

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125277

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

RISK EVALUATION AND MITIGATION STRATEGY

NDA/Serial Number: 125277/0035

Drug Name: Kalbitor (ecallantide)

Indication(s): Treatment of hereditary angioedema (HAE)

Applicant: Dyax Corp.

Date(s): Received date: June 1, 2009
PADUFA date: December 1, 2009

Review Priority: Priority

Biometrics Division: Division of Biometrics II / Office of Biostatistics

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Project Manager: Colette Jackson

Keywords: BLA review, REMS

This resubmission does not contain new efficacy information, thus there is no statistical review for this cycle. In the resubmission, the sponsor updated the labeling. Following are the comments from the statistical reviewer on section 14 clinical studies in the labeling.

1.

(b) (4)

*In both studies, the effects of KALBITOR were evaluated using the Mean Symptom Complex Severity (MSC) score and the Treatment Outcome Score (TOS), which are validated patient reported outcome measures for HAE. These measures evaluated the severity of attack symptoms at **all anatomic locations** (MSCS score) and response to therapy (TOS).*

2. Suggest to add a sentence in the end of paragraph 4 to explain that an improvement in symptoms from baseline is reflected by a positive TOS value.
3. Suggest to present a concise table 2. Cut off the section for integrated summary of efficacy. For each study, only report N, mean, standard deviation, and P values on MSCS and TOS. Take out median and inter-quartile range.
4. For the results on number of patients required medical intervention, only report the numerical trend, do not discuss statistical significance.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Dongmei Liu, Ph.D.
Date: October 26, 2009



Oct. 26, 2009

Statistical Team Leader: Qian Li, Sc.D.



Oct-26-09



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCES
OFFICE OF BIostatISTICS

Secondary Statistical Review CLINICAL STUDIES

BLA: 125277/0002

Name of product: Kalbitor (ecallantide)

Indication: hereditary angioedema

Applicant: Dyax

Dates: Received 9/23/08; user fee (6 months) 3/23/09

Review priority: P

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1 INTRODUCTION

This is a secondary review considering the findings of Dongmei Liu, Ph.D., the primary statistical reviewer, as well as discussion by the advisory committee. I have concurred with Dr. Liu's principal conclusion, "that there is a lack of consistent and substantial evidence to support the efficacy claim." It may be useful, however, to elaborate my perspective a little.

The application relies for evidence of efficacy on two studies, EDEMA3 and EDEMA4. In EDEMA3, the apparent statistical significance is somewhat vitiated by a problem in defining treatment groups for analysis. In EDEMA4, the problem is a remarkable difference in outcomes before and after a protocol amendment. In addition, Dr. Liu raises some issues in regard to the imputation of data for patients who had certain emerging symptoms or interventions after the administration of the treatment under study.

2 ALLOCATION ERROR IN EDEMA3

Two patients in EDEMA3 had their treatments switched from what was assigned in the randomization schedule. The Treatment Outcome Score was statistically significantly better ($p = 0.045$) for ecallantide than for placebo if those patients were included in the group with the treatment they actually received, but not ($p = 0.14$) if they were included in the group to which they had been assigned.

To me the issue here is not "robustness" but multiplicity. While the analysis as treated is sound and arguably better, there is little doubt that if the results had been reversed, with the analysis as randomized significant, that analysis would have been considered primary. If we accept these results as significant at level 0.05, and we also would have accepted those, we would make a Type I error, if the treatment had no effect, whenever one or the other or both tests were significant. The probability of such an error would be very slightly more than 0.05, because each test would reject the null hypothesis with probability 0.05 and they would usually but not always agree. It is fair to suggest, therefore, that the nominally significant result is not truly significant at level 0.05. It is also fair to point out, however, that if it is not, it is nevertheless significant at some level between 0.05 and 0.1, and surely much closer to 0.05.

3 INTERACTION IN EDEMA4

EDEMA4 was conducted under a Special Protocol Agreement. The protocol was amended, however, to change the sample size during the trial. At the time of the amendment, the sponsor was advised to include in the study report an analysis of possible differences in outcomes before and after the amendment was in force. As Dr. Liu pointed out, a remarkable difference was found: almost all the effect of the drug compared to placebo can be attributed to the outcomes after the change.

Notwithstanding the Special Protocol Agreement, I think this analysis is highly relevant. Indeed, I think it should be considered part of the agreed analysis, as it was requested at the time the protocol was amended.

There are several possible interpretations of this treatment-by-period interaction. One possibility is that the seeming interaction is a Type I error: there was no difference in the real treatment effect before and after the change, only random variation. As Dr. Liu pointed out, significance testing on the interaction suggests this is unlikely. Of course, there is some latent multiplicity here, though not a lot: Dr. Liu would have been bound to notice similar interactions of treatment with age, race or sex, for example. So, we cannot exclude the possibility that this apparent interaction is a chance occurrence.

Naturally, we also cannot exclude the possibility that it is real. The most likely explanation for a difference in the effect of the test product before and after the change is a difference in the patient populations. Dr. Liu reports several differences observed by the applicant, and some members of the advisory committee speculated on others.

What if it is real? We then have a product that was ineffective not only in some patients but in the entire sample of patients originally intended to be recruited in EDEMA4. By the same token, it was then definitely effective in another sample, the late-recruited patients.

The role such interactions should play in approval decisions is a difficult question. We can approve a product that will fail to work for many patients, without a clear understanding of what patients it will succeed for. Alternatively, we can withhold a product that will work for some patients. The decision must be based on benefits and risks: the benefits to the patients the product works for, and the risks not only to them but to others uselessly treated.

4 IMPUTATION

Attacks of hereditary angioedema can be difficult to manage and sometimes life-threatening. The protocols specified a primary measure of outcome, but sometimes interventions would be necessary that would affect the interpretation of that measure. It is not inconceivable that a bad treatment would improve symptoms by worsening patients' conditions enough that alternative therapies would have to be used. To obviate such a result, the protocols specified that certain emerging symptoms or interventions would require the assignment of an unfavorable score to patients regardless of what otherwise would have been the primary measure. As it happens, more placebo patients had such artificial bad scores assigned.

Dr. Liu points out that this procedure may exaggerate the effect of the test article. The sense in which this is true must be considered carefully. Patients with artificially bad scores assigned did not in fact have outcomes as bad as their scores would indicate, so that the numerical difference between active and placebo groups may indeed overstate the difference in average outcomes. On the other hand, more emerging symptoms and interventions in the placebo group are themselves evidence of a beneficial effect of the test article, over and above the difference in the primary outcome variable.

Dr. Liu suggested other possible analyses which have merit, especially for describing numerically the effect of the product. I do not think, however, that a finding of effectiveness requires these additional analyses.



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STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

BLA/Serial Number: 125277/0002
Drug Name: Kalbitor (ecallantide)
Indication(s): Treatment of hereditary angioedema (HAE)
Applicant: Dyax Corp.
Date(s): Received Sep. 23, 2008
Review Priority: Priority

Biometrics Division: Division of Biometrics II / Office of Biostatistics
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Keywords: BLA review, Clinical studies, Data imputation

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1. EXECUTIVE SUMMARY

1.1 Conclusions

Dyax Corp. proposes ecallantide for the treatment of acute attacks of hereditary angioedema in patients who are 10 years of age and older. Ecallantide is a plasama kallikrein inhibitor intended for subcutaneous injection. The applicant conducted two phase 3 studies to support the efficacy and safety of ecallantide and claimed that with the recommended dose of 30mg (3.0mL) administered in three 1 mL injections, ecallantide eliminates or reduces signs and symptoms of HAE attacks and offers a significant benefit over available treatments. Issues identified in the phase 3 studies suggest that there is a lack of consistent and substantial evidence to support the efficacy claim of ecallantide. From statistical stand point of view, there is weak evidence to support the approval of this drug.

The issues in phase 3 studies are summarized below.

The main issue identified in one phase 3 study is the significant interaction between the treatment effect and enrollment pre and post sample size change. The efficacy result of this study was largely driven by the enrollment after the decision of sample size adjustment. In the other phase 3 study, statistical significance is only confirmed for intention to treat (ITT) as treated population and per protocol population, but not in ITT as randomized population. The difference between ITT as randomized and ITT as treated population is due to two patients who received wrong drugs.

The primary efficacy end points used in the clinical studies are patient report outcome (PRO) measures --- Treatment Outcome Score (TOS) and Mean Symptom Complex Severity (MSCS). The endpoint using MSCS was changes at 4 hours post-dose from baseline. This change from baseline uses the evaluation of MSCS at two time points (baseline and 4 hours post-dose) and ignored the change pattern in between. We are concerned the adequacy of the endpoint as it does not capture additional efficacy information such as how soon the change starts. For example, for patients whose symptoms completely disappear before 4 hour post-dose, the recovery may occur at 1 hour post-dose, or 2 hours post-dose. Therefore more frequent symptom assessments may provide more complete efficacy information.

The data imputations used by the sponsor in this application are not conservative in assessing treatment differences. The data imputations tend to favor ecallantide. Alternative imputation rules or methods should be considered.

Another deficiency in this submission is the adequacy of number of patients in the age group between 10 to 18 years of age. The applicant proposes the treatment for patients who are 10 years of age and older. However, only 14 patients (8% of the sample size) in the study were less than 18 years old, and of these, only 4 received ecallantide. There are not enough data to support the efficacy and safety for pediatric group.

1.2 Brief Overview of Clinical Studies

The applicant conducted two phase 3, double-blinded, placebo-controlled, parallel arm, multi-center studies comparing ecallantide to placebo. The studies were similar in design. The first phase 3 study (EDEMA3) has a sample size of 72 with patient randomized into the two arms in 1:1 ratio. The second study (EDEMA4) has a larger sample size, 96, with the same randomization ratio. In both studies, patients recruited were age of 10 years old or above. At enrollment, patient presented to the study center within 8 hours of recognition of an acute attack of HAE with symptom complexes assessed as moderate or severe. After initial dosing, responses to the treatment were recorded through either an electronic diary or paper diary. Symptom complex severity assessment was performed by patients at enrollment (baseline) and at 4 and 24 hours post-dose. Response assessment for the individual symptom complexes was performed by patients at 1, 2, 3, 4, and 24 hours post-dose. Patients were discharged at 4 hours post-dose. Follow up visit or phone calls were scheduled during the study participation. In EDEMA3, after double blind phase, all patients including the ones in the placebo arm advanced to open label repeat dosing phase.

The primary efficacy endpoint for EDEMA3 was Treatment Outcome Score (TOS). The secondary efficacy endpoints for EDEMA3 included change of Mean Symptom Complex Severity (MSCS) at 4 hours post-dose from baseline and time to report of significant improvement in overall responses. Followed by the recommendation of FDA, the primary efficacy end point for EDMA4 changed to change of MSCS at 4 hours post-dose from baseline. Except TOS at 4 hours post-dose and time to report of significant improvement in overall responses, there were two additional secondary efficacy end points for EDEMA4 --- proportion of patients maintaining a significant improvement in overall response and proportion of responders at 4 hours based on change from baseline in MSCS.

1.3 Statistical Issues and Findings

Majority of the patients completed the study. Only one patient in the ecallantide arm in each of the two phase 3 studies was lost to follow up. In both studies, most of the demographic and baseline characteristics were balanced in the two study arms. The only exceptions were gender ratio and the percentage of patients with the primary HAE attack locations classified as cutaneous and GI/abdominal in EDEMA4. The results from analyses based on ITT as treated populations in both studies showed patients in the ecallantide arm had statistically significantly greater reduction in MSCS at 4 hours post-dose from baseline, as well as higher TOS at 4 hours post-dose compared to patients in the placebo arm. In both studies, patients treated with ecallantide reached significant improvement earlier than the placebo group, but there was no statistically significant difference. The difference in proportions of patients with response, based on change of MSCS at 4 hours post-dose from baseline ≤ -1 , was only 16% in EDEMA3, while as the difference was 30% in EDEMA4. The difference in EDEMA4 is statistically significant, but the difference in EDEMA3 is not.

The main statistical issues for this application are the interaction between treatment effect and enrollment period (pre and post sample size change) in one of the efficacy study and data imputation in both studies.

In the study which has confirmed statistical significance, there was significant interaction between the treatment effect and enrollment period (pre and post sample size change). If the trial was conducted the same way before and after sample size change, the chance to see such an interaction is very small. The statistical significance of the study was driven by the post sample size change enrollment. Without replicated study to demonstrate the same large treatment effect observed in the post sample size change enrollment, it is hard to accept the evidence in efficacy results due to the small probability to make this observation.

For data imputation, since there were more emerging symptom complexes and medical interventions in the placebo arm than in the ecallantide arm, more data were imputed in the placebo arm than in the ecallantide arm. The imputation rules proposed by the sponsor increased the difference of treatment effect between the ecallantide arm and the placebo arm. To have a balanced assessment of the treatment robustness, alternative imputation rules that are relatively conservative in assessing treatment differences are explored in this review.

After the advisory committee meeting, a few additional issues were identified. We sent out enquiry on these issues to the applicant and are waiting for responses. The questions include a). clarification on data imputation in EDEMA3 with and without severe upper airway compromise (SUAC) failure; b). analysis to show whether the primary efficacy end point depends on the mean lowest historical functional C1-INH level or the mean lowest historical C4 level; c). change in MSCS recalculated as the arithmetic mean for 3 possible symptom complexes instead of 5. The 3 complexes are abdominal/GI, internal head/neck, and peripheral (external head/neck, genital/buttocks, and cutaneous grouped together); d). change in MSCS recalculated as the area under the curve measure (detail is available in section 3.1.6 Data Imputation).

2. INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Ecallantide is a plasma kallikrein inhibitor. The applicant is requesting approval for use of ecallantide to treat patients who are 10 years of age and older with acute attacks of hereditary angioedema (HAE). The proposed dose is 30mg (3.0mL) administered in three 1 mL by subcutaneous injections. 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.

2.1.2 History of Drug Development

BBIND 10426 (CBER) opened for the drug development on ecallantide as intended treatment for HAE on April 30, 2002. On February 4, 2003, orphan drug designation was granted. On June 26, 2003, initial application for fast track designation was submitted and denied by CBER on the grounds that the application did not focus on severe, life-threatening aspects of HAE attacks nor addressed unmet medical needs. In the meeting with sponsor on April 5, 2006, dosing, efficacy endpoints, long-term safety data requirement, and correction on indications were discussed. In the end of phase 2 meeting with sponsor on August 29, 2006, agreement on efficacy end points was reached. There was further discussion on study design and number of clinical trials needed for the efficacy and safety evaluation. On October 13, 2006, request for Special Protocol Assessment (SPA) was made for EDEMA4. FDA recommended change of the primary efficacy end point. Fast track designation was granted on November 17, 2006. The original protocol for EDEMA4 was submitted on February 21, 2007. Protocol amendment was made on December 3, 2007 to increase sample size and to allow use of paper diaries. Rolling review was granted on January 15, 2008. The final rolling portion of BLA was submitted on September 23, 2008. An advisory committee meeting was held on February 4, 2009.

2.1.3 Specific Studies Reviewed

The summary of all clinical studies the applicant submitted to support this application was given in section 5.2 (Tabular listing of all clinical studies) of the study report. My statistical review focuses on the double blind part of the two phase 3 studies designed for efficacy evaluation --- EDEMA3 and EDEMA4. EDEMA3 was conducted in US, Canada, Europe and Israel. EDEMA4 was conducted only in North America.

2.2 Data Sources

All data was supplied by the applicant to the CBER electronic data room in SAS transport format. The data and final study report for the electronic submission were archived under the network path location <\\cbsap58\M\CTD_Submissions\STN125277\125277.enx>. The information needed for this review was contained in modules 1, 2.5, 2.7, and 5.3.5.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design of EDEMA3

General Design

EDEMA3 is a phase 3, double-blinded, placebo-controlled, parallel arm, multi-center study followed by an open-label repeat dosing phase. The objective of the study was to assess the efficacy and safety of ecallantide (30mg liquid administered by subcutaneous injection) for the treatment of acute attacks of hereditary angioedema (HAE). The study was conducted in 25 sites in US, Canada, Europe, and Israel. The double blinded part was done from December 2005 to February 2007. The open label repeat dosing phase was completed in September 2007.

At enrollment, eligible patients who presented to the study center within 8 hours of recognition of an acute attack of HAE with symptom complexes assessed as moderate or severe were randomized in a 1:1 ratio to receive either a treatment of ecallantide or a matching placebo by subcutaneous injection. Randomization followed a block design, stratified according to prior use of ecallantide and attack locations (laryngeal vs. abdominal vs. peripheral). After initial dosing, responses to the treatment were recorded through an eDiary. Symptom complex severity assessment was performed by patients at enrollment (baseline) and at 4 and 24 hours post-dose. Response assessment for the individual symptom complexes was performed by patient at 1, 2, 3, 4, and 24 hours post-dose. Patients were discharged at 4 hours after receiving the injections, with 3 follow-up visits planned. After a minimum of 1 follow-up visit, patients continued to the open label stage. In special circumstances, i.e. after the initial dosing with study drug if the patient was at risk for severe upper airway compromise (SUAC), a single dose of ecallantide 30mg SC (referred to as a SUAC dose) could have been administered within 0 to 4 hours of the study drug treatment. Total duration of study participation was up to 97 days including the follow-up visits.

Efficacy Endpoints

The efficacy was measured by patient reported outcomes (PRO). The applicant stated that the motivation of using PRO measures was due to the highly variable constellation of HAE symptoms. PRO instruments developed in this study 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. The primary end point of this study was the Treatment Outcome Score (TOS) at 4 hours post-dosing. The definition of TOS is as follows:

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

where symptom complex score was recorded on a 5-category scale (significant improvement [100], improvement [50], same [0], worsening [-50], and significant worsening [-100]) and

symptom complex weight was recorded on a 4-category scale (normal [0], mild [1], moderate [2], severe [3]). In this study, applicant defined that a clinically meaningful improvement was indicated by a TOS of 30 or above.

One secondary end point was the change of Mean Symptom Complex Severity (MSCS) at 4 hours post-dose from baseline. MSCS is defined as

$$MSCS = \frac{\sum \text{symptom complex severity}}{\text{Number of symptom complexes}}$$

MSCS score is a point-in-time global measure of symptom severity. Patient's assessment of severity on each individual symptom complex was recorded on a 0 to 3 categorical scale (normal [0], mild [1], moderate [2], and severe [3]) for 5 symptom complexes (Oropharyngeal Head/Neck, GI/Abdominal, Genital/Buttocks, Non-oropharyngeal head/Neck, and Cutaneous). A decrease in score reflects improvement in symptoms. In this study, applicant defined that a clinically meaningful improvement was indicated by a reduction of 0.3 or greater.

Another secondary endpoint is the time to report of significant improvement in overall responses. It was defined as the first time (in minutes) post-dose that the patient reported the overall assessment as "a lot better or resolved." Patients not reporting the overall assessment as "a lot better or resolved" from 15 minutes through 4 hours post-dose were censored at 240 minutes. Patients who received additional HAE therapy within 4 hours were censored at the time of the medical intervention.

Analysis Populations

Analysis of the primary and secondary efficacy endpoints was conducted on Intent-to-Treat (ITT) population and the Per Protocol (PP) population. The ITT population consisted of all patients who received any amount of study drug and who completed their 4 hour follow-up assessment. This included patients receiving open-label ecallantide treatment for SUAC. Since two patients received the wrong study drug (one patient randomized to ecallantide received placebo and one patient randomized to placebo received ecallantide), ITT population was further defined as ITT-as-randomized and ITT-as-treated. The Per Protocol population consisted of all patients who received a complete dose of study drug and completed their 4 hour follow-up assessment with no major protocol deviations.

Patient Disposition

A total of 72 patients were randomized in a 1:1 ratio to the two arms. Only one patient didn't complete the double-blinded study and it was due to lost to follow-up. The summary of patient disposition is given in Table 1.

Table 1 Summary of patient disposition for EDEAM3

	Ecallantide	Placebo
Randomized	36	36
ITT as randomized population	36	36
ITT as treated population	36	36
Per Protocol population	35	36
Discontinued after study drug was administered	1*	0

* Due to lost to follow-up.

Patient Demographics and Baseline Characteristics

The patient demographics and baseline characteristics are summarized for the ITT-as-randomized population in Table 2. The two study arms were well balanced with respect to age, gender, race, and the stratification factors (prior use of ecallantide and attack locations) applied in randomization. Majority of symptom complexes reported at baseline were stomach/GI symptoms and cutaneous symptoms.

Table 2 Patient demographics and baseline characteristics (ITT-as-randomized population)

		Ecallantide (N=36)	Placebo (N=36)
Age	Mean	39	32
	Median	37	30
	Std. Dev.	15	14
	Range (Min, Max)	(18, 77)	(11, 57)
Gender	Male	12 (33%)	13 (36%)
	Female	24 (67%)	23 (64%)
Race	White	33 (92%)	32 (89%)
	Black	1 (3%)	4 (11%)
	Hispanic	2 (6%)	0 (0%)
Prior use of ecallantide	Yes	8 (22%)	11 (31%)
	No	28 (78%)	25 (69%)
Attack location	Oropharyngeal Head/Neck	9 (25%)	4 (11%)
	GI/Abdominal	20 (77%)	21 (58%)
	Genital/Buttocks	2 (6%)	4 (11%)
	Non-oropharyngeal head/Neck	4 (11%)	9 (25%)
	Cutaneous	21 (58%)	14 (39%)

3.1.2 Study Design of EDEMA4

General Design

The design of EDEMA4 was similar to the design of EDEMA3 with a few exceptions. EDEMA4 was conducted in 30 sites in US and Canada. The study period of EDEMA4 was from April 2007 to June 2008. There was no open label repeat dosing phase in EDEMA4.

There were six major differences in the design of the two studies. Firstly, randomization in EDEMA4 was stratified based on prior use of ecallantide and anatomic locations of HAE attack categorized in 2 strata, laryngeal vs. all other locations; while in EDEMA3, randomization was stratified based on prior use of ecallantide and attack locations categorized in 3 strata, laryngeal vs. abdominal vs. peripheral.

Secondly, in addition to the SUAC dose, in EDEMA4, if patient's symptoms failed to improve or resolve incompletely at 4 hours after initial dosing, or if an attack relapsed within 24 hours after initial dosing, a single open-label dose of 30 mg SC ecallantide (referred to as Dose B) or standard care was administered. Patients were discharged at 4 hours after the initial dosing as well. Total duration of the study participation in EDEMA4 was up to 7 days including the follow-up visits.

Thirdly, the primary efficacy end point in EDEMA4 was the change of MSCS at 4 hours post-dose from baseline. The primary efficacy end point in EDEMA3, TOS at 4 hours post-dose, was used as the secondary efficacy end point in EDEMA4. This change was recommended by FDA, because MSCS was considered a more straightforward measure of response to treatment than TOS. Two more secondary efficacy endpoints, proportion of patients maintaining a significant improvement in overall response and proportion of patients with successful response at 4 hours post-dose based on change from baseline in MSCS, were added to EDEMA4 by a special protocol assessment (SPA). Maintenance of significant improvement was defined as achieving and maintaining a significant improvement in overall response (i.e. maintaining an assessment of "a lot better or resolved") through 24 hours after dosing. A successful response was defined as improvement in existing laryngeal symptom complex, stabilization of an existing peripheral symptom complex, or a change from baseline in the MSCS score at 4 hours of at least -1.0.

Fourthly, no data imputations were employed for the primary and secondary analyses in EDEMA4. In EDEMA3, TOS and MSCS were imputed for emerging symptom complexes and medical interventions that may have an effect on drug assessment. In both studies, sensitivity analyses were performed using imputations for emerging symptoms and medical interventions to test the robustness of the study conclusions. In this review, to make comparison between the two studies on consistent basis, all the analysis, except the results presented in section of data imputation, were based on unimputed data.

Fifthly, in EDEMA4, no patient received wrong drug, so there was no further classification of ITT-as-randomized and ITT-as-treated. Prior to unblinding, the statistical analysis plan was amended with new definitions of ITT and PP populations. ITT population for EDEMA4 was redefined as patients who received any amount of drug regardless of whether there was a 4-hour assessment. Per Protocol population was defined as all patients who received a complete dose of study drug with no major protocol deviation.

Lastly, a protocol amendment was made on Dec. 3, 2008 to increase the sample size of 52 in the original protocol to 96. Another modification of the protocol was allowing the use of paper diaries.

Patient Disposition

A total of 96 patients enrolled in EDEMA4. Ninety-five patients completed the study with only one patient in the placebo group withdrew from the study after enrollment. The patient voluntarily left the study site against medical advice. The summary of patient disposition for EDEMA4 is given in Table 3.

Table 3 Summary of patient disposition for EDEMA4

	<u>Ecallantide</u>	<u>Placebo</u>
Randomized	48	48
Intent-to-treat population	48	48
Per protocol population	47	48
Patients withdrew from study	1*	0

* Left study site against medical advice.

Patient Demographics and Baseline Characteristics

In EDEMA4, the demographic and baseline characteristics were similar in the ecallantide and the placebo arms except for gender ratio and attack locations. A higher proportion of females (77%) were in the ecallantide group than in the placebo group (58%). A higher proportion of patients in the ecallantide group (71%) entered the study with cutaneous symptom complexes compared to patients in the placebo group (44%), whereas a higher proportion of patients in the placebo group entered with GI/abdominal symptom complexes (56%) compared to patients in the ecallantide group (38%). The summary of patient demographics and baseline characteristics is given in Table 4. Considering the study had a small sample size, it is not unusual to observe that some baseline characteristics are unbalanced.

Table 4 Patient demographics and baseline characteristics (ITT population)

		Ecallantide (N=48)	Placebo (N=48)
Age	Mean	31	38
	Median	35	39
	Std. Dev.	13	12
	Range (Min, Max)	(16, 73)	(14, 72)
Gender	Male	11 (23%)	20 (42%)
	Female	37 (77%)	28 (58%)
Race	White	39 (81%)	43 (90%)
	Black	3 (6%)	3 (6%)
	Hispanic	4 (8%)	1 (2%)
	Asian	1 (2%)	1 (2%)
	Other	1 (2%)	0 (0%)
Prior use of ecallantide	Yes	17 (53%)	19 (40%)
	No	31 (65%)	29 (60%)
Attack location	Oropharyngeal Head/Neck	8 (17%)	13 (27%)
	GI/Abdominal	18 (38%)	27 (56%)
	Genital/Buttocks	6 (13%)	5 (10%)
	Non-oropharyngeal head/Neck	14 (29%)	9 (19%)
	Cutaneous	34 (71%)	21 (44%)

3.1.3 Statistical Methods

Non-parametric Wilcoxon rank sum test was applied to analyses of Treatment Outcome Score (TOS) and change of Mean Symptom Complex Severity (MSCS). Log-rank test was used to compare the time to report of significant improvement in overall responses. Logistic regression was applied to analysis of proportion of patients with responses.

3.1.4 Efficacy Results of EDEMA3 and EDEMA4

The summary of analysis on TOS and MSCS are given in Table 5 and Table 6 respectively. The results reported in this section were from analysis based on ITT-as-treated population. The results show that patients in the ecallantide arm had statistically significant greater reduction in MSCS at 4 hours post-dose from baseline, as well as higher TOS at 4 hours post-dose, compared to patients in the placebo arm. However, the analysis result of EDEAM3 based on ITT-as-randomized population doesn't give a significant P value ($p=0.138$). The treatment difference measured by TOS between the ecallantide arm and the placebo arm changed from 26 by analysis based on ITT as treated population to 31 by analysis based on ITT as randomized population. By sponsor's definition, TOS of 30 or above indicates meaningful improvement. The difference between ITT-as-randomized and ITT-as-treated population is only due to two patients who received wrong drugs, one patient who was randomized to the placebo arm received ecallantide and the other patient who was randomized to the ecallantide arm received placebo. Data from two patients are enough to change the study conclusion indicates that the treatment difference

was not robust in EDEMA3. This is one of the concerns this reviewer has on the efficacy results of EDEMA3. This issue was discussed at the advisory committee meeting. The statistician on the committee thought this result was reasonable in orphan drug studies. It is not unusual to observe this outcome due to the swap of two patients, because the sample size of the study was only big enough to detect the expected effect size, but not much room for fiddling with data.

There was some minor update on data from EDEMA3 after the application was submitted. The efficacy results of EDEMA3 based on updated data are slightly different from the reported results in submission. Data from EDEMA4 remain the same.

Table 5 Summary of analyses results on TOS at 4 hours post-dose for EDEMA3 and EDEMA4 (ITT-as treated population)

	EDEMA3		EDEMA4	
	Ecallantide (N=36)	Placebo (N=36)	Ecallantide (N=48)	Placebo (N=48)
Mean	63	36	53	8
Std. Dev.	39	54	50	63
Median	50	50	50	0
IQR	(50, 100)	(0, 100)	(0, 100)	(-50, 50)
P value	0.045		0.003	

Table 6 Summary of analyses results on change of MSCS at 4 hours post-dose from baseline for both EDEMA3 and EDEMA4 (ITT-as-treated population)

	EDEMA3		EDEMA4	
	Ecallantide (N=36)	Placebo (N=36)	Ecallantide (N=48)	Placebo (N=48)
Mean	-1	-0.6	-0.8	-0.4
Std. Dev.	0.9	0.6	0.6	0.8
Median	-1	-1	-1	0
IQR	(-1.5, -0.5)	(-1, 0)	(-1, 0)	(-1, 0)
P value	0.04		0.01	

Since both TOS and MSCS were analyzed by non-parametric Wilcoxon rank sum test, the reviewer has the concern on difference between statistical significance and meaningful clinical difference. Since Wilcoxon rank sum test does not provide descriptive statistics to summarize the distribution, alternative test that better describes the effect size is desired. Particular attention was paid to a secondary efficacy end point, proportion of patients with successful responses at 4 hours post-dose based on change of MSCS ≤ -1 . This secondary efficacy end point was only in the statistical analysis plan for EDEMA4. The reviewer applied similar analysis to EDEMA3 and compared the results from the two studies. The summary is given in Table 7. As shown in Table 7, the difference in proportion of patients with response at 4 hours was only 16% in EDEMA3, while the difference was 30% in EDEMA4.

Table 7 Proportion of patients with successful responses based on change of MSCS at 4 hours post-dose from baseline less than or equal to -1 (ITT-as-treated population)

	EDEMA3		EDEMA4	
	Ecallantide (n=36)	Placebo (n=36)	Ecallantide (n=48)	Placebo (n=48)
Yes	22 (66%)	18 (50%)	29 (60%)	14 (29%)
No	14 (39%)	18 (50%)	19 (40%)	34 (71%)
P value	0.3		0.003	

To gain better understanding in the treatment difference, the reviewer conducted additional analysis based on different definitions of responder. The definition used for this analysis was only based on cut offs of TOS and change in MSCS regardless of HAE attack locations. The results are summarized in Table 8. Results of EDEMA4 are consistent with various cut-offs. Regardless of cut offs applied to the definition of successful responses, significant difference between the placebo arm and the ecallantide arm are confirmed by all tests. The results of EDEMA3 are variable. The treatment differences for all the responder definitions were relatively small.

Table 8 Summary results of proportion of patient with successful response based on different definitions (ITT-as-treated population)

		EDEMA3			EDEMA4		
		Ecallantide	Placebo	Difference	Ecallantide	Placebo	Difference
TOS	≥70	44%	31%	13%	46%	19%	27%
	≥50	75%	50%	25%	69%	27%	42%
	≥30	75%	50%	25%	69%	27%	42%
MSCS	≤-1	61%	50%	11%	60%	29%	31%
	≤-0.3	78%	61%	17%	69%	38%	31%

3.1.5 Comparison of the EDEMA4 efficacy results between pre and post sample size change

The study period of EDEMA4 was from April 2007 to June 2008. The original protocol for EDEMA4 was submitted on February 21, 2007. Protocol amendment was made on December 3, 2007 to increase sample size and allow use of paper diaries. Before the protocol amendment, electronic diaries had been required. No change on patient selection or conduction of study was made.

The sponsor provided the summary of baseline and disease characteristics for patients who enrolled before and after sample size change. The detail is given in the appendices. In a brief summary, the proportion of females in the pre sample size change enrollment was lower than the proportion of female in the post sample size change enrollment; there was also a difference in the relative distribution of patients with primary attack locations at laryngeal, abdominal, and peripheral sites between the pre and post sample size change enrollment.

To assess whether sample size change had impact on treatment effect, comparison of the efficacy results between pre and post sample size change enrollment was conducted. The results are summarized in Table 9, Table 10, and Table 11.

Table 9 summarizes the efficacy results on change of MSCS at 4 hours post-dose pre and post sample size change. The results show that the treatment difference between the ecallantide arm and the placebo arm was -0.09 with P value of 0.826 in pre sample size change enrollment and was -0.88 with P value less than 0.001 in post sample size change enrollment. Before sample size change, there was merely no difference between the two arms; after sample size change, the treatment difference was enlarged significantly.

Table 9 Summary of change in MSCS at 4 hours post-dose in EDEMA4 pre and post sample size change enrollment (ITT population)

	Pre sample size change		Post sample size change	
	Ecallantide (N=28)	Placebo (N=24)	Ecallantide (N=20)	Placebo (N=24)
Mean	-0.7	-0.6	-0.9	-0.06
Std. Dev.	0.6	0.8	0.7	0.8
Median	-1	-0.3	-1	0
IQR	(-1,0)	(-1,0)	(-1.3,-0.3)	(-0.5,0.3)
P value	0.826		<0.001	

The results on TOS at 4 hours post-dose in Table 10 are similar to the results on change of MSCS. Again, the treatment difference between the two arms was 24.08 with P value of 0.24 before the sample size change; it increased to 72.39 with P value of 0.006 after sample size change.

Table 10 Summary of TOS at 4 hours post-dose in EDEMA4 pre and post sample size change enrollment (ITT populations)

	Pre sample size change		Post sample size change	
	Ecallantide (N=28)	Placebo (N=24)	Ecallantide (N=20)	Placebo (N=24)
Mean	43	19	67	-5
Std. Dev.	47	58	51	68
Median	50	0.00	100	0
IQR	(0,100)	(-28.57,100)	(50,100)	(-67,50)
P value	0.24		0.006	

The proportion of responders based on different cut offs on TOS and change in MSCS in Table 11 gives the similar conclusions to Table 9 and Table 10.

Table 11 Summary of proportions of responders based on cut offs on TOS and change in MSCS in EDEMA4 pre and post sample size change enrollment (ITT population)

		Pre sample size change			Post sample size change		
		Ecallantide (N=28)	Placebo (N=24)	Difference	Ecallantide (N=20)	Placebo (N=24)	Difference
TOS	≥70	32%	25%	7%	65%	13%	52%
	≥50	57%	33%	24%	85%	21%	64%
	≥30	57%	33%	24%	85%	25%	60%
MSCS	≤-1	54%	46%	8%	70%	13%	57%
	≤-0.3	64%	54%	10%	75%	21%	54%

To further clarify the problem, the reviewer made scatter plot on change of MSCS at 4 hours post-dose vs. enrollment time (Figure 1). Each point indicates a patient. Y axis is change of MSCS at 4 hours post-dose; X axis is the enrollment date; the red dots indicate patients in the ecallantide arm; the black dots indicate patients in the placebo arm; the green dotted line shows when the protocol amendment was granted; the black dotted line shows where the population was split into pre and post sample size change enrollment. Six patients in the placebo arm enrolled after sample size change performed very poorly, i.e. change of MSCS at 4 hours post-dose from baseline was greater than 0; while no patients enrolled before sample size change performed the same. The pattern observed before sample size change is similar to the pattern observed in EDEMA3 where change of MSCS at 4 hours post-dose from baseline for all patients were negative except one patient in the ecallantide arm (whose change of MSCS at 4 hours post-dose was 0.5).

This raised the reviewer's concern on an interaction between treatment effect and enrollment period in EDEMA4. The reviewer conducted logistic regression on proportion of responders based on change of MSCS ≤-1 with treatment effect, enrollment period (categorized as pre and post sample size change), and the interaction between treatment effect and enrollment period as covariates. The model is

$$\text{Responder} = \beta_0 + \beta_1 \text{treatment} + \beta_2 \text{enrollment.period} + \beta_3 * \text{treatment:enrollment.period.}$$

The results are summarized in Table 12. Significant interaction effect was detected with P value of 0.04. The null hypothesis of the test is that the treatment difference between the two study arms is the same before and after sample size increment. P value of 0.04 indicates that the chance to observe such inconsistency is rare. What we can conclude is that the treatment differences changed substantially after sample size adjustment. There is no treatment difference before sample size adjustment, but large treatment difference after sample size adjustment.

Based on the sponsor's analysis, excluding the placebo outliers, the significant result of primary efficacy analysis disappeared (p=0.085). This means the efficacy observed in EDEMA4 was mainly due to the placebo patients performed poorly in the later part of the study.

In addition to that, there is another concern. Although the overall efficacy was observed in EDEMA4, when extrapolating the study result to target population, the inconsistency between

the two study periods in EDEMA4 means that in some HAE patients, ecallantide would have some effect; while in other HAE patients, ecallantide would have no effect. At the finalization of this review, the sponsor has not been able to figure out what made the patients in the two study periods performed so differently, it is not predictable what type of patients could benefit from this drug.

Based on the latest response from the sponsor, this inconsistency was partially explained by the differences in response of placebo patients with abdominal attacks and ecallantide patients with peripheral attacks treated before and after sample size change. For the ecallantide patients with peripheral attacks, the response to treatment was substantially better for those who enrolled the study after sample size increment than the ones who enrolled before sample size increment. For placebo patients with an abdominal attack, the response to treatment was substantially better for those who enrolled early in the study compared to those who enrolled later in the study. Among the 5 placebo outliers recruited after sample size change, 3 of them entered the study with an abdominal attack. There was no indication that baseline characteristics could predict a poor or good response. This only explained what caused the inconsistency, but it still can not explain why patients performed so differently before and after sample size change. The sponsor proposed further analysis to explore the issue. However, the new analysis reached similar conclusion. With Wilcoxon rank sum test blocked by participation in prior EDEMA studies and primary attack locations, again no treatment difference was observed between the two study arms before sample size change and substantial treatment difference was observed after sample size change.

This issue was discussed at the advisory committee meeting. One of the voting questions was whether data provided substantial and convincing evidence that ecallantide provides a clinically meaningful beneficial effect on acute attack of HAE. Four out of 13 committee members voted yes; 8 of 13 committee members voted no; and one abstained. The committee suggested additional analysis to study the inconsistency between the two study periods in EDEMA4. Two analyses were thought to be useful for further understand of the issue: a). the analysis to show whether the primary efficacy end point depends on the mean lowest historical functional C1-INH level or the mean lowest historical C4 level; b). change in MSCS recalculated as the arithmetic mean for 3 possible symptom complexes instead of 5. The 3 complexes are abdominal/GI, internal head/neck, and peripheral (external head/neck, genital/buttocks, and cutaneous grouped together). The agency already sent out information request to the sponsor for data that are necessary for these analyses, but it is not available yet. The committee also commented that although the efficacy results were not consistent, efficacy was confirmed at least in some patients.

EDEMA4 pre vs. post sample size change

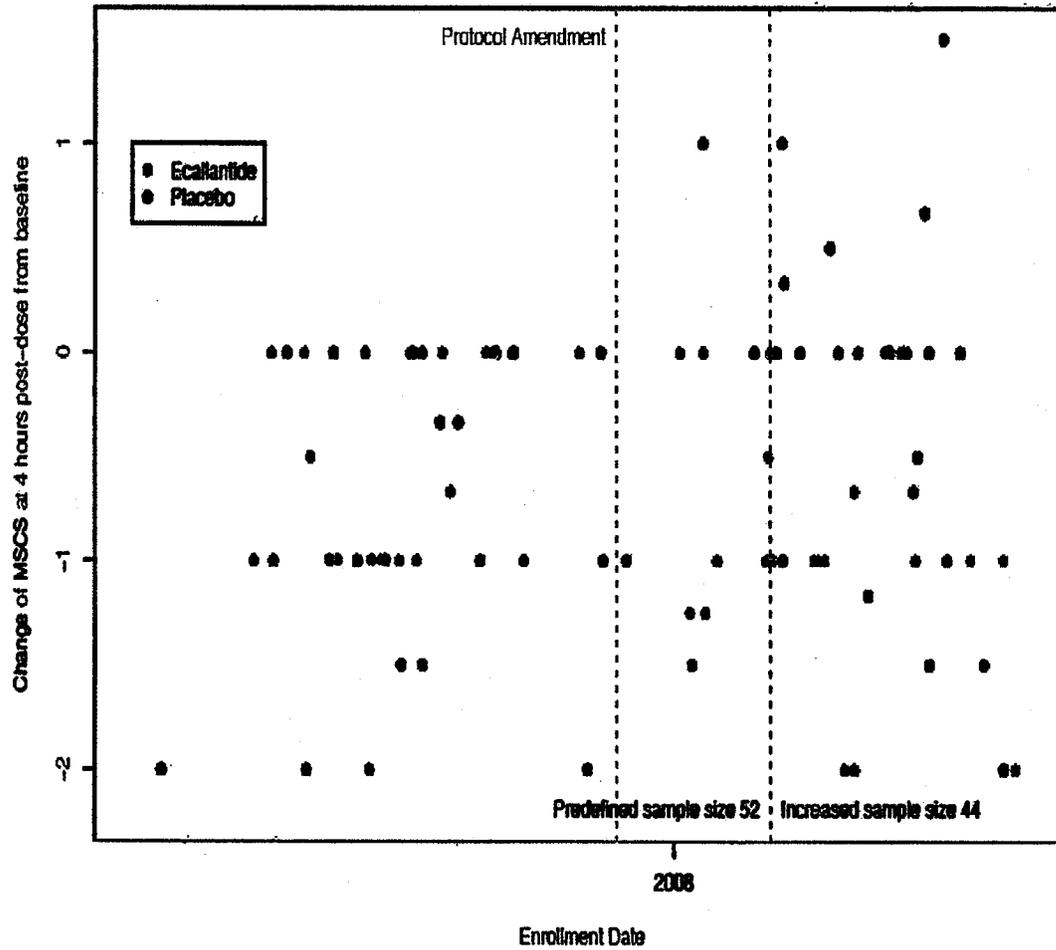


Figure 1 Scatter plot of change in MSCS at 4 hours post-dose vs. enrollment date in EDEMA4 (ITT population)

Table 12 Summary of interaction between treatment effect and enrollment period in EDEMA4 (ITT population)

	Estimate	Std. Error	P value
Intercept	-1	0.5	0.02
Treatment	2	0.6	0.01
Enrollment period	-2	1	0.07
Interaction	3	1	0.04

3.1.6 Data Imputation

The occurrence of emerging symptom complexes (i.e. any new symptom complex that occurred after dosing with study drug and was classified outside of symptom complexes identified at baseline) and medical interventions during an attack affects the evaluation of Treatment Outcome Score (TOS) and change of Mean Symptom Complex Severity (MSCS) at 4-hour and 24-hour post-dose. In the BLA submission, data used for the primary and secondary analyses in EDEMA3 were imputed, data used for the primary and secondary analyses in EDEMA4 were not. Sensitivity analysis on data with and without imputation was conducted for TOS and change in MSCS in EDEMA3, EDEMA4, and integrated summary of efficacy (ISE) to check the robustness of results.

The detail rules for data imputation proposed by the sponsor are available in appendices. Here is a brief summary of it. When there was emerging symptom complex, the baseline severity for the emerging symptom was classified as "normal". If the emerging symptom was still present at 4/24 hours post-dose, its severity was used to calculate the MSCS at these time points. If the emerging symptom was not present at the evaluation time point, its severity was classified as "normal". For TOS, the emerging symptom complex was weighted according to its peak severity assessment. If the emerging symptom was still present at 4/24 hours post-dose, the response assessment was assigned as "significant worsening", otherwise "normal". When there was medical intervention during an attack before unblinding, for MSCS, symptom complexes that were potentially affected were given a severity assessment of "severe"; for TOS, symptom complexes that were potentially affected were given a response assessment of "significant worsening". If medical intervention was not clearly directed to a specific symptom complex, all symptom complexes were affected in MSCS and TOS calculations.

The imputation rules proposed by the sponsor were designed for a conservative measure on TOS and MSCS. However, it does not guarantee the treatment differences on imputed data lead to a conservative conclusion on efficacy of the study drug. Because there were more emerging symptom complexes and medical interventions in the placebo arm than in the ecallantide arm, more data in the placebo arm were imputed than in the ecallantide arm. This increased the difference in treatment effect between the two arms. Thus the imputation favored the study drug.

Table 13 summarizes the percentage of data imputed in each study. Table 14 gives the corresponding P values from the test on various imputed data. We see that the higher percentage of data was imputed in the placebo arm than in the ecallantide arm, the more significant the result became.

Table 13 Summary of percentage of data imputed in EDEMA3 and EDEMA4 (ITT-as-treated population)

	EDEAM3				EDEMA4			
	TOS		MSCS		TOS		MSCS	
	Ecallantide	Placebo	Ecallantide	Placebo	Ecallantide	Placebo	Ecallantide	Placebo
Unimputed	0%	0%	0%	0%	0%	0%	0%	0%
Imputed for Emg. Symp.	0%	3%	0%	6%	8%	15%	0%	15%
Imputed for Emg. Symp. + Med. Inv	3%	11%	3%	11%	8%	21%	0%	21%

Table 14 Summary of P values resulted from different data imputations in EDEMA3 and EDEMA4 (ITT-as-treated population, not treating patients with SUAC as treatment failure)

	EDEMA3		EDEMA4	
	TOS	MSCS	TOS	MSCS
Unimputed	0.045	0.041	0.003	0.01
Imputed for emerging symptom complexes	0.033	0.027	0.002	0.001
Imputed for emerging symptom complexes and medical intervention	0.017	0.016	<0.001	<0.001

This raises the concern that data imputation rules proposed by the sponsor may exaggerate the treatment difference.

The so-called unimputed data are in fact imputed as well, since it ignored the information from emerging symptom complex and potential effect on treatment outcome by medical intervention.

Because the imputation rules proposed by the sponsor favored the study drug, alternative imputation rules that are expected to lead to conservative results are necessary to assess the robustness of the study results. Considering there were more emerging symptoms and medical interventions in the placebo arm than in the ecallantide arm, this reviewer suggests reversing the imputation rules proposed by the sponsor and see if statistical significance can still be confirmed by analysis based on data imputed according to the new rules. For example, instead of assigning significant worsen (-100) to emerging symptom in TOS calculation, assign significant improvement (100) to it. The detail of imputation rules proposed by this review is available in appendices. This new imputation rule is not reasonable in the sense of estimating single treatment outcome. It is only proposed to check how big effect the imputation rule could have on estimation of treatment difference between ecallantide and placebo. Because the imputation rule proposed by the sponsor is not conservative, it is desirable to see what the result would be if the opposite imputation rule is applied.

The summary of analysis results based on data imputed according to both imputation rules are given in Table 15. The unfilled cells are the analysis we requested from sponsor but not available yet. We see that the primary efficacy end point is highly sensitive to imputation. These analyses

can be considered extreme imputation rules, which may not be reasonable in estimating treatment difference, but provide information in assessing treatment robustness.

In addition, the result based on data including imputation due to SUAC failure is very different from the result based on data not including imputation due to SUAC failure in EDEMA3. The p values for unimputed data in EDEMA3 analyzed based on ITT as treated population was 0.041 and 0.045 for change of MSCS and TOS respectively, when not treating patients with SUAC as treatment failure; the same p values was 0.096 and 0.092 for change of MSCS and TOS respectively, when treating patients with SUAC as treatment failure. There were 2 patients in the ecallantide arm in EDEMA3 with SUAC failure, one patient in the placebo arm in EDEMA3 with SUAC failure. These patients were included in the ITT population in EDEMA3. In EDEMA4, there were one patient in the ecallantide arm with SUAC failure and 3 patients in the placebo arm with SUAC failure. Because in EDEMA4 the primary analysis was done based on data without imputation, patients with SUAC failure did not have their 4 hour post-dose evaluation and thus not included in the primary analysis, but included in the sensitivity analysis.

Table 15 P values using different approaches to data imputation

	Treating patients with SUAC as treatment failure						Not treating patients with SUAC as treatment failure					
	Based on rule 2a in appendices			Based on rule 2b in appendices			Based on rule 2a in appendices			Based on rule 2b in appendices		
	E3- As TX	E3- ITT	E4 ITT	E3- As TX	E3- ITT	E4 ITT	E3- As TX	E3- ITT	E4 ITT	E3- As TX	E3- ITT	E4 ITT
	Change from baseline in MSCS score at 4 hours											
Unimputed	0.096	---	---	0.096	---	---	0.041	0.096	0.01	0.041	0.096	0.01
Imputed for emerging symptom complexes	0.069	---	---	---	---	---	0.027	---	0.001	---	---	0.006
Imputed for emerging symptom complexes and medical intervention	0.044	---	---	---	---	---	0.016	---	<0.001	---	---	0.372
	TOS at 4 hours											
Unimputed	0.092	---	---	0.092	---	---	0.045	0.138	0.003	0.045	0.138	0.003
Imputed for emerging symptom complexes	0.071	---	---	---	---	---	0.033	---	0.002	---	---	0.002
Imputed for emerging symptom complexes and medical intervention	0.037	---	---	---	---	---	0.017	---	<0.001	---	---	0.143

As the efficacy assessments were only made at baseline and 4 hours post-dose, MSCS was only evaluated at two time points. It only captures the change between the two time points, but ignores the pathway of changing. The shortcomings of this approach are illustrated in the examples below. In the following discussion, we also discuss the advantages of an alternative efficacy end point for consideration in future studies, which requires more frequent measurements of MSCS and calculates the area under the curve. This efficacy end point will have less issue with emerging symptom complexes.

As an example, in Figure 2, the patient in case 1 starts with a single severe symptom at baseline and gets improved at 3 hours post-dose, the symptom severity reduces to mild. The change of MSCS at 4 hours post-dose from baseline in case 1 is -2. The patient in case 2 also starts with a single severe symptom at baseline, but gets improved at 0.5 hour post-dose, which is much earlier than that in case 1. The severity of symptom also reduces to mild. The change of MSCS at 4 hours post-dose from baseline in case 2 is -2 as well, the same as that in case 1. However, clinically case 2 is much better than case 1, because the treatment shows benefit more quickly. This difference is not captured by change in MSCS at 4 hours post-dose from baseline. A better measure would be proportion of area under the curve (i.e. AUC --- the area labeled in red) of severity path. In case 1, the AUC is 10. Compare to the total area of 12 which we consider as the maximum potential suffering the patient could experience, the proportion of suffering over the period is $10/12=83.3\%$ of the maximum potential suffering. The treatment helps to reduce the suffering by 16.7%. In case 2, the AUC is 5, the proportion is $5/12=41.7\%$, the treatment helps to reduce the potential suffering by 48.3%. The difference of 16.7% and 41.7% reflects the difference in the treatment effect of the two cases. This measure could be applied to case 3 and case 4 in the same way. In the two cases with emerging symptom complexes, case 3 and case 4, the change of MSCS is 1. However, the patient in case 3 is in a worse case than the patient in case 4. In case 3, the AUC is 6.5, the proportion of AUC is $6.5/12=54.2\%$, which is the measure of failure of the treatment. In case 4, the AUC is 0.5, the proportion of AUC is $0.5/12=4.2\%$. The difference of 54.2% and 4.2% reflects the treatment difference in two cases. If we assign the primary end points of the four cases to be -0.167, -0.417, 0.542, and 0.42 respectively, it reflects the idea of change in MSCS, but in a much more effective way.

Furthermore, because AUC is a continuous measure, we can apply test on continuous variables, which is usually better at describing the effect size, to it. It also solves the problem with imputation due to emerging symptom complexes, because it doesn't require arbitrary symptom severities to be assigned to emerging symptom complexes. If the new efficacy end point is available, there will be less problems in data imputation.

We sent out request to the sponsor on recalculation of MSCS by AUC approach and re-analyzing data based on the recalculated MSCS. The result is not available yet at the finalization of this review.

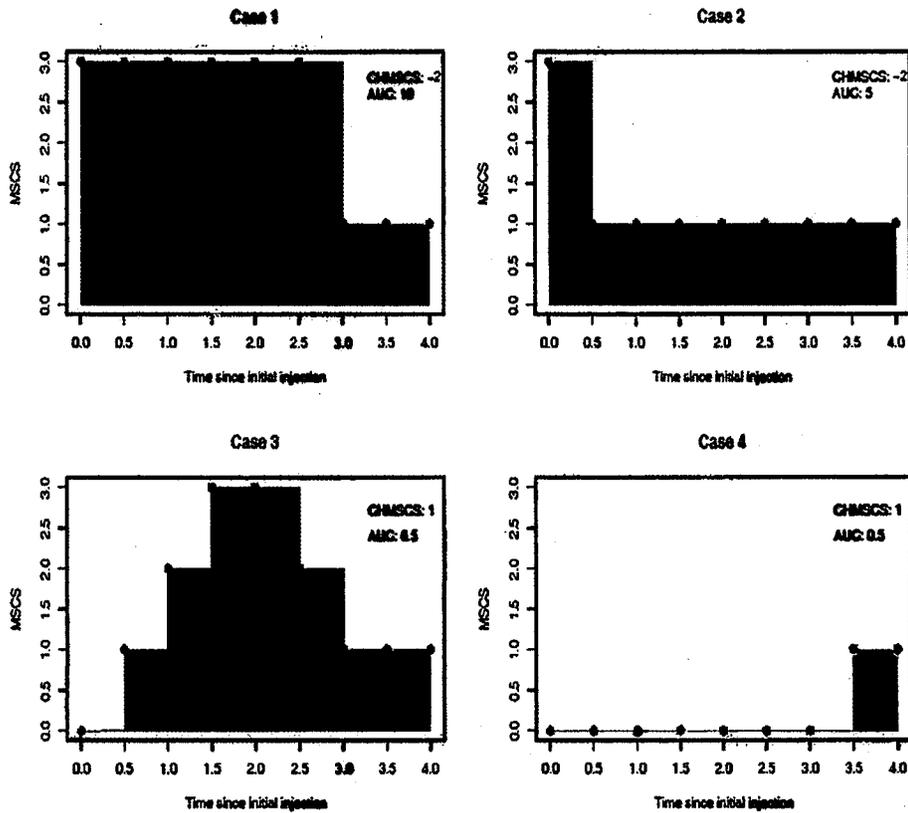


Figure 2 Illustration of an alternative efficacy end point --- AUC.

3.2 Evaluation of Safety

The evaluation of safety was conducted by Dr. Susan Limb. No special analysis on safety evaluation was requested by the clinical review team. Reader is referred to Dr. Susan Limb's review for this section.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analysis on efficacy end points was done for age, gender, race, prior use of ecallantide, and attack locations of HAE. However, due to the small sample size and majority of patients coming from a single stratum in subgroups, no meaningful conclusions could be drawn from subgroup analysis.

Because the applicant proposes ecallantide for the treatment of acute attacks of hereditary angioedema in patients who are 10 years of age and older, the results of subgroup analysis on age are summarized in Table 16 and Table 17 to show that there were no enough data on pediatric group to support efficacy in patients who are younger than 18 years of age.

Table 16 Summary of results on change of MSCS at 4 hours post-dose from baseline by age group in EDEMA3 and EDEMA4 (ITT as treated population)

	EDEMA3				EDEMA4			
	Pediatric (<18yr)		Adult (>=18yr)		Pediatric (<18yr)		Adult (>=18yr)	
	Ecallantide	Placebo	Ecallantide	Placebo	Ecallantide	Placebo	Ecallantide	Placebo
N	2	7	32	28	2	3	45	39
Mean	-1	-0.6	-1	-0.5	-1.1	-1	-0.8	-0.3
Std. Dev.	0	0.5	1	0.7	0.2	0	0.6	0.8
Median	-1	-1	-1	-0.2	-1.1	-1	-1	0
IQR	(-1,-1)	(-1,0)	(-1.8,-0.5)	(-1,0)	(-1.3,-1)	(-1,-1)	(-1,0)	(-1,0)
P value	0.4		0.02		0.5		0.005	

Table 17 Summary of results on TOS at 4 hours post-dose by age group in EDEMA3 and EDEMA4 (ITT as treated population)

	EDEMA3				EDEMA4			
	Pediatric (<18yr)		Adult (>=18yr)		Pediatric (<18yr)		Adult (>=18yr)	
	Ecallantide	Placebo	Ecallantide	Placebo	Ecallantide	Placebo	Ecallantide	Placebo
N	2	7	34	29	2	3	45	39
Mean	75	36	48	14	100	58	51	4
Std. Dev.	35	48	60	72	0	38	50	63
Median	75	0	50	0	100	50	50	0
IQR	(50,100)	(0,100)	(0,100)	(-25,100)	(100,100)	(25,100)	(0,100)	(-50,50)
P value	0.4		0.05		0.4		0.001	

APPENDICES

1. Demographic and baseline characteristics in the patients enrolled pre and post sample size change.

Quotation from study report DX-88/20(EDEMA4).

Table 12. Summary of Baseline and Disease Characteristics for the First 52 and Last 44 Patients Treated in EDEMA4

Statistic	First 52 Enrolled	Last 44 Enrolled
	(N=28)	(N=20)
Mean age at informed consent (y)	37.9	35.8
Female, n (%)	20 (71.4)	17 (85.0)
Caucasian, n (%)	25 (89.3)	14 (70.0)
Mean age at first HAE symptom onset (yr)	13.6	13.2
Mean lowest historical functional C1 INH level (%)	30.1	35.4
Mean lowest antigenic C1 INH level (mg/dL)	7.7	15.0
Mean lowest historical C4 level (mg/dL)	6.2	12.9
Moderate/Severe Internal Head/Neck, n (%)	3 (10.7)	5 (25.0)
Moderate/Severe Stomach/GI, n (%)	7 (25.0)	6 (30.0)
Moderate/Severe Genital/Buttocks, n (%)	4 (14.3)	2 (10.0)
Moderate/Severe External Head/Neck, n (%)	6 (21.4)	4 (20.0)
Moderate/Severe Cutaneous, n (%)	18 (64.3)	14 (70.0)

Statistic	Placebo	
	(N=24)	(N=24)
Mean age at informed consent (y)	36.2	39.8
Female, n (%)	12 (50.0)	16 (66.7)
Caucasian, n (%)	22 (91.7)	21 (87.5)
Mean Age at first attack (y)	10.7	15.3
Mean lowest historical functional C1 INH level (%)	29.4	13.4
Mean lowest antigenic C1 INH level (mg/dL)	14.8	10.8
Mean lowest historical C4 level (mg/dL)	9.9	10.1
Moderate/Severe Internal Head/Neck, n (%)	2 (8.3)	5 (20.8)
Moderate/Severe Stomach/GI, n (%)	16 (66.7)	10 (41.7)
Moderate/Severe Genital/Buttocks, n (%)	4 (16.7)	0
Moderate/Severe External Head/Neck, n (%)	3 (12.5)	6 (25.0)
Moderate/Severe Cutaneous, n (%)	8 (33.3)	9 (37.5)

Source: Summary Tables 14.1.6.1.1, 14.1.6.1.2, 14.1.10.1.1, 14.1.10.1.2, 14.2.1.1.1, 14.2.1.1.2

2. Data imputation rules.

a. Rules for data Imputation proposed by the sponsor.

Quotation from clinical study report: DX-88/20 (EDEMA4)

EMERGING SYMPTOM COMPLEXES

Per the SAP, the occurrence of an emerging symptom complex (i.e. any new symptom complex that occurred after dosing with study drug and was classified outside of symptom complexes identified at baseline) affected the MSCS score and the TOS calculations in the sensitivity analyses as follows:

• *MSCS score*

- *An emerging symptom complex was included in the baseline MSCS score calculation, with its baseline severity classified as "normal."*
- *An emerging symptom complex was included in the 4-hour and/or 24-hour calculations. If the emerging symptom complex was still present at 4 hours and/or 24 hours, its severity was used to calculate the MSCS score at these times. If the emerging symptom complex was not present at 4 hours and/or 24 hours, its severity was classified as "normal."*

• *TOS*

- *An emerging symptom complex was weighted according to its peak severity assessment.*
- *An emerging symptom complex that was still present at 4 hours and/or 24 hours was assigned a response assessment of "significant worsening." An emerging symptom complex that was not present at 4 hours and/or 24 hours was assigned a response assessment of "same."*

MEDICAL INTERVENTION

Per the SAP, patients receiving medical intervention during an attack were to be identified before unblinding, and a medical determination was to be made as to whether the intervention had the potential to affect treatment outcome. Medical intervention that was clearly directed to a specific symptom complex affected only that specific symptom complex in the MSCS score and the TOS calculations; medical intervention that was not clearly directed to a specific symptom complex, as well as open-label dosing with ecallantide for SUAC or as Dose B, affected all symptom complexes in the MSCS score and the TOS calculations. The following was applied to the MSCS score, the TOS, and the overall response assessment calculations:

- *For the MSCS score, symptom complexes that were potentially affected were given a severity assessment of "severe" at 4 hours and/or 24 hours.*

- For the TOS, symptom complexes that were potentially affected were given a response assessment of "significant worsening" and a severity assessment of "severe" at 4 hours and/or 24 hours.

- The overall response assessment was classified as "significant worsening" and a severity assessment of "severe" at 4 hours and/or 24 hour.

b. Rules for data imputation proposed by the reviewer.

EMERGING SYMPTOM COMPLEXES

• MSCS score

- An emerging symptom complex was included in the baseline MSCS score calculation, with its baseline severity classified as peak severity before the evaluation timepoint.

- An emerging symptom complex was included in the 4-hour and/or 24-hour calculations. If the emerging symptom complex was still present at 4 hours and/or 24 hours, its severity was used to calculate the MSCS score at these times. If the emerging symptom complex was not present at 4 hours and/or 24 hours, its severity was classified as "normal."

• TOS

- An emerging symptom complex was weighted according to its severity assessment at the first appearance of the symptom.

- An emerging symptom complex that was still present at 4 hours and/or 24 hours was assigned a response assessment of "significant improvement." An emerging symptom complex that was not present at 4 hours and/or 24 hours was assigned a response assessment of "normal"

MEDICAL INTERVENTION

- For the MSCS score, symptom complexes that were potentially affected were given a severity assessment of "normal" at 4 hours and/or 24 hours.

- For the TOS, symptom complexes that were potentially affected were given a response assessment of "significant improvement" and a severity assessment of "normal" at 4 hours and/or 24 hours.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer:
Date:

Dongmei Liu, Ph.D.
February 11, 2009

 2-17-2009

Statistical Team Leader:

Qian H. Li, Sc.D.

 2-17-09

Biometrics Division Director:

Thomas Permutt, Ph.D.

Examples of filing issues	Yes	No	Resolution & Status
of product			
data supporting the proposed dose and dose interval	<input checked="" type="radio"/> Y	<input type="radio"/> N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	<input checked="" type="radio"/> Y	<input type="radio"/> N	
adequate characterization of product specificity or mode of action	<input checked="" type="radio"/> Y	<input type="radio"/> 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	<input type="radio"/> Y	<input type="radio"/> N	NA
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	<input type="radio"/> Y	<input type="radio"/> N	
all information reasonably known to the applicant and relevant to the safety and efficacy described?	<input checked="" type="radio"/> Y	<input type="radio"/> N	

List of Clinical Studies (protocol number)	Final study report submitted?		Financial disclosure or certification submitted?			SAS & other electronic datasets complete & usable?		BIMO sites identified?		
	Y	N	Y	N	NR	Y	N	Y	N	NR
EDEMA 3	<input checked="" type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR	<input checked="" type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR
EDEMA 4	<input checked="" type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR	<input checked="" type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR
	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR
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	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR
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	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> NR	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> Y	<input type="radio"/> N	<input type="radio"/> 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).

None

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

Yes

Is an Advisory Committee needed?

Yes

Recommendation (circle one): File RTF

Reviewer: [Signature] ^{NOV. 3, 2008} Type (circle one): Clinical Clin/Pharm **Statistical**

Concurrence:

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

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

CTD Module / Contents	Present?	Final, justification, action & status
Overall CTD Table of Contents [2.1]	<input checked="" type="checkbox"/> Y N	
Introduction to the summary documents (1 page) [2.2]	<input checked="" type="checkbox"/> Y N	
Clinical overview [2.5]	<input checked="" type="checkbox"/> Y N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	<input checked="" type="checkbox"/> 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]	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> Clinical Safety	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> Synopses of individual studies	<input checked="" type="checkbox"/> Y N	

CTD Module / Contents	Present?	Final, justification, action & status
Module Table of Contents [5.1]	<input checked="" type="checkbox"/> Y N	
Tabular Listing of all clinical studies [5.2]	<input checked="" type="checkbox"/> Y N	
Study Reports and related information [5.3]	<input checked="" type="checkbox"/> 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	
<input type="checkbox"/> Pharmacodynamic (PD)	Y N	
<input type="checkbox"/> Efficacy and Safety	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> Postmarketing experience	Y <input checked="" type="checkbox"/> N	
<input type="checkbox"/> Case report forms	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> Individual patient listings (indexed by study)	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> electronic datasets (e.g. SAS)	<input checked="" type="checkbox"/> Y N	
Literature references and copies [5.4]	Y N	

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

Examples of Issues			Compliance Issues		
<input type="checkbox"/> summary reports reference the location of individual data and records	<input checked="" type="checkbox"/> Y	N			
<input type="checkbox"/> protocols for clinical trials present	<input checked="" type="checkbox"/> Y	N			
<input type="checkbox"/> all electronic submission components usable	<input checked="" type="checkbox"/> Y	N			
statement for each clinical investigation:					
<input type="checkbox"/> conducted in compliance with IRB requirements	<input checked="" type="checkbox"/> Y	N			
<input type="checkbox"/> conducted in compliance with requirements for informed consent	<input checked="" type="checkbox"/> Y	N			
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	<input checked="" type="checkbox"/> 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			2 studies
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	<input checked="" type="checkbox"/> Y	N			
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y	N			Not applicable
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)	<input checked="" type="checkbox"/> 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	<input checked="" type="checkbox"/> Y	N			
drug interaction studies communicated as during IND review as necessary are included	Y	N			NA
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	<input checked="" type="checkbox"/> Y	N			
comprehensive analysis of safety data from all current world-wide knowledge	Y	N			only for the studies submitted