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RESEARCH**

APPLICATION NUMBER:

BLA 125277

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	November 30, 2009
From	Sally Seymour, MD <i>MS 11/30/09</i>
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	BLA# 125277
Supplement#	
Applicant	Dyax Corp.
Date of Submission	May 31, 2009
PDUFA Goal Date	December 1, 2009
Proprietary Name / Established (USAN) names	Kalbitor / ecallantide
Dosage forms / Strength	solution for injection; 10mg/mL
Proposed Indication(s)	acute attacks of hereditary angioedema (HAE)
Recommended:	Approval

1. Introduction

This is a summary of the Complete Response for the Biologics Licensing Application (BLA) for ecallantide for the treatment of acute attacks of hereditary angioedema (HAE) in patients 16 years of age and older. On September 23, 2008, Dyax submitted a BLA for ecallantide for the treatment of acute attacks of hereditary angioedema (HAE) in patients 10 years of age and older. Ecallantide is a recombinant human plasma kallikrein inhibitor, which is a new molecular entity (NME). The proposed trade name is Kalbitor. Because of the rarity of HAE, ecallantide has Orphan Drug Status. The original BLA submission included the results of two placebo controlled phase 3 clinical trials designed to establish the efficacy and safety of ecallantide for the treatment of HAE. A Complete Response (CR) action was taken on March 25, 2009, with clinical deficiencies regarding inadequate data to support approval of patients below 18 years of age and the requirement for a Risk Evaluation and Mitigation Strategy (REMS) to mitigate the risk of anaphylaxis. The requested REMS included a Medication Guide, Communication Plan, and Elements to Assure Safe Use (ETASU). In addition, there were numerous product quality issues that Dyax needed to address.

On May 31, 2009, Dyax submitted a Complete Response. To address the issue regarding pediatric patients, Dyax adjusted the proposed lower age limit from 10 years of age to 16 years of age. To support approval in patients 16 to 18 years of age, Dyax included a summary of data available in this age group and included validated pharmacokinetic (PK) data to support the dose in pediatric patients. The CR included a REMS that contained all the requested elements, including a restricted distribution program. However, after review of the REMS, the Agency had concerns that the restricted distribution program did not mitigate the risk of anaphylaxis and could hinder patient access to ecallantide. The Agency determined that a REMS including a Communication Plan and Medication Guide would be adequate to assure safe use of ecallantide. A revised REMS was requested on October 16, 2009. Dyax submitted a revised REMS containing a Communication Plan and Medication Guide on October 26, 2009.

With the revised REMS and revised pediatric age range, Dyax has adequately addressed the clinical deficiencies outlined in the March 25, 2009 CR letter. In addition, Dyax has adequately addressed the outstanding CMC issues and has agreed to multiple post-marketing requirements (PMRs) to address clinical, carcinogenicity, and immunoassay issues. The recommendation for this application is Approval. This memo focuses only on the CR issues that warrant discussion, including the pediatric data, REMS, and issues with immunogenicity assays. The CDTL memo dated March 25, 2009, has a summary of the original application. The PDUFA date for this BLA is December 1, 2009.

2. Background

Hereditary angioedema (HAE) is a rare, autosomal dominant disorder estimated to affect 1 in 10,000 to 50,000 individuals. HAE is a condition characterized by intermittent, unpredictable attacks of pain and subcutaneous or submucosal edema of the face, larynx, gastrointestinal tract, limbs, and/or genitalia. Attacks can be life-threatening, particularly those attacks involving the airway. Ecallantide is a recombinant human plasma kallikrein inhibitor. In HAE, kallikrein activity is not regulated, which can lead to increased bradykinin and signs/symptoms of HAE. The treatment options for HAE are limited. Until recently no products were approved for the treatment of acute attacks of HAE in the United States. However, on October 9, 2009, a recombinant C1 esterase inhibitor (Berinert) was approved for the treatment of acute abdominal or facial attacks of HAE in adult and adolescent patients.

On September 23, 2008, Dyax submitted a BLA for ecallantide for the treatment of acute attacks of HAE in patients 10 years of age and older. A CR action was taken on March 25, 2009, with clinical deficiencies regarding inadequate data to support approval of patients below 18 years of age and the requirement for a REMS to mitigate the risk of anaphylaxis. The following are the clinical deficiencies in the CR letter (REMS deficiency is paraphrased).

The results of the submitted clinical studies do not support the efficacy and safety of Kalbitor (ecallantide) at a dose of 30 mg SC for the treatment of acute attacks of hereditary angioedema (HAE) in patients 10 years of age and older. Particularly, the number of patients below 18 years of age exposed to Kalbitor (ecallantide) is limited and not adequate to assess efficacy or safety in this age group. To support efficacy and safety of Kalbitor (ecallantide) for treatment of acute attacks of HAE in patients 10 years of age and older, provide the following: Efficacy and safety data from controlled clinical studies or open label clinical studies in a reasonable number of patients below 18 years of age and covering each year age group. Also provide validation of the ecallantide bioanalytical assay, and comparative ecallantide exposure data in adults and pediatric patients to support the recommended pediatric dose.

Requirement for proposed Risk Evaluation and Mitigation Strategy (REMS). In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for ecallantide to ensure that the benefits of the drug outweigh the risks of anaphylaxis. Anaphylaxis was noted as a safety signal in the clinical data submitted to support the efficacy and safety of ecallantide. Your proposed REMS must include the following elements: Medication Guide, Communication Plan, Elements to Assure Safe Use (ETASU), Implementation System and a

Timetable for Assessments. The ETASU must include: A) a requirement that healthcare providers who prescribe ecallantide have particular training or experience or are specially certified; B) a requirement that ecallantide is only dispensed by pharmacies, practitioners, or healthcare settings that are specially certified; C) a requirement that ecallantide is dispensed or administered to patients with documentation of safe-use conditions; D) a requirement that each patient using ecallantide be subject to certain monitoring; and E) a requirement that patients who receive ecallantide are enrolled in a registry.

The two clinical deficiencies and Dyax's response to address these deficiencies will be discussed in the Clinical Section. In addition, there were numerous product quality issues that Dyax needed to address, including issues with immunoassays that will be discussed further in the next section (CMC). The CR letter also included the following four post-marketing requirements (PMRs) if the BLA is approved:

- 1. Conduct a study with Kalbitor (ecallantide) in patients with hereditary angioedema to evaluate anaphylaxis and type I hypersensitivity. The study should include objectives to identify predictive risk factors and develop effective screening tools to mitigate the risk of hypersensitivity and anaphylaxis.*
- 2. Conduct a study with Kalbitor (ecallantide) in patients with hereditary angioedema to evaluate immunogenicity. The study should include objectives to correlate antibody levels with adverse events and lack of efficacy.*
- 3. Conduct a study with Kalbitor (ecallantide) in patients with hereditary angioedema to evaluate the effects on coagulation parameters.*
- 4. Conduct a study in rats to evaluate the carcinogenic potential of Kalbitor (ecallantide). We recommend that you submit a dose escalation proposal for the carcinogenicity study with rats for our review and concurrence prior to initiation of the study. The 6-month subcutaneous toxicology study with rats could serve as the basis of dose selection.*

The first 3 PMRs will be discussed in the Clinical section and the carcinogenicity PMR will be addressed in the Nonclinical Pharmacology/Toxicology section.

3. CMC

Ecallantide is a plasma kallikrein inhibitor derived from human tissue factor pathway inhibitor (TFPI). Ecallantide is a 60 amino acid protein and the molecular weight is 7054 Daltons. Ecallantide shares 88% identity with TFPI. Ecallantide is produced by expression in the yeast, *Pichia pastoris*. The drug product is a sterile solution for injection containing ecallantide in phosphate buffered saline. There are no preservatives and the pH of the solution is 7.0. The solution is contained in a clear glass vial, in which each vial contains 1mL of ecallantide solution 10mg/mL. The proposed dose of ecallantide is 30mg (3mL), which is to be administered subcutaneously (SC) in three (1mL) divided doses away from the angioedema location. No dilution is necessary. The proposed commercial shelf life for ecallantide is 36 months at 5°C. Secondary packaging (cardboard box) is necessary to protect the ecallantide drug product from excessive light. Inspection of the manufacturing sites was performed during the original review period and the sites were deemed acceptable.

The Division of Therapeutic Proteins (DTP) reviewed the CMC aspect of the application and noted deficiencies that precluded approval. The major deficiencies that needed to be addressed included (b) (4) testing, (b) (4) testing, host cell protein Ki assays, and release tests for the drug substance. Dyax submitted information to address the CMC deficiencies in the Complete Response. DTP reviewed the submitted information and found the information acceptable. DTP recommended two post-marketing commitments regarding stability and overfill, which Dyax agreed to address.

Microbiology Considerations

Because ecallantide is a sterile solution, a microbiology consult was obtained to evaluate microbial controls and sterility assurance. Based upon the microbiology review of the original submission, there were microbiology deficiencies that Dyax needed to address. The deficiencies were the following: insufficient information regarding depyrogenation of the glass vials; validation of stopper sterilization; sensitivity of the dye ingress container-closure integrity test, and a waiver request for (b) (4). In the Complete Response, Dyax submitted information to address the deficiencies. Anastasia Lolas reviewed the resubmission and found the information satisfactory to address the microbiological deficiencies and she recommends approval.

Immunoassay Considerations

Because ecallantide is a biologic product, immunogenicity is a concern. Immunogenicity assays were developed to detect the following antibodies in serum: 1) ecallantide antibodies, 2) ecallantide neutralizing antibodies, 3) ecallantide IgE antibodies, and 4) *Pichia* yeast IgE antibodies. In the original submission, Dr. Jack Ragheb noted deficiencies with the sensitivity and specificity of the assays and insufficient information regarding the potential for ecallantide antibodies to cross react with TFPI.

In the Complete Response, Dyax submitted information to address the issues identified by Dr. Ragheb. While some of the issues were adequately addressed, Dr. Ragheb noted 3 remaining issues that could be addressed as post-marketing requirements. The issues were the following: 1) to refine the neutralizing anti-ecallantide IgG assay, 2) to develop and validate new anti-ecallantide and anti *P. pastoris* IgE assays, and 3) to further evaluate for cross reactivity of anti-ecallantide antibodies with TFPI. Refer to Dr. Ragheb's review for more details. Dyax agreed to the PMRs to address the 3 issues and has submitted the requested timelines, which are acceptable.

4. Nonclinical Pharmacology/Toxicology

Dyax submitted a complete pharmacology/toxicology program to support the chronic intermittent use of ecallantide in the original BLA that supported the safety of the proposed clinical dose. The recommendation from the pharmacology/toxicology team on the first cycle was approval. There were no pharmacology/toxicology deficiencies. However, a carcinogenicity study was not included in the original BLA submission, which was acceptable given the serious, potentially life-threatening nature of HAE. In the March 25, 2009, CR letter, a post-marketing requirement (PMR) of a carcinogenicity study in rats was conveyed. Dyax agreed to the PMR for a carcinogenicity study for ecallantide and has submitted the requested timelines, which are acceptable.

5. Clinical Pharmacology/Biopharmaceutics

Although the clinical pharmacology team found the original BLA acceptable, the team noted outstanding issues with validation of the bio-analytical assays, which is important for the population PK analysis. The population PK analysis provides comparative exposure data in adults and pediatric patients to support the recommended pediatric dose. In the CR, Dyax submitted additional information to address the bio-analytical assay issues. The clinical pharmacology team has determined that submitted information addresses the validation issues with the bio-analytical assays. The key findings are the following: 1) insufficient information to claim that no dosage adjustment is needed in patients 65 years and older; 2) clearance is 24% lower in healthy volunteers than in HAE patients; and 3) population PK analysis showed that gender, body weight, and age did not have an effect on ecallantide exposure. This last finding is important and provides support for the proposed pediatric dose of ecallantide in children 10 years of age and older. However, to further confirm this conclusion, it is recommended that PK samples be taken in future pediatric studies for patients < 16 years of age. Dr. Yun Xu concluded the resubmission was acceptable.

6. Clinical/Statistical

In the original application, Dyax proposed an indication for acute treatment of HAE attacks in children 10 years of age and older. To support the safety and efficacy of ecallantide for the proposed indication, Dyax submitted a full clinical program including two small placebo controlled clinical trials, EDEMA3 and EDEMA4. Dr. Susan Limb reviewed the clinical program in detail. Her conclusions were that the totality of efficacy data was sufficient to support the efficacy of ecallantide for the proposed indication in patients 18 years of age and older; however the data were not adequate to support the efficacy in patients less than 18 years of age. In addition, the clinical review identified hypersensitivity and anaphylaxis as a safety signal. Because of the safety signal of anaphylaxis, a Risk Evaluation and Mitigation Strategy (REMS) was required. Therefore, the recommendation from the clinical team was a Complete Response with deficiencies as outlined in Section 2 regarding insufficient pediatric information and a REMS. These recommendations are generally consistent with the Pulmonary Allergy Drugs Advisory Committee held on February 4, 2009. Refer to Dr. Limb's review of the original application dated February 13, 2009, and my CDTL memo dated March 25, 2009, for details of the clinical program.

In the Complete Response, Dyax revised the lower age bound for the indication from 10 to 16 years of age and Dyax submitted a summary of pediatric data to support the indication in patients 16 years and older. Dyax also submitted a REMS as requested by the Agency as well as updated safety information for the ongoing open-label study. This memo will focus on these two issues.

Pediatric

Clinical review of the original submission concluded that efficacy was supported in patients 18 years and older. In this Complete Response, Dyax proposed 16 years of age as the lower age bound for the indication. To support efficacy and safety in patients 16-18 years of age, Dyax submitted a summary of data in this age group as well as validation of the PK data to support use of the proposed dose. In the clinical development program, 6 patients 16 years of age and

6 patients 17 years of age received 30mg ecallantide SC for 11 and 30 HAE attacks, respectively. The number of patients is reasonable and is consistent with the Division's expectation for this orphan indication. Dr. Limb reviewed the efficacy and safety information of each patient 16 and 17 years of age and compared to the data in adults (18 years and older). Due to the limited number of patients, statistical analysis was not performed. Dr. Limb concluded that the efficacy data was supportive in patients 16-17 years of age and consistent with the adult population. The safety data was also supportive and did not identify a new safety signal. As discussed in Section 5, Dyax submitted validated PK information. The population PK analysis shows no effect of age on exposure and supports the proposed dose of 30mcg ecallantide SC in pediatric patients. For patients < 16 years of age, Dyax proposes to conduct a phase 4, open-label study to obtain additional information. Dr. Limb has concluded that the information provided is adequate to support the efficacy and safety of ecallantide in patients 16 years of age and older.

REMS

During review of the original submission, Dr. Limb noted a safety signal of anaphylaxis. Using the data in the original application, an anaphylaxis rate of 3.7% patients (9 cases of 243 HAE patients) or 1.1% doses (9 of 846 doses) was observed. Most of these reactions occurred following repeat dosing of ecallantide. In addition to these events, other various hypersensitivity reactions, including: urticaria, flushing, pruritis, itchy throat, erythematous rash, shortness of breath, conjunctival erythema, and eye swelling were noted. The safety signal was discussed during the February 2009 PADAC meeting and Dyax presented a risk minimization strategy, including a mandatory registry and restricted distribution via a central pharmacy. After internal discussion between OSE and DPAP, a REMS was deemed necessary to assure the safe use of ecallantide. Because of the priority review timeline of 6 months, a REMS could not be reviewed and agreed upon in the first cycle; therefore, a deficiency for a REMS was outlined in the March 25, 2009 CR letter as described in Section 2. The Agency requested a REMS with specific elements, including a Medication Guide, Communication Plan, and Elements to Assure Safe Use.

In the Complete Response, Dyax submitted a REMS with all the requested elements: Medication Guide, Communication Plan, and Elements to Assure Safe Use (ETASU). The REMS include a restricted distribution program that included a single specialty pharmacy distributor, certification of healthcare prescribers, and distribution only to enrolled healthcare providers and enrolled pharmacies. During review, the Division and OSE determined that a elements to assure safe use (restricted distribution program) were not necessary to ensure the safe use of ecallantide. The risk of hypersensitivity reactions is not unique to ecallantide and is an expected adverse event for a foreign protein-derived biologic product. Other drug products with a similar risk of anaphylaxis have not exhibited the need for a restricted program with elements to assure safe use, and there is no evidence to suggest that the nature of hypersensitivity reactions associated with ecallantide differs from more well-known drug-induced hypersensitivity reactions. In addition, it was unclear that the proposed elements to assure safe use would actually mitigate the risk of anaphylaxis and there was concern the proposed elements could hinder patient access. On October 16, 2009, the Agency requested that Dyax submit a revised REMS that included a Medication Guide and Communication Plan

to communicate important information to patients and providers about the unique characteristic of anaphylaxis that may overlap with symptoms of HAE.

On October 26, 2009, Dyax submitted a revised REMS consisting of a Medication Guide and Communication Plan to communicate the risk of anaphylaxis and that the signs/symptoms of anaphylaxis and HAE attacks may overlap. The Communication Plan includes the product labeling and a Dear Healthcare Professional Letter (DHCP). Dyax plans to distribute the DHCP at the product launch and yearly thereafter for 2 years via direct mail to allergy/immunology providers and emergency medicine providers. Dyax representatives will also provide the DHCP letter and product labeling to potential prescribers during the first year of product availability. The information will also be available on the product website. Assessment of the REMS will include patients' and HCPs' understanding of the serious risks of ecallantide. After further minor modifications of the REMS goals and the DHCP letter, the REMS was found to be acceptable by DPAP and OSE.

7. Pediatrics

In this Complete Response, Dyax proposed 16 years of age as the lower age bound for the indication. The population PK analysis shows no effect of age on exposure, which supports the proposed of 30mcg ecallantide SC in pediatric patients. As discussed in Section 6, the data submitted is adequate to support the efficacy and safety in patients 16-18 years of age. Younger patients were included in the clinical program, but the numbers are small and additional safety data is necessary in patients < 16 years of age. For patients < 16 years of age, Dyax proposes to conduct a phase 4, open-label study to obtain additional information. Because of the orphan indication, PREA is not triggered by this application.

8. Other Relevant Regulatory Issues

A Pulmonary Allergy Drugs Advisory Committee (PADAC) was held on February 4, 2009, to discuss the original BLA submission. Important discussion items included the adequacy of the efficacy and safety data, anaphylaxis and hypersensitivity data, and the adequacy of the pediatric data. Details of the meeting can be found in the transcript. Generally, panel members noted the limitations of the efficacy and safety data, but noted the limitations of the population. Panel members discussed the hypersensitivity and anaphylaxis data. They noted that ecallantide was highly immunogenic and the data may underestimate the risk. The voting indicated that the efficacy data for ecallantide was sufficient in patients 18 years and older (8 Yes, 4 No, 1 Abstain), but not in patients less than 18 years of age (3 Yes, 10 No). The committee voted that the safety of ecallantide was not adequately established in all age groups (5 Yes, 8 No (adults) and 2 Yes, 11 No (peds)) and further information is necessary. With regards to recommendation for approval, the committee was split (6 Yes, 5 No, 2 Abstain), but some panel members noted that if limited to adults only, they would recommend approval. Generally, the committee favored approval in adults, but not in patients less than 18 years of age. The panel recommended appropriate risk management strategies for anaphylaxis.

A DSI audit was performed for the original submission and Dyax, Corporation was also inspected. The inspection did not identify any major deficiencies and the conclusion was that the findings support the validity of data as reported by Dyax.

9. Labeling

Dyax submitted a product label in the new PLR format. Labeling negotiations were conducted during the review period and labeling was agreed upon. The following are pertinent labeling issues:

- The proposed labeling included a Boxed Warning regarding anaphylaxis and Medication Guide, both of which are appropriate. The Boxed Warning emphasizes that 1) ecallantide should only be administered under the supervision of a healthcare professional with appropriate support to manage anaphylaxis; 2) the similarity of symptoms of HAE and hypersensitivity reactions; and 3) ecallantide should not be administered to patients with a history of hypersensitivity reactions
- The agreed upon lower age limit for the indication is 16 years of age.

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

Consults from DRISK, DDMAC, SEALD, and DMEPA were obtained regarding product labeling. The proposed tradename of Kalbitor was found acceptable by DMEPA. The comments from DRISK, SEALD, and DDMAC were conveyed to Dyax.

10. Recommendations/Risk Benefit Assessment

- Recommended regulatory action

The recommended regulatory action is **Approval**. The clinical and CMC deficiencies in the March 25, 2009, CR letter have been adequately addressed. The original BLA supported the efficacy and safety of ecallantide in patients 18 years of age and older. Dyax has modified the indication to a lower age bound of 16 years of age instead of 10 years of age. Dyax submitted data to support the efficacy and safety of ecallantide in patients 16-18 years of age. Thus, the lower age limit of 16 is acceptable. Dyax has adequately addressed outstanding CMC deficiencies. In addition, to mitigate the risk of anaphylaxis, Dyax submitted a REMS, which

includes a Medication Guide and Communication Plan. The REMS was found acceptable by the Division and OSE.

- Risk Benefit Assessment

Acute HAE attacks are serious and can be potentially life-threatening. Until recently, there had been no approved therapies for the treatment of acute HAE attacks. Because of the orphan indication, the clinical program is limited in size. Efficacy limitations were noted in the original review and discussed at the PADAC meeting. However, given the serious and potential life threatening nature of HAE attacks, the efficacy data is adequate for patients 16 years of age and older. This is consistent with the primary medical officer recommendation and the PADAC recommendation. Ecallantide is immunogenic and anaphylaxis is the primary safety signal of concern. The serious risk of anaphylaxis, the need to be administered by a healthcare professional with support to manage anaphylaxis, and the overlapping symptoms of HAE attacks and anaphylaxis are all concerns with ecallantide. The submitted REMS with Medication Guide and Communication plan addresses these concerns. With the REMS and modified age for indication (>16 years of age), the risk benefit assessment of ecallantide for patients 16 years of age and older is favorable.

- Recommendation for Postmarketing Risk Management Activities

Ecallantide has a safety signal of hypersensitivity reactions, including anaphylaxis. The Agency requested a REMS to assure the safe use of ecallantide. The agreed upon REMS include a Medication Guide and Communication Plan to communicate the risk of anaphylaxis and that the signs/symptoms of anaphylaxis and HAE attacks may overlap. The Communication Plan includes the product labeling and a Dear Healthcare Professional Letter (DHCP). The information will also be available on the product website. Assessment of the REMS will include patients' and HCPs' understanding of the serious risks of ecallantide. The REMS was reviewed by DPAP and OSE and found to be acceptable.

- Recommendation for other Postmarketing Study Commitments

Dyax has agreed to the following post-marketing requirements in a submission dated November 17, 2009, as outlined below:

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

Submission of Final Protocol: December 2009

Completion of Study: February 2014

Submission for Final Report: August 2014

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

Submission of Final Report: March 2010

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

Submission of Final Report: August 2010

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

Submit Method Development Reports for FDA Review: April 2010

Submission of Final Report: September 2010

Conduct a study in rats to evaluate the carcinogenic potential of Kalbitor (ecallantide). The 6-month subcutaneous toxicology study with rats could serve as the basis of dose selection.

Submission of Final Protocol: June 2010

Completion of Study: September 2012

Final Report: September 2013

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

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

Final Protocol Submission: January 2010

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

Final Report Submission: April 2010

- Recommended Comments to Applicant

There are no comments to convey to Dyax.