

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

BLA 125277

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

BLA-125277	Re-submission Date(s): 31 May, 2009
Brand Name	Kalbitor
Generic Name	Ecallantide
Primary Clin Pharm Reviewer	Yun Xu, M.D. Ph.D.
Team Leader (Acting)	Partha Roy, Ph. D.
OCP Division	DCPII
Primary PM Reviewer	Hao Zhu, Ph.D.
PM Team Leader	Yaning Wang, Ph.D.
OND division	DPAP
Sponsor	Dyax
Relevant IND(s)	IND 10,426
Submission Type	Original Submission
Priority Status	Priority
Formulation; Strength(s)	1 mL (10 mg drug) per vial
Dosage and Administration	30 mg (3.0 mL), administered S.C. in three 1 mL injections. If the attack persists, an additional dose of 30 mg may be administered
Indication	Acute attacks of Hereditary Angioedema (HAE), age 10 and up

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1 Executive Summary

This is a resubmission of the biologics license application (BLA) for Kalbitor (Ecallantide), recombinant human plasma kallikrein inhibitor. This product has been studied under IND 10,426 and was granted Orphan and Fast Track Designations in 2003 and 2006, respectively. The sponsor submitted the original BLA on Sept 23, 2008 and received a complete response. After

discussing with the Agency about the deficiency in the previous submission, the sponsor re-submitted the BLA on May 31, 2009.

Kalbitor (ecallantide) is a plasma kallikrein inhibitor intended for subcutaneous injection to treat acute attacks of hereditary angioedema (HAE) in patients who are 16 years of age and older. HAE is a rare and sometimes life-threatening disease. There is presently no marketed or approved treatment for acute attacks, or cure for HAE in the United States.

KALBITOR is a clear, colorless liquid free of preservatives. Each vial of KALBITOR contains 1 mL ecallantide at a concentration of 10 mg/mL. The recommended dose of KALBITOR is 30 mg (3.0 mL), administered subcutaneously in three 1 mL injections. If the attack persists, an additional dose of 30 mg may be administered.

1.1 Recommendation

The Office of Clinical Pharmacology/Division 2 (OCP/DCP-2) has reviewed BLA 125277 re-submitted on 31 May, 2009 and finds it acceptable, provided that satisfactory agreement is reached between the sponsor and the Agency regarding language in the labeling text.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

According to the Agency's request in the CR letter, the sponsor submitted the in-study bio-analytical reports containing the requested performance data from (b) (4) for studies DX-88/5, DX-88/13, and DX-88/15. The assay performance and study results were acceptable and the data are considered valid.

According to the previous review, the analytical results from study DX-88/1 was not acceptable due to lack of quality control. Therefore, the bio-analytical results from acceptable studies (DX-88/2, DX-88/4 and DX-88/6, DX-88/5, DX-88/13 and DX-88/15) are re-analyzed in the population PK analysis. Based on the population PK analysis, no significant difference in results was found between this review cycle and the previous review cycle. The key findings are summarized below.

1. The sponsor claimed that based on population pharmacokinetic analysis, it is not necessary to adjust dose for patients greater than 65 years of age. However, it was found that this claim cannot be fully justified based on population PK analysis using the currently available data.
2. The sponsor claimed that the concentration data from both healthy subjects and patients demonstrated no difference in the pharmacokinetics of ecallantide. However, population PK analysis indicated that the clearance (CL/F) is significantly different between healthy subjects and patients. CL/F in patients is about 24% lower in healthy subjects than in patients.
3. Based on the current data, gender, body weight, and age are not statistically significant covariates. Since age is not a statistically significant covariate for pharmacokinetics of ecallantide, no dose adjustment is necessary in the future clinical trials to test safety and efficacy in patients under 16 years of age. However, it is still recommended that the PK samples be taken in these studies to further confirm this conclusion.

2 Review on new information in re-submission

2.1 Drug assays

Three assays (developed by (b) (4) and (b) (4), respectively) were used to measure ecallantide in plasma during clinical development. In the previous review, the results from the study analyzed by (b) (4) (study DX/88-1) are considered invalid due to lack of quality control. The results from the studies analyzed by (b) (4) (studies DX-88/6, DX-88/2 and DX-88/4) are considered acceptable. For results from the studies analyzed by (b) (4) (studies DX-88/5, DX-88/13 and DX-88/15), the sponsor did not submit the complete in-study bio-analytical reports with QC information before the end of previous review cycle. The Agency requested the sponsor to submit the information in the re-submission.

In this new submission, the sponsor submitted the in-study bio-analytical reports from (b) (4) for studies DX-88/5, DX-88/13, and DX-88/15. The results of sample analysis in each of the individual studies are acceptable as evidenced by QC sample precision and accuracy within $\pm 15\%$. Therefore, the bio-analytical results in studies DX-88/5, DX-88/13, and DX-88/15 are considered acceptable.

2.2 Re-analysis of population pharmacokinetics

In the previous review, the population PK analysis was conducted assuming that the bio-analytical results from all studies are valid. Because the sponsor did not submit the in-study bio-analytical reports from (b) (4), it was unclear whether the results analyzed by (b) (4) were acceptable. In this resubmission, the acceptable bio-analytical results (studies DX-88/2, DX-88/4 and DX-88/6, DX-88/5, DX-88/13 and DX-88/15) are re-analyzed in the population PK analysis.

The re-analysis of population pharmacokinetics can be found in the attached pharmacometrics review. And the key findings are summarized below.

1. The sponsor claimed that based on population pharmacokinetic analysis, it is not necessary to adjust dose for patients greater than 65 years of age. However, it was found this claim cannot be fully justified based on population PK analysis using the currently available data.
2. The sponsor claimed that the concentration data from both healthy subjects and patients demonstrated no difference in the pharmacokinetics of ecallantide. However, population PK analysis indicated that the clearance (CL/F) is significantly different between healthy subjects and patients. CL/F in patients is about 24% lower in healthy subjects than in patients.
3. Based on the current data, gender, body weight, and age are not statistically significant covariates.

Based on the current data, age is not a statistically significant covariate for pharmacokinetics of ecallantide. Therefore, no dose adjustment is necessary in the future clinical trials to test safety and efficacy in patients under 16 years of age. However, it is recommended that the PK samples will be taken in these studies to further confirm this conclusion.

4 Appendix

4.1 Pharmacometrics Review

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is the proposed dose for patients greater than 65 years of age justified based on population pharmacokinetic analysis?

The sponsor claimed that based on population pharmacokinetic analysis, it is not necessary to adjust dose for patients greater than 65 years of age. However, we found this claim cannot be fully justified based on population PK analysis using the currently available data. The reasons were listed as the following:

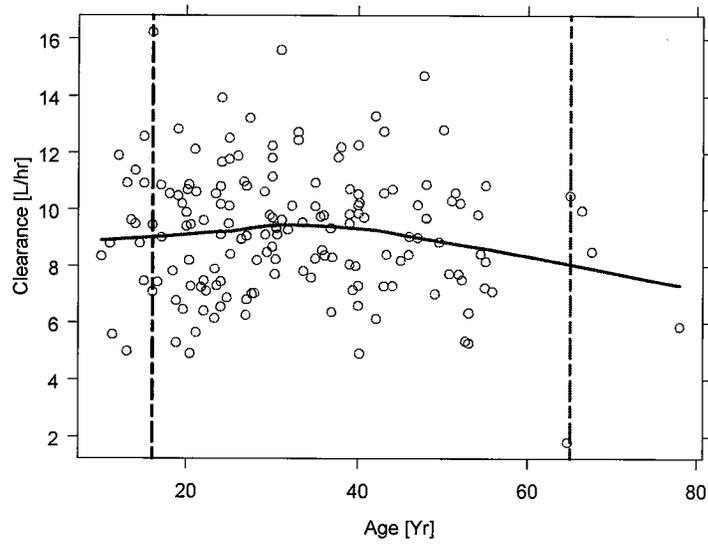
- The sample size is too small to determine an appropriate dose for geriatric patients based on population PK analysis. The current population PK dataset includes observations from 161 subjects. Only 3 patients are greater than 65 years of age (Table 1). Among them, 2 patients are less than 68 years of age. Intensive PK samples were collected in only 2 patients. The small sample size with the narrow age distribution is insufficient to detect the clinical relevant difference, if it exists, between the geriatric patients and rest of the other patients.
- It appears that slightly smaller values in clearance and volume of distribution is shown in old patients (> 65 years of age), even though the relationships are not statistically significant based on population PK analysis (Figure 1).
- Mechanistically, it is difficult to rule out the possibility that ecallantide is eliminated at a different rate in geriatric patients as compared to the rest of other patients. Ecallantide is a small protein with a molecular weight of 7054 Da. It is shown to be eliminated through kidney and is found in urine. A decreased renal function is generally seen in old patients. Therefore, it is possible that ecallantide is eliminated at a lower rate in old patients.

Table 1. Information for Patients > 65 Years of Age in the Current Analysis Dataset

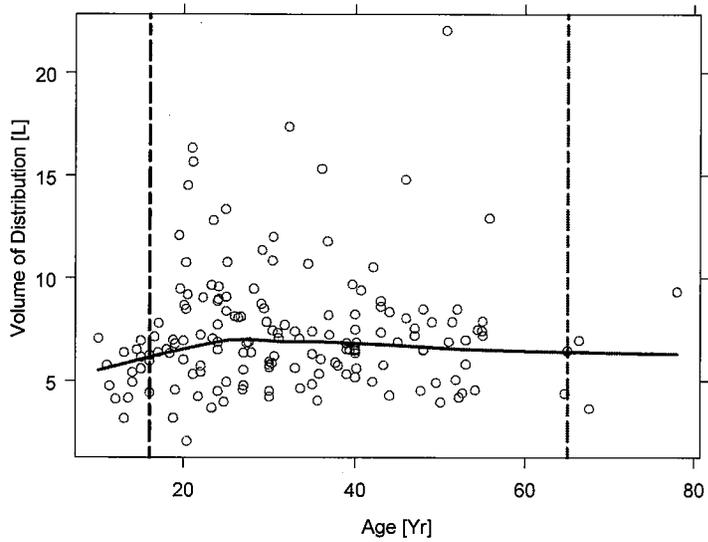
Patient ID	Age [Yr]	Sex	Weight [kg]	BSA [m ²]	Study ID DX88/	Samples / subject	Dosing
210.2	67.6	1	60	1.59	2	4	10 i.v. for 10 minutes
217.2	66.4	0	78	1.97	2	7	80 i.v. for 10 minutes

5198.5	78	1	63.1	1.63	5	4	16.3 i.v. for 10 minutes*
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Figure 1 Clearance (A) and Volume of Distribution (B) vs. Age Relationships



(A)



(B)

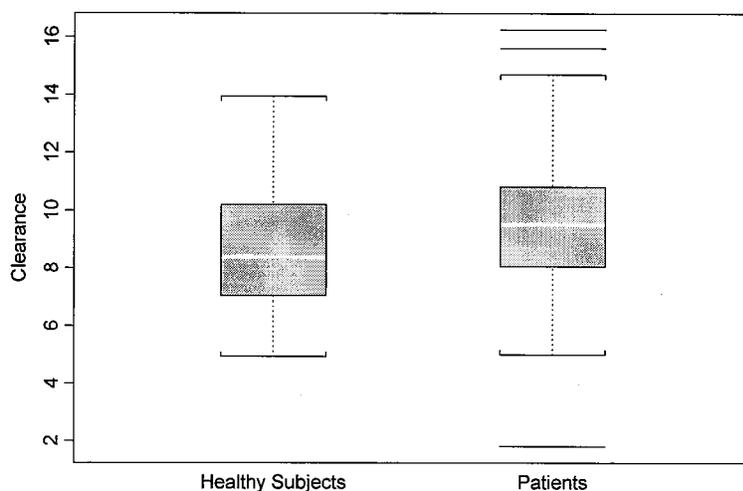
Note: Green dashed line = 65 years of age, Black dashed line = 16 years of age, Dots with open cycle = model fitted major PK parameters. Red line = lowest line.

Clearance = CL/F, and Volume of Distribution = Vc/F

1.1.2 Is the label statement of no difference in ecallantide pharmacokinetics between healthy subjects and patients justified?

No. The sponsor claimed that the concentration data from both healthy subjects and patients demonstrated no difference in the pharmacokinetics of ecallantide. However, population PK analysis indicated that the clearance (CL/F) is significantly different between healthy subjects and patients. As demonstrated in Figure 2, CL/F is about 24% lower in healthy subjects than in patients.

Figure 2. CL/F Stratified by Subject Type (Patients vs. Healthy Subjects)



1.1.3 The sponsor claimed in the label that body weight, age, and gender are not significant covariates based on population pharmacokinetic analysis. Is this statement justified?

Yes. Based on the current data, gender, body weight, and age are not statistically significant covariates.

1.2 Recommendations

None.

1.3 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

8 USE IN SPECIFIC POPULATIONS

Ecaltantide

BLA125277, Sequence 0035

PM Review.Ecaltantide final with number.doc

8.4 Pediatric Use

Safety and effectiveness of KALBITOR in patients below 16 years of age have not been established. [M2.7.4, Section 2.1.1.6.4; M2.7.3, Section 3.3.2 and Section 6; M5.3.3.5, Population PK Report; M1.11.4, DX88-107 Pediatric Report]

8.5 Geriatric Use [REDACTED] (b) (4)

Clinical studies of did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. [REDACTED] (b) (4)

[REDACTED] In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

No exposure-response relationships for KALBITOR to components of the complement or kallikrein-kinin pathways have been established. [REDACTED] (b) (4)

12.3 Pharmacokinetics

[REDACTED] (b) (4)

[REDACTED] (b) (4)

(b) No pharmacokinetic data are available in patients or subjects with hepatic or renal impairment. [M5.3.3.5, Population PK Report]

2 PERTINENT REGULATORY BACKGROUND

The resubmission dated on 31 May 2009 incorporated the FDA's requirements from the complete response letter. The agency received the original submission between 31 December 2007 and 23 Sep 2008 as a rolling submission. The sponsor was seeking the marketing approval of ecallantide for the treatment of acute attacks of hereditary angioedema, which is an orphan indication and can be life-threatening. This submission was granted fast track review in 2006. The division issued a complete response letter on 25 March 2009.

In the current resubmission, additional information related to bioanalytical assay used to measure ecallantide plasma concentration was provided. In addition, the safety, efficacy, and exposure (PK) data for pediatric patients, covering each age group was included. The updated information can potentially affect the pharmacometric analyses results previously reviewed by Dr. Ping Ji for the original submission. The sponsor also provided an updated label with changes in Section 8 (Use in specific population), Section 12.2 (Pharmacodynamics), and Section 12.3 (Pharmacokinetics).

3 RESULTS OF SPONSOR' S ANALYSIS

No additional pharmacometric analyses report was provided in the resubmission. The sponsor's analysis results from the original submission were summarized in Dr. Ping Ji's pharmacometrics review.

4 REVIEWER' S ANALYSIS

4.1 Introduction

The reviewer's analysis was performed based on a subset of the original population PK analysis dataset. The original population PK dataset included samples analyzed by three different assays. The clinical pharmacology reviewer indicated that the assay developed by (b) (4), and described in report DX005-VAL was not validated (Please refer to Dr. Yun Xu's review). Therefore, the data generated by this assay should not be included in the population PK analysis. In the current review, we updated the population PK analysis with the dataset excluding PK observations generated by the invalidated assay.

4.2 Objectives

Analysis objective is to assess the proposed label claims based on the Population PK analysis.

4.3 Methods

4.3.1 Data Sets

The original dataset is summarized in Table 2. This dataset includes PK observations from 7 clinical trials (Study DX-88/1, Study DX-88/2, Study DX-88/4, Study DX-88/5, Study DX-88/6, Study DX-88/13, and Study DX-88/15). Pharmacokinetic data from Study DX-88/1 used invalidated PK assay. Therefore, it was not included in the current analysis.

Table 2. Analysis Data Sets

Study Number	Name	Link to EDR
DX-88-1, 2, 4, 5, 6, 13, 15	*Mega-dat.txt	\\cbsap58\m\cTD_Submissions\STN125277\0009\m5\datasets\dx88-pop-pk\analysis\programs\input\mega-dat.txt

*Note: PK observations from Study DX-88/1 were excluded from current population PK analysis.

4.3.2 Software

NONMEM and S₊ Plus were used for the reviewer's analysis.

4.3.3 Models and Results

4.3.3.1 Data Preview

Current analysis dataset includes 2996 observations from 161 subjects in 6 clinical trials. The features of the major covariates in the current population PK dataset were summarized in Table 3.

**Table 3 Summary of Major Categorical Covariates (A)
and Continuous Covariates (B)**

	Dataset	Subjects	Observations	Note
	Total Number	161	2996	
Categorical Covariates				
Age Group	> 65 Yr	3	16	
	16-65 Yr	145	2836	
	< 16 Yr	13	144	
Subject	Healthy Subjects	50	2153	From Study DX88/6, DX88/13, and DX88/15
	Patients	111	843	
Gender	Male	105	2123	
	Female	56	873	
(A)				
Continuous Covariates		Mean	Median (5th - 95th percentile)	
Body weight (kg)		75.6	70.8 (53.3 - 115.5)	
Age (yr)		32.7	30.3 (14 - 54.9)	
(B)				

In the current analysis dataset, only 3 subjects were older than 65 years of age. The detailed information for each subject greater than 65 years of age was summarized in Table 4. A preview of the pharmacokinetic profiles from the three patients was shown in Figure 3.

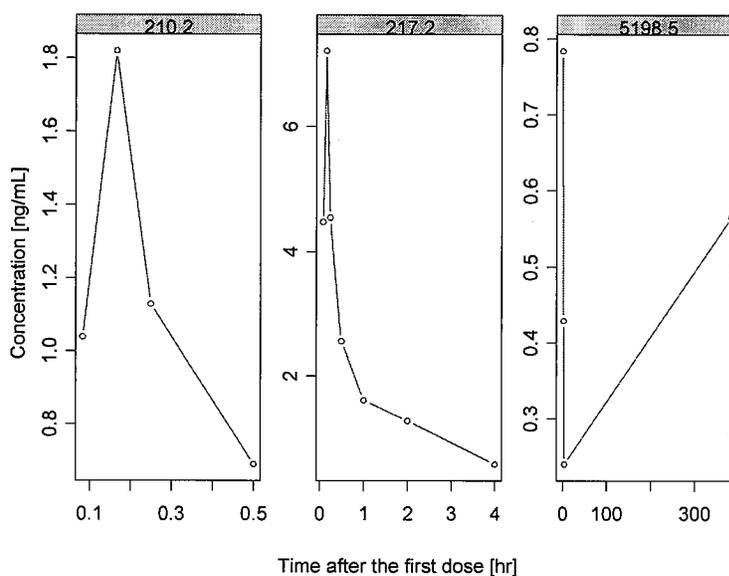
Table 4 Information for Patients > 65 Years of Age in the Current Analysis Dataset

Patient ID	Age [Yr]	Sex	Weight [kg]	BSA [m ²]	Study ID DX88/	Samples / subject	Dosing
210.2	67.6	1	60	1.59	2	4	10 i.v. for 10 minutes

217.2	66.4	0	78	1.97	2	7	80 i.v. for 10 minutes
5198.5	78	1	63.1	1.63	5	4	16.3 i.v. for 10 minutes*

* Note: This patient received two doses. The other 2 patients received a single dose.

Figure 3 Preview of the Pharmacokinetic Profile for Patients > 65 Years of Age



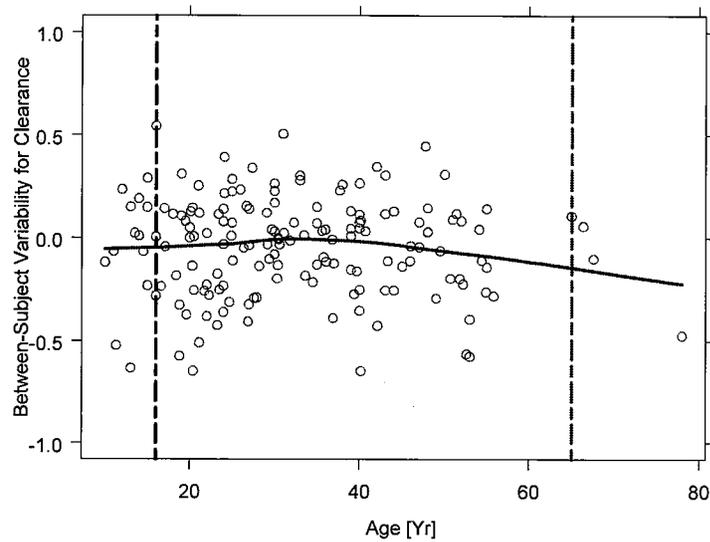
4.3.3.2 Population Pharmacokinetics Modeling

Population PK modeling was conducted based on Dr. Ping Ji's model in the review. The PK models (such as the final model and the base model) are not expected to be different from the previous review because our analysis dataset retains 97% of the PK observations from the original dataset. The data was adequately described by a three-compartment model with first-order absorption (including a lag time) and first-order elimination. The final model included patient type on CL/F and assay difference on Vc/F. In addition, body weight was included as a covariate for Ka. Different formulations and different injection sites were related to different Ka, lag time, and bioavailability.

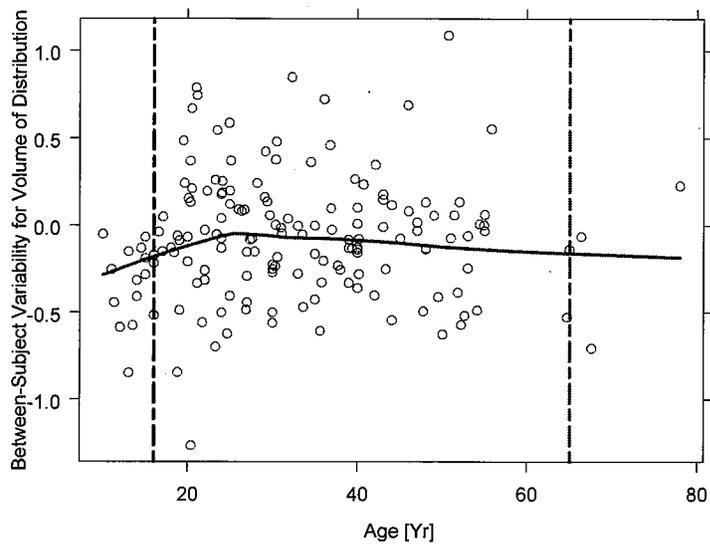
The between-subject variability and age relationships for two major pharmacokinetic parameters (i.e., CL/F and Vc/F) were demonstrated in Figure 4. It appears that slightly smaller values in CL/F and Vc/F can be seen in old patients (> 65 years of age). No apparent trend can be identified for CL/F between patients less than and greater than 16 years of age. Nevertheless, Vc/F appears to be smaller in adolescent patients (< 16 years

of age) as compared to the adults (> 16 years of age). Further population PK analysis by using the forward addition from the base model indicated that age is not a statistically significant covariate for both CL/F and Vc/F.

Figure 4 Between-Subject Variability vs. Age Relationships for CL/F (A) and Vc/F (B)



(A)



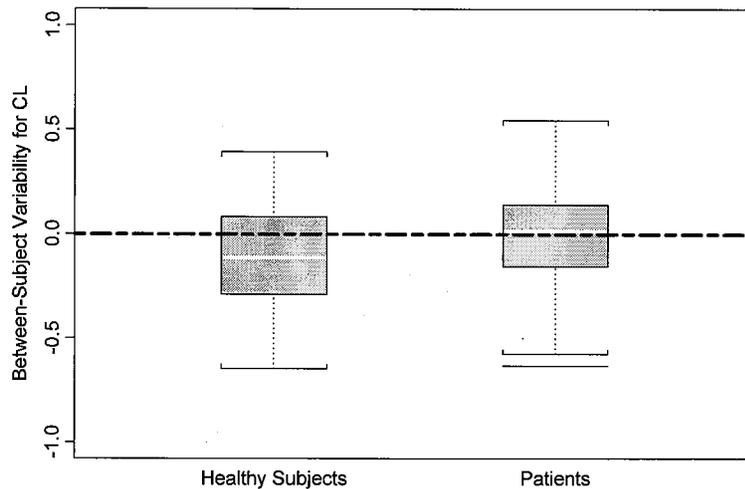
(B)

Note: Green dashed line = 65 years of age, Black dashed line = 16 years of age

Clearance = CL/F, Volume of Distribution = Vc/F

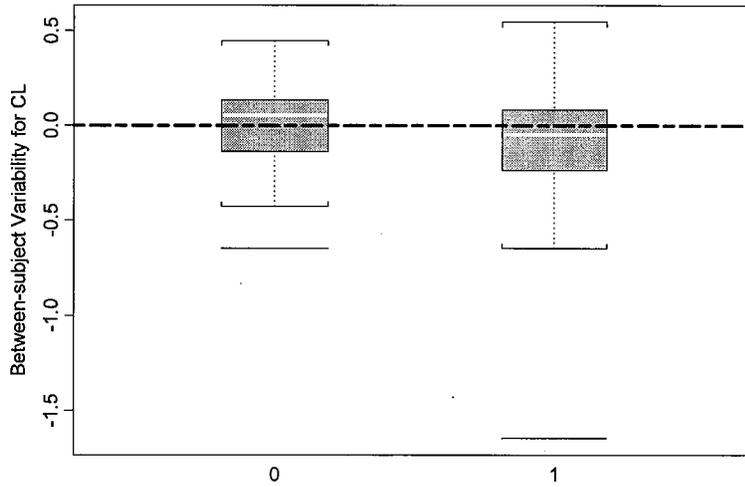
Figure 5 demonstrated the between-subject variability for CL/F stratified by subject type (patients versus healthy subjects). Population PK analysis by using the back forward elimination from the final model indicated that the difference in CL/F between healthy subjects and patients was statistically significant. CL/F in patients was about 24% lower in healthy subjects than in patients.

Figure 5 Between-Subject Variability for CL/F Stratified by Subject Type (Patients vs. Healthy Subjects)

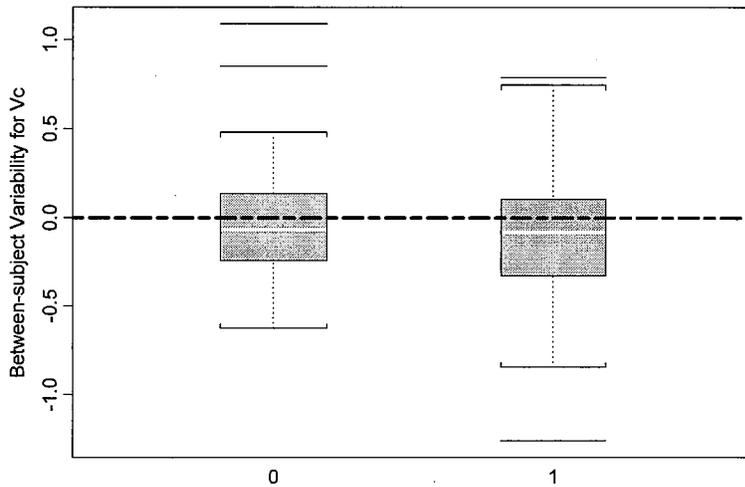


In addition, the between-subject variabilities for CL/F and Vc/F stratified by gender were shown in Figure 6. No apparent trend can be identified for the distributions of CL/F and Vc/F between male and female subjects. Population PK analysis by using forward addition from the base model indicated that gender was not a significant covariate for both CL/F and Vc/F.

**Figure 6 Between-Subject Variability for CL/F (A)
and Vc/F (B) Stratified by Gender**



(A)

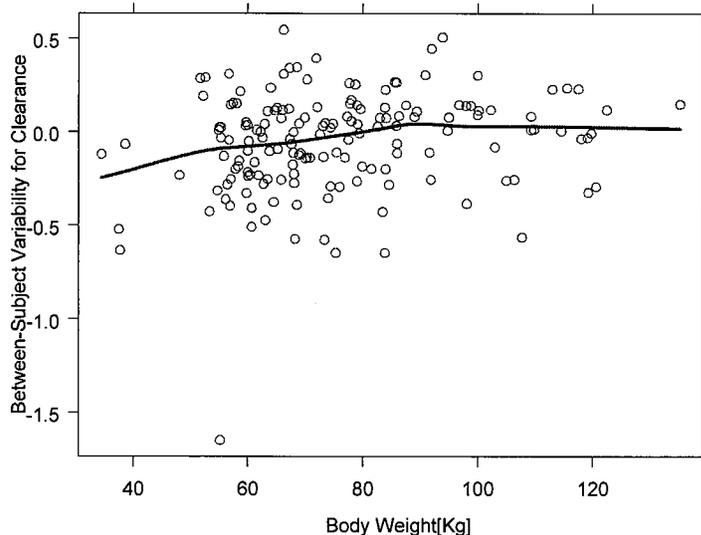


(B)

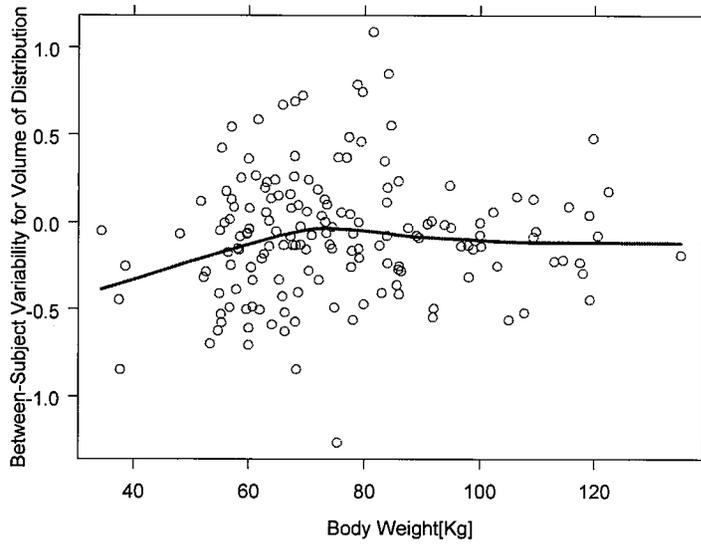
Note: 0 = Female, 1 = Male

Furthermore, the between-subject variabilities for CL/F and Vc/F were plotted against body weight (Figure 7). No apparent trend can be identified for the distribution of CL/F over body weight. However, it appears that Vc/F increases with body weight for a patient less than 70 kg. Population PK analysis by using forward addition from the base model indicated that body weight was not a significant covariate for both CL/F and Vc/F.

Figure 7 Between-Subject Variability vs. Body Weight Relationships for CL/F (A) and Vc/F (B)



(A)



(B)

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\

6 APPENDIX

Table 5 Modeling Procedure

Procedure	Model	Description	OFV *	Change in OFV (b) (4)
[Redacted content]				

Note: *: Objective function value

Signature

Yun Xu 10/21/2009

Yun Xu, M.D. Ph.D., Primary Clinical Pharmacology Reviewer

Partha Roy 10/21/2009

Partha Roy, Ph.D., Clinical Pharmacology Team Leader (Acting)

 10/21/2009

Hao Zhu, Ph.D., Primary Pharmacometrics Reviewer

 10/21/2009

Yaning Wang, Ph.D., Pharmacometrics Team Leader

CLINICAL PHARMACOLOGY REVIEW

BLA-125277	Submission Date(s): 23 Sept, 2008
Brand Name	Kalbitor
Generic Name	Ecallantide
Primary Clin Pharm Reviewer	Yun Xu, M.D. Ph.D.
Team Leader (Acting)	Wei Qiu, Ph. D.
OCP Division	DCPH
Primary PM Reviewer	Ping Ji, Ph.D.
Secondary PM Reviewer	Christoffer Tornoe, Ph.D.
PM Team Leader	Yaning Wang, Ph.D.
OND division	DPAP
Sponsor	Dyax
Relevant IND(s)	IND 10,426
Submission Type	Original Submission
Priority Status	Priority
Formulation; Strength(s)	1 mL (10 mg drug) per vial
Dosage and Administration	30 mg (3.0 mL), administered S.C. in three 1 mL injections. If the attack persists, an additional dose of 30 mg may be administered
Indication	Acute attacks of Hereditary Angioedema (HAE), age 10 and up

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1 Executive Summary

This is a biologics license application (BLA) for Kalbitor (Ecallantide), recombinant human plasma kallikrein inhibitor. This product has been studied under IND 10,426 and was granted Orphan and Fast Track Designations in 2003 and 2006, respectively. Kalbitor (ecallantide) is a plasma kallikrein inhibitor intended for subcutaneous injection to treat acute attacks of hereditary angioedema (HAE) in patients who are 10 year of age and older. HAE is a rare and sometimes life-threatening disease. There is presently no marketed or approved treatment for acute attacks, or cure for HAE in the United States.

KALBITOR is a clear, colorless liquid free of preservatives. Each vial of KALBITOR contains 1 mL ecallantide at a concentration of 10 mg/mL. The recommended dose of KALBITOR is 30 mg (3.0 mL), administered subcutaneously in three 1 mL injections. If the attack persists, an additional dose of 30 mg may be administered.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCP/DCP-2) has reviewed BLA 125277 submitted on 23 Sept, 2008 and finds it acceptable. However, the sponsor has not submitted some required information on bio-analytical assays as of Feb 11, 2009, which will have direct impact on the individual and population pharmacokinetic results. Therefore, pharmacokinetic data may be re-analyzed upon arrival of the requested information. Recommendation and labeling comments will be made after reviewing the requested information.

Comments to Medical Team:

It appears that there is a steady increase in the probability of seroconversion with increased dose numbers. Considering most patients enrolled in the clinical trial only received limited number of ecallantide doses, and the HAE patients may be given the drug for lifetime, close monitoring and report of immunogenicity is recommended as a post marketing commitment or Risk Evaluation and Mitigation Strategy (REMS) if it is approved.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Following the administration of a single SC dose of ecallantide to healthy subjects, mean maximum plasma concentration was observed approximately 2 to 3 hours after dosing. The bioavailability of SC dose is about 90%. No clinical or preclinical studies were conducted to assess mass balance, route of excretion, or metabolism. Neither human drug-drug interaction studies, nor studies in impaired renal and hepatic patients, have been performed.

As confirmed by population pharmacokinetic modeling, three covariates affected ecallantide pharmacokinetics: population, body weight and assay type. However, none of them appeared to affect ecallantide pharmacokinetics in a clinically significant manner. Neither age nor sex had an effect on ecallantide exposure. However, the relatively small sample distribution of elderly population may not allow the labeling recommendation in this age group.

In the phase 3 studies (EDEMA3 and EDEMA4), 8.4 % of patients seroconverted to anti-ecallantide antibodies. Neutralizing antibodies to ecallantide were determined to be present in 1.6% of patients. There was no apparent correlation between effectiveness or safety and presence of neutralizing antibodies. However, several problems were identified with the immunogenicity assays and sampling schedule, which may affect the results of immunogenicity. Therefore, the immunogenicity results should be interpreted with caution. It appears that there is a steady increase in the probability of seroconversion with increased dose numbers.

2 Question Based Review

2.1 General Attributes of the Drug

1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Kalbitor (ecallantide) is a plasma kallikrein inhibitor intended for subcutaneous injection to treat acute attacks of hereditary angioedema (HAE) in patients who are 10 year of age and older. HAE is a rare and sometimes life-threatening disease. There is presently no marketed or approved treatment for acute attacks, or cure for HAE in the United States.

The clinical development program has been conducted under IND 10,426 since May 2002. Review of this IND was initially conducted by CBER in the Office of Therapeutics Research and Review. In October 2003, review of this IND was transferred from CBER to CDER, ODE VI. In October 2005, review of this IND was transferred from ODE VI to ODE II, Division of Pulmonary and Allergy Products. Kalbitor was granted Orphan and Fast Track Designations by the agency in 2003 and 2006, respectively. During the development program for HAE indication, key issues were discussed comprehensively with the agency, including patient reported outcome (PRO) development, dose selection, size of the safety database, the Special Protocol Assessment (SPA) agreement of the Phase 3 clinical study, and the timing and format of the BLA rolling submission.

2. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

ecallantide is a recombinant peptide inhibitor of plasma kallikrein. It is composed of 60 amino acids and has a molecular weight of 7054 Daltons. Ecallantide is formulated as a 10 mg/mL clear

and colorless, sterile, preservative-free and nonpyrogenic solution in (b) (4)
 (b) (4) Each vial contains 10 mg ecallantide, 8.0 mg sodium chloride, 0.76 mg disodium hydrogen orthophosphate (dihydrate), 0.2 mg monopotassium phosphate, and 0.2 mg potassium chloride in water for injection, USP (Table 1). The recommended dose of ecallantide is 30 mg (3.0 mL), administered SC as a divided dose.

Table 1. Quantitative composition per mL of liquid ecallantide

Ingredient	Quantity per mL	Function	Reference to Standard
Active			
EcAllantide	10 mg	Active	House
Inactive			
Na ₂ HPO ₄ ·2H ₂ O	0.76 mg	pH	USP
KH ₂ PO ₄	0.2 mg	pH	USP
NaCl	8.0 mg	Tonicity	USP
KCl	0.2 mg	Tonicity	USP
		(b) (4)	USP

USP = United States Pharmacopeia; WFI = Water for Injection; qs = quantity sufficient

EcAllantide drug product manufacturing consists of (b) (4) of drug substance into vials followed by stoppering. (b) (4)

During the development of ecallantide, nonclinical and clinical drug product manufacturing has been performed at 4 different contract manufacturers including

(b) (4) Genzyme (Framingham, MA), and (b) (4). Analytical testing indicated that drug product manufactured at these different sites was of comparable quality, and no separate nonclinical comparability studies were performed. At the intended dose, route, and to-be-marketed form, ecallantide demonstrates consistent and predictable exposure following SC administration.

During the development, two formulations have also been tested in clinical studies. In early clinical trials, ecallantide was administered as a single 10 minute intravenous (IV) infusion. The later switch to the SC route of administration was intended to improve patient compliance and ease of use. A prototype lyophilized formulation containing 30 mg ecallantide was also developed for SC administration. It was evaluated in a clinical Study DX-88/15 which was a double-blind, crossover study in healthy subjects designed to evaluate pharmacokinetic parameters and bioequivalence. The lyophilized formulation was not considered bioequivalent to the liquid formulation and was not further evaluated.

3. What are the proposed mechanism(s) of action and therapeutic indication(s)?

EcAllantide is a novel, potent plasma kallikrein inhibitor (K_i=25pM). It was selected on the basis of its high affinity and high specificity for human plasma kallikrein, a serine protease that is active in the intrinsic coagulation, pain, and inflammation pathways. The activity of human plasma kallikrein is normally regulated by complement component-1 esterase inhibitor (C1-INH). HAE patients are characterized by genetic mutations affecting the C1-INH gene located on chromosome 11q, which is inherited as an autosomal dominant trait. 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.

Although HAE attacks can, in some cases, be induced by known stimuli, 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 by kallikrein with the release of bradykinin.

Bradykinin acts on the vasculature to increase capillary and endothelial permeability, resulting in extravasation of fluids producing the pathognomonic signs and symptoms of HAE attacks. This leads to the characteristic acute attacks of HAE: episodes of swelling affecting any part of the body, including the abdominal viscera (which can result in episodes of pain, nausea, and vomiting), and the oropharynx and larynx (which can result in airway obstruction, asphyxiation, and death). By inhibiting the activation of plasma kallikrein, ecallantide works to prevent the elevated levels of bradykinin. As an inhibitor of plasma kallikrein, 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 the symptoms of acute attacks of HAE.

4. What are the proposed dosage(s) and route(s) of administration?

KALBITOR is a clear, colorless liquid free of preservatives. Each vial of KALBITOR contains 1 mL ecallantide at a concentration of 10 mg/mL. The recommended dose of KALBITOR is 30 mg (3.0 mL), administered subcutaneously in three 1 mL injections. If the attack persists, an additional dose of 30 mg may be administered.

2.2 General Clinical Pharmacology

1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The clinical development program for ecallantide consists of 12 clinical studies, 10 of which are completed and 2 of which are ongoing. The 10 completed studies include: 4 studies in healthy subjects, 5 studies in the HAE patient population, and 1 study in cardio-thoracic surgery (CTS) indication, another indication in development for ecallantide. The 2 ongoing studies include: 1 open-label HAE study and 1 study in CTS (which is not yet reported). In addition, patients received ecallantide by compassionate use and through a re-challenge procedure. The overall efficacy evaluation of ecallantide for treatment of HAE includes the 5 clinical studies in HAE. The overall safety evaluation for HAE treatment includes the safety data from the 10 completed studies, SAEs from the 2 ongoing studies, and the compassionate use and re-challenge experience. Tabulate listing of completed clinical studies in HAE indication is summarized in Table 2.

Table 2. Tabulate listing of completed clinical studies in HAE indication

Study Identifier	Study type	Study Design and Type of Control	Test Product(s), Dosage Regimen, Route of Administration	Number of Subjects by Arm Completed / Treated	Duration of Treatment/ Population
DX-88/1	PK	Double-blind, escalating single-dose Placebo	Ecallantide 10, 20, 40, or 80 mg IV	10 mg: 2 20 mg: 2 40 mg: 4 80 mg: 4 Placebo: 4 16/16	Single dose Healthy subjects
DX-88/2 EDEMA0	Efficacy	Open-label, escalating single-dose	Ecallantide 10, 40, or 80 mg IV	10 mg: 3 40 mg: 3 80 mg: 3	Single dose HAE/ AAE

		N/A		9/9	patients
DX-88/4 EDEMA1	Efficacy	Double-blind, escalating single-dose Placebo	Ecallantide 5, 10, 20, or 40 mg/m ² IV	5, 10, 20 mg/m ² 10 patients each 40 mg/m ² : 11 Placebo: 8 49/49	Single dose HAE patients
DX-88/5 EDEMA2	Efficacy	Open-label, ascending repeat-dose N/A	Ecallantide 5, 10, 20 mg/m ² IV; 30 mg SC	5 mg/m ² IV: 18 10 mg/m ² IV: 55; 20 mg/m ² IV: 9 30 mg SC: 31 77/77	Multiple doses (≥7 days apart per dose) HAE patients
DX-88/6	PK	Open-label, repeat-dose N/A	Ecallantide 20 mg/m ² , 10 min IV, 3 weekly doses; 20 mg/m ² , 4 hr IV, 1 dose	Dose 1: 8 Dose 2: 8 Dose 3: 7 Dose 4: 6 6/8	4 doses (7 days apart per dose) Healthy subjects
DX-88/13	PK	Open-label, repeat-dose, crossover Active	Ecallantide 30 mg 10-minute IV; 10 mg SC injection and two 1 mL placebo SC injections; 30 mg SC Once-weekly, cross-over	6 subjects each 16/18	3 doses (7 days apart per dose) Healthy subjects
DX-88/14 Double- Blind Part EDEMA3 -DB	Efficacy	Double-blind, single-dose Placebo	Ecallantide 30 mg, three 1 mL SC injections	36 patients each 71/72	Single dose HAE patients
DX-88/14 Repeat- Dosing Part EDEMA3 -RD	Efficacy	Open-label, repeat dose N/A	Ecallantide 30 mg, three 1 mL SC injections	67 patients 66/67	Multiple doses (≥72 hours apart per dose) HAE patients
DX-88/15	BA/BE	Double-blind, randomized, crossover Placebo	Ecallantide (liquid) 30 mg as three 1 mL SC injections and placebo (lyophilized), one 1 mL SC injection OR	12 subjects each 23/24	2 doses (7 days apart per dose) Healthy Subjects

			Ecallantide (lyophilized), 30 mg as one 1 mL SC injection and placebo (liquid) three 1mL SC injections		
DX-88/20 EDEMA4	Efficacy	Double-blind, single dose followed by possible open-label dose for severe upper airway compromise, incomplete response, or relapse Placebo	Ecallantide 30 mg, three 1 mL SC injections	48 patients each (double-blind) 95/96 37 patients (open-label)	Single double-blind dose; Single open-label dose for severe upper airway compromise, incomplete response, or relapse HAE patients

2. What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (collectively called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

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 tract, extremities, and/or genitals. 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. The sponsor approached the issue of measuring HAE symptom and treatment response by developing patient reported outcome (PRO) instruments that could evaluate all signs and symptoms of an HAE attack at any anatomical site, as well as capture severity and change in severity of each symptom across anatomical sites in response to treatment for the full constellation of symptoms. These instruments are patient-completed in electronic data capture mode at the clinical site during an acute attack at 15- and 30- minute intervals for the first 4 hours after dosing and at 24 hours after dosing. The validated PRO instruments accurately and comprehensively assess symptom severity and response to treatment. Five symptom complexes were established and assessed to capture all symptoms of an HAE attack: oropharyngeal head/neck, GI/abdominal, genital/buttocks, nonoropharyngeal head/neck, and cutaneous.

The PRO instruments comprise 2 measures: a composite assessment of all symptoms of the acute attack (MSCS score) and an assessment of the overall response to a therapeutic intervention (TOS score). MSCS score is a point-in-time global measure of symptom severity. Patients' assessment of severity was recorded on a 0 to 3 categorical scale (0 = normal, 1 = mild, 2 = moderate, 3 = severe) for the 5 symptom complexes. The change in MSCS score from baseline at 4 and 24 hours indicates the change in symptom severity over time. A decrease in score reflects improvement in symptoms. Clinically meaningful improvement is indicated by a reduction of

0.30 or greater. TOS is a composite measure of response to treatment and includes an overall assessment of response. Patients' assessment of response was recorded on a 5-category scale (significant improvement [100], improvement [50], same [0], worsening [-50], significant worsening [-100]), for each symptom complex at 4 and 24 hours and weighted based on severity assessment at baseline. Clinically meaningful improvement is indicated by a TOS of 30 and above.

Development of the PRO occurred throughout the HAE indication development program. The MSCS score and TOS were developed using data from these early clinical studies (EDEMA0, EDEMA 1 and EDEMA 2) with input from experts and regulatory authorities, and validated using cognitive debriefing interviews and analysis of their psychometric properties within the EDEMA3 study. The final versions of the PRO instruments were used in EDEMA3 and EDEMA4, pivotal studies of the HAE indications. In EDEMA3, the primary endpoint was TOS, and the main secondary efficacy measure was the change from baseline MSCS score at 4 hours. As recommended by FDA, EDEMA4 subsequently utilized the MSCS at 4 hours as the primary and TOS as the secondary efficacy endpoint. Because EDEMA3 and EDEMA4 had similar study designs, including eligibility criteria for moderate to severe attacks of HAE, populations and endpoints (MSCS score and TOS), and were well-matched at baseline, these 2 Phase 3 clinical studies were pooled into an "Integrated Phase 3 Analysis." The parameters of this pooling were predefined before the unblinding of EDEMA4.

In addition, an expert panel convened by the sponsor recommended a 4-hour post-dosing assessment as the primary endpoint assessment as providing a meaningful and sensitive marker of treatment benefit, which was used in early clinical development. In early clinical efficacy studies (EDEMA0, EDEMA1 and EDEMA2), proportion of success outcomes 4-hour post-dosing were used as the primary efficacy outcome. Two principal bodies of data support this choice. First, a placebo-controlled study examining efficacy and safety of C1-INH concentrate demonstrated that 95% of C1-INH-treated patients vs 12% placebo-treated reported the beginning of symptom resolution by 4 hours. Secondly, a sensitivity analysis of primary endpoint data from EDEMA1 conducted at 30-minute intervals up to 5 hours post-infusion showed that the early placebo response remained constant until the end of the 4-hour assessment point.

3. Exposure-response

- 1) What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

One controlled and 2 uncontrolled Phase 2 studies were conducted in HAE patients during early development: EDEMA1, EDEMA2 and EDEMA0, respectively. The final dose selected in the pivotal clinical study, EDEMA3 and EDEMA4, is selected based on the results from these previous studies. In EDEMA0, while a small number of patients were treated and the ecallantide doses used in the study varied, the efficacy data demonstrated that ecallantide had an effect on reducing the duration of attack symptoms. The results of EDEMA1 demonstrated that ecallantide administered at IV doses 5, 10, 20, or 40 mg/m² showed clinical activity against attacks at all anatomic locations (abdominal, peripheral, and laryngeal). The 10 mg/m² dose (approximately 20 mg, the average human body surface area is about 1.8 m²) provided significant benefit in mitigating acute signs and symptoms of HAE, and that increasing the dose to a level of 20 mg/m² and 40 mg/m² provided incremental, although slight, improvement in activity.

A clinical study in healthy subjects (DX-88/13) established comparability in AUC values between 30 mg IV and 30 mg SC ecallantide doses. EDEMA2 evaluated 5, 10, and 20 mg/m² IV doses and the 30 mg SC dose in a total of 240 HAE attacks in 77 patients. The study showed a clinical response at each dose level with a more impressive response in the 30 mg SC group compared with the other dose groups. Successful outcome based on improvement of response at 4 hours and maintained for more than 24 hours (the primary endpoint evaluation) was achieved following treatment with 30 mg SC in 49 of 60 (81.7%) of attacks treated, as compared with 11 of 24 (45.8%) of attacks treated at 5 mg/m², 96 of 141 (68.1%) at 10 mg/m², and 9 of 15 (60.0%) at 20 mg/m². Time to onset of response was similar across doses. Based on the overall response data, the 30 mg SC dose was deemed an appropriate dose to achieve efficacy. Furthermore, the 30 mg SC dose was studied in HAE patients in EDEMA2 and in healthy subjects in DX-88/13, and found to be well tolerated and showed comparable safety profile to other dose levels. In summary, the 30 mg SC dose showed improved efficacy and comparable safety to other dose levels studied, and was selected as the dose used in the pivotal study, compared to placebo.

- 2) What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

In vitro enzyme inhibition measurements demonstrated that ecallantide is a potent, selective, and reversible inhibitor of human plasma kallikrein with an equilibrium inhibition constant (K_i) of 25 pM. Enzyme specificity studies demonstrated that ecallantide weakly inhibited 5 additional proteases including neutrophil elastase (K_i = 0.75 μM), tissue kallikrein 2 (K_i = 0.29 μM), pancreatic trypsin (K_i = 69 nM), plasmin (K_i = 29 nM), and factor XIa (K_i = 1.7 nM). Ecallantide demonstrates selectivity for plasma kallikrein over these other enzymes of between 60-fold to 30,000-fold.

In a series of in vitro coagulation studies, ecallantide at 1.0 ug/ml did not inhibit factor XI and only partially (approximately 20%) inhibited plasmin. The maximum ecallantide concentration in HAE patients receiving a 30 mg SC dose is approximately from 0.6 to 1 μg/mL. It is therefore less likely that ecallantide would display any clinically meaningful inhibition of plasmin or factor XIa. In preclinical safety studies, administration of ecallantide results in a dose-dependent, reversible prolongation of activated partial thromboplastin time (aPTT). This is a direct pharmacologic action of ecallantide and is due to the inhibition of kallikrein-mediated activation of factor XII to factor XIIa, which is the initial step in the initiation of the intrinsic clotting cascade. 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/m². However, 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.

The maximum ecallantide concentration (C_{max}) in HAE patients receiving IV dosing in excess of 20 mg/m² (~ 6.5 μg/mL at 20 mg/m²) is much higher compared to that in patients receiving 30 mg SC dose (~0.6 to 1 μg/mL). Considering the change of activated partial thromboplastin time is mainly driven by drug concentration, the difference in C_{max} between the IV and SC dose could explain the transient prolongation of aPTT following IV dose.

- 3) Does this drug prolong the QT or QTc interval?

In preclinical development, ecallantide was shown to have no direct effects in standard

cardiovascular assays, including human ether-a go-go related gene (hERG) assay, isolated Purkinje fiber preparations, inward sodium current (INa), or transient outward potassium current (Ito) in isolated male and female rat cardiomyocytes. For patients taking ecallantide, no clinically significant QT prolongation has been seen or is expected. As agreed with the agency, a thorough QT/QTc study was not conducted. ECG monitoring as proposed in EDEMA4 protocol was accepted as an alternative. In EDEMA4, the randomized, placebo-controlled study to assess 30 mg SC dose vs placebo, 12-lead electrocardiograms (ECGs) were obtained at baseline, around the Cmax window at 2 hours and 4 hours post-dose, and at follow-up (Day 7). ECGs were evaluated for PR interval, QRS complex, and QTc interval. Ecallantide had no significant effect on the QTc interval, heart rate, cardiac conduction, or any other components of the ECG. Of note, there were no outliers at extremes (>500 msec absolute or >60 msec change from baseline) of QTc in response to treatment with ecallantide at and around the Cmax window of 2 to 4 hours.

- 4) Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

One controlled and 2 uncontrolled Phase 2 studies were conducted in HAE patients during early development: EDEMA1, EDEMA2 and EDEMA0, respectively. The final dose selected in the pivotal clinical study, EDEMA3 and EDEMA4, are selected based on the results from these previous studies. In EDEMA0, while a small number of patients were treated and the ecallantide doses used in the study varied, the efficacy data demonstrated that ecallantide had an effect on reducing the duration of attack symptoms. The results of EDEMA1 demonstrated that ecallantide administered at IV doses 5, 10, 20, or 40 mg/m² showed clinical activity against attacks at all anatomic locations (abdominal, peripheral, and laryngeal). The 10 mg/m² dose (approximately 20 mg, the average human body surface area is about 1.8 m²) provided significant benefit in mitigating acute signs and symptoms of HAE, and that increasing the dose to a level of 20 mg/m² and 40 mg/m² provided incremental, although slight, improvement in activity.

A clinical study in healthy subjects (DX-88/13) established comparability between 30 mg IV and 30 mg SC ecallantide doses based on PK parameters, including clearance, elimination half-life, and volume of distribution. As a result, the dose-ranging studies conducted with IV ecallantide (DX-88/1 and DX-88/6) supported ecallantide tolerability and efficacy when administered SC. EDEMA2 evaluated 5, 10, and 20 mg/m² IV doses and the 30 mg SC dose in a total of 240 HAE attacks in 77 patients. The study showed a clinical response at each dose level with a more impressive response in the 30 mg SC group compared with the other dose groups. Successful outcome based on improvement of response at 4 hours and maintained for more than 24 hours (the primary endpoint evaluation) was achieved following treatment with 30 mg SC in 49 of 60 (81.7%) of attacks treated, as compared with 11 of 24 (45.8%) of attacks treated at 5 mg/m², 96 of 141 (68.1%) at 10 mg/m², and 9 of 15 (60.0%) at 20 mg/m². Time to onset of response was similar across doses. Based on the overall response data, the 30 mg SC dose was deemed an appropriate dose to achieve efficacy. Furthermore, the 30 mg SC dose was studied in HAE patients in EDEMA2 and in healthy subjects in DX-88/13, and found to be well tolerated and showed comparable safety profile to other dose levels. In summary, the 30 mg SC dose showed improved efficacy and comparable safety to other dose levels studied.

In addition to the available efficacy and safety data from studies in healthy subjects and HAE patients, the 30 mg SC dose was also selected based on practical considerations associated with fixed SC dosing. By moving to the administration of a standard dose of 30 mg SC in all patients, potential errors in dosing due to incorrect calculations of the body surface area are eliminated. In

addition, SC administration of any drug provides an ease of administration, which is generally preferred by clinicians and patients compared with IV dosing.

The sponsor communicated with the agency in Aug, 2006 about selecting the 30 mg SC dose. The Agency responded that the dose ranging study with the IV formulation is adequate given the comparative exposure (AUC) of the IV and SC formulation, and suggested the sponsor to compare 30 mg SC dose and placebo dose in the subsequent efficacy studies.

4. What are the PK characteristics of the drug and its major metabolite?

1) What are the single dose and multiple dose PK parameters?

The pharmacokinetics of ecallantide was evaluated in both intravenous (IV) and subcutaneous (SC) administration in healthy volunteers and HAE patients. The pharmacokinetics of liquid ecallantide following intravenous (IV) administration was evaluated in 2 studies in healthy subjects (Studies DX-88/1 and DX-88/6) and 3 studies in patients with HAE (Studies DX-88/2 [EDEMA0], DX-88/4 [EDEMA1], and DX-88/5 [EDEMA2] at fixed doses ranging from 10 to 80 mg, or body weight adjusted doses ranging from 5 to 40 mg/m². The pharmacokinetics of ecallantide following subcutaneous (SC) administration was evaluated in 2 studies in healthy subjects (Studies DX-88/13 and DX-88/15) and 1 study in HAE patients (Study DX-88/5). In these studies, ecallantide was administered at nominal doses of 10 mg or 30 mg. In study DX-88/5 and study DX-88/13, ecallantide was administered subcutaneously in liquid formulation. While in study DX-88/15, ecallantide was administered subcutaneously in both liquid and lyophilized formulation.

Individual pharmacokinetic parameters, which described the disposition of ecallantide, were calculated in 3 single-dose studies in healthy subjects (Studies DX-88/1, DX-88/13, and DX-88/15) and in 1 repeat-dose study in healthy subjects (Study DX-88/6). A summary of the studies designs could be found in Table 3. Pharmacokinetic parameters in all these 4 studies were derived using traditional methods and plasma concentration data profiles were analyzed either noncompartmentally (Studies DX-88/1, DX-88/13, and DX-88/15) or using a 2-compartment model (Study DX-88/6). Pharmacokinetic data from Studies DX-88/2, DX-88/4, and DX-88/5 were very sparse and accurate individual pharmacokinetic parameters could not be derived using traditional methods. Data from these studies, however, were included in the population pharmacokinetic analysis.

After this BLA was submitted on Sept 23, 2008, it was found some key information was missing in the bio-analytical reports. The agency requested the sponsor to provide the missing information, and the sponsor replied on Dec 11, 2008, indicating such information would be submitted within approximately one month. Because of the tight review timeline, all the PK data were assumed acceptable and used in the individual and population PK analysis. On Jan 29, 2009, the sponsor submitted part of the requested information. It was found due to lack of Quality Control (QC) data, the results from DX-88/1 was considered not acceptable. However, it still could not be concluded whether the results from study DX-88/5, DX-88/13, and DX-88/15 are acceptable because of incomplete QC data, more information was requested from the sponsor and has not been submitted yet as of Feb 11, 2009. Because the review is due on Feb 13th and some key information is still missing, all the PK data were assumed acceptable and used in the individual and population PK analysis, and the results were presented in this version of the review. However, all results derived from the studies mentioned above (especially the results from the population PK analysis) should be considered temporary and be interpreted with caution.

Table 3. Description of Pharmacokinetic Studies in Healthy Subjects

Study No. (Country)	Product Desc. (Lot No.)	Study Phase Design	Study Objectives	Regimen, Dose, Route	No. Subj.	Gender (M/F)	Sampling Scheme
DX-88/1 (Scotland)	Liquid (317392)	Phase I Double-blind Ascending-dose	Tolerability Pharmacokinetics	Single, 10 mg IV inf.	2	2M/0F	PK: predose, 5, 10, 15, 30, 45 min, 1, 2, 4, 8, 12, and 24 hrs post-dose AET: predose, 1, 4, and 24 hrs and 7 days post dose Anti-DX-88 antibodies: predose, 35 days post dose
				Single, 20 mg IV inf.	2	0M/2F	
				Single, 40 mg IV inf.	4	3M/1F	
				Single, 80 mg IV inf.	4	4M/0F	
DX-88/6 (UK)	Liquid (493034)	Phase I Open-label Repeat-dose	Pharmacokinetics Safety Immunogenicity	Repeat, 20 mg/m ² IV inf. Q7 days for 4 weeks	8	2M/6F	PK: predose, 15, 30, 45 min, 1, 1.5, 2, 4, 8, 12, 16, and 24 hrs post (10 min inf) or predose, 15, 30, 45 min, 1, 1.5, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7.5, 8, 12, 16, and 24 hrs post dose (4 hr inf) AET: predose, 1, 4, 12, and 24 hrs post each dose Anti-DX-88 antibodies: Days -1, 6, 13, 20, 28, 49
DX-88/13 (UK)	Liquid (227-01-004)	Phase I Open-label Three-period crossover	Pharmacokinetics Safety Immunogenicity	Single, 27.3 mg IV inf. Single, 27.3 mg SC inj. Single, 9.1 mg SC inj.	18	9M/9F	PK: predose, 5, 10, 15, 30, 45 min, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 22, 24 hrs post each dose AET: predose, 15 min 1, 4, and 12 hrs post each dose Non-IgE, IgE anti-DX-88 IgE anti-P _{antaria} Antibodies: Days -1, 6, 13, 21, 42
DX-88/15 (UK)	Liquid (227-05-002) Lyophilized (716 2742)	Phase I Double-blind Two-period crossover Bioequivalence	Pharmacokinetics Safety Tolerability Immunogenicity	Single, 30 mg SC inj.	24	9M/15F	PK: predose, 5, 10, 15, 30, 45 min, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 22, 24 hrs post each dose AET: predose, 1, 4, and 12 hours post then Days 15 and 36 Non-IgE, IgE anti-DX-88 IgE anti-P _{antaria} Antibodies: Days -1, 7, 15, 36

A summary of the pharmacokinetic parameters after single dose in healthy subjects is presented in Table 4. Following the administration of a single IV dose of ecallantide, C_{max} and AUC increased proportionally with the dose from 10 to 80 mg. Plasma clearance ranged from 71 to 141 mL per minute and the volume of distribution ranged from 5.9 to 18.8 L. Plasma ecallantide concentration declined rapidly with a mean elimination half life of 0.6 to 2.0 hours. Following the administration of a single SC dose of ecallantide to healthy subjects, C_{max} and AUC increased proportionally with the dose from 10 to 30 mg. A mean maximum plasma concentration of 586 ng/mL was observed approximately 2 to 3 hours after dosing at 27.3 mg dose (nominal dose 30 mg). Following SC administration, plasma ecallantide concentration also declined rapidly with an elimination half life of approximately 2 hours. The bioavailability of the 27.3 mg SC dose (nominal dose 30 mg) is about 90%.

Table 4. Summary of Mean Pharmacokinetic Parameters Following Single-Dose Administration of Ecallantide in Healthy Subjects

Study	Route	Dose (mg)	N	C _{max} (ng/mL)	t _{max} (hr)	AUC (ng·hr/mL)	V _d * (L)	Cl* (mL/min)	t _{1/2} (hr)
DX-88/1	IV	10	2	2000	0.2	1400	5.9	122	0.6
		20	2	4750	0.2	4709	7.4	71	1.2
		40	4	7680	0.2	8823	10.2	76	1.6
		80	4	14800	0.2	17656	11.2	76	1.7
DX-88/6	IV (10 min)	20 mg/m ²	6	6497	n/c	5890	13.2	110	2.0
		20 mg/m ²	6	1170	n/c	5300	11.2	118	1.3
DX-88/13	IV	27.3	16	3741	0.2	3327	18.8	141	1.6
		27.3	17	586	2.7	3017	26.4	153	2.0
		9.1	18	179	2.2	837	29.3	189	1.8
DX-88/15	SC (liquid)	30	23	995	2.4	4232	23.1	124	2.2

Source: DX-88/1 CSR; DX-88/6 CSR; DX-88/13 CSR; DX-88/15 CSR.

Abbreviations: C_{max}—observed maximum serum concentration after administration, t_{max}—time to reach C_{max}, AUC—area under the concentration time-curve, V_d—volume of distribution, Cl—clearance, t_{1/2}—terminal half-life, n/c—not calculated.

* For SC dose, V_d/F and Cl/F is calculated

Study DX-88/6 also assessed pharmacokinetic profiles and safety of ecallantide in healthy subjects following repeat IV dosing at 20 mg/m² (Days 0, 7, 14, 21). Subjects were administered a dose of ecallantide once weekly for 4 weeks. For the first 3 doses, ecallantide was administered as a 10-minute IV infusion. The final dose was administered as an IV infusion over 4 hours. The pharmacokinetic parameters after each dose were summarized in Table 5. No drug accumulation was observed after repeated weekly IV dose at 20 mg/m². Based on the time-concentration profile, the majority of the administered ecallantide was cleared from the plasma within 6 hours following each dosing. Considering the short half-life of ecallantide, no drug accumulation is expected at a weekly dose.

Table 5. Summary of PK Parameters from Compartmental Models of Plasma Samples Collected from Healthy Volunteers after 10-Minutes and 4-Hour Intravenous Infusion of Ecallantide

Parameter	10-minute Infusion			4-h Infusion
	Dose 1 (N=6)	Dose 2 (N=6)	Dose 3 (N=6)	Dose 4 (N=6)
Dose (mg)	36.5 ± 6.02	36.5 ± 6.02	36.5 ± 6.02	36.5 ± 6.02
AUC (h*µg/mL)	5.06 ± 0.94	5.75 ± 1.26	6.86 ± 2.90	5.25 ± 0.92
Half-life				
Alpha t _{1/2} (h)	0.10 ± 0.04	0.13 ± 0.07	0.13 ± 0.04	0.03 ± 0.01 ^a
Beta t _{1/2} (h)	1.18 ± 0.44	1.89 ± 0.80	2.78 ± 2.26	1.27 ± 0.52 ^b
C _{max} (µg/mL)	7.02 ± 1.36	6.47 ± 0.67	6.00 ± 0.88	1.17 ± 0.12
CL (mL/h)	7405 ± 1833	6597 ± 1849	5750 ± 1276	7101 ± 1615
V _{dis} (mL)	9731 ± 3152	13056 ± 3326	16770 ± 9989	11152 ± 1743

Source: Appendix 16.1.13.1 (Tables 3, 4, 5, 6)

Note: AUC = area under the curve; C_{max} = maximum plasma concentration achieved; CL = clearance; SD = standard deviation; V_{dis} = volume of distribution at steady state

a. (n=2) Plasma concentration data for Subjects 001-0002 and 001-0004 were consistent with a 2-compartment model, whereas data from the other 4 subjects (Subjects 001-0003, 001-0006, 001-0007, and 001-0011) were consistent with a 1-compartment model.

b. This includes terminal half-life estimated from both 1-compartment (Subjects 001-0002 and 001-0004) or 2 compartment (Subjects 001-0003, 001-0006, 001-0007, and 001-0011) modeling.

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DX-88/15 evaluated the bioequivalence of liquid and lyophilized formulations of ecallantide in healthy subjects. Subjects were administered 2 SC doses of 30 mg ecallantide at one-week intervals (Days 1 and 8). The test-to-reference ratio (lyophilized/liquid formulation) was summarized in Table 6. The 90% CIs for liquid and lyophilized DX-88 C_{max}, and AUC_{0-last} ratios were not within 80% to 125%. Therefore, lyophilized DX-88 formulation was not bioequivalent to the liquid formulation and was not used in later studies.

Table 6. Pharmacokinetic Equivalence Assessment for Liquid and Lyophilized Formulations of Ecallantide

Parameter	Ratio	90% Confidence Interval	
		Lower	Upper
C _{max}	65.6	54.8	78.4
AUC _{0-last}	80.5	74.2	87.4

- 2) How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

According to the results of population PK analysis, the effect of disease on the pharmacokinetics of ecallantide was assessed. The clearance of ecallantide was 23.4% lower in patients (7.56 L/h) than in healthy subjects (9.87 L/h).

- 3) What are the characteristics of drug absorption?

Following the administration of a single SC dose of ecallantide to healthy subjects, mean maximum plasma concentration was observed approximately 2 to 3 hours after SC dosing (Table 4). The bioavailability of the 27.3 mg (nominal dose 30 mg) SC dose is about 90%.

- 4) What are the characteristics of drug distribution?

Following the administration of a single IV dose of ecallantide, the volume of distribution ranged from 5.9 to 18.8 L.

- 5) Does the mass balance study suggest renal or hepatic as the major route of elimination?

No clinical or preclinical studies were conducted to assess mass balance, route of excretion, or metabolism, as the expected consequence of the metabolism of biotechnology-derived polypeptide is the degradation to small peptides and individual amino acids.

Ecallantide is a small protein (7054 Da) and it is expected that elimination is by renal filtration followed by tubular re-absorption and metabolic catabolism. Renal elimination of ecallantide has been confirmed by demonstration of ecallantide activity in urine of treated subjects. Neither formal human drug-drug interaction studies, nor studies in impaired renal and hepatic patients, have been performed; this is consistent with biologic agent development. Since no information is available on ecallantide pharmacokinetics in renal and hepatic impairment patients, guidance on exercising caution is appropriate if ecallantide use for a patient with impaired organ function.

- 6) What are the characteristics of drug metabolism?

No clinical or preclinical studies were conducted to assess drug metabolism, as the expected consequence of the metabolism of biotechnology-derived polypeptide is the degradation to small peptides and individual amino acids.

- 7) What are the characteristics of drug excretion?

Ecallantide is a small protein (7054 Da) and it is expected that elimination is by renal filtration followed by tubular reabsorption and metabolic catabolism. Renal elimination of ecallantide has been confirmed by demonstration of ecallantide activity in urine of treated subjects. However, no mass balance study was conducted in animal or human. Therefore, the fraction excreted by urine is unknown.

- 8) Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Following the administration of a single IV dose of ecallantide, C_{max} and AUC increased approximately proportional with the dose from 10 to 80 mg (Table X). Following the administration of a single SC dose of ecallantide to healthy subjects, C_{max} and AUC increased approximately proportional with the dose from 10 to 30 mg.

9) How do the PK parameters change with time following chronic dosing?

Study DX-88/6 assessed pharmacokinetic profiles and safety of ecallantide in healthy subjects following repeat IV dosing (Days 0, 7, 14, 21). No drug accumulation was observed after repeated weekly IV dose at 20 mg/m². Based on the time-concentration profile, the majority of the administered ecallantide was cleared from the plasma within 6 hours following each dosing. Based on the short half-life of ecallantide, it is expected that no drug accumulation was observed on a weekly dosing regimen.

10) What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Pharmacokinetic data from Studies DX-88/2, DX-88/4, and DX-88/5 were very sparse and accurate pharmacokinetic parameters could not be derived using traditional methods. Data from these studies, however, were included in the population pharmacokinetic analysis. Individual pharmacokinetic parameter could only be calculated in 3 single-dose studies in healthy subjects (Studies DX-88/1, DX-88/13, and DX-88/15) and in 1 repeat-dose study in healthy subjects (Study DX-88/6). Because of the relatively homogenous characteristics of healthy volunteers in these studies, the inter- and intra-subject variability of PK parameters was evaluated by population PK analysis by using all the available PK data in both healthy volunteers and patients.

Inter- and intra-subject variability of PK parameters in volunteers and patients could be found in "APPENDIX 2: MODEL PARAMETER ESTIMATES FOR THE FINAL COVARIATE PHARMACOKINETIC MODEL FOR DX-88" in the pharmacometric review. Three covariates affected ecallantide pharmacokinetics: population, body weight and assay type. An inverse relationship was observed between the subject body weight and the rate of absorption after SC administration; as weight increased the rate of absorption decreased with no change on the extent of absorption. The assay type affected the central volume of distribution, which was 20% smaller for patients whose samples were assayed using an LC-MS/MS (LLOQ: 0.473 mg/L) assay compared to patients whose samples were assayed using an ELISA (LLOQ: 0.156 mg/L) or LC-MS (LLOQ: 0.5 mg/L) assay.

2.3 Intrinsic Factors

1. What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response and what is the impact of any differences in exposure on efficacy or safety response?

A population pharmacokinetic model was established with a three-compartment disposition model with first-order absorption and elimination. Three covariates affected ecallantide pharmacokinetics: population, body weight and assay type. The clearance of ecallantide was found to be 23.4% lower in HAE or AAE patients (7.56 L/h) than in healthy subjects (9.87 L/h). An inverse relationship was observed between body weight and the rate of absorption after SC administration; as weight increased the rate of absorption decreased with no change on the extent of absorption. The assay type affected the central volume of distribution, which was 20% smaller for patients whose samples were assayed using an LC-MS/MS (LLOQ: 0.473 mg/L) assay compared to patients whose samples were assayed using an ELISA (LLOQ: 0.156 mg/L) or LC-

MS (LLOQ: 0.5 mg/L) assay. Neither age nor sex had an effect on ecallantide exposure. However, the relatively small sample distribution of elderly population may not allow the labeling recommendation in this age group. The whole population PK model dataset (development + validation) consisted of 173 individuals with 3090 concentrations, among which 3 subjects were greater than 65 yr of age (16 concentrations, <1%).

2. Based upon what is known about exposure-response relationships and their variability, and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendations.

Based on dose-exposure relationship and the intrinsic factors that may affect ecallantide PK, one fixed dose regimen (30 mg S.C. dose) is appropriate for all patients.

2.4 Immunogenicity

2.4.1 Anti-Ecallantide Antibodies (all-class)

Three ELISA methods were developed for the detection of anti-ecallantide antibodies in early development stage (Phase 1 and Phase 2 stage). However, none of these assays have been validated. Therefore, the results of immunogenicity assays in the Phase 1 and Phase 2 study was not validated and was not included in immunogenicity (all-class) calculation. The frequency of anti-Ecallantide Antibodies (all-class) was calculated based on the results of the final validated anti-ecallantide antibody assays (ECL assay), which was used in phase 3 studies (EDEMA3 and EDEMA4).

The ECL assay was used to detect antibodies in samples obtained from patients participating in EDEMA3 and EDEMA4. Serum samples were assayed from 156 unique patients who participated in EDEMA3 and EDEMA4. These patients received a variable number of doses of ecallantide, ranging from none to approximately 15 doses, with approximately one-third of the patients receiving a single dose. Twenty-three of these patients (20 naïve to ecallantide and 3 with prior ecallantide exposure) participated in one or both of these studies and received only placebo. Twenty-one of the 23 patients had both a pre-dose and at least 1 post-dose sample assayed using ECL assay. There were no samples that were confirmed positive. The remaining 2 patients had only a pre-dose (1 patient) or post-dose (1 patient) sample assayed. Neither of these patients had a confirmed positive sample. Thus, in this group of 23 patients who entered the studies with negative assay results, all remained negative, and there was no seroconversion following placebo administration.

One hundred thirty-three patients participated in 1 or both of the studies and received at least 1 dose of ecallantide. Of these, 110 patients were naïve to ecallantide upon entry into these studies, and 23 patients had prior exposure to ecallantide. There were 121 patients (combined naïve and non-naïve) who had pre-dose serum samples negative for anti-ecallantide antibodies, and 119 of these patients had 1 or more post-dose samples assayed. Among these 119 patients, 10 patients had one or more post-dose samples that tested positive for anti-ecallantide antibodies for a seroconversion rate of 8.4% (Table 7).

Table 7. Baseline versus Post-Dose Anti-Ecallantide Antibody Status for Patients Tested by the ECL Assay in EDEMA3 and EDEMA4

Baseline	Post-Dose			Total
	Negative	Positive	Missing	
Negative	109	10	2	121
Positive	0	10	0	10
Missing	2	0	0	2
Total	111	20	2	133

However, the percentage of seroconversion to anti-ecallantide antibody may be underestimated due to incomplete data. In study DX88/14 (EDEMA3), samples for serum antibody testing were reported at screening and/or enrollment prior to dosing, Follow-Up Visit 1 (Study Day 6 to 10), Follow-Up Visit 2 (Study Day 23 to 37), and Follow-Up Visit 3 (Study Day 83 to 97). Totally 22.4% patients had at least 1 serum sample that produced confirmed positive assay results for antibodies to ecallantide. However, in study DX88/20 (EDEMA4), serum antibody testing were only reported at enrollment (pre-dose) and Follow-up Visit 1 (Study Day 7 [± 2 days]), and 1.5% patients had serum sample that produced confirmed positive assay results for antibodies to ecallantide. The immunogenicity results at later time points have not been reported yet. Considering the incomplete data in study EDEMA4, the incidence of seroconversion to anti-ecallantide antibody may be underestimated since it may take longer than one week to development antibody in human. Therefore, the percentage of seroconversion should be interpreted with caution. When the immunogenicity results from later time points are available in study EDEMA4, they should be included to calculate the incidence of immunogenicity.

Only the results of immunogenicity assays (all-class) performed in the Phase 3 Clinical Studies were validated. However, no pharmacokinetic samples were taken in Phase 3 studies. Therefore, the effect of immunogenicity on pharmacokinetics could not be evaluated.

2.4.2 Neutralizing Anti-Ecallantide Antibodies

Serum samples negative for anti-ecallantide antibodies (all-class) in EDEMA 3 and EDEMA 4 were assumed to be negative for neutralizing antibodies to ecallantide as well, and samples were not assayed. All serum samples confirmed positive for anti-ecallantide antibodies in EDEMA 3 and EDEMA 4, regardless of titer, were assayed for neutralizing antibodies to ecallantide. One or more samples from each of 4 patients tested positive for neutralizing antibodies to ecallantide. The pre-dose sample from 2 patients (both with prior exposure to ecallantide) tested positive for neutralizing antibodies, as did the post-dose samples. For the other 2 patients, neutralizing antibodies developed after ecallantide exposure in EDEMA3 and/or EDEMA4. Of the total 133 patients who received ecallantide in these studies, 2 had no pre-dose sample, 2 had no post-dose sample, and 2 tested positive for neutralizing antibodies prior to exposure in these studies, leaving 127 at risk for developing neutralizing antibodies. Two of these patients developed neutralizing antibodies for a seroconversion rate of 1.6% in EDEMA3 and or EDEMA4 (Table 8).

Table 8. Baseline versus Post-Dose Neutralizing Antibody Status for Patients Tested by the ECL Assay

Baseline	Post-Dose			Total
	Negative	Positive	Missing	
Negative	125	2	2	129
Positive	0	2	0	2
Missing	2	0	0	2
Total	127	4	2	133

Source: Antibody Retest Report and EDEMA4 CSR Listings 16.2.8.8.1 and 16.2.8.8.2.2.

In summary, two of 127 patients (1.6%) who were tested by the ECL assay seroconverted (neutralizing antibodies). The 129 comes from 131 patients with at least 1 post-dose evaluation minus the 2 patients who were positive at baseline. Patients with a missing baseline were presumed negative at baseline.

2.4.3 IgE antibodies to ecallantide

Two ELISA methods were developed for the detection of IgE anti-ecallantide antibodies. (b) (4)

(b) (4) This required the use of 2 different ELISA formats in this assay: an indirect ELISA for the IgE myeloma standards, and direct capture ELISA for the unknown samples. Following discussions with the FDA in 2006, it was felt that the format of this assay did not conform to industry consensus recommendations (Mire-Sluis et al, 2004). So the (b) (4) as replaced with a unique hybrid reagent that allowed for a direct capture ELISA format to be used for both unknowns and standards.

The number of patients at risk to seroconvert (ie, the denominator) includes those who have at least 1 post-baseline value but excludes those who are positive at both pre- and post-treatment. Patients who are missing the pre-treatment evaluation are considered to be negative pre-treatment. The number of seroconversion is determined as the number of patients whose pre-treatment evaluation is either negative or missing (ie, the denominator) and who have a post-treatment evaluation that is positive (ie, the numerator). Therefore, in the ecallantide HAE program, 4 of 195 (2.1%) patients seroconverted to anti-ecallantide IgE antibodies (Table 9),

Table 9 Seroconversion to Anti-Ecallantide IgE Antibodies

Baseline	Post-Dose Ecallantide (N=219)				
	Negative		Positive		Missing
	n	(%)	n	(%)	
IgE Antibodies to Ecallantide					
Negative	165	(98.8)	2	(1.2)	3
Positive	0	(0.0)	0	(0.0)	0
Missing	26		2		21

Source: ISS Summary Table 10.1.

Note: Percentages are based on the number of patients with both baseline and at least 1 post-baseline result.

The assay for anti-ecallantide IgE described in the submission is unexpectedly sensitive for a chromogenic, antigen-specific IgE assay. The extraordinary sensitivity of this assay is likely an artifact of the surrogate positive control used to establish the limit of detection and limit of

quantitation, which could result in an excess of false negative results when clinical samples are tested. Therefore, the percentage of seroconversion should be interpreted with caution.

2.4.4 IgE antibodies to (b) (4)

Two specific ELISA methods were developed for the detection of human IgE antibodies to *P. pastoris* host cell proteins. (b) (4)
(b) (4)

Following discussions with the FDA in 2006, it was felt the format of this assay did not conform to industry consensus recommendations (Mire-Sluis et al, 2004) and the assay format was changed. The assay utilized a new (b) (4) which consisted of a (b) (4)

The number of patients at risk to seroconvert (ie, the denominator) includes those who have at least 1 post-baseline value but excludes those who are positive at both pre- and post-treatment. Patients who are missing the pre-treatment evaluation are considered to be negative pre-treatment. The number of seroconversion is determined as the number of patients whose pre-treatment evaluation is either negative or missing (ie, the denominator) and who have a post-treatment evaluation that is positive (ie, the numerator). Therefore, in the ecallantide HAE program, and 14 of 175 (8.0%) patients seroconverted to anti-*P. pastoris* IgE antibodies (Table 10).

Table 10 Seroconversion to Anti-*Pichia pastoris* IgE Antibodies

Baseline	Post-Dose Ecallantide (N=219)				
	Negative		Positive	Missing	
	n	(%)	n	(%)	n
IgE Antibodies to <i>P. Pastoris</i>					
Negative	134	(87.0)	8	(5.2)	3
Positive	0	(0.0)	12	(7.8)	0
Missing	27		6		29

Source: ISS Summary Table 10.1.

Note: Percentages are based on the number of patients with both baseline and at least 1 post-baseline result.

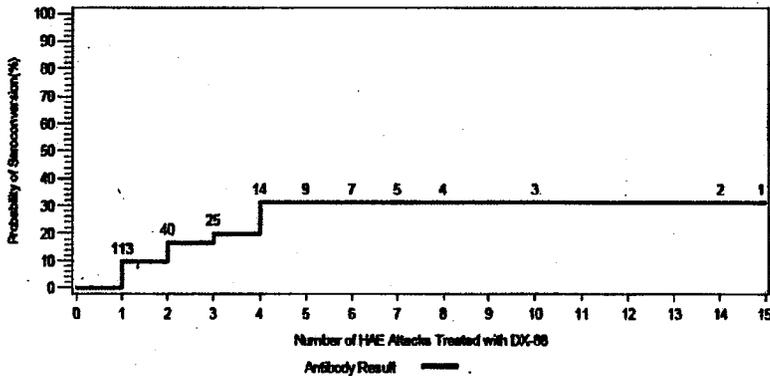
The assay for anti- *Pichia pastoris* IgE described in the BLA is unexpectedly sensitive for a chromogenic, antigen-specific IgE assay. The extraordinary sensitivity of this assay is likely an artifact of the surrogate positive control used to establish the limit of detection and limit of quantitation, which could result in an excess of false negative results when clinical samples are tested. Therefore, the percentage of seroconversion should be interpreted with caution.

2.4.5 Number of Attacks to Seroconversion

Figure 1 displays the number of ecallantide-treated HAE attacks to seroconversion for anti-ecallantide (all classes) antibodies in EDEMA 3 and EDEMA 4 patients. For anti-ecallantide (all classes) antibodies in EDEMA3 and EDEMA 4 patients, there is a steady increase in the probability of seroconversion with each treated episode through the fourth episode, with no further increases through the fifteenth episode. Based on the curve, the probability of seroconversion to

anti-ecallantide (all classes) antibodies after 5 HAE attacks is estimated to be approximately 30%.

Figure 1 Number of DX-88 Treated HAE Attacks to Seroconversion of All Antibodies to DX-88 EDEMA3-DB, EDEMA3-RD, and EDEMA4 Patients Treated with DX-88



Note: The estimates 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.
 Excludes patients who were antibody positive at the time of their first DX-88 exposure in EDEMA3-DB, EDEMA3-RD, or EDEMA4 or who were antibody negative before their first DX-88 exposure in EDEMA3-DB, EDEMA3-RD, or EDEMA4 and then had no post-baseline antibody evaluations. This figure also includes patients who were antibody negative at baseline but positive at post-baseline.
 Eight (8) patients were excluded because the patient seroconverted during EDEMA2.

2.4.6 Antibody status to pharmacokinetics, efficacy and adverse effect

Only the results of immunogenicity assays (all-class) performed in the Phase 3 Clinical Studies were validated. However, no pharmacokinetic samples were taken in Phase 3 studies. Therefore, the effect of immunogenicity on pharmacokinetics could not be evaluated.

Details of the effect of immunogenicity on efficacy and safety could be found in the pharmacometrics review. In general, there was no apparent correlation between effectiveness or safety and presence of neutralizing antibodies. In clinical studies, anti-ecallantide and IgE anti-ecallantide antibody status do not appear to correlate with the percentage of patients who experienced treatment emergent adverse events (TEAEs). There was no apparent correlation between safety or effectiveness and presence of neutralizing antibodies. Positive anti-ecallantide antibody status does not appear to increase the incidence of TEAEs. There was no obvious relationship between the time of onset of the TEAE and when a patient became antibody positive.

As a protein therapeutic, anaphylaxis and anaphylactoid to ecallantide is expected and is considered the major severe adverse effect. The following part discusses the relationship between anaphylaxis and immunogenicity.

Three cases of anaphylaxis and one case of anaphylactoid reaction were identified by the sponsor.

•Patient 8805051099 (EDEMA3) experienced anaphylaxis twice – the first time after her 17th dose of ecallantide and the second during a re-challenge procedure. The patient was noted to

have tested intermittently positive to IgE against *P. pastoris* up to 2 years before the first event as well as non-IgE to ecallantide.

•Patient 8820401009 (EDEMA4) developed anaphylaxis after her 4th dose of ecallantide. The patient had intermittently tested positive for non-IgE and IgE antibodies to ecallantide since her 2nd dose and 3rd doses, respectively, although she tested negative for IgE to ecallantide immediately prior to the event.

•Patient 8805024097 (EDEMA2) developed anaphylaxis 10 minutes after her 6th dose. The patient tested positive for non-IgE antibodies to ecallantide after the 5th dose and positive for IgE 7 days after the anaphylaxis. The patient went on to complete a successful rechallenge procedure and received 11 additional doses of ecallantide.

•Patient 8802003005 (EDEMA0) was identified as having an anaphylactoid reaction 5 minutes after her first dose of ecallantide (40 mg/m² IV). She test positive for ecallantide antibodies per the investigator's own immunoblot, but subsequently negative on the Applicant's ELISA assays.

During the review process, the clinical review team identified four additional potential case of anaphylaxis.

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

•Patient 8804013003 (EDEMA1) developed rhinitis, itchy throat, and shortness of breath following receipt of her 1st dose of ecallantide 20 mg/m² IV. The patient has not tested positive for antibody formation to ecallantide or *P. pastoris*.

•Patient 8805019001 (EDEMA2) experienced symptoms suggestive of anaphylaxis during a rechallenge procedure 2 minutes after the start of the 1st ecallantide dose (10 mg/m² IV). The patient tested positive for IgE antibodies to *P. pastoris* 1 year prior to the reaction but had tested negative in subsequent assays. On re-challenge 18 months later, she developed sneezing, nasal congestion, throat itchiness, and cough.

•Patient 8805050097 (EDEMA2) developed abdominal pain, nausea, vomiting, throat itchiness, and nasal congestion following receipt of the 1st dose of ecallantide for treatment of an external head/neck HAE attack. Study drug infusion was stopped. No antibodies were detected and the patient did not undergo a re-challenge procedure.

2.4.7 Comments on immunogenicity results

Several deficiencies were identified with the immunogenicity assays and incomplete data, which may significantly affect the results of immunogenicity. Therefore, the immunogenicity results may not be reliable and should be interpreted with caution. When the immunogenicity results from later time points are available in study EDEMA4, they should be included to calculate the incidence of immunogenicity. In addition, it appears that there is a steady increase in the probability of seroconversion with increased dose. Considering most patients enrolled in the clinical trial only received limited number of treatments of ecallantide, and the HAE patients

may be given the drug for lifetime, close monitoring and report of immunogenicity is recommended as a post marketing commitment or REMS if it is approved.

2.5 Extrinsic Factors

1. What extrinsic factors (drugs herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or response and what is the impact of any differences in exposure on response?

No study on influence of extrinsic factors was conducted.

2. Drug-drug interactions

No drug-drug interaction evaluations were conducted.

2.6 General Biopharmaceutics

1. Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Ecaltantide is a polypeptide. Therefore, the BCS class does not apply to this drug.

2. What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trials?

The ecaltantide drug substance manufacturing process has evolved during the course of development. (b) (4)

(b) (4)

The sponsor indicated that pivotal nonclinical and clinical studies were conducted using material made according to the commercial (b) (4) process. The majority of ecaltantide drug substance batches (b) (4) were manufactured using the commercial (b) (4) process and the 2nd generation (b) (4) process; these 2 processes consist of the same unit operations but employ different scales. Therefore, no relative bioavailability study was conducted from the proposed to-be-marketed formulation to the pivotal clinical trials formulation.

2.7 Analytical Section

2.7.1 Drug assays

1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

No clinical or preclinical studies were conducted to assess metabolism of the drug. Only the parent drug was measured.

2. What bioanalytical methods are used to assess concentrations?

The assays used to measure ecallantide in plasma evolved during clinical development. The assays used to measure ecallantide concentration can be found in Table 11. The plasma concentration of ecallantide was initially measured using a high performance liquid chromatography method with mass spectral detection (HPLC/MS and HPLC/MS/MS). Due to poor detection limits, a sandwich enzyme-linked immunosorbent assay (ELISA) was then developed with a 100-fold greater sensitivity.

Table 11 Validation Parameters for Ecallantide Bio-analytical Assays

Calibration Curve Range	0.5-20 µg/mL	0.473-39.4 µg/mL	0.156-10 ng/mL
Linearity	0.99	>0.99	>0.99
LLOQ	0.5 µg/mL*	0.473 µg/mL	0.156 ng/mL
Precision	%RSD<11.3%*	%CV<13.3%	%CV<16.8
Accuracy	96.4%-116.3%	85.6%-102.1%	98.1%-105.4%
Recovery	Not performed due to extraction method	Not performed due to extraction method	80%-112%
Selectivity/Specificity	Pass	Pass	Pass
Freeze-thaw Stability	Not Performed	87.1%-109.9% 4 cycles	%CV<7.6% 5 cycles
Short-term Stability	80.1%-103.6% 24 hours ambient	89.2%-110.6% 28 hours ambient	Not Performed
Long-term Stability	Not Performed	95.8%-101.4% 113 days at -80°C	Not Performed
Stock stability	91.9%-122.9% 7 days at 4°C	104.4% 350 days at -20°C	Not Performed
Post-preparative stability	Not Performed	99.6%-103.2% 217.9 hours ambient	Not Performed
Clinical study	DX-88/1	DX-88/2 (EDEMA0) DX-88/4 (EDEMA1) DX-88/6	DX-88/5 (EDEMA2) DX-88/13 DX-88/15

*Primary validation was performed in rat serum with subsequent partial validation in cynomolgus monkey and human plasma.

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Two HPLC/MS methods were developed for the detection of ecallantide. In the first HPLC/MS method developed by (b) (4), the assay was first validated in rat serum. The assay was cross-validated to monkey and human plasma where linearity, accuracy, specificity, and stability were determined in those matrices. However, in the in-study bio-analytical reports, information on QC (quality control) samples precision and accuracy could not be found. The agency sent an information request letter requesting this information from the sponsor on Dec 4th, 2008, and the sponsor replied on Dec 11th, 2008, indicating QC information will be submitted within approximately one month. On Jan 29th 2009, the sponsor submitted additional information, indicating the precision and accuracy of QC were not calculated in the study analyzed by (b) (4)(DX/88-1). Therefore, the pharmacokinetic result from DX/88-1 is considered invalid.

A second HPLC/MS/MS method was developed and validated by (b) (4) in (b) (4). Samples from three studies (DX-88/6, DX-88/2 and DX-88/4) were analyzed using this method within the time frame of January 2000 and December 2004. Because of the possible bio-analytical issues with (b) (4) within this time frame, the sponsor contracted with external auditors (b) (4) along with (b) (4) to conduct a comprehensive audit of (b) (4) and the affected studies. One consistent audit finding was the lack of a standard operating procedure (SOP) for the management of chromatographic data integration, which can allow for unstandardized modifications to the chromatographic peak

baselines by the analyst per their scientific judgment. However, the auditors concluded that based on the numbers of samples with corrected baselines, the possible deviations in the analytical results would have minimal effects on the pharmacokinetic analyses. The results of sample analysis in individual study are acceptable as evidenced by QC sample precision and accuracy within $\pm 15\%$. Therefore, the bio-analytical results from (b) (4); are considered acceptable.

An ELISA method with greater sensitivity (LLOQ (b) (4); was developed and validated by (b) (4) (b) (4) (b) (4)

Certain issues were identified with this ELISA method. First, ecallantide shares 88% identity with TFPI, a.k.a. lipoprotein-associated coagulation inhibitor, between TFPI amino acid residues 59 and 118. TFPI is a glycosylated protein found predominantly in the vascular endothelium and plasma in both free forms and bound with plasma lipoproteins. The sponsor did not provide any discussion or data on the potential of antibodies directed against the ecallantide to cross-react with endogenous TFPI. Such cross-reactivity may interfere with the ecallantide immunoassays and affect the results. Secondly, no stability protocol was performed following the initial validation. The sponsor indicated that a long term stability study of ecallantide PK samples is currently ongoing in support of the ELISA PK method employed in another indication of this drug (cardiothoracic surgery indication). This method is performed by (b) (4); and is similar to (b) (4); A method. At the present time, the samples have been stored below -60°C for a total of 16 months with no apparent loss of signal through the 12-month time point and support the (b) (4) ELISA method. Thirdly, no QC information could be found in the in-study bio-analytical reports by using the ELISA methods. In the IR letter dated Dec 4th, 2008, the agency requested the sponsor to re-submit each in-study bio-analytical report with QC information, and provide a summary table to summarize the parameters for each individual study. The sponsor replied on Dec 11, 2008, indicating QC information has been requested from (b) (4) and will be submitted within approximately one month. On Jan 29th 2009, the sponsor submitted new information on QC. However, the sponsor only submitted a summary table about the QC information; no complete in-study bio-analytical reports with QC information were submitted. The agency contacted the sponsor again on Feb 09, 2009, asking for the complete in-study bio-analytical reports. As of Feb 11, 2009, the sponsor has not submitted the information yet. Therefore, it can not be concluded whether the results from the studies analyzed by (b) (4) (DX-88/5, DX-88/13 and DX-88/15) are acceptable.

In summary, among the three bio-analytical methods used to measure ecallantide concentration, only the results from (b) (4) are considered acceptable based on current information. However, when comparing the individual PK parameters from the Phase I studies (DX-88/1, DX-88/6, DX-88/13, and DX-88/15), the results are comparable among similar dosing regimens, although the samples from these four Phase I studies are analyzed by the three separate analytical lab and the results are comparable. Because of the review timeline, the results from all three analytical methods are temporarily considered valid and used in the individual and population PK analysis. The final decision will be made based on the new information that the sponsor will submit.

2.7.2 Immunogenicity assays

The methodology of the immunogenicity assays in this submission was reviewed by Dr. Jack A Ragheb from CMC. Complete review of the assay methodology could be found in the CMC review. In summary, it was found the immunoassay methods are generally adequate except for the anti-IgE assay. However, the current validated assay for the anti-ecallantide antibodies (all-class) was used only in Phase 3 Clinical Studies DX-88/14 and DX-88/20. Thus, the results of immunogenicity assays performed in the Phase 1 and 2 Clinical Studies was not used to calculate the frequency anti-ecallantide antibodies (all-class).

A serious deficiency of this submission is the sponsor's failure to provide any discussion or data on the potential of antibodies directed against the drug substance to cross-react with endogenous TFPI. Such cross-reactivity may interfere with the DX-88 immunoassays, which was not explored by the sponsor, which may be reflected in the 20% background signal observed in the drug confirmatory ECL assay when results with human serum normal controls (HSNC) are reported as signal/background (S/B) ratios and the need for a relatively high PC antibody concentration (421 ng/mL) to demonstrate selectivity in the neutralizing antibody (Nab) assay.

The assay for both anti-DX-88 and anti-P.pastoris IgE described in the BLA is unexpectedly sensitive for a chromogenic, antigen-specific IgE assay. The extraordinary sensitivity of this assay is likely an artifact of the surrogate positive control used to establish the limit of detection and limit of quantitation, which could result in an excess of false negative results when clinical samples are tested.

Additionally, the sponsor concluded that cut-point determinations based on normal human serum are not equivalent to those based on serum from treatment naïve HAE patients. However, the sponsor has not provided any data generated with treatment naïve HAE patient serum or plasma.

2.7.3 Anti-Ecallantide Antibodies (all-class)

Three ELISA methods were developed for the detection of anti-ecallantide antibodies in early development stage (Phase 1 and Phase 2 stage). However, none of these assays have been validated. Therefore, the results of immunogenicity assays in the Phase 1 and Phase 2 study was not validated and was not included in immunogenicity (all-class) calculation.

(b) (4)

The assay for anti- *Pichia pastoris* IgE described in the BLA is unexpectedly sensitive for a chromogenic, antigen-specific IgE assay. The extraordinary sensitivity of this assay is likely an artifact of the surrogate positive control used to establish the limit of detection and limit of quantitation, which could result in an excess of false negative results when clinical samples are tested. Therefore, the percentage of seroconversion should be interpreted with caution.

Comments on immunogenicity assay

Several deficiencies were identified with the immunogenicity assays, which may significantly affect the results of immunogenicity. Therefore, the immunogenicity results may not be reliable and should be interpreted with caution.

3 Detailed Labeling Recommendations

The sponsor has not submitted the required QC information from (b) (4) yet as of Feb 11, 2009. So it can not be concluded whether the pharmacokinetic results based on studies analyzed by (b) (4); (DX-88/5, DX-88/13 and DX-88/15) are acceptable, which will have direct impacts on labeling statements. Therefore, the detailed labeling recommendations were not included in this version of the review.

4 Appendix

4.1 Pharmacometrics Review

**OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW**

Application Number	125277
Submission Number (Date)	Sep 23, 2008
Clinical Division	DADP
Primary PM Reviewer	Ping Ji, Ph.D.
Secondary PM Reviewer	Christoffer W. Tornoe, Ph.D.

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Summary of Findings

The key pharmacometric findings from Ecalantide BLA125277 submission are:

- A three-compartment disposition model with first-order absorption and elimination was found to adequately describe the ecallantide concentration-time profiles in the dose range studied (10-80 mg and 5-40 mg/m²). The model estimated clearance (CL) and steady-state volume of distribution (V_{ss}) were 7.56 L/h and 15 L.
- Three covariates affected ecallantide pharmacokinetics: population, body weight and assay type.
 - The clearance of ecallantide was found to be 23.4% lower in HAE or AAE patients (7.56 L/h) than in healthy subjects (9.87 L/h).
 - An inverse relationship was observed between body weight and the rate of absorption after SC administration; as weight increased the rate of absorption decreased with no change on the extent of absorption.
 - The assay type affected the central volume of distribution, which was 20% smaller for patients whose samples were assayed using an LC-MS/MS (LLOQ: 0.473 mg/L) assay compared to patients whose samples were assayed using an ELISA (LLOQ: 0.156 mg/L) or LC-MS (LLOQ: 0.5 mg/L) assay.
- Neither age nor sex had an effect on ecallantide exposure. However, the relatively small sample distribution of elderly population may not allow the labeling recommendation in this age group. The whole population PK model dataset (development + validation) consisted of 173 individuals with 3090 concentrations, among which 3 subjects were greater than 65 yr of age (16 concentrations, <1%).
- There appeared to be a dose-response relationship for effectiveness (successful outcome) (Study DX-88-5). The proportion of patients with successful outcome was less for 5 mg/m² IV (0.458) compared to 10 mg/m² IV (0.681) and 20 mg/m² IV (0.6) dosing regimens. Patients treated with ecallantide 30 mg SC (~17 mg/m²) had the highest proportion of successful outcomes (0.817) and was the dose used in the pivotal trials.
- A cumulative increase in treatment emergent adverse events (TEAEs) was observed as the number of doses given increased.
- The incidence of seroconversion appears to increase with increasing number of ecallantide treatments.
- There was no apparent correlation between effectiveness or safety and presence of neutralizing antibodies.

Note: The population PK analysis was based on all available ecallantide concentrations assuming that all concentrations were measured using validated analytical methods. Because of unresolved bio-analytical issues, the results in population PK analysis should be considered temporary and subject to change.

1.1 Key Review Questions

The purpose of this pharmacometrics review is to address the following key questions.

1.1.1 Is there evidence supporting one fixed dose for all patients?

Yes, one fixed dose regimen is appropriate for all patients.

Three covariates affected ecallantide pharmacokinetics: population, body weight and assay type. An inverse relationship was observed between the subject body weight and the rate of absorption after SC administration; as weight increased the rate of absorption decreased with no change on the extent of absorption. The assay type affected the central volume of distribution, which was 20% smaller for patients whose samples were assayed using an LC-MS/MS (LLOQ: 0.473 mg/L) assay compared to patients whose samples were assayed using an ELISA (LLOQ: 0.156 mg/L) or LC-MS (LLOQ: 0.5 mg/L) assay.

Body weight, age, gender, and laboratory values examined did not significantly influence the PK of ecallantide total exposure (*Source: Sponsor's Population Pharmacokinetic Report-DX-88, page 36-37*). As body weight is not a significant covariate on the exposure of ecallantide, the reviewer agrees with the sponsor's proposal of a fixed, i.e. not body weight adjusted, dosing regimen of 8 mg q2w.

1.1.2 Is the number of elderly or pediatric subjects in the POP PK model adequate for the labeling recommendation?

The number of pediatric subjects in the POP PK model appears adequate, but the number of elderly subjects is not adequate for labeling recommendation.

The whole population PK model dataset (development + validation) consisted of 173 individuals with 3090 concentrations, among which 19 subjects were below 18 yrs of age (191 concentrations, 6%) and 3 subjects were greater than 65 yr of age (16 concentrations, <1%). Thus, the relatively small sample distribution of elderly population may not be adequate for the labeling recommendation in this age group.

1.1.3 Is there evidence of exposure-response for effectiveness and safety?

Yes, exposure-response relationships appear to exist for both effectiveness and safety.

A dose response relationship appeared to exist from study DX-88-5 for the successful outcome (defined as attack resolution begun within 4 hours after treatment and maintained for 24 hours) (Table 1.1.3A). Patients treated with ecallantide 5 mg/m² IV had lower proportion of successful outcomes (0.458) than patients treated with 10 mg/m² IV, 20 mg/m² IV and 30 mg SC (~17 mg/m²). It is of note that the absolute bioavailability of SC ecallantide was more than 90% (DX-88/13).

Table 1.1.3A: Number (proportion) of patients with successful outcome (DX-88-5)

Dosing Regimen	5 mg/m ² , IV	10 mg/m ² , IV	20 mg/m ² , IV	
Number (success/attack)	11/24	96/141	9/15	
proportion	0.458	0.681	0.6	

Source: Summarized from dx-88-5 CSR, summary table 14.1.2-2B

Because of small sample size, it is difficult to assess the dose response relationship from studies DX-88-2 and DX-88-4 statistically (Tables 1.1.3B and C), although the success

rate in the treated group (29/40, 72%) appeared to be higher than placebo group (8/32, 25%) from study DX-88-4.

Table 1.1.3B: Number (proportion) of patients who reported beginning of resolution of attack symptoms by 4 hours post-treatment with DX-88 (DX-88-2)

Dose Level	Total Patients (N)	Patient Reports n (%)
Overall	8	4 (50.0%)
10 mg	3	2 (66.7%)
40 mg	3	1 (33.3%)
80 mg	2	1 (50.0%)

Source: dx-88-2 final report, Table 11-4, page 54

Table 1.1.3C: Number (proportion) of patients with successful outcome (DX-88-4)

Dose Level	DX-88 (Ecallantide)		Pooled Placebo		p-value
	Response	Percent	Response	Percent	
5 mg/m ²	8/10	80.0%	2/8	25.0%	0.0536*
10 mg/m ²	5/10	50.0%	2/8	25.0%	0.3665
20 mg/m ²	7/10	70.0%	2/8	25.0%	0.1534
40 mg/m ²	9/10	90.0%	2/8	25.0%	0.0128**

* borderline statistically significant (0.05 < p-value < 0.1); ** statistically significant (p-value < 0.05)

Source: dx-88-5 final study report, table 11-7, page 66

In general, a cumulative increase in treatment emergent adverse events (TEAEs) was observed as the number of doses given increased (Table 1.1.3D). However, the observation of more TEAEs could be also the consequence of the presence of more HAE attacks (eg, TEAEs in the gastrointestinal SOC that are related to HAE).

Table 1.1.3D: Selective cumulative TEAEs by system oral class occurring in patients in population I by exposure to ecallantide

	1 Dose (N=108)		2-4 Doses (N=80)		5-9 Doses (N=19)		>9 Doses (N=12)	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients with ≥1 TEAE	52	(48.1)	60	(75.0)	18	(94.7)	12	(100.0)
Blood and Lymphatic System Disorders	2	(1.9)	5	(6.3)	2	(10.5)	3	(25.0)
Cardiac Disorders	0	-	1	(1.3)	3	(15.8)	2	(16.7)
Congenital, Familial and Genetic Disorders	3	(2.8)	7	(8.8)	6	(31.6)	2	(16.7)
Ear and Labyrinth Disorders	1	(0.9)	0	-	1	(5.3)	1	(8.3)
Eye Disorders	4	(3.7)	4	(5.0)	1	(5.3)	1	(8.3)
Gastrointestinal Disorders	21	(19.4)	28	(35.0)	15	(78.9)	11	(91.7)
General Disorders and Administration Site Conditions	17	(15.7)	17	(21.3)	12	(63.2)	11	(91.7)
Immune System Disorders	2	(1.9)	0	-	0	-	1	(8.3)
Infections and Infestations	12	(11.1)	21	(26.3)	11	(57.9)	9	(75.0)
Injury, Poisoning and Procedural Complications	0	-	7	(8.8)	5	(26.3)	3	(25.0)
Investigations	7	(6.5)	12	(15.0)	7	(36.8)	8	(66.7)
Metabolism and Nutrition Disorders	0	-	3	(3.8)	3	(15.8)	1	(8.3)
Musculoskeletal and Connective Tissue Disorders	10	(9.3)	9	(11.3)	7	(36.8)	4	(33.3)
Neoplasms Benign, Malignant, and Unspecified	0	-	1	(1.3)	0	-	0	-
Nervous System Disorders	11	(10.2)	22	(27.5)	9	(47.4)	9	(75.0)
Psychiatric Disorders	2	(1.9)	3	(3.8)	2	(10.5)	3	(25.0)
Renal and Urinary Disorders	3	(2.8)	5	(6.3)	2	(10.5)	2	(16.7)
Reproductive System and Breast Disorders	1	(0.9)	4	(5.0)	2	(10.5)	4	(33.3)
Respiratory, Thoracic and Mediastinal Disorders	12	(11.1)	10	(12.5)	8	(42.1)	6	(50.0)
Skin and Subcutaneous Tissue Disorders	11	(10.2)	20	(25.0)	5	(26.3)	7	(58.3)
Surgical and Medical Procedures	0	-	3	(3.8)	1	(5.3)	0	-
Vascular Disorders	4	(3.7)	4	(5.0)	3	(15.8)	3	(25.0)

Source: ISS Summary Table 5.4.

Abbreviations: TEAE=treatment-emergent adverse event, SOC=system organ class.

Note: (1) Patients reporting more than 1 event with the same SOC are counted only once for that SOC.

(2) Percentages based on number of unique patients in the safety population for each exposure group.

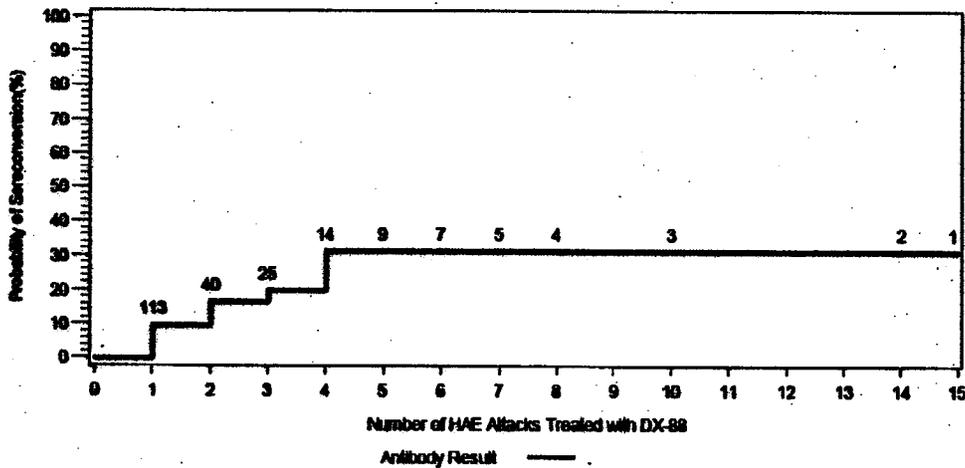
Source: 2.7.4 Summary of clinical safety-Table 2.7.4.19, page 66.

1.1.4 Does the immunogenicity affect the effectiveness, safety, and PK?

There was no apparent correlation between effectiveness or safety and presence of neutralizing antibodies. The effect of immunogenicity on PK in clinical studies was not evaluated.

The incidence of seroconversion appears to increase with increasing exposure to ecallantide. For anti-ecallantide (all classes) antibodies, there is a steady increase in the probability of seroconversion with each treated episode through the fourth episode. Based on the curve, the probability of seroconverting to anti-ecallantide (all classes) antibodies after 4 HAE attacks is estimated to be approximately 30%.

Fig. 1. Number of DX-88 Treated HAE Attacks to Seroconversion of All Antibodies to DX-88 (IgE and/or Non-IgE) EDEMA3-DB, EDEMA3-RD, and EDEMA4 Patients Treated with DX-88



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.
Excludes patients who were antibody positive at the time of their first DX-88 exposure in EDEMA3-DB, EDEMA3-RD, or EDEMA4 or who were antibody negative before their first DX-88 exposure in EDEMA3-DB, EDEMA3-RD, or EDEMA4 and then had no post baseline antibody evaluations. This figure also includes patients who were antibody unknown at baseline but positive at post baseline.
Eight (8) patients were excluded because the patient seroconverted during EDEMA2.

(Source: Response to FDA Request for Information, sequence 0017, p 3)

Figure 1.1.1. Number of ecallantide-treated HAE Attacks to seroconversion - anti-ecallantide (all classes) antibodies (all patients in HAE studies)

The antibody detection was intermittent. For example, patient 5199 in DX-88/5 was tested positive for IgE antibodies to *P pastoris* after treatment for Episodes 4, 6, 7, 9, 10, 11, and 12, and negative in other episodes. It is noteworthy that the immunogenicity assay method Phase 1 and 2 studies had not been validated and no pharmacokinetic samples were collected in the Phase 3 studies, so no definitive conclusion can be made on the effect of immunogenicity on ecallantide exposure in the clinical studies.

In preclinical studies, 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 10 mg/kg and 20 mg/kg dose groups. In rats, 22 of 30 (73%) of animals in the 25 mg/kg dose group were antibody-positive and in the cynomolgus monkey, 12 of 12 (100%) of animals in the 10 mg/kg and 25 mg/kg dose groups were antibody-positive. Antibodies generally were detected 1 month following the initiation of dosing and persisted throughout the 180 day, every third day dosing study. Incidence at the 0.4 mg/kg dose level was 30% in rats and 63% in monkeys. Antibody-positive animals tended to have increased exposure to ecallantide compared to antibody-negative animals or animals with lower antibody titers or concentrations. In rats, the mean C_{max} and AUC_{last} more than doubled in the 25 mg/kg dose group on day 177 compared to day 0. A similar trend was observed in monkeys with mean C_{max} , AUC_{last} , and $t_{1/2}$ more than doubling in antibody-positive animals in the 10 mg/kg and 25 mg/kg dose groups at the end of the dosing phase when compared to day 0. The increased exposure did not result in a differential toxicity profile and ecallantide was tolerated similarly in both antibody-positive and antibody-negative animals. (Source: 2.6.6 Toxicology written summary, Page 40)

In clinical studies, anti-ecallantide and IgE anti-ecallantide antibody status do not appear to correlate with the percentage of patients who experienced treatment emergent adverse events (TEAEs). There was no apparent correlation between safety or effectiveness and presence of neutralizing antibodies. Thirty-six of 216 patients (16.7%) were 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 incidence of TEAEs. There was no obvious relationship between the time of onset of the TEAE and when a patient became antibody positive. (Source: 2.7.4 Summary of clinical safety, page 90)

1.2 Recommendations

None.

1.3 Labeling Statements

Labeling statements to be removed are shown in ~~red-strikethrough font~~ and suggested labeling to be included is shown in underline blue font. Because of unresolved bio-analytical issues, the recommendations should be considered temporary and subject to change.

8.4 Pediatric Use

(b) (4)

8.5 Geriatric Use

(b) (4)

12.3 Pharmacokinetics

Following the administration of a single 30 mg subcutaneous dose of KALBITOR to healthy subjects, a mean (\pm standard deviation) maximum plasma concentration of 586 ± 106 ng/mL was observed approximately 2 to 3 hours post-dose. The mean area under the concentration-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. A population pharmacokinetic analysis, using concentration data from both healthy subjects and patients, (b) (4)

(b) (4) (b) (4) Body weight, age, and gender were also shown to have no impact on KALBITOR exposure. Ecallantide is a small protein (7054 Da) and renal elimination in the urine of treated subjects has been demonstrated.

No pharmacokinetic data are available in patients or subjects with hepatic or renal impairment.

2 PERTINENT REGULATORY BACKGROUND

None.

3 RESULTS OF SPONSOR'S ANALYSIS

The key findings from sponsor's population PK analysis are summarized below:

- The final model was best fit with a 3-compartment mathematical model.
- DX-88 had linear pharmacokinetics between tested doses of 8 mg and 96 mg.
- Subject age, sex, disease state had no effect on DX-88 exposure.
- Two covariates affected DX-88 pharmacokinetics: total body weight on the rate of absorption after SC administration and assay type on the central volume of distribution.
- The relative bioavailability after SC administration was ~100% for 30 mg dose of the liquid formulation, 87% for 10 mg dose of the liquid formulation, and 79% for 30 mg dose of the lyophilized formulation.
- The volume of distribution at steady state was ~15.1L, which is consistent to the distribution to the extracellular fluid.
- The clearance was 7.56 L/h, and the half-life was short with α -, β -, and γ -half-lives as 0.4 hours, 0.8 hours, and 4.5 hours, respectively.

Reviewer's comments:

Sponsor's population PK analysis is generally adequate and the significant covariates identified by the sponsor were reproduced.

However, the following limitations of sponsor's population PK analysis were identified:

- *The model estimation using the combined dataset including both modeling and validating datasets could not converge due to an infinite objective function. Sponsor explained this as possibly due to large number of patients in the validation dataset and the discrepancy between the two datasets. (Population PK report, Page 36-37)*

In reviewer's analysis, the population pharmacokinetic model of ecallantide was developed using the combined dataset.

4 REVIEWER'S ANALYSIS

4.1 Introduction

In sponsor's analysis, the pharmacokinetic model estimation minimized successfully with the modeling dataset, however, the model estimation using the combined dataset including both modeling and validating dataset could not converge due to an infinite objective function. In reviewer's analysis, the population pharmacokinetic model of ecallantide was developed and evaluated using the combined dataset.

4.2 Objective

- To assess the proposed labeling claims based on the PopPK analysis

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table .

Table 4.3.1: Analysis Data Set

Study Number	Name	Link to EDR
DX-88-1, 2, 4, 5, 6, 13, 15	Mega-dat.txt	\\cbsap58\m\leCTD_Submissions\STN125277\0009\m5\datasets\dx88-pop-pk\analysis\programs\input\mega-dat.txt

4.3.2 Software

SAS, S-PLUS, NONMEM were used for the reviewer's analyses.

4.3.3 Covariates investigated

In sponsor's analysis, covariates effects had been extensively investigated, including visit number, assay type, age, gender, body mass index, body surface area, body weight and baseline laboratory results. Only body weight and assay type were shown to be significant covariates and this result was reexamined in reviewer's analysis. In addition, the effect of body weight, age and gender on drug clearance and central volume of distribution was also re-evaluated.

4.4 Results

4.4.1 Population Pharmacokinetic Analysis

The listing of base and covariate model development is displayed in the Appendix 1. The parameter estimates and goodness-of-fit graphs for the reviewer's final PK model are presented in Appendixes 2 and 3, respectively.

Similar to sponsor's population PK findings, a three-compartment disposition model with first-order absorption and elimination was found to adequately describe the ecallantide concentration-time profiles in the dose range studied (10-80 mg and 5-40 mg/m²). The estimated steady-state volume of distribution (V_{ss}) estimate was 15 L.

The effect of disease on the pharmacokinetics of ecallantide was also assessed. The clearance of ecallantide was 23.4% lower in HAE or AAE patients (7.56 L/h) than in healthy subjects (9.87 L/h). Body weight and Assay method were found to be significant PK covariates (see Figure 4.4.1) consistent with sponsor's findings. An inverse relationship was observed between body weight and the rate of absorption after SC administration; as weight increased the rate of absorption decreased with no change on the extent of absorption. The assay type affected the central volume of distribution, which was 20% less for patients whose samples were assayed using an LC-MS/MS (LLOQ: 0.473 mg/L) assay compared to patients whose samples were assayed using an ELISA (LLOQ: 0.156 mg/L) or LC-MS (LLOQ: 0.5 mg/L) assay. Age, body weight and sex were not found to affect the CL and central volume of distribution of ecallantide.

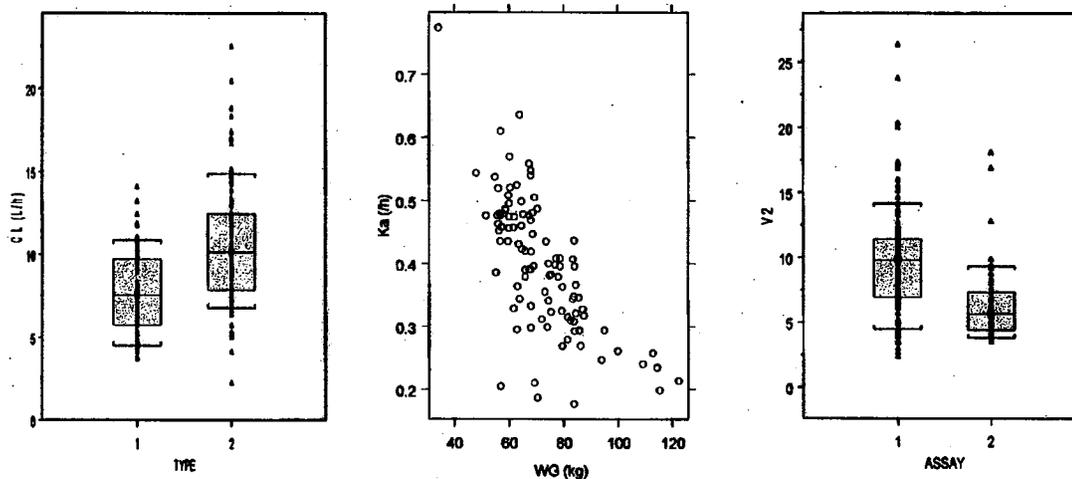


Figure 4.4.1: Identified covariate – PK parameter relationships for ecallantide. (Left) Disease type vs CL, (Middle) Ka vs. Weight, and (Right) Assay vs. V2.

APPENDIX 1: LISTING OF ANALYSES FILES AND OUTPUT FILES

LISTING OF ANALYSES FILES AND OUTPUT FILES					
No.	File Name	Output files	Description	OFV	Comments
1	m1fo.mod	m1fo.lst	1-comp	4409.644	
2	m2fo.mod	m2fo.lst	2-comp	-1701991	
3	m3fo.mod	m3fo.lst	3-comp	-1745.298	
4	m3fo_err.mod	m3fo_err.lst	Model m3fo-nmn.mod with different residual error terms for the different assays used in the studies	-2053.303	
5	m3fo_A.mod	m3fo_A.lst	Model m3fo_err.mod with different absorption for different form and SC doses.	-2357.372	
6	m3fo_B.mod	m3fo_B.lst	Model m3fo_err.mod with lag time added to 10 mg liquid form	-2381.530	
7	m3fo_C.mod	m3fo_C.lst	Model m3fo_err.mod with lag time added overall	-2420.423	
8	base_foce.mod	base_foce.lst	Sponsor's base model	-2463.213	
9	base_foce_type_CL.mod	base_foce_type_CL.lst	Model base_foce.mod with difference in CL between healthy and patients	-2478.905	Base model
10	base_foce_type_V2.mod	base_foce_type_V2.lst	Model base_foce.mod with difference in V2 between healthy and patients	-2466.011	
11	base_foce_1.mod	base_foce_1.lst	Model base_foce_type_CL.mod with thigh factor on ALAG1 removed	-2471.646	
12	base_foce_2.mod	base_foce_2.lst	Model base_foce_type_CL.mod with thigh factor on ka removed	-2416.458	
13	base_foce_3.mod	base_foce_3.lst	Model base_foce_type_CL.mod with same absorption kinetics between 10 and 30 mg SC formulation	-2266.406, terminated	
14	Base_foce_4.mod	Base_foce_4.lst	Model base_foce_type_CL.mod with same absorption kinetics between liquid and lyophilized SC formulation	-2209.512, terminated	

LISTING OF ANALYSES FILES AND OUTPUT FILES					
No.	File Name	Output files	Description	OFV	Comments
15	Base_foce_WT.mod	Base_foce_WT.lst	Model base_foce_type_CL.mod with wt added to ka	-2443.702	
16	Base_foce_assay.mod	Base_foce_assay.lst	Model base_foce_type_CL.mod with assay added to v2	-2485.97, terminated	
17	final_foce.mod	final_foce.lst	Sponsor's final model	-2579.842	
18	Base_foce_CLV.mod	Base_foce_CLV.lst	Model base_foce_type_CL.mod to allow CL and V2 to correlate	-2541.806, Rmatrix	
19	Base_foce_CLV_A.mod	Base_foce_CLV_A.lst	Model Base_foce_CLV.mod to remove thigh on ka	-2478.981	
20	Base_foce_CLV_B.mod	Base_foce_CLV_B.lst	Model Base_foce_CLV.mod to remove thigh on ka	-2535.359	
21	Base_foce_CLV_C.mod	Base_foce_CLV_C.lst	Model Base_foce_CLV.mod to add wt on ka	-2563.599	
22	Base_foce_CLV_D.mod	Base_foce_CLV_D.lst	Model base_foce_CLV.nmn.txt to add assay to V2	-2545.982	
23	Base_foce_CLV_E.mod	Base_foce_CLV_E.lst	Model base_foce_C.nmn.txt to remove thigh on alag1	-2556, terminated	
24	Base_foce_CLV_F.mod	Base_foce_CLV_F.lst	Model Base_foce_CLV_C.mod to add assay to V2	-2567.973	
25	Base_foce_CLV_G.mod	Base_foce_CLV_G.lst	Model Base_foce_CLV_F.mod to remove thigh on alag1	-2513	
26	Base_foce_CLV_H.mod	Base_foce_CLV_H.lst	Model Base_foce_CLV_D.mod to add power function on wt for ka	-2560.561	
27	Base_foce_CLV_I.mod	Base_foce_CLV_I.lst	Model Base_foce_CLV_H.mod to remove eta on alag	-2574.697	
28	Base_foce_CLV_J.mod	Base_foce_CLV_J.lst	Model Base_foce_CLV_I.mod to remove eta on Q4	-2565.857	
29	Base_foce_CLV_K.mod	Base_foce_CLV_K.lst	Model Base_foce_CLV_I.mod to	-2573	

LISTING OF ANALYSES FILES AND OUTPUT FILES

No.	File Name	Output files	Description	OFV	Comments
			add wt on CL		
30	Base_foce_C LV_L.mod	Base_foce_CL V_L.lst	Model Base_foce_CLV_I.mod to add age on CL	-2592	
31	Base_foce_C LV_M.mod	Base_foce_CL V_M.lst	Model Base_foce_CLV_I.mod to add sex on CL	-2576.419	
32	Base_foce_C LV_N.mod	Base_foce_CL V_N.lst	Model Base_foce_CLV_I.mod to add wt on V2	-2577.086	
33	Base_foce_C LV_O.mod	Base_foce_CL V_O.lst	Model Base_foce_CLV_I.mod to add age on V2	-2595.665	
34	Base_foce_C LV_P.mod	Base_foce_CL V_P.lst	Model Base_foce_CLV_I.mod to add sex on V2	-2575.269	
35	Base_foce_C LV_Q.mod	Base_foce_CL V_Q.lst	Model Base_foce_CLV_I.mod to remove thigh effect on alag	-2573.363	
36	Base_foce_C LV_R.mod	Base_foce_CL V_R.lst	Model Base_foce_CLV_I.mod to remove eta on V4	-2563.944	
37	Final_3.mod	Final_3.lst	Model Base_foce_CLV_Q.mod to remove thigh factor	-2605.154	Final model

APPENDIX 2: MODEL PARAMETER ESTIMATES FOR THE FINAL COVARIATE PHARMACOKINETIC MODEL FOR DX-88

Model Parameter Estimates for the Final Covariate Pharmacokinetic Model for DX-88				
Parameter	θ	Estimate	RSE%	BSV%
CL (L/h) (healthy subject)	θ1	9.87	6.6	39
V2 (L)	θ2	8.86	10.5	55
Q3 (L/h)	θ3	1.26	23.2	-
V3 (L)	θ4	2.2	23.1	130
Q4 (L/h)	θ5	9.87	29.6	29
V4 (L)	θ6	3.91	11	83
Ka for liquid formulation (per h per kg weight)	θ7	28.5	6.18	20
F1 on logistic scale for 10 mg dose of the liquid formulation	θ8	-1.9	22.6	73
Ka for 30 mg dose of the lyophilized formulation	θ9	0.317	14	32
F1 on logistic scale for 30 mg dose of the lyophilized formulation	θ10	-1.28	18.2	73
Lagtime for 10 mg dose of the liquid formulation (min)	θ11	7.6	10.5	18
Lagtime for 30 mg dose of the liquid formulation (min)	θ12	2.72	16.5	22
Assay effect on V2	θ13	-0.202	43.5	
Patient effect on CL (%)	θ14	-23.4	28.9	
Correlation between CL and V2		0.40		
Residual variability for Study DX-88/1		0.0174		
Residual variability for Studies DX-88/2, 4, and 6		0.0322		
Residual variability for Studies DX-88/5, 13 and 15		0.133		

The final model was a 3-compartment model estimated with first-order conditional estimation after Ln-Ln transformation

APPENDIX 3: SCATTER PLOTS OF GOODNESS OF FIT OF FINAL MODEL

Best Possible Copy

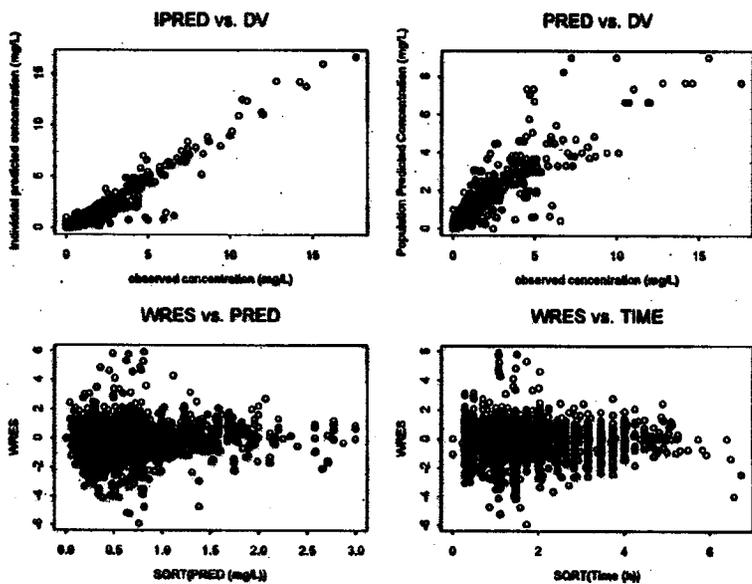


Figure: Scatter plots of goodness of fit of final model (final_3.mod)

APPENDIX 4: SPONSOR'S POPULATION PK ANALYSIS

Title:

Population Pharmacokinetics of DX-88 in Healthy Volunteers, Patients with Hereditary Angioedema, and Patients with Acquired Angioedema

Objectives:

To characterize the pharmacokinetics of the recombinant protein DX-88 (ecallantide), a novel plasma kallikrein inhibitor, in healthy subjects and patients with hereditary angioedema (HAE) or acquired angioedema (AAE).

Study Design:

DX-88/1: Double Blind Placebo Controlled Single Ascending Intravenous Dose Study to Assess the Tolerability and Pharmacokinetic Parameters of DX-88 (plasma kallikrein inhibitor) in Healthy Volunteers. A total of 12 post-dose samples per subject were collected.

DX-88/2: Open-Label, Single Ascending Intravenous Dose Study to Assess the Tolerability and Efficacy of DX-88 (Plasma Kallikrein Inhibitor) Administered Following Onset of Peripheral and/or Facial Edema or Abdominal Symptoms in Patients with Angioedema. A total of 11 post-dose samples per subject were collected.

DX-88/4: An Ascending Four Dose Placebo Controlled Study to Assess the Efficacy and Tolerability of DX-88 (recombinant plasma kallikrein inhibitor) Administered Following Onset of Acute Attacks of Hereditary Angioedema. A total of 3 to 4 post-dose samples per subjects were collected.

DX-88/5: EDEMA2: Evaluation of DX-88's Effects in Mitigating Angioedema—An Open Label Study to Assess the Efficacy and Tolerability of Repeated Doses of DX-88 (recombinant plasma kallikrein inhibitor) in Patients with Hereditary Angioedema. A total of three post-dose samples per subject were collected.

DX-88/6: An Open-Label Study Designed to Assess the Pharmacokinetic Profiles and Safety of Repeated Dosing of DX-88 in Volunteers Given 4 Intravenous Dose Regimens of DX-88. A total of 12 or 24 samples per subject were collected.

DX-88/13: An Open-Label Study Designed to Assess and Compare the Pharmacokinetic Profiles and Safety of Intravenous versus Subcutaneous Dosing of DX-88, Recombinant Inhibitor of Human Plasma Kallikrein, in Volunteers. A total of 26 post-dose samples per subject were collected.

DX-88/15: A Randomized, Double-Blind, Crossover Study to Assess the Bioequivalence and Safety Profiles of 30 mg DX-88 Liquid versus Lyophilized Formulations in Healthy Volunteers. A total of 26 post-dose samples per subject were collected.

Methods:

Standard population pharmacokinetic modeling methods were used. A suitable base structural pharmacokinetic model was developed first. Covariates were then included in the base structural model in a forwards/backwards stepwise manner using the likelihood ratio test (LRT) as the criteria for model selection. Covariates were confirmed using first-order conditional estimation (FOCE) with a p-value of < 0.01 needed for inclusion in the

model. Once the final pharmacokinetic model was identified, the model was evaluated using the influence diagnostics and predictive checks and then validated using an external validation dataset. The covariates evaluated in the model included visit number, assay type (LC-MS/MS versus ELISA), and subject-specific covariates (subject age, gender, body mass index [BMI], body surface area [BSA], and weight) and baseline laboratory results (alkaline phosphatase, SGOT (AST), SGPT (ALT), total protein, and hematocrit). Subject serum creatinine concentration and creatinine clearance (CrCL), which was calculated by the Cockcroft-Gault equation using actual body weight, were evaluated as covariates only for drug clearance.

Number of Subjects:

The population pharmacokinetic parameters of DX-88 were characterized in 35 angioedema patients (33 with HAE and 2 with AAE; 11 males and 24 females) and 62 healthy subjects (28 males and 34 females) between 11 to 68 years of age and were validated in 76 HAE patients (26 males and 50 females).

Test Product, Dose and Mode of Administration:

DX-88 liquid formulation for IV and SC administration was provided as a sterile, isotonic solution formulated at pH (b) Each mL contained 10 mg ecallantide in (b) (4) (b) (4) containing sodium and potassium phosphate, sodium chloride, and potassium chloride (DX-88/1, 2, 4, 6, 5, 13, 15). Lyophilized DX-88 formulation was a (b) (4)

. The administered doses in each individual study were:

DX-88/1: 10 mg (n=2) IV, 20 mg (n=2) IV, 40 mg (n=2) IV, 80 mg (n=2) IV

DX-88/2: 10 mg (n=3) IV, 40 mg (n=3) IV, 80 mg (n=3) IV

DX-88/4: 5 mg/m² (n=10) IV, 10 mg/m² (n=10) IV, 20 mg/m² (n=10) IV, 40 mg/m² (n=11) IV

DX-88/5: 5 mg/ m² (n=18) IV, 10 mg/ m² (n=55) IV, 10 mg/ m² (n=9) IV, 30 mg/ m² (n=31) SC

DX-88/6: 20 mg/ m² (n=8) IV

DX-88/13: 30 mg (n=17) IV, 30 mg (n=16) SC, 10 mg (n=6) upper arm, 10 mg (n=6) thigh, 10 mg (n=6) abdomen

DX-88/15: 30 mg (n=24) liquid crossover to lyophilized

Duration of Treatment:

DX-88/1, 2, 4, 13, and 15: single dose administration

DX-88/5: the overall duration of treatment was dependant on the episodic nature of HAE attacks, and the number of HAE attacks for which each patient was treated, to a aximum of 20 attacks. The study period was 28 ± 3 days per treated HAE attack.

DX-88/6: Each subject received four 20 mg/ m² doses of DX-88 (ecallantide) over 4 weeks.

Main Measurements and variables:

The covariates evaluated in the model included visit number, assay type (LC-MS/MS versus ELISA), and subject-specific covariates (subject age, gender, body mass index [BMI], body surface area [BSA], and weight) and baseline laboratory results (alkaline phosphatase, SGOT (AST), SGPT (ALT), total protein, and hematocrit). Subject serum

creatinine concentration and creatinine clearance (CrCL), which was calculated by the Cockcroft-Gault equation using actual body weight, were evaluated as covariates only for drug clearance.

Results:

No difference was noted in the model-derived pharmacokinetic parameters between healthy subjects and HAE patients. The clearance of DX-88 was 7.56 L/h with a volume of distribution at steady-state of 15.1 L. Between-subject variability was 38% for clearance and 52% for central volume. The α -, β -, and γ -half-lives of DX-88 were 0.4 hours, 0.8 hours, and 4.5 hours, respectively. Pharmacokinetic parameters were similar after single, intermittent or repeated doses and were not affected by subject age or gender. After subcutaneous administration, the relative bioavailability was approximately 100% for the 30 mg dose of the liquid formulation, 87% for the 10 mg dose of the liquid formulation, and 79% for the 30 mg dose of the lyophilized formulation.

Two covariates affected DX-88 pharmacokinetics: subject weight and assay type. An inverse relationship was observed between the subject body weight and the rate of absorption after SC administration; as weight increased the rate of absorption decreased with no change on the extent of absorption. The assay type affected 1 pharmacokinetic parameter, the central volume of distribution, which was 35% smaller for patients whose samples were assayed using an LC-MS/MS assay compared to patients whose samples were assayed using an ELISA or LC-MS assay. Neither patient age nor sex had an effect on DX-88 exposure.

DX-88 had linear pharmacokinetics and was dose proportional for doses up to 96 mg, the highest dose examined. Peak concentrations occurred immediately after the end of infusion and 2 to 3 hours after subcutaneous administration, although drug absorption was slower in heavier subjects.

Conclusions:

DX-88 pharmacokinetics was dose proportional between doses of 8 and 96 mg, the highest dose tested, and the relative bioavailability after SC administration was high: approximately 100% for 30 mg dose of the liquid formulation, 87% for 10 mg dose of the liquid formulation, and 79% for 30 mg dose of the lyophilized formulation. DX-88 had a limited volume of distribution at steady state (~15.1L), which is consistent with distribution to the extracellular fluid, and was cleared rapidly (7.56 L/h) with a relatively short γ -half-life (4.5 hours). Given the short half-life, administration of daily doses of DX-88 would not be expected to result in any significant plasma accumulation.

4.2 Cover Sheet and OCP Filing/Review Form

Regulatory Filing Review Memo for BLAs and Supplements

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CDER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy (<http://www.fda.gov/cber/regsopp/8404.htm>). An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD) (see <http://www.fda.gov/cber/ich/ichguid.htm>).

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications. You cannot have multiple indications under supplement submissions. If the sponsor submits multiple indications under a supplement, you must unbundle the submission.

CDER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN: 125277 Product: Kalbitor Applicant: Dyax

Final Review Designation (circle one): Standard Priority

Submission Format (circle all that apply): Paper Electronic Combination

Submission organization (circle one): Traditional CTD

Filing Meeting: Date 10/30/2008 Committee Recommendation (circle one): File RTF

RPM: _____
(signature/date)

Attachments:

- Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):

____ Part A – RPM

____ Part B – Product/CMC/Facility Reviewer(s): _____

____ Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): _____

____ Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical)
Reviewers _____

- Memo of Filing Meeting

Part A. Regulatory Project Manager (RPM)

Cover Letter	Y	N	
Form 356h completed	Y	N	
<input type="checkbox"/> including list of all establishment sites and their registration numbers	Y	N	
<input type="checkbox"/> If foreign applicant, US Agent signature.	Y	N	
Comprehensive Table of Contents	Y	N	
Debarment Certification with correct wording (see * below)	Y	N	
User Fee Cover Sheet	Y	N	
User Fee payment received	Y	N	
Financial certification &/or disclosure information	Y	N	
Environment assessment or request for categorical exclusion (21 CFR Part 25)	Y	N	
Pediatric rule: study, waiver, or deferral	Y	N	
Labeling:	Y	N	
<input type="checkbox"/> PI –non-annotated	Y	N	
<input type="checkbox"/> PI –annotated	Y	N	
<input type="checkbox"/> PI (electronic)	Y	N	
<input type="checkbox"/> Medication Guide	Y	N	
<input type="checkbox"/> Patient Insert	Y	N	
<input type="checkbox"/> package and container	Y	N	
<input type="checkbox"/> diluent	Y	N	
<input type="checkbox"/> other components	Y	N	
<input type="checkbox"/> established name (e.g. USAN)	Y	N	
<input type="checkbox"/> proprietary name (for review)	Y	N	

* The Debarment Certification must have correct wording , e.g. "I, the undersigned, hereby certify that XXX Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug, and Cosmetic Act in connection with the studies listed in Appendix XXX." Applicant may not use wording such as "To the best of my knowledge,..."

Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y	N	
<input type="checkbox"/> legible	Y	N	
<input type="checkbox"/> English (or translated into English)	Y	N	
<input type="checkbox"/> compatible file formats	Y	N	
<input type="checkbox"/> navigable hyper-links	Y	N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	Y	N	
<input type="checkbox"/> summary reports reference the location of individual data and	Y	N	

records <input type="checkbox"/> protocols for clinical trials present <input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	Y N Y N	
companion application received if a shared or divided manufacturing arrangement	Y N	
if CMC supplement: <input type="checkbox"/> description and results of studies performed to evaluate the change <input type="checkbox"/> relevant validation protocols <input type="checkbox"/> list of relevant SOPs	Y N Y N Y N	
if clinical supplement: <input type="checkbox"/> changes in labeling clearly highlighted <input type="checkbox"/> data to support all label changes <input type="checkbox"/> all required electronic components, including electronic datasets (e.g. SAS)	Y N Y N Y N	
if electronic submission: <input type="checkbox"/> required paper documents (e.g. forms and certifications) submitted	Y N	

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Has orphan drug exclusivity been granted to another drug for the same indication?

If yes, review committee informed? _____

Does this submission relate to an outstanding PMC? _____

If an Advisory Committee (AC) discussion may be needed, list applicable AC meetings scheduled to occur during the review period:

- Name: _____
- Dates: _____

Recommendation (circle one): File RTF

RPM Signature: _____

Branch Chief concurrence: _____

Part B – Product/CMC/Facility Reviewer(s)

Overall CTD Table of Contents [2.1]	Y	N
Introduction to the summary documents (1 page) [2.2]	Y	N
Quality overall summary [2.3]	Y	N
<input type="checkbox"/> Drug Substance	Y	N
<input type="checkbox"/> Drug Product	Y	N
<input type="checkbox"/> Facilities and Equipment	Y	N
<input type="checkbox"/> Adventitious Agents Safety Evaluation	Y	N
<input type="checkbox"/> Novel Excipients	Y	N
<input type="checkbox"/> Executed Batch Records	Y	N
<input type="checkbox"/> Method Validation Package	Y	N
<input type="checkbox"/> Comparability Protocols	Y	N

Module Table of Contents [3.1]	Y	N
Drug Substance [3.2.S]		
<input type="checkbox"/> general info	Y	N
<input type="checkbox"/> nomenclature		
<input type="checkbox"/> structure (e.g. sequence, glycosylation sites)		
<input type="checkbox"/> properties		
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	Y	N
<input type="checkbox"/> description of manufacturing process	Y	N
<input type="checkbox"/> batch numbering and pooling scheme		
<input type="checkbox"/> cell culture and harvest		
<input type="checkbox"/> purification		
<input type="checkbox"/> filling, storage and shipping		
<input type="checkbox"/> control of materials	Y	N
<input type="checkbox"/> raw materials and reagents		
<input type="checkbox"/> biological source and starting materials		
<input type="checkbox"/> cell substrate: source, history, and generation		
<input type="checkbox"/> cell banking system, characterization, and testing		
<input type="checkbox"/> control of critical steps and intermediates	Y	N
<input type="checkbox"/> justification of specifications		
<input type="checkbox"/> analytical method validation		
<input type="checkbox"/> reference standards		
<input type="checkbox"/> stability		
<input type="checkbox"/> process validation (prospective	Y	N

<p>validation; excipients of human/animal origin)</p> <p><input type="checkbox"/> control of drug product (justification of specifications; analytical method validation)</p> <p><input type="checkbox"/> container closure system [3.2.P.7]</p> <ul style="list-style-type: none"> <input type="checkbox"/> specifications (vial, elastomer, drawings) <input type="checkbox"/> availability of DMF <input type="checkbox"/> closure integrity <input type="checkbox"/> administration device(s) <p><input type="checkbox"/> stability</p> <ul style="list-style-type: none"> <input type="checkbox"/> summary <input type="checkbox"/> post-approval protocol and commitment <input type="checkbox"/> pre-approval <ul style="list-style-type: none"> <input type="checkbox"/> protocol <input type="checkbox"/> results <input type="checkbox"/> method validation 	<p>Y N</p> <p>Y N</p> <p>Y N</p>	
<p>Diluent (vials or filled syringes) [3.2P']</p> <p><input type="checkbox"/> description and composition of diluent</p> <p><input type="checkbox"/> pharmaceutical development</p> <p><input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)</p> <p><input type="checkbox"/> batch formula</p> <p><input type="checkbox"/> description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)</p> <p><input type="checkbox"/> controls of critical steps and intermediates</p> <p><input type="checkbox"/> process validation including aseptic processing & sterility assurance:</p> <ul style="list-style-type: none"> <input type="checkbox"/> 3 consecutive lots <input type="checkbox"/> other needed validation data <p><input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)</p> <p><input type="checkbox"/> control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)</p>	<p>Y N</p>	

<input type="checkbox"/> reference standards <input type="checkbox"/> container closure system <ul style="list-style-type: none"> ○ specifications (vial, elastomer, drawings) ○ availability of DMF ○ closure integrity <input type="checkbox"/> stability <ul style="list-style-type: none"> □ summary □ post-approval protocol and commitment □ pre-approval <ul style="list-style-type: none"> ○ protocol ○ results 	Y	N	
Other components to be marketed (full description and supporting data, as listed above): <ul style="list-style-type: none"> □ other devices □ other marketed chemicals (e.g. part of kit) 	Y	N	
Appendices for Biotech Products [3.2.A] <ul style="list-style-type: none"> □ facilities and equipment <ul style="list-style-type: none"> ○ manufacturing flow; adjacent areas ○ other products in facility ○ equipment dedication, preparation and storage ○ sterilization of equipment and materials ○ procedures and design features to prevent contamination and cross-contamination □ adventitious agents safety evaluation (viral and non-viral) e.g.: <ul style="list-style-type: none"> ○ avoidance and control procedures ○ cell line qualification ○ other materials of biological origin ○ viral testing of unprocessed bulk ○ viral clearance studies ○ testing at appropriate stages of production □ novel excipients 	Y	N	
USA Regional Information [3.2.R] <ul style="list-style-type: none"> □ executed batch records □ method validation package 	Y	N	

<input type="checkbox"/> comparability protocols	Y	N	
Literature references and copies [3.3]	Y	N	

content, presentation, and organization sufficient to permit substantive review?	Y	N	
<input type="checkbox"/> legible	Y	N	
<input type="checkbox"/> English (or translated into English)	Y	N	
<input type="checkbox"/> compatible file formats	Y	N	
<input type="checkbox"/> navigable hyper-links	Y	N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	Y	N	
<input type="checkbox"/> summary reports reference the location of individual data and records	Y	N	
<input type="checkbox"/> all electronic submission components usable	Y	N	
includes appropriate process validation data for the manufacturing process at the commercial production facility?	Y	N	
includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)?	Y	N	
includes data demonstrating consistency of manufacture	Y	N	
includes complete description of product lots and manufacturing process utilized for clinical studies	Y	N	
describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y	N	
data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y	N	
certification that all facilities are ready for inspection	Y	N	
data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y	N	
if not using a test or process specified by regulation, data is provided to show the	Y	N	

alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> mycoplasma <input type="checkbox"/> sterility <input type="checkbox"/> <input type="checkbox"/>	Y N Y N Y N	
identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y N	
floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y N	
description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y N	
information and data supporting validity of sterilization processes for sterile products and aseptic manufacturing operations	Y N	
if this is a supplement for post-approval manufacturing changes, is animal or clinical data needed? Was it submitted?	Y N	

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Recommendation (circle one): File RTF

Reviewer: _____ Type (circle one): Product (Chair) Facility (DMPQ)
 (signature/ date)

Concurrence:
 Branch/Lab Chief: _____ Division Director: _____
 (signature/ date) (signature/ date)

Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s)

Overall CTD Table of Contents [2.1]	Y	N	
Introduction to the summary documents (1 page) [2.2]	Y	N	
Non-clinical overview [2.4]	Y	N	
Non-clinical summary [2.6]	Y	N	
<input type="checkbox"/> Pharmacology	Y	N	
<input type="checkbox"/> Pharmacokinetics	Y	N	
<input type="checkbox"/> Toxicology	Y	N	

Module Table of Contents [4.1]	Y	N	
Study Reports and related info. [4.2]	Y	N	
<input type="checkbox"/> Pharmacology	Y	N	
<input type="checkbox"/> Pharmacokinetics	Y	N	
<input type="checkbox"/> Toxicology	Y	N	
Literature references and copies [4.3]	Y	N	

content, presentation, and organization sufficient to permit substantive review?	Y	N	
<input type="checkbox"/> legible	Y	N	
<input type="checkbox"/> English (or translated into English)	Y	N	
<input type="checkbox"/> compatible file formats	Y	N	
<input type="checkbox"/> navigable hyper-links	Y	N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	Y	N	
<input type="checkbox"/> summary reports reference the location of individual data and records	Y	N	
<input type="checkbox"/> protocol-specified (as opposed to a different, post-hoc analysis) and other critical statistical analyses included	Y	N	
<input type="checkbox"/> all electronic submission components usable	Y	N	
data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y	N	
for each non-clinical laboratory study, either a statement that the study was conducted in compliance with the good laboratory practice requirements set forth in 21 CFR Part 58 or, if the study was not conducted in compliance with such regulations, a brief statement justifying the non-compliance	Y	N	

Part D – Clinical (Pharmacology, Efficacy, Safety, and Statistical) Reviewers

Overall CTD Table of Contents [2.1]	Y	N	
Introduction to the summary documents (1 page) [2.2]	Y	N	
Clinical overview [2.5]	Y	N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	Y	N	
<input type="checkbox"/> Biopharmaceutics and associated analytical methods	Y	N	
<input type="checkbox"/> Clinical pharmacology [includes immunogenicity]	Y	N	
<input type="checkbox"/> Clinical Efficacy [for each indication]	Y	N	
<input type="checkbox"/> Clinical Safety	Y	N	
<input type="checkbox"/> Synopses of individual studies	Y	N	

Module Table of Contents [5.1]	Y	N	
Tabular Listing of all clinical studies [5.2]	Y	N	
Study Reports and related information [5.3]	Y	N	
<input type="checkbox"/> Biopharmaceutic	Y	N	
<input type="checkbox"/> Studies pertinent to Pharmacokinetics using Human Biomaterials	Y	N	
<input type="checkbox"/> Pharmacokinetics (PK)	Y	N	See attached clin pharm memo for details.
<input type="checkbox"/> Pharmacodynamic (PD)	Y	N	
<input type="checkbox"/> Efficacy and Safety	Y	N	The product has not been approved yet.
<input type="checkbox"/> Postmarketing experience	Y	N	
<input type="checkbox"/> Case report forms	Y	N	
<input type="checkbox"/> Individual patient listings (indexed by study)	Y	N	
<input type="checkbox"/> electronic datasets (e.g. SAS)	Y	N	
Literature references and copies [5.4]	Y	N	

Content, presentation, and organization sufficient to permit substantive review?	Y	N	
<input type="checkbox"/> legible	Y	N	
<input type="checkbox"/> English (or certified translation into English)	Y	N	
<input type="checkbox"/> compatible file formats	Y	N	
<input type="checkbox"/> navigable hyper-links	Y	N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	Y	N	

<input type="checkbox"/> summary reports reference the location of individual data and records	Y	N	
<input type="checkbox"/> protocols for clinical trials present	Y	N	
<input type="checkbox"/> all electronic submission components usable	Y	N	
statement for each clinical investigation:			
<input type="checkbox"/> conducted in compliance with IRB requirements	Y	N	
<input type="checkbox"/> conducted in compliance with requirements for informed consent	Y	N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	Y	N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	Y	N	
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	Y	N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y	N	
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	Y	N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	Y	N	
drug interaction studies communicated as during IND review as necessary are included	Y	N	
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	Y	N	
comprehensive analysis of safety data from all current world-wide knowledge	Y	N	

of product			
data supporting the proposed dose and dose interval	Y	N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	Y	N	
adequate characterization of product specificity or mode of action	Y	N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	<u>Y</u>	N	The sponsor claims that pivotal nonclinical and clinical studies were conducted using material made according to the commercial (b) (4) process.
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y	N	
all information reasonably known to the applicant and relevant to the safety and efficacy described?	Y	N	

	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
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	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR

Y= yes; N=no; NR=not required

Clinical Pharmacology Memo:

For clinical pharmacology review, the following clarifications/actions are required from the sponsor.

1. The sponsor used three different bioanalytical assays to measure the drug concentrations. If the sponsor has conducted any bridging studies to compare the performance among these different analytical assays, we request the sponsor to submit the report.
2. We have identified three studies (DX-88/6, DX-88/2 and DX-88/4) that should be confirmed since the bioanalytical analysis was conducted by (b) (4) within the time frame of Jan 2000 and December 2004. Our general recommendation is that the sponsor may repeat these studies, reanalyze the samples, or commit an independent scientific audit of the studies. The sponsor indicated an external audit of MDS Pharma Services was conducted to determine to what extent any analytical deviations would affect pharmacokinetic conclusions. We request the sponsor to submit the audit report.
3. In Data Listing Dataset session of study report DX88/1 (session 5.3.3.1.25.2.1), the concentration-time profile for individual subject is missing. We request the sponsor to submit the dataset as a SAS transport files (*.xpt).
4. For study report "Population Pharmacokinetics and Pharmacodynamics of DX-88", we request the sponsor to submit the following items:
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 - c. Please submit a combined dataset from Phase 2 and/or Phase 3 studies that would allow us to perform exploratory exposure (C_{max}, AUC, C_{min}, and dose)-response (primary and secondary endpoints) analysis.

Signature



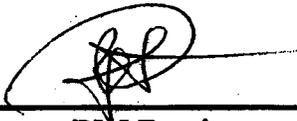
2/13/09

Primary Clin Pharm Reviewer: Yun Xu, M.D. Ph.D.



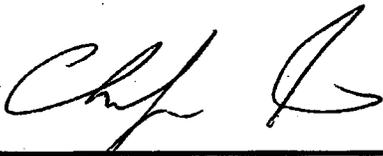
2/13/09

Team Leader (Acting): Wei Qiu, Ph. D.



2/13/09

Primary PM Reviewer: Ping Ji, Ph.D.



2/13/09

Secondary PM Reviewer: Christoffer Tornoe, Ph.D.



2/13/09

PM Team Leader: Yaning Wang, Ph.D.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 125277 Applicant: Dyax

Stamp Date: Sept. 23, 2008

Drug Name: Kalbitor NDA/BLA Type: BLA

On initial overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	Comment
Criteria for Refusal to File (RTF)				
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		X	The sponsor claims that pivotal nonclinical and clinical studies were conducted using material made according to the commercial (b) (4) process.
2	Has the applicant provided metabolism and drug-drug interaction information?		X	Usually metabolism and DDI studies are not required for BLA submission.
Criteria for Assessing Quality of an NDA				
Data				
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g. CDISC)?	X		See additional comments.
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?		X	N/A
Studies and Analyses				
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X		
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?	X		
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?	X		
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X		
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?		X	The sponsor requests a pediatric exemption based on the orphan status of the drug to treat HAE.
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?		X	See comments to Q 9.
11	Is the appropriate pharmacokinetic information submitted?	X		
12	Is there adequate information on the pharmacokinetics	X		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR A NEW NDA/BLA

	and exposure-response in the clinical pharmacology section of the label?			
General				
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?	X		
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X		
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	X		
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X		
17	Was the translation from another language important or needed for publication?		X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Y

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

For clinical pharmacology review, the following clarifications/actions are required from the sponsor.

1. The sponsor used three different bioanalytical assays to measure the drug concentrations. If the sponsor has conducted any bridging studies to compare the performance among these different analytical assays, we request the sponsor to submit the report.
2. We have identified three studies (DX-88/6, DX-88/2 and DX-88/4) that should be confirmed since the bioanalytical analysis was conducted b (b) (4) (b) (4) within the time frame of Jan 2000 and December 2004. Our general recommendation is that the sponsor may repeat these studies, reanalyze the samples, or commit an independent scientific audit of the studies. The sponsor indicated an external audit of (b) (4) was conducted to determine to what extent any analytical deviations would affect pharmacokinetic conclusions. We request the sponsor to submit the audit report.
3. In Data Listing Dataset session of study report DX88/1 (session 5.3.3.1.25.2.1), the concentration-time profile for individual subject is missing. We request the sponsor to submit the dataset as a SAS transport files (*.xpt).

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING CHECKLIST FOR A NEW NDA/BLA**

4. For study report "Population Pharmacokinetics and Pharmacodynamics of DX-88", we request the sponsor to submit the following items:
- a. All datasets used for model development and validation. They should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
 - b. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
 - c. Please submit a combined dataset from Phase 2 and/or Phase 3 studies that would allow us to perform exploratory exposure (Cmax, AUC, Cmin, and dose)-response (primary and secondary endpoints) analysis.

Yan Xu

11/13/2008

Reviewing Pharmacologist

Date

M. D.

11/13/08

Team Leader/Supervisor

Date

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR A NEW NDA/BLA

Clinical Pharmacology Study Summary

Pharmacokinetics

The pharmacokinetics of liquid ecallantide following intravenous (IV) administration was evaluated in 2 studies in healthy subjects (Studies DX-88/1 and DX-88/6) and 3 studies in patients with HAE (Studies DX-88/2 [EDEMA0], DX-88/4 [EDEMA1], and DX-88/5 [EDEMA2] at fixed doses ranging from 10 to 80 mg, or body weight adjusted doses ranging from 5 to 40 mg/m². The pharmacokinetics of ecallantide following subcutaneous (SC) administration was evaluated in 2 studies in healthy subjects (Studies DX-88/13 and DX-88/15) and 1 study in HAE patients (Study DX-88/5). In these studies, ecallantide was administered at nominal doses of 10 mg or 30 mg. Full PK profiles were taken in studies DX-88/1, DX-88/6, DX-88/13 and DX-88/15. The results are summarized in the table below.

Study	Route	Dose (mg)	# Subj	C _{max} (ng/mL)	T _{max} (hr)	AUC (ng*hr/mL)	V _d (L)	CL (mL/min)	T _{1/2} (hr)
DX-88/1	IV inf	10	2	2000	0.2	1400	5.9	122	0.6
	IV inf	20	2	4750	0.2	4709	7.4	71	1.2
	IV inf	40	4	7680	0.2	8823	10.2	76	1.6
	IV inf	80	4	14800	0.2	17656	11.2	76	1.7
DX-88/6	IV inf ^a (10 min)	20 mg/m ²	6	6497	n/c	5880	13.2	110	2.0
	IV inf (4 hr)	20 mg/m ²	6	1170	n/c	5300	11.2	118	1.3
DX-88/13	IV inf	27.3	16	3741	0.2	3327	18.8	141	1.6
	SC inj	27.3	17	586	2.7	3017	26.4	153	2.0
	SC inj	9.1	18	179	2.2	837	29.3	189	1.8
DX-88/15	SC inj	30 (liquid)	23	995	2.4	4232	23.1	124	2.2
	SC inj	30 (lyophilized)	23	671	2.4	3449	30.7	153	2.4

^a mean of 3 separate doses

A comprehensive population pharmacokinetic analysis was performed by nonlinear mixed effects modeling using NONMEM software that included all available plasma concentration data from both healthy subjects and patients irrespective of route. The final model with the best fit was a 3-compartment model. Given the short half-life, administration of daily doses of ecallantide would not be expected to result in any significant plasma accumulation. Pharmacokinetic parameters were similar after single, intermittent or repeated doses and were not affected by subject age or gender. Two covariates were found to affect ecallantide pharmacokinetics: subject weight and assay type. Subject body weight and the rate of absorption following SC administration were inversely related, (ie, the heavier the person, the slower the rate of absorption). The assay type was a significant covariate for a single pharmacokinetic parameter, the central volume of distribution, which was 35% smaller for patients whose samples were assayed using an LC-MS/MS assay, compared to patients whose samples were assayed using an ELISA or LC-MS assay. Assay type had no effect on the other parameters.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR A NEW NDA/BLA

Pharmacodynamics

No exposure-response relationships for KALBITOR to components of the complement or kallikrein-kinin pathways have been established. A dose response between 5 and 20 mg/m² IV has been demonstrated for measures of clinical efficacy in HAE. Exposure in this dose range is dose-proportional and encompasses the 30 mg subcutaneous dose (DX88/5).

A transient prolongation of activated partial thromboplastin time (aPTT), approximately two-fold, has been observed following IV dosing of ecallantide at doses in ≥ 20 mg/m². This is a direct pharmacologic action of ecallantide and is due to the inhibition of kallikrein-mediated activation of factor XII to factor XIIa, which is the initial step in the initiation of the intrinsic clotting cascade. aPTT prolongation has been used as a pharmacodynamic marker of ecallantide activity in nonclinical studies. No consistent aPTT prolongation has been observed in healthy volunteers and patients administered ecallantide SC at doses of 30 mg.

In preclinical development, ecallantide was shown to have no direct effect in standard cardiovascular assays. In agreement with the Agency, no thorough QT/QTc study was required for the development. Instead, ECGs were evaluated in EDEMA4, the randomized, placebo-controlled Phase 3 study to assess 30 mg SC dose vs placebo. In this study, 12-lead ECGs were obtained at baseline, 2 hours and 4 hours post-dose (covering the time of expected C_{max}), and at follow-up (day 7). ECGs were evaluated for PR interval, QRS complex, and QTc interval. KALBITOR had no significant effect on the QTc interval, heart rate, or any other components of the ECG.

Immunogenicity

The presence of anti-ecallantide antibodies was tested. Assays for non-IgE, IgE as well as neutralizing antibodies to ecallantide were developed. In total, 12.9% of patients seroconverted to anti-ecallantide antibodies, 2.1% to anti-ecallantide IgE antibodies, and 8.0% of patients seroconverted to anti-*P pastoris* IgE antibodies. In study EDEMA3 and EDEMA4, the double-blind, placebo-controlled Phase 3 studies, 8.4% of patients seroconverted to anti-ecallantide antibodies. There was a seroconversion rate of 1.6% for patients who tested positive for neutralizing antibodies to ecallantide in vitro.

Part D – Clinical (Pharmacology, Efficacy, Safety, and Statistical) Reviewers

Overall CTD Table of Contents [2.1]	Y	N	
Introduction to the summary documents (1 page) [2.2]	<u>Y</u>	N	
Clinical overview [2.5]	<u>Y</u>	N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	<u>Y</u>	N	
<input type="checkbox"/> Biopharmaceutics and associated analytical methods	<u>Y</u>	N	
<input type="checkbox"/> Clinical pharmacology [includes immunogenicity]	<u>Y</u>	N	
<input type="checkbox"/> Clinical Efficacy [for each indication]	Y	N	
<input type="checkbox"/> Clinical Safety	Y	N	
<input type="checkbox"/> Synopses of individual studies	<u>Y</u>	N	

Module Table of Contents [5.1]	Y	N	
Tabular Listing of all clinical studies [5.2]	<u>Y</u>	N	
Study Reports and related information [5.3]	<u>Y</u>	N	
<input type="checkbox"/> Biopharmaceutic	<u>Y</u>	N	
<input type="checkbox"/> Studies pertinent to Pharmacokinetics using Human Biomaterials	<u>Y</u>	N	
<input type="checkbox"/> Pharmacokinetics (PK)	Y	<u>N</u>	See attached clin pharm memo for details.
<input type="checkbox"/> Pharmacodynamic (PD)	<u>Y</u>	<u>N</u>	
<input type="checkbox"/> Efficacy and Safety	Y	<u>N</u>	
<input type="checkbox"/> Postmarketing experience	Y	<u>N</u>	The product has not been approved yet.
<input type="checkbox"/> Case report forms	Y	<u>N</u>	
<input type="checkbox"/> Individual patient listings (indexed by study)	Y	<u>N</u>	
<input type="checkbox"/> electronic datasets (e.g. SAS)	Y	<u>N</u>	
Literature references and copies [5.4]	<u>Y</u>	<u>N</u>	

Content, presentation, and organization sufficient to permit substantive review?	Y	<u>N</u>	
<input type="checkbox"/> legible	Y	<u>N</u>	
<input type="checkbox"/> English (or certified translation into English)	Y	<u>N</u>	
<input type="checkbox"/> compatible file formats	Y	<u>N</u>	
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of product			
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data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	<u>Y</u>	N	The sponsor claims that pivotal nonclinical and clinical studies were conducted using material made according to the commercial (b) (4) process.
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all information reasonably known to the applicant and relevant to the safety and efficacy described?	Y	N	

	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR

Y= yes; N=no; NR=not required

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Is clinical site(s) inspection (BiMo) needed?

Is an Advisory Committee needed?

Recommendation (circle one): File RTF

Reviewer: Yun Xu, 11/15/2008 Type (circle one): Clinical Clin/Pharm Statistical
(signature/ date)

Concurrence:

Branch Chief: [Signature] 11/17/08 Division Director: [Signature] 11/17/08
(signature/ date) (signature/ date)

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