

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

BLA 125277

CHEMISTRY REVIEW(S)



Center for Drug Evaluation and Research - Food and Drug Administration
Office of Biotechnology Products, Office of Pharmaceutical Science
29 Lincoln Drive, Bethesda, MD 20892

BL: 125277
SERIAL: Response to CR
START DATE: October 16, 2009
FINISH DATE: October 22, 2009
REVISION DATE: October 28, 2009, November 9, 2009, November 16, 2009,
November 24
FROM: Kathy Lee, M.S. *ML 11/25/09*
THROUGH: Barry Cherney, Ph.D. *Barry Cherney 11-25-09*
PRODUCT: Kalbitor (ecallantide or DX-88), *Pichia pastoris*
INDICATION: the treatment of acute attacks of hereditary angiodema
ROUTE OF ADMIN.: 3 SC injection
DOSE REGIMEN: 3 x 10 mg/mL
SPONSOR: Dyax
CLINICAL DIVISION: DPAP
PRIMARY REVIEWS: August 23, 2009
FIRST ACTION DUE DATE: December 1, 2009
REVIEW TEAM:
Product Team: Kathy Lee, Jack Ragheb, Susan Kirshner, Kimberly Rains, Ingrid Markovic
CDTL: Sally Seymour
Medical Officer: Susan Limb
P/T: Jean Wu
Facilities: Patricia Hughes and Anastasia Lolas
Clinical Pharmacology: Yun Xu
Stats: Dongmei Liu
PM: Colette Jackson

I. POST MARKETING COMMITMENTS

The sponsor will submit real time stability data in the annual report for a request for extension of shelf-life. The purpose of an annual stability study is not to reevaluate the dating period but rather confirm that all the process changes (including personnel) made during the last year had no impact on product quality. Since a stability study performed at 5°C is expected to have limited ability to detect significant changes that might affect product quality; the sponsor should include an accelerated or stress stability study that would be more sensitive to small but significant changes in product quality. Because this requirement involves the design of a study to be implemented next year, this study can be submitted following approval and can therefore be requested as a PMC.

Sponsor Language

1. To include an accelerated or stress stability study as part of the annual stability program for the drug product. The final approved protocol will be submitted in a PAS supplement to the license by January 2010.

There is a low risk of overdosing from the excess fill volume. Some liquid remains of the vial for withdrawal, (b) mL. Therefore, it is likely that occasionally health care providers will administer the excess volume to patients even though the PI gives detailed instructions on administration. While there have been no reports of overdose with Kalbitor and HAE patients have received single doses up to (b) mg intravenously without evidence of dose-related toxicity, it is prudent to limit any potential overdose. There is also a risk for pooling containers and compromising the sterility of the product that excess volumes might increase. Given that the actual amount of overage is relatively low and the use of the product in a clinical setting (i.e., the temptation to pool is very low) the risk to patient safety is also low. Thus, excessive overfill is not an approvability issue because of the low theoretical risks associated with this issue.

Sponsor Language

2. To evaluate the minimal fill volume required for appropriate dosage withdrawal and to adjust the final fill volume for the drug product to reduce the likelihood that a patient could be overdosed with the excess (b) (4) drug product. The final study report and new fill volume, if found necessary, will be submitted in a supplement to the license by April 2010.

II. COMMENTS SENT TO SPONSOR OCTOBER 27, 2009.

RESPONSES TO THESE COMMENTS HAVE BEEN REVIEWED AND ARE INCORPORATED INTO THIS REVIEW MEMO.

1. In your response to CR you have provided information on you Inhibition Constance Ki assay. You have based the preliminary acceptance criteria on the validation data, 4 drug substance batches and 3 drug product batches. However, in your release and stability table you have listed the specification TBD. This is not acceptable, please set interim specifications with upper and lower limits.

2.

(b) (4)

3.

[REDACTED] (b) (4)

4. [REDACTED] (b) (4)

5. You provided the updated reference standard qualification protocol. As part of this protocol you have added the Inhibition Constance Ki assay to the list of assays. However, the suggested specification should also be sufficiently stringent to control for (b) (4) [REDACTED] of the reference standard. Please tighten the specification for the Inhibition Constance Ki assay to control for this (b) (4) [REDACTED]

III. OVERVIEW

The FDA's questions will be listed in italics followed by Dyax's response to our questions in normal text and a review of the information sent to the FDA in blue italics.

8. Regarding the release and stability specifications:

[REDACTED] (b) (4)

Dyax optimized and validated an Inhibition Constant Ki method for release and stability testing for the drug substance and drug product. They developed the assay with the following characteristics:

1. A total enzyme concentration throughout the assay that is equal to (b) (4) [REDACTED]

12 pages withheld immediately after this page as (b)(4) CCI/TS.
[REDACTED]

Response: Per our request, the Sponsor included the test for host cell protein (HCP) in the drug substance specification. The Sponsor states that they analyzed the HCP results in drug substance from batches B2007-007 through B2007-015 using 99% Tolerance Interval. The results showed the average HCP value to be 47 ng/mL with a range of (b) (4) and 99% Tolerance Interval of 0 - 161 ng/mL. Therefore, the Sponsor states that they will tighten the original acceptance criterion of (b) (4)..

Table 6. HCP Levels of Ecallantide Used in Clinical Studies

| Lot # | Description | HCP (ng/mL) | Clinical Use |
|---------|---------------------------|-------------|---------------------------------------------------------------------------------------|
| (b) (4) | Avecia (b) (4) | (b) (4) | Phase 2: DX-88/2 (EDEMA0) and DX-88/3 |
| | Avecia (b) (4) (b) (4) | | Phase 1: DX-88/6 Phase 2: DX-88/2 (EDEMA0), DX-88/4 (EDEMA1), and DX-88/5 (EDEMA2) |
| | Avecia (b) (4) (b) (4) | | Phase 2: DX-88/5 (EDEMA2) |
| | | | Phase 2: DX-88/5 (EDEMA2) Phase 1: DX-88/13 |
| | Avecia Commercial Process | | Phase 1: DX-88/15 Phase 3: DX-88/14 (EDEMA3) |
| | Avecia Commercial Process | | Phase 1: DX-88/15 Phase 2: DX-88/16 Phase 3: DX-88/19, DX-88/20 (EDEMA4) |
| | | | Phase 3: Open label |
| | | | Phase 3: Open label |

Reviewer Comment: Dyax has tightened the specification to better reflect their manufacturing process. Although the specification is (b) (4) and patients have had anaphylactic reactions with IgE antibodies to P. pastoris, this measure of HCP levels alone may not accurately reflect why a patient may develop IgE antibodies to P. pastoris (e.g., reaction to (b) (4), repeats or unknown sensitivity to yeast). Therefore, the proposed specification is acceptable.

(g) CR Request: Because large protein aggregates in therapeutic protein products may enhance immunogenicity of target antigens, these product related variants should be appropriately monitored and control. While USP method <788>, monitors particulates that are greater than 10 µm, protein particulates that are smaller than 10 µm have not been monitored. (b) (4)

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1.0 LETTER SUMMARY

Lot Release, Manufacturing sites, Names, shelf-life and storage conditions, and PMCs and PMR

2.0 QUALITY OVERALL SUMMARY (Executive Summary)

2.1. Recommendations

A. Recommendation and Conclusion on Approvability

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, does not recommend approval of 125277 for Kalbitor (ecallantide) manufactured by Dyax. The data submitted in this application are not adequate to support the conclusion that the manufacture of Kalbitor (ecallantide) is well controlled, and leads to a product that is pure and potent. It is recommended that this product not be approved for human use (under conditions specified in the package insert).

B. Major Deficiency CMC Comments

1. Regarding cell bank characterization;

- a. We acknowledge that assessment of the cell banking system for the presence of (b) (4) has been conducted and that no (b) (4) was detected in the working cell bank. However, information describing the assay's Limit of Detection (LOD), a critical measure indicating that the assay provides meaningful results, has not been submitted. You will need to provide information regarding the procedures used and the results obtained for determination of the LOD for the (b) (4) assay.
- b. You have included a protocol to assess qualification of a new working cell bank which, if approved, would allow you to submit results of the qualification study in the subsequent annual report. Although you have characterized the current working cell bank to ensure consistent production of the intended product, the proposed protocol is deficient in ensuring the consistency of critical product quality attributes. Thus, while consistency of the coding sequence of the expression construct is a critical parameter, it is not sufficient to ensure that the intended product is consistently produced since some product attributes (e.g. glycosylation) cannot be predicted from sequence alone. You will need to revise your protocol to include a full characterization of the intended product and results to be achieved.

2. Regarding the release and stability specifications;

- a. Your potency assay used for release and stability testing of drug substance and drug product appears to be inadequate because under the conditions of the proposed assay, K_{iapp} is much less than the amount of enzyme (E) and therefore, all inhibitor will be bound to enzyme irrespective of significant changes in the affinity of Ecallantide to Kallikrein. Thus, a given lot of Ecallantide would not be out of specification until the K_{iapp} is approximately (b) (4) higher than the expected value of (b) (4). We believe that determination of K_{iapp} as a release assay will provide a better measure of product potency than the currently proposed test, if the precision of the K_{iapp} determination is improved. Furthermore, the K_{iapp} assay should be designed so that inhibitor concentrations are tested in a range of concentrations relative to enzyme active site concentrations (less than, equal to, and greater than) with an emphasis on data points in the region where $[I]$ approximates $[E]$. You will need to revise the specifications to include a measurement of K_{iapp} .

b. [REDACTED] (b) (4)

[REDACTED] (b) (4)

- c. Regarding your specifications for the RP-HPLC assay;

- i. You have proposed to group oxidized variants together with glycosylated species in your release and stability specifications. However, because each variant is associated with different risks to patient safety, we believe each of these variants should have

individual acceptance criteria. You will need to revise the acceptance criteria to include separate limits for oxidized and glycosylated species.

- ii. Currently, your specification for main peak plus product related substance is (b)%. This allows for up to (b)% of unknown total impurities. However, actual results show that product related substances compose (b)% of the total material with no other substances observed.^b You will need to revise your acceptance criteria to better reflect actual manufacturing history.
- iii. While you have specified that no single impurity will be (b)%, this does not take into account the risk associated with a specific impurity. You will need to revise your specifications to include action limits that require an assessment of impact to product quality as it may relate to safety and efficacy, for any new impurity that is observed in the RP-HPLC assay.
- iv. The acceptance criteria for (b) (4) for release and stability are (b) and (b)% respectively. However, you have not adequately justified these levels. While we understand this is a product related substance (i.e., has biological activity), (b) (4) levels may also influence immunogenicity of the product. You will need to submit data that support these acceptance criteria together with your justification.

d. You will need to express the acceptance criterion for results from the (b) assay using 2 significant figures (b) (4)

(b) (4)



(b) (4)

3. Given that you ship drug substance to a contract manufacturer for fill/finish, it is important that an identity test be performed at the contract manufacturer to ensure the correct identity of the product to be manufactured. You will need to describe the identity testing performed for receipt at the contract manufacturer for fill/finish.
4. The acceptance criteria listed in your reference standard qualification protocol are not sufficiently stringent to control for potential drift in the characteristics of the reference standard. For example, the acceptance criterion for bioactivity is (b) (4) (b) (4)% and thus allows for a standard having an actual activity value of (b) (4)% to represent (b) (4)% activity for a test sample, thereby introducing a (b) (4)% change in the true potency of the product. You will need to tighten each acceptance criterion to minimize drift in product characteristics. Please include objective criteria for assessing what “comparable to reference standard” means.
5. You established (b) (4) process based on manufacturing experience and a statistical analysis using (b) (4) tolerance intervals. This approach allows for action limits for step yields that are significantly (b) (4) than current manufacturing experience indicates has no impact on product quality. Therefore, you will need to tighten the range to better reflect your actual manufacturing experience and your understanding of how yield can impact product quality.

2.2 Summary of Chemistry Assessments

A. Description of the Product

Ecaltantide is a recombinant protein that is a high affinity and high specificity reversible tight-binding protein inhibitor of human plasma kallikrein. Ecaltantide acts on the upstream elements in the kinin pathway, to block plasma kallikrein, thereby reducing excess endogenous bradykinin. The protein was discovered through the iterative selection and screening of phage display libraries containing variants of the first Kunitz domain of the naturally occurring human protein, tissue-factor pathway inhibitor. Ecaltantide is produced using a yeast (*Pichia pastoris*) production system and is purified from the yeast

(b) (4)

Ecallantide drug substance is formulated in phosphate buffered saline (PBS) at pH 7.0 with no preservatives. The drug substance is (b) (4) to prepare the drug product and filling into vials. The drug product is a sterile solution for injection containing 10 mg/ml of ecallantide in PBS (pH 7.0). The proposed dose of ecallantide is 30 mg (3mL), which is administered subcutaneously (SC) in three 1mL doses away from the angioedema location. The proposed commercial shelf life for ecallantide is 36 months at 5°C.

Mechanism of Action:

Hereditary angioedema (HAE) is a rare, autosomal dominant disease caused by low levels of the plasma protein C1 inhibitor. Patients suffer from intermittent attacks of subcutaneous or submucosal oedema of the face, larynx, gastrointestinal track, limbs or genitalia. C1 inhibitor regulates many proteases in the complement system, contact and clotting cascades including kallikrein. The low levels of C1 inhibitor in HAE patients leads to higher endogenous levels of plasma kallikrein. Plasma kallikrein is responsible for cleaving high molecular weight kininogen, which once cleaved releases bradykinin. Bradykinin is responsible for the edema seen in the HAE patients. Ecallantide binds to plasma kallikrein and blocks the binding site, thereby inhibiting the conversion of HMW kininogen to bradykinin, which inhibits the edema. See diagram below for detailed schematic.¹

¹ Levy et al. The therapeutic potential of a kallikrein inhibitor for treating HAE. *Expert Opin. Investig. Drugs.* (2006) 15(9): 1077-1090.

(b) (4)

Hollister-Stier Laboratories, LLC (Spokane, Washington) produces the ecallantide drug product. To produce the ecallantide drug product the ecallantide drug substance is (b) (4)d through two (b) (4), packaged and label. The process validation study demonstrates that the DP manufacturing process is consistently able to produce sterile ecallantide drug product.

Release specifications:

The methods and acceptance criteria required for the release and stability of ecallantide DS and DP are provided in tables below. The tests include methods for the determination of physical/chemical properties, potency, identity, purity and heterogeneity, impurities, and safety.

Dyax based their release and stability specifications for the drug substance on release data from the 12 batches of ecallantide drug substance manufactured using the second (b) (4) and commercial (b) (4) scale. For quantitative tests, statistical analysis (mean, standard deviation, range, and 99% Tolerance Interval) of historical batch data was performed to support the acceptance limits.

Dyax based their release and stability specifications for the drug product on release data from all ten ecallantide drug product batches produced at (b) (4) and Hollister-Stier. For quantitative tests, statistical analysis (mean, standard deviation, range, and 99% Tolerance Interval) of historical batch data was performed to support the acceptance limits.

Release Specification for DS:



(b) (4)

Release Specification for DP:



(b) (4)

Degradation and Stability:

The proposed commercial shelf life for ecallantide DS is 36 months at -20°C. Dyax identified stability-indicating methods through evaluation of stability data at elevated temperatures and through forced degradation and stress studies. The formation of (b) (4)) product related species and loss of ecallantide main peak (both detected by reverse phase high performance liquid chromatography [RP-HPLC]) and the formation of (b) (4) detected by (b) (4) are the only chemical modifications detected at the elevated temperatures of 5°C and 25°C. Dyax performed forced degradation studies to provide additional information regarding degradation pathways that examined high temperature and low pH which are conditions known to induce oxidized and deamidated species, respectively. However, these modifications do not occur at the proposed commercial storage temperature of -20°C after 36 months of storage.

The proposed commercial shelf life for ecallantide DP is 36 months at 5°C. Dyax identified stability-indicating methods through evaluation of stability data at the recommended storage temperature (5°C) and elevated temperatures, and through forced-

degradation and stress studies. The only trends observed at 5°C were increase of the (b) (4) and loss of ecallantide main peak (both detected by RP-HPLC). Under conditions (4) forced degradation, elevated temperature (25°C), additional modifications have been identified including formation of (b) (4)

Photo-stability studies conducted on drug product show an increase in (b) (4) indicating a requirement for the secondary packaging (cardboard box) to protect the ecallantide drug product from excessive light. Due to the potential photolytic sensitivity observed in the primary container (Type I clear glass vial), Dyax added a statement to the drug product label stating to protect DP from light.

B. Description of How the Drug Product is Intended to be Used

Kalbitor™ (ecallantide) is intended for subcutaneous administration to treat patients experiencing acute attacks of hereditary angioedema.

C. Basis for Approvability or Not-Approval Recommendation

The information outlined in this review memo provides the basis for a complete response letter.

3.0 DRUG SUBSTANCE

3.1 General Information

- Recommended International Nonproprietary Name (INN): **ecallantide**
- Company or laboratory code: **DX-88**
- USAN: **ecallantide**
- Chemical Abstracts Service (CAS) registry number: **460738-38-9**
- Proposed proprietary name for drug product: **Kalbitor™**

ecallantide is a recombinant protein with high affinity and high specificity for human plasma kallikrein. It functions as a reversible tight-binding inhibitor of kallikrein. Ecallantide is expressed in a yeast (*Pichia pastoris*) production system and is purified from the yeast culture supernatant. Ecallantide contains 60 amino acid residues and three intramolecular disulfide bonds. The mass of ecallantide as determined by electro-spray-mass spectrometry (ES-MS) is 7054 Daltons, which is consistent with the predicted molecular weight of 7054 Daltons. Disulfide bond mapping of ecallantide confirms the expected intramolecular disulfide bond arrangement; (b) (4)

(b) (4)

(b) (4)

The sequence of ecallantide was identified through the iterative selection and screening of phage display libraries containing variants of the first Kunitz domain (K1) of the naturally occurring human protein tissue-factor pathway inhibitor (TFPI), also known as lipoprotein-associated coagulation inhibitor (LACI). The primary amino acid sequences of ecallantide and TFPI-K1 are homologous, and the amino acid sequences differ by

(b) (4)

(b) (4)

3.2 CHARACTERIZATION

3.2.1 Summary

Dyax sufficiently characterized Ecallantide using a variety of characterization assays. Dyax determined the primary, secondary, and tertiary structure of ecallantide. They assessed the identity, purity, aggregation, mass, pI, heterogeneity, and biological activity of ecallantide. Six distinct ecallantide product-related substances (PRS) were identified. All six ecallantide species were purified and characterized. Dyax determined the types and locations of modifications on each of the six different ecallantide species. These modifications include

(b) (4)

. Dyax performed comprehensive stability assays investigating a variety of parameters. Samples of ecallantide were subjected to stress conditions and product-related impurities (aggregated ecallantide, deamidated ecallantide, and mis-folded ecallantide) were purified and characterized.

3.2.2 General Information

Ecallantide was discovered through the iterative selection and screening of phage display libraries containing variants of the first Kunitz domain of the naturally occurring human protein, tissue-factor pathway inhibitor. Ecallantide is produced using a yeast (*Pichia pastoris*) production system and is purified from the yeast culture supernatant.

Dyax studied the physicochemical characteristics of ecallantide drug substance using a variety of analytical methods. They characterized the biological activity of ecallantide using an activity-based potency method and by determination of the



MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
CENTER FOR DRUG EVALUATION AND RESEARCH

FROM: Ingrid Markovic, Ph.D., Quality Reviewer, DTP/OBP/OPS/CDER

TO: STN # 125277 file

THROUGH: Barry Cherney, Ph.D., Deputy Director, DTP/OBP/OPS/CDER

SPONSOR: Dyax Pharmaceuticals

PRODUCT: Kalbitor™ (ecallantide; kalikrein inhibitor)

SUBJECT: Review of sections of BLA STN # 125277 pertaining to the genetic construct analysis, cell banks, adventitious agents safety evaluation, container closure systems and extractables & leachables analysis

DUE DATE: March 23, 2009

In 3/23/09
Barry Cherney
 3-23-09

RECOMMENDATION:

Based on the provided information, with exception of the specified action items, no additional safety issues were noted in the submission in relationship to the following: 1) generation and genetic analysis of the expression construct; 2) qualification of the cell banking system; 3) DS and DP container/closure systems and 4) evaluation of extractables and leachables. Therefore, the risks for adverse impact on product quality and/or patient safety due to reviewed categories do not appear excessively high. However, as part of the quality risk management strategy deficiencies listed below in the text should be addressed by the Sponsor in order to reduce the level of uncertainty further and to minimize the adverse impact to patient safety and efficacy.

Action items to be included in the CR letter:

- We acknowledge that assessment of the cell banking system for the presence of (b) (4) has been conducted and that no (b) (4) was detected in the working cell bank. However, information describing the assay's Limit of Detection (LOD), a critical measure indicating that the assay provides meaningful results, has not been submitted. You will need to provide information regarding the procedures used and the results obtained for determination of the LOD for the (b) (4) assay.
- You have included a protocol to assess qualification of a new working cell bank which, if approved, would allow you to submit results of the qualification study in the

subsequent annual report. Although you have characterized the current working cell bank to ensure consistent production of the intended product, the proposed protocol is deficient in ensuring the consistency of critical product quality attributes. Thus, while consistency of the coding sequence of the expression construct is a critical parameter, it is not sufficient to ensure that the intended product is consistently produced since some product attributes (e.g. glycosylation) cannot be predicted from sequence alone. You will need to revise your protocol to include a full characterization of the intended product and results to be achieved.

- We note that studies pertaining to examination of extractable and leachable substances associated with the drug substance (DS) and drug product (DP) container/closure systems have not been performed using the relevant DS and DP vehicles. While extractable data generated by the vendor is useful and the risk due to the potential toxicity of these leachates appears minimal, the risks associated with potential for enhanced immunogenicity due to an adjuvant effect have not been addressed. You will need to evaluate the amounts and types of leachables that accumulate over time under the recommended storage conditions, using robust analytical methods. Please submit the results of these evaluations.

1. GENERAL OVERVIEW

Current review provides evaluation of the following sections of the BLA:

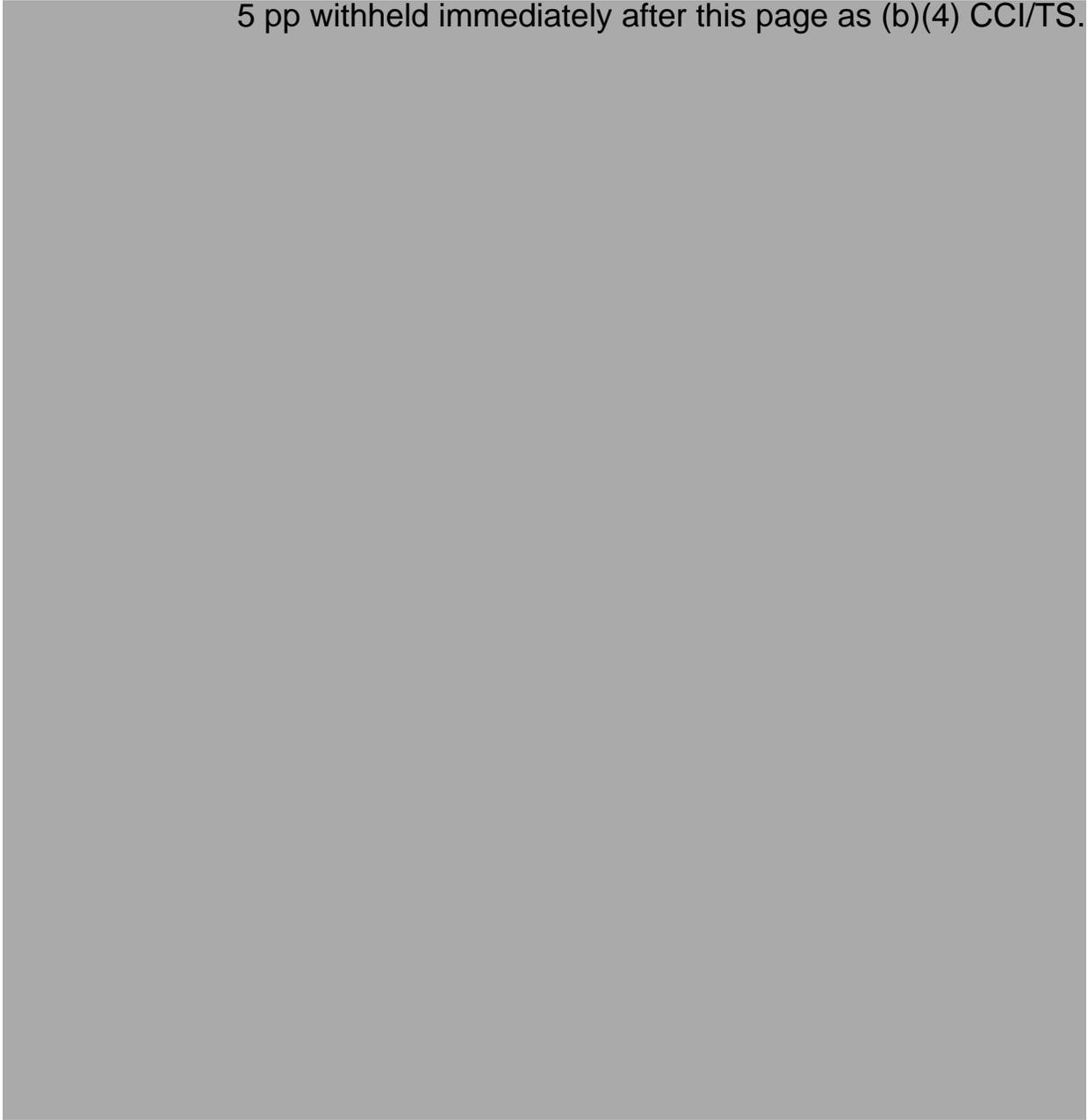
- Generation and genetic analysis of the expression construct
- Qualification of the cell banking system
- DS and DP container/closure systems
- Evaluation of extractables and leachables

2. Generation and genetic analysis of the expression construct

(b) (4)



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6.0 Conclusions

Based on the provided information, with exception of the specified action items, no additional safety issues were noted in the submission in relationship to the following: 1) generation and genetic analysis of the expression construct; 2) qualification of the cell banking system; 3) DS and DP container/closure systems and 4) evaluation of extractables and leachables. Therefore, the risks for adverse impact on product quality and/or patient safety due to reviewed categories do not appear excessively high. However, to reduce the level of risk further in order to minimize the adverse impact to patient safety and efficacy the deficiencies listed elsewhere in the text should be addressed by the Sponsor. There are three comments for inclusion in the CR letter sent to the Sponsor.

Jackson, Colette

From: Jackson, Colette
At: Thursday, March 19, 2009 1:41 PM
To: Carter, Vicky
Cc: Schneider, Kay
Subject: FW: 125277 Product Information Sheet

Attachments: 125277 Product Information Sheet.PDF

Vicky,

Here is the Product Information Sheet for BLA 125277.

Please let me know if you need any additional information for BLA 125277 in order for us to complete our action.

Thank you,

Colette Jackson

*Senior Regulatory Health Project Manager
Division of Pulmonary and Allergy Products
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From: JACKSONC [<mailto:Colette.Jackson@fda.hhs.gov>]
Sent: Thursday, March 19, 2009 12:25 PM
To: Jackson, Colette
Subject: 125277 Product Information Sheet



125277 Product
Information She...

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

CENTER FOR DRUG EVALUATION AND RESEARCH

TEL: 301-827-1790

FAX: 301-480-3256

TO: Collette Jackson

FROM: Kathy Lee

FAX#: 301 796 9718

Number of pages: 5

COMMENTS: Per your request.
Kathy

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Product Information Sheet - Indication

STN: 1257701

Reg. Coordinator: Colette Jackson

Document Date: 3/19/09

FDA Rcvd Date: 9/1/08

CBER Rcvd Date: _____

Applicant Dyax

Product Kalbitor ecallantide

Proprietary/Trade Name(s) Kalbitor

Complete a box for each indication

Indication Treatment of acute Attacks of HAE

Dose 30mg (BUT 3 x 1ml vials (10mg each))

Age groups - check all that apply

Adult 18+ All Child 3-12 Geriatric 65+ Pediatric 0-3 Young Adult 13-18 Other _____

Indication Product Use - check all that apply

Ancillary Diagnostic/Therapeutic Therapeutic Prophylaxis Other _____

Further Manufacturing Injectable Further Manufacturing Non Injectable

Indication _____

Dose _____

Age groups - check all that apply

Adult 18+ All Child 3-12 Geriatric 65+ Pediatric 0-3 Young Adult 13-18 Other _____

Indication Product Use - check all that apply

Ancillary Diagnostic/Therapeutic Therapeutic Prophylaxis Other _____

Further Manufacturing Injectable Further Manufacturing Non Injectable

Guidance for completion of this form

Indication -- As stated in the P.I. This should also go into the short summary under the submission screen

Dose -- From the "Dosage and Administration" section of P.I. -- This is what the patient actually gets.

Dosage/Physical Form Details -- From the "How Supplied" section of P.I. -- Enter final dosage strengths

3 pp withheld immediately after this page as (b)(4) CCI/TS.

STN 125277

Product Kalibitor

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

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

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

STN 125277

Product

Kallitor

Part B Page 3

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

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Product Kalbitar

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

Literature references and copies [3.3] Y N

| | | | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|---|--|
| content, presentation, and organization sufficient to permit substantive review? | <input checked="" type="radio"/> Y | N | |
| <input type="checkbox"/> legible | <input checked="" type="radio"/> Y | N | |
| <input type="checkbox"/> English (or translated into English) | <input checked="" type="radio"/> Y | N | |
| <input type="checkbox"/> compatible file formats | <input checked="" type="radio"/> Y | N | |
| <input type="checkbox"/> navigable hyper-links | <input checked="" type="radio"/> Y | N | |
| <input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays | <input checked="" type="radio"/> Y | N | |
| <input type="checkbox"/> summary reports reference the location of individual data and records | <input checked="" type="radio"/> Y | N | |
| <input type="checkbox"/> all electronic submission components usable | <input checked="" type="radio"/> Y | N | |
| includes appropriate process validation data for the manufacturing process at the commercial production facility? | <input checked="" type="radio"/> Y | N | |
| includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)? | <input checked="" type="radio"/> Y | N | |
| includes data demonstrating consistency of manufacture | <input checked="" type="radio"/> Y | N | |
| includes complete description of product lots and manufacturing process utilized for clinical studies | <input checked="" type="radio"/> Y | N | |
| describes changes in the manufacturing process, from material used in clinical trial to commercial production lots | <input checked="" type="radio"/> Y | N | |
| data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred) | <input checked="" type="radio"/> Y | N | |
| certification that all facilities are ready for inspection | Y | N | |
| data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment. | <input checked="" type="radio"/> Y | N | |
| if not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: | Y | N | |

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Product

kalbiton

Part B Page 6

| Examples of Filing Issues | Yes? | | If not, justification, action & status |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|---|----------------------------------------|
| <input type="checkbox"/> LAL instead of rabbit pyrogen | <input checked="" type="checkbox"/> | N | |
| <input type="checkbox"/> mycoplasma | <input checked="" type="checkbox"/> | N | |
| <input type="checkbox"/> sterility | <input checked="" type="checkbox"/> | N | |
| <input type="checkbox"/> | | | |
| <input type="checkbox"/> | | | |
| identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples | Y | N | |
| floor diagrams that address the flow of the manufacturing process for the drug substance and drug product | <input checked="" type="checkbox"/> | N | |
| description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment | <input checked="" type="checkbox"/> | N | |
| information and data supporting validity of sterilization processes for sterile products and aseptic manufacturing operations | <input checked="" type="checkbox"/> | N | |
| if this is a supplement for post-approval manufacturing changes, is animal or clinical data needed? Was it submitted? | Y | N | NA |

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

Recommendation (circle one): File RTF

Reviewer: WMP 10/21/08 Type (circle one): Product (Chair) Facility (DMPQ)
 (signature/ date)

Concurrence:
 Branch/Lab Chief: E. Shacht
 (signature/ date)

Division Director: Amy Rosenkey
 (signature/ date)

Immunogenicity

Memo

Date: September 28, 2009

From: Jack A. Ragheb M.D., Ph.D.

To: STN 125277/0

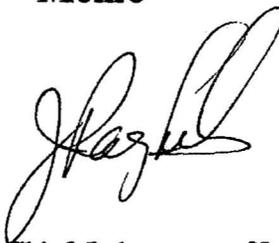
Through: Susan Kirshner, Associate Chief, Laboratory of Immunology, DTP

Subject: Response to CR of DX-88 BLA; Immunoassay Review

Product: DX-88 (Ecallantide, Kalbitor, Kallikrein Inhibitor)

Sponsor: Dyax

Indication: Treatment of acute episodes of Hereditary AngioEdema (HAE)



10/23/09

Jessica L. Kirshner
10/23/09

Summary

The original review covered the immunoassays submitted in the BLA for detection of Drug Substance (DS) in plasma and the detection of anti-DS binding and neutralizing antibodies in serum, as well as the presence of anti-yeast antibodies as described in the rolling BLA STN 125277. This review covers the sponsor's response to the BLA CR.

In HAE, diminished inhibition of kallikrein due to C1INH deficiency is thought to lead to the dysregulated generation of bradykinin. Produced in yeast (*Pichia pastoris*), DX-88 is a 60 amino acid, recombinant, kallikrein inhibitor derived following targeted mutation and reiterative phage display affinity maturation of a peptide encompassing amino acids 10-21 and 31-39 of the first Kunitz domain of the human tissue factor pathway inhibitor (TFPI). It shares 88% identity with TFPI between TFPI amino acid residues 59 and 118.

Upon review of the BLA, the immunoassay methods were found to have been adequately validated, however, there were significant deficiencies with respect to the sensitivity and specificity of these assays. One such deficiency in the BLA was the sponsor's failure to provide any discussion or data on the potential of antibodies directed against the DS to cross-react with endogenous TFPI. Partial deficiency of TFPI is associated with hypercoagulable states (e.g. venous thrombosis) and the targeted deletion of the TFPI gene is an embryonic lethal mutation in mice. Beyond its clinical implications, such cross-reactivity may interfere with the DX-88 immunoassays, which also was not explored by the sponsor.

In addition to a possible loss of specificity due to potential cross-reactivity with TFPI, the lots of some, if not all, the DX-88 drug substance used in the immunoassays is contaminated with *P. pastoris* host cell protein (HCP). While this would not be expected to impact the ELISA used for measuring DX-88 during the PK studies or the non-IgE or Nab DX-88 assays, it will confound interpretation of the anti-DX-88 IgE assay as the wells in that assay will contain both DX-88 and *P. pastoris* host cell protein.

Memo

Date: February 11, 2009

From: Jack A. Ragheb M.D., Ph.D.

To: STN 125277/0

Through: Susan Kirshner, Acting Associate Chief, Laboratory of Immunology, DTP

Subject: DX-88 BLA Immunoassay Review

Product: DX-88 (Ecallantide, Kalbitor, Kallikrein Inhibitor)

Sponsor: Dyax

Indication: Treatment of acute episodes of Hereditary AngioEdema (HAE)

Background, Rationale and Summary

This review covers the immunoassays for detection of Drug Substance (DS) in plasma and the detection of anti-DS binding and neutralizing antibodies in serum, as well as the presence of anti-yeast antibodies.

The proposed indication for this BLA is the treatment of Hereditary Angioedema (HAE), a genetic disorder (autosomal dominant) characterized by acute attacks of localized swelling and inflammation that may be life-threatening. Disease is a result of C1 esterase inhibitor (C1-INH) deficiency. C1-INH has pleotropic effects, with roles in controlling the activation of the complement, kinin-generating, fibrinolytic, and intrinsic clotting pathways. In HAE, diminished inhibition of kallikrein, leading to the dysregulated generation of bradykinin, is thought to be responsible for the attacks of angioedema.

Bradykinin, a member of the kinin family, is a potent vasodilator that increases vascular permeability, resulting in local edema. Bradykinin is generated by the action of the kinin protease kallikrein on high molecular weight kininogen. DX-88 is a 60 amino acid, recombinant, kallikrein inhibitor derived following targeted mutation and reiterative phage display affinity maturation of a peptide encompassing amino acids 10-21 and 31-39 of the first Kunitz domain of the human tissue factor pathway inhibitor (TFPI). DX-88 reversibly binds and inhibits the proteolytic activity of plasma kallikrein with a K_i of 30-40 pM.

Produced in yeast (*Pichia pastoris*), DX-88 has a molecular weight of 7054 Da. It shares 88% identity with TFPI, a.k.a. lipoprotein-associated coagulation inhibitor, between TFPI amino acid residues 59 and 118. Therefore one safety concern for DX-88 is that anti-DX-88 antibodies could potentially cross react with TFPI.

TFPI is a glycosylated protein found predominantly in the vascular endothelium and plasma in both free forms and complexed with plasma lipoproteins. TFPI is a protease

inhibitor that regulates the tissue factor (TF)-dependent pathway of blood coagulation. The coagulation process initiates with the formation of a factor VIIa-TF complex, which proteolytically activates additional proteases (factors IX and X) and ultimately leads to the formation of a fibrin clot. TFPI inhibits the activated blood clotting factor X and VIIa-TF proteases in an autoregulatory loop. In addition, TFPI interacts with the proteases trypsin IV and thrombospondin 1, which have inflammatory roles. While not its proposed indication in this BLA, DX-88 is under investigation as a [REDACTED] (b) (4)

In general, the immunoassay methods have been adequately validated, however, as indicated below, there are significant deficiencies with respect to the sensitivity and specificity of these assays. Furthermore, the current validated assay for the anti-DS antibodies was used only in Phase 3 Clinical Studies DX-88/14 and DX-88/20. Thus, the results of immunogenicity assays performed in the Phase 1 and 2 Clinical Studies may not be valid.

A serious deficiency of this BLA is the sponsor's failure to provide any discussion or data on the potential of antibodies directed against the DS to cross-react with endogenous TFPI. Partial deficiency of TFPI is associated with hyper-coagulable states (e.g. venous thrombosis) and the targeted deletion of the TFPI gene is an embryonic lethal mutation in mice. Beyond its clinical implications, such cross-reactivity may interfere with the DX-88 immunoassays, which was not explored by the sponsor. This may be particularly problematic for the immunoassay based PK studies. Such cross-reactivity may also be reflected in the 20% background signal observed in the drug confirmatory ECL assay when results with human serum normal controls (HSNC) are reported as signal/background (S/B) ratios and the need for a relatively high positive control (PC) antibody concentration (421 ng/mL) to demonstrate selectivity in the neutralizing antibody (Nab) assay.

In addition to a possible loss of specificity due to potential cross-reactivity with TFPI, the lots of some, if not all, the DX-88 drug substance used in the immunoassays is contaminated with *P. pastoris* host cell protein (HCP). While this would not be expected to impact the ELISA used for measuring DX-88 during the PK studies or the non-IgE or Nab DX-88 assays, it will confound interpretation of the anti-DX-88 IgE assay as the wells in that assay will contain both DX-88 and *P. pastoris* host cell protein.

The assay for both anti-DX-88 and anti-*P.pastoris* IgE described in the BLA is unexpectedly sensitive for a chromogenic, antigen-specific IgE assay. The extraordinary sensitivity observed for this assay is likely an artifact of the surrogate PC used to establish the limit of detection and limit of quantitation. Overestimation of assay sensitivity could result in an excess of false negative results when clinical samples are tested. This potential problem with the sensitivity of the IgE assays may underlie the observation that 4 of the 8 subjects identified by the Agency as having experienced an anaphylactic reaction had no detectable IgE antibodies to DX-88 or HCP. If, as suggested by the advisory committee, IgE screening of patients be instituted, it will be essential to

have a sufficiently sensitive and specific IgE assay on which to base clinical decisions as to the risk benefit ratio of administering DX-88. These assays are also problematic because the sponsor has no information on the generation or characterization of the PC used in either assay.

Additionally, the sponsor concluded that cut-point determinations based on normal human serum are not equivalent to those based on serum from treatment naïve HAE patients. However, the sponsor has not provided any data generated with treatment naïve HAE patient serum or plasma. Inappropriately high cut-points based on normal human serum may also result in an excess of false negative results when HAE clinical samples are tested.

(b) (4)