

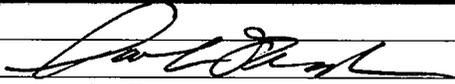
**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125338

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	November 24, 2009
From	Sarah Okada, M.D. 
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	BLA 125338
Supplement#	0
Applicant	Auxilium Pharmaceuticals Inc.
Date of Submission	February 27, 2009
PDUFA Goal Date	August 29, 2009
Proprietary Name / Established (USAN) names	Xiaflex / Collagenase clostridium histolyticum
Dosage forms / Strength	Lyophilized powder with diluent, reconstituted for local injection; 0.58 mg/injection, 0.9 mg/vial
Proposed Indication(s)	1. Advanced Dupuytren's Disease
Recommended:	<i>Approval with revisions to proposed labeling</i>

1. Introduction

Dupuytren's Disease is a condition involving fibroblast proliferation, collagen deposition, and myofibroblast contraction, resulting in nodules and cords of the fascial fibers running longitudinally in the subcutaneous tissues of the palm. The fascial bands thicken and enlarge, drawing the contiguous digital fascia in, resulting in flexion contracture of the affected digits. The overlying skin thickens and the subcutaneous fat becomes more fibrotic, leading to attachment of the skin to the underlying fascial structures. Currently, surgery (fasciectomy or fasciotomy) is the mainstay of treatment and is considered when hand function is impaired; typically, when there is a contracture of a metacarpophalangeal joint of at least 30 degrees, or when there is any degree of proximal interphalangeal joint contracture. However, these procedures are not curative, as the pathophysiology of the disease continues and recurrence of lesions or development of new lesions is common. Although the prevalence of the disease varies, with the highest predilection being in older men of Northern European descent, in the Caucasian population overall prevalence estimates range from 4 to 6% of the population, with a 2:1 male:female ratio. Prevalence increases with age, with men and women being affected with equal frequency after the age of 80 years. Men typically present for treatment in the fifth decade, and women a decade later [Thurston, 2003]. A number of factors have been reported to be associated with the development of the disease, including alcohol use, smoking, manual work/trauma, diabetes, and hyperlipidemia.

The subject of this application is collagenase clostridium histolyticum (also known as AA4500, or Xiaflex), which is a fixed-ratio mixture of two purified collagenolytic enzymes produced by *Clostridium histolyticum*, proposed as a non-surgical treatment for Dupuytren's contractures. When injected into Dupuytren's cords, the postulated mechanism of action of

AA4500 is essentially an enzymatically-mediated fasciotomy, with disruption of the cord leading to a reduction in contracture and improvement in range of motion of the affected joints. The proposed dosage and administration is for up to 3 injections of 0.58 mg of AA4500 per cord, given at 4-week intervals. If an injection does not result in release of contracture by 24 hours, finger extension procedures are recommended to facilitate cord disruption. BLA 125338 includes efficacy and safety data from 12 clinical studies, including 6 randomized, double-blind, placebo-controlled studies, which encompass 1082 patients with 1780 treated cords, who received a total of 2630 injections. The two largest of the completed randomized and controlled studies, AUX-CC-857 and AUX-CC-859, serve as the primary evidentiary basis for the efficacy evaluation. The clinical review focused not only on the efficacy and safety results, which appeared to be clearly favorable, but also on whether there were any data that could shed light on the question of how generalizable these results might be to clinical practice, if approved.

2. Background

The Class I and II Clostridial collagenases that comprise AA4500 have different preferred substrates and cleavage sites. Together, as per the Applicant, these two collagenases exert maximal effects against Type I and Type III collagens—the types that make up the bulk of a Dupuytren's lesion. Type I collagen is the most abundant collagen of the human body, present in scar tissue, tendons, skin, artery walls, the endomysium of myofibrils, fibrocartilage, and the organic part of bones and teeth. Type III collagen forms the bulk of granulation tissue and reticular fibers, and is produced quickly by young fibroblasts before the tougher type I collagen is synthesized. It is also found in artery walls, skin, intestines and the uterus. Type IV collagen, the primary component of basement membranes and the perineurium of peripheral nerves, is also recognized by Class I Clostridial collagenase; however, the Applicant asserts AA4500 is not effective at degrading type IV collagen in vivo, and that no effects on blood vessels, nerves, and epithelia were noted following local injection in non-clinical studies. Nonetheless, injection of enzymes that can lyse the major structural components of most tissues necessitates precision and caution.

Although systemic absorption of AA4500 is negligible, local injection of these bacterial proteins results in a very high incidence of anti-product antibodies, with almost 100% of patients developing these antibodies after 3 injections. The safety evaluation of the data in this submission assessed the magnitude of the risk of hypersensitivity, and whether the anti-product antibodies could possibly cross react with endogenous matrix metalloproteinases (MMPs).

These potential concerns must be taken in light of the fact that Dupuytren's contractures are currently only successfully treated with surgery, with the inherent risks that these procedures entail, and that Dupuytren's contractures are often recurrent and multifocal. An effective non-surgical treatment would represent an important alternative.

Auxilium Pharmaceuticals, Inc. acquired the global development rights for AA4500 from BioSpecifics Technologies Corp. (BTC) in June 2004. Dupuytren's has also been ~~designated~~

an orphan indication, as requested by BTC and granted by FDA in May 1996. Pre-submission regulatory meetings include an End of Phase 2 (EOP2) meeting between BTC and the Agency in 2001, a meeting granted to Auxilium in September 2006 after their acquisition of the product to discuss their Phase 3 plans, and a pre-BLA meeting in September 2008. These meetings included discussion of endpoints, imputation methods for missing data, and the size of the safety database. All issues have been addressed in accordance with Agency guidance. AA4500 is not currently licensed for marketing in any country.

3. CMC/Device

*CMC Reviewers: Ashutosh Rao, V. Ravichandran, Baolin Zhang, Jee Chung, Kimberly Rains.
CMC Team Leader: Kathy Lee
Much of the following information was excerpted from Ms. Lee's review.*

- **General product quality considerations**

AA4500 is a parenteral, lyophilized product comprised of two highly purified (b) (4) bacterial collagenases in an approximate (b) (4) mass ratio, collagenase AUX-I (Clostridial type I collagenase, and collagenase AUX-II (Clostridial type II collagenase). These collagenases are isolated and purified from the fermentation of *Clostridium histolyticum*. Collagenase AUX-I is a single polypeptide chain containing (b) (4) amino acids of known sequence and has a molecular weight of 114 kDa. AUX-II is (b) (4) amino acids long and has a molecular weight of 113 kDa. There is a 47% homology in the amino acid sequence of these two products. Both collagenases digest collagen by hydrolyzing the triple helical region of collagen under physiological conditions. Each collagenase has different specificity; Class I enzymes hydrolyze loci near the amino and carboxy termini of the triple helical domains of the collagen molecule and Class II collagenases make their initial cleavage near the interior of the molecule.

During the course of its development, the AA4500 drug substance has been manufactured at three sites, Biospecifics Technologies Corp. (BTC) Lynbrook, NY, (b) (4); (b) (4) and Auxilium's active pharmaceutical ingredient (API) manufacturing facility located in Horsham, PA, which is the proposed commercial manufacturing site. Comparability data have been submitted to support each of these changes and were determined to be adequate. The drug product has been sterilized, filled, and lyophilized by three different manufacturers (b) (4). The drug product and sterile diluent vials are currently labeled and final-packaged by (b) (4).

Both calcium and zinc are required for the function of AA4500 drug product¹. The calcium is supplied in the sterile diluent and the zinc (b) (4).

¹Mookhtiar & van Wart, 1992; Matrix Supplement No.1, pp116-126

(b) (4)

No additional exogenous Zn is required for the activity of AA4500 drug product.

The proposed commercial shelf life for AA4500 drug substance is 24 months at a storage condition of less than or equal to -60°C. Auxilium established the shelf life based on stability data at -70°C through the 36 months, 24 months and 12 months pull points for three batches Drug Substance manufactured at (b) (4) (CTL2006#0809O, CTL2006#1031N and CTL2006#1583I) as well as 24 months data for one lot drug substance manufactured by Auxilium.

The proposed commercial shelf life for AA4500 drug product is 24 months at a storage condition of 5°C (2-8°C). Auxilium established the shelf life based on stability data at 5°C through the 24 month pull point for four primary drug product lots manufactured by (b) (4)

AA4500 is a non-specified biologic and is subject to the CBER lot release program (21 CFR 610.2(a)). Given that Auxilium has a well controlled manufacturing process based on principles from ICH Q9 and has demonstrated through process validation and batch analysis that they can consistently produced high quality material, the product reviewers have concluded that this product is not required to be on the CBER lot release program.

- **Facilities review/inspection**

Office of Compliance reviewers: Kalavati Suvarna, Ph.D.

Office of Compliance Team Leader: Patricia Hughes, Ph.D.

Facilities inspected:

For drug substance: Auxilium Pharmaceutical, Inc.

102 Witmer Road, Horsham, PA 19044. USA

FEI No. 3006537159

For drug product and sterile diluent:

(b) (4)

(b) (4)

Pending facilities inspection (QC and stability release testing of drug substance):

(b) (4)

The facilities inspection was originally scheduled for June 1-5, 2009, but was delayed after contamination with *Bacillus cereus* was noted in 3 successive product runs in March 2009. The source of contamination was identified as a leaking valve seal that occurred after preventive maintenance was performed on the 15L and 200L fermenters by a contractor. After evidence of successful corrective actions with a clean run, inspection was re-scheduled for August 17-21, 2009. The facilities were classified VAI (voluntary action indicated) and a 3-item Form 483 was issued.

Facilities inspection (b) (4) has been scheduled for 10-5-09. The need for inspection of this facility was identified late, when it was discovered that the clinical lots proposed for initial release upon approval had been tested at this site rather than at the Horsham facility. Preliminary results of the inspection indicate no approvability issues but the final report is pending at the time of this review.

The inspection of the drug product fill-finish site, (b) (4), was waived based on current acceptable cGMP status.

Auxilium Pharmaceuticals, Inc., is claiming a categorical exclusion from the requirement to file an Environmental Assessment (EA) for AA4500; Clostridial collagenase for Injection under 21 CFR 25.31(c). This regulation provides for categorical exclusion for "Action on an NDA, abbreviated application, application form marketing approval of a biologic product, or a supplement to such applications, or actions on an OTC monograph, for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment." To Auxilium's knowledge, no extraordinary circumstances exist that would warrant the preparation of an EA. The product review team thus concurs with a categorical exclusion from an EA for AA4500.

- **Immunogenicity**

Immunogenicity Review by Fred Mills (primary) and Susan Kirschner (secondary)

Screening Assays for anti-Aux I and anti-Aux II antibodies

Screening for anti-product antibodies utilizes bridging antibody assays that are not dependent on the isotype of response and show high sensitivity. The sensitivity for the rabbit anti-AUX-I polyclonal positive control is (b) (4), with an estimated cut-off of (b) (4). The sensitivity for the rabbit anti-AUX-II polyclonal positive control is (b) (4), with an estimated cut-off of (b) (4). The assays are appropriately validated, except for the fact that absence of High Dose Hook effect is not demonstrated at high antibody concentrations. The lack of High Dose Hook effect in this case is not a concern because almost all patients tested positive after 3 AA4500 injections, making under-estimation of positivity unlikely. Additionally, positive screening results are confirmed by competition with AUX-I or AUX-II, which is also appropriately validated.

As previously noted, all patients became seropositive after 3 injections, and the average titers are very high ($\sim 10^5$). Auxilium has provided data showing a decline in titer with time after patients have received a single dose. The long-term persistence of antibodies for patients who have received multiple doses is not fully known although clinical data are available for patients who have received up to 8 injections.

Potential for cross-reactivity with human proteins

As AUX-I and AUX-II are bacterially derived proteins, the fact that AA4500 is highly immunogenic is not unexpected. This immunogenicity poses a safety concern in two primary ways: 1) the potential for hypersensitivity, and 2) the potential for toxicity related to the cross-reactivity of anti-product antibodies with endogenous proteins. The clinical safety concerns

related to immunogenicity are addressed in greater detail in Section 8, below. As shown in Table 1, below, AUX-I and AUX-II have a low but not insignificant amount of sequence homology with a number of human matrix metalloproteinases (MMPs).

Table 1: Amino Acid Sequence Homology Between AUX-I and AUX-II versus Human Matrix Metalloproteinases (MMPs)

Major Collagenolytic Human MMPs		Primary Substrate(s)	% Sequence Homology vs.	
Protein name	Alternative Name		AUX-I	AUX-II
MMP-1	Collagenase-1	Fibrillar collagen	37	35
MMP-2	Gelatinase-A	Gelatin	28	42
MMP-3	Stromelysin-1	Non-fibrillar collagen MMP proenzymes	24	24
MMP- 8	Collagenase-2	Fibrillar collagen	50	53
MMP- 9	Gelatinase-B	Gelatin	39	39
MMP-13	Collagenase-3	Fibrillar collagen	34	29
MMP-14	MT1-MMP	Fibrillar collagen MMP proenzymes	44	32

Source: Table 1 from Module 5.3.5.3. Integrated Summary of Immunology

Auxilium performed studies to investigate possible cross-reactivity between patient sera and human MMPs by adding recombinant MMPs to the bridging antibody assays for Aux I and Aux II. For the five patient sera tested, the MMPs did not appear to produce an appreciable inhibition of antibody binding to AUX-I. However, one of the patients did show MMP inhibition of antibody binding to AUX-II, indicating the presence of cross-reactive antibodies.

Agency immunologists identified two other potential homologous proteins in the NCBI protein human protein database—polycystin I and KIAA0319—which have not been investigated by Auxilium, and which have as much or greater similarity to AUX-II as do the MMPs. Polycystin I is involved in polycystic kidney disease (Chang and Ong, *Nephron Physiol* 2008; 108 pp. 1–7), and KIAA0319 is involved in neural migration, and may have a role in dyslexia (*Human Molecular Genetics* 2006, 15 pp. 1659–1666). Agency immunologists recommend evaluation of the potential for cross-reactivity against these two proteins as a post-marketing commitment.

Neutralizing antibody formation

Neutralizing antibodies were assessed as inhibition of AUX-I or AUX-II enzyme activity by antibody-positive patient sera (from Study AUX-CC-857). The assay utilized captures neutralization of the collagen binding domain, as well as neutralization of the active site.

There was a high rate of neutralizing Abs: 22 of 200 samples had anti-Aux-I neutralization and 44 of 204 samples had anti-Aux II neutralization. This high neutralizing rate may in part be explained by the high titers observed and the fact that in general there is a correlation between antibody titer and raising neutralizing antibodies. Neutralizing antibodies would not be anticipated to interfere with the efficacy of the product since Dupuytren’s lesions are not

well vascularized and access of these antibodies to the local site of injection is likely to be extremely limited.

Hypersensitivity

At the request of the FDA, Auxilium provided justification for not performing IgE or skin prick testing, consisting of the following elements:

1. In early development, IgE testing was performed, and some subjects were positive for anti-product IgE. However, this did not correlate with hypersensitivity.
2. Auxilium was concerned that continued skin prick testing might result in sensitization, and that positive test results might result in un-blinding of the study. Therefore, with the approval of the FDA, IgE or skin prick testing was not used in the pivotal trials.
3. Auxilium argues that in the absence of systemic hypersensitivity, there was no perceived clinical value for performing IgE testing in the clinical trial program, nor in the target subject population following approval.

Seven adverse events (AEs) were reported with the preferred term, "hypersensitivity." Allergic events and hypersensitivity are discussed in greater detail in Section 8, below.

- **Other notable issues (resolved or outstanding)**

At inspection, the product review team requested release testing method transfers for the change in release testing sites from the (b) facility to the Horsham facility. The full method validation information was submitted with the original BLA, but the method transfer reports were submitted 9-2-09. Similarly, additional information on the working cell bank and reference standard qualification protocols for the Horsham facility were requested at inspection, and was submitted 9-4-09. Because product from the Horsham facility will be critical for the commercial launch if the product is approved, these recent submissions will need to be reviewed and determined to be acceptable by Agency product reviewers before the BLA can be approved. During the course of these discussions with the applicant, it was discovered that the clinical lots proposed for initial release upon approval were tested at the (b) (4) facility and not the Horsham facility, necessitating inspection of the (b) facility as well. Inspection of the (b) facility was performed on October 5-6, 2009 and determined to be acceptable.

From a product and compliance perspective, BLA 125338 is recommended for approval. The product review team has drafted the following post-marketing requirement (PMR) and post-marketing commitment (PMC) recommendations:

PMRs (from the Office of Compliance):

1. Conduct and submit data from an adequate container-closure integrity study for the diluent product with container-closure components that have been subjected to the same or worse (b) (4) cycle. The proposed (b) (4) test protocol and method for stability testing can be used to fulfill this requirement.

Provide (b) (4) test validation results for container-closure integrity testing of lyophilized product and diluent vials in the stability program. *Submit validation report and data in a CBE supplement by March 2010.*

- This PMR pertains to a lack of “challenging” container-closure data and is not an approvability issue because otherwise adequate data were submitted to support container-closure integrity.
2. Determine the D121-value of the biological indicator *G.stearothermophilus* in the diluent product solution and reassess the validation studies conducted. Provide a comparison to the D-values used in the product validation studies. *Submit data in a CBE supplement by March 2010.*
 - This PMR pertains to lack of data on the heat resistance of biological indicator spores suspended in diluent, and is not an approvability issue because the sterilization process itself is adequately robust (b) (4) and the diluent is (b) (4) prior to (b) (4)

PMCs (Office of Compliance):

1. Conduct a study to demonstrate microbial control at end of hold (10 days) for the individual AUX-I and AUX-II intermediates. The hold time study included in the submission for the individual AUX-I and AUX-II intermediates is inadequate as the study was performed using formulation buffer. *Submit the data from the study in a CBE-30 supplement by December 2010.*
 - This PMC arises from the theoretical concern that the ability of microorganisms to grow may be affected by the presence of collagenase enzymes in the formulation buffer
2. Qualify the bioburden test for in-process intermediates. The qualification should be performed using 3 different lots. *Submit the data in a CBE-30 supplement by December 2010.*
3. The endotoxin test was qualified using one lot of AUX-I and AUX-II intermediates, and one lot of drug substance. Please perform additional qualification using 2 lots of AUX-I intermediate, AUX-II intermediate, and drug substance, and 3 lots of HIC eluate and TFF-1 concentrate, to demonstrate reproducibility of the test results. *Submit the summary data in a CBE-30 supplement by December 2010.*

PMCs (Office of Biologic Products):

4. To develop and validate an immune-based host cell protein (HCP) assay: (b) (4) the Sponsor should incorporate a validated ELISA as soon as feasible. While this is an important product quality issue it should not hold up approvability for two main reasons: 1) Auxilium already has a crude but qualitative assay for detecting host cell proteins by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and silver staining, and 2) they provided sufficient rationale for the technical

difficulty of developing an immune-based HCP assay for clostridial proteins.

(b) (4)

5. To characterize the types and amounts of subvisible particles (b) (4) in the drug product under stress conditions, at release, and throughout the dating period; and to propose an appropriate control strategy, based on the risk to product quality. Auxilium proposed to set a limit of (b) (4) per vial for subvisible particles. This is not an approvability issue because they are committed to performing subvisible particle testing. However, they have not provided data to support the proposed specification, as they have not performed the testing yet.
6. To establish individual acceptance criteria for AUX-I and AUX-II profile, and their mass ratio, for the RP-HPLC for release and stability testing of the drug substance and drug product. Establishment of these acceptance criteria should be a PMC item. It is not an approvability issue because control over individual enzymes is not the basis for the final product's biological activity; rather it is the synergistic action of the two enzymes on collagen. However to ensure consistent product manufacture and control, they must demonstrate control over the mixing stage of the drug substance by establishing criteria for each peak of drug intermediate.
7. To calculate the protein recovery for each HPLC method validation (SEC and RP-HPLC) using an orthogonal protein measurement assay that provides added assurance that the method is suitable for its intended purpose.
8. To develop and validate the RP-HPLC method to quantify potential impurities for AUX I intermediate, DS, and DP.
9. To establish and validate a staining and destaining control (e.g., BSA) for SDS-PAGE Coomassie and Silver Stain to ensure appropriate level of detection for product-related impurities for every test result.
10. To confirm the accuracy of the SEC-HPLC method for detecting aggregates using stress samples (e.g., light, heat, oxidation) using orthogonal testing methods (e.g., AUC or FFF). Auxilium currently uses size exclusion chromatography (SEC-HPLC) as their identity test method. (b) (4)

Implementation of this testing into the specifications should be a PMC. This issue does not affect approvability because the ~~Sponsor~~ currently has two assays that are capable of detecting high-molecular weight

species, namely SDS-PAGE (b) (4) gel assay for product-related impurities) and SEC-HPLC (for aggregates).

11. To develop and validate an immune-based identity assay and to add the validated assay to the release specifications for the drug substance and the drug product. Auxilium has a reversed-phase high performance liquid chromatography (RP-HPLC) assay as the primary identity test but the product team believes an orthogonal immune-based assay should also be put in place.
12. To include an accelerated or stress stability condition as part of the annual stability program for the drug substance and drug product. This is not approvability issue because Auxilium has performed comprehensive forced degradation studies (b) (4)
[REDACTED]
13. To evaluate the minimal fill volume required 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 reconstituted drug product.
14. To evaluate the potential for cross-reactivity of anti-product antibodies with endogenous proteins polycystin I and KIAA0319.
15. To evaluate the long-term persistence of anti-product antibodies for patients who have received multiple doses of Xiaflex. This study should assess total and neutralizing antibodies.

4. Nonclinical Pharmacology/Toxicology

*Primary Pharmacology/Toxicology Review by Asoke Mukherjee, Ph.D.
Pharmacology/Toxicology Supervisor: R. Dan Mellon, Ph.D. Much of the following information was excerpted from Dr. Mukherjee's review.*

- **General nonclinical pharmacology/toxicology considerations**

At an EOP2 teleconference in September 2001, the Agency advised the applicant that "Preclinical requirement for chronic toxicity, reproductive toxicity and carcinogenicity studies are waived due to the nature of the product, and its intended use in this specific clinical setting." The nonclinical studies submitted in the BLA include mutagenicity assays, two multi-dose intravenous (IV) toxicity studies in rats, a local toxicity study in dogs, fertility and embryofetal development studies (IV) in rats, and sensitization experiments in guinea pigs exposed to AA4500 by intraperitoneal (IP) or intracardiac route.

Clostridial collagenase made by BTC, (b)(1) and Auxilium processes showed a similar toxicity profile and immunogenicity. Antibody formation to AUX-I and AUX-II was observed at all doses tested following IV injections (rats) and local injections (dogs).

Two multidose intravenous (IV) toxicity studies were conducted in rats up to 16 days. Following IV injection, AUX-I rapidly degraded in plasma, but AUX-II could be measured on days 1 and 7. The NOAEL was 0.029 mg protein/dose. Liver toxicity was noted at 0.13 and 0.29 mg protein/dose. Injection site perivascular inflammation and fibrosis were noted at all doses. Both these toxicities were non-reversible.

A local toxicity study was conducted after injection of AA4500 in the dog penis. The study was conducted to support the safety of the drug in Peyronie's disease (b)(4), and the study report was submitted with this BLA submission. Data showed injection site inflammation in the treated groups at single and multiple doses. Doses ranged from 0.8 to 14.9 ug/kg. Both AUX-I and AUX-II were detectable in the plasma only within 60 min after dosing, suggesting minimal bioavailability of the drug in systemic circulation following local administration. However, antibodies to AUX-I and AUX-II were present in the serum even at recovery day 28. The Applicant conducted sensitization experiments in guinea pigs and did not observe immediate hypersensitivity reactions in guinea pigs when challenged by AA4500 by IP or intracardiac route.

The non-clinical data provided in the BLA clearly showed development of anti-product antibodies in the serum both after single and multiple injections, irrespective of the route of administration or species. The consequences of the development of these antibodies are unknown, and none were apparent in the non-clinical studies.

The toxicities observed in the non-clinical studies were consistent with the mechanism of action of the collagenases. The immunogenicity to the product is also an anticipated reaction to these bacterial proteins. No systemic allergic response was identified in the nonclinical studies.

- **Carcinogenicity**

Mutagenicity studies are generally not required for biologics because large protein molecules do not readily enter cells. However, mutagenicity studies can still provide insights regarding process impurities that could be mutagenic. The Applicant conducted mutagenicity studies in Ames assay, in vitro chromosomal aberration in peripheral human lymphocytes and mouse micronucleus assay using clostridial collagenase prepared by BTC batches. The drug substance was not mutagenic in these assays. However, the batch used in these studies was not intended for marketing under the BLA and thus, in terms of impurities, the genetic toxicology studies submitted in the BLA are not relevant to the proposed marketing batches. AA4500 is not an immunosuppressant, is not absorbed systemically, and is not intended for chronic regular use; therefore carcinogenicity studies were not required for the BLA submission.

- **Reproductive toxicology**

Reproductive toxicology studies were conducted with product obtained from the (b) (4) manufacturing process. The Applicant provided data for fertility, early embryonic development, and embryofetal development safety studies in rats. Male and female rats did not show any effect on fertility and early embryonic development up to 0.13 mg protein/dose by IV bolus injections of AA4500 manufactured by (b) (4). Pregnant rats also did not show developmental toxicity to pups when injected during the organogenicity period.

Anti-AUX-I and -AUX-II antibodies were present in most of the rat studies but were not directly measured in the embryofetal development study. There were no reproductive or developmental toxicities noted related to the development of anti-product antibodies.

The Applicant did not conduct pre- and post-natal development studies in rats; however, during the Pre-BLA meeting with the Division, the Applicant was asked to provide justification for not conducting these studies in the BLA. The Applicant's rationale included the lack of systemic bioavailability of AA4500 following local injection and lack of toxicities in the reproductive studies conducted. The Pharmacology/Toxicology team concurs with the Applicant's rationale, but recommends including labeling language to address the theoretical concerns arising from the possibility of anti-product antibodies that cross react with endogenous MMPs and the unknown impact of this on embryofetal development.

- **Other notable issues (resolved or outstanding)**

The Pharmacology/Toxicology team recommends approval of the BLA with revisions to the proposed labeling. No non-clinical postmarketing requirements or commitments are recommended.

Dr. Mukherjee recommended consideration of language regarding a possible tetracycline interaction in labeling. This issue was discussed amongst the review team and the consensus was that since the concern with tetracycline would be a loss of efficacy rather than a safety concern, and that the likelihood of this interaction is low due to the avascular nature of Dupuytren's cords, that this theoretical interaction does not merit inclusion into labeling.

Dr. Mukherjee's concerns regarding the potential for hypersensitivity are being addressed via labeling and pharmacovigilance, as per recommendations from our Allergy/Immunology consultants in the Division of Pulmonary and Allergy Products (DPAP). See Section 8 immunogenicity section, below, for details.

5. Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology Reviewer: Srikanth Nallani, Ph.D.

Clinical Pharmacology Team Leader: Suresh Doddapaneni, Ph.D.

- **General clinical pharmacology/biopharmaceutics considerations**

AA4500 is intended for local injection into Dupuytren's cords. Systemic absorption is neither desired nor observed at therapeutic doses. In an early stage dose-escalation study, Dupuytren's patients received 600, 1200, 2400, 4800, 9600 and 10,000 U of collagenase into the cord that was causing contracture of the metacarpophalangeal (MP) joints (Badalamante MA, Hurst LC, et. al. The Journal of Hand Surgery; 25A (4): 629 to 636). Based on the improvement noted at the 10,000 U (equivalent to 0.58 mg) of collagenase, the efficacy and safety of 0.58 mg of XIAFLEX was evaluated in 2 randomized, double-blind, placebo-controlled, multi-center trials in 374 adult patients with advanced Dupuytren's disease (Studies AUX-CC-857 and -859). In addition, studies # 02 and # 55 assessed the safety, tolerability and pharmacokinetics after single intra-cord injections of 0.58 mg of AA4500 in Dupuytren's disease patients.

In PK study # 55, an open label safety, tolerability and PK study, sixteen subjects were enrolled and treated with one injection of AA4500. Blood samples were collected for the determination of AUX-I and AUX-II plasma concentrations at the following time points relative to dosing: 15 minutes before, 5, 10, 20, 30 minutes after, 1, 2, 4, 8, 12, and 24 hours after (i.e., following the finger extension procedure to disrupt the cord), and seven and 30 days after (in 15 subjects). AUX-I and AUX-II levels were determined by validated double-sandwich enzyme-linked immunosorbent assays (ELISA). AUX-I and AUX-II levels were not detected in any subject at any time point through the first 24 hours, on Day 7, or on Day 30 following administration of a single 0.58 mg injection of AA4500 into a Dupuytren's cord. All samples were below the lower level of quantification (i.e., ≤ 5 ng/mL for AUX I and ≤ 25 ng/mL for AUX II). There were no major adverse events observed in this study.

- **Drug-drug interactions**

Not applicable; the product is not absorbed systemically.

- **Pathway of elimination**

Elimination is likely by local proteolysis. Elimination and excretion were not formally examined due to lack of systemic exposure following local injection into the Dupuytren's cord.

- **Intrinsic factors potentially affecting elimination: age, gender, hepatic insufficiency and renal impairment.**
- **Demographic interactions/special populations**

The current Phase 3 clinical studies conducted by Auxilium have evaluated the safety and efficacy of AA4500 in a subject population that is representative (i.e., in age, gender, and race) of the population targeted for commercialization. As systemic exposure to AA4500 after intralesional injection into Dupuytren's cords has not been detected, studies were not conducted to evaluate the metabolism of AA4500 PK in subjects with impaired hepatic or renal function.

- **Thorough QT study or other QT assessment**

The product is not absorbed systemically and is not expected to affect the cardiac conduction system, therefore QT assessments were neither required nor performed.

- **Other notable issues (resolved or outstanding)**

The Clinical Pharmacology team finds the data in the submission adequate to support approval and no Phase 4 commitments are recommended.

6. Clinical Microbiology -Not applicable

7. Clinical/Statistical- Efficacy

Primary clinical review by Eric Brodsky, M.D.

Primary statistical review by Jonathan Norton, Ph.D.

Statistical Team Leader: Dionne Price, Ph.D.

The data that provide the primary evidentiary basis of the efficacy assessment are from two randomized, double-blind, placebo-controlled studies involving 374 patients at 21 clinical sites. AUX-CC-857 was conducted at 16 sites in the US, and AUX-CC-859 was conducted at 5 sites in Australia. In both these studies, patients were randomized 2:1 (active:placebo) to receive up to 3 injections of 0.58 mg AA4500 vs. placebo, at 4 week intervals. The primary endpoint for the studies is the proportion of patients achieving a reduction in contracture to 5 degrees or less (“clinical success”), 30 days after the last injection.

The baseline demographics and disease characteristics were similar between treatment groups in both the studies, and are consistent with the underlying patient population. Most patients were Caucasian males in their early to mid-sixties. In AUX-CC-857, 2/3 of the primary lesions selected affected a metacarpophalangeal (MP) joint, whereas in AUX-CC-859 about half of the primary lesions affected an MP joint and half affected a proximal interphalangeal (PIP) joint. There were very few dropouts in these studies. Refer to Tables 6.1 to 6.4 in Dr. Brodsky’s review for further details.

As shown in Table 2, below, a much higher proportion of patients experienced an almost complete resolution of their targeted contracture (reduction to 5 degrees or less) after up to 3 injections with AA4500, compared to placebo—64% vs. 7% in AUX-CC-857 and 44% vs. 5% in AUX-CC-859. As might be expected based on historical results with surgical procedures, lesions affecting MP joints appeared to be more amenable to correction compared to lesions affecting PIP joints. However, within each of these studies, a similar proportion of patients in each treatment group had lesions affecting MP joints identified; thus the inherent refractoriness of selected lesions was not likely to have biased study results.

While a little over half of those responding did so after the first injection (see Table 3), approximately a third of patients receiving additional injections achieved the primary endpoint with the second and third injections. Patients in AUX-CC-857 and 859 had approximately 1.7 injections, on average.

Table 2: Primary Endpoint Results for the Pivotal Trials (Table 6.5 from Dr. Brodsky's review)

	Study 57 ¹ (U.S.)		Study 59 ² (Australian)	
	CCH 0.58 mg	Placebo	CCH 0.58 mg	Placebo
Primary Efficacy Endpoint (All Primary Joints – MP or PIP)				
Proportion of patients with clinical success (MP or PIP joint)	n=203 64%	n=103 7%	n=45 44%	n=21 5%
p-value	< 0.001	–	< 0.001	–
Difference	57%	–	39%	–
95% CIs for the Difference	(48%, 65%)	–	(18%, 56%)	–
Subgroup Analyses by Primary Joint Type				
Proportion of patients with clinical success (MP joint)	n=133 77%	n=69 7%	n=20 65%	n=11 9%
Proportion of patients with clinical success (PIP joint)	n=70 40%	n=34 6%	n=25 28%	n=10 0%

CIs = confidence intervals (using an exact method)

1 MITT population was the primary statistical population for the efficacy analyses in Study 57.

The MITT population included all treated patients who had at least one post-treatment contracture measurement and had baseline contracture > 5 degrees. There was 1 patient in each of the CCH and placebo groups who were included in the treated population (ITT) and excluded from the MITT population.

2 ITT population (all treated patients) was the primary statistical population for the efficacy analyses in Study 59.

Reference: Adapted from the CSR for Study 57, Table 14.2.2.1; and the CSR for Study 59, Table 14.2.2.2.

Table 3: Primary Endpoint Results by Injection (Table 6.6 from Dr. Brodsky’s review)

	Study 57 ¹ (U.S.)		Study 59 ² (Australian)	
	CCH	Placebo	CCH	Placebo
Last injection (up to 3 injections)³	n=203 64%	n=103 7%	n=45 44%	n=21 5%
First injection⁴	n=203 39%	n=103 1%	n=45 27%	n=21 5%
Second injection⁴	n=99 35%	n=100 1%	n=22 27%	n=19 0%
Third injection⁴	n=45 36%	n=91 6%	n=8 25%	n=18 0%

1 MITT population (all treated patients with at least one post-treatment contracture measurement and had baseline contracture > 5 degrees) was the primary statistical population in Study 57.

2 ITT population (all treated patients) was the primary statistical population in Study 59.

3 Clinical success after the last injection (up to 3 injections) was the primary efficacy endpoint in Studies 57 and 59.

4. The proportion of patients that achieved clinical success after the 1st injection was a secondary endpoint included in the statistical hierarchy. The proportion of patients that achieved clinical success after the 2nd and 3rd injections were not pre-specified endpoints.

Reference: Adapted from the CSR for Study 57, Table 14.2.2.1, Page 97; CSR for Study 59, Table 14.2.2.1, Page 147.

Results from the supportive randomized and controlled trials in the AA4500 clinical development program are consistent with the results from AUX-CC-857 and -859. (Refer to Table 6.7 in Dr. Brodsky’s review for detailed results.)

Secondary endpoints assessed in the pivotal studies included:

- ≥50% reduction from baseline in degree of contracture 30 days after the last injection
- percentage change from baseline in degree of contracture 30 days after the last injection
- Change from baseline in range of motion (degrees) 30 days after the last injection
- Time to achievement of reduction of contracture to 5 degrees or less

The first three secondary endpoints listed above are very similar to the primary endpoint, and are consistent with the primary endpoint results in supporting a treatment effect in favor of AA4500 for the treatment of Dupuytren’s contractures. Refer to Table 6.8 and 6.9 in Dr. Brodsky’s review for additional details. The median time to achievement of reduction of contracture to 5 degrees or less was 56 and 57 days for all primary joints treated with AA4500 in AUX-CC-857 and -859, respectively, reflecting the need for more than one injection, as injections were spaced at 30 day intervals. Median time for MP joints treated with AA4500 was 36 and 34 days, reflecting the comparatively fewer injections needed to successfully treat lesions affecting MP joints.

- **Includes discussion of notable efficacy issues both resolved and outstanding**

The efficacy results from the AA4500 clinical studies provide convincing evidence that AA4500 is effective in reducing Dupuytren’s contractures when administered by a healthcare

professional experienced in the management of disorders of the hand, such as hand surgeons or orthopedic surgeons. Of the 272 subjects injected with AA4500 in the Phase 3 trials, all but 11 were treated by hand or orthopedic surgeons. Exploratory analyses of efficacy by professional background of the investigator were performed (see the primary clinical and statistical reviews for additional details), with no clear differences noted; however the relative homogeneity of the investigator background in these studies precludes definitive conclusions.

Agency statistical reviewers were able to confirm the primary efficacy analyses and concurred with the clinical review team that studies AUX-CC-857 and AUX-CC-859 provide substantial evidence of efficacy of AA4500 for the treatment of Dupuytren's contractures.

8. Safety

- **Adequacy of the database, major findings/signals, special studies, foreign marketing experience, if any, and plans for postmarketing as discussed in the Pre-Approval Safety Conference (if NME will be approved)**

In the entire safety database of the 12 submitted clinical studies, 1082 patients received at least one intra-cord injection of 0.58 mg of AA4500 (2630 injections). The mean (\pm SD) duration of safety follow-up for these 1082 patients was 9.5 (\pm 4.6) months. The size of the safety database and the duration of safety follow-up are consistent with the Agency's advice during pre-submission meetings. Of the 1082 patients in the safety database, only 14 patients received up to 8 injections total (for multiple Dupuytren's lesions); however, 116 received up to 5 injections. In the 90-day controlled portions of the 2 pivotal trials (Studies 57 and 59), 249 and 125 patients received at least one injection of 0.58 mg of CCH and placebo into the cord affecting the primary joint, respectively. In addition to the 1082 patients who received the proposed CCH dose (0.58 mg), 22 and 18 patients received a lower CCH dose (0.29 mg and 0.145 mg, respectively). AA4500 is not currently marketed in any country.

Table 4: Overview of total AA4500 (Xiaflex) exposure by patients and number of injections received (Table 7.1 from Dr. Brodsky's review)

# of Xiaflex injections received	n (%)
≥ 1	1082 (100%)
1	443 (41%)
2	219 (20%)
3	170 (16%)
4	93 (9%)
5	116 (11%)
6	14 (1%)
7	13 (1%)
8	14 (1%)

Reference: Safety Update, Table 4, Page 13.

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.**

Deaths

No deaths were observed during the 90-day controlled portion of AUX-CC-857 and -859. During the entire follow-up period of the 12 submitted clinical studies, there were 5 deaths reported: a 68 year old male with a history of COPD who died of a COPD exacerbation, a 63 year old male with a history of diabetes, hypertension, and colon cancer who died of liver cancer, a 77 year old male with hyperlipidemia and a history of coronary artery disease who died of an MI, a 79 year old male with diabetes, hypertension, and hyperlipidemia who died of an MI, and a 76 year old male with hypertension, hyperlipidemia, COPD, and coronary artery disease who died of an MI. The nature and occurrence of these events is consistent with what might be expected in the underlying patient population of older males with multiple comorbidities.

Serious Adverse Events

As shown in Table 5, serious adverse events (SAE) of the injected extremity occurred only in patients treated with AA4500. The difference between treatment groups overall in the occurrence of SAE is attributable to SAE of the injected extremity. As might be expected of a product that results in collagen lysis, two cases of tendon rupture were noted (1% incidence).

Table 5: SAEs in the 90-day Controlled Period of AUX-CC-857 and -859 (Table 7.4 from Dr. Brodsky's review)

	0.58 mg of CCH (n=249)	Placebo (n=125)
Patients with ≥ 1 SAE	7 (3%)	1 (1%)
Patients with ≥ 1 SAE involving the injected extremity	5 (2%)	0 (0%)
Tendon rupture	2 (1%)	0 (0%)
Complex regional pain syndrome	1 (< 1%)	0 (0%)
Ligament disorder	1 (< 1%)	0 (0%)
Ligament injury	1 (< 1%)	0 (0%)
Patients with ≥ 1 SAE that did not involve the injected extremity	2 (1%)	1 (1%)
Spine fusion surgery	1 (< 1%)	0 (0%)
Panic attack	1 (< 1%)	0 (0%)
Acute cholecystitis	0 (0%)	1 (1%)

Reference: Adapted from the CSR of Study 57, Table 29, Page 69 and CSR of Study 59, Table 59, Page 111

A third tendon rupture was observed in the larger safety database of the 12 submitted clinical studies (see Table 6). However, overall, considering the number of patients (1082) and injections (2630), the incidence of treatment-emergent SAE of the injected extremity is low. As an exploratory analysis, Table 6 also contains information on the background professional training of the investigator. Very few events were linked to non-surgeons, consistent with the study population of investigators, which contained very few non-surgeons. While no definitive conclusions can be drawn, it does not appear that lack of surgical background was associated with a greater risk or severity of AEs of the injected extremity.

Table 6: All SAE of the Injected Extremity in the 12 Submitted Clinical Studies (Table 7.5 from Dr. Brodsky's review)

	Patient #	Study	SAE of the injected extremity	Time Between Last CCH Injection & AE	# of Injections into Cord ²	Treatment/Outcome	Investigator Training ³
Controlled Portions of the Pivotal Trials Through Day 90							
1	1157-4203	57	Tendon ruptures	4 days	3	Surgery	Hand surgeon or plastic surgeon
2	1154-2710	57	Tendon ruptures	7 days	1	Surgery	Hand surgeon
3	1157-4201	57	Complex regional pain syndrome	13 days	1	Steroids, pregabalin & hand therapy	Hand surgeon or plastic surgeon
4	1170-3801	57	Ligament disorder	20 days	3	Event ongoing	Hand surgeon
5	6003-1601	59	Flexor pulley ruptures	43 days	2	Surgery	Hand surgeon
Open-Label, Uncontrolled Portions of the CCH Studies							
6	1167-1011	55	Tendon rupture	≤ 7 days	1	Surgery	Hand surgeon
7	6002-1502	59	Sensory abnormality of left hand	13 days	2	Resolved	Rheumatologist
8	6006-4528	54	Fracture of the tip of right 2 nd finger with a ligament tear	14 days	1	Recovered without surgery	Hand surgeon
9	6008-4705	54	Tendonitis	14 days	4	Managed conservatively, Outcome unknown	Rheumatologist
10	1170-3816	58	Boutonniere deformity	28 days	1	Splint, ongoing	Hand surgeon
11	1173-7222	56	Elective amputation of the right 5th finger	103 days	1	Surgery	Hand surgeon

1 CCH Studies include Studies 02, 03, 04, 51, 52, 53, 54, 55, 56, 57, 58, and 59.

2 Number of CCH injections into the relevant cord prior to the SAE. CCH may have been injected at other sites.

3 Investigator training who performed the injection. Data on the particular investigator (principal investigator or sub-investigator) who performed the injection at every site was not known.

Reference: Narratives and case reports forms of Studies 54, 55, 56, 57, and 59 and from the Integrated Summary of Safety. Also adapted from Auxilium's response to clinical information request #1 on June 23, 2009 and clinical information request #3 on August 12, 2009.

Discontinuation due to AE

There were very few discontinuations due to AE in the pivotal studies. The three patients who discontinued, however, were all in the AA4500 treatment group.

Table 7: Discontinuations due to Adverse Events (DAE); (Table 7.9 from Dr. Brodsky's review)

	0.58 mg of CCH (n=249)	Placebo (n=125)
Patients with ≥ 1 DAE	3 (1%)	0 (0%)
Severe injection site pain	1 (<1%)	0 (0%)
Dizziness	1 (<1%)	0 (0%)
Complex regional pain syndrome	1 (<1%)	0 (0%)

Reference: Adapted from the CSR of Study 57, Page 69 and Safety Update, Table 30, Page 75.

Common AE

Adverse events occurred in almost all patients who were treated with AA4500, versus half of the patients who were treated with placebo. Most of these adverse events appeared to be local reactions to treatment.

Table 8: Common Adverse Events in AUX-CC-857 and -859 (Table 7.10 from Dr. Brodsky’s review)

	0.58 mg of CCH (n=249)	Placebo (n=125)
Patients with ≥ 1 AE	243 (98%)	61 (49%)
Peripheral edema ²	183 (73%)	6 (5%)
Contusion	137 (55%)	4 (3%)
Injection site hemorrhage	95 (38%)	4 (3%)
Pain in extremity	87 (35%)	6 (5%)
Injection site pain	83 (33%)	7 (6%)
Injection site swelling	59 (24%)	7 (6%)
Tenderness	60 (24%)	0 (0%)
Ecchymosis	51 (20%)	1 (1%)
Lymphadenopathy	31 (12%)	0 (0%)
Pruritus	27 (11%)	1 (1%)
Skin laceration	22 (9%)	0 (0%)
Lymph node pain	21 (8%)	0 (0%)
Axillary pain	15 (6%)	0 (0%)
Erythema	14 (6%)	0 (0%)
Injection site pruritus	13 (5%)	0 (0%)
Blister	11 (4%)	0 (0%)
Arthralgia	10 (4%)	1 (1%)
Blood blister	10 (4%)	0 (0%)
Inflammation	8 (3%)	0 (0%)
Paresthesia	7 (3%)	1 (1%)
Nasopharyngitis	6 (2%)	9 (7%)
Headache	6 (2%)	5 (4%)
Injection site vesicles	6 (2%)	1 (1%)
Joint swelling	6 (2%)	0 (0%)
Swelling	6 (2%)	0 (0%)
Hypoesthesia	5 (2%)	0 (0%)
Sinusitis	2 (1%)	3 (2%)
URI	1 (<1%)	3 (2%)

1 The pivotal trials were Studies 57 and 59. Includes all patients who received at least one injection of double-blind injection. Preferred term was coded using MedDRA dictionary (Version 8.0). If multiple AEs were reported for a given preferred term, only 1 event was counted per patient.

2 The overwhelming majority of edema AEs were swelling of the injected hand.

Reference: CSR of Study 57, Table 14.3.1.3, Pages 209-215 and CSR of Study 59, Table 14.3.1.3a, Pages 204-207.

• **Immunogenicity**

Over 86% of patients had anti-AUX-I and/or anti-AUX-II antibodies after the first injection, and 100% of patients had anti-AUX-I and/or anti-AUX-II antibodies after the third injection. Although anti-product antibodies would not be expected to affect efficacy, given the relative lack of blood flow to a typical Dupuytren’s lesion, allergic reactions would be an anticipated

result of exposure to foreign proteins. An efficacy subgroup analysis of the primary endpoint for Study AUX-CC-857 by neutralizing anti-product antibody status suggests that efficacy does not appear to be significantly affected. However, the numbers of patients with neutralizing antibodies was relatively small, precluding definitive conclusions.

Table 9: Efficacy Subgroup Analysis by Neutralizing Antibody Status for the Primary Endpoint, Study AUX-CC-857 (Table 7.14 of Dr. Brodsky’s review)

	Neutralizing Antibody Status		
	Positive	Negative	Unknown
Neutralizing Antibody to AUX-I			
All Joints	12/20 (60%)	106/168 (63%)	12/15 (80%)
Neutralizing Antibody to AUX-II			
All Joints	21/42 (50%)	97/146 (66%)	12/15 (80%)

1 In Study 57, 130/203 (64%) of CCH-treated patients achieved the primary endpoint.
 Reference: Adapted from response to clinical information request #3 (August 12, 2009).

With respect to allergic reactions, there were surprisingly no severe reactions that could have been the result of systemic hypersensitivity. Of the 1082 subjects who received at least 1 injection of AA4500 0.58 mg, there were seven events coded as hypersensitivity reactions; four of these were considered unrelated to study drug (rash behind knee, nasal allergy, allergic symptoms, allergic cough) and three were considered related (local allergic reactions of redness, itch, and swelling at injection site) by the investigator concerned. All of the adverse events classified as related hypersensitivity reactions occurred with the first injection. There were no cases of clinically diagnosed anaphylaxis, and there were no severe events, i.e., those requiring hospitalization or involving hypotension or respiratory compromise. There were two cases of urticaria and several other cases of various rashes, all of mild or moderate severity, that were listed under treatment-emergent adverse events (Table 14.2.7 in Module 5.3.5.3 Integrated Summary of Safety).

To the extent that pruritis can represent histamine-mediated phenomena, there was evidence that these events correlated with an increasing number of injections during the controlled period of the pivotal trials, as shown in Table 10. This could indicate an increased propensity toward at least mild allergic reactions with repeated exposures.

Table 10: Pruritis AEs by Injection in Studies AUX-CC-857 and -859 (Table 7.12 from Dr. Brodsky’s review)

	Study 57		Study 59	
	CCH n=203	Placebo n=103	CCH n=45	Placebo n=21
After up to 3 injections	33/203 (16%)	1/103 (1%)	6/45 (13%)	0/21 (0%)
After 1 injection	10/203 (5%)	1/103 (1%)	1/45 (2%)	0/21 (0%)
After 2 injections	15/99 (15%)	0/100 (0%)	4/22 (18%)	0/19 (0%)
After 3 injections	20/45 (44%)	0/91 (0%)	3/8 (38%)	0/18 (0%)

1 Pruritus AEs were from pooled MedDRA terms “pruritus, injection site pruritus, or pruritus generalized AE.”
 Reference: Safety analysis by reviewer using ADAE JMP datasets for Studies 57 and 59.

IgE Serum Testing

Serum IgE antibodies were not measured in the Auxilium-sponsored studies. As noted above in Section 3, Auxilium's rationale for this was the lack of correlation of IgE with hypersensitivity events early in clinical development. There was additional concern that skin prick testing to assess for pre-existing allergy to the proteins might result in sensitization and that positive test results might result in un-blinding of the study. Therefore, with the approval of the FDA, IgE or skin prick testing was not used in the pivotal trials. However, serum IgE antibodies were measured in 3 early Phase 1 and Phase 2 studies of Xiaflex conducted by the prior academic sponsor.

During the open public hearing at the Arthritis Advisory Committee (AAC) meeting, Dr. Robert Hamilton, a Johns Hopkins immunologist, provided the results of IgE testing following Xiaflex injections in the early Phase 1 and Phase 2 studies from the prior academic sponsor. In these Phase 1 studies, a high percentage of patients had IgE antibodies and titers following intra-lesional Xiaflex injections. These data were not formally submitted to the FDA.

Dr. Hamilton also performed IgE testing in an early Phase 2 trial (Study DUPY-202), sponsored by the prior academic sponsor. This study was a dose-ranging, randomized, double-blind, placebo-controlled trial of Xiaflex in patients with Dupuytren's contracture. Patients received single doses of placebo or 0.145, 0.29, or 0.58 mg Xiaflex injections into one Dupuytren's cord. During the open-label extension, patients may have received 4 additional 0.58 mg Xiaflex injections at 4-6 week intervals for a total of up to 5 Xiaflex injections. Patients were excluded from receiving study medication if they had IgE antibodies to collagenase exceeding 15 ng/mL. Patients who had IgE antibodies below 15 ng/mL could not receive additional Xiaflex injections if they had a positive skin scratch test to Xiaflex.

In this Phase 2 trial, Xiaflex-treated patients had a greater incidence of IgE antibodies with more injections (see Table 10 below) and greater titers were seen with more injections (see Figure 1 below), though the number of patients with successive injections was small. No cases of severe systemic hypersensitivity reactions were seen in the early trials or in the late phase trials. Nonetheless, the data on increasing pruritis events (Table 9, above), coupled with increasing incidence and titers of IgE antibodies, raise the question of whether there might be a threshold above which severe hypersensitivity might occur that has not yet been reached with the extent of exposure thus far in the clinical trials. To assist in the determination of whether this is a realistic possibility, and whether additional postmarketing studies should be performed to address this question, DAARP consulted the Division of Pulmonary and Allergy Products (DPAP).

DPAP's conclusions and recommendations are as follows (excerpted from their consult):

- The increasing incidence and titers of drug-specific IgG and IgE upon repeated dosing of Xiaflex indicate the potential for hypersensitivity reactions including anaphylaxis. The absence of anaphylaxis cases in the available safety database of limited size does not rule-out the potential for such reactions.
- Given the apparent low frequency of drug-related hypersensitivity events, the questionable systemic exposure to antigen, and the orphan status of the drug product, it would be difficult to

conduct an adequately powered post-marketing study capable of assessing the hypersensitivity risk attributable to Xiaflex. Moreover, such a study would likely be of low yield. However, DPAP suspects that the rate and severity of hypersensitivity reactions may increase with wider usage of the drug and over time.

- Thus, DPAP recommends that product labeling for Xiaflex clearly indicate the potential for severe allergic reactions, including anaphylaxis. DPAP also recommends that Xiaflex be labeled for use in a clinical setting that is capable of treating hypersensitivity reactions including anaphylaxis. Moreover, DPAP recommends a pharmacovigilance program that will track hypersensitivity adverse events and facilitate periodic analysis of these adverse events. The pharmacovigilance program should obtain any available information on the temporal relationship of the reaction to Xiaflex administration, reported signs and symptoms of systemic allergic reactions, including cutaneous, cardiopulmonary, and gastrointestinal manifestations, changes in vital signs, and any pertinent laboratory parameters such as serum tryptase. Allergic skin prick testing and drug-specific IgE titers are not recommended at this time, as these findings cannot be used to reliably exclude subjects at increased risk of hypersensitivity.

Table 11: IgE Response by Number of AA4500 injections in Study DUPY-202

Number Exposure Results	Day 0/Pre- Injection	Day 7	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12
1 st Exposure ^a (Active Injection# 1) N ^b	62	51	64	50	29	21	24	21
Positive	0	0	2 (3.1%)	0	0	1 (4.8%)	3 (12.5%)	1 (4.8%)
Equivocal	0	0	1 (1.6%)	0	0	0	1 (4.2%)	0
Negative	62 (100.0%)	51(100.0%)	61 (95.3%)	50(100.0%)	29(100.0%)	20 (95.2%)	20 (83.3%)	20 (95.2%)
2 nd Exposure (Active Injection# 2) N ^b	36	36	44	21	14	12	10	6
Positive	1 (2.8%)	25 (69.4%)	10 (22.7%)	4 (19.0%)	4 (28.6%)	4 (33.3%)	2 (20.0%)	2 (33.3%)
Equivocal	0	3 (8.3%)	6 (13.6%)	1 (4.8%)	0	1 (8.3%)	2 (20.0%)	0
Negative	35 (97.2%)	8 (22.2%)	28 (63.6%)	16 (76.2%)	10 (71.4%)	7 (58.3%)	6 (60.0%)	4 (66.7%)
3 rd Exposure (Active Injection#3) N ^b	25	24	28	19	13	8	6	5
Positive	2 (8.0%)	12 (50.0%)	11 (39.3%)	6 (31.6%)	4 (30.8%)	2 (25.0%)	3 (50.0%)	3 (60.0%)
Equivocal	2 (8.0%)	5 (20.8%)	2 (7.1%)	4 (21.1%)	2 (15.4%)	0	1 (16.7%)	0
Negative	21 (84.0%)	7 (29.2%)	15 (53.6%)	9 (47.4%)	7 (53.8%)	6 (75.0%)	2 (33.3%)	2 (40.0%)
4 th Exposure (Active Injection# 4) N ^b	19	19	19	15	14	11	5	8
Positive	6 (31.6%)	16 (84.2%)	12 (63.2%)	8 (53.3%)	11 (78.6%)	6 (54.5%)	3 (60.0%)	6 (75.0%)
Equivocal	1 (5.3%)	1 (5.3%)	2 (10.5%)	5 (33.3%)	0	1 (9.1%)	0	0
Negative	12 (63.2%)	2 (10.5%)	5 (26.3%)	2 (13.3%)	3 (21.4%)	4 (36.4%)	2 (40.0%)	2 (25.0%)
5 th Exposure (Active Injection# 5) N ^b	9	9	7	8	8	9	8	8
Positive	2 (22.2%)	9 (100.0%)	4 (57.1%)	7 (87.5%)	5 (62.5%)	5 (55.6%)	3 (37.5%)	3 (37.5%)
Equivocal	4 (44.4%)	0	3 (42.9%)	1 (12.5%)	1 (12.5%)	3 (33.3%)	2 (25.0%)	3 (37.5%)
Negative	3 (33.3%)	0	0	0	2 (25.0%)	1 (11.1%)	3 (37.5%)	2 (25.0%)

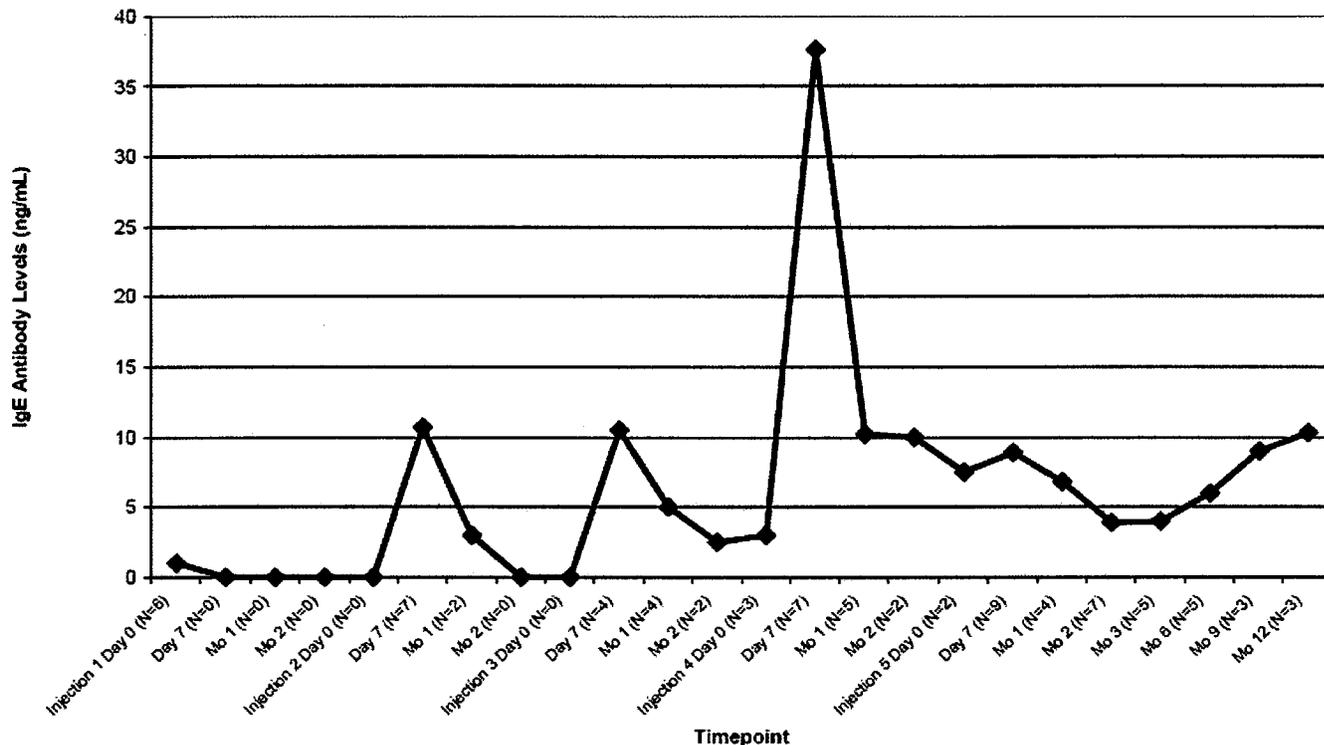
Results were reported as positive (>1 ng/mL) or naïve (<1 ng/mL).

a For placebo, the Injection 2-Day 0 value is used for Active Injection 1-Baseline/Pre-Admission.

b Number of patients who had immunological test results at a visit.

Reference: CSR of Study DUPY-202, Pages 58-59.

Figure 1: Mean IgE (ng/mL) levels in patients who received 5 AA4500 injections and had a positive IgE response in Study DUPY-202



Reference: CSR of Study DUPY-202, Pages 58-59.

Potential for Cross-Reactivity

What if anti-product antibodies were cross-reactive to endogenous proteins, such as MMPs? As noted in Section 3, above, several MMPs have 24 to 53% sequence homology to AUX-I and AUX-II. MMP expression and activity are increased in tissue injury and inflammatory disease processes, particularly through regulation of barrier function, cytokine/chemokine activity, or gradient formation. Although knock-out mouse models have limitations in terms of the translatability of results in already mature systems—as knocking out genes early in development may allow for compensatory mechanisms not available later—there are a number of MMP knock-out mouse models available. These models demonstrate a complex phenotype that makes it difficult to predict what might arise from MMP inhibition, as it appears that MMPs can either protect against or contribute to pathology in inflammatory processes [Manicone 2008].

Although not conclusive, there does not appear to be a trend toward increased AEs with successive injections (see Table 12 below). Since all patients were anti-product antibody positive after the 3rd or 4th injection, the lack of increase in AEs is somewhat reassuring. Furthermore, there was no increase in patients experiencing pre-defined clinically significant laboratory abnormalities observed with increasing exposure (see Table 13, below), as evidenced by similarly low numbers of abnormalities in the updated safety data. Thus far, the

data submitted do not suggest that the development of anti-product antibodies correlates with adverse clinical outcomes.

Table 12: Most Frequently Reported Treatment-Related AEs, by Number of Injections

Preferred Term ^b	AA4500 0.58 mg							
	Injection 1 (N=1082)	Injection 2 (N=639)	Injection 3 (N=420)	Injection 4 (N=250)	Injection 5 (N=157)	Injection 6 (N=41)	Injection 7 (N=27)	Injection 8 (N=14)
Number (%) of subjects with ≥ 1 treatment-related AE	1028 (95.0)	603 (94.4)	381 (90.7)	230 (92.0)	139 (88.5)	36 (87.8)	25 (92.6)	13 (92.9)
Peripheral edema	727 (67.2)	406 (63.5)	256 (61.0)	165 (66.0)	110 (70.1)	30 (73.2)	21 (77.8)	11 (78.6)
Contusion ^a	514 (47.5)	238 (37.2)	125 (29.8)	71 (28.4)	48 (30.6)	12 (29.3)	10 (37.0)	4 (28.6)
Injection site pain	346 (32.0)	171 (26.8)	112 (26.7)	55 (22.0)	39 (24.8)	11 (26.8)	7 (25.9)	4 (28.6)
Pain in extremity	278 (25.7)	142 (22.2)	78 (18.6)	42 (16.8)	21 (13.4)	7 (17.1)	6 (22.2)	2 (14.3)
Injection site hemorrhage	275 (25.4)	176 (27.5)	109 (26.0)	66 (26.4)	38 (24.2)	7 (17.1)	3 (11.1)	3 (21.4)
Tenderness	221 (20.4)	101 (15.8)	60 (14.3)	41 (16.4)	17 (10.8)	4 (9.8)	4 (14.8)	1 (7.1)
Injection site swelling	179 (16.5)	117 (18.3)	84 (20.0)	49 (19.6)	26 (16.6)	6 (14.6)	2 (7.4)	2 (14.3)
Ecchymosis	140 (12.9)	73 (11.4)	54 (12.9)	25 (10.0)	14 (8.9)	6 (14.6)	1 (3.7)	2 (14.3)
Pruritus	40 (3.7)	50 (7.8)	50 (11.9)	25 (10.0)	25 (15.9)	9 (22.0)	3 (11.1)	2 (14.3)
Skin laceration	76 (7.0)	27 (4.2)	16 (3.8)	11 (4.4)	5 (3.2)	2 (4.9)	0 (0.0)	0 (0.0)
Lymphadenopathy	91 (8.4)	29 (4.5)	15 (3.6)	7 (2.8)	2 (1.3)	0 (0.0)	1 (3.7)	0 (0.0)
Blood blister	50 (4.6)	40 (6.3)	10 (2.4)	4 (1.6)	4 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)
Axillary pain	47 (4.3)	17 (2.7)	7 (1.7)	3 (1.2)	1 (0.6)	0 (0.0)	0 (0.0)	1 (7.1)
Hematoma	39 (3.6)	20 (3.1)	5 (1.2)	2 (0.8)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site pruritus	17 (1.6)	15 (2.3)	19 (4.5)	15 (6.0)	9 (5.7)	1 (2.4)	2 (7.4)	0 (0.0)
Injection site vesicles	24 (2.2)	16 (2.5)	6 (1.4)	4 (1.6)	2 (1.3)	0 (0.0)	1 (3.7)	0 (0.0)
Lymph node pain	24 (2.2)	12 (1.9)	5 (1.2)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Erythema	16 (1.5)	14 (2.2)	9 (2.1)	4 (1.6)	1 (0.6)	1 (2.4)	0 (0.0)	0 (0.0)
Pain	21 (1.9)	11 (1.7)	7 (1.7)	5 (2.0)	3 (1.9)	1 (2.4)	1 (3.7)	1 (7.1)
Arthralgia	25 (2.3)	5 (0.8)	3 (0.7)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Swelling	19 (1.8)	10 (1.6)	6 (1.4)	3 (1.2)	2 (1.3)	0 (0.0)	1 (3.7)	0 (0.0)
Joint swelling	16 (1.5)	5 (0.8)	1 (0.2)	9 (3.6)	2 (1.3)	1 (2.4)	0 (0.0)	0 (0.0)
Edema	12 (1.1)	7 (1.1)	7 (1.7)	5 (2.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Blister	17 (1.6)	7 (1.1)	2 (0.5)	3 (1.2)	3 (1.9)	0 (0.0)	1 (3.7)	0 (0.0)

Note: Includes TEAEs occurring in ≥ 2.0% of subjects with a start date on or after the date of the first injection of AA4500 0.58 mg to the Day 30 visit after the last injection of AA4500 that had a relationship to study drug of either possible, probable, or missing. If the Day 30 visit was missing, then the next available visit after the Day 7 visit after the last injection was used.

a Includes all subjects who received at least 1 injection of AA4500 0.58 mg.

b Preferred term was coded using MedDRA dictionary (Version 8.0). An AE was counted only once if occurred multiple times for the same injection cycle, but counted multiple times if occurred within different injection cycles.

c 1 subject's report of contusion (considered treatment related) was mapped to musculoskeletal and connective tissue disorders SOC (applies to Injection 1); all other reports of contusion were mapped to injury, poisoning and procedural complications SOC.

Data source: ISS Table 14.2.19.1

Source: Table 32 of ISS

Table 13: Sponsor-defined clinically significant laboratory abnormalities

Laboratory Parameter	SI Criteria	Placebo N=125		AA4500 0.58 mg N=974			
		BLA Submission		BLA Submission		Safety Update	
Hematology		n ^b	N (%)	n ^b	N (%)	n ^b	N (%)
Hematocrit	CS+: ≥ 0.6 L/L	120	0 (0.0)	908	0 (0.0)	924	0 (0.0)
	CS-: ≤ 0.3 L/L	120	0 (0.0)	908	1 (0.1)	924	1 (0.1)
Hemoglobin	CS+ ≥ 190 g/L (female)	120	0 (0.0)	911	0 (0.0)	927	0 (0.0)
	≥ 200 g/L (male)						
Platelets	CS-: ≤ 100 g/L (female)	120	0 (0.0)	911	4 (0.4)	927	4 (0.4)
	≤ 110 g/L (male)						
Chemistry	CS+: ≥ 650 G/L	120	0 (0.0)	906	1 (0.1)	923	1 (0.1)
	CS-: ≤ 100 G/L	120	0 (0.0)	906	3 (0.3)	923	4 (0.4)
BUN	CS+: ≥ 12 mmol/L	120	1 (0.8)	911	8 (0.9)	925	9 (1.0)
Creatinine	CS+: ≥ 300 μmol/L	120	0 (0.0)	911	0 (0.0)	925	0 (0.0)
ALT (U/L)	CS+: > 3xULN	120	1 (0.8)	908	5 (0.6)	924	6 (0.7)
AST (U/L)	CS+: > 3xULN	120	1 (0.8)	908	6 (0.7)	923	6 (0.7)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CS+ = clinically significant high; CS- = clinically significant low; ULN = upper limit of normal

^a Includes all subjects who received at least 1 injection of AA4500 0.58 mg.

^b Number of subjects with at least 1 postbaseline measurement of the analyte. Percents were based on this count.

Data source: Safety Update Table 14.1.12 and ISS Table 14.1.14

Source: Table 13 of 120-day Safety Update, 5/18/09 submission

- **Discussion of primary reviewer's comments and conclusions**

Dr. Brodsky has concluded that AA4500 has an acceptable safety profile based on the data in this submission. AA4500 injection is likely to cause local adverse reactions related to its mechanism of action, including edema, contusions, and pain in the injected extremity. Severe adverse reactions, such as tendon ruptures, were uncommon and no significant clinical hypersensitivity events were observed. The relative homogeneity of the professional background of study investigators raises questions regarding generalizability of study results, particularly since efficacy and safety of the product is reliant on the product being injected in an appropriate manner and in appropriate locations. To further address these questions, Dr. Brodsky is recommending a postmarketing study requirement of a large simple trial to assess for the risk of SAE of the injected extremity, including tendon ruptures, when a broad range of healthcare professionals inject AA4500. He also recommends the study be of sufficient duration to evaluate long-term safety (e.g., risk of hypersensitivity events with repeated treatment courses over longer periods) and contracture recurrence.

- **Highlight differences between CDTL and review team with explanation for CDTL's conclusion and ways that the disagreements were addressed**

I concur with Dr. Brodsky that AA4500 has an acceptable safety profile and that the risk:benefit profile of AA4500 is favorable for the treatment of Dupuytren's contractures.

How best to handle the issue of generalizability of study results was a matter of extensive internal discussions that occurred after the Arthritis Advisory Committee meeting, including the review team and the Office of Surveillance and Epidemiology (OSE). If current clinical practice patterns hold true, then most of the healthcare professionals administering Xiaflex to Dupuytren's patients will in fact be either hand surgeons or orthopedic surgeons with an extremity focus. If this is the case, then efficacy and safety results would be expected to vary in a manner consistent with the difference between clinical trial results for any product versus the results for that product seen in clinical practice. In fact, if a postmarketing study requirement of a large simple trial was enacted, that large simple trial is very likely to enroll mostly hand surgeons and orthopedic surgeons, as these professionals would be the most likely early adopters of Xiaflex use if approved. Thus the goal of the postmarketing study—to assess differences in safety relative to background professional training—would not be achievable unless targeted efforts were made to enroll professionals of other backgrounds, which may not be consistent with normal clinical practice patterns. A postmarketing requirement for an epidemiology study, e.g., an evaluation of healthcare databases, would be unlikely to provide useful information for similar reasons—the data will reflect the efficacy/safety of the product in the hands of hand surgeons and orthopedic surgeons and will not address the generalizability concern driving the postmarketing requirement.

For the safety concern of the potential of repeated Xiaflex treatment courses to result in serious hypersensitivity reactions, Agency experts (DPAP) have determined that a postmarketing study is impractical and unlikely to provide meaningful results, and I concur.

The concern driving Dr. Brodsky's recommendation for a long-term assessment of contracture recurrence is not technically a safety concern, as contracture recurrence is part of the natural history of the disorder. While such an assessment is certainly of interest, in particular to address the question of whether Xiaflex injection would be similar to surgical options with respect to long-term recurrence, the question is academic in nature, as it is clear that the risk:benefit profile of an effective non-surgical alternative would be favorable, even if data ultimately show that time to recurrence is less than that for surgery.

In light of these considerations, I do not believe that a clinical postmarketing study requirement would be useful to address the safety concerns of tendon rupture or the potential for hypersensitivity and therefore do not recommend clinical postmarketing studies based on the currently available information. The review team and OSE are aware of this and have concurred that this is a reasonable approach.

- **Discussion of notable safety issues (resolved or outstanding)**

Because of the serious risk of tendon rupture (and subsequent requirement for surgical correction) and the potential serious risk of hypersensitivity reactions, the review team and OSE have determined that a risk evaluation and mitigation strategy (REMS) is warranted, and I concur. See Section 13, below, for additional details of the recommended REMS elements and assessments.

9. Advisory Committee Meeting

A meeting of the Arthritis Advisory Committee (AAC) was convened on September 16, 2009 to discuss this BLA. In addition to the standing members, the panel for this AAC included 3 hand surgeons and two members of the Drug Safety and Risk Management Advisory Committee. A summary of the questions asked of the panel, and the ensuing discussion, follows (adapted from the summary minutes of the meeting):

Question 1: Investigator training in the clinical studies included injection technique instruction via manuals and DVDs, workshops, and investigator meetings. This may be more extensive than the training proposed for the education of healthcare professionals in clinical practice if Xiaflex is approved. Please discuss the adequacy of the proposed training.

- *Some members commented that clinicians may not pay full attention to the training provided through the DVD and recommended that a check be put in place to ensure completion of the training process.*
- *Some members commented that the proposed training was not sufficient for many rheumatologists to perform the procedures. Other members disagreed and stated that the proposed training was adequate for rheumatologists or other medical specialists to inject Xiaflex.*
- *Some members commented that the proposed training was adequate for those clinicians who are knowledgeable of the anatomy of the hand and comfortable with performing the procedure. One member commented that it was necessary for the Sponsor to provide tutorials or models to demonstrate*

Xiaflex injections and finger extension procedures to those rheumatologists not familiar with the anatomy of the hand.

- *Some members stated that other office procedures (e.g., injections for varicose veins, steroid injections of the hand for trigger fingers) do not require credentialing and access to these procedures are not restricted by the FDA.*

Question 2: In view of the data available for safety and efficacy, do you recommend approval of Auxilium's Xiaflex for the treatment of patients with advanced Dupuytren's Disease?

Vote: **Yes=12** **No = 0** **Abstain = 0**

- *Members agreed that Xiaflex was beneficial in the treatment of Dupuytren's contracture and met an unmet need. Many members stated that the benefit/risk ratio was positive.*

Question 3: Depending on your response to Question 2, please address the following questions:

Question 3a: If you recommend approval, what additional studies, if any, should be conducted post-approval to further assess the safety of Xiaflex?

- *One member noted that a mandatory registry of patients may help determine whether the proposed physician training was adequate and would be needed to monitor the safety of Xiaflex long-term. Other members stated that any restriction on the use of Xiaflex including a mandatory patient registry would be onerous and restrict access to Xiaflex, and the decision to inject Xiaflex should be left to each physician. Other members noted that they were opposed to a mandatory registry and felt that the necessary information could be gained through a Phase 4 post marketing study.*
- *Some members recommended active data mining of Xiaflex-associated events in healthcare databases.*
- *Some members commented that a post marketing study would be helpful to address data gaps pertaining to efficacy and safety with a broader range of administering physicians, and to address questions of long-term efficacy (i.e. contracture recurrence) and safety (i.e. risks of hypersensitivity with repeated exposures over extended periods).*

Other Comments from Committee Members:

- *Some members commented that it would be difficult to monitor Xiaflex-treated patients in the office setting as those that do well after treatment may not be willing to return for follow up visits. Other members stated that patients with serious complications (e.g., tendon ruptures) would not likely be lost to follow-up.*
- *A few members noted that a standardized national consent form should be developed to inform all patients of the risks of Xiaflex injection; however, others noted that this may not be feasible.*

- *Some committee members stated that voluntary registries in current use in the United States do not provide adequate information.*
- *One member was concerned about the clinical implications of high IgE titers following Xiaflex injections.*
- *Some members expressed concern regarding off-label use of Xiaflex for different indications including the treatment of Peyronie's disease, adhesive capsulitis, scarring, or plantar fasciitis.*
- *One member expressed concerned that Xiaflex would be used in Dupuytren's patients with mild disease severity (e.g., patients with less than a 20 degree contracture, patients without functional impairment).*
- *One member noted that of 8 Xiaflex-treated patients, 6 had recurrences after long-term follow-up.*
- *Some members commented that the annual number of Xiaflex injections and finger manipulations may be an important fact in the proficiency of the procedure.*
- *Some members were concerned about non-responders. Dr. Thomas Kaplan, a hand surgeon who was an investigator in several Xiaflex studies and who presented for Auxilium at the AAC, stated that non-responders could be limited by injecting only patients with a palpable cord.*
- *Some members were concerned about the difficulty of repairing a Xiaflex-associated tendon rupture. Dr. Kaplan stated that in general these tendon ruptures are difficult to repair and may require two surgical procedures.*

10. Pediatrics

AA4500 received orphan designation for Dupuytren's, thus the requirements of the Pediatric Research Equity Act (PREA) do not apply. Furthermore, Dupuytren's disease does not occur in children.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**—No issues were identified.

- **Exclusivity or patent issues of concern**

This product is covered by US patent number RE39941, which expires on August 22, 2014. The applicant is also claiming orphan exclusivity for AA4500.

- **Financial disclosures**

Two investigators may receive royalties if the product is approved: Drs. Hurst and Badalamente. Dr. Hurst's site was inspected. Dr. Badalamente did not participate in AUX-CC-857 or AUC-CC-859.

- **Other GCP issues**—No issues were identified.
- **DSI audits**

From the consult review by Roy Blay and Tejashri Purohit Sheth:

Three clinical sites and the Applicant’s records were assessed by the Division of Scientific Investigation. The clinical sites were selected on the basis of the highest enrollment with the greatest treatment effect-size in favor of the product. Preliminary results of the inspection are shown in Table 14 below.

Table 14: DSI Inspection results by site

Name of CI, Location	Protocol #/ # of Subjects/	Inspection Dates	Final Classification
Lawrence Hurst, M.D. SUNY at Stony Brook Health Sciences Center, T-18 Stony Brook, NY 11794-0001	DUPY 303A / 35 and AUX-CC-857/ 28	17 Jun-6 Jul 2009	Pending. Interim classification is VAI.
Vincent Hentz, M.D. 770 Welch Road, Suite 400 MC 5715 Stanford University Hand and Upper Extremity Surgery Palo Alto, CA 94304	AUX-CC-857/ 37	28 May-16 Jun 2009	Pending. Interim classification is VAI.
F. Thomas Kaplan, M.D. Indiana Hand Center 8501 Harcourt Road Indianapolis, IN 46280	AUX-CC-857/ 25	17-19 Jun 2009	Pending. Interim classification is NAI.
Auxilium Pharmaceuticals, Inc. 40 Valley Stream Parkway, Malvern, PA 19355 Benjamin Del Tito, Jr., Ph.D. Ph: (484) 321-5989	DUPY 303A and AUX-CC-857	4-7 Aug 09	Pending. Interim classification is NAI.

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;
 EIR has not been received from the field and complete review of EIR is pending

At Dr. Hurst’s site, complete physical examinations as required by protocol were not performed for any of the enrolled subjects. However, DSI considers the data acceptable in support of efficacy and safety, as key components of the physical examination as pertinent to efficacy were conducted. At Dr. Hentz's site, eight subjects did not have complete goniometric data. Otherwise, the data generated by the clinical sites of Drs. Hurst, Hentz, and Kaplan appear acceptable in support of the application.

- **Other discipline consults**—Allergy/Immunology consult was obtained; see Section 8 immunogenicity section above for details.
- **Any other outstanding regulatory issues**—None.

12. Labeling

- **Proprietary name**

Xiaflex is the proposed proprietary name for AA4500. This name was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and by the Division of Drug Marketing Advertising and Communications (DDMAC) and was found to be acceptable.

- **Address important issues raised by brief discussion of DDMAC and OSE Division comments.**

Representatives from DDMAC and the OSE have been present at the labeling meetings for this BLA. No major issues were identified; however refinements and clarifications of the package insert were discussed and effected.

- **Physician labeling**

1. Dosage and Administration:

- The applicant proposes.

(b) (4)

(b) (4) Dr. Brodsky

proposes to modify this to “XIAFLEX should be administered by a physician experienced in injection procedures of the hand and in the treatment of Dupuytren’s contracture.” I concur with Dr. Brodsky’s clarifications. The Advisory Committee panel concluded that restricting the administration of the product to physicians of certain specialties (e.g., hand surgeons) would be unnecessarily restrictive, and the review team concurs.

- The review team recommends revisions to the injection and finger extension procedure sections of the dosage and administration section to enhance clarity.

2. Warnings:

- The applicant proposes warnings regarding tendon ruptures, use in patients with coagulation disorders, and potential for allergic reaction. The review team concurs that these three basic issues should be included in the Warnings section, but would revise the labeling to include more detail.

3. Clinical Studies section:

(b) (4)

- The secondary endpoint of mean percent decrease from baseline in the degree of contracture may be useful to clinicians in estimating treatment effect in a typical group

of patients; thus the review team concurs that these endpoint results may remain in the label.

Additional revisions and clarifications are recommended by the review team throughout the label.

- **Highlight major issues that were discussed, resolved, or not resolved at the time of completion of the CDTL review.**

Labeling negotiations with the applicant have not yet been completed at the time of this review.

- **Carton and immediate container labels** (if problems are noted)—no problems noted.
- **Patient labeling/Medication guide** (if considered or required):

A medication guide will be required as part of the REMS for Xiaflex. The submitted patient information labeling is inadequate and will need to be revised and resubmitted as a medication guide.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I concur with the BLA 125338 review team and recommend approval, with revisions to the proposed labeling.

- **Risk Benefit Assessment**

Dr. Brodsky has concluded that the clinical data in this submission support the conclusion that the risk:benefit profile of AA4500 injections for the treatment of Dupuytren's contracture is favorable, and I concur. The Advisory Committee panel also determined this to be the case when they recommended approval. When performed by study investigators, intralesional injections of AA4500 were highly efficacious in effecting contracture reduction with a low risk of serious injury to the injected extremity.

As shown in Table 15, below, in studies AUX-CC-857 and -859, two patients were treated with up to 3 injections of AA4500 for every patient achieving almost complete contracture reduction (0 to 5 degrees). In contrast, 125 patients were treated for every tendon rupture occurrence in these trials. Local adverse reactions, related to the mechanism of action of the product, were common, and observed in almost all patients receiving AA4500 injections. No serious hypersensitivity events were observed in the clinical trials.

It would be expected that these highly favorable results may not be replicated in clinical practice, where both patients and their injectors will be less highly selected and the ratio of

success to severe adverse event may be reduced. This question does not preclude approval, as the benefit:risk ratio is highly favorable, thus an anticipated reduction in the ratio would still not alter the overall favorable conclusion.

Table 15: Risk:Benefit Summary of AUX-CC-857 and -859 Study Results (Table 1.1 from Dr. Brodsky's review)

Possible Benefit			
	Xiaflex	Placebo	Number Needed to Treat (NNT)
Patients who had a contracture reduction to 0° to 5°	150/248 (60%)	8/124 (6%)	~ 2
Patients who had a ≥ 50% decrease in contracture from baseline	207/248 (83%)	15/124 (12%)	~ 1
Possible Risk			
	Xiaflex	Placebo	Number Needed to Harm (NNH)
Local AEs (e.g., edema, contusion, extremity pain)	243/249 (98%)	61/125 (49%)	~ 1*
Tendon Ruptures	2/249 (1%)	0/125 (0%)	~ 125
Other SAEs involving the injected extremity (not tendon ruptures)	3/249 (1%)	0/125 (0%)	~ 83

1 The benefit and risk calculations were based on the efficacy and safety results of the pooled pivotal trials through Day 90 (Studies 57 and 59). The Xiaflex denominator for the benefits was based on the number of patients in the primary efficacy population (n=248) and the Xiaflex denominator for the risks was based on the number of patients in the primary safety population (n=249). The mean (±SD) number of Xiaflex injections given in the pivotal trials through Day 90 was 1.7 (±0.8) injections.

* The NNH for local reactions was ~ 1 because the incidence of local reactions in patients not given Xiaflex injections would likely be 0%.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

A REMS is necessary for Xiaflex to ensure the benefits of the drug outweigh the risks of tendon rupture and other serious adverse events affecting the injected extremity, and the potential risk of serious hypersensitivity reactions.

The REMS should include:

1) A Medication Guide, because Xiaflex is a product that has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use, Xiaflex.

2) A Communication Plan targeted to healthcare providers who are likely to prescribe and administer Xiaflex, which will provide for the dissemination of information about the risks of Xiaflex, including tendon ruptures and hypersensitivity events (including anaphylaxis), how to properly inject Xiaflex and perform finger extension procedures, and the requirement to disseminate the Medication Guide with each Xiaflex injection.

Furthermore, the REMS assessment plan will include a requirement for a narrative summary and analysis of all cases of serious adverse events of the injected extremity and all cases of hypersensitivity reactions. The Applicant should submit their proposed targeted adverse event reporting forms in the REMS supporting document. The REMS assessment should also include a report on the status of healthcare provider professional background, the number and percentage of these providers who received educational materials, and an evaluation of the healthcare providers' understanding of proper injection technique as well as of the serious risks associated with Xiaflex injection. Additionally, the REMS assessment should include an evaluation of patients' understanding of the serious risks of Xiaflex and periodic reports on the distribution and dispensing of the Medication Guide.

- **Recommendation for other Postmarketing Requirements and Commitments**

I do not believe that a clinical postmarketing study requirement would be useful to address the safety concerns of tendon rupture or the potential for hypersensitivity and therefore do not recommend clinical postmarketing studies based on the currently available information. The review team and OSE are aware of this and have concurred that this is a reasonable approach. (See Section 8, above.)

The CMC review teams have recommended 2 postmarketing requirements and 14 postmarketing commitments, as enumerated in Section 3, above.

- **Recommended Comments to Applicant—None.**

REFERENCES:

Bayat A, DA McGrouther, "Management of Dupuytren's disease—clear advice for an elusive condition," *Ann R Coll Surg Engl* 2006; 88:3-8

Manicone AM and JK McGuire, "Matrix metalloproteinases as modulators of inflammation," *Seminars in Cell & Developmental Biology* 19 (2008) 34–41

(Chang and Ong, *Nephron Physiol* 2008; 108 pp. 1–7), and KIAA0319 is involved in neural migration, and may have a role in dyslexia (*Human Molecular Genetics* 2006, 15 pp. 1659–1666).

Rodriguez D, CJ Morrison, CM Overall, "Matrix Metalloproteinases: What don't they do? New substrates and biological roles identified by murine models and proteomics," *BBA-Molecular Cell Research* (2009)

Shaw RB et al., "Dupuytren's Disease: History, Diagnosis, and Treatment," *Plast. Reconstr. Surg.* 2007, 120:44e

Thurston AJ, "Dupuytren's Disease," *Journal of Bone & Joint Surgery (Br)*, 2003; 85-B:469-77