CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125338

SUMMARY REVIEW

Summary Basis for Regulatory Action

Date	February 2, 2010
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	125338
Applicant Name	Auxilium Pharmaceuticals Inc.
Proprietary / Established (USAN) Names	Xiaflex Collagenase clostridium histolyticum
Dosage Forms / Strength	Local injection Lyophilized powder with diluent, 0.58 mg/injection, 0.9 mg/vial
Proposed Indication(s)	Advanced Dupuytren's Disease
Action:	*Approval*

1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding collagenase clostridium histolyticum (CCH) for the orphan indication listed above and I refer the reader to the reviews in the action package for a more detailed discussion. CCH is a fixed ratio mixture of two purified collagenolytic enzymes produced by Clostridium histolyticum for use in the non-surgical treatment of Dupuytren's contractures. Dupuytren's contracture is a hand deformity in which collagen deposition occurs in the palmar fascia connective tissue under the skin forming a thick cord that ultimately results in a fixed flexion contracture of one or more fingers that can be quite debilitating complicating everyday activities. Usually the ring and little finger are most commonly affected, although other digits can be involved. Usual therapy consists of surgery or needle aponeurotomy, neither of which is curative. Surgery, depending on the technique and how extensive the disease is, can be quite arduous with a prolonged recovery and rehabilitation period. CCH was developed as a non-surgery alternative consisting of injection of collagenase enzymes into the cord which results in enzymatically-mediated fasciotomy, dissolving the cord and freeing any tendon entrapment. This type of procedure would be anticipated to have minimal invasion of the tissue and require less rehabilitation than a surgical procedure.

The sponsor has proposed administration of up to 3 injections of 0.58 mg per cord at 4-week intervals. After each injection, if release does not spontaneously occur, a finger extension procedure is recommended to finish disruption of the cord. The application package demonstrated that CCH was effective and safe if used appropriately, although the patients have not yet been followed long enough to see how reoccurrence rates may compare with historical rates of surgical patients. In any event, this treatment requires significantly less rehabilitation and offers patients an important non-surgical alternative and I recommend approval.

Efficacy

Efficacy was evaluated by two randomized, double-blind, placebo-controlled studies of 374 subjects. The results are thoroughly discussed in Drs. Brodsky, Norton and Okada's reviews. The primary endpoint was the proportion of subjects achieving a reduction in contracture to five degrees or less, 30 days after the last injection. Both metacarpophalageal (MP) and interphalangeal (PIP) joints were studied and were represented in both the CCH and placebo groups. Studying both of these joint is important as historical results from surgical studies suggest that lesions affecting MP joints are more amenable to correction than those affecting PIP joints.

The two tables below from Dr. Okada's review demonstrate the results (pages 15-16).

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 1: 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	n=103	n=45	n=21
	64%	7%	44%	5%
First injection[4]	n=203	n=103	n=45	n=21
	39%	1%	27%	5%
Second injection[4]	n=99	n=100	n=22	n=19
	35%	1%	27%	0%
Third injection[4]	n=45	n=91	n=8	n=18
	36%	6%	25%	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.

It is important to note that this treatment was administered by hand or orthopedic surgeons in most cases, with a few cases administered by rheumatologists. Subgroup evaluations did not detect a difference in efficacy results based on the professional background of the investigator.

These results demonstrate clear efficacy with CCH and also indicate that for those failing to have resolution with the first course of therapy, repeat dosing may provide benefit. As with the historical surgical studies, CCH treatments of affected MP joints enjoy greater success than affected PIP joints. Secondary endpoints also mirrored the results demonstrated above. Reoccurrence of symptoms was noted, and depending on the definition used, occurred in 4-11% of subjects followed for a mean of 7 months. It is difficult to compare these rates to those of historic controls for patients treated by surgery because of definitions used and follow-up periods, but this rate does not seem dissimilar to what would be expected by invasive techniques. Longer periods of follow-up will be necessary to further delineate how this treatment may compare to historically reported rates with surgery.

Safety

The following table from Dr. Okada's review details the exposures contained within the database (Page 17).

Table 2: 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.

Mean duration for follow-up was 9.5 months. The most concerning adverse event was tendon rupture, which occurred with about 1% incidence. This complication did not seem to be related to whether the investigator had surgical training or not, but very few non-surgeons were included in the database. The most common reaction was local inflammation and pruritus at the injection site.

100% of subjects developed antibodies to the collagenase. This did not appear to affect efficacy and there were not any indications of severe reactions or anaphylaxis; however immunogenicity may have accounted for the local pruritus noted above.

As noted in Dr. Okada's review, during the open public hearing at the Arthritis Advisory Committee (AAC) meeting, Dr. Robert Hamilton provided the results of IgE testing that had been conducted by a prior academic sponsor in early phase testing. In these studies a high percentage of patients had IgE antibodies and titers following intra-lesional injections which increased with the number of exposures. No cases of anaphylaxis were noted in any of these subjects. Although increasing IgE titers and increasing number of exposures in the clinical trials did not appear to result in clinical hypersensitivity events, the Division of Pulmonary and Allergy Products (DPAP) was consulted regarding the possible ramifications of the immunogenicity data.

Their conclusions were that, even though no cases of anaphylaxis were seen, the limited size of the safety database could not rule-out the potential for reactions at low frequencies. Given this apparently low frequency (if it occurs) and the limited number of patients that may be exposed, it would probably be difficult to power a study capable of assessing hypersensitivity risk attributable to CCH. As such, labeling should indicate our concern and a pharmacovigilance program initiated that will track hypersensitivity adverse events over time.

CCH has an acceptable safety profile when viewed in the context of its benefits. The most common reactions are local. There is a theoretical concern for systemic reactions that has yet to be expressed clinically. The most concerning safety issue is tendon rupture associated with its use, but fortunately this is uncommon.

There is concern internally by some that approval of CCH may lead physicians with less involvement in procedures to treat Dupuytren's contractures which may lead to a higher percentage of tendon rupture which has lead to the recommendation for a large safety study. Dr. Okada addresses this issue in detail in her review and I agree with her conclusions which are that a large safety study would most likely include the same type of practitioners that were included in the trials. As such, I do not think this study would be useful and feel that most of the concerns can be handled with the proposed REMS which would include a medication guide, a communication plan and an assessment plan. The assessment plan will include a requirement for a narrative summary of all cases of serious adverse events including potential hypersensitivity reactions and a report on the status of healthcare provider professional background, the number and percentage of providers receiving educational materials and their understanding of proper injection technique.

2. Conclusions and Recommendations

The data included in this application demonstrate that CCH will be an important non-surgical treatment for patients suffering with Dupuytren's contractures. Dr. Okada has a table that demonstrates that only two patients need to be treated to achieve one contracture reduction to less than five degrees. The optimism engendered by this potential efficacy needs to be somewhat modulated, however, as this database also indicates that for every 125 subjects treated there is one tendon rupture. Since these numbers come from a controlled environment, they will likely change when this drug is released to general practice. Also, we do not have data regarding reoccurrence rates except for limited time of observation, and increased reports of reoccurrences will likely happen with more accumulated time of observation. However, any safety concerns with this drug must also be viewed in the context of risks with the current standard of care. As noted by Dr. Rappaport, the current standard of care with surgery also has significant complications with reports of nerve injury, arterial injury/transaction, gangrene, amputation, Complex Regional Pain Syndrome, infection and healing difficulties.

Dupuytren's contractures can have a dramatic impact on people's lives, and the surgery is quite onerous and also has risks. As such, this is an important addition to medical therapy and should be approved.

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

Summary Review for Regulatory Action

Date	February 1, 2010
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia and Rheumatology Products
Subject	Division Director Summary Review
BLA #	125338
Applicant Name	Auxilium Pharmaceuticals Inc.
Date of Submission	February 27, 2009
PDUFA Goal Date	August 29, 2009
Proprietary Name / Established (USAN) Name	Xiaflex Collagenase clostridium histolyticum
Dosage Forms / Strength	Lyophilized powder with 0.3mg/mL calcium chloride dihydrate in 0.9% sodium chloride as a diluent, reconstituted for local injection/0.58 mg/injection, 0.9 mg/vial
Proposed Indication	For the treatment of advanced Dupuytren's Disease
Recommendation for action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Eric Brodsky, M.D.
Statistical Review	Jonathan Norton, Ph.D.; Dionne Price, Ph.D.; Thomas Permutt, Ph.D.
Pharmacology Toxicology Review	Asoke Mukherjee, Ph.D.; Daniel Mellon, Ph.D.; Paul C. Brown, Ph.D.
OBP Quality Review	Ashutosh Rao, Ph.D.; V. Ravichandran, Ph.D.; Baolin Zhang, Ph.D.; Jee Chung, Ph.D.; Kimberly Rains, Ph.D.; Kathy Lee, MS.; Fred Mills, Ph.D.; Susan Kirshner, Ph.D.; Amy Rosenberg, M.D..
Office of Compliance/DMPQ	Kalavati Suvarna, Ph.D.; Patricia F. Hughes, Ph.D.;
Microbiology Review	N/A
Clinical Pharmacology Review	Srikanth C. Nallani, Ph.D.; Suresh Doddapaneni, Ph.D.
DPAP	Brian Oscar Porter, M.D., Ph.D., M.P.H.; Susan Limb,

	M.D.; Badrul Chowdhury, M.D., Ph.D.
DDMAC	Mathilda Fienkeng; Twyla Thompson; Sangeeta Waswani; Michael Sauers
DSI	Roy Blay, Ph.D.; Tejashri Purohit-Sheth, M.D.; Constance Lewin, M.D., M.P.H.
CDTL Review	Sarah Okada, M.D.
OSE/DMEPA	Walter Fava, R.Ph.; Carlos M. Mena-Grillasca, R.Ph.; Denise Toyer, Pharm.D.; Carol Holquist, R.Ph.
OSE/DAEA	N/A
OSE/DRISK	Mary Dempsey; Christopher Wheeler, Pharm.D.;Kathy O'Connell, M.D.; Elizabeth Donohoe; Kate Heinrich, Latonia Ford; Kendra Worthy, Pharm.D.; Suzanne Berkman Robottom; Claudia Karwoski, Pharm.D.
OSE/DEPI	N/A

OBP=Office of Biotechnology Products
DMPQ=Division of Manufacturing and Product Quality
OND=Office of New Drugs
DPAP=Division of Pulmonary and Allergy Products
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK= Division of Risk Management
DAEA=Division of Adverse Event Analysis
CDTL=Cross-Discipline Team Leader
DEPI= Division of Epidemiology

1. Introduction

Dupuytren's Disease is a condition in which there is proliferation of fibroblasts with collagen deposition and myofibroblast contraction. This pathology leads to the development of fascial bands, or cords, that run longitudinally in the subcutaneous tissues of the palm. As these cords thicken and enlarge they draw the contiguous digital fascia in and resulting in flexion contractures of the affected digits. Surgery, either fasciectomy or fasciotomy, is the current mainstay of treatment when hand function becomes impaired. The sponsor has submitted this application in support of licensing for their collagenase clostridium histolyticum product, Xiaflex. Xiaflex is a fixed-ratio mixture of two purified collagenolytic enzymes produced by *Clostridium histolyticum*. When injected into the Dupuytren's cords the enzymatic action disrupts the collagen structure leading to a reduction in contracture; though mechanical manipulation of the contracted digit to fully disrupt the cords is often required post-treatment. The proposed dosage and administration is for up to three injections of 0.58 mg per cord, given at four-week intervals. Finger extension procedures are initiated approximately 24 hours after product injection if the treatment has not resulted in release of the contracture.

2. Background

During the development of Xiaflex and the review of this application, the main concerns that were raised by the Agency were related to the product's immunogenicity and whether the collagenases would result in damage to other collagen-containing tissues in the hand. Even though systemic absorption of Xiaflex is negligible, 100% of subjects developed anti-product antibodies after four injections. The sponsor has assessed the risk of hypersensitivity due to this effect and whether the anti-product antibodies cross react with endogenous matrix metalloproteinases (MMPs). Xiaflex is composed of Class I and II collagenases (AUX-I and AUX-II) which can work on different substrates and cleavage sites, exerting maximal effects against the types of collagen that make up the bulk of the Dupuytren's cords according to the sponsor.

Xiaflex has not received marketing approval in any country thus far. The Agency has granted Xiaflex an orphan designation for the treatment of advanced Dupuytren's Disease. The product review team has recommended a number of post-marketing requirements and commitments; but overall they are recommending approval along with the other review teams and Dr. Okada, the Cross-Discipline Team Leader. Dr. Brodsky has recommended an additional post-marketing study. However, Dr. Okada does not agree with that recommendation, for the reasons explicated in Section 13, and I concur with her assessment and recommendation. Dr. Mukherjee has recommended specific labeling regarding the potential for drug-drug interactions between Xiaflex and tetracycline-type antibiotics, as well as a clinical registry to assess immune-related adverse events. While Dr. Mellon concluded, based on discussions with the clinical review team, that the antibiotic interaction concern was not likely to be relevant, he deferred to the clinical review team regarding the safety registry. As noted above, Dr. Okada and the DPAP consultants do not think that an additional post-marketing study will provide any useful information above and beyond careful pharmacovigilance. Dr. Mukherjee also suggested that, based on the potential cross-reactivity of the antibodies seen in the animals exposed to Xiaflex, the labeling for Xiaflex should reflect a Category C pregnancy designation. However, Dr. Mellon disagrees with this recommendation as he considers it speculative.

3. CMC

During development Xiaflex was manufactured at three different sites. The current manufacturing site, Auxilium's facility in Horsham, PA, is the proposed commercial manufacturing site. Comparability data were submitted for products manufactured at these different sites and were determined to be adequate by the OBP review team. Calcium and zinc are required for the enzymatic activity of Xiaflex. The calcium is supplied in the sterile diluent packaged with the drug product (b) (4) Auxilium has provided adequate data to support a shelf life for Xiaflex of 24 months, stored at 5° C.

The original date for the facilities inspection was delaved (b) (4) A source for the contamination was identified and the sponsor submitted evidence of successful correction with a clean run. A late inspection a (b) (4). also resulted in clearance of this site. The sponsor claimed a categorical exclusion from the requirement for an Environmental Assessment and the products review team concluded that this request was appropriate.

The two collagenases in Xiaflex have a low but not insignificant amount of sequence homology with a number of human MMPs. Auxilium performed studies to investigate possible cross-reactivity between patient sera and human MMPs. For the five patient sera tested, there did not appear to be an appreciable inhibition of antibody binding to AUX-I; but one subject's serum did demonstrate MMP inhibition of antibody binding to AUX-II. The products review team identified two additional potentially homologous proteins not investigated by Auxilium. These two proteins have as much or greater similarity to one of the collagenases in Xiaflex. As such, the review team has recommended evaluation of the potential for cross reactivity against these two proteins as a post-marketing requirement. The Office of Compliance and the Office of Biologics Products have recommended a total of the one post-marketing requirement (PMR) and sixteen post-marketing commitments (PMCs). See Section 13 for a summary of the PMR and PMCs.

4. Nonclinical Pharmacology/Toxicology

Chronic toxicity studies, reproductive toxicity studies and mutagenic toxicity and carcinogenicity studies were not required for this product as Xiaflex will not be used on a chronic basis and there is no apparent systemic absorption in humans. The sponsor submitted mutagenicity assays, two multi-dose intravenous toxicity studies in rats, a local toxicity study in dogs, a fertility and embryofetal development study in rats, and sensitization studies in guinea pigs. While hepatic toxicity and injection site perivascular inflammation and fibrosis were noted in the intravenous studies, these findings are not relevant to the clinical setting considering the absence of significant systemic absorption. The local toxicity study was conducted after injection of Xiaflex into the dog penis in support of safety for use in Peyronie's disease. Injection site inflammation occurred with single and multiple dosing. Although AUX-I and AUX-II were only detectable in the plasma for 60 minutes after injection suggesting minimal systemic absorption, antibodies to both were noted in the serum even at Recovery Day 28. Immediate hypersensitivity reactions were not noted in the guinea pig experiments after challenge by the intraperitoneal or intracardiac routes of administration.

The drug product was not mutagenic in the standard battery of assays. However, the batch used in these studies was not the batch intended for marketing and, therefore, these studies are not relevant to the to-be-marketed product as the impurity profiles of these batches are not identical. There were no abnormalities noted in the fertility and embryofetal development study. The pharmacology/toxicology review team agreed that Segment I and III reproductive toxicology studies would not be necessary for this application due to the absence of systemic absorption in the clinical setting. However, Dr. Mukherjee recommended that the product be

labeled as Pregnancy Category C due to the presence of anti-product antibodies that may react with endogenous proteins. Dr. Mellon disagreed with Dr. Mukherjee's recommendation as noted on page 7 of his review:

> As the Division has concluded that the full battery of reproductive and developmental toxicology studies are not needed for this product due to a lack of detectable systemic exposure, and is not requiring the remaining studies from this battery, I do not think that a Pregnancy Category C is justified. Although virtually all individuals who have received XIAFLEX have developed anti-product antibodies, and there are some data that these antibodies may interfere with endogenous MMP activity (see product immunogenicity review completed by Dr. Mills), this is a theoretical concern and the current options listed in 21CFR§201.57 do not support the designation of a Pregnancy Category C for a theoretical concern. Nonetheless, I do think that it is reasonable to include some language to specifically raise the unknown clinical impact of the anti-product antibodies on the fetus.

I concur with Dr. Mellon's conclusion and recommendation.

Dr. Mukherjee has also recommended a post-marketing registry to monitor for immune-related adverse events occurring in conjunction with antibody development and labeling to recommend against the use of certain antibiotics such as tetracycline which have collagenase inhibitory properties in proximity to the administration of Xiaflex. On page 3 of Dr. Mellon's supervisory review he states:

> Dr. Mukherjee has noted that there is potential for tetracycline antibiotics to interfere with the efficacy of the enzyme. There are no clear data to demonstrate this one way or another for this product; however, upon further discussion with the clinical pharmacology and clinical review teams, the likelihood that systemic tetracycline will impact local tissue efficacy appears minimal. Therefore, the labeling does not need to include drug-drug interaction information on tetracycline.

I concur with Dr. Mellon's conclusion. In an addendum to his review, he states:

> I concur with Dr. Mukherjee that the nonclinical data will not provide useful information regarding the potential clinical significance of anti-product antibodies, should they form in patients administered this product. The option of a user registry to monitor for a potential association of the antibodies to the development of systemic or local inflammatory diseases following use of Xiaflex should be based on the strength of the clinical data reviewed by product immunology reviewer and the existing clinical safety database.

On page 12 of her review, Dr. Okada states:

> 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).

I concur with this decision.

5. Clinical Pharmacology/Biopharmaceutics

As the sponsor provided adequate data to document that Xiaflex is not absorbed systemically to any significant degree, studies of its metabolism, its pharmacokinetics in patients with renal or hepatic impairment, its interactions with other drugs and its effects on the QT interval were neither required nor performed.

6. Clinical Microbiology

No clinical microbiology data were necessary for this application.

7. Clinical/Statistical-Efficacy

The sponsor submitted six studies in support of efficacy. Three of these studies were not considered "pivotal" by the sponsor due to their small size and study design features. The sponsor proposed Study DUPY-303 (Study 03) as a pivotal trial, but the review team disagreed with this interpretation as Study 03:

- Enrolled patients at only one site
- Was terminated early and enrolled only 30% of the planned number of subjects
- Was conducted by an investigator with a potential conflict of interest
- Did not include appropriate statistical gate-keeping for secondary endpoints; and
- Did not include a prespecified plan to collect protocol violations

While I don't agree that the statistical concern raised by the clinical review team for secondary endpoints should necessarily result in this study being considered inadequate as primary support of efficacy, I do agree that the other four concerns relegate it to supporting status.

The two adequate and well-controlled studies, AUX-CC-857 (Study 857) and AUX-CC-859 (Study 859) were considered by the review team to provide the primary evidentiary basis in support of the efficacy of Xiaflex. Both studies were randomized, double-blind, placebo-controlled trials in subjects with a fixed flexion deformity resulting in an MP or PIP joint contracture of at least 20 degrees but less than or equal to 100 degrees for an MP joint or less than or equal to 80 degrees in a PIP joint, in at least one finger other than the thumb. Up to three injections of Xiaflex 0.58 mg or placebo were administered into a Dupuytren's cord at 4-week intervals. If the contracture persisted for 24 hours after an injection, the investigator performed a finger extension procedure in an attempt to rupture the cord. Both studies were multi-site; all sites for 857 were in the U.S. and all sites for 859 were in Australia. The primary outcome endpoint for the studies was the proportion of subjects achieving a reduction in contracture to 5 degrees or less by 30 days after the last injection.

The following two tables reproduced from pages 15 and 16 of Dr. Okada's review summarize the results of the primary and secondary outcome analyses:

Table 1: 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 2: 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 injection[4]	n=203 39%	n=103 1%	n=45 27%	n=21 5%
Second injection[4]	n=99 35%	n=100 1%	n=22 27%	n=19 0%
Third injection[4]	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.

As with surgical treatment of Dupuytren's disease, lesions affecting the MP joints appeared to be more amenable to correction than lesions affecting the PIP joints. Just over half of the subjects who responded to treatment did so after the first injection.

The results noted in the other clinical studies and the secondary outcome analyses from Studies 857 and 859 were generally supportive of the primary outcome analyses.

8. Safety

A total of 1082 subjects received at least one injection of 0.58 mg of Xiaflex. The following table reproduced from page 17 of Dr. Okada's review summarizes the exposure by number of injections:

Table 3: 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.

There were no deaths during the 90-day controlled portions of the pivotal studies. There were five deaths in the full safety database. Drs. Brodsky and Okada have concluded that these deaths were the result of underlying disorders and were not associated with exposure to Xiaflex and I concur with their conclusion.

Serious adverse events were uncommon. As would have been expected, there were three tendon ruptures in subjects treated with Xiaflex and none in the placebo subjects. One Xiaflex-treated subject developed Complex Regional Pain Syndrome, another potential adverse event seen in surgical treatment of Dupuytren's. Discontinuations were also uncommon. While the common adverse events occurred in nearly all of the Xiaflex-treated subjects and only half of the placebo-treated subjects, these events were predominantly reversible local treatment reactions and there were no other events of particular clinical concern.

Over 86% of subjects had anti-AUX-I and/or anti-AUX-II antibodies after the first injection and 100% had these antibodies after the fourth injection. However, I agree with Drs. Brodsky and Okada that these antibodies would not be likely to have any effect on efficacy due to the relative lack of blood flow to Dupuytren's lesions. There were no severe allergic reactions as a result of systemic hypersensitivity. There were seven events coded as hypersensitivity

reactions, four clearly unrelated to study drug and three mild injection site reactions thought to be related to Xiaflex administration. However, there were two cases of urticaria and several other generalized rashes all of mild to moderate severity. In addition, the incidence of pruritus was correlated with the number of injections. During the open public hearing portion of the advisory committee meeting held for this application, Dr. Robert Hamilton, a Johns Hopkins University immunologist provided the results of IgE testing following Xiaflex injections from early Phase 1 and 2 studies performed by academic investigators. In these studies, a high percentage of patients had drug-specific IgE antibodies and titers following the Xiaflex injections. However, the observation of these IgE antibodies may not be relevant to the current product, as the early trials were performed using collagenase prepared by a different manufacturer (b) (4), using a manufacturing process (b) (4)

To better understand the risk of systemic hypersensitivity reactions that might be associated with Xiaflex after approval, the Division of Pulmonary and Allergy Products (DPAP) was consulted. The following conclusions have been reproduced from page 2 of Dr. Porter's review:

> 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. 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.

Specifically in regard to cross-reactivity to endogenous proteins such as MMPs, on page 24 of her review, Dr. Okada notes that:

> Although not conclusive, there does not appear to be a trend toward increased AEs with successive injections...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..., 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.

9. Advisory Committee Meeting

This BLA was discussed at a meeting of the Arthritis Advisory Committee (AAC) on September 16, 2009. Three hand surgeons and two members of the Drug Safety and Risk

Management Advisory Committee were included as panel members in addition to the standing members of the AAC. The following questions were posed to the committee members:

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.

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?

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?

Question 3b: If you do not recommend approval, what additional data are needed to support approval?

In response to a vote on Question 2, the results were as follows:

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

Dr. Okada has summarized the responses overall and a transcript of the meeting is available on the FDA website:

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisDrugsAdvisoryCommittee/UCM186962.pdf.

There were a variety of opinions regarding Question 1 that ranged from some members expressing concern that some form of certification of training be required to others saying that the sponsor's proposed training was adequate and that attestation or credentialing should not be required as it would be onerous and potentially restrict access. Overall, most of the members felt that the training was appropriate and adequate for those physicians who would be likely to use Xiaflex to treat their patients with Dupuytren's contracture. Some members felt that a registry or post-marketing safety study would be helpful to better understand the risks of tendon rupture and/or hypersensitivity reactions. However, other members felt that these studies would not be any more helpful than standard post-marketing vigilance.

10. Pediatrics

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

11. Other Relevant Regulatory Issues

There are no other relevant regulatory issues.

12. Labeling

No major differences of opinion occurred during discussions regarding the product labeling. The Agency and the sponsor have concurred on appropriate language for the labeling.

13. Decision/Action/Risk Benefit Assessment

- Recommendation for Regulatory Action

  Approval

- Risk Benefit Assessment

  Auxilium has provided adequate evidence of the efficacy, safety and product quality for Xiaflex for use in the treatment of Dupuytren's contracture with a palpable cord. Xiaflex injections were highly efficacious in effecting contracture reduction. The risk of tendon rupture was low. With the current standard of care, surgical intervention, there have been numerous serious outcomes reported that include nerve injuries, arterial injury/transection, gangrene, amputation, Complex Regional Pain Syndrome, infection, wound healing difficulties and systemic complications. While there is a potential risk for clinically significant hypersensitivity reactions, none were seen in the clinical studies and this risk can be adequately addressed via product labeling, careful post-marketing pharmacovigilance, and the post-marketing risk evaluation and mitigation strategy (REMS) described below. While the product quality appears adequate for marketing, the product review team has recommended a number of post-marketing requirements and commitments which are summarized below. I agree with their recommendations.

  Dr. Brodsky has recommended an additional post-marketing study requirement for a large simple study to assess the differential risk of serious adverse events and long-term safety based on practitioner training and background, as well as to assess contracture recurrence. Dr. Okada disagrees with this recommendation for a number of reasons:

  - The investigators for this study would likely be the more highly trained hand surgeons and rheumatologists based on clinical practice patterns. Therefore, it would not provide the information it was designed to find.

  - As per the recommendations from the DPAP consultants, this study would be impractical and unlikely to provide meaningful results.

- Contracture recurrence is not a safety concern, but rather a part of the natural history of Dupuytren's disease. Therefore, this is an academic question and not appropriate for a post-marketing requirement.

I concur with Dr. Okada's conclusion that this study is not necessary.

- Recommendation for Postmarketing Risk Management Activities

The clinical review team and the OSE review team have recommended a REMS for Xiaflex in order to ensure that the benefits of the product outweigh the risks of tendon rupture and other serious adverse events affecting the injected extremity, as well as the potential risk of serious hypersensitivity reactions. The REMS should consist of a Medication Guide to inform patients of the potential risks and a Communication Plan to inform health care providers of those risks. The proposed REMS contains a number of REMS assessments that include assessment of the extent of Xiaflex use by physicians of different specialties as well as collection and analysis of serious adverse events occurring with the use of this product.

- Recommendation for Required Post-marketing Study Requirements

1) Submit an *in vitro* study of human sera from patients who have received multiple Xiaflex injections to evaluate the potential for cross-reactivity of anti-product antibodies (i.e., anti-AUX-I and anti-AUX-II) with endogenous human MMPs including MMP-1, MMP-2, MMP-3, MMP-8, MMP-13) with similar homology and relevance to the protein components of Xiaflex. This study should assess the frequency of inhibition of the enzymatic activity of these human proteins by anti-product antibodies and by neutralizing anti-product antibodies. This study should also be designed to assess whether repeated treatment courses of Xiaflex injection result in anti-product antibodies that are more persistent and cross-reactive to endogenous proteins compared to initial anti-product antibody responses.

- Recommendation for Postmarketing Study Commitments

2) 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 reconstituted drug product.

3) 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.

- 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

4) Qualify the bioburden test for in-process intermediates. The qualification should be performed using three different lots.

5) The endotoxin test was qualified using one lot of AUX-I and AUX-II intermediates, and one lot of drug substance. Perform additional qualification using two lots of AUX-I intermediate, AUX-II intermediate, and drug substance, and three lots of HIC eluate and TFF-1 concentrate, to demonstrate reproducibility of the test results.

6) 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.

- This PMC pertains to a lack of "challenging" container-closure data but is not an approvability issue because otherwise adequate data were submitted to support container-closure integrity.

7) 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.

- This PMC 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)

8) Evaluate the potential for cross-reactivity of anti-product antibodies with endogenous proteins polycystin I and KIAA0319.

9) Develop and validate an immune-based host cell protein (HCP) assay: After (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)

10) 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 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.

11) 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. 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.

12) 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.

13) Develop and validate the RP-HPLC method to quantify potential impurities for AUX I intermediate, DS, and DP.

14) 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.

15) 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).

16) 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.

17) Include an accelerated or stress stability condition as part of the annual stability program for the drug substance and drug product. This is not an approvability issue because Auxilium has performed comprehensive forced degradation studies (b) (4)