, MSCS score will average the severity of 3 symptoms).

EDEMA3 MSCS score calculation scheme
A baseline value of 0 (= normal) is assigned for emerging symptoms.

Imputation for Medical Intervention

EDEMA4 MSCS score calculation scheme
Patients who received open-label ecallantide for SUAC did not have an MSCS score at 4 hours post-dose (ie, dosing with blinded study drug); therefore, they were not included in the analyses of these endpoints at 4 hours.

EDEMA3 MSCS score calculation scheme
The occurrence of a medical intervention affected the MSCS score calculation as follows:

- Assignment of a severity assessment of “severe” at 4 and 24 hours.
  - Medical interventions that were clearly directed to specific symptom complex(es) only affected that specific symptom complex (eg, anti-nausea medications taken by a patient’s reporting GI/abdominal and cutaneous symptom complexes would lead to an response assessment of “severe” for GI/abdominal but would not affect cutaneous severity assessment).

- Medical interventions that were not clearly directed to specific symptom complex(es) affected all symptom complexes.

The occurrence of open-label treatment with ecallantide for SUAC affected the MSCS score calculation as follows:

- Assignment of a severity assessment of "severe" at 4 and 24 hours.

Formula for Calculating TOS

The TOS is a composite score that is calculated using the following components:

Symptom complex identification: Internal Head/Neck, Stomach/GI, Genital/Buttocks, External Head/Neck, or Cutaneous.

Baseline Symptom Complex Severity Assessment – "Severe" with a score of 3, "Moderate" with a score of 2, and "Mild" with a score of 1.

Response assessment of each symptom complex after dosing – "Significant Improvement" with a score of 100, "Improvement" with a score of 50, "Same" with a score of 0, "Worsening" with a score of -50 and "Significant Worsening" with a score of -100.

The TOS is calculated by taking the sum of individual symptom complex response assessments multiplied by the symptom complex severity assessment at baseline, divided by the sum of all individual symptom complex severity assessments as presented in the following formula:

$$TOS = \frac{\Sigma(\text{symptom complex response assessment score } \mathbf{x} \text{ baseline severity assessment})}{\Sigma \text{ baseline symptom complex severity assessment}}$$

Imputation for Emerging Symptoms

EDEMA4 TOS calculation scheme
Severity used for TOS weighting is the severity provided by the patient the first time they identify the symptom as part of their attack. Outcome score is the one reported by the patient at 4 hours.

EDEMA3 TOS calculation scheme
Emerging symptom complex(es) are weighted according to their peak severity assessment.
Emerging symptom complex(es) that are still present at 4 and/or 24 hours are assigned a response assessment of "significant worsening" (= -100).
Emerging symptom complex(es) that are no longer present at 4 and/or 24 hours are assigned an assessment of "same".

Imputation for Medical Intervention

EDEMA4 TOS calculation scheme

Patients who received open-label ecallantide for SUAC did not have TOS at 4 hours post-dose (ie, dosing with blinded study drug); therefore, they were not included in the analyses of these endpoints at 4 hours.

EDEMA3 TOS calculation scheme

The receipt of medical intervention during the 4 hours post-dose affected the TOS calculation as follows:

Symptom Complex Response Assessments: The response assessment was classified as "significant worsening" at 4 and/or 24 hours.

- Medical interventions that were clearly directed to specific symptom complex(es) only affected that specific symptom complex response (eg, anti-nausea medications taken by a patient reporting GI/abdominal and cutaneous symptom complexes would have led to a response assessment of "significant worsening" for GI/abdominal but would not have affected the cutaneous response assessment).
- Medical interventions that were not clearly directed to specific symptom complex(es) affected all symptom complexes.

If a patient was treated with open-label ecallantide for SUAC, the response assessment was classified as "significant worsening" at 4 and/or 24 hours for the TOS calculation.

Appendix B Tabular Summary of Anaphylactoid and Generalized Hypersensitivity Reactions and Anaphylaxis Diagnostic Criteria

Table 34. Summary of Anaphylactoid Reactions

Patient	Symptoms	Dose	Time to Onset	Treatment Required	Skin Test Results	Rechallenge Dose	Antibody Status	Meets NIAID Criteria for Anaphylaxis [33]
880200305	Dysphagia, pruritus, urticaria, edema, dyspnea, abdominal pain, enteritis No hypotension	1st dose	5 mins	Adrenaline, hydrocortisone, Antihistamine (polarmine)	Rechallenge not done	Rechallenge not done	Antibody status at dosing + non-IgE and IgE to DX-88 per investigator (immunoblot), both negative in ELISA	Yes
8805051099	pruritus, generalized erythema, and a ↓BP from 108/60 mmHg to 82/56 mmHg	17th dose	12 mins	Epinephrine, benadryl, lorazepam, oxygen	positive skin reaction (wheal and flare)	7 minutes after 1mg SC dosing, the patient experienced AEs of dyspnea, generalized rash, anxiety, pharyngeal edema, vomiting, diarrhea, urinary incontinence, and hypoxia.	Antibody status at dosing Positive for IgE antibodies to P pastoris. Earliest obtained approx. 2 yrs before the anaphylactic reaction Tested positive for antibodies to ecallantide (non-IgE) at low titers prior reaction	Yes
8805024097	pruritus, tingling, papular rash, flushing, nausea, dizziness, diaphoresis and a drop in BP (102/67mm/Hg to 87/60 mmHg)	6th dose	10 mins	diphenhydramine, epinephrine, hydrocortisone, cetirizine, and ranitidine,	Positive skin reaction (wheal and flare) but Investigator determined it likely to be an irritation reaction	No reaction	Positive non-IgE (1st positive assay obtained immediately prior to the 6th dose) Positive IgE anti-ecallantide antibodies (7 days following)	Yes
401-103	pruritus and tingling of tongue, generalized pruritus, erythema of neck and arm, nausea and dizziness, confusion, lethargy	4th dose in continuation study	Within 1 minute	Epinephrine SC hydroxyzine IM, solumedrol and IV fluids.	Pending	Pending	Positive anti DX-88 (ECL) + IgE, (seroconversion at 28-day follow-up for 2nd exposure) anti DX-88- IgE (seroconversion at 7-day follow-up for 3rd exposure)	Yes

Table 35. Generalized Hypersensitivity Cases

Patient	Symptoms	Dose	Time to Onset	Treatment Required	Skin Test Results	Rechallenge Dose	Antibody Status	Meets NIAID Criteria for Anaphylaxis[33]
8805054099	headache, blurred vision, flushing, urticaria, pruritus, conjunctival injection, with an ↑HR, ↑BP	6th dose iv	1 minute	Diphenhydramine	ID phase positive skin reactions with wheal and flare. The Investigator determined all ID reactions to be an irritation reaction	No reaction	Positive consistently non-IgE antibodies to ecallantide, with seroconversion first noted in the 7 day follow-up for the 5th exposure to ecallantide Positive IgE antibodies to P pastoris at 7 day follow-up for 6th exposure	No
8814326002	pruritus, nausea and local site reactions	4th dose	12 min	No treatment	During Intradermal test developed wheal and flare	Not given	Antibody status at dosing + non-IgE antibodies to ecallantide seroconversion noted on the 7-day follow-up after 3rd exposure + IgE antibodies to P pastoris seroconversion noted on the 7-day follow-up after 2nd exposure	No

Anaphylaxis is highly likely when any one of the following 3 NIAID criteria is fulfilled**:**

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula);

And at least one of the following:

- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
- Reduced BP or associated symptoms of end-organ dysfunction (eg, 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):

- Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
- Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
- Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):

- Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
- Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

Appendix C EDEMA3-DB: ITT-as-Randomized Population

In EDEMA3-DB, several study endpoints that showed a statistically-significant treatment effect of ecallantide in the ITT-as-treated population were not statistically significant for the ITT-as-randomized population, although strong trends were observed. Both TOS at 4 hours (primary endpoint) and change from baseline in MSCS score at 4 hours (secondary endpoint) were not statistically-significantly improved with ecallantide treatment compared with placebo (P=0.100 and P=0.094, respectively). Although the key study endpoints were not met with the ITT-as-randomized population, this is believed to be due to the small study population included in EDEMA3-DB (as expected for this orphan condition). As a result of the treatment administration error in 2 patients, 2.8% (1 of 36 patients) of the ecallantide group was treated with placebo and 2.8% (1 of 36 patients) of the placebo group was treated with ecallantide. A summary of baseline characteristics and efficacy results for these 2 patients is provided in Table 36.

Table 36. Baseline Characteristics and Efficacy Results of Patients Who Received the Wrong Treatment in EDEMA3-DB

	Randomized to Placebo Received Ecallantide	Randomized to Ecallantide Received Placebo
Age (yr)	16	66
Gender	Male	Female
Race	White	White
Primary attack location	Peripheral, severe	Abdominal, moderate
Symptom complex	External head/neck, severe	Stomach/GI, moderate
MSCS score at baseline	3.0	2.0
MSCS score at hour 4	2.0	2.0
Change in MSCS score at 4 hours	-1.0	0.0
TOS at 4 hours	100	0

A summary of efficacy results for the EDEMA3-DB ITT-as-randomized population is provided in Table 37.

Table 37. Summary of Efficacy Results for EDEMA3-DB: ITT-as-Randomized Population

	Ecallantide (N=36)		Placebo (N=36)		
	n		n		P-value
Primary Endpoint					
TOS at 4 hours (median [IQR])					
Imputed	36	50.0 (0.0, 100.0)	36	0.0 (0.0, 100.0)	0.100[a]
Unimputed	34	50.0 (50.0, 100.0)	35	50.0 (0.0, 100.0)	0.138[a]
Secondary Endpoints					
MSCS score - Change from baseline at 4 hours (median [IQR])					
Imputed	36	-1.0 (-1.5, -0.0)	36	-0.5 (-1.0, 0.0)	0.094[a]
Unimputed	34	-1.0 (-1.5, -0.5)	35	-1.0 (-1.0, 0.0)	0.096[a]
Proportion of patients with significant improvement in overall response[b], n (%)					
Imputed	36	18 (50.0)	36	12 (33.3)	ND
Time to significant improvement in overall response (estimated median [IQR]), minutes					
Imputed	36	165.0 (83.0, --)	36	-- (135.0, --)	0.136[c]
Tertiary Endpoints					
MSCS score - Change from baseline at 24 hours (median [IQR])					
Imputed	33	-1.0 (-2.0, 0.0)	33	-0.5 (-1.0, 0.0)	0.142[a]
TOS at 24 hours (median [IQR])					
Imputed	33	75.0 (0.0, 100.0)	34	0.0 (-100.0, 100.0)	0.044[a]
Proportion of patients with sustained improvement in overall response[b] n (%)					
Imputed	36	25 (69.4)	36	18 (50.0)	ND
Time to onset of sustained improvement in overall responsee (estimated median [IQR]), minutes					
Imputed	36	67.0 (37.0, --)	36	165.0 (49.0, --)	0.075[c]
Proportion of patients receiving medical intervention within 24 hours, n (%)					
Imputed	36	5 (13.9)	36	13 (36.1)	0.012[d]

Source: SCE Tables 2.7.3.10, 2.7.3.11, 2.7.3.12, 2.7.3.14, 2.7.3.15, 2.7.3.16, 2.7.3.17, 2.7.3.18, 2.7.3.19, and 2.7.3.38
ITT=intent-to-treat, IQR=interquartile range, MSCS=Mean Symptom Complex Severity, TOS=Treatment Outcome Score
ND = not done; -- indicates not reached
[a] Wilcoxon rank sum test
[b] Not an endpoint, but a statistic that results from the time-to-analysis
[c] Log-rank test (Kaplan-Meier)
[d] Logistic regression model

Appendix D EDEMA4 Patient Narratives for QT Assessment

No EDEMA4 patient in either treatment group had a QTc value of >500 msec during double-blind treatment, and 1 patient (placebo group, 7 days post-dose) had a QTc of 480 to 499 msec. Three patients in ecallantide group and 4 patients in the placebo group had QTc values of 450 to 479 msec. Patients with at least one post-dose QTc value ≥450 msec are described as follows:

Patient 415003, a female in the ecallantide group had a QTc value of 451 msec at 4 hours during double-blind treatment. This patient had a pre-dose QTc value of 441 msec, 2-hour QTc value of 448 msec, and a Follow-up QTc value of 421 msec. This patient had ECG findings that were assessed as clinically significant by the Investigator, although the findings were not considered TEAEs. The patient was observed on ECG as having clinically significant first-degree AV block at screening and throughout the study. The overall clinical impression was noted as abnormal. The patient's medical history included a history of atrial fibrillation (resolved) and ongoing arrhythmia.

Patient 424005, a male in the ecallantide group had QTc values ranging from 452 to 469 msec at all assessment times. This patient had the following QTc values during the study: pre-dose=457 msec; 2 hours=469 msec; 4 hours=453 msec; and Follow-up 1=452 msec. This patient's overall ECG was within normal limits. The patient's medical history was unremarkable.

Patient 437001, a female in the ecallantide group had a single QTc value ≥450 msec. The patient had a QTc value at screen=445 msec; re-screen=430 msec; pre-dose=425 msec; 2 hours=435 msec; 4 hours=459 msec; 2 hours open-label=435 msec; 4 hours open-label=430 sec; and Follow-up 1=420 msec. The ECG was abnormal at screen, with a clinically significant finding of "poor R wave progression V1-V3." This patient also had ECG findings that were not clinically significant that included "poor R wave progression V1-V4" at re-screen, pre-dose, and at 2 and 4 hours during open-label treatment, as well as "right intraventricular conduction delay noteworthy" at 4 hours post-dose during double-blind treatment. The patient's medical history was unremarkable.

Patient 414001, a female who received placebo during double-blind treatment had 2 QTc values ≥450 msec during the study. The patient had a prolonged QTc interval of 459 msec at pre-dose, 463 msec at 2 hours, 454 msec at 4 hours, and 438 msec at Follow-up. This patient's overall ECG was within normal limits, with no clinically significant ECG findings. The patient's medical history was unremarkable.

Patient 417007, a female who received placebo during double-blind treatment had 2 QTc values ≥450 msec during the study. The patient had the following QTc values: screen=439 msec; pre-dose=435 msec; 2 hours=465 msec; and Follow-up=429 msec. This patient's overall ECG was within normal limits, with no clinically significant ECG findings. The patient's medical history included ongoing arrhythmia and ongoing systolic hypertension.

Patient 426012, a female who received placebo during double-blind treatment had 2 QTc values ≥450 msec during the study, of which one QTc value was ≥480 msec. The patient had the following QTc values: pre-dose=432 msec; 2 hours=438 msec; 4 hours=468 msec; and Follow-up=485 msec. This patient's overall ECG at 2 hours was within normal limits, although there was a clinically significant finding of "minor nonspecific ST and T wave flattening." At 4 hours post-dose, the ECG overall and ST segment were abnormal, although the "nonspecific ST and T wave abnormalities" were assessed as not clinically significant by the Investigator. The patient's medical history was unremarkable.

Patient 438002, a female who received placebo during double-blind treatment had 1 QTc value ≥450 msec during double-blind treatment. The patient had the following QTc values: screen=438 msec; pre-dose=457 msec; 2 hours=465 msec; 4 hours=447 msec; and Follow-up=439 msec. This patient's overall ECG was within normal limits, with no clinically significant ECG findings, although "right intraventricular conduction delay noteworthy" was noted at screening. The patient's medical history was unremarkable.

During double-blind treatment, no patient in either group had a change in QTc value ≥60 msec. Two patients in the ecallantide group had changes in QTc values of 30 to 59 msec and are detailed below. Patient 437001 had one post-dose QTc value ≥450 msec and is also presented above.

Patient 426017, a female who received ecallantide during double-blind treatment had 2 changes from baseline QTc values ≥30 msec during the study. The patient had the following changes from baseline in QTc values: 2 hours=51 msec; 4 hours=51 msec; 2 hours open-label=36 msec; 4 hour open-label=34 msec; and Follow-up=27 msec. This patient's overall ECG at pre-dose was within normal limits, although "sinus bradycardia noteworthy" was noted as a non-clinically significant finding. At 2 hours, 4 hours, 2 hours open-label, and 4 hours open-label the ECG overall and ST segment were abnormal, although the "nonspecific ST and T wave abnormalities" were assessed as not clinically significant by the Investigator. The patient's medical history was unremarkable.

Patient 437001, a female in the ecallantide group had a single change from baseline QTc value ≥30 msec. The patient had a QTc value at screen=445 msec; re-screen=430 msec; pre-dose=425 msec; 2 hours=435 msec; 4 hours=459 msec; 2 hours open-label=435 msec; 4 hours open-label=430 sec; and Follow-up 1=420 msec. At 4 hours, the patient had a change from baseline QTc of 34 msec. The ECG overall was abnormal at screen, with a clinically significant finding of "poor R wave progression V1-V3." This patient also had ECG findings that were not clinically significant that included "poor R wave progression V1-V4 at re-screen, pre-dose, and at 2 and 4 hours during open-label treatment, as well as "right intraventricular conduction delay noteworthy" at 4 hours post-dose during double-blind treatment. The patient's medical history was unremarkable.