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*APPLICATION NUMBER:*  
**125338**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

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Reviewer Name	Eric Brodsky, M.D. <i>Eric Brodsky</i> October 5, 2009
CDTL	Sarah Okada, M.D. <i>Sarah Okada</i> 10-5-09
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Established Name	Collagenase clostridium histolyticum
Trade Name	Xiaflex
Applicant	Auxilium Pharmaceuticals
Proposed Formulation	Lyophilized powder, reconstituted with supplied diluent
Proposed Dosing Regimen	Up to three 0.58 mg injections into a cord affecting a contracture given at 4-week intervals. Additional cords can be injected sequentially.
Proposed Indication	Advanced Dupuytren's disease

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# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

From a clinical perspective, recommend **approval** of Biologic License Application (BLA) 125338 for Xiaflex (collagenase clostridium histolyticum) for the treatment of **adult patients with Dupuytren's contracture (DC)**, with revisions to the proposed label. Recommend approval of up to 3 injections of Xiaflex (0.58 mg), given at 4-week intervals, into a palpable cord that is associated with a significant contracture of a metacarpophalangeal (MP) joint or a proximal interphalangeal (PIP) joint (additional cords can be injected sequentially). Recommend that Xiaflex should be administered by a healthcare professional experienced in injection procedures of the hand **and the treatment of Dupuytren's contractures**.

## 1.2 Risk Benefit Assessment

### Overview of the Clinical Program

Auxilium submitted BLA 125338 on February 27, 2009, to support the approval of Xiaflex for the **treatment of patients with advanced Dupuytren's disease**. Xiaflex consists of two microbial collagenases (AUX-I and AUX-II), isolated and purified from *Clostridium histolyticum*, which hydrolyze native collagen. When injected into Dupuytren's cords, the postulated mechanism of action is collagen lysis resulting in enzymatic disruption of the cord, leading to a reduction in contracture and improvement in range of motion of the affected joints. Auxilium's **proposed dosage and administration** for Xiaflex is up to 3 injections of 0.58 mg of Xiaflex per Dupuytren's cord, given at 4-week intervals. If an injection does not result in a meaningful reduction of the contracture by 24 hours, Auxilium recommends finger extension procedures to facilitate cord disruption. Additional cords are to be handled sequentially. There are currently no approved non-surgical treatments for Dupuytren's contracture (DC).

The primary support for the efficacy and safety of Xiaflex for the treatment of DC are from the results of two similarly-designed randomized, double-blind, placebo-control, multi-centered, 90-day Phase 3 trials — Studies 57 and 59. Study 57 enrolled patients at 16 U.S. sites with a total of 308 treated patients and Study 59 enrolled patients at 5 Australian sites with a total of 66 treated patients. In these two trials, patients must have had a fixed flexion contraction of an MP or PIP joint at least 20 degrees (°) but  $\leq 100^\circ$  (for MP joint) or  $\leq 80^\circ$  (for a PIP joint) caused by a palpable cord. Patients may have received up to 3 injections every 30 days on Days 0, 30, and 60 of Xiaflex or placebo directly into one cord that caused the contracture of the primary MP or PIP joint. If the contracture persisted 24 hours after the injection procedure, the investigator extended the treated finger in an attempt to rupture the cord (finger extension procedure). The primary efficacy endpoint for the pivotal trials (Studies 57 and 59) was the proportion of patients that achieved a reduction of the contracture of the primary joint (MP or PIP joint) to 0 to 5 degrees, 30 days after the last injection (clinical success) after up to 3 injections.

Additional support for the efficacy and safety of Xiaflex for the treatment of DC are from the results of four smaller randomized, double-blind, placebo-control trials — Studies 02, 03, 51, and 53. Six

open-label, uncontrolled studies of Xiaflex in patients with DC (Studies 04, 52, 54, 55, 56, and 58) were designed to collect safety data after one year of follow-up and to collect data on the durability of response (incidence of recurrence).

In the entire safety database (the controlled and uncontrolled portions of the 12 submitted Xiaflex studies), **1082 patients with 1780 Dupuytren's cords** received at least one intra-cord injection of the proposed Xiaflex dose, 0.58 mg, (**2630 Xiaflex injections**). The mean ( $\pm$ SD) duration of safety follow-up for these 1082 patients was 9.5 ( $\pm$ 4.6) months. In addition, 22 and 18 patients received one intra-cord injection of a lower Xiaflex dose (0.29 mg and 0.145 mg, respectively). 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 Xiaflex and placebo into the cord affecting the primary joint, respectively.

#### Summary of Efficacy

Intra-cord injections of Xiaflex (0.58 mg) demonstrated efficacy for the treatment of DC, based on large absolute treatment margins of 57% and 39% compared to placebo injections for the primary efficacy endpoint (contracture reduction of the primary joint to 0° to 5° degrees after up to 3 injections) in Studies 57 and 59, respectively. In both trials, after up to 3 injections, Xiaflex treatment demonstrated significant improvements compared to the placebo group in the change from baseline in contracture degree and the change from baseline in range of motion.

#### Summary of Safety

No patients died in the placebo-controlled portions of the pivotal trials through Day 90. In the complete clinical development program for Xiaflex, there were a total of 7 deaths in patients who received intra-cord injections of 0.58 mg of Xiaflex and no deaths in a limited number of placebo-treated patients. It is not likely that the deaths were due to the Xiaflex injections since the reported causes of death were consistent with the underlying patient population and their comorbidities, the incidence of death did not increase with greater number of Xiaflex injections, most of these deaths occurred several months after the last Xiaflex injection, and there is no evidence of systemic Xiaflex exposure after intra-cordal Xiaflex injections.

In the controlled portions of the pooled pivotal trials through Day 90, 2% and 0% of the Xiaflex-treated and placebo-treated patients had a SAE that involved the treated extremity. In the controlled and uncontrolled portions of the 12 submitted Xiaflex studies, out of 1082 patients treated with 0.58 mg of Xiaflex (with a total of 2630 Xiaflex injections), 11 (1.0%) patients had SAEs that involved the injected extremity. Of these 11 SAEs, 3 were flexor tendon ruptures that occurred within 7 days of intra-cordal Xiaflex injection of the affected digit, required surgical correction, and were likely related to Xiaflex treatment. Although there are major limitations of cross study comparisons, it appears that the incidence of SAEs of the treated extremity observed in the Xiaflex studies, and the incidence of flexor tendon rupture in particular, does not appear to be out of proportion to the incidence of surgical complications following fasciectomy and/or fasciotomy for DC reported in the published literature.

In the controlled portions of the pivotal trials through Day 90, after up to 3 injections, two times as many Xiaflex-treated patients than placebo-treated patients had an AE (98% vs. 49%). The overwhelming majority of Xiaflex-associated AEs were local reactions (e.g., hand edema, contusion, hemorrhage, and extremity pain) and were likely related to Xiaflex injection.

Xiaflex treatment was associated with an increased proportion of mild allergic reactions (e.g., pruritus) compared to placebo treatment; however, there were no severe reactions, e.g., those associated with respiratory compromise, hypotension, or end-organ dysfunction. In the pivotal trials, almost all of the Xiaflex-treated patients had antibodies against AUX-I or against AUX-II after the first injection. However, there was no evidence of changes in efficacy or safety of Xiaflex based on antibody status.

### **Risk-Benefit Assessment**

Table 1.1 contains an estimate of the potential benefits versus risks of Xiaflex treatment based on selected efficacy and safety outcomes observed during the controlled periods of the pooled pivotal studies (Studies 57 and 59) after up to 3 injections of study medication. In the clinical trial setting, 2 patients needed up to Xiaflex treatment to have a clinically meaningful improvement in contracture reduction in 1 patient. One patient needed Xiaflex treatment to obtain the more modest benefit of improvement of 50% in the contracture degree in 1 patient. Also in the clinical trial setting, 1 patient needed Xiaflex treatment in order for one patient to have a local adverse reaction (e.g., edema, contusion, extremity pain, pruritus). Many patients needed Xiaflex treatment in order for one patient to have a tendon rupture or another SAE of the injected extremity.

The risk-benefit calculations do not compare Xiaflex treatment to current standard of care (surgery). Since causality was not assessed for the SAEs involving the injected extremity, the number needed to harm calculations may be an overestimation the risk of these events. On the other hand, since the overwhelming majority of investigators who performed the injections were hand or orthopedic surgeons who were thoroughly trained in Xiaflex injection procedures, the outcomes may underestimate the risks and overestimate the benefits if Xiaflex was used in a clinical practice setting.

The September 16, 2009 Arthritis Advisory Committee (AAC) voted 12:0 in favor of Xiaflex approval and stated that the benefits of Xiaflex outweigh the risks in the treatment of DC. Most members of the AAC **agreed that Auxilium's proposed labeling, training and education, and managed distribution plan** is sufficient to minimize the risks of Xiaflex-associated tendon ruptures. Most of the AAC members thought that a FDA-controlled restricted distribution program, e.g., elements to assure safe use (ETASU) in a Risk Evaluation and Mitigation Strategy (REMS), would be too burdensome and the decision to use Xiaflex should be left up to each physician. This reviewer agrees with these AAC **members that Auxilium's proposed education and managed distribution plan with modified labeling** is sufficient to minimize the risks of tendon ruptures.

Overall, this reviewer believes that the results support the efficacy and safety of intra-cordal injections of 0.58 mg of Xiaflex for the treatment of DC. The Xiaflex labeling should include the risks of serious local complications including flexor tendon ruptures. A post-marketing requirement (PMR) will help elucidate the risks of SAEs of the injected extremity for non-hand surgeons performing Xiaflex injections (see Section 1.4 Recommendations for Postmarket Requirements and Commitments).

**Table 1.1: Benefit-Risk overview after up to 3 intra-cord injections<sup>1</sup>**

<b>Possible Benefit</b>			
	<b>Xiaflex</b>	<b>Placebo</b>	<b>Number Needed to Treat (NNT)</b>
<b>Patients who had a contracture reduction to 0° to 5°</b>	150/248 (60%)	8/124 (6%)	~ 2
<b>Patients who had a ≥ 50% decrease in contracture from baseline</b>	207/248 (83%)	15/124 (12%)	~ 1
<b>Possible Risk</b>			
	<b>Xiaflex</b>	<b>Placebo</b>	<b>Number Needed to Harm (NNH)</b>
<b>Local AEs (e.g., edema, contusion, extremity pain)</b>	243/249 (98%)	61/125 (49%)	~ 1
<b>Tendon Ruptures</b>	2/249 (1%)	0/125 (0%)	~ 25
<b>Other SAEs involving the injected extremity (not tendon ruptures)</b>	3/249 (1%)	0/125 (0%)	~ 83

<sup>1</sup> 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%.

### 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Post-marketing Risk Evaluation and Mitigation Strategies are not recommended.

### 1.4 Recommendations for Postmarket Requirements and Commitments

A post-marketing requirement (PMR) is recommended “to assess a known serious risk” of Xiaflex — serious adverse reactions of the injected extremity including tendon ruptures. The majority of Xiaflex injections in the clinical database were performed by hand surgeons who were carefully selected and well-trained in the Xiaflex injection technique and finger extension procedures. The Xiaflex safety database from the controlled and uncontrolled portions of the 12 submitted Xiaflex studies was sufficient to assess the risk of SAEs of the injected extremity following Xiaflex injection by these well-trained hand surgeons. However, since Auxilium plans to market Xiaflex to other surgery specialists (i.e., orthopedic, plastic, and general surgeons) and non-surgeons (i.e., rheumatologists) and the safety database of Xiaflex injections by non-hand surgeons was limited; it is important to assess if the risk of SAEs of the injected extremity would increase after Xiaflex use by non-hand surgeons. To assess these serious risks, a large simple trial should be conducted, where physicians and their patients are enrolled irrespective of physician specialty, and given the training tools proposed for clinical practice, with a long-term (e.g., 5 year) follow up period to assess for serious reactions of the injected extremity, severe hypersensitivity events, and contracture recurrence. Efficacy and safety analyses by professional background and training of the healthcare provider should be performed. Although efficacy assessments will not be required for the PMR, data on contracture recurrence should be collected.

Although there were no severe allergic reactions in the clinical database, increasingly high titers of anti-product antibodies with successive injections raises the concern that severe allergic reactions may occur in the post-marketing setting. The Division of Pulmonary and Allergy Products (DPAP) was consulted regarding the need for a PMR to address this safety concern. This reviewer will defer to **DPAP's recommendations for the need for a PMR to assess severe allergic reactions.** DPAP's consult review is pending at this time.

There were limited follow-up data on the risk of contracture recurrence following successful treatment with Xiaflex (i.e., the mean follow-up period was about 7 months in the clinical database). A post-marketing commitment (PMC) is recommended to assess recurrence following successful treatment with Xiaflex. Since recurrence is **not a "serious risk"** of Xiaflex, but rather part of the underlying **disease process of Dupuytren's**, this post-marketing study would not meet the requirements for a PMR. This PMC could be achieved by collecting recurrence data as part of the PMR as described above.

## 2 Introduction and Regulatory Background

### 2.1 Product Information

**Proposed Trade Name (established name):** Xiaflex is the proposed trade name and collagenase clostridium histolyticum is the established name adopted by the United States Adopted Names (USAN) Council.

**Proposed Indication:** "Treatment of advanced Dupuytren's disease"

**Proposed Age Group:** Adult patients

**Proposed Dosage and Administration:** (b) (4)

Inject 0.58 mg into the Dupuytren's cord.

Administration of a local anesthetic agent prior to injection of Xiaflex is not recommended, as it may interfere with proper placement of the injection. Place the needle in the cord and inject one-third of the 0.58 dose into the area where the contracting cord is maximally separated from the underlying flexor tendons and where the skin is not intimately adhered to the cord. Withdraw the needle tip from the cord and reposition it in a distal location, injecting the second third and finally withdraw the needle again and injection the last third into a proximal location to the initial injection. Approximately 24 hours after injection, a finger extension procedure (apply moderate stretching pressure for 10 to 20 seconds) may be performed with local anesthesia, if needed, to facilitate cord disruption.

If the injection was not successful, two additional repeat injections (every 4 weeks) may be attempted for a total of 3 injections into the same cord. It is recommended that only one cord should be treated at a time. If the disease has resulted in multiple contractures, treatment of each cord should be undertaken in a sequential order.

**Chemical Class:** New Molecular Entity

**Description:** Xiaflex consists of two microbial collagenases, AUX-I and AUX-II, which are isolated and purified from *Clostridium histolyticum*. Both collagenases are single polypeptide chains and each consists of approximately 1000 amino acids. Collagenase AUX-I and AUX-II have observed molecular weights of 114 and 113 kDa and belong to the class I and class II *Clostridium histolyticum* collagenases, respectively.

**Mechanism of Action:** AUX-I and AUX-II, collagenases, are proteinases which hydrolyze native collagen resulting in lysis of collagen. Injection of Xiaflex (AUX-I and AUX-II) into a Dupuytren's cord comprised mostly of collagen can result in a non-surgical, enzymatic disruption of the cord. Results of *in vitro* studies suggest that the collagenases (AUX-I and AUX-II) worked synergistically to provide broad hydrolyzing activity towards collagen. There are no clinical data regarding the relative contributions of the individual collagenases (AUX-I or AUX-II) to the efficacy of Xiaflex in the treatment of Dupuytren's contracture.

**How supplied:** Xiaflex is supplied as a sterile, lyophilized powder in a single-use glass vial containing 0.9 mg of Xiaflex to deliver a 0.58 mg dose after reconstitution. Sterile diluent for reconstitution is supplied (3 mL of 0.03% calcium chloride in 0.9% sodium chloride). For cords affecting MP and PIP joints, each 0.58 mg dose should be administered in an injection volume of 0.25 and 0.2 mL, respectively.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

There are no medically approved products for the treatment of DC. Surgery is effective for treatment of contractures associated with functional impairment. Table 2.1 displays the types of surgery for DC in order of less extensive to more extensive surgery. In general, the more extensive surgery is associated with greater incidence of contracture reduction but it is also associated with a higher incidence of complications (e.g., nerve or arterial injury, infection, skin loss, wound-healing difficulties, hematoma, complex regional pain syndrome).

**Table 2.1: Types of surgery for DC**

Type of Surgery	Description	Comments
<b>Closed Surgery</b>		
Percutaneous Fasciotomy (needle aponeurotomy)	Simple division of the fascia	Highest chance for recurrence
<b>Open Surgery</b>		
Open Fasciotomy	Simple division of the fascia	—
Limited Fasciectomy (selective, regional partial)	Excision of the disease tissue only	—
Extensive Fasciectomy (complete, total)	Excision of disease tissue and potentially diseased fascia	—
Dermofasciectomy	Excision of diseased tissue and skin	A skin graft is usually required. Usually performed for recurrent and severe disease and when the skin is adherent to the underlying diseased fascia.
Elective Amputation	Amputation at the PIP joint or through the proximal phalanx.	May be necessary when nerve and vascular damage results in loss of sensory function and cold intolerance. May be indicated if flexion contracture of PIP, especially 5th finger, is severe and cannot be corrected enough to make the finger useful.

## 2.3 Availability of Proposed Active Ingredient in the United States

Xiaflex is not approved in the United States or any other country.

## 2.4 Important Safety Issues With Consideration to Related Drugs

There are no approved collagenases in the United States or any other country.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

See Table 2.2 for the important Pre-BLA submission interactions between the FDA and the original Xiaflex sponsor (Dr. Hurst) and the current Xiaflex sponsor (Auxilium) regarding the clinical

development program for Xiaflex for the treatment of DC. In general, the FDA agreed with Auxilium's proposed design including primary efficacy endpoints of the Phase 3 trials to support the efficacy of Xiaflex and Auxilium agreed to submit safety results on 1000 patients exposed to Xiaflex injections to support the safety of Xiaflex in DC. In May 1996, Xiaflex was given an orphan designation by the FDA for the treatment of advanced Dupuytren's disease.

**Table 2.2: Important clinical issues during pre-BLA interactions between the FDA and the Xiaflex sponsor regarding the clinical development of Xiaflex for DC<sup>1</sup>**

Type of Meeting (Meeting Date) [Date minutes finalized]	FDA recommendations/comments
<b>Auxilium sponsored the development of Xiaflex</b>	
<p><b>Pre-BLA</b> (9/15/08) [10/8/08]</p>	<ol style="list-style-type: none"> <li>1. The results of Study 55 suggest lack of systemic exposure of Xiaflex after injection of 0.58 mg of Xiaflex into a cord.</li> <li>2. The proposed safety database for the BLA submission will comprise of 1000 patients who have received at least one Xiaflex injection at the proposed dose (over 2500 injections) and 100 patients will have one-year follow-up after the first injection. The proposed safety database is acceptable.</li> <li>3. The BLA should include proposals for managing potential safety concerns that may not have been seen in the clinical trials including the possibility of anti-product antibodies that are cross-reactive with endogenous collagenase (especially if these antibodies could cross the placenta during fetal development). Also the BLA should propose, if Xiaflex were approved, how to ensure proper administration by providers and how Auxilium plans to assess post-marketing tendon rupture to determine if the incidence is higher than noted in the trials.</li> <li>4. It is likely that Xiaflex will qualify for a full waiver to conduct pediatric studies to satisfy PREA because the number of pediatric patients with DC is small and studies would be highly impracticable.</li> </ol>
<p><b>Clinical Development</b> (4/4/06) [5/12/06]</p>	<ol style="list-style-type: none"> <li>1. Include a method for imputation for missing data for your primary efficacy endpoint (e.g., non-responder imputation) and rank the secondary endpoints.</li> <li>2. Inclusion of 10 sites in one proposed study to support efficacy is sufficient to demonstrate reproducibility across practitioners.</li> <li>3. Need at least 1000 Xiaflex-treated patients and least 100 Xiaflex-treated patients who have at least 12 months of follow-up safety data.</li> <li>4. Need durability of response data (i.e., percent with recurrence and time to recurrence using a pre-specified definition of reoccurrence).</li> <li>5. The primary efficacy endpoint for a proposed Phase 3 trial (the proportion of patients with contracture reduction to 0 to 5 degrees after up to 3 injections) is acceptable.</li> </ol>
<b>Individual Investigator (Dr. Hurst) sponsored the development of Xiaflex<sup>2</sup></b>	
<p><b>EOPII</b> (8/22/01) [9/21/01]</p>	<ol style="list-style-type: none"> <li>1. The use of open-label (b) (4) is not suitable to support the efficacy of Xiaflex (efficacy assessment of multiple Xiaflex treatments under controlled conditions is required).</li> <li>2. Assess durability of response (reoccurrence) out to 9 to 12 months.</li> <li>3. At least 2 studies with sufficiently large populations are required to assess safety and efficacy of Xiaflex. Additional studies should provide a larger safety database to assess the rate of specific AEs including antibody response.</li> <li>4. Describe the specific injection techniques, post-injection manipulation, splint usage, and ROM exercises for physicians and patient instructions.</li> </ol>
<p><b>Orphan Designation</b> 5/23/96</p>	<p>Xiaflex was given an orphan designation for the "treatment of advanced (b) (4) Dupuytren's disease" on May 23, 1996.</p>

<sup>1</sup> The sponsor of Xiaflex changed from Dr. Hurst to Auxilium on December 14, 2005.

<sup>2</sup> Dr. Hurst was the original Xiaflex sponsor and conducted Studies 02, 03, 04. Biospecifics Technology Corporation (BTC) supplied Xiaflex under investigation for these trials.

### **3 Ethics and Good Clinical Practices**

#### **3.1 Submission Quality and Integrity**

Auxilium's original electronic submission and responses to the FDA's clinical information requests were sufficient for a review of this BLA.

#### **3.2 Compliance with Good Clinical Practices**

According to Auxilium, the 2 pivotal trials were conducted in compliance with good clinical practice (GCP) guidelines as required by the major regulatory authorities, the Declaration of Helsinki concerning medical research in humans, and in **accordance with Auxilium's procedures**. A signed informed consent form was obtained from each patient prior to the initiation of study procedures and IRB approval was obtained by the investigators.

As is customary for new molecular entities such as Xiaflex, the Division of Scientific Investigations (DSI) was requested to perform routine audits of clinical sites (see Table 3.1). Three sites were chosen for inspection including 1 site (Dr. Hurst at Stony Brook) that treated patients in two Xiaflex trials (Studies 03 and 57) and 2 other sites in Study 57. These 3 sites included the highest enrolling site (Site 1157), the third highest enrolling site in which there was greater treatment effects of Xiaflex compared to the overall study results (Site 1160), and the fourth highest enrolling site in which there was greater treatment effects of Xiaflex compared to the overall study results (Site 1154). Inspection of the only site in Study 03 — the single-center U.S. trial — was requested because the absolute treatment effects of Xiaflex at this site compared to the other studies appeared greater than in Study 57 (91% vs. 56%) and because the co-investigators (Dr. Lawrence Hurst and Dr. Marie Badalamente) had a potential conflict of interest with the study results.

**Table 3.1: Selected sites for DSI inspection in Studies 03 and 57**

Site# (Name, Address, Phone#)	Patients Enrolled (% of entire study population)	Xiaflex-treated / placebo-treated patients	Absolute treatment margin of Xiaflex compared to placebo <sup>1</sup>
<b>Site in Study 03 (single-center study)<sup>2</sup></b>	<b>35 (100%)</b>	<b>23/12</b>	<b>91%</b>
<b>Dr. Lawrence Hurst and Dr. Marie Badalamente Health Sciences Center, T-18, SUNY at Stony Brook, NY 11794; (631) 444-3145</b>	<b>35 (100%)</b>	<b>23/12</b>	<b>91%</b>
<b>Sites in Study 57</b>	<b>308 (100%)</b>	<b>204/104</b>	<b>56%</b>
<b>Site# 1157: Dr. Vincent Hentz Stanford University School of Medicine Hand &amp; Upper Extremity Surgery 770 Welch Rd Ste 400, MC 5715, Palo Alto, CA 94304 (650) 723-6796</b>	<b>37 (12%)</b>	<b>25/12</b>	<b>52%</b>
<b>Site# 1160: Dr. Lawrence Hurst Health Sciences Center, T-18, SUNY at Stony Brook, NY 11794; (631) 444-3145</b>	<b>28 (9%)</b>	<b>20/8</b>	<b>86%</b>
<b>Site# 1154: Dr. F. Thomas Kaplan Indiana Hand Center, 8501 Harcourt Road, Indianapolis, IN 46280 (800) 888-4263</b>	<b>25 (8%)</b>	<b>16/9</b>	<b>77%</b>

<sup>1</sup> For the primary efficacy endpoint (proportion of patients that achieved a reduction of the primary contracture to 0 to 5 degrees, 30 days after the last injection)

<sup>2</sup> The one selected site in Study 03 (Dr. Hurst at Stony Brook) was the only site in Study 03. Dr. Hurst was also the principal investigator at Site #1160 in Study 57.

The DSI audited a portion of records from the patients at these 3 sites including, but not limited to, laboratory reports, sponsor correspondence, source documentation, Institutional Review Board communications, monitoring reports, protocol deviations, adverse events, concomitant medications, and test article accountability. The DSI found that data collected from these 3 sites were reliable and there were no significant data integrity issues.

### 3.3 Financial Disclosures

Auxilium certified that almost all the clinical principal and sub-investigators in the 12 submitted Xiaflex studies did not have compensation that could be affected by the outcome of the study as defined by 21 CFR 54.2(a); proprietary interest in Xiaflex as defined in 21 CFR 54.2(b); a significant equity in Auxilium as defined in 21 CFR 54.2(b); or was the recipient of significant payments as defined in 21 CFR 54.2(f).

Auxilium disclosed that Dr. Lawrence Hurst (a principal investigator) and Dr. Marie Badalamente (a sub-investigator) — who participated as investigators in 1 pivotal trial (Study 57), 2 supportive smaller trials (Studies 02 and 03), and 3 open-label, safety Studies 04, 55, and 58 — had proprietary interest in Xiaflex and had significant payments from Auxilium as defined in CFR 54.2(c). Therefore, Dr. Hurst and Dr. Badalamente had a potential conflict of interest. However, the DSI audited a portion of **patient records Dr. Hurst's site in Studies 03 and 57** and found no significant data integrity issues. **Furthermore, even if patients at Dr. Hurst's sites in all these studies were excluded the overall efficacy and safety results of Xiaflex in the clinical database would be unchanged.**

## 4 Significant Issues Related to Other Review Disciplines

### 4.1 Chemistry, Manufacturing, and Controls

The chemistry, manufacturing, and controls data in this section was extracted from Kathy Lee's secondary review (the CMC team leader), the manufacturing site inspection data was extracted from Dr. Kalavati Suvarna's review (the drug substance manufacturing quality reviewer) and Dr. Anastasia Lolos (the drug product manufacturing quality reviewer), and the immunogenicity data was extracted from Fred Mill's review (the therapeutic product reviewer).

**Description of the Drug Product:** Xiaflex is a parental, lyophilized product comprised of two highly purified (b) (4) bacterial collagenases in an approximate (b) (4) mass ratio, AUX-I and AUX-II. These collagenases are isolated and purified from the fermentation of *Clostridium histolyticum*. Collagenases are also known as matrix metalloproteinases (MMPs). AUX-I is a single polypeptide chain containing (b) (4) amino acids of known sequence with a molecular weight of 114 kDa. AUX-II is (b) (4) amino acids long with a molecular weight of 113 kDa. There is a 47% homology in the amino acid sequence of AUX-I and AUX-II.

Both collagenases digest collagen by hydrolyzing the triple helical region of collagen under physiological conditions. Each collagenase has different specificity. Results of *in vitro* studies suggest that the collagenases (AUX-I and AUX-II) worked synergistically to provide broad hydrolyzing activity towards collagen. However, there are no clinical data regarding the relative contributions of the individual collagenases (AUX-I or AUX-II) to the efficacy of Xiaflex in the treatment of DC.

Both calcium and zinc are required for the function of Xiaflex. The calcium is supplied in the sterile diluent and the zinc (b) (4); (b) (4). No additional exogenous Zinc is required for the activity of Xiaflex.

**Biological Activity Assays:** Auxilium uses two biological activity assays to measure the potency of collagenase clostridium histolyticum. The Soluble Rat Collagen (SRC) measures the proteolytic activity of AUX-I using a rat-tail tendon while the synthetic peptide-based (GPA) potency assay measures the proteolytic activity of AUX-II using a synthetic peptide. The CMC reviewers found no major issues with the biologic activity assays.

**Stability:** Dr. Ashutosh Rao, the therapeutic product reviewer, agreed with Auxilium's following proposed commercial shelf life for Xiaflex based on the submitted stability data of the lyophilized drug product: 24 months at 2°-8°C.

**Manufacturing Sites:** During the course of its development, the drug substance (collagenase clostridium histolyticum) was manufactured at the following 3 sites (the drug substance was found to be comparable at all 3 sites):

- 1) Biospecifics Technologies Corporation (BTC) in Lynbrook, NY;

- 2) [REDACTED] (b) (4)
- 3) **Auxilium's manufacturing facility in Horsham, PA** (the proposed commercial manufacturing site).

The drug product (Xiaflex) was sterilized, filled, and lyophilized by three different contract manufactures: [REDACTED] (b) (4). The drug product and sterile diluent vials are currently labeled and final packaged by [REDACTED] (b) (4).

The drug substance manufacturing was inspected at the Auxilium site at 102 Witmer Road, Horsham, PA 19044 and the drug product and sterile diluent manufacturing was inspected at the [REDACTED] (b) (4). These two sites are the proposed commercial production of the drug substance and drug product, respectively. According to the product reviewers, the facility inspections were acceptable.

**Immunogenicity Assays:** For discussions of the clinical implications of immunogenicity including allergic reactions and anti-product antibody cross-reactivity to human matrix metalloproteinases (MMPs) see Sections 7.3.6 (Clinical Implications of Immunogenicity).

Dr. Fred Mills reviewed the immunogenicity assays for antibodies to AUX-I and AUX-II. The antibody assays in the Auxilium-sponsored Xiaflex studies included total immunoglobulins; however, no specific isotypes were assessed, such as IgE, IgG, or IgM. Dr. Mills stated that the immunoglobulin assays are appropriately validated.

Neutralizing antibodies were assessed as inhibition of the enzymatic activity of AUX-I or AUX-II by patient sera. See Section 7.3.6 (Clinical Implications of Immunogenicity) for the incidence of neutralizing antibodies and a subgroup efficacy analysis by neutralizing antibody status.

Dr. Mills recommends the following post-marketing commitments (PMCs):

- Assess the cross-reactivity of anti-AUX-I and anti-AUX-II to human MMPs.
- Monitor and collect injection site pruritus and hypersensitivity Xiaflex-associated reactions in the post-marketing setting.
- Assess the long-term persistence of antibodies in patients who received multiple Xiaflex doses.

**CMC Approvability Issues:** At the inspection, the product review team requested release testing method transfers for the change in release testing sites from the [REDACTED] (b) (4) to the Horsham facility. The method transfer reports were submitted on September 2, 2009. Because product from the Horsham facility will be critical for commercial launch if Xiaflex is approved, this recent submission will need to be reviewed and determined to be acceptable by the Agency product reviewers before the BLA can be approved. An additional inspection of the [REDACTED] (b) (4) also needs to be performed before approval, as the clinical batches proposed for marketing at approval have been tested at the [REDACTED] (b) (4). This inspection is still pending at the time of this review.

In addition, the CMC reviewers will recommend several post-marketing commitments (PMCs). For a complete list of these PMCs, see the product reviews or Dr. Sarah Okada's cross-discipline team leader's review.

## 4.2 Clinical Microbiology

Xiaflex is not a product intended to treat infections. There are no clinical microbiology issues that would prevent approval of Xiaflex.

## 4.3 Preclinical Pharmacology/Toxicology

According to Dr. Asoke Mukherjee, the pharmacology/toxicology reviewer, the major non-clinical collagenase clostridium histolyticum (CCH) studies submitted in the BLA included two multi-dose intravenous toxicity studies in rats, a local toxicity study in dogs, intravenous fertility and embryofetal development studies in rats, and intraperitoneal and intracardiac sensitization studies in guinea pigs. The findings from the non-clinical studies were extracted from Dr. Mukherjee's review.

Systemic Toxicology Studies: Two controlled intravenous toxicity studies of CCH given every 48 hours for 16 days (8 doses) were conducted in Sprague Dawley rats. Following intravenous injection, AUX-I rapidly degraded in plasma, but AUX-II was measured on Days 1 and 7. The NOAEL was 0.029 mg of protein/dose. Liver toxicity was noted at 0.13 and 0.29 mg of protein/dose. Non-reversible injection site perivascular inflammation and fibrosis were noted at all doses. In these studies, antibodies to AUX-I and AUX-II were present; however, there were no non-clinical consequences of these antibodies.

The clinical implications of anti-AUX-I and anti-AUX-II antibodies seen in these rat toxicology studies are not known. The inflammation observed in the non-clinical studies is consistent with the mechanism of action of collagenases. There was no evidence of liver toxicity in the clinical Xiaflex studies (see Section 7.4.3, Laboratory Findings).

Local Toxicology Study: A local controlled toxicity study of CCH in male beagle dogs was conducted. CCH was injected into the penis 3 times a week for 3 treatment cycles (with 3 weeks between treatment cycles). There was injection site inflammation after single and multiple doses of CCH. Both AUX-I and AUX-II were detectable in the plasma within 60 minutes after dosing, suggesting minimal bioavailability of CCH in systemic circulation following local administration. There was local toxicity with a primary inflammatory response (i.e., hemorrhage, edema, necrosis, inflammation, neovascular proliferation, lymphoid hyperplasia) and there were inflammatory findings in the draining lymph nodes. There was no significant systemic toxicity (i.e., changes in body weight; food consumption; hematology, chemistry, or urinalysis values; or organ weights). There were no effects on arteries, nerves, and large veins.

Immunogenicity in the Toxicology Study: Immunogenicity was an anticipated event to the foreign bacterial proteins. The non-clinical data from the three toxicology studies showed development of anti-AUX-I and anti-AUX-II antibodies in the serum after single and multiple injections, irrespective of the route of administration or species. There was no evidence of non-clinical allergic reactions to CCH. The clinical consequences of the development of these antibodies are unknown.

**Reproductive Toxicology Studies:** Fertility, early embryonic development, and embryofetal development safety studies in rats were conducted. Male and female rats did not show any effect on fertility and early embryonic development up to 0.13 mg protein/dose by intravenous bolus injections of CCH. Pregnant rats also did not show developmental toxicity to pups when injected during the organogenicity period. In these studies, anti-AUX-I and -AUX-II antibodies were present; however, there were no reproductive or developmental toxicities that were related to the anti-product antibodies. The pharmacology/toxicology team agreed with Auxilium that pre- and post-natal development studies of CCH in rats were not required because there was no evidence of toxicity in the completed reproductive toxicity studies and there was no evidence of systemic exposure following Xiaflex injections into Dupuytren's cords in humans. Dr. Mukherjee recommends a Pregnancy Category C Classification instead of Auxilium's proposed Category B to reflect the absence of pre- and post-natal development data.

**Sensitization studies:** Sensitization studies in guinea pigs and did not show evidence of immediate hypersensitivity reactions to CCH when given by intraperitoneal or intracardiac routes.

**Carcinogenicity Studies:** Since Xiaflex is not an immunosuppressant, is not absorbed systemically, and is not intended for chronic regular use, carcinogenicity studies were not required for the Xiaflex BLA submission.

**Summary:** The Pharmacology/Toxicology team recommends approval of the Xiaflex BLA with revisions to the proposed labeling. No non-clinical post-marketing requirements or commitments are recommended. Overall, there were no pharmacology/toxicology issues that would prevent approval of Xiaflex for DC.

## 4.4 Clinical Pharmacology

### 4.4.1 Mechanism of Action

Xiaflex consists of two microbial collagenases (AUX-I and AUX-II) that hydrolyze native collagen. Auxilium proposes that when Xiaflex is injected into Dupuytren's cords, collagen lysis results in enzymatic disruption of the cord, leading to a reduction in contracture and improvement in range of motion of the affected joints.

### 4.4.2 Pharmacodynamics

There were no pharmacodynamic studies of Xiaflex.

### 4.4.3 Pharmacokinetics

Studies 55 and 02 assessed the pharmacokinetics of Xiaflex after single intra-cord injections of 0.58 mg of Xiaflex. AUX-I and AUX-II enzyme levels were not detected in any patient at any time point at baseline or on Days 0, 1, 7, and/or 30 following administration of a single intra-cord injection of 0.58 mg in 20 patients with DC. All samples were below the lower level of quantification for AUX-I and

AUX-II. See Table 4.1 for the timing and assay sensitivity of PK assessments, and number of patients with PK samples in Studies 55 and 02.

**Table 4.1: Timing of PK assessments, assay sensitivity, and number of patients with PK samples in Studies 55 and 02**

Study	Timing of PK Assessments	Analytical sensitivity of immunoenzymetric assay	# of patients with PK samples
55	Baseline and the following times post-injection: 5, 10, 20, 30, and 60 minutes; 2, 4, 8, 12, and 24 hours; and 7 and 30 days	5 ng/mL for AUX I 25 ng/mL for AUX II	16
02	Baseline and the following times post-injection: 10, 20, and 30 minutes; 1, 4, and 24 hours after the injection.	4 ng/mL	4

Reference: Adapted from the protocols for Studies 02 and 55.

## **5 Sources of Clinical Data**

### **5.1 Tables of Xiaflex Clinical Studies**

Auxilium submitted data from 12 completed studies of Xiaflex in their BLA to support approval of Xiaflex for the treatment of DC (see Table 5.1):

1. 2 pivotal trials (Studies 57 and 59): Randomized, double-blind, placebo-controlled Phase 3 trials through Day 90.
2. 4 supportive trials (Studies 03, 53, 51, and 03): Randomized, double-blind, placebo-controlled trials.
3. 6 safety studies (Studies 54, 56, 58, 04, 55, and 52): open-labeled, uncontrolled safety studies.

Data from 1 ongoing study of Xiaflex [Study AUX-CC-860 (Study 860)] was not submitted in the BLA. Study 860 is an uncontrolled, multi-center, long-term follow-study of patients with DC who were injected with Xiaflex in Studies 54, 56, 57, 58, and 59. In this study, patients will not receive additional Xiaflex treatments, but recurrence data will be collected once a year for 4 years and the following safety data will be collected once a year for 4 years: immunogenicity data (total immunoglobulins to AUX-I and AUX-II) and adverse events. Enrollment in Study 860 began in September 2009 and the estimated date for study completion is March 2013.

**Table 5.1: Key design features of the 12 Xiaflex submitted studies in patients with DC<sup>1</sup>**

Study	Design	Treatment Groups	# of Sites <sup>2</sup>	Actual/Planned Enrollment
<b>Pivotal Trials (R, DB, PC, 90-day, Phase 3 Trials)<sup>3</sup></b>				
57	Up to 3 Xiaflex injections into 1 cord.	0.58 mg Xiaflex (n=204) Placebo (n=104)	16	308/216 (>100%)
59	Up to 3 Xiaflex injections into 1 cord.	0.58 mg Xiaflex (n=45) Placebo (n=21)	5	66/60 (>100%)
<b>Supportive Trials (R, DB, PC Trials)<sup>3</sup></b>				
03 <sup>4</sup>	90-day study of up to 3 Xiaflex injections into 1 cord.	0.58 mg Xiaflex (n=23) Placebo (n=12)	1	35/116 (30%)
53 <sup>5</sup>	90-day study of up to 3 Xiaflex injections into 1 cord. If patients had untreated cords they were allowed to receive open-label Xiaflex treatment (up to 5 additional injections).	0.58 mg Xiaflex (n=17) Placebo (n=6)	2	23/48 (48%)
51 <sup>5</sup>	90-day study of up to 3 Xiaflex injections into 1 cord. Patients only received 1 injection of study medication.	0.58 mg Xiaflex (n=5) Placebo (n=2)	3	7/216 (3%)
02	Dose-ranging, Phase 2 study of 1 Xiaflex injection into 1 cord. Allowed to receive up to 4 additional open-label Xiaflex injections every 4-6 weeks. Also, 4 other patients had open-label PK tests after intracord injections of 0.58 mg of Xiaflex.	0.58 mg Xiaflex (n=23) 0.29 mg Xiaflex (n=22) 0.145 mg Xiaflex (n=18) Placebo (n=17)	2	80/52 (>100%)
<b>Open-Label, Uncontrolled Safety Studies</b>				
54	9-month study of up to 5 Xiaflex injections on Days 0, 30, 60, 90, and 120 (maximum 3 injections into a 1 cord).	0.58 mg Xiaflex (n=386)	20	386/240 (>100%)
56	9-month study of up to 5 Xiaflex injections on Days 0, 30, 60, 90, and 120 (maximum 3 injections into a 1 cord).	0.58 mg Xiaflex (n=201)	14	201/100 (>100%)
58	Long-term extension study of Study 57 (9 additional months for a total of 12 months). If significant contracture may have received up to 5 additional Xiaflex injections on Days 0, 30, 60, 90, and 120 (maximum 3 injections into a 1 cord).	0.58 mg Xiaflex (n=286)	16	286/216 (>100%)
04 <sup>5</sup>	Long-term extension study of Study 03 (14 additional months for a total of 17 months). If a significant contracture may have received up to 5 Xiaflex injections of every 4 to 6 weeks (up to 3 injections per joint).	0.58 mg Xiaflex (n=19)	1	35/116 (30%)
55	Single-dose, PK, Phase 1 study of 1 Xiaflex injection into 1 cord.	0.58 mg Xiaflex (n=16)	1	16/16 (100%)
52 <sup>6</sup>	Long-term extension study of Study 51 (9 additional months for a total of 12 months). Patients with a significant contracture may have received up to 5 Xiaflex injections.	N/A <sup>6</sup>	N/A <sup>6</sup>	0/216 (0%)

R = randomized, DB = double-blind, PC = placebo-controlled, N/A = not applicable

1 Studies DUPY-202, DUPY-303, DUPY-404, AUX-CC-851, AUX-CC-852, AUX-CC-853, AUX-CC-854, AUX-CC-855, AUX-CC-856, AUX-CC-857, AUX-CC-858, and AUX-CC-859 are abbreviated as Studies 02, 03, 04, 51, 52, 53, 54, 55, 56, 57, 58, and 59, respectively.

2 Sites in which patients received study medication. All of the studies only included U.S. sites except Studies 53 and 59 (only Australian sites) and Study 54 (only European and Australian sites).

3 The primary efficacy endpoint for the important trials (Studies 57 and 59) and the supportive trials (Studies 03, 53, 51, and 02) was the proportion of patients that achieved a contracture reduction of the primary joint to 0 to 5 degrees, 30 days after the last injection.

4 After Auxilium acquired the rights for Xiaflex from the prior sponsor, enrollment was discontinued in Studies 03 and 04.

5 Due to a manufacturing issue, enrollment was discontinued in Studies 51, 52, and 53.

6 No patients received study medication in Study 52.

Reference: BLA, Tabular-listing, Table 1, Pages 1-12.

As shown in Table 5.2, Auxilium also submitted deaths from 2 academic pilot studies of Xiaflex which were conducted by the prior sponsor of Xiaflex (Dr. Hurst). The source data (e.g., efficacy and safety results) for these studies were not submitted to the FDA and could not be verified.

**Table 5.2: Three single-site academic U.S. studies of Xiaflex in patients with DC**

Reference	Design	Treatment Groups
	Open-label, uncontrolled, single-dose	0.58 mg Xiaflex (n=16)
<b>Badalamente, Marie and Hurst, Lawrence. "Enzyme Injection as Nonsurgical Treatment of Dupuytren's Disease." <i>The Journal of Hand Surgery</i> 2000;25A: 629-636.<sup>1</sup></b>	Open-label, uncontrolled, single-dose escalation study of ultrasound-assisted injections of Xiaflex. Patients were allowed to receive repeat injections of Xiaflex if the joint angle did not correct to 0 to 5 degrees.	0.02 mg Xiaflex (n=1) 0.03 mg Xiaflex (n=1) 0.07 mg Xiaflex (n=1) 0.14 mg Xiaflex (n=1) 0.28 mg Xiaflex (n=1) 0.56 mg Xiaflex (n=1) 0.58 mg Xiaflex (n=29)
<b>Study DUPY-101: Badalamente, Marie and Hurst, Lawrence. "Collagen as a Clinical Target: Nonoperative Treatment of Dupuytren's Disease." <i>The Journal of Hand Surgery</i> 2002;27A: 788-798.</b>	R, DB, PC, single-dose study of ultrasound-assisted injections. Patients were allowed to enter the extension phase of the study and receive up to 4 additional open-label injections of Xiaflex every 4-6 weeks.	0.58 mg Xiaflex (n=25) Placebo (n=24)

<sup>1</sup> In Badalamente and Hurst 2000, a primary joint was not noted. In this study, 29 patients had 34 joints with significant contractures from cords and several patients received injections of 0.58 mg of Xiaflex in multiple cords that were causing contractures.

## 5.2 Review Strategy

**Efficacy:** Studies 57 and 59 through Day 90 served as the pivotal trials for the evaluation of the efficacy of Xiaflex in the treatment of DC because these trials were adequate and well-controlled and had acceptable endpoints. For the efficacy evaluation of these studies see Section 6 and for the study reports see Sections 9.4.1 and 9.4.2.

Additional support for the efficacy of Xiaflex for the treatment of DC are from the results of four smaller randomized, double-blind, placebo-control trials — Studies 02, 03, 51 and 53. This reviewer agrees with Auxilium's contention that Studies 53, 51, and 02 are supportive trials; however, this reviewer disagrees with Auxilium that Study 03 is a pivotal trial. This reviewer considers Study 03 as a supportive trial for the following reasons:

- Study 03 enrolled patients at 1 site (a total of 35 patients were treated) compared to the pivotal trials which enrolled patients at 5 to 16 sites (a total of 66 to 308 patients were treated). In Study 03, only 2 investigators performed all the injections; whereas, in the pivotal trials, up to 7 to 34 investigators (principal investigators and sub-investigators) performed the injections. The efficacy results of trials with fewer sites, patients, and investigators may not be as generalizable as efficacy results of trials with more sites, patients, and investigators.
- Study 03 was terminated early and enrolled only 30% of the planned number of patients due to a change in the pharmaceutical sponsor.
- The investigator who performed the injections in Study 03 had a potential conflict of interest.
- Study 03 did not include appropriate statistical gate-keeping for the secondary endpoints and did not include a plan to collect protocol violations.

**Safety:** The primary support for the safety of Xiaflex in patients with DC was evaluated in the double-blinded, placebo-controlled portions of the pooled pivotal trials through Day 90 (Studies 57 and 59). These safety data were pooled because these trials had very similar designs, safety evaluations, and patient populations. Additional support for the safety of Xiaflex in patients with DC was from pooled

results from the controlled and uncontrolled portions of all 12 submitted Xiaflex studies through the last safety cut-off date (Studies 02, 03, 04, 51, 52, 53, 54, 55, 56, 57, 58, and 59).

### 5.3 Discussion of Individual Studies/Clinical Trials

Two pivotal trials served as the primary support for the efficacy and safety of Xiaflex for DC (Studies 57 and 59). Below is an overview of the design of these trials (see Sections 9.4.1 and 9.4.2 for the individual study reports for these 2 trials).

Study 57 (Study AUX-CC-857): Study 57 was a randomized, double-blind, placebo-controlled, multi-center (16 U.S. sites), 2-arm, Phase 3 trial of Xiaflex in 308 treated patients with Dupuytren's contracture (DC). Patients must have had a fixed flexion deformity (caused by a palpable cord) resulting in an MP or PIP joint contracture at least 20° but ≤ 100° (for a MP joint) or ≤ 80° (for a PIP joint) in at least one finger, other than the thumb. Investigators selected the "primary joint" in which all the important efficacy evaluations were based. Patients may not have received a treatment for DC on the primary joint within 90 days prior to the first dose of study drug.

Patients were randomized 2:1 to receive an injection of Xiaflex or placebo directly into the cord affecting the primary joint. Patients may have received up to 3 injections on Days 0, 30, and 60 of Xiaflex or placebo directly into the Dupuytren's cord that caused the contracture of the primary MP or PIP joint. If the contracture persisted 24 hours after the injection procedure, the investigator extended the treated finger in an attempt to rupture the cord (finger extension procedure). The range of motion of the MP and PIP joints was assessed using a finger goniometer at 1, 7, and 30 days after study medication injections. Upon completion of the Day 90 follow-up visit, all patients may have entered Study 58, a 9-month, open-label extension study, if they required treatment of remaining contractures.

The primary efficacy endpoint was the proportion of patients who achieved a reduction of the contracture of the primary joint (either MP or PIP) to 0 to 5 degrees, 30 days after the last injection (clinical success) up to 3 injections. Comparison of the primary efficacy endpoint results between the Xiaflex and placebo groups was performed using a Cochran-Mantel-Haenszel (CMH) statistic for 2 x 2 tables, controlling for joint type (MP or PIP) and baseline contracture severity.

Study 59 (Study AUX-CC-859): Study 59 was a randomized, double-blind, placebo-controlled, multi-center (5 Australian sites), 2-arm, Phase 3 trial of Xiaflex in 66 treated patients with Dupuytren's contracture (DC). Study 59 had two parts: part one was a 3-month, double-blind, placebo-controlled portion with up to 3 injections of study medication every 30 days and a 9-month open-label, uncontrolled extension portion where patients could receive up to 5 additional injections of Xiaflex every 30 days. The placebo-controlled portion of Study 59 had the same design, evaluation and procedures, primary endpoint, and statistical analyses as Study 57.

## 6 Review of Efficacy

### Efficacy Summary

In the pivotal trials (Studies 57 and 59), a numerically and statistically significantly greater proportion of Xiaflex-treated patients compared to placebo-treated patients achieved the primary efficacy endpoint [the proportion of patients that achieved a contracture reduction of the primary MP or PIP joint to 0 to 5 degrees, 30 days after the last injection (clinical success) after up to 3 injections]. The absolute treatment margins of Xiaflex compared to placebo for the primary efficacy endpoint were 57% and 39% in Studies 57 and 59, respectively. For the subgroup efficacy analyses by primary joint type (MP or PIP), Xiaflex-treated patients had a greater proportion of clinical success compared to placebo-treated patients for each of these joint types (MP or PIP) in each pivotal trial. Also, a numerically greater proportion of Xiaflex-treated patients compared to placebo-treated patients achieved clinical success after 1 injection.

In the pivotal trials, after up to 3 injections, Xiaflex treatment resulted in a significantly greater decrease in the mean percent change from baseline in the contracture degree of the primary joint (MP and PIP) and each joint type compared to placebo treatment. After up to 3 injections, Xiaflex treatment resulted in a significantly greater increase in the range of motion (ROM) from baseline for the primary joint and each joint type compared to placebo treatment.

In Studies 54, 56, 57, 58, and 59, a recurrence was pre-specified as an increase in contracture  $\geq 20^\circ$  associated with the presence of a palpable cord after successful Xiaflex treatment. Of the 830 Xiaflex-treated cords that achieved clinical success in these studies, 30 (4%) cords had a recurrence (the mean follow-up period after clinical success was 7.4 months). Although there are major limitations to cross-study comparisons with the surgery literature, it appeared that the incidence of recurrence following successful Xiaflex-treatment was not greater than the incidence of recurrence following fasciectomy and/or fasciotomy for DC.

The majority of investigators who performed injections were hand surgeons in the pivotal trials; although, a limited number of injectors were orthopedic surgeons or rheumatologists. In an efficacy subgroup analysis by surgical training in Study 57, orthopedic surgeons who performed the injections obtained similar results for the primary efficacy endpoint as hand surgeons. In a subgroup efficacy analysis in Study 59, rheumatologists who performed the injections obtained similar results for the primary efficacy endpoint as hand and orthopedic surgeons.

Overall, the results of the Xiaflex trials support the efficacy of Xiaflex in the treatment of DC.

### 6.1 Indication

Auxilium proposes the following indication for Xiaflex: “for the treatment of advanced Dupuytren’s disease.”

### 6.1.1 Methods

Studies 57 and 59 served as the pivotal trials for the evaluation of efficacy of Xiaflex in the treatment of DC. These trials were adequate and well-controlled (double-blinded, placebo-controlled) and had acceptable endpoints.

### 6.1.2 Demographics

As shown in Table 6.1, the Xiaflex and placebo groups within each pivotal trial (Studies 57 and 59) were generally balanced with respect to baseline demographics and demographics were similar across the two pivotal trials [the U.S. trial (Study 57) and the Australian trial (Study 59)]. The greater proportion of individuals older than 65 years or 75 years in the placebo group in Study 59 was assessed in light of the relatively small number of total placebo patients in this study, and was determined not to have impacted overall study results [see Section 6.1.7 (Subpopulations)]. The majority of patients in these trials were Caucasian men and the mean age was in the early to mid-sixties which is consistent with the known demographics of patients with DC.

**Table 6.1: Baseline demographics in the pivotal trials<sup>1</sup>**

		Study 57 (U.S.)		Study 59 (Australian)	
		Xiaflex (n=204)	Placebo (n=104)	Xiaflex (n=45)	Placebo (n=21)
Age	Mean (SD)	62 (10)	63 (9)	63 (8)	66 (11)
	≥ 65	41%	45%	44%	57%
	≥ 75	10%	14%	2%	24%
Gender	Male	84%	71%	87%	81%
	Female	16%	29%	13%	19%
Race	White	100% <sup>2</sup>	100%	100%	100%
	Hispanic	1% <sup>2</sup>	0%	0%	0%
	Black	0%	0%	0%	0%
	Asian	0%	0%	0%	0%
Weight	kg, mean (SD)	83 (16)	79 (18)	86 (15)	76 (12)
Height	ft, mean (SD)	5.8 (0.3)	5.7 (0.3)	5.8 (0.2)	5.7 (0.2)

<sup>1</sup> ITT population (all treated patients)

<sup>2</sup> There was one Hispanic patient who received Xiaflex

Reference: Adapted from the CSR for Study 57, Table 14.1.2, Page 84 and the CSR of Study 59, Table 14.1.2, Pages 135-136.

### 6.1.3 Baseline Disease Characteristics

As shown in Table 6.2, the baseline characteristics of DC including prior treatments were similar in the Xiaflex and placebo groups within each pivotal trial and similar across the two trials (Studies 57 and 59). However, a slightly greater proportion of patients in Study 59 had prior surgery for DC than patients in Study 57 (53% vs. 36%). Since the overwhelming majority of Xiaflex-treated patients with prior DC surgery had surgery on a different finger or hand than the selected primary joint, treatment of the primary contracture in the pivotal trials represented initial treatment of these cords. Of the patients with a documented type of prior surgery in Study 57, 49% and 38% had a prior fasciotomy and

fasciectomy, respectively. In the pivotal trials, 98% to 100% of the patients were naive to Xiaflex treatment at baseline.

**Table 6.2: Baseline characteristics of DC in the pivotal trials<sup>1</sup>**

	Study 57 (U.S.)		Study 59 (Australian)	
	Xiaflex (n=204)	Placebo (n=104)	Xiaflex (n=45)	Placebo (n=21)
Mean (SD) duration of symptoms in years	4.9 (6)	5.4 (7)	5.7 (7)	5.7 (7)
DC symptoms developed	gradually	97%	98%	100%
	overnight	3%	2%	0%
History of hand trauma	28%	20%	27%	19%
Family history of Dupuytren's	42%	51%	49%	43%
Prior treatment for DC	39%	48%	53%	52%
Prior surgery for DC <sup>2</sup>	36%	42%	53%	52%
Prior surgery on the same hand and finger as the primary joint	5%	N/A <sup>4</sup>	7%	N/A <sup>4</sup>
Prior Xiaflex injection <sup>3</sup>	2%	1%	0%	0%
Prior cortisone injection <sup>3</sup>	1%	1%	0%	0%

<sup>1</sup> ITT population (all treated patients)

<sup>2</sup> In Study 57, of the 115 patients who had prior hand surgery, only 45 (39%) had a recorded type of hand surgery [70 (61%) had an unknown type of hand surgery]. Of these 45 patients, 22 (49%) and 17 (38%) had a prior fasciectomy and fasciectomy, respectively. In Study 59, of the patients who had a prior surgery, in 91% of these cases the type of surgery was not known.

<sup>3</sup> In Study 57, only 2 of the 9 patients with a prior injection were treated with an injection to the primary joint in the past (1 received cortisone and 1 received Xiaflex). In Study 59, no patients received an injection for DC in the past.

<sup>4</sup> N/A is not available.

Reference: Adapted from CSR of Study 57, Table 7, Page 36, Table 14.1.3, Pages 86-87 and Table 14.1.4, Pages 88-89; from CSR of Study 59, Table 11, Page 47, Table 14.1.3, Pages 137-138, Table 14.1.4, Pages 139-140. Also adapted from the June 23, 2009 response to FDA's information requests, Table 4, Page 11 and Table 6, Page 14.

As summarized in Table 6.3 below, treatment groups within the pivotal trials (Studies 57 and 59) were generally balanced with respect to baseline severity of joint contractures in the primary joint (the joint selected for the primary efficacy assessments). In Studies 57 and 59, the baseline range of motion (ROM) — full flexion minus full extension — for the MP primary joints were 44 and 40 degrees, respectively, and the baseline ROM for the PIP primary joints were 46 and 43 degrees, respectively. The normal ROM is considered to be about 90 degrees (not including hyperextension) for MP joints and about 100 degrees for PIP joints. Patients in both trials had **extensive Dupuytren's disease with a mean number of fixed flexion contractures of 3.0 and 3.3 in Studies 57 and 59, respectively.**

**Table 6.3: Baseline characteristics including disease severity of the primary joints and all joints affected by DC in the pivotal trials<sup>1</sup>**

		Study 57 (U.S.)		Study 59 (Australian)	
		Xiaflex (n=204)	Placebo (n=104)	Xiaflex (n=45)	Placebo (n=21)
<b>Primary Joint<sup>3</sup></b>					
MP or PIP, mean (SD)	Degrees of ROM <sup>4,5</sup>	44 (20)	45 (19)	40 (15)	44 (16)
	Degrees of full extension <sup>4</sup>	50 (20)	49 (20)	53 (15)	50 (16)
	Degrees of full flexion <sup>4</sup>	94 (9)	95 (10)	94 (8)	94 (11)
MP joint was the primary joint		66%	67%	44%	52%
PIP joint was the primary joint		34%	33%	56%	48%
% of MP joints > 50° of full extension		39%	39%	50%	36%
% of PIP joints > 40° of full extension		70%	74%	80%	80%
Little (5 <sup>th</sup> ) finger/MP joint - primary joint		34%	31%	27%	29%
Little (5 <sup>th</sup> ) finger/PIP joint - primary joint		27%	24%	42%	38%
Ring (4 <sup>th</sup> ) finger/MP joint - primary joint		28%	31%	16%	19%
Ring (4 <sup>th</sup> ) finger/PIP joint - primary joint		5%	4%	7%	5%
Another MP or PIP was the primary joint		7%	11%	8%	10%
<b>All Joints affected by Cords</b>					
Total contracture index <sup>2</sup> , mean (SD) degrees		149 (128)	149 (111)	175 (107)	150 (84)
Mean (SD) # of affected joints per patient	MP or PIP	3.0 (2.2)	3.0 (2.1)	3.4 (2.3)	3.0 (1.5)
	MP	1.6 (1.5)	1.7 (1.4)	1.5 (1.6)	1.5 (1.5)
	PIP	1.4 (1.3)	1.3 (1.3)	2.0 (1.6)	1.4 (1.2)
Both hands with contracture		40%	35%	49%	57%
Only one hand with contracture		60%	65%	51%	43%

1 ITT population (all treated patients)

2 The total contracture index is the sum of fixed-flexion contractures (≥ 20 degrees caused by DC) for 16 joints (8 MP and 8 PIP joints in the hands).

3 The primary joint served as the basis for the primary endpoint and important secondary endpoints in Studies 57 and 59.

4 In these trials, 0 degrees was defined as the anatomic position of the MP and PIP joints. According to the Society for Surgery of the Hand, typical ROM of the PIP joint is 100 degrees (0 degrees of full extension to 100 degrees of full flexion) and the typical ROM of the MP joint is 90 degrees (0 degrees of extension and 90 degrees of full flexion). The degree of hyperextension of the MP joint was not included in the assessment of the important efficacy endpoints (typical hyperextension is 45 degrees of the MP joint).

5 The MP and PIP joints had similar baseline ROM.

Reference: Adapted from CSR of Study 57, Table 7, Page 36, Table 14.1.3, Pages 86-87, Table 14.1.7.1, Page 92, Table 14.1.7.2, Page 93, Table 14.1.7.3, Page 94; from CSR of Study 59, Table 11, Page 47, Table 14.1.3, Pages 137-138, Table 14.1.4, Pages 139-140, Table 14.1.7.1, Page 143, Table 14.1.7.2, Page 144, and Table 14.1.7.3, Page 145.

### 6.1.3 Subject Disposition

Table 6.4 displays the disposition of patients in the double-blind, controlled portions of the pivotal trials through Day 90 (Studies 57 and 59). Overall, very few patients discontinued during the 90-day double-blind phase of the trials. Those who did discontinue withdrew for a variety of reasons with no category predominating.

**Table 6.4: Disposition through the placebo-controlled portions of the pivotal trials through Day 90**

	Study 57 (U.S.)		Study 59 (Australian)	
	Xiaflex	Placebo	Xiaflex	Placebo
Randomized	204 (100%)	104 (100%)	45 (100%)	21 (100%)
ITT <sup>1</sup>	204 (100%)	104 (100%)	45 (100%)	21 (100%)
MITT <sup>2</sup>	203 (100%)	103 (99%)	N/A <sup>3</sup>	N/A <sup>3</sup>
Completed DB phase	191 (94%)	100 (96%)	45 (100%)	19 (91%)
Discontinued DB phase	13 (6%)	4 (4%)	0 (0%)	2 (10%)
Withdrawn consent	4 (2%)	3 (3%)	0 (0%)	2 (10%)
Lost to follow-up	4 (2%)	1 (1%)	0 (0%)	0 (0%)
DAEs <sup>4</sup>	3 (2%)	0 (0%)	0 (0%)	0 (0%)
Other	2 (1%)	0 (0%)	0 (0%)	0 (0%)

<sup>1</sup> In Study 59 all efficacy analyses were based on the ITT population (treated patients) and in both studies, all safety analyses were based on the ITT population.

<sup>2</sup> In Study 57, the modified intent-to-treat (MITT) population was all ITT patients who had pre-injection fixed flexion contracture measurements of the primary joint > 5 degrees and at least one post first-injection measure obtained on the primary joint. In Study 57, all the important efficacy evaluations were based on the MITT population.

<sup>3</sup> N/A is not applicable. Study 59 did not have a MITT population.

<sup>4</sup> DAEs are adverse events leading to discontinuation.

Reference: Adapted from the CSR of Study 57, Table 6, Page 33 and also adapted from CSR of Study 59, Table 14.1.1a, Pages 133-134.

#### 6.1.4 Analysis of Primary Endpoints

The primary efficacy endpoint for the pivotal trials (Studies 57 and 59) and the supportive trials (Studies 03, 53, 51, and 02) was the **proportion of patients who achieved a reduction of the contracture of the primary joint (either MP or PIP) to 0 to 5 degrees, 30 days after the last injection (clinical success)**. In the pivotal trials and supportive Studies 03 and 53, up to 3 injections of study medication may have been injected into the cord (associated with the contracture of the primary joint) every 30 days on Days 0, 30, and 60, and in supportive Studies 02 and 51, only 1 intra-cord injection of study medication was administered on Day 0.

Table 6.5 displays the results of the primary efficacy endpoint in the pivotal trials. A numerical and statistically significantly greater proportion of Xiaflex-treated patients compared to placebo-treated patients achieved clinical success after up to 3 injections with absolute treatment margins of 57% and 39% in Studies 57 and 59, respectively. For the Xiaflex-treated patients, the mean (SD) number of injections administered in the 90-day period was 1.7 (0.8) in each trial. For the subgroup efficacy analyses by primary joint type (MP or PIP), Xiaflex-treated patients had a greater proportion of clinical success compared to placebo-treated patients for each of these joint types in each pivotal trial.

**Table 6.5: Proportion of patients that achieved a reduction of the contracture of the primary joint to 0 to 5 degrees (clinical success) after up to 3 injections in the pivotal trials**

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

CI = 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 Xiaflex 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.

As shown in Table 6.6, the proportion of patients in the Xiaflex and placebo groups who achieved clinical success **after the first injection** was 39% and 1% in Study 57, and 27% and 5% in Study 59, respectively. The proportion of Xiaflex-treated patients with clinical success was similar after the first, second, and third injections (ranging from 35% to 39% in Study 57 and 25% to 27% in Study 59).

**Table 6.6: Proportion of patients that achieved a contracture reduction to 0 to 5 degrees, 30 days after the first, second, third, or last injection of the primary joint in the pivotal trials**

	Study 57 <sup>1</sup> (U.S.)		Study 59 <sup>2</sup> (Australian)	
	Xiaflex	Placebo	Xiaflex	Placebo
<b>Last injection (up to 3 injections)<sup>3</sup></b>	n=203 <b>64%</b>	n=103 <b>7%</b>	n=45 <b>44%</b>	n=21 <b>5%</b>
<b>First injection<sup>4</sup></b>	n=203 <b>39%</b>	n=103 <b>1%</b>	n=45 <b>27%</b>	n=21 <b>5%</b>
<b>Second injection<sup>4</sup></b>	n=99 <b>35%</b>	n=100 <b>1%</b>	n=22 <b>27%</b>	n=19 <b>0%</b>
<b>Third injection<sup>4</sup></b>	n=45 <b>36%</b>	n=91 <b>6%</b>	n=8 <b>25%</b>	n=18 <b>0%</b>

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 (see Table 6.5) 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 2<sup>nd</sup> 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 shown in Table 6.7, the results of the primary efficacy endpoint (clinical success) in the supportive trials (Studies 03, 53, 51, and 02) demonstrated numerically greater responses in Xiaflex-treated patients compared to placebo-treated patients. In Study 02, the single-dose-ranging trial, patients treated with the 0.58 mg Xiaflex dose demonstrated a numerical improvement in clinical success compared to patients treated with lower Xiaflex doses.

**Table 6.7: Proportion of patients that achieved a contracture reduction of the primary joint to 0 to 5 degrees, 30 days after the last injection (clinical success) in the supportive trials<sup>1</sup>**

Study	Treatment Groups	n	Clinical Success of Primary Joint (MP & PIP)
<b>Trials with up to 3 injections on Days 0, 30, and 60</b>			
Study 03 <sup>2</sup>	Xiaflex 0.58 mg	23	91%
	Placebo	12	0%
Study 53 <sup>3</sup>	Xiaflex 0.58 mg	17	77%
	Placebo	6	0%
<b>Trials with only 1 injection on Day 0</b>			
Study 51 <sup>3</sup>	Xiaflex 0.58 mg	5	20%
	Placebo	2	0%
Study 02 <sup>2</sup>	Xiaflex 0.58 mg	23	78%
	Xiaflex 0.29 mg	22	46%
	Xiaflex 0.145 mg	18	50%
	Placebo	17	0%

<sup>1</sup> The supportive trials were Studies 03, 53, 51, and 02.

<sup>2</sup> Randomized population was the primary statistical population for the efficacy analyses in Studies 02 and 03.

<sup>3</sup> ITT population (all treated patients) was the primary statistical population for the efficacy analyses in Studies 51 and 53.

Reference: Adapted from the final study reports for Studies 03, 53, 51, and 02.

### 6.1.5 Analysis of Secondary Endpoints

Results of the secondary efficacy endpoints in the pivotal trials (Studies 57 and 59) were consistent with the results of the primary efficacy endpoint in demonstrating a treatment benefit with Xiaflex. As shown in Table 6.8, after up to 3 injections, Xiaflex treatment resulted in a significantly greater decrease in the mean percent change from baseline in the contracture degree of the primary joint (MP and PIP) compared to placebo treatment. Results for this endpoint when subgrouped by primary joint type (MP or PIP) were consistent with the overall results supporting a treatment benefit of Xiaflex treatment in the change in degree of contracture.

For Xiaflex-treated patients, the mean percentage decreases in degree of contracture after the first, second, and third injections were 65%, 67%, and 60% in Study 57 and 59%, 63%, and 51% in Study 59.

**Table 6.8: Mean percent change from baseline in contracture degree after up to 3 injections of the primary joint by joint type in the pivotal trials**

	Study 57 <sup>1</sup>		Study 59 <sup>2</sup>	
	Xiaflex	Placebo	Xiaflex	Placebo
<b>Primary MP or PIP Joints</b>	n=203	n=103	n=45	n=21
Baseline contracture degree, mean (SD)	50 (20)	49 (20)	53 (15)	50 (16)
Contracture degree 30 days after injection, mean (SD)	12 (19)	46 (24)	17 (19)	44 (20)
<b>Primary MP Joints</b>	n=133	n=69	n=20	n=11
Baseline contracture degree, mean (SD)	48 (20)	45 (21)	50 (14)	47 (18)
Contracture degree 30 days after injection, mean (SD)	8 (8)	41 (22)	7 (15)	43 (23)
Mean % decrease from baseline in degree of contracture, 30 days after injection	87%	7%	84%	14%
<b>Primary PIP Joints</b>	n=70	n=34	n=25	n=10
Baseline contracture degree, mean (SD)	54 (19)	57 (17)	56 (15)	54 (13)
Day 30 contracture degree, mean (SD)	22 (22)	51 (25)	24 (22)	48 (18)
Mean % decrease from baseline in degree of contracture, 30 days after injection	65%	11%	59%	14%

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

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

Reference: Adapted from CSR of Study 57, Table 14.2.4.1, Page 124, Table 14.2.4.2, Page 128, Table 14.2.4.3, Page 132; also adapted from the CSR of Study 59, Table 21, Page 64.

As shown in Table 6.9, after up to 3 injections, Xiaflex treatment resulted in a significantly greater increase in the range of motion (ROM) from baseline for the primary joint (MP and PIP) and each joint type (MP or PIP) compared to placebo treatment in the pivotal trials.

For Xiaflex-treated patients, the mean ( $\pm$ SD) change from baseline in ROM (in degrees) after first, second, and third injections were 28 ( $\pm$ 20), 34 ( $\pm$ 22), and 35 ( $\pm$ 23), respectively, in Study 57, and 29 ( $\pm$ 17), 35 ( $\pm$ 20), and 33 ( $\pm$ 19), respectively, in Study 59.

**Table 6.9: Mean (SD) change from baseline in ROM (in degrees) after up to 3 injections of the primary joint by joint type in the pivotal trials<sup>1</sup>**

	Study 57 <sup>2</sup>		Study 59 <sup>3</sup>	
	Xiaflex	Placebo	Xiaflex	Placebo
<b>All Primary Joints (MP or PIP)</b>	n=197	n=102	n=45	n=21
Baseline ROM	44 (±20)	45 (±19)	40 (±15)	44 (±16)
ROM 30 days after injection	80 (±20)	50 (±22)	76 (±18)	52 (±20)
<b>Primary MP Joints</b>	n=129	n=68	n=20	n=11
Baseline ROM	43 (±20)	46 (±19)	40 (±12)	41 (±21)
ROM 30 days after injection	83 (±16)	50 (±21)	80 (±11)	50 (±21)
Change from baseline in ROM 30 days after injection	41 (±20)	4 (±13)	40 (±13)	9 (±15)
<b>Primary PIP Joints</b>	n=67	n=34	n=25	n=10
Baseline ROM	46 (±20)	44 (±18)	41 (±18)	47 (±10)
ROM 30 days after injection	75 (±24)	49 (±24)	73 (±21)	54 (±18)
Change from baseline in ROM 30 days after injection	28 (±22)	5 (±19)	32 (±20)	7 (±16)

<sup>1</sup> Primary joint was either MP or PIP of either hand. The numbers of patients at each time point with a ROM value differed.

<sup>2</sup> MITT population (all treated patients who had at least one post-treatment contracture measurement and had baseline contracture > 5 degrees) was the primary statistical population for the efficacy analyses in Study 57.

<sup>3</sup> ITT population (all treated patients) was the primary statistical population for the efficacy analyses in Study 59.

Reference: Adapted from the July 15, 2009 response to a statistical information request (submission #14), Table 1, Pages 1-4, Table 2, Page 8, Table 3, Page 12; from CSR of Study 59, Table 14.2.5.1, Pages 170- 173, Table 14.2.5.2, Page 177; Table 14.2.5.3, Page 181

### 6.1.6 Recurrence of Contracture

During the controlled and uncontrolled portions of Studies 54, 56, 57, 58, and 59, the investigator was asked to document the recurrence of contracture for patients who achieved a contracture reduction to 0 to 5 degrees (clinical success). In these studies **a recurrence was pre-specified as an increase in contracture to  $\geq 20^\circ$  associated with the presence of a palpable cord after successful Xiaflex treatment.** In the pooled controlled and uncontrolled portions of these studies, of the 830 Xiaflex-treated cords that achieved clinical success 30 (4%) cords had a contracture recurrence (the mean follow-up period after clinical success was 7.4 months). Of these 30 recurrences, 23% occurred within 3 months of follow-up and 50% occurred between 3 to 6 months of follow-up after clinical success.

In an exploratory analysis, **a recurrence was defined as a joint with an increase in contracture  $\geq 20^\circ$  after successful Xiaflex treatment (irrespective of the presence of a palpable cord).** In pooled controlled and uncontrolled portions of Studies 03, 04, 53, 54, 56, 57, 58, and 59, of the 897 Xiaflex-treated joints affected by a palpable cord that achieved contracture reduction to 0 to 5 degrees 97 (11%) had a recurrence of the contracture (exploratory definition). This analysis is likely to be more sensitive for contracture recurrence than the pre-specified recurrence definition; however, some of these cases may be due to non-DC etiologies.

In an attempt to place the incidence of contracture recurrence in the Xiaflex studies in perspective, a literature search was performed on the contracture recurrence following fasciectomy and/or fasciotomy for DC (see Table 6.10). Articles were selected if they included **a recurrence definition**

in which the contracture was severe enough to require another operation. These articles included retrospective, observational studies and prospective cohort studies. The incidence of recurrence was 0% to 23% following fasciectomy and 19% to 66% following fasciotomy. Although the follow-up period available for Xiaflex-treated patients is shorter and still accruing, the incidence of recurrence following Xiaflex-treatment thus far does not appear to be greater than literature reports of recurrence following surgery.

**Table 6.10: Literature reports of contracture recurrence (severe enough to require another surgery) following fasciectomy and fasciotomy for DC**

Literature Report	Recurrence Incidence (# of Patients)	Mean Follow-up	Study Type <sup>1</sup>	Recurrence Definition
<b>Fasciectomy</b>				
Foucher 1992	23% (n=107)	5.6 years	Retrospective (Same surgeon)	Severe enough to require another operation. Extension of disease at and outside surgical site
Skoff 2004	3% (n=30)	2.7-3.5 years	Prospective cohort (Same surgeon)	Required a second operation
Searle <sup>2</sup> 1992	0% (n=32)	3.2 years	Retrospective	Recurrent cord formation
Hall <sup>2</sup> 1997	0% (n=67)	4 years	Retrospective	Recurrent flexion contracture
<b>Fasciectomy or Fasciotomy</b>				
Dias 2006	15% (n=1037)	2.3 years	Retrospective (several surgeons)	Any deformity more than a mild MP joint contracture (severe enough to require another operation)
McFarlane 1990	6%-8% (n=434)	At 2 years <sup>3</sup>	Retrospective (several surgeons)	Appearance of disease within the area of operation that required reoperation
	6%-8% (n=48)	At 10 years <sup>3</sup>		
<b>Fasciotomy</b>				
Van Rijssen 2006	42% (n=55)	2.8 years	Retrospective (several surgeons)	Severe enough to require another operation
Duthie 1997	66% (n=82)	10 years	Retrospective (Same surgeon)	Required a second operation
Foucher 2003	19% (n=100)	3.2 years	Retrospective (several surgeons)	Required a second operation

<sup>1</sup> All these studies were observational

<sup>2</sup> Patients in the Hall 1997 and Searle 1992 articles had radical dermofasciectomy.

<sup>3</sup> These are not mean follow-up times; rather, they are incidences of recurrence at 2 and 10 years.

### 6.1.7 Subpopulations

Table 6.11 displays the exploratory subgroup efficacy analyses of intra-cordal Xiaflex injections compared to placebo injections, using the primary efficacy endpoint, by baseline demographics and disease characteristics in the pivotal trials (Studies 57 and 59). Treatment with Xiaflex appeared to exert a positive effect for all demographic subgroups. Subgroup efficacy analyses by race could not be performed, because there were too few non-Caucasians [371/372 (100%) of the patients in the pivotal trials were Caucasian (only 1 patient was Hispanic)]. Treatment with Xiaflex also appeared to exert a positive effect in patients whether or not they had prior DC surgery or prior DC surgery on the injected ray. Finally, Xiaflex treatment appeared to exert a positive effect for important baseline characteristics of the primary joint (joint type, contracture severity, and involved finger).

**Table 6.11: Subgroup efficacy (clinical success after up to 3 injections) by baseline demographics and disease characteristics in the pivotal trials<sup>1</sup>**

		Study 57 (U.S.)		Study 59 (Australian)	
		Xiaflex 0.58 mg	Placebo	Xiaflex 0.58 mg	Placebo
<b>Overall Population</b>		130/203 (64%)	111/172 (64%)	89/151 (59%)	124/160 (78%)
<b>Demographics</b>					
Age	< 65 years old	77/120 (64%)	5/57 (9%)	13/25 (52%)	1/9 (11%)
	65 ≥ but < 75 years old	41/62 (66%)	2/32 (6%)	7/19 (37%)	0/7 (0%)
	≥ 75 years old	12/21 (57%)	0/14 (0%)	0/1 (0%)	0/5 (0%)
Gender	Male	107/171 (63%)	3/30 (10%)	17/39 (44%)	0/17 (0%)
	Female	23/32 (72%)	4/73 (5%)	3/6 (50%)	1/4 (25%)
<b>Baseline Disease Characteristics</b>					
Prior DC Surgery <sup>2</sup>	Yes	46/72 (64%)	1/43 (2%)	9/24 (38%)	1/11 (9%)
	No	84/131 (64%)	6/60 (10%)	11/21 (52%)	0/10 (0%)
Prior DC Surgery on same ray that was injected	Yes	10/16 (63%)	N/A <sup>3</sup>	3/9 (33%)	N/A <sup>3</sup>
	No	120/187 (64%)	N/A <sup>3</sup>	17/36 (47%)	N/A <sup>3</sup>
<b>Baseline Characteristics of Primary Joint</b>					
Primary Joint Type	MP	102/133 (77%)	5/69 (7%)	13/20 (65%)	1/11 (9%)
	PIP	28/70 (40%)	2/34 (6%)	7/25 (28%)	0/10 (0%)
Severe joint contracture (> 50° for MP joint or > 40° for PIP joint)	Yes	41/101 (41%)	1/51 (2%)	11/30 (37%)	0/12 (0%)
	No	89/102 (87%)	6/52 (12%)	9/15 (60%)	1/9 (11%)
Finger	Little	68/123 (55%)	3/57 (5%)	14/31 (45%)	1/14 (7%)
	Ring	53/67 (79%)	3/35 (9%)	5/10 (50%)	0/5 (0%)
	Middle	6/10 (60%)	1/7 (14%)	0/2 (0%)	0/2 (0%)
	Index	3/3 (100%)	0/4 (4%)	1/2 (50%)	—

1 The primary efficacy endpoint was the proportion of patients with a contracture reduction to 0 to 5 degrees (clinical success) after up to 3 injections.

2 Primary surgery may have been on the same or different cord (involved the same or different finger) as the primary joint. In Study 57, the mean (SD) baseline degree of contracture of the primary joint was 50 (20) and 51 (20) for patients with prior surgery and without prior surgery, respectively. In Study 59, the mean (SD) baseline degree of contracture of the primary joint was 51 (17) and 56 (12) for patients with prior surgery and without prior surgery, respectively.

3 N/A is not available

Reference: June 23, 2009 submission (response to clinical IRs), Table 3, Page 11, Table 4, Page 11, and Table 5, Page 12. Also adapted from the JMP ADTJ\_I and ADDUPHX datasets in Studies 57 and 59.

In the pivotal trials, the majority of study medication injections were performed by hand surgeons or orthopedic surgeons. This raises questions regarding whether healthcare professionals without surgical training would have similar efficacy and safety results after having had similar product-related training and instruction. To further explore this issue, efficacy subgroup analyses were conducted by specialization. In Study 57, all investigators injecting study medication were surgeons. As shown in Table 6.12, orthopedic surgeons and hand surgeons who performed the injections obtained similar results for the primary efficacy endpoint (73% vs. 63%).

**Table 6.12: Efficacy by specialty subgroup analysis in Study 57**

Principal Investigator, (PI) (Location; Site #)	Total # (%) of patients	Proportion of Patients with Clinical Success (Primary Efficacy Endpoint) <sup>1</sup>	
		Xiaflex	Placebo
<b>All Sites</b>	<b>306 (100%)</b>	<b>130/203 (64%)</b>	<b>7/103 (7%)</b>
<b>1 Hentz (Palo Alto, CA; 1157)</b>	<b>37 (12%)</b>	<b>13/25 (52%)</b>	<b>0/12 (0%)</b>
<b>2 Lubahn (Erie, PA; 1158)</b>	<b>33 (11%)</b>	<b>14/23 (61%)</b>	<b>2/10 (20%)</b>
<b>3 Hurst (Stony Brook, NY; 1160)</b>	<b>28 (9%)</b>	<b>17/20 (85%)</b>	<b>0/8 (0%)</b>
<b>4 Kaplan (Indianapolis, IN; 1154)</b>	<b>25 (8%)</b>	<b>14/16 (88%)</b>	<b>1/9 (11%)</b>
<b>5 Costas (Atlanta, GA; 1164)</b>	<b>21 (7%)</b>	<b>7/14 (50%)</b>	<b>1/7 (14%)</b>
<b>6 Hotchkiss (NY, NY; 1159)</b>	<b>19 (6%)</b>	<b>8/13 (62%)</b>	<b>0/6 (0%)</b>
<b>7 Belsky (Newton, MA; 1175)</b>	<b>16 (5%)</b>	<b>4/11 (36%)</b>	<b>0/5 (0%)</b>
<b>8 Bear (Rockford, IL; 1166)</b>	<b>16 (5%)</b>	<b>7/11 (64%)</b>	<b>0/5 (0%)</b>
<b>9 Akelman (Providence, RI; 1161)</b>	<b>15 (5%)</b>	<b>6/9 (67%)</b>	<b>0/6 (0%)</b>
<b>10 McPherson (Minneapolis, MN; 1165)</b>	<b>13 (4%)</b>	<b>4/8 (50%)</b>	<b>1/5 (20%)</b>
<b>11 Blazar (Boston, MA; 1170)</b>	<b>12 (4%)</b>	<b>4/8 (50%)</b>	<b>0/4 (0%)</b>
<b>12 Britton (Denver, CO; 1152)</b>	<b>10 (3%)</b>	<b>5/6 (83%)</b>	<b>0/4 (0%)</b>
<b>13 Peimer (Marquette, MI; 1182)</b>	<b>10 (3%)</b>	<b>4/6 (67%)</b>	<b>2/4 (50%)</b>
<b>14 Frazier (Oklahoma City, OK; 1153)</b>	<b>18 (6%)</b>	<b>7/11 (64%)</b>	<b>0/7 (0%)</b>
<b>15 Meals (Los Angeles, CA; 1155)</b>	<b>19 (6%)</b>	<b>9/13 (69%)</b>	<b>0/6 (0%)</b>
<b>16 Roeshot (State College, PA; 1172)</b>	<b>14 (5%)</b>	<b>7/9 (78%)</b>	<b>0/5 (0%)</b>

The yellow highlights the results of all patients at all 16 sites in Study 57.

1 Primary efficacy endpoint was the proportion of patients that achieved a contracture reduction to 0 to 5 degrees of the primary joint, 30 days after the last injection, using the MITT population (all treated patients who had at least one post-treatment contracture measurement and had baseline contracture > 5 degrees).

2 Of the 26 investigators who performed injections at these 14 sites, 25 were hand surgeons except 1 was a plastic surgery fellow.

3. Of these 7 investigators who performed injections at these 2 sites, 6 were orthopedic surgeons except 1 was a hand surgeon.

Reference: Adapted from CSR from Study 57, Table 14.2.2.5, Pages 101-102; also adapted from the June 23, 2009 response to information requests, Table 1, Pages 4-7.

Study 59 included a subgroup of rheumatologists who injected study medication. Table 6.13 displays the results of a subgroup efficacy analysis, using the primary efficacy endpoint, subgrouped by medical specialist who performed the injections (hand surgeons, orthopedic surgeons, or rheumatologists). Although rheumatologists performed injections on a limited number of patients, the rheumatologists achieved similar results for the primary efficacy endpoint as the hand surgeons or orthopedic surgeons (45% vs. 47% vs. 40%).

**Table 6.13: Efficacy by specialty subgroup analysis in Study 59<sup>1</sup>**

Principle Investigator (Site #)		Total # (%) of patients	Proportion of Patients with Clinical Success (Primary Efficacy Endpoint) <sup>1</sup>	
			Xiaflex	Placebo
<b>All sites</b>		<b>66 (100%)</b>	<b>20/45 (44%)</b>	<b>1/21 (5%)</b>
<b>Hand Surgeons</b>		<b>12 (18%)</b>	<b>9/10 (90%)</b>	<b>0/10 (0%)</b>
1	<b>Coleman, Stephen (6005)</b>	<b>15 (23%)</b>	<b>6/10 (60%)</b>	<b>0/5 (0%)</b>
2	<b>Gilpin, David (6006)</b>	<b>12 (18%)</b>	<b>3/9 (33%)</b>	<b>0/3 (0%)</b>
<b>Orthopedic Surgeon</b>		<b>23 (35%)</b>	<b>6/15 (40%)</b>	<b>1/8 (13%)</b>
3 & 4	<b>Karrasch, Jeff (6003) and Houston, Anthony (6007)<sup>3</sup></b>	<b>23 (35%)</b>	<b>6/15 (40%)</b>	<b>1/8 (13%)</b>
<b>Rheumatologists</b>		<b>16 (24%)</b>	<b>5/11 (45%)</b>	<b>0/5 (0%)</b>
4	<b>Hall, Stephen (6002)<sup>4</sup></b>	<b>16 (24%)</b>	<b>5/11 (45%)</b>	<b>0/5 (0%)</b>

1 The primary efficacy endpoint was the proportion of patients that achieved a reduction of the contracture to 0 to 5 degrees of the primary joint, 30 days after the last injection, using the ITT population (all treated patients).

2 All of the principal investigators and sub-investigators who performed the injections and finger extension procedures were hand surgeons.

3 The results for Sites 6003 and 6007 were combined in this row because Dr. Houston did all the injections and finger extension procedures at both sites. Dr. Houston is an orthopedic surgeon with hand surgery training.

4 At Site 6002, the 4 injectors were rheumatologists.

Reference: Adapted from CSR from Study 59, Table 14.2.2.5, Page 151; also adapted from the June 23, 2009 response to information requests, Table 1, Pages 4-7.

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

In their pivotal trials, Auxilium only evaluated the efficacy of one Xiaflex dose in the treatment of patients with DC (0.58 mg). In Study 02, the single-dose-ranging trial, patients treated with one 0.58 mg Xiaflex injection demonstrated a numerical improvement in clinical success compared to patients treated with single injections of lower Xiaflex doses (0.29 mg and 0.145 mg). See these results in Table 6.7 in Section 6.1.4 (Analysis of Primary Endpoints). Therefore, Auxilium proposes only one Xiaflex dose (0.58 mg).

In the pivotal trials, Xiaflex injections were administered once every 30 days. There is no information regarding the efficacy of Xiaflex after administration at different frequencies. Auxilium proposes that Xiaflex injections be repeated at 4-week intervals if necessary.

In the pivotal trials, up to 3 Xiaflex injections into the primary joint were allowed. Xiaflex-treated patients who received up to 3 injections every 30 days had greater responses than Xiaflex-patients who received only 1 injection (64% vs. 39% in Study 57 and 44% vs. 27% in Study 59). Auxilium proposes that each cord associated with a contracture may receive up to 3 Xiaflex injections every 4 weeks. There is no controlled data regarding the efficacy the use of 4 or more injections in the treatment of DC.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Table 6.14 displays an analysis of the time to reach clinical success of the primary joint (contracture reduction to 0 to 5 degrees) for patients who reached clinical success in the pivotal trials. Of the Xiaflex-treated patients who reached clinical success, 60% to 61% reached clinical success within 30 days of the first injection.

**Table 6.14: Time to reach clinical success for patients who achieved clinical success in the pivotal trials through Day 90<sup>1</sup>**

	Day <sup>2</sup>	Study 57 (U.S.)		Study 59 (Australian)	
		Xiaflex 0.58 mg	Placebo	Xiaflex 0.58 mg	Placebo
# of patients who achieved clinical success		130 patients	7 patients	20 patients	1 patient
Injection # 1	1	26 (20%)	0 (0%)	1 (5%)	0 (0%)
	7	25 (19%)	0 (0%)	3 (15%)	1 (100%)
	30	29 (22%)	1 (14%)	8 (40%)	0 (0%)
Injection # 2	0	1 (1%)	0 (0%)	0 (0%)	0 (0%)
	1	10 (8%)	0 (0%)	0 (0%)	0 (0%)
	7	11 (8%)	0 (0%)	2 (10%)	0 (0%)
	30	13 (10%)	1 (14%)	4 (20%)	0 (0%)
Injection # 3	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	1	4 (3%)	0 (0%)	2 (10%)	0 (0%)
	7	5 (4%)	0 (0%)	0 (0%)	0 (0%)
	30	5 (4%)	5 (71%)	0 (0%)	0 (0%)
	90	1 (1%)	0 (0%)	0 (0%)	0 (0%)

<sup>1</sup> Contracture measurements were only assessed by goniometer 1, 7, and 30 days after study medication injections.

Only patients who reached clinical success are included in this table.

<sup>2</sup> Days after injection in which joint contractures were measured.

Reference: Adapted from the CSR in Study 59, Table 14.2.7.1, Page 197; also adapted from the CSR in Study 57, Table 14.2.7.1, Page 199.

There was no evidence of tolerance to Xiaflex because the proportion of Xiaflex-treated patients who achieved clinical success remained constant after each of the first three injections. In Study 57, 35% to 39% of Xiaflex-treated patients had clinical success after the first, second, or third injections and in Study 59, 25% to 27% of Xiaflex-treated patients had clinical success after the first, second, or third injections.

For discussion of the recurrence of contractures, see Section 6.1.6 (Recurrence of Contracture).

## 7 Review of Safety

### Safety Summary

**Exposure:** In entire safety database (the controlled and uncontrolled portions of the 12 submitted Xiaflex studies), 1082 patients received at least one intra-cord injection of 0.58 mg of Xiaflex (2630 Xiaflex injections). The mean ( $\pm$ SD) duration of safety follow-up for these 1082 patients was 9.5 ( $\pm$ 4.6) months. The numbers of Xiaflex-treated patients and the duration of safety follow-up were adequate to evaluate the safety of Xiaflex in the treatment of DC and are consistent with the Agency's advice during clinical development meetings.

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 Xiaflex and placebo into the cord affecting the primary joint, respectively. In addition to the 1082 patients who received the proposed Xiaflex dose (0.58 mg), 22 and 18 patients received a lower Xiaflex dose (0.29 mg and 0.145 mg, respectively).

**Major Safety Results:** No patients died in the placebo-controlled portions of the pivotal trials through Day 90. In the complete clinical development program for Xiaflex, there were a total of 7 deaths in patients who received intra-cord injections of 0.58 mg of Xiaflex and no deaths in a limited number of placebo-treated patients and patients treated with lower Xiaflex doses (0.145 or 0.29 mg). Two of the deaths occurred in extended follow up from an earlier, academic pilot study of Xiaflex. It is not likely that these deaths were due to the Xiaflex injections given the following reasons:

- There is no evidence of systemic Xiaflex exposure after intra-cordal Xiaflex injections.
- There was no temporal relationship between the Xiaflex injections and the deaths (the deaths occurred several months after the last Xiaflex injection).
- There was no evidence of an increase in the incidence of death with a greater number of Xiaflex doses.
- The reported causes of death were consistent with the underlying patient population and their comorbidities.

In the controlled portions of the pooled pivotal trials through Day 90, 2% and 0% of the Xiaflex-treated and placebo-treated patients had a SAE that involved the treated extremity. In the controlled and uncontrolled portions of the 12 submitted Xiaflex studies, out of 1082 patients treated with 0.58 mg of Xiaflex (with a total of 2630 Xiaflex injections), 11 (1.0%) patients had SAEs that involved the injected extremity. Of these 11 SAEs, 3 were flexor tendon ruptures which occurred within 7 days of intra-cordal Xiaflex injection of the affected digit, were likely related to Xiaflex treatment, and required surgery to correct the tendon ruptures of the affected digit. Although there are major limitations of cross study comparisons, it appears that the incidence of SAEs of the treated extremity observed in the Xiaflex studies, and the incidence of tendon rupture in particular, does not appear to be out of proportion to the incidence of surgical complications following fasciectomy and/or fasciotomy for DC reported in the published literature.

In the controlled portions of the pivotal trials through Day 90, there were few adverse events leading to discontinuation (1% and 0% of the Xiaflex-treated and placebo-treated patients had DAEs, respectively). Of the 3 Xiaflex-associated DAEs, 2 involved the treated extremity (severe injection site pain and exacerbation of a regional pain syndrome).

In the controlled portions of the pivotal trials through Day 90, **after up to 3 injections**, two times as many Xiaflex-treated patients than placebo-treated patients had an AE (98% vs. 49%). The overwhelming majority of Xiaflex-associated AEs were local reactions. The most commonly reported Xiaflex-associated AEs were edema (mostly edema of the treated hand), contusion, hemorrhage, and pain involving the treated extremity and were likely related to Xiaflex injection. For Xiaflex-treated patients, the types and proportion of AEs were similar after 1 Xiaflex injection to after up to 3 Xiaflex injections, although fewer placebo-treated patients experienced an AE after a single injection.

**Clinical Implications of Immunogenicity:** In the pivotal trials, almost all of the Xiaflex-treated patients had antibodies against AUX-I (89% to 95%) or against AUX-II (82% to 88%) after the first injection. All Xiaflex-treated patients who received a total of 4 or more injections (i.e., because more than one cord was treated) had antibodies to AUX-I and AUX-II.

There was no difference in the proportion of Xiaflex-treated patients with positive or negative neutralizing antibody status to AUX-I who achieved the primary endpoint of clinical success. A slightly lower proportion of Xiaflex-treated patients with positive neutralizing antibody status to AUX-II achieved the primary endpoint than patients with negative neutralizing antibody status, although the numbers of patients were too small to make definitive conclusions.

Xiaflex treatment was associated with an increased proportion of mild allergic reactions (e.g., pruritus) compared to placebo treatment and the likelihood of these reactions increased with successive injections. However, severe reactions, e.g., those requiring hospitalization, or adrenergic agents, or those associated with respiratory compromise, hypotension, or end-organ dysfunction, were not observed. Although there is a theoretical concern of cross-reactivity of anti-product antibodies to human matrix metalloproteinases (MMPs), there was no clinical evidence of this in the clinical database.

**Limitations of the Data:** Since the overwhelming majority of investigators who performed the injections were hand surgeons who were thoroughly trained in Xiaflex injection procedures, the incidence of SAEs involving the treated extremity in the clinical trials may underestimate the risk of serious local complications of Xiaflex injections in a typical clinical practice. A post-marketing requirement (PMR) will help elucidate the incidence of serious adverse reactions of the injected extremity following Xiaflex injections by all intended specialists.

**Summary:** In summary, the safety of Xiaflex in the controlled and uncontrolled portions of the Xiaflex studies supports its approval for the treatment of Dupuytren's **contracture**. **The Xiaflex** labeling should include the risks of serious local complications such as tendon ruptures and a PMR is recommended to assess the incidence of serious adverse reactions of the injected extremity following Xiaflex injections by all intended specialists.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

See Section 5.2 (Review Strategy) for the safety pools that will be used to evaluate the safety of intra-cord injections of Xiaflex in the treatment of DC. See Table 5.1 in Section 5.1 (Tables of Xiaflex Clinical Studies) for the design of the major safety trials for the safety analyses (Studies 57 and 59).

### 7.1.2 Categorization of Adverse Events

Auxilium's categorization of adverse events (AEs) with preferred terms are consistent with the investigator's verbatim terms including the AEs leading to discontinuation (e.g., injection site pain, complex regional pain syndrome).

### 7.1.3 Pooling of Data Across Studies to Estimate and Compare Incidence

See Section 5.2 (Review Strategy) for the safety pools that will be used to evaluate the safety of Xiaflex intra-cord injections in the treatment of DC.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Exposure at Appropriate Doses and Durations of Target Populations

In entire safety database (the controlled and uncontrolled portions of the 12 submitted Xiaflex studies), **1082 patients with 1780 Dupuytren's cords** received at least one intra-cord injection of 0.58 mg of Xiaflex (**2630 Xiaflex injections**). See Table 7.1 for the number of Xiaflex injections that patients received in the 12 submitted studies (Studies 02, 03, 04, 51, 52, 53, 54, 55, 56, 57, 58, and 59). The mean ( $\pm$ SD) duration of safety follow-up for these 1082 patients was 9.5 ( $\pm$ 4.6) months. In the safety database, 22 and 18 patients received one intra-cord injection of a lower Xiaflex dose (0.29 mg and 0.145 mg, respectively).

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 Xiaflex and placebo into the cord affecting the primary joint, respectively.

**Table 7.1: Xiaflex exposure in controlled and uncontrolled portions of the 12 submitted Xiaflex studies**

# 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.

### 7.2.2 Exposure at Appropriate Demographics of Target Populations

See Section 6.1.2 (Demographics) for the baseline demographics in the two pivotal trials. There were no significant differences in the baseline demographics for the primary efficacy and safety populations.

### 7.2.3 Special Animal and/or In Vitro Testing

According to Dr. Mukherjee, the pharmacology/toxicology reviewer, the pharmacology and toxicology studies of Xiaflex were **adequate to explore Xiaflex’** potential adverse reactions [see Section 4.3 (Preclinical Pharmacology/Toxicology) for more details].

### 7.2.4 Routine Clinical Testing

The types and frequencies of safety tests used to assess AEs, vital signs, labs, and other tests were adequate to assess the safety of intra-cordal Xiaflex injections in the treatment of DC.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

No specific drug-drug interactions studies were required for Xiaflex since there was no evidence of systemic absorption.

## 7.3 Major Safety Results

Table 7.2 presents the major safety results in the double-blinded, placebo-controlled portions of the pooled pivotal trials through Day 90 and the controlled and uncontrolled portions of the 12 submitted Xiaflex studies. Almost all Xiaflex-treated patients had an AE and a greater proportion had an AE compared to placebo-treated patients. The overwhelming majority of these AEs were local reactions.

A similar proportion of Xiaflex-treated and placebo-treated patients had an SAE that did not involve the injected extremity. These results are not unexpected since there was no evidence of systemic Xiaflex exposure after single intra-cord injections of 0.58 mg of Xiaflex.

A slightly greater proportion of Xiaflex-treated patients compared to placebo-treated patients had SAEs that involved the treated extremity. No patients died during the 90-day placebo-controlled period, and 5 deaths occurred during the total follow-up period through data cut-off in the 12 submitted studies. The causes of death in the Xiaflex clinical program appear to be consistent with what might be expected for the underlying patient population.

**Table 7.2: Major safety results**

<b>Double-Blind, Placebo-Controlled Portions of Pooled Pivotal Trials Through Day 90<sup>1</sup></b>		
	<b>0.58 mg of Xiaflex (n=249)</b>	<b>Placebo (n=125)</b>
<b>Patients who died</b>	<b>0 (0%)</b>	<b>0 (0%)</b>
<b>Patients with ≥ 1 SAE</b>	<b>7 (3%)</b>	<b>1 (1%)</b>
<b>Patients with ≥ 1 SAE involving the injected extremity</b>	<b>5 (2%)</b>	<b>0 (0%)</b>
<b>Patients with ≥ 1 SAE that did not involve the injected extremity</b>	<b>2 (1%)</b>	<b>1 (1%)</b>
<b>Patients with ≥ 1 DAE</b>	<b>3 (1%)</b>	<b>0 (0%)</b>
<b>Patients with ≥ 1 AE</b>	<b>243 (98%)</b>	<b>61 (49%)</b>
<b>Controlled and Uncontrolled Portions of all 12 Submitted Xiaflex Studies<sup>2</sup></b>		
	<b>0.58 mg of Xiaflex</b>	
<b>Number of Xiaflex-treated patients (0.58 mg)</b>	<b>n=1082</b>	
<b>Patients who died<sup>3</sup></b>	<b>5/1082 (0.5%)</b>	
<b>Patients with ≥ 1 SAE involving the treated extremity<sup>4</sup></b>	<b>11/1082 (1.0%)</b>	
<b>Patients with ≥ 1 tendon rupture involving the treated extremity</b>	<b>3/1082 (0.3%)</b>	
<b>Number of Xiaflex injections (0.58 mg)</b>	<b>n=2630</b>	
<b>SAEs involving the treated extremity per Xiaflex injection<sup>4</sup></b>	<b>11/2630 (0.4%)</b>	
<b>Tendon ruptures involving the treated extremity per Xiaflex injection</b>	<b>3/2630 (0.1%)</b>	

<sup>1</sup> Includes all patients who received ≥ 1 injection of study medication in the pooled Studies 57 and 59 through Day 90

<sup>2</sup> Includes all patient who received at least one injection of 0.58 mg of Xiaflex in the pooled submitted studies (Studies 02, 03, 04, 51, 52, 53, 54, 55, 56, 57, 58, and 59).

<sup>3</sup> Two Xiaflex-associated deaths from an academic study in the literature are not included in this incidence (see Table 7.3 for the narratives of the 5 deaths in the 12 submitted Xiaflex studies and the 2 deaths from the academic study).

<sup>4</sup> There were 11 SAEs that involved the treated extremity in the 12 submitted studies including 3 tendon ruptures. Several of these SAEs may have not been related to Xiaflex; therefore, this incidence likely represents an upper bound of related SAEs involving the treated extremity.

Reference: Adapted from the CSR of Study 57, Table 22, Page 60 and CSR of Study 59, Table 39, Page 88; also adapted from the ISS and Safety Update.

### 7.3.1 Deaths

There were no deaths in Xiaflex-treated or placebo-treated patients in the controlled portions of the pivotal trials.

As shown in Table 7.3, in the complete clinical development program for Xiaflex, there were a total of 7 deaths in patients who received intra-cord injections of 0.58 mg of Xiaflex and no deaths in a limited number of placebo-treated patients. Two of the deaths occurred in extended follow up from an earlier, academic pilot study of Xiaflex. In an early phase dose-ranging clinical study, there were no deaths in

the Xiaflex-treated patients who received lower doses (either 0.145 or 0.29 mg of Xiaflex), but exposure periods for patients in these groups were brief. Given the following reasons, it is not likely that these deaths were due to the Xiaflex injections:

- There is no evidence of systemic Xiaflex exposure after intra-cordal Xiaflex injections.
- There was no temporal relationship between the Xiaflex injections and the deaths (the deaths occurred several months after the last Xiaflex injection).
- There was no evidence of an increase in the incidence of death with a greater number of Xiaflex doses.
- The reported causes of death were consistent with the underlying patient population and their comorbidities.

**Table 7.3: Narratives of the 7 deaths in the controlled and uncontrolled portions of all the Xiaflex studies and literature reports of Xiaflex in DC<sup>1</sup>**

	Patient # (Study)	Narrative	Time between last Xiaflex injection & Death Date [# of Injections] <sup>2</sup>
<b>Auxilium's Submitted Studies of Xiaflex<sup>3</sup></b>			
1	101-CMP (Study 02)	68 year old male with COPD over 20 years, prostate cancer, and prior alcoholism received one placebo injection on Day 1 and two Xiaflex injections on Days 84 and 396. On Day 560, he was hospitalized for iliac artery stenosis and on Day 604 he died of COPD (during the first quarter of (b) (4)).	208 days [2]
2	004-CMP (Study 02)	63 year old male with DM, HTN, colon cancer (s/p hemicolectomy 9 years prior to study admission). Received 0.145 mg of Xiaflex on Day 1 and subsequently received 2 injections of 0.58 mg of Xiaflex on Days 168 and 378. On Day 388, he reported weight loss, fever, and cough. Around Day 454 he was diagnosed with liver cancer and subsequently died (date of death not provided) (about fourth quarter of 2001).	≥ 76 days [3]
3	1168-7010 (Study 56)	77 year old male, CAD, hyperlipidemia, glaucoma, and arthritis. Received 1 Xiaflex injection on Day 1 and had symptoms of an MI and died of an MI on Day 157 (second quarter of (b) (4)).	157 days [1]
4	1178-7704 (Study 56)	79 year old male with DM type II, HTN, hyperlipidemia, GERD, and hypothyroidism. Received 1 Xiaflex injection on Day 1 and died on Day 180 due to a MI (second quarter of (b) (4)).	180 days [1]
5	6002-4242 (Study 54)	76 year old male with CAD (MI in 1997 and 2006), HTN, hyperlipidemia, seizures, COPD, and prostate cancer. Received 1 Xiaflex injection on Day 1 and had an MI on Day 261 and died on Day 267 (fourth quarter of 2008).	267 days [1]
<b>Pilot Academic Study<sup>4</sup></b>			
6	1008 <sup>4</sup>	75 year old male with COPD over 20 years died from complications of pulmonary fibrosis about one year after his last injection of Xiaflex.	About 365 days [1]
7	100028 <sup>4</sup>	68 year old male with history of cardiac disease died 2 months after his last injection of Xiaflex from a rupture of aortic aneurysm.	About 60 days [1]

1 All of the patients who died received 0.58 mg of Xiaflex.

2 Number of Xiaflex injections received prior to death.

3 These 5 deaths were from 12 submitted Xiaflex studies (Studies 02, 03, 04, 51, 52, 53, 54, 55, 56, 57, 58, and 59).

4 These 2 deaths, reported by Auxilium, were from a pilot academic study.

Reference: Adapted from the case report forms and narratives in Studies 02, 54, and 56 and the Integrated Summary of Safety.

### 7.3.2 Nonfatal Serious Adverse Events

In the double-blind, controlled portions of the pivotal trials through Day 90, 3% and 1% of the

Xiaflex-treated and placebo-treated patients had a SAE (see Table 7.4). Of these SAEs, a similar proportion of Xiaflex-treated and placebo-treated patients had SAEs that did not involve the injected extremity; however, a greater proportion of Xiaflex-treated patients, compared to placebo-treated patients, had SAEs involving the injected extremity (2% vs. 0%).

**Table 7.4: SAEs during placebo-controlled portion of the pooled pivotal trials through Day 90<sup>1</sup>**

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

<sup>1</sup> Pivotal trials were Studies 57 and 59.

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

As shown in Table 7.5, in the controlled and uncontrolled portions of the 12 submitted Xiaflex studies, out of 1082 patients treated with 0.58 mg of Xiaflex (with a total of 2630 Xiaflex injections), 11 (1.0%) patients had SAEs that involved the injected extremity. See Tables 7.6 and 7.7 for detailed narratives regarding these SAEs involving the injected extremity that occurred in the controlled and uncontrolled portions of the trials, respectively. Of the 11 SAEs, 7 (64%) occurred within 2 weeks of the last Xiaflex injection. Many of these patients required surgery or additional medical treatment to correct the SAE. Of these 11 SAEs, 3 were flexor tendon ruptures, which occurred within 7 days of intracordal Xiaflex injection of the affected digit, and 1 was a flexor pulley rupture occurring 43 days after intracordal Xiaflex injection of the affected digit. These events appeared to be related to study treatment. These four patients required surgery to correct the tendon or pulley rupture. The patient who underwent an elective amputation of the right 5th finger had received Xiaflex injection near the 5th MP joint, but also had a severe untreated contracture near the 5th PIP which rendered the digit nonfunctional; she later injured the 5th digit in an unrelated traumatic event, resulting in the recommendation for elective amputation.

Of the 11 Xiaflex-treated patients who had SAEs that involved the injected extremity, 9 (82%) received injections by a hand surgeon or plastic surgeon and 2 (18%) received injections by a rheumatologist. All 4 Xiaflex-treated patients who had a tendon rupture or pulley rupture received injections by a hand surgeon. From these data, it does not appear that non-surgeon injectors (e.g., rheumatologists) had a greater incidence of SAEs that involved the treated extremity compared to hand or plastic surgeons. However, since there were few SAEs that involved the treated extremity and data on which investigator performed injections was not collected at sites in which there were multiple

injectors with different specialties, no definitive conclusions can be made regarding the association between these SAEs and the medical specialty of the injectors.

**Table 7.5: Summary of the SAEs that involved the injected extremity in the controlled and uncontrolled portions of all the Xiaflex studies<sup>1</sup>**

	Patient #	Study	SAE of the injected extremity	Time Between Last Xiaflex Injection & AE	# of Injections into Cord <sup>2</sup>	Treatment/Outcome	Investigator Training <sup>3</sup>
<b>Controlled Portions of the Pivotal Trials Through Day 90</b>							
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
<b>Open-Label, Uncontrolled Portions of the Xiaflex Studies</b>							
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 <sup>nd</sup> 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 5 <sup>th</sup> finger	103 days	1	Surgery	Hand surgeon

<sup>1</sup> Xiaflex Studies include Studies 02, 03, 04, 51, 52, 53, 54, 55, 56, 57, 58, and 59.

<sup>2</sup> Number of Xiaflex injections into the relevant cord prior to the SAE. Xiaflex may have been injected at other sites.

<sup>3</sup> 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.

**Table 7.6: Narratives of the 5 SAEs that involved the injected extremity in the double-blind, placebo-controlled portions of the pivotal trials through Day 90<sup>1</sup>**

Patient # (Study)	Narrative	Time Between Last Xiaflex Injection & AE (# of Injections) <sup>2</sup>
1157-4203 (Study 57)	76-year-old male with prior fasciotomy for DC (left 3 <sup>rd</sup> and 5 <sup>th</sup> fingers), HTN, received 1 Xiaflex injection into the cord affecting the left 5 <sup>th</sup> MP joint on Day 1 and on Day 2 had 3 finger extensions. On Day 28, had a second Xiaflex injection into the cord affecting the left 5 <sup>th</sup> MP joint and on Day 29 had 3 finger extension procedures. On Day 54, had a first Xiaflex injection into the cord affecting the left 5 <sup>th</sup> PIP joint and required 2 finger extension procedures on Day 55. On Day 59, unable to flex his finger. On Day 61, had no active flexion of the FDS or the FDP to the left fifth finger. On Day 62, [REDACTED] was performed. Findings revealed that there were tendon ruptures (FDS and the FDP) with obliteration of the A2 pulley. A 4 mm Hunter silicone rod was placed and definitive surgery scheduled for a later time. The Dupuytren's cord was ruptured.	4 days (3)
1154-2710 (Study 57)	61 year old male with HTN, depression, and insomnia. Administered Xiaflex on Day 1 into the cord affecting the PIP joint of the 5th finger and had finger manipulation on Day 2. On Day 8, after pulling a handle at work, felt a pop at the injection site and had bruising, swelling, and decreased ability to flex the finger. On Day 10, an MRI showed tendon ruptures: full thickness tear of the flexor digitorum profundus (FDP), severe partial tear of the flexor digitorum superficialis tendon (FDS), and probable tear of the A2 pulley of the fifth digit. On Day 49, surgery was performed and a complete rupture of FDP tendon was found and the FDS tendon was intact. [REDACTED]: tenolysis of FDS tendon, excision of FDP tendon remnant in palm, and lumbrical release left small finger. Following surgery, flexion to approximately 90 degrees was achieved and passive extension to 5 degrees of flexion was obtained. On Day 140, active flexion of the left small MP joint (0-85°) and PIP joint (40-50°).	7 days (1)
1157-4201 (Study 57)	67 year old woman with history of DVT, history of pneumonia, interstitial cystitis, anxiety, osteoporosis, and a history of complex regional pain syndrome (CRPS) following bilateral distal radius fractures in 2002. On Day 1, Xiaflex into the cord affecting the left 5th PIP. Day 2 manipulation of the finger resulted in rupture of the cord and an increase in extension but not to success endpoint. On Day 13, had persistent swelling and increased pain and tenderness over the dorsum of the PIP joint. On Day 14, the investigator reported findings that strongly suggested the development of CRPS. She was [REDACTED].	13 days (1)
1170-3801 (Study 57)	73-year-old female with HTN, hyperlipidemia, gastritis, and hypothyroidism. Received Xiaflex injections on Day 1, 25, and 56, which were injected into the cord affecting the right 5th MP joint. On Day 2, 26, and 57 had 3, 0, and 3 finger extension procedures, respectively. On Day 76, the extensor at the 5 <sup>th</sup> right finger was deficient. An examination showed sagittal band disruption with nonreducer tendon. The investigator considered this ligament disorder [REDACTED], which became apparent only after the MP joint of the small right 5th finger regained some extension (i.e., contracture reduced from 75° to 40° after treatment with Xiaflex). [REDACTED].	20 days (3)
6003-1601 (Study 59)	61 year old male. On Day 1 received Xiaflex into the cord associated with the left 5 <sup>th</sup> PIP and then had a second Xiaflex injection on Day 28. On Day 71, had worsening of his left 5 <sup>th</sup> finger contracture. On examination on Day 84, left 5 <sup>th</sup> PIP had greater contraction and worse function. An MRI showed an A2 and A4 pulley rupture (flexor pulley ruptures) with an intact flexor tendon without evidence of Dupuytren's contracture and without neurovascular compromise. On Day 238, the patient had [REDACTED]: a left 5 <sup>th</sup> PIP joint fusion and tenotomy (cutting or dividing a tendon).	43 days (2)

1 Studies 02, 03, 04, 51, 52, 53, 54, 55, 56, 57, 58, and 59. All of these SAEs occurred with 0.58 mg of Xiaflex injections.

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

Reference: Narratives and case reports forms from the final study reports of Studies 54, 55, 56, 57, and 59 and from the Integrated Summary of Safety.

**Table 7.7: Narratives of the 6 SAEs that involved the injected extremity in the uncontrolled, open-label portions of all the Xiaflex studies<sup>1</sup>**

Patient # (Study)	Narrative	Time Between Last Xiaflex Injection & AE [# of Injections] <sup>2</sup>
1167-1011 (Study 55)	62 year old male with HTN, asthma, GERD, BPH, hyperlipidemia, back pain, and a Boutonniere deformity of the 5th finger. Received Xiaflex on Day 0 into the PIP of the 5th finger on the right hand and on Day 1, had hand manipulation resulting in rupture of the cord. On Day 7, had weakness of the treated finger and on Day 8, MRI showed a complete tendon rupture of the 5 <sup>th</sup> (right) flexor digitorum superficialis tendon and a significant attenuation of the size of the flexor digitorum profundus tendon.	≤ 7 days [1]
6002-1502 (Study 59)	51 year old male with hyperlipidemia. On Day 1, given Xiaflex and on Day 29 given a second Xiaflex injection in the cord associated with the left 2 <sup>nd</sup> MP joint. On Day 42 had left hand tingling. On Day 182 and Day 276 the cord thickened. On Day 360, diagnosed with proliferation of the cord and a sensory abnormality of left hand. On Day 434, had a fasciectomy and removal of the cord of the left 2 <sup>nd</sup> finger. Post-surgery the patient had full ROM.	13 days [2]
6006-4528 (Study 54)	67 year old male with history of hyperlipidemia. On Day 1 received 1 Xiaflex injection into the cord associated with right 2 <sup>nd</sup> MP joint. On Day 14, had a farming accident and his right 2 <sup>nd</sup> finger was caught in a cattle crush. On Day 29, diagnosed with a fracture of the tip of right 2 <sup>nd</sup> finger with a ligament tear.	14 days [1]
6008-4705 (Study 54)	47 year old male with a prior surgery for DC of left 5th finger about 11 years prior to study. Received Xiaflex injection into cord involving the right 5th MP joint on Day 0 and did not require finger extensions because the cord ruptured. On Day 7, received 1 Xiaflex injection into the cord involving the right 5 <sup>th</sup> PIP joint and on Day 2 required 2 finger extensions. On Day 30, received 1 Xiaflex injection into the cord involving the left 5 <sup>th</sup> MP joint. On Day 133, received his fourth Xiaflex injection into the cord involving the right 3 <sup>rd</sup> PIP. On Day 134, received 1 finger extension procedure. He had local reactions after this injection. On Day 147, had loss of DIP joint movement in the right 3 <sup>rd</sup> finger. MRI showed hypertrophic tendonitis and intrasubstance but not complete tear.	14 days [4]
1170-3816 (Study 58)	67 year old female with anxiety, hyperlipidemia, GERD, HTN. Received Xiaflex injection in the cord affecting the left 5 <sup>th</sup> PIP on Day 1 and on Day 28 developed a Boutonniere deformity of the left 5 <sup>th</sup> DIP and a splint was placed to correct the deformity.	28 days [1]
1173-7222 (Study 56)	75-year-old female with history of prior surgery for DC, HTN, GERD, essential tremors, spinal stenosis, herniated discs, osteopenia, OA, prior history of thrombophlebitis from an IV, prior history of pyelonephritis, and prior intestinal obstruction. Given Xiaflex on Day 0 and on Day 0 had right hand bruising, swelling, injection site tenderness (MP joint) and hematoma. All of these AEs resolved by Day 14. For her the primary MP joint, the baseline fixed flexion contracture was 30 degrees and on Day 1 and Day 90, the MP had 45 and 20 degrees of contracture, respectively. Baseline, Day 1, and Day 2 PIP contractures of her untreated right 5 <sup>th</sup> finger were 105, 105, and 100 degrees, respectively. On Day 103, injured her right 5 <sup>th</sup> finger (1.5 cm skin laceration with exposed flexor tendon) from a handle of a plastic shopping bag. On Day 106, her hand surgeon (non-investigator) saw no evidence of an infection and offered the patient either a skin flap procedure or an elective amputation because the right 5 <sup>th</sup> finger was not functional was constantly in her way due to the severe PIP contracture and the skin flap procedure would not likely be successful. Patient had an elective amputation of the right 5th finger on Day 115. She had no post-surgical complications.	103 days [1]

<sup>1</sup> Studies 02, 03, 04, 51, 52, 53, 54, 55, 56, 57, 58, and 59. All of these SAEs occurred with 0.58 mg of Xiaflex injections.

<sup>2</sup> Number of Xiaflex injections into the relevant cord prior to the SAE. Xiaflex may have been injected at other sites.

Reference: Narratives and case reports forms from the final study reports of Studies 54, 55, 56, 57, and 59 and from the Integrated Summary of Safety.

Because there are no currently available non-surgical treatments for DC, in an attempt to place the incidence of these SAE in perspective, a literature search on complications following fasciectomy and/or fasciotomy for DC was performed. The search included retrospective, observational studies and prospective cohort studies. As shown in Table 7.8, the incidence of SAEs of the treated extremity observed in the Xiaflex studies, and the incidence of tendon rupture in particular, does not appear to be out of proportion to the incidence of surgical complications reported in the published literature.

**Table 7.8: Intraoperative and postoperative complications after fasciectomy or fasciotomy for DC compared to Xiaflex-associated SAEs involving the treated extremity in the Xiaflex studies**

<b>Surgical Complications in the Literature<sup>1</sup></b>	
<b>Intra-operative complications</b>	<b>Proportion</b>
Nerve injuries	0-8%
Arterial injury/transection	0-10%
<b>Post-operative complications</b>	<b>Proportion</b>
Infection	0-10%
Skin loss	0-5%
Wound healing difficulties	0-4%
CRPS	0-18%
Hematoma	0-3%
Gangrene	0-0.1%
Amputation	0-0.6%
Non-hand systemic complications (e.g., MI, left ventricular failure, urinary retention)	< 1%
<b>Local Extremity SAEs<sup>2</sup> in the 12 Submitted Xiaflex Studies</b>	
SAEs involving the treated extremity <sup>2</sup>	0.3%
Tendon Ruptures <sup>2</sup>	0.1%

<sup>1</sup> Data are from retrospective and prospective observational studies.

<sup>2</sup> SAEs are reported as events per Xiaflex injection. These data are from the controlled and uncontrolled portions of the 12 submitted Xiaflex studies. The tendon ruptures were a subset of the SAEs involving the treated extremity.

Reference: Bulstrode 2005, McFarlane 1990, Foucher 1992, Foucher 2003, Gelberman 1982, Moermans 1991, Rodrigo 1976, Sennwald 1990, Skoff 2004, Van Rijssen.

### 7.3.3 Dropouts and/or Discontinuations

In the pooled double-blinded, placebo-controlled portions of the pivotal trials through Day 90 (Studies 57 and 59), there were few adverse events leading to discontinuation (1% and 0% of the Xiaflex-treated and placebo-treated patients had DAEs, respectively). See Table 7.9 for a listing of these DAEs. All 3 DAEs were associated with Xiaflex treatment. Of the 3 Xiaflex-associated DAEs, 2 involved the treated extremity (severe injection site pain and exacerbation of a regional pain syndrome).

**Table 7.9: DAEs during the controlled portions of the pivotal trials through Day 90**

	<b>0.58 mg of Xiaflex (n=249)</b>	<b>Placebo (n=125)</b>
<b>Patients with ≥ 1 DAE</b>	<b>3 (1%)</b>	<b>0 (0%)</b>
<b>Severe injection site pain</b>	<b>1 (&lt; 1%)</b>	<b>0 (0%)</b>
<b>Dizziness</b>	<b>1 (&lt; 1%)</b>	<b>0 (0%)</b>
<b>Complex regional pain syndrome</b>	<b>1 (&lt; 1%)</b>	<b>0 (0%)</b>

DAEs are AEs leading to discontinuation

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

### 7.3.4 Common Adverse Events

As shown in Table 7.10, in the placebo-controlled portion of the pooled pivotal trials through Day 90 (Studies 57 and 59), **after up to 3 injections**, two times as many Xiaflex-treated patients than placebo-treated patients had an AE (98% vs. 49%). The overwhelming majority of Xiaflex-associated AEs were local reactions. The most commonly reported Xiaflex-associated AEs were edema (mostly edema of the injected hand), contusion, hemorrhage, and pain involving the treated extremity and were likely related to Xiaflex injection.

Patients did not receive local analgesic medication or analgesic blocks prior to the injections, but may have received analgesic medications for the finger extension procedures. A greater proportion of Xiaflex-treated compared to placebo-treated patients had pain in the extremity (35% vs. 5%) or injection site pain (33% vs. 6%).

**Table 7.10: AEs ( $\geq 2\%$  in either treatment group) in the placebo-controlled, double-blind periods in the pooled pivotal trials through Day 90<sup>1</sup>**

	<b>0.58 mg of Xiaflex (n=249)</b>	<b>Placebo (n=125)</b>
<b>Patients with <math>\geq 1</math> AE</b>	<b>243 (98%)</b>	<b>61 (49%)</b>
Peripheral edema <sup>2</sup>	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%)

<sup>1</sup> Includes all patients who received at least 1 injection of study medication. If multiple AEs were reported for a given preferred term, only 1 event was counted per patient.

<sup>2</sup> 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 14.3.1.3, Pages 204-207.

See Table 7.11 for the proportion of patients with at least one AE after a single injection in the pooled pivotal trials. For Xiaflex-treated patients, the types and proportion of AEs were similar after 1 Xiaflex injection to after up to 3 Xiaflex injections, although fewer placebo-treated patients experienced an AE after a single injection (26%).

**Table 7.11: AEs ( $\geq 5\%$  in either treatment group) after one injection in the double-blind, placebo-controlled periods in pooled pivotal trials<sup>1</sup>**

	<b>0.58 mg of Xiaflex (n=249)</b>	<b>Placebo (n=125)</b>
<b>Patients with <math>\geq 1</math> AE</b>	<b>236 (95%)</b>	<b>32 (26%)</b>
<b>Edema<sup>2</sup></b>	<b>169 (68%)</b>	<b>3 (2%)</b>
<b>Contusion</b>	<b>127 (51%)</b>	<b>3 (2%)</b>
<b>Injection site hemorrhage</b>	<b>76 (31%)</b>	<b>2 (2%)</b>
<b>Pain in extremity</b>	<b>71 (29%)</b>	<b>5 (4%)</b>
<b>Injection site pain</b>	<b>65 (26%)</b>	<b>5 (4%)</b>
<b>Tenderness</b>	<b>52 (21%)</b>	<b>0 (0%)</b>
<b>Ecchymosis</b>	<b>40 (16%)</b>	<b>0 (0%)</b>
<b>Injection site swelling</b>	<b>33 (13%)</b>	<b>4 (%)</b>
<b>Lymphadenopathy</b>	<b>30 (12%)</b>	<b>0 (0%)</b>
<b>Lymph node pain</b>	<b>19 (8%)</b>	<b>0 (0%)</b>
<b>Skin laceration</b>	<b>14 (6%)</b>	<b>0 (0%)</b>

<sup>1</sup> Includes all patients who received at least one injection of study medication. The pivotal trials were Studies 57 and 59. 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.

<sup>2</sup> The overwhelming majority of edema AEs were swelling of the injected hand.

Reference: ADAE analysis datasets from Studies 57 and 59.

### 7.3.5 Immunogenicity

Immunogenicity data were collected in almost all of the Auxilium-sponsored multiple-dose Xiaflex studies (controlled and uncontrolled portions of Studies 54, 56, 57, 58, and 59). Samples for antibodies against AUX-I (anti-AUX-I) and against AUX-II (anti-AUX-II) were collected from patients during screening, at Day 30 of each injection cycle, and at quarterly visits after the last injection. In the pivotal trials (Studies 57 and 59), almost all of the Xiaflex-treated patients had anti-AUX-I (89% to 95%) or anti-AUX-II (82% to 88%) after the first injection (see Table 7.12). All Xiaflex-treated patients who received a total of 4 or more injections (i.e. because more than one cord was treated) had antibodies to AUX-I and AUX-II in Studies 54, 56, 57, 58, and 59.

**Table 7.12: Antibodies to AUX-I or AUX-II after the first Xiaflex injection in the pivotal trials**

	Study 57		Study 59	
	Anti-AUX-I	Anti-AUX-II	Anti-AUX-I	Anti-AUX-II
N <sup>1</sup>	203	203	45	45
<b>Xiaflex-treated patients with anti-product antibody</b>				
<b>Baseline</b>	<b>3/188 (2%)</b>	<b>7/188 (4%)</b>	<b>0/45 (0%)</b>	<b>0/45 (0%)</b>
<b>After first injection<sup>2</sup></b>	<b>171/192 (89%)</b>	<b>158/192 (82%)</b>	<b>40/42 (95%)</b>	<b>37/42 (88%)</b>

<sup>1</sup> Xiaflex-treated patients

<sup>2</sup> Xiaflex-treated patients who had an anti-product sample

Reference: Adapted from CSR of Study 57, Table 14.3.10.1, Page 371; Table 14.3.10.3, Page 376; also adapted from CSR of Study 59, Table 14.3.10.1, Page 654; Table 14.3.10.2, Page 655.

### 7.3.6 Clinical Implications of Immunogenicity

Xiaflex was highly immunogenic, which was not unexpected because Xiaflex consists of two bacterially derived proteins. It is important to assess the clinical implications of the high incidence of anti-product antibodies to the components of Xiaflex. This immunogenicity could be associated with a decrease in effectiveness of the product and also poses two possible safety concerns: 1) the potential for allergic reactions and 2) the potential for toxicity related to the cross-reactivity of anti-product antibodies with endogenous proteins.

**Subgroup Efficacy Analysis by Neutralizing Antibody Status:** To assess the relationship of immunogenicity and effectiveness of Xiaflex, a subgroup efficacy analysis by neutralizing status was performed. Neutralizing antibodies to AUX-I and AUX-II were assessed using the last available post-injection sample in Study 57. In Study 57, 12/203 (6%) and 21/203 (10%) of Xiaflex-treated patients with adequate samples had a positive neutralizing antibody to AUX-I or AUX-II, respectively. There was no difference in the proportion of Xiaflex-treated patients with positive or negative neutralizing antibody status to AUX-I who achieved the primary endpoint of clinical success (see Table 7.13). A slightly lower proportion of Xiaflex-treated patients with positive neutralizing antibody status to AUX-II achieved the primary endpoint than patients with negative neutralizing antibody status, although the numbers of patients were too small to make definitive conclusions.

**Table 7.13: Proportion of Xiaflex-treated patients with contracture reduction to 0 to 5 degrees after up to 3 injections by neutralizing antibody status in Study 57<sup>1</sup>**

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

<sup>1</sup> In Study 57, 130/203 (64%) of Xiaflex-treated patients achieved the primary endpoint.

Reference: Adapted from response to clinical information request #3 (August 12, 2009).

**Allergic Adverse Events:** Xiaflex contains foreign proteins, so immunogenicity and allergic reactions would not be unexpected, particularly with repeated exposures. Data from the Xiaflex clinical development program suggest mild reactions do occur at an increased rate, and that the likelihood of

these increases with successive injections. However, severe reactions, e.g., those requiring hospitalization, or adrenergic agents, or those associated with respiratory compromise, hypotension, or associated symptoms of end-organ dysfunction, were not observed. Two cases of hives and several rashes were reported in the 12 submitted studies.

In an exploratory analysis, the occurrence of pruritus AEs (using MedDRA terms "pruritus", "injection site pruritus", or "pruritus generalized AE") was performed. Other MedDRA terms such as local edema, tenderness, injection site swelling, and ecchymosis were not included in this analysis because these AEs likely include effects that may be related to post-procedural trauma or collagenase-related tissue inflammation which would confound assessment of allergic etiologies. As shown in Table 7.14, a greater proportion of Xiaflex-treated patients had pruritus AEs after up to 3 injections in each pivotal trial through Day 90, compared to placebo-treated patients. The incidence of pruritus increased after more Xiaflex doses were administered. Overall, these data suggest Xiaflex is an allergen, as might be expected for a product comprised of foreign proteins, but do not suggest severe allergies are likely with typical clinical exposures.

**Table 7.14: Pruritus AEs after up to 1, 2, or 3 injections in the placebo-controlled pivotal trials through Day 90<sup>1</sup>**

	Study 57		Study 59	
	Xiaflex n=203	Placebo n=103	Xiaflex 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%)

<sup>1</sup> 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.

Although there were no severe allergic reactions in the Xiaflex clinical database, since Xiaflex was highly immunogenic with increasingly high antibody titers (including IgE isotypes in early Xiaflex studies) with successive exposures high titers, DAARP consulted the Division of Pulmonary Allergy Products (DPAP) and posed the following questions:

1. Do increasingly high titers of anti-product antibody with successive injections, and/or the high magnitude of the titers raise a concern for future development of clinical hypersensitivity responses, in the absence of corroborating clinical events in the experience to date?
2. Would you recommend a post-marketing study requirement to further assess the allergenicity of Xiaflex?
3. If so, please comment on key study design issues that would be important to relay to the Sponsor (i.e., antigen-specific IgE testing, skin testing, what time interval between exposures would be necessary to rule out booster responses that might result in clinical hypersensitivity events, what adverse events should be included as representative of clinical hypersensitivity events).

The DPAP consult review was pending at the time of completion of this reviewer's memo.

Potential for Cross-Reactivity of Anti-Product Antibodies with Human MMPs: According to Auxilium, there is no evidence that Xiaflex caused adverse reactions potentially indicative of cross-reactivity to human matrix metalloproteinases (MMPs):

- In the clinical database, there were no reports of Xiaflex-associated musculoskeletal events such as polyarthritis, osteolysis, and shoulder girdle pain that would be indicative of cross reactivity.
- There is no directly comparable homolog to AUX-I or AUX-II that exists in humans. The closest structural and functional human analogs (i.e., MMPs), which can degrade collagen are both structurally and functionally different than AUX-I and AUX-II.
- A subset of relevant purified recombinant human MMPs (MMP-1, -2, -3, -8 and -13) did not interfere with the detection of anti-AUX-I and/or anti-AUX-II in titer-positive plasma samples from patients with DC.
- The activity of MMPs *in vivo* is tightly regulated by a number of endogenous protease inhibitors so antibodies to AUX-I and AUX-II would not be expected to have a significant impact on overall MMP activity in the face of pool of proteases present in the blood.
- In the non-clinical multiple-dose studies in rats and dogs of collagenase clostridium histolyticum, there was no evidence of the systemic effects indicative of systemic MMP inhibition such as bone and joint changes, decreased fertility, abnormal placentation and/or developmental anomalies, even in the face of high and persistent anti-AUX-I and anti-AUX-II antibody titers.

According to Dr. Mills, the homology of AUX-I and AUX-II to human MMPs ranges from about 24% to 53%. The sera of 5 Xiaflex-treated patients was collected and cross-reactivity to human MMPs were analyzed. Out of the 5 patients tested, human MMPs did not appear to bind to anti-AUX-I; however, human MMPs appeared to bind to anti-AUX-II in 1 of the 5 patients, indicating the possible presence of cross-reactive antibodies.

The clinical implications of inhibition of human MMPs are not well characterized. Products that have inhibitory activity to MMPs (e.g., tetracycline products, investigational products that inhibit human MMP in development for the treatment of cancer, arthritis, arteriosclerosis, and congestive heart failure) do not have specific toxicities related to inhibition of MMPs. Besides local toxicity (e.g., tendon ruptures, hand edema, contusion, injection site pain), there were no other clearly Xiaflex-related toxicities in the clinical database with 1082 and 420 patients exposed to at least 1 and 3 Xiaflex injections, respectively. Therefore, cross-reactivity of anti-AUX-I and anti-AUX-II to endogenous human proteins (MMPs) remains theoretical at this time.

## 7.4 Supportive Safety Results (vital signs, labs, ECGs)

### 7.4.1 Vital Signs

Table 7.15 displays the proportion of patients with an AE of hypotension, hypertension, bradycardia, or tachycardia in the controlled portions of the pivotal trials through Day 90. No patient had a bradycardia or tachycardia AE. Of the 4 hypertension AEs in the Xiaflex group, 1 occurred after the injection, 1 occurred on the finger extension procedure day, and the 2 others occurred at other times

during the 90-day controlled period. There were few hypertension or hypotension AEs to draw definitive conclusions about the association of Xiaflex injections and hypotension or hypertension.

**Table 7.15: Proportion of patients with AE of hypotension, hypertension, bradycardia, or tachycardia in the controlled portions of the pivotal trials through Day 90<sup>1</sup>**

	Study 57 (U.S.)		Study 59 (Australian)	
	0.58 mg of Xiaflex (n=203)	Placebo (n=103)	0.58 mg of Xiaflex (n=45)	Placebo (n=21)
Hypotension	1/203 (<1%)	0/103 (0%)	0/45 (0%)	0/21 (0%)
Hypertension <sup>2</sup>	4/203 (2%)	1/103 (1%)	1/45 (2%)	0/21 (0%)
Bradycardia	0/203 (0%)	0/103 (0%)	0/45 (0%)	0/21 (0%)
Tachycardia	0/203 (0%)	0/103 (0%)	0/45 (0%)	0/21 (0%)

<sup>1</sup> Blood pressure and heart rate were measured immediately after injection and 5, 10, 20, 30, and 60 minutes after each injection, and before discharge on the injection day and 1, 7, and 30 days after each injection.

<sup>2</sup> Hypertension includes AEs of hypertension and blood pressure increased  
Reference: ADAE datasets in Studies 57 and 59

In the controlled periods in the pivotal trials through Day 90, vital signs (systolic and diastolic blood pressure, respiratory rate, pulse, and temperature) were measured at Screening, injection day, and 1, 7, and 30 days after each injection. On the injection day, systolic and diastolic blood pressure, respiratory rate, and pulse were measured immediately before each injection, and immediately after injection and 5, 10, 20, 30, and 60 minutes after injection, and before discharge. In addition, on injection day, temperature was measured immediately before, immediately after and 5 minutes after injection, and before discharge.

Table 7.16 displays vital sign assessments of low or high blood pressure or low or high heart rate after injections on the injection day in controlled portions of the pivotal trials through Day 90. Note, this reviewer used post-hoc cut-off values for these analyses and these events may not have been associated with any clinical symptoms. Xiaflex-treated patients had similar or lower proportions of vital sign measurements suggestive of low or high blood pressure or low or high heart rates.

**Table 7.16: Vital sign assessments of low or high blood pressure or low or high heart rate blood post-injection on injection day in controlled portions of the pivotal trials through Day 90<sup>1</sup>**

	Study 57 (U.S.)		Study 59 (Australian)	
	0.58 mg of Xiaflex (n=203)	Placebo (n=103)	0.58 mg of Xiaflex (n=45)	Placebo (n=21)
<b>Low Blood Pressure</b>				
Proportion of patients with $\geq 20$ mmHg decrease in SBP from baseline	77/203 (38%)	36/103 (35%)	21/45 (47%)	10/21 (48%)
Proportion of patients with absolute SBP $\leq 90$ mmHg <sup>2</sup>	6/203 (3%)	7/103 (7%)	0/45 (0%)	0/21 (0%)
<b>High Blood Pressure</b>				
Proportion of patients with $\geq 20$ mmHg increase in SBP from baseline	49/203 (24%)	31/103 (30%)	24/45 (53%)	14/21 (67%)
Proportion of patients with absolute SBP $\geq 180$ mmHg <sup>2</sup>	12/203 (6%)	4/103 (4%)	9/45 (20%)	5/21 (24%)
<b>Low Heart Rate</b>				
Proportion of patients with decrease in HR $\geq 20$ bpm from baseline	9/203 (4%)	7/103 (7%)	3/45 (7%)	2/21 (10%)
Proportion of patients with absolute heart rate $< 60$ bpm <sup>2</sup>	72/203 (35%)	42/103 (41%)	22/45 (49%)	14/21 (67%)
<b>High Heart Rate</b>				
Proportion of patients with increase in HR $\geq 20$ bpm from baseline	9/203 (4%)	7/103 (7%)	6/45 (13%)	1/7 (14%)
Proportion of patients with absolute heart rate $\geq 100$ bpm <sup>2</sup>	10/203 (5%)	6/103 (6%)	4/45 (9%)	0/21 (0%)

bpm is beats per minute

1 Anytime on injection day post-injection. On injection day, vital signs were measured immediately after injection and 5, 10, 20, 30, and 60 minutes after injection, and before discharge.

2 Patients with abnormal absolute values post-injection may have had abnormal baseline values.

Reference: ADVSINJ datasets in Studies 57 and 59

#### 7.4.2 Laboratory Findings

##### Assessment of Hepatotoxicity and Liver Enzyme Elevations

In the controlled and uncontrolled portions of the 12 submitted Xiaflex studies, there were no cases of acute liver failure or cases of Hy's Law and 3 Xiaflex-treated patients and 1 placebo-treated patient had a Hepatobiliary AE (all 4 patients had gallstones or cholecystitis). See Table 7.17 for the Hepatobiliary AEs in the controlled portions of the pivotal trials through Day 90 and the controlled and uncontrolled portions of the 12 submitted Xiaflex studies.

**Table 7.17: Hepatobiliary AEs in the controlled portions of the pivotal trials through Day 90 and the controlled and uncontrolled portions of the 12 submitted Xiaflex studies<sup>1</sup>**

<b>Controlled Portions of the Pivotal Trials Through Day 90</b>		
	<b>0.58 mg of Xiaflex (n=249)</b>	<b>Placebo (n=125)</b>
<b>Cholecystitis acute</b>	<b>0 (0%)</b>	<b>1 (1%)</b>
<b>Controlled and Uncontrolled Portions of the 12 Submitted Xiaflex Studies</b>		
	<b>0.58 mg of Xiaflex (n=1082)</b>	
<b>Hepatobiliary disorders SOC</b>	<b>1 (0.1%)</b>	
<b>Cholecystitis</b>	<b>1 (0.1%)</b>	
<b>Cholecystitis chronic</b>	<b>1 (0.1%)</b>	
<b>Cholelithiasis</b>	<b>1 (0.1%)</b>	

<sup>1</sup> The pivotal trials were Studies 57 and 59 and the 12 submitted studies were Studies 02, 03, 04, 51, 52, 53, 54, 55, 56, 57, 58, and 59.

Reference: Adapted from the ISS, Table 14.1.6, Page 9 and Table 14.2.6, Page 110

In the pivotal trials, a hepatic panel was performed at baseline and 30 days after injections and on Day 90. As shown in Table 7.18, there was no difference in the proportion of Xiaflex-treated and placebo-treated patients who had ALT or AST elevation  $\geq 3$  times the upper limit of normal (ULN) and no patients had ALT or AST elevations  $\geq 5$  ULN. There appeared to be no evidence of Xiaflex-associated hepatotoxicity in the clinical Xiaflex database.

**Table 7.18: Percent of patients with liver test abnormalities in the placebo-controlled portions of the pooled pivotal trials through Day 90<sup>1</sup>**

	<b>0.58 mg of Xiaflex</b>	<b>Placebo</b>
	<b>N=235<sup>2</sup></b>	<b>N=120<sup>2</sup></b>
<b>ALT or AST <math>\geq 3x</math> ULN</b>	<b>2 (1%)</b>	<b>2 (2%)</b>
<b>ALT or AST <math>\geq 5x</math> ULN</b>	<b>0 (0%)</b>	<b>0 (0%)</b>

<sup>1</sup> ITT population (patients who received at least one dose of study medication) in Studies 57 and 59. Patients may have had an abnormal baseline AST or ALT.

<sup>2</sup> Patients who had at least one post-baseline lab measurement of the analyte in Studies 57 and 59.

Adapted from the ISS, Table 14.1.14, Page 95

### Other Laboratory Tests

In the pivotal trials, the following laboratory tests were performed at baseline and 30 days after injections and on Day 90: CBC with differential, BUN, creatinine, sodium, potassium, calcium, phosphorus, uric acid, total protein, glucose, cholesterol, triglycerides, a hepatic panel, and a urinalysis. Very few patients had significant abnormalities of BUN, creatinine, hematocrit, hemoglobin, or platelet counts after injection. There was no significant difference in the proportion of patients in the Xiaflex and placebo groups who had significant changes in these lab tests (see Table 7.19).

**Table 7.19: Percent of patients with significant changes in hematocrit, hemoglobin, platelet, BUN, or creatinine tests in the placebo-controlled portions of the pivotal trials through Day 90<sup>1</sup>**

	Clinically significant value <sup>2</sup>	0.58 mg of Xiaflex (n=239) <sup>3</sup>	Placebo (n=120) <sup>3</sup>
High hematocrit	≥ 60%	0 (0%)	0 (0%)
Low hematocrit	≤ 30%	0 (0%)	0 (0%)
High hemoglobin	≥ 19 (female) or ≥ 20 (male), g/dL	0 (0%)	0 (0%)
Low hemoglobin	≤ 10 (female) or ≤ 11 (male), g/dL	2 (1%) <sup>4</sup>	0 (0%)
High Platelet count	≥ 650,000/μL	0 (0%)	0 (0%)
Low Platelet count	≤ 100,000/μL	2 (1%) <sup>5</sup>	0 (0%)
High BUN	≥ 35 mg/dL	3 (1%)	1 (1%)
High Creatinine	≥ 3.0 mg/dL	0 (0%)	0 (0%)

1 ITT population (patients who received at least one dose of study medication) in Studies 57 and 59. Patients may have had an abnormal baseline value.

2 Clinically significant value determined post-hoc by Auxilium

3 Patients who had at least one post-baseline lab measurement of the analyte in Studies 57 and 59. There were only 237 Xiaflex-treated patients who had post-baseline measurements of BUN and creatinine and 238 Xiaflex-treated patients who had post-baseline measurements of platelet counts.

4 The 2 Xiaflex-treated patients who had clinically significantly low hemoglobin levels after injection had low baseline values.

5 At least 1 of these Xiaflex-treated patients had a baseline platelet count less than 100,000/μL.

Adapted from the ISS, Table 14.1.14, Page 95.

### 7.4.3 Electrocardiograms (ECGs)

Xiaflex is not expected to prolong the QT interval or cause arrhythmias because it is not systemically absorbed; therefore, thorough QT/QTc studies or post-treatment ECG assessments were not required.

## 7.5 Safety Explorations for Probable Xiaflex-Related Adverse Reactions

### 7.5.1 Dose Dependency for Adverse Events

Table 7.20 displays SAEs of the injected extremity in the controlled and uncontrolled portions of the Xiaflex studies and common AEs in Study 02 by Xiaflex treatment group. Lower Xiaflex doses were associated with lower proportion of common AEs in Study 02. However, since there was limited number of patients who received lower Xiaflex doses, no definitive statements can be made regarding dose dependence for common AEs or SAEs involving the injected extremity.

**Table 7.20: SAEs of the injected extremity and common AEs by Xiaflex treatment group**

	Xiaflex			Placebo
	0.58 mg	0.29 mg	0.145 mg	
<b>SAEs of the injected extremity per injection in all the Xiaflex studies<sup>1</sup></b>				
# of injections	2630	22	18	125
SAEs of injected extremity	11 (0.4%)	0 (0%)	0 (0%)	0 (0%)
<b>SAEs of the injected extremity and Common AEs in Study 02<sup>2</sup></b>				
# of patients	23	22	18	17
SAEs of injected extremity	0 (0%)	0 (0%)	0 (0%)	0 (0%)
AEs	21 (91%)	18 (82%)	14 (78%)	11 (66%)

<sup>1</sup> Controlled and uncontrolled portions of Studies 02, 03, 04, 51, 52, 53, 54, 55, 56, 57, 58, and 59

<sup>2</sup> Study 02 included a single dose, placebo and dose-control portion of the trial.

### 7.5.2 Time Dependency for Adverse Events

There was no evidence that AEs increased with greater number of Xiaflex injections. A similar proportion of patients in the controlled pivotal trials through Day 90 had an AE after 1 injection (95%) or after up to 3 injections (98%). Furthermore, as shown in Table 7.21 a similar proportion of patients who received 1, 2, 3, or 4 Xiaflex injections had SAEs that involved the injected extremity (1%). There were few patients who received 6, 7, or 8 Xiaflex injections.

**Table 7.21: SAEs of the injected extremity by the number of Xiaflex injections<sup>1</sup>**

# of Xiaflex injections	# of patients (%)	SAEs of the injected extremity
≥ 1	1082 (100%)	11/1082 (1%)
1	443 (41%)	6/443 (1%)
2	219 (20%)	2/219 (1%)
3	170 (16%)	2/170 (1%)
4	93 (9%)	1/93 (1%)
5	116 (11%)	0/116 (0%)
6	14 (1%)	0/14 (0%)
7	13 (1%)	0/13 (0%)
8	14 (1%)	0/14 (0%)

<sup>1</sup> Controlled and uncontrolled portions of Studies 02, 03, 04, 51, 52, 53, 54, 55, 56, 57, 58, and 59.

### 7.5.3 Drug-Demographic Interactions

Table 7.22 presents demographic characteristics of the 11 patients with SAEs of the injected extremity compared to the 1082 Xiaflex-treated patients in the entire clinical database. Racial subgroups were not included in this analysis because there were few non-Caucasians in the clinical database [5 (0.5% of the 1082 patients were non-Caucasian). The mean age and locations of the patients with SAEs were similar to those in the entire clinical database. Female patients had a slightly greater proportion of SAEs involving the injected extremity than their proportion in the entire Xiaflex database; however, no definite conclusions can be drawn regarding the relationship between gender and these SAEs given the small number of SAEs. Of the 11 SAEs, 3 were tendon ruptures and all 3 tendon ruptures occurred in men.

**Table 7.22: Demographics of patients with SAEs of the injected extremity and demographics of all Xiaflex-treated patients<sup>1</sup>**

		<b>Demographics of Xiaflex-Treated Patients<sup>1</sup></b>	<b>Demographic of 11 Patients with SAEs of the Injected Extremity</b>
<b>N</b>		<b>1082</b>	<b>11</b>
<b>Age, mean (±SD)</b>		<b>63 (±10)</b>	<b>64 (±9)</b>
<b>Gender</b>	<b>Males</b>	<b>83%</b>	<b>7/11 (64%)</b>
	<b>Females</b>	<b>17%</b>	<b>4/11 (36%)</b>
<b>Location</b>	<b>United States</b>	<b>58%</b>	<b>7/11 (64%)</b>
	<b>Australia</b>	<b>30%</b>	<b>4/11 (36%)</b>
	<b>Europe</b>	<b>13%</b>	<b>0/11 (0%)</b>

<sup>1</sup> Xiaflex-treated patients who received at least one injection of 0.58 mg in the controlled and uncontrolled portions of the 12 submitted studies.

Reference: Narratives and case reports forms from the final study reports of Studies 54, 55, 56, 57, and 59 and from the Integrated Summary of Safety, Table 17, Page 55.

#### 7.5.4 Drug-Drug Interactions

No formal Drug-Drug Interactions (DDI) of Xiaflex were performed because there was no systemic exposure of Xiaflex after intra-cord injections of Xiaflex.

Since intra-cordal Xiaflex injections were associated with a high frequency of contusion and injection site hemorrhage in patients who did not receive anti-coagulant medications, other than low dose-aspirin, the concomitant use of anticoagulant medication, other than low-dose aspirin, with Xiaflex injections is not recommended.

#### 7.5.5 Other Safety Explorations for Probable Xiaflex-Related Reactions

It is important to assess whether the injection technique had a role in the 3 flexor tendon ruptures. Auxilium modified the Xiaflex injection technique during the clinical development because 2 tendon ruptures occurred after Xiaflex injections of cords associated with PIP joint contractures of the fifth finger. The new technique instructed investigators not inject more than 4 mm distal to the palmar digital crease and not to insert the needle more than 2 to 3 mm in depth when injecting the cords associated with PIP joint contractures in the fifth finger.

Prior to the modified injection technique, there were 2 (0.27%) tendon ruptures following 734 Xiaflex injections. After the modified technique was instituted, there was 1 (0.05%) tendon rupture following 1896 Xiaflex injections. Given the small number of tendon ruptures, it is not possible to draw definitive conclusions whether the modified technique reduced the incidence of tendon ruptures. For additional safety explorations of the tendon ruptures and other SAEs of the injected extremity, see Section 7.3.2 (Nonfatal Serious Adverse Events).

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

In the controlled portions of the pivotal trials (Studies 57 and 59) through day 90, no Xiaflex-treated or placebo-treated patient developed a malignancy other than non-melanoma skin cancer (NMSC). In the controlled and uncontrolled portions of the 12 submitted Xiaflex studies, of the 1082 Xiaflex-treated patients, 11 (1%) had a malignancy other than NMSC [the mean ( $\pm$ SD) duration of safety follow-up was 9.5 ( $\pm$ 4.6) months]. The types and frequency of malignancies were consistent with the patient population and their comorbidities.

No formal non-clinical studies of carcinogenic effects of Xiaflex were performed because the proposed indication is of short duration; Xiaflex is not likely to suppress the immune system; and there was no evidence of human exposure after intra-cordal injections.

### 7.6.2 Human Reproduction and Pregnancy Data

There were few women of child-bearing potential in the 12 submitted Xiaflex studies which was not unexpected because DC is a disease of older men. In the 12 submitted Xiaflex studies, only 10 (0.9%) of the patients were female **and** under 50 years old and only 3 (0.3%) of the patients were female **and** under 40 years old. There were no patients who became pregnant in the 12 submitted Xiaflex studies.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

In this BLA, Auxilium did not submit any studies of Xiaflex in pediatric patients and Auxilium does not plan to study Xiaflex in pediatric patients because DC is primarily a disease of older patients. In the 12 submitted Xiaflex studies, the mean age ( $\pm$ SD) was 63 ( $\pm$ 10) years old and there were no patients younger than 33 years of age. Since Xiaflex has been granted an orphan designation for the treatment of DC, the Pediatric Research Equity Act (PREA) of 2007 requirement does not apply.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

According to Auxilium, no patient received an overdose of Xiaflex. Excessive doses of Xiaflex may be more likely to produce serious local complications such as tendon rupture and ligament damage.

No assessment of physiological or psychological dependency or withdrawal was performed because Xiaflex had no systemic absorption and dependency and withdrawal are not expected to occur after intra-cordal Xiaflex injections.

## 7.7 Additional Submissions / Safety Issues

### 7.7.1 Additional Submissions

Table 7.23 displays additional safety submissions to this BLA. All of the safety information in these submissions has been incorporated into this review.

**Table 7.23: Additional clinical safety submissions**

Date of Submission (sequence #)	Type of Submission	Date of DAARP IR	Comments
2/27/09 (0)	Original BLA Submission <sup>1</sup>	N/A	—
5/18/09 (6)	120-day Safety Update <sup>2</sup>	N/A	—
6/16/09 (7)	Response to FDA's information requests about the carton and container labels	4/28/09 (filing letter)	New labeling added the established name from USAN Council, modified the wording for recurrence of contracture to include all the data from the Xiaflex studies from the Safety Update, added a patient information section, and modified the carton and container labels as recommended by the FDA.
6/23/09 (8)	Response to FDA clinical information requests #1	4/28/09 (filing letter)	—
7/8/09 (11)	Response to FDA clinical information requests #2	6/10/09	—
7/15/09 (14)	Response to FDA statistical information request #1	6/24/09	ROM endpoint using statistical methods as outlined in the SAP
7/28/09 (17)	Response to FDA statistical information request #2	6/8/09	Lack of protocol deviations in Study 03
8/12/09 (18)	Response to FDA clinical information requests #3	7/14/09	—
8/25/09 (22)	Updated Risk Management Plan and updated label	N/A	—
8/28/09 (24)	Response to FDA CMC information request	8/25/09	Justification for the excess overage (approximately (b) of the reconstituted drug product will be discarded). (4)

IR is information request

USAN Council is the United States Adopted Names Council

### 7.7.2 Auxilium's Proposed Risk Management Plan

Table 7.24 outlines Auxilium's propose risk management plan to assess and minimize Xiaflex-associated SAEs of the injected extremity including flexor tendon ruptures.

Auxilium proposes routine pharmacovigilance with a standard questionnaire to obtain safety data about tendon ruptures. This reviewer recommends that a post-marketing requirement (PMR) should

be required to assess the magnitude of tendon ruptures in the clinical practice setting (see Section 1.4, Recommendations for Postmarket Requirements and Commitments).

To reduce the risk of SAEs of the injected extremity, Auxilium proposes safety-related labeling changes and education to healthcare professionals (i.e., video, website, and/or manual) regarding the proper injection procedures and finger extension procedures. Auxilium also proposes a managed distribution program (outside of the FDA's purview) that requires physicians to sign a form prior to receiving Xiaflex. Physicians must agree that they understand the risks of Xiaflex and the injection and finger extension procedures. If physicians do not sign the form, then Xiaflex will not be provided. Most members of the September 16, 2009 Arthritis Advisory Committee (AAC) agreed that Auxilium's proposed labeling, education, and managed distribution plan is sufficient to minimize the risks of Xiaflex-associated tendon ruptures. Most of the AAC members thought that a FDA-controlled restricted distribution program, e.g., elements to assure safe use (ETASU) in a Risk Evaluation and Mitigation Strategy (REMS), would be too burdensome. This reviewer agrees with these AAC members that Auxilium's proposed education and restricted distribution plan with modified labeling is sufficient to minimize the risks of tendon ruptures.

**Table 7.24: Auxilium's proposed risk management plan for SAEs involving the injected extremity**

<b>Risk Assessment</b>
<b>Routine Pharmacovigilance</b>
Includes standard follow-up questionnaire to obtain safety information about tendon or ligament ruptures.
Aggregate review of AEs monthly for first year then quarterly
<b>Risk Minimization</b>
<b>Labeling</b>

(b) (4)

<b>Education to healthcare professionals<sup>1</sup></b>
<b>Video, Web Site, and/or &amp; Manual for Proper Injection Technique &amp; Finger Extension Procedure.</b>
<b>Auxilium's restricted distribution program (self-attestation prior to receiving Xiaflex)</b>
Physicians must sign an enrollment form that states that they understand the injection procedures, Xiaflex risks including tendon rupture, and they have viewed a Xiaflex video.
If physicians do not sign this form, Xiaflex will not be provided. If physicians sign the form, they will be entered into a central enrollment database. The distributor will ship Xiaflex to the physician after checking that the physician is enrolled.

<sup>1</sup> Training activities will be supplemented by support from Auxilium liaisons to clinicians.

Reference: Adapted from the Risk Management Plan also from the August 25, 2009 response to a clinical information request.

Also adopted from Auxilium's September 16, 2009 Arthritis Advisory Committee presentation.

## 8 Postmarket Experience

There is no post-marketing experience for Xiaflex because Xiaflex is not approved in any country.

## 9 Appendices

### 9.1 References

- 1 Bulstrode NW, Jemec B, Smith PJ. The Complications of Dupuytren's Contracture Surgery. *The Journal of Hand Surgery* 2005;30A,5:1021-1025.
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14 Van Rijssen, AL, Werker PMN. Percutaneous Needle Fasciotomy in Dupuytren's Disease. *Journal of Hand Surgery (British and European)* 2006;31B,5:498-501.

## 9.2 Labeling Recommendations

The following are the major changes recommended for proposed labeling for Xiaflex. These recommendations may change after internal labeling discussions and after labeling discussions with Auxilium:

### INDICATIONS AND USAGE:

1. Auxilium proposes the following Indication: (b) (4)  
Since in the pivotal trials patients must have had a palpable cord associated with a significant contracture of a MP or PIP joint (at least a 20 degree contracture), the following indication is recommended: "treatment of adult patients with Dupuytren's contracture associated with a palpable cord." Dr. Thomas Kaplan — a hand surgeon, principal investigator for several Xiaflex studies, and a speaker for Auxilium at the September 16, 2009 Advisory Committee Meeting — recommended that only Dupuytren's patients with palpable cords be treated. Dr. Kaplan stated that patients with DC without palpable cords should not be treated to minimize the risks and maximize the benefits of Xiaflex. Since there are no data on the efficacy and safety of Xiaflex in patients without a palpable cord, the indication should not include these patients.

### DOSAGE AND ADMINISTRATION

2. Auxilium proposes that Xiaflex (b) (4)  
(b) (4) since Xiaflex injections require professional training in hand injections and in product-specific training, it is recommended that Xiaflex be "administered by a healthcare professional experienced in injection procedures of the hand and in the treatment of patients with Dupuytren's contracture."
3. This section is reorganized into the following subsections to improve clarity of the dosage and administration: "Dosing, Reconstitution of the Lyophilized Powder, Preparation Prior to Injection, Injection Procedure, and Finger Extension Procedure."

### CONTRAINDICATIONS:

4. Auxilium's proposes that Xiaflex be (b) (4)  
(b) (4) Since there were no cases of severe allergic reactions in over 1000 Xiaflex-treated patients including 639 patients who received more than one dose, this contraindication should be removed.

### WARNINGS AND PRECAUTIONS:

5. The subsection title (b) (4) should be renamed to "Tendon Rupture or Ligament Damage."

### ADVERSE REACTIONS:

6. The information about contracture recurrence should be removed because the follow-up period was limited to assess recurrence.

### DRUG INTERACTIONS:

7. Anticoagulation medication should be included in this section because in the pivotal trials the use of anticoagulation medications other than low-dose aspirin was not allowed. Thus, the safety of Xiaflex in patients taking anticoagulant medications is unknown.

**CLINICAL STUDIES:**

8. Results of clinical success after 1 injection of study medication should be included in this section because it will be useful for healthcare providers and patients to understand the efficacy of Xiaflex after 1 injection.
9. The information in the demographic table should be moved to the ADVERSE REACTIONS section.
10. The results from Studies 57 and 59 should be included in this section; however, the results from Study 03 should not be included because Study 03 is a supportive trial.
11. The p-values should be removed from all the tables.
12. The secondary endpoint (clinical improvement, or the proportion of patients with  $\geq 50\%$  reduction in the contracture degree) should be removed from this section because it contains redundant information as the other efficacy data included in this section.

**REFERENCES:**

13. The two references should be removed because these articles were not reviewed by the Agency.

**PATIENT PACKAGE INSERT:**

14. The patient package insert should be removed because it is promotional and a patient package insert is not required.

### 9.3 Advisory Committee Meeting

The Agency decided that an Arthritis Advisory Committee (AAC) was needed because Xiaflex is a new molecular, would be the first-in-class intra-lesional injection (a bacterial collagenase), and would be the first approved medical product for the treatment of Dupuytren's contracture. The following items were discussed at the September 16, 2009 AAC 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).*

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

The committee did not address this question as approval was unanimously recommended.

**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 concern 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 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.*

## 9.4 Individual Study Reports

### 9.4.1 Study AUX-CC-857 (Study 57)

The following description of the protocol for Study AUX-CC-857 (Study 57) is based on amendment 2 of the protocol (dated November 19, 2007) and Version 1.2 of the SAP (dated May 22, 2008). See Table 9.1 for the dates of all amendments to the protocol and SAP for Study 57.

In Study 57, the first patient enrolled on August 28, 2007 and the last patient completed the study on October 24, 2008. According to Auxilium, the final protocol (amendment #2) and the final SAP (Version 1.2) occurred while Study 57 was blinded.

**Table 9.1: Amendments to the protocol and SAP of Study 57<sup>1</sup>**

	Amendment	Date
Protocol	Original	3/6/07
	Amendment #1	6/21/07
	Amendment #2	11/19/07
SAP	Original (1.0)	1/8/08
	Version 1.1	5/15/08
	Version 1.2	5/22/08

<sup>1</sup> According to Auxilium, the protocol changes and the final SAP (version 1.2) were produced while Study 57 was blinded.

**Title:** "A Phase 3, Double-Blind, Randomized, Placebo-Controlled Study of the Safety and Efficacy of AA4500 in the Treatment of Subjects With Dupuytren's Contracture"

**Objectives of Study 57:** The primary objective of Study 57 was to evaluate the efficacy and safety of up to 3 injections of Xiaflex as compared to placebo in reducing the degree of contracture (flexion deformity) in a primary joint (MP or PIP) of patients with advanced Dupuytren's disease (DD). The secondary objective of this study was to evaluate the efficacy and safety of up to 3 injections of Xiaflex in reducing the degree of contracture (flexion deformity) in multiple joints (MPs and PIPs) of patients with advanced DD.

**Overall Design of Study 57:** A 90-day, randomized, double-blind, placebo-controlled, multi-center (16 U.S. sites), Phase 3 trial of Xiaflex in patients with Dupuytren's contracture (DC). Patients must have had a fixed flexion deformity (caused by a palpable cord) resulting in an MP or PIP joint contracture at least 20 degrees but  $\leq 100^\circ$  (for MP joint) or  $\leq 80^\circ$  (for a PIP joint) in at least one finger, other than the thumb. Patients may not have received a treatment for DC on the primary joint within 90 days prior to the first dose of study drug. Upon completion of the Day 90 follow-up visit, all patients may have entered Study 58 (9-month, open-label extension study) if they required further treatment of DC (joints that were not successfully treated in Study 57 or joints that were not treated in Study 57).

**Eligibility Criteria of Study 57:** Table 9.2 displays the eligibility criteria in Study 57.

**Table 9.2: Eligibility Criteria in Study 57**

<p><b>Inclusion Criteria:</b> To have been eligible to participate in the study, patients had to have met all of the following criteria:</p> <ol style="list-style-type: none"> <li>1. Was at least 18 years of age</li> <li>2. Had a diagnosis of Dupuytren’s contracture with a fixed flexion deformity of at least one finger, other than the thumb, that was <math>\geq 20^\circ</math> caused by a palpable cord that had never been treated with Xiaflex. If a MP joint, the fixed flexion deformity had to be <math>\leq 100^\circ</math> or if a PIP joint had to be <math>\leq 80^\circ</math>.</li> <li>3. Had a positive “table top test” defined as the inability to simultaneously place the affected finger(s) and palm flat against a table top.</li> <li>4. Had to be in good health, based upon the results of a medical history, physical examination, and safety laboratory profile.</li> <li>5. Voluntarily signed and dated an informed consent agreement approved by the Institutional Review Board/Independent Ethics Committee (IRB/IEC).</li> <li>6. Female subjects of child bearing potential had to have used an acceptable method of birth control, be surgically sterilized, or be a post menopausal female (i.e., no menses for at least 1 year).<sup>1</sup></li> </ol>	<p><b>Exclusion Criteria:</b> If patients had any of the following conditions, they were not eligible to participate in the study:</p> <ol style="list-style-type: none"> <li>1. Had received a treatment for Dupuytren’s contracture including surgery (fasciectomy or surgical fasciotomy), needle aponeurotomy/fasciotomy, or injection of verapamil and/or interferon on the selected primary joint within 90 days before the first dose of study drug.</li> <li>2. Received any Xiaflex treatments within 30 days before the first dose of study drug.</li> <li>3. Had a chronic muscular, neurological, or neuromuscular disorder that affected the hands.</li> <li>4. Had a known recent history of bleeding or received anticoagulant medication (except for aspirin <math>\leq 150</math> mg daily) within 7 days before the first dose of study drug.</li> <li>5. Had a known recent history of stroke, a disease process that affected the hands, or other medical condition which in the investigator’s opinion would make the patient unsuitable for enrollment in the study.</li> <li>6. Received doxycycline or doxycycline derivative during the 14 days before the first dose of study drug.</li> <li>7. Had a known allergy to collagenase or any other excipient of Xiaflex.</li> <li>8. Female subjects who were nursing or pregnant, or planned to become pregnant during the treatment phase.</li> <li>9. Received an investigational drug within 30 days before the first dose of study drug.</li> </ol>
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<sup>1</sup> A pregnancy test was performed prior to enrollment in the study.

Reference: Adapted from amendment #2 of Protocol 57 (last amendment)

**Selection of the Primary Joint in Study 57:** Before treatment, the investigator evaluated all fingers, except for the thumb, of both hands and selected the “primary joint” on the selected hand. The investigators had discretion in the selection of the hand if bilateral contractures were present and in selection of the finger to be treated (e.g., 5<sup>th</sup>, 4<sup>th</sup>, 3<sup>rd</sup>, or 2<sup>nd</sup>) if multiple fingers had contractures. On the selected hand, the primary joint was the MP joint if the contracture occurred solely in the MP or was the PIP joint if the contracture occurred solely in the PIP joint. If both the MP and PIP joints were contracted in the same finger, then the MP joint was selected as the primary joint.

After the primary joint was successfully treated, subsequent MP or PIP joints were selected as secondary joint and tertiary joints with the goal of providing the patient with complete functionality of the treated hand. After complete functionality of one hand was attained, joints on the other hand may have been selected for treatment.

**Treatments in Study 57:** Patients were randomized 2:1 to receive an injection of Xiaflex or placebo directly into the Dupuytren’s cord.

Xiaflex was administered in a volume of 0.25 and 0.2 mL for MP and PIP joints, respectively. Each patient may have received a maximum of 3 injections of Xiaflex or placebo on Days 0, 30, and 60. The primary joint could have received up to 3 injections, the secondary joint could have received up to 2 injections, and the tertiary joint could have only received 1 injection (see Table 9.3).

**Table 9.3: Algorithm for selection of joints (MP or PIP) to be injected in Study 57<sup>1</sup>**

Injection Day		
Day 0		First injection of primary joint
Day 30	Outcome of primary joint after the first injection (given on Day 0)	If outcome of primary joint was a failure, primary joint was given a second injection
		If outcome of primary joint was a success (i.e., reduction of contracture to $\leq 5^\circ$ of normal), the secondary joint was injected
Day 60	Outcome of primary joint after 2 injections (given on Days 0 and 30)	If outcome of primary joint after the second injection was a failure, the primary joint had a third injection
		If outcome of primary joint after the second injection was a success, the secondary joint was injected
	Outcome of secondary joint after the first injection (given on Day 30)	If outcome of secondary joint after the first injection was a failure, the secondary joint was given a second injection
		If outcome of secondary joint after the first injection was a success, the tertiary joint was injected

<sup>1</sup> In Study 57, there could have been up to 3 injections on Days 0, 30, and 60. The 3 injections could all have been in the primary, secondary, and/or tertiary joints. The injections could have been in the cord that affected the MP or PIP in all fingers, except the thumb, of either hand.

Before discharge, the patient was instructed not to flex or extend the fingers on the treated hand for 12 hours after the injection to prevent extravasation of the study product out of the cord. The follow-up visit (about 24 hours after the injection), the investigator manipulated (extended) the treated finger in an attempt to rupture the cord. The amount of force applied to extend the finger was according to each patient's pain tolerance. Following manipulation, appropriate personnel (e.g., hand therapist) fitted the patient with a splint and instructed the patient to wear the splint each night for up to 4 months. Patients were instructed to perform a series of finger flexion/extension exercises at home.

**Concomitant Medication in Study 57:** Doxycycline or doxycycline derivatives should not have been administered within 14 days before and 7 days after injection of study drug. According to Auxilium, doxycycline has been shown to be a collagenase inhibitor *in vitro*. Patients could not have received an anticoagulant medication for 7 days before and 7 days after each injection (except for  $\leq 150$  mg aspirin daily).

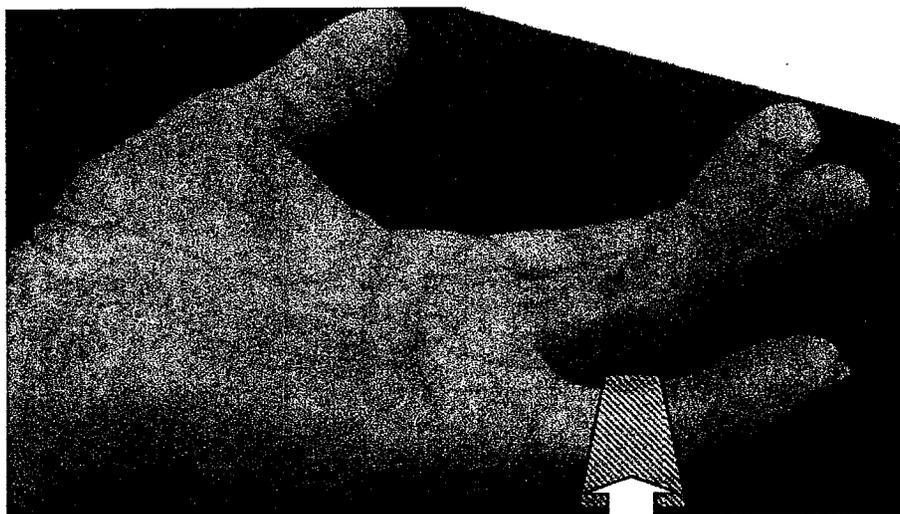
**Training of the Investigators and Sub-Investigators Who Administered Injections and Performed Finger Extensions:** The goals of training were to familiarize principle investigators (PI) with Xiaflex and to provide instruction to assure consistency of the injection technique and finger manipulation technique across all centers and countries. The PIs were responsible for training the applicable sub-investigators (SIs) if they were performing injections and/or finger extension procedures.

All investigative sites received the same core training materials, which included the following:

1. **Manual:** Injection technique training. The injection technique training manual was reviewed with investigators during the individual site initiation visits.
2. **DVD:** Injection training and finger manipulation (12-minutes).

3. **Workshop:** Of the 16 PIs in Study 57, 8 (50%) attended a 30 minute workshop meeting, in which Dr. Hurst gave the PIs a demonstration of the injection technique by way of a slide presentation and viewing of the injection technique video. Specific injection simulation was not provided nor deemed necessary.
4. **Teleconference:** Demonstrated a modified injection technique into the cord affecting the 5<sup>th</sup> finger (30-minutes). During the early phase of Studies 57 and 59 two tendon ruptures and a ligament injury occurred. As a result, the injection technique for the 5th finger was modified in Protocol Amendment #2 and a training modification teleconference was held to highlight the modifications to the injection technique of the cords involving the 5<sup>th</sup> finger. The major modification included identification of an area of the 5th finger that should not be injected (see Figure 9.4). The modified injection procedures included the following:
  - When injecting the cord contracting the PIP of the 5<sup>th</sup> finger, do not inject more than 4 mm distal to the palmar digital crease.
  - The needle insertion into the cord contracting the PIP joint in the 5th finger should never be more than 2 to 3 mm in depth.
  - Due to their close proximity to tendon, be extremely cautious with central cords as they approach the PIP flexion crease area.
  - If there is any doubt about the needle being in the cord or having passed through the cord, withdraw the needle and reposition in a new area.
  - If there is a suspicion of the needle being in a tendon, move the tip of the injected finger to ascertain that the needle does not move with finger tip motion.
  - When injecting, be sure the tip of needle does not advance with pressure on plunger of syringe during injection.
  - Avoid very strenuous force (power gripping) across the tendons of the injected joint for several weeks post injection.

**Figure 9.4: Zone of the 5<sup>th</sup> finger in which injections should not be made**



Reference: June 23, 2009 response to clinical information request, Page 16.

See Table 9.5 for a summary of the investigator training in Study 57.

**Table 9.5: Investigator training in Study 57**

<b>Training</b>	<b>Time Devoted</b>	<b>Comments</b>
<b>Injection Technique Manual</b>	<b>N/A</b>	<b>Reviewed with investigators during site initiation visits</b>
<b>Injection Technique DVD</b>	<b>12 minutes</b>	<b>Instructions on injection and finger extension procedures</b>
<b>Workshop/Investigator Meetings</b>	<b>30 minutes</b>	<b>Of the 16 PIs in Study 57, 8 (50%) attended a workshop. PIs given a slide demonstration of injections &amp; finger extensions.</b>
<b>Teleconference to highlight modified technique</b>	<b>30 minutes</b>	<b>During the early parts of Studies 57 and 59, there were 2 Xiaflex-associated tendon ruptures and 1 ligament injury. Injection technique for cords involving the 5th finger was modified.</b>
<b>Other Information</b>	<b>N/A</b>	<b>PIs did not perform simulations. PIs were responsible for training all the sub-investigators in injections and finger extensions</b>

PIs = principal investigators

Reference: Adapted from the June 23, 2009 response to FDA clinical information request #1.

**Study Monitoring and Evaluation in Study 57:** See Table 9.6 for the procedures and evaluations in Study 57. Follow-up visits were at 1, 7, and 30 days after each injection.

**Table 9.6: Procedures and evaluations in Study 57**

Procedures <sup>a</sup>	Screening	Injection Day <sup>b</sup>		Days after each injection <sup>c</sup>			Day 90 <sup>d</sup>
	Within 60 days of 1 <sup>st</sup> injection	Before each injection	After each injection	1	7	30	
Obtain informed consent	X						
Medical history including history of Dupuytren's disease	X						
Physical examination	X						
Body weight and height	X						
Table top test	X						
Vital signs	X	X	X*	X	X	X	X
Finger goniometry	X <sup>i</sup>	X		X	X	X	X <sup>i</sup>
Hand grip strength	X	X			X	X	X
Clinical laboratories	X					X	X
Serum pregnancy testing (if applicable)	X						
Urine pregnancy testing (if applicable)		X					X
12-lead ECG	X						
Immunogenicity sample <sup>f</sup>		X <sup>h</sup>				X	X
Finger manipulation				X			
Adverse event recording	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X
Study drug administration			X				
Physician global assessment		X <sup>h</sup>					X
Subject global assessment		X <sup>h</sup>					X
Splinting of treated finger				X <sup>i</sup>			

a If two visits occurred on the same day overlapping procedures did not need to be repeated.

b Patients could have received up to 3 injections on Days 0, 30, and 60.

c Assessments on Days 1, 7, and 30 were repeated after each injection (up to 3 injections)

d All patients were supposed to have a follow-up visit on Day 90, which was the end of double-blind study (Study 57) and also the start of the open-label extension study (Study 58).

e Immediately after injection and 5, 10, 20, 30, and 60 minutes after injection, and before discharge, vital signs must have been stable for a period of at least 60 minutes before the patient could have been discharged from the study unit.

f Finger goniometry measured the angles of extension and flexion of all joints on the affected hand(s). Extension angles were measured as a passive evaluation.

g For immunogenicity testing, a 10 mL blood sample was needed.

h Before the initial injection only.

i The patient was fitted with a splint and instructed to wear the splint each night for up to 4 months. The patient was also instructed how to perform a series of finger flexion/extension exercises at home.

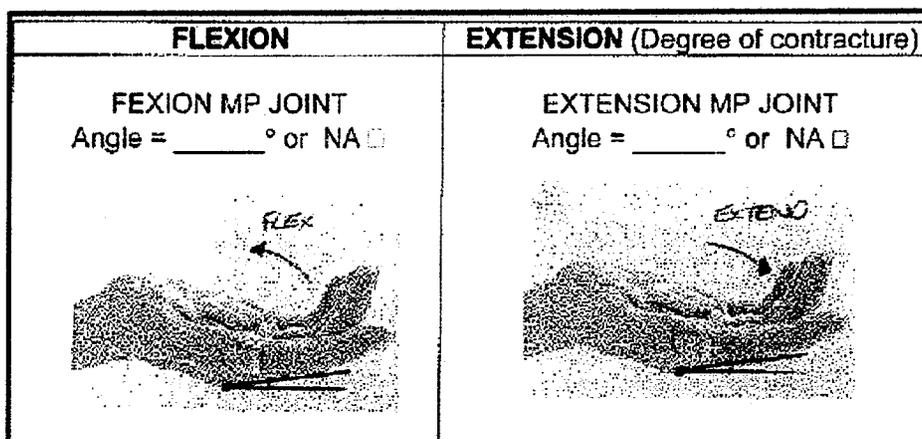
Range of motion of the hand joints were measured using a finger goniometer. Full extension was measured when the finger was passively extended (straightened) as far as possible toward the neutral position of zero degrees and full flexion was measured when the finger when passively curled as close to the palm as possible. In this trial, 0 degrees was defined as the normal full extension of the MP and PIP joints (see Table 9.7 for the types of finger measurements and Figure 9.8 for a diagram of angles for ROM measurements).

**Table 9.7: MP and PIP range of motion measurements using a finger goniometer in Study 57**

Measurement	Definition
Full Extension (fixed flexion contracture) <sup>1</sup>	Joint extended away from the palm
Full Flexion	Joint flexed towards the palm
Range of Motion	Full Flexion minus Full Extension

<sup>1</sup> Normal extension of a MP or PIP joint is an angle of 0°. Fingers that can be extended beyond straight (0°) were reported with a full extension angle of 0°.

**Figure 9.8: Angles used for the range of motion measurements for the MP joint in Study 57<sup>1</sup>**



<sup>1</sup> Similar measurements were used for PIP joints

Hand grip strength was assessed using dynamometry. See Table 9.9 for the patient and physician global assessments responses at Screening and Day 90.

**Table 9.9: Patient and physician global assessments at Screening and Day 90 in Study 57**

Evaluation Visit	Assessment	Possible Responses
<b>Patient Global Assessment</b>		
Screening	Current status	Normal (no contracture), Mild, Moderate, Severe
Day 90	Degree of improvement in treated contractures	0% to 100% in increments of 10%
	Overall satisfaction with treatment	Very Satisfied, Quite Satisfied, Neither Satisfied nor Dissatisfied, Quite Dissatisfied and Very Dissatisfied
<b>Physician Global Assessment</b>		
Screening	Current status	Normal (no contracture), Mild, Moderate, Severe
Day 90	Current status	Normal (no contracture), Mild, Moderate, Severe
	Change in disease severity	Very Much Improved, Much Improved, Minimally Improved, No Change, Minimally Worse, Much Worse, Very Much Worse

Lab tests at baseline and on Days 30 and 90 included CBC with differential, BUN, creatinine, sodium, potassium, calcium, phosphorus, uric acid, total protein, glucose, cholesterol, triglycerides, a hepatic panel, and a urinalysis. For WOCB, a serum pregnancy test was performed at screening and a urine pregnancy test was performed prior to each injection and on Day 90.

**Efficacy Endpoints in Study 57:** The primary and secondary efficacy endpoints in Study 57 were all based on injection of the primary joint.

The primary efficacy endpoint in Study 57 was the proportion of patients who achieved a reduction in contracture (i.e., flexion deformity) of the primary joint to 0-5° (clinical success), 30 days after the last

injection. Thirty days after the last injection was on Days 30, 60, and 90 for patients who received 1, 2, and 3 injections of the primary joint, respectively.

In Study 57, the secondary efficacy endpoints, based on injection of the primary joint, were the following:

- Proportion of patients with  $\geq 50\%$  reduction from baseline in contracture (clinical improvement) after the last injection.
- Percent change from baseline in contracture degree after the last injection.
- Change from baseline in the range of motion, ROM, (difference between the finger extension angle and finger flexion angle expressed in degrees) after the last injection.\*
- Time (in days) to achieve and maintain clinical success after the last injection.\*\* It was possible to achieve clinical success on Days 1, 7, and 30 after each injection (approximately Days 1, 7, 30, 31, 38, 60, 61, 68, and 90 if there were 3 injections). See Table 9.10 for examples of how the time to achieve and maintain clinical success was determined.
- Proportion of patients who achieved a reduction in contracture (clinical success) to 0-5°, after the first injection (Day 30).
- Proportion of patients with  $\geq 50\%$  reduction from baseline in contracture (clinical improvement) after the first injection.
- Percent reduction from baseline in contracture degree after the first injection.
- Change from baseline in ROM after the first injection.\*

\* This endpoint originally was the percent reduction from baseline in the ROM in the protocol. According to Auxilium, it was changed in the Version 1.2 SAP (dated May 22, 2008) because in patients with DC the ROM could have been small (e.g., 0) in which case the percent change from baseline would have been unstable.

\*\* This endpoint was changed from time to clinical success to time to first achieve and maintain clinical success. It was changed in the Version 1.2 SAP (dated May 22, 2008).

**Table 9.10: Examples of how time to clinical success were determined**

- If the treated joint measurement was  $\leq 5^\circ$  on Day 1, Day 7, and Day 30, then the joint was a success and the time to reach clinical success was Day 1.
- If the treated joint measurement was  $\leq 5^\circ$  on Day 7 and Day 30, but not on Day 1, then the joint was a clinical success and the time to reach clinical was Day 7.
- If the treated joint measurement was  $\leq 5^\circ$  on Day 1 and Day 30, but not on Day 7, then the joint was a clinical success and the time to reach clinical success was on Day 30.
- If a treated joint measurement was  $\leq 5^\circ$  on Day 1 and/or Day 7 and was  $> 5^\circ$  on Day 30, then the joint was not a clinical success for that injection cycle.

### **Statistics in Study 57:**

**Population:** The following were the pre-specified populations:

1. The intent-to-treat (ITT) population (all randomized patients who received at least 1 injection). All safety analyses were based on the ITT population.
2. The modified intent-to-treat (MITT) population was all ITT patients who had pre-injection fixed flexion contracture measurements of the primary joint  $> 5$  degrees and at least one post first-injection

measure obtained on the primary joint. All efficacy evaluations, except for physician and patient global assessments, were based on the MITT population. The MITT population was not in the protocol and was defined in Version 1.2 of the SAP (May 22, 2008).

3. The per-protocol (PP) population was ITT patients who had a day 30 post-injection evaluation of contracture after the last treatment to the primary joint, and had no protocol violations that would have affected efficacy evaluation of the primary joint including:

- Received the wrong treatment
- Received > 3 doses of study medication in the DB phase
- Received < 3 injections of study medication without reaching clinical success, did not have a supportive reason for not giving additional injections (e.g. no palpable cord, AEs)
- Final evaluation after the final treatment occurred before the Day 30 visit
- Fixed flexion contracture measurement that did not meet the minimum requirement ( $\geq 20$  degrees) or meet the maximum requirement ( $\leq 100$  degrees for MP joints or  $\leq 80$  degrees for PIP joints)

Database Lock: The study was un-blinded after the final patient completed the Day 90 visit. Un-blinding before the Day 90 visit was not permitted unless it was deemed necessary for appropriate treatment of a medical emergency.

#### Primary Efficacy Endpoint

Baseline Stratification: According to Auxilium, previous clinical studies of Xiaflex in DC showed different response rates between MP and PIP joints and contractures of different severity. Therefore, Study 57 stratified by severity of primary joint contracture at baseline ( $\leq 50^\circ$  or  $> 50^\circ$  for a MP joint and  $\leq 40^\circ$  or  $> 40^\circ$  for a PIP joint) and by joint (MP or PIP).

Methods: Comparison of the primary efficacy endpoint results between the Xiaflex and placebo groups was performed using a Cochran-Mantel-Haenszel (CMH) statistic for 2 x 2 tables, controlling for joint type (MP or PIP) and baseline contracture severity. If the contracture measured at baseline is  $5^\circ$  or less, then clinical success was not computed for the joint and was listed as missing.

Handling of Treatment Failure, Dropouts, and Missing Data: If the efficacy values were missing 30 days after the last injection (Day 30, 60, or 90), the last observation carried forward (LOCF) was used to determine the primary efficacy endpoint (7 days or 1 day after the last injection). If all post-injection data are missing, then these data were not used.

Pre-Specified Sensitivity Analysis: A sensitivity analysis was performed where all patients who were missing data 30 days after last injection were counted as not achieving the primary efficacy endpoint.

Secondary Efficacy Endpoints: The secondary efficacy analyses were performed only if the primary efficacy analysis was significant at a significance level of 0.05. Each of the secondary efficacy analyses were performed in a hierarchical closed loop testing procedure based on a two-sided hypothesis with a 0.05 significance level for each hypothesis. The first 14 hypotheses assessed

efficacy measurements after up to 3 injections and the last 12 hypotheses assessed efficacy measurements after the first injection (see Table 9.11).

If the contracture measured at baseline is 5° or less, then clinical success and clinical improvement were not computed for the joint and were listed as missing.

Comparisons in the combined population of the MP and PIP joints of clinical success rates and clinical improvement rates between the Xiaflex and placebo groups was performed using a CMH statistic for 2x2 tables, controlling for joint type (MP or PIP) and baseline contracture severity. Comparison in the sub-populations of MP or PIP joints was performed using a CMH statistic for 2x2 tables, controlling for baseline contracture severity. Percent reduction from baseline contracture and change from baseline ROM were analyzed with full factorial analysis of variance (ANOVA) with factors for treatment group, baseline contracture severity, and joint type. Survival curve (Kaplan-Meier) was used to display the time to first achieve and maintain clinical success after the last injection. Log-rank test was used to compare time to first achieve and maintain clinical success curves between the treatment groups. When clinical success was not achieved by the Day 30 visit after the last injection, the time to first achieve success was right censored at the last evaluation after the last injection.

**Table 9.11: Hierarchy of hypothesis tests for the primary and secondary efficacy parameters in Study 57**

Order	Parameter	Injection	Joints	Controlled by
1	Clinical Success	Last	MP+PIP	Joint Type and Baseline Severity
2	Clinical Improvement			
3	% Reduction From Baseline			
4	Time to First Achieve and Maintain Clinical Success			
5	Change from Baseline in ROM			
6	Clinical Success	Last	MP	Baseline Severity
7	Clinical Improvement			
8	% Reduction From Baseline			
9	Time to First Achieve and Maintain Clinical Success			
10	Change from Baseline in ROM			
11	Clinical Success	Last	PIP	Baseline Severity
12	Clinical Improvement			
13	% Reduction From Baseline			
14	Time to First Achieve and Maintain Clinical Success			
15	Change from Baseline in ROM			
16	Clinical Success	First	MP+PIP	Joint Type and Baseline Severity
17	Clinical Improvement			
18	% Reduction From Baseline			
19	Change from Baseline in ROM			
20	Clinical Success	First	MP	Baseline Severity
21	Clinical Improvement			
22	% Reduction From Baseline			
23	Change from Baseline in ROM			
24	Clinical Success	First	PIP	Baseline Severity
25	Clinical Improvement			
26	% Reduction From Baseline			
27	Change from Baseline in ROM			

Clinical success was the proportion of patients who achieved a reduction in contracture (i.e., flexion deformity) of the primary joint to 0-5°

Clinical improvement was the proportion of patients with ≥ 50% reduction from baseline in contracture

**Results of the 24-Week Efficacy Data and 52-Week Safety Data for Study 57:**

**Study 57 Dates Conducted:** The first patient enrolled in Study 57 on August 28, 2007 and the last patient completed the study on April 14, 2008. For all of the efficacy and safety results of Study 57 see Sections 6 and 7.

**Protocol Deviations in Study 57:** In Study 57, 156 (76%) and 81 (77%) of the patients in the Xiaflex and placebo groups had at least 1 protocol violation, respectively, and 11% and 13% of the patients in the Xiaflex and placebo groups had significant protocol deviations, respectively. See Table 9.12 for the significant protocol deviations in Study 57.

**Table 9.12: Significant protocol deviations in the controlled portion of Study 57 through Day 90**

	Xiaflex (n=204)	Placebo (n=104)
<b>Significant Protocol Violations</b>	<b>22 (11%)</b>	<b>13 (13%)</b>
Patients who remained eligible for treatment did not receive up to 3 injections (primary joint contracture >5°; palpable cord present; and no report of an AE contraindicating further treatment)	14 (7%)	8 (8%)
Did not have the Day 30 measurement after the last injection (Day 30, 60, or 90 for the first, second, and third injections, respectively)	4 (2%)	4 (4%)
Received the wrong treatment	3 (1%)	2 (2%)
Did not have a baseline fixed-flexion contracture ≥ 20 degrees	2 (1%)	0 (0%)

Reference: CSR of Study 57, Page 34; ADDV Datasets

9.4.2 Study AUX-CC-859 (Study 59)

The following description of the protocol for Study AUX-CC-859 (Study 59) is based on amendment #3 of the protocol (dated December 5, 2007) and Version 3.0 of the SAP (dated November 21, 2008). See Table 9.13 for the dates of all amendments to the protocol and SAP for Study 59.

In Study 59, the first patient enrolled on August 24, 2007, the last patient completed the double-blind phase on January 21, 2008, and the last patient completed the open-label phase on September 29, 2008.

**Table 9.13: Major amendments to the protocol and SAP of Study 59**

	Amendment	Date
<b>Protocol</b>	Original	3/1/07
	Amendment #1	6/22/07
	Amendment #2	11/19/07
	Amendment #3	12/5/07
<b>SAP</b>	Original (1.0)	11/19/07
	Version 1.3	12/13/07
	Version 1.4	12/31/07
	Version 2.0	7/30/08
	Version 3.0	11/21/08

**Title:** "A Phase 3, Double-Blind, Randomized, Placebo-Controlled Study of the Safety and Efficacy of AA4500 in the Treatment of Subjects With Dupuytren's Contracture Followed by an Open-Label Extension Phase"

**Objectives of Study 59:** The primary and secondary objectives of Study 59 were identical to the objectives in Study 57 (see the objectives in Study 57). The tertiary objective of study 59 was to evaluate the recurrence rate in joints that were successfully treated during the 12-month study period.

**Overall Design of Study 59:** A 90-day, randomized, double-blind, placebo-controlled, multi-center (5 Australian sites), Phase 3 trial of Xiaflex in patients with advanced DD. Patients must have had a fixed flexion deformity (caused by a palpable cord) resulting in an MP or PIP joint contracture at least 20 degrees but  $\leq 100^\circ$  (for MP joint) or  $\leq 80^\circ$  (for a PIP joint) in at least one finger, other than the thumb. Patients may not have received a treatment for DC on the primary joint within 90 days prior to the first dose of study drug. Study 59 had two parts: part one was a 3-month, DB, PC phase with up to 3 injections of study medication every 30 days and part two was a 9-month open-label, uncontrolled extension phase where patients could receive up to 5 additional injections of Xiaflex every 30 days.

**Eligibility Criteria of Study 59:** The eligibility criteria in Study 59 were identical to the eligibility criteria in Study 57 (see the eligibility criteria in Study 57).

**Selection of the Primary Joint in Study 59:** The selection of the primary joints in Study 59 was identical to the selection criteria in Study 57 (see the selection criteria in Study 57).

**Treatments in Study 59:** In Study 59, the treatments, dosage and administration, allowed concomitant medications, and the algorithm for selection of primary joints for injection were identical to Study 57.

**Study Monitoring and Evaluation in Study 59:** The procedures and evaluations in the DB phase in Study 59 were identical to the procedures and evaluations in Study 57 (see Table 9.6). See Table 9.14 for the procedures and evaluations in the open-label phase in Study 59. Follow-up visits were at 1, 7, and 30 days after each injection in the DB and open-label phases.

**Table 9.14: Procedures and evaluations in the open-label period in Study 59**

Procedures	Injection day <sup>a</sup>		Days after each injection <sup>b</sup>			Follow-up <sup>c</sup>		
	Before each injection	After each injection	1	7	30	Month 6	Month 9	Month 12
Vital signs	X	X <sup>d</sup>	X	X	X	X	X	X
Finger goniometry	X		X	X	X	X	X	X <sup>e</sup>
Hand grip strength	X			X	X	X	X	X
Clinical laboratories								X
Urine pregnancy testing (if applicable)	X							X
Immunogenicity sample <sup>f</sup>	X				X	X	X	X
Finger manipulation			X					
Adverse event recording	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X
Study drug administration	X							
Physician global assessment								X
Subject global assessment								X
Splinting of treated finger			X <sup>g</sup>					

a In addition to the 3 injections in the DB phase, patients could have received up to 5 additional injections on Day 90 (end of DB and start of open-label phase), and at Months 4, 5, 6, and 7.

b Assessments on Days 1, 7, and 30 were repeated after each injection (up to 5 injections) in the open-label phase.

c All patients had follow-up at Months 6, 9, and 12.

d Immediately after injection and 5, 10, 20, 30, and 60 minutes after injection, and before discharge, vital signs were assessed. Vital signs must have been stable for a period of at least 60 minutes before the patient could have been discharged from the study unit.

e The angles of extension and flexion of all joints on the affected hand(s) were measured.

f For immunogenicity testing, a 10 mL blood sample was collected.

g The patient was fitted with a splint and instructed to wear the splint each night for up to 4 months. The patient was instructed how to perform a series of finger flexion/extension exercises at home.

**Training of the Investigators and Sub-Investigators Who Administered Injections and Performed Finger Extensions:** The training of investigators who administered injections and performed finger extension procedures was identical in Studies 57 and 59 (see the training of investigators in the Individual Study Report for Study 59 (Section 9.4.2)). In Study 59, investigator meetings that were held in Australia devoted about 30 minutes to the injection technique and finger manipulation. At these meetings, the injection procedure (for 15 minutes) and finger manipulation procedure was described during an audiovisual presentation by Dr. Lawrence Hurst. This was followed by a 40 minute demonstration of product reconstitution, central laboratory procedures, and a review of the injection training/finger manipulation DVD (12 minutes).

**Efficacy Endpoints in Study 59:** The primary and secondary efficacy endpoints in Study 59 were all based on injection of the primary joint and were identical to the primary and secondary endpoints in Study 57.

**Population:** The following were the pre-specified populations in Study 59:

1. The intent-to-treat (ITT) population (all randomized patients who received at least 1 injection). All efficacy and safety analyses were based on the ITT population.

2. The per-protocol (PP) population was ITT patients who had a day 30 post-injection evaluation of contracture after the last treatment to the primary joint, and had no protocol violations that would have affected efficacy evaluation of the primary joint including:

- Received the wrong treatment
- Received > 3 doses of study medication in the DB phase
- Received < 3 injections of study medication without reaching clinical success, did not have a supportive reason for not giving additional injections (e.g. no palpable cord, AEs)
- Final evaluation after the final treatment occurred before the Day 30 visit
- Fixed flexion contracture measurement that did not meet the minimum requirement ( $\geq 20$  degrees) or meet the maximum requirement ( $\leq 100$  degrees for MP joints or  $\leq 80$  degrees for PIP joints)

**Database Lock:** The study was un-blinded after the final patient completed the Day 90 visit. Unblinding before the Day 90 visit was not permitted unless it was deemed necessary for appropriate treatment of a medical emergency.

**Primary and Secondary Efficacy Endpoints:** In Study 59, the baseline stratification, statistical methods, and handling of missing data were identical to the statistical procedures in Study 59.

**Results of Study 59:** See Sections 6 and 7 for all the efficacy and safety results in Study 59.

**Protocol Deviations:** In Study 59, 35 (78%) and 17 (81%) of the patients in the Xiaflex and placebo groups had protocol violations, respectively, and 2 (4%) and 0 (0%) of the patients in the Xiaflex and placebo groups had significant protocol violations, respectively. See Table 9.15 for all protocol deviations in the controlled portions of Study 59 through Day 90.

**Table 9.15: All protocol deviations in the controlled portions of Study 59 through Day 90<sup>1</sup>**

	Xiaflex (n=45)	Placebo (n=21)
<b>All Protocol Violations</b>	<b>35 (78%)</b>	<b>17 (81%)</b>
<b>Patients who remained eligible for treatment did not receive up to 3 injections (primary joint contracture <math>&gt;5^\circ</math>; palpable cord present; and no report of an AE contraindicating further treatment)</b>	21 (47%)	0 (0%)
<b>Delay of study medication injection</b>	4 (9%)	0 (0%)
<b>Received the wrong treatment</b>	1 (2%)	0 (0%)
<b>Did not do procedure<sup>2</sup></b>	18 (40%)	13 (62%)
<b>Procedure not done on time<sup>2</sup></b>	6 (13%)	3 (14%)

<sup>1</sup> Only 2 protocol violations were considered significant: 1 patient received placebo instead of Xiaflex for a second injection and 1 Xiaflex-treated patient missed a Day 30 assessment after a second injection

<sup>2</sup> Procedure included lab tests, vital signs, and efficacy measurements (grip strength, ROM measurement)

Reference: CSR of Study 59, Page 45

**DIVISION OF PULMONARY AND ALLERGY PRODUCTS**  
**MEDICAL OFFICER CONSULTATION**

Date: September 28, 2009  
To: Christopher Hilfiger, Consumer Safety Officer, Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)  
From: Brian Oscar Porter, M.D., Ph.D., M.P.H., Medical Officer  
Through: Susan Limb, M.D., Medical Team Leader  
Through: Badrul Chowdhury, M.D., Ph.D., Division Director  
Subject: Clinical implications of antigen-specific IgE to Xiaflex

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**General Information**

BLA#: BLA 125338  
Sponsor: Auxilium Pharmaceuticals, Inc.  
Drug Product: Xiaflex (collagenase clostridial histolyticum)  
Request From: Christopher Hilfiger, Consumer Safety Officer, DAARP  
Date of Request: September 23, 2009  
Date Received: September 28, 2009  
Materials Reviewed: Summary consult document and proposed product label wording

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**I. Executive Summary**

This is a medical officer review in response to a consultation request from the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) regarding Xiaflex, a bacterial collagenase product derived from *Clostridium histolyticum*, with a proposed indication for the treatment of Dupuytren's contracture, a designated orphan disease. Xiaflex is highly immunogenic, with 100% of recipients developing progressively increasing titers of circulating antigen-specific immunoglobulins after 4 intralesional injections into Dupuytren's cords of the hand. Limited analysis of samples from Phase I and II studies demonstrated that antigen-specific IgE titers also increased with repeated doses of Xiaflex, raising concern for a potential anaphylaxis risk. Of note, patients in the Phase I and II studies with IgE levels exceeding 15 ng/ml were excluded from further receipt of the drug product. To date, 1082 patients have received Xiaflex, with 59% (639) having received 2 or more injections. Seven cases of documented hypersensitivity have been reported, although none of these reactions were severe. Two of these hypersensitivity reactions occurred on the day of dosing, although anaphylaxis has not yet been reported. While an Arthritis Advisory Committee voted unanimously 12 to 0 to approve Xiaflex for this orphan designation, concerns were raised as to the need for post-market monitoring of adverse events related to the use of Xiaflex in non-research, clinical practice settings.

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.

A review of the background and submitted materials and responses to questions are provided below.

## **II. Background**

Submitted under BLA 125338 (2/27/09), Xiaflex is a dual collagenase containing biologic product derived from the bacterium *Clostridium histolyticum*, with a proposed indication of the treatment of Dupuytren's contracture, a debilitating condition of the hands, in which the palm and lateral fingers become progressively contracted due to the development of tight connective tissue cords, which impair mobility. Designated an orphan disease, Dupuytren's contracture typically requires surgical correction in its advanced stages to release these cords, as no medical products are currently approved for its treatment. Xiaflex is given in up to 3 intralesional injections per cord of 0.58 mg each in approximately 0.2 ml, given at 4-6 week intervals. Xiaflex has shown efficacy for the proposed indication based on 12 studies, which demonstrated an adequate safety profile for a 3-dose course. Given concerns that results of clinical studies of this biologic agent performed by specialized hand surgeons may not reflect results gleaned from real-world clinical practice, an Arthritis Advisory Committee met on September 16, 2009, to discuss the Sponsor's risk minimization plan, which included training physicians in the administration of Xiaflex. Although the committee voted unanimously to approve Xiaflex for the proposed indication, some members recommended post-marketing safety studies be completed, particularly for patients receiving multiple injections.

### **Systemic exposure and drug-specific antibody development**

Of note, the two collagenase components of Xiaflex were not detected in the circulation of 20 patients who underwent pharmacokinetic testing. However, two pivotal trials of this drug demonstrated that total drug-specific (anti-collagenase) immunoglobulins were detected in 82-95% of patients after the first exposure to Xiaflex and 100% of patients after 4 or more drug exposures. Moreover, these antibody titers directly correlated with the number of doses received. Although total immunoglobulin levels (presumably IgG

and IgM) did not appear to have an impact on the clinical efficacy of Xiaflex, antigen-specific IgE levels were not measured in these pivotal trials. In contrast, 3 early Phase I and II studies conducted by a prior academic Sponsor included antigen-specific IgE measurements. These data were not submitted to the BLA but were included in the presentation at the Arthritis Advisory Committee meeting. Results from 2 Phase I studies were reported as indicating a high percentage of subjects developed drug-specific IgE. Data from a dose-ranging, randomized, double-blind, placebo-controlled Phase II trial confirmed this observation. In this study, patients initially received a single dose of 0.145, 0.29, or 0.58 mg of Xiaflex versus placebo, followed by an open-label extension phase of up to 4 additional 0.58 mg doses of study drug given at 4-6 week intervals for up to 5 injections. Results indicated that while drug-specific IgE was not detected pre-Xiaflex exposure in any of the 62 drug recipients in the trial, both the incidence and titer of specific IgE increased with repeated injections of Xiaflex to nearly 10 times baseline levels at 1 year after last study drug administration. Of note, patients in the Phase I and II studies with IgE levels exceeding 15 ng/ml were excluded from further receipt of the drug product. Drug-specific IgE levels were not assayed in the Phase III program.

#### **Hypersensitivity reactions to Xiaflex**

The clinical relevance of the immunoassay data is unclear, as no severe hypersensitivity reactions have been reported in a safety database of 1082 Xiaflex recipients involving 2630 total injections across 12 clinical trials, including the Phase II trial mentioned above. However, 36 Xiaflex recipients and 4 placebo-treated patients were reported as having had one or more of the following adverse events (AEs; MedRA terms): blood pressure decreased, bronchospasm, dyspnea, hypersensitivity, hypotension, loss of consciousness, orthostatic hypotension, swelling face, syncope, syncope vasovagal, and urticaria. To clarify whether any of these reactions may have reflected a systemic hypersensitivity reaction, DAARP requested the Sponsor (Auxilium) provide the following additional information:

- a. The temporal relationship between AE and last study drug injection
- b. If other symptoms or signs of a systemic hypersensitivity reaction occurred, e.g., hives, flushing, swollen lips/tongue/uvula; respiratory compromise (dyspnea, wheeze-bronchospasm, stridor, hypoxemia); vascular compromise (hypotension, syncope);
- c. Whether there was a response to re-challenge.

The Sponsor indicated that none of the aforementioned AEs had a temporal relationship with study drug administration nor were associated with signs and symptoms of hypersensitivity. While DAARP concurred that no severe hypersensitivity reactions had been noted, 7 cases of hypersensitivity were identified. Five occurred 4-21 days after last study drug administration and did not require treatment, while 2 occurred on the day of Xiaflex administration, consisting of localized symptoms (pruritus, arm redness, swelling) for which hydrocortisone was given. Furthermore, the DAARP Clinical Review Team found the incidence of pruritus through Day 90 increased with repeated drug dosing and was consistently greater than placebo at all time points.

### **III. Questions**

*1) Do increasingly high titers of anti-product antibody with successive injections, and/or the high magnitude of the titers, raise a concern for future development of clinical hypersensitivity responses, in the absence of corroborating clinical events in the experience to date?*

#### **DPAP Response**

Yes—progressively increasing titers of drug-specific IgE seen with repeated dosing of Xiaflex indicates the potential for significant immediate hypersensitivity reactions, despite the absence of reported drug-related anaphylaxis to date. While the severity of hypersensitivity reactions does not reliably correlate with antigen-specific IgE titers, the overall incidence of hypersensitivity reactions does correlate with the presence and increasing titers of antigen-specific IgE. The lack of anaphylaxis or other severe hypersensitivity cases in this database of limited size does not diminish the concern for such reactions to develop in a larger patient population with repeated, chronic use—particularly given that immediate hypersensitivity reactions including localized pruritus, erythema, and edema have already been observed.

Of note, the documented increases in total drug-specific antibody levels (presumably IgG and IgM) observed in several pivotal studies, raise a theoretical concern for immune complex-mediated adverse reactions, such as renal deposition disease (glomerulonephritis), joint deposition, and serum sickness. Such reactions typically manifest 10-14 days after receipt of study drug and may occur after only a single dose. The absence of circulating drug in pharmacokinetic studies, however, suggests a low likelihood of such reactions.

*2) Would you recommend a post-marketing study requirement to further assess the allergenicity of this product?*

#### **DPAP Response**

No—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. To this end, we recommend product labeling that explicitly discusses the risk of hypersensitivity reactions including anaphylaxis. We also recommend that Xiaflex be labeled for administration in clinical settings capable of providing treatment for hypersensitivity reactions including anaphylaxis. In addition, DPAP recommends a pharmacovigilance program that will collect the following information, if available, for reported hypersensitivity adverse events:

- 1) Timing of reaction in relation to Xiaflex administration
- 2) Description of any cutaneous (e.g., urticaria, erythema, pruritus, edema), respiratory (e.g., airway edema, bronchoconstriction), cardiovascular (e.g., hypotension, syncope), and gastrointestinal (e.g., nausea, vomiting, abdominal pain) signs and symptoms consistent with hypersensitivity.
- 3) Changes in vital signs
- 4) Pertinent laboratory parameters (e.g., serum tryptase)

Pre-dose or reflexive allergic skin testing with Xiaflex and drug-specific IgE titers for Xiaflex recipients are not recommended, as there is currently no justification for excluding patients from Xiaflex dosing based on the results of such tests.

*3) If so, please comment on key study design issues that would be important to relay to the Sponsor (i.e., antigen-specific IgE testing, skin testing, what time interval between exposures would be necessary to rule out booster responses that might result in clinical hypersensitivity events, what adverse events should be included as representative of clinical hypersensitivity events).*

**DPAP Response:** See Response to Question 3.