FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Arthritis Advisory Committee

September 16, 2009

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Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Rheumatology Products

MEMORANDUM

DATE: August 17, 2009

FROM: Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and Rheumatology Products
Office of Drug Evaluation II, CDER, FDA

TO: Chair, Members, and Invited Guests
Arthritis Advisory Committee (AAC)

RE: Overview of the September 16, 2009 AAC Meeting to Discuss BLA 125338 for AA4500-Collagenase Clostridium Histolyticum (Xiaflex) for the treatment of advanced Dupuytren's Disease

AA4500, also known as collagenase clostridium histolyticum, is a fixed-ratio mixture of clostridial type I and type II collagenase isolated from the culture medium of the gram-positive bacteria *Clostridium histolyticum*, and developed as a non-surgical treatment for Dupuytren's contractures. When injected into Dupuytren's cords, the postulated mechanism of action is local lysis of collagen resulting in enzymatic disruption of the cord, leading to a reduction in contracture and improvement in range of motion of the affected joint(s). The proposed dose and administration of AA4500 is 0.58 mg as a single injection into the target cord, followed by a finger extension procedure approximately 24 hours later to facilitate disruption of the cord in those individuals who did not experience spontaneous disruption, and up to two follow-up injections at 4-week intervals, if necessary. Currently, surgery is the mainstay of treatment of Dupuytren's contractures and there are no approved non-surgical treatments for the disorder.

The clinical development program for AA4500 includes multiple randomized, controlled studies and open-label studies that provide the evidentiary basis for the efficacy and safety of this treatment for Dupuytren's Disease. The predominant professional background of the healthcare professionals performing the AA4500 injections in the clinical studies was surgical in nature, with most being either hand surgeons or orthopedic surgeons. The investigators received product-specific training in injection

procedures via multiple mechanisms including manuals and DVDs, workshops, and investigator meetings. This extensive level of background professional training and product-specific injection procedure training may have optimized study outcomes, but also raises questions about how much professional and product-specific training might be required in clinical practice, if the product is approved.

During this meeting, you will hear presentations from the Applicant, Auxilium Pharmaceuticals, Inc., and from the Agency, which will encompass details of the clinical development program and clinical trial results in support of AA4500, as well as the risk management program and training proposed for the product if it becomes licensed for use in clinical practice. Following these presentations you will be asked for your recommendations regarding whether the risks and benefits of the product merit approval, and your opinions regarding the requisite professional background of the healthcare professionals who would administer AA4500 in clinical practice, as well as the adequacy of the proposed product-specific training.

The Division and the Agency are grateful to the members of the committee and our invited guests for taking time from your busy schedules to participate in this important meeting. Thank you in advance for your advice, which will aid us in making the most informed and appropriate decisions possible.

FDA Briefing Document for the September 16, 2009 Arthritis Advisory Committee Meeting

Xiaflex
(AA4500/collagenase clostridium histolyticum) for Advanced Dupuytren's Disease

Biologic License Application 125338

Department of Health & Human Services
Food & Drug Administration
Center for Drug Evaluation & Research
Office of New Drugs
Division of Anesthesia, Analgesia, and Rheumatology Products

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1.0 Background

Dupuytren's disease (DD) is a condition characterized by progressive, fibrous thickening of the palmar fascia with the formation of nodules and cords. Patients with advanced DD develop a fixed flexion contracture of finger joints [Dupuytren's contracture (DC)], most commonly metacarpophalangeal (MP) and proximal interphalangeal (PIP) joints, limiting the normal extension of their finger joints. Currently, surgery is the mainstay of treatment but is not curative; there is a high likelihood of recurrence, as discussed in Section 3.3 below. There are currently no approved non-surgical treatments for DC.

Auxilium Pharmaceuticals (Auxilium) submitted a Biologic License Application (BLA), BLA 125338, on February 27, 2009 for **Xiaflex [AA4500, or collagenase clostridium histolyticum (CCH)]** for the proposed indication of treatment of patients with advanced DD. CCH consists of two microbial collagenases (AUX-I and AUX-II) ─ single polypeptide chains that contain approximately 1000 amino acids ─ which are isolated and purified from *Clostridium histolyticum*. These proteinases 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 CCH is up to 3 injections of 0.58 mg of CCH per Dupuytren's cord, given at 4-week intervals. If an injection does not result in release of the contracture by 24 hours, finger extension procedures are recommended to facilitate cord disruption. Additional cords are to be handled sequentially. See Table A1 in the Appendix for a detailed description of Auxilium's Proposed Dosage and Administration of CCH (Reconstitution, Preparing for Injection, and Injection and Finger Extension Procedures).

The sections that follow include a summary of the clinical trials and major efficacy and safety results, special considerations pertaining to the background professional training of study investigators (i.e., surgical vs. non-surgical), and a summary of the CCH-injection-specific training received by study investigators. The Committee is being asked to consider how background professional training and CCH-specific training may have impacted study outcomes, and the implications of this for healthcare professionals who may use CCH in clinical practice if CCH is approved (see Items for Discussion in Section 8).

2.0 Description of Clinical CCH Trials

2.1 Overview of the Submitted Clinical CCH Trials

The primary support for the efficacy and safety of CCH for the treatment of DC are from the results of two randomized, double-blind, placebo-control, multi-centered, 90-day Phase 3 trials ─ Studies 57 and 59 (see Table 1). Studies 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 trials, 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 ≤ 100° (for MP joint) or ≤ 80° (for a PIP joint) in at least one finger, other than the thumb. Patients may have received up to 3 injections (each injection separated by 4-week intervals) of CCH 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 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. About 24 hours after the injection procedure, patients were fitted with a splint to be worn each night for four months and instructed to perform finger flexion/extension exercises.

Additional support for the efficacy and safety of CCH for the treatment of DC are from the results of four smaller randomized, double-blind, placebo-control trials ─ Studies 03, 53, 51, and 02 (see Table 1). The Agency agrees with Auxilium that Studies 53, 51, and 02 are supportive trials; however, the Agency disagrees with Auxilium's contention that Study 03 is a pivotal trial. The Agency 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 1 investigator performed all the injections; whereas, in the pivotal trials, up to 7 to 33 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.

In Studies 57, 59, 03, and 53, up to 3 injections of study medication may have been administered into the cord (associated with a contracture of the primary joint) every 30 days on Days 0, 30, and 60, and in Studies 02 and 51, only 1 dose of study medication was injected into the cord on Day 0. 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 that achieved a reduction of the contracture of the primary joint to 0 to 5 degrees, 30 days after the last injection (clinical success).

During the course of clinical development, the Agency recommended that safety data be collected on over 1000 CCH-treated patients and over 100 CCH-treated patients with over one year of follow-up. Additionally, the Agency recommended that data on durability of response be collected (e.g., incidence of recurrence). Six open-label, uncontrolled studies of CCH in patients with DC were designed to collect these data (Studies 04, 52, 54, 55, 56, and 58, ─ see Table 1).

Table 1: Key design features of the 12 CCH studies in patients with DC[1]

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

R = randomized, DB = double-blind, PC = placebo-controlled, SD = single-dose, 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 After Auxilium acquired the rights for CCH from the prior sponsor, enrollment was discontinued in Studies 03/04.

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

5 No patients received study medication in Study 52.

Reference: Adapted from the BLA submission, Tabular-listing, Table 1.

2.2 Baseline Patient Population Characteristics in the Pivotal Trials

As shown in Table 2, the CCH 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 higher 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. 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.

In Studies 57 and 59, 36% and 53% of the CCH-treated patients had prior surgery for DC, respectively. The overwhelming majority of these CCH-treated patients with prior DC surgery had surgery on a different finger than the location of the selected primary joint (see Table 2). In Study 57 and 59, only 39% and 9% of the patients with prior DC surgery, respectively, had documentation of the type of prior surgery. Of the patients with a documented type of prior surgery in Study 57, 49% and 38% had a prior fasciotomy and fasciectomy, respectively.

Table 2: Baseline demographics and disease characteristics in the pivotal trials[1]

		Study 57 (U.S.)		Study 59 (Australian)	
		CCH (n=204)	Placebo (n=104)	CCH (n=45)	Placebo (n=21)
Baseline Demographics					
Age, mean (SD)		62 (10)	63 (9)	63 (8)	66 (11)
Age ≥ 65		41%	45%	44%	57%
Age ≥ 75		10%	14%	2%	24%
Gender	Male	84%	71%	87%	81%
	Female	16%	29%	13%	19%
Race	White	100%[2]	100%	100%	100%
	Hispanic	1%[2]	0%	0%	0%
	Black	0%	0%	0%	0%
	Asian	0%	0%	0%	0%
Weight in kg, mean (SD)		83 (16)	79 (18)	86 (15)	76 (12)
Height in feet, mean (SD)		5.8 (0.3)	5.7 (0.3)	5.8 (0.2)	5.7 (0.2)
Baseline Disease Characteristics					
Duration of symptoms in years, mean (SD)		4.9 (6)	5.4 (7)	5.7 (7)	5.7 (7)
History of hand trauma		28%	20%	27%	19%
Family history of DD		42%	51%	49%	43%
Prior treatment for DC		39%	48%	53%	52%
Prior surgery		36%	42%	53%	52%
Prior surgery on the same hand and finger as the primary joint		5%	N/A[3]	7%	N/A[3]
Prior CCH injection		2%	1%	0%	0%
Prior cortisone injection		1%	1%	0%	0%

1 ITT population (all treated patients)
2 There was one Hispanic patient who received CCH in Study 57.
3 These data were not available.

Sources: Study 57 final study report
Information request response, June 23, 2009

As summarized in Table 3 below, treatment groups within the pivotal trials (Studies 57 and 59) were generally balanced with respect to baseline severity of DC as measured in the primary joint affected by DC (the joint selected for the primary efficacy assessment). 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.

Table 3: Baseline disease severity in the pivotal trials[1]

		Study 57 (U.S.)		Study 59 (Australian)	
		CCH (n=204)	Placebo (n=104)	CCH (n=45)	Placebo (n=21)
All Joints affected by Cords					
Total contracture index[2], 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%
Primary Joint affected by Cords[3]					
MP or PIP, mean (SD)	Degrees of ROM[4,5]	44 (20)	45 (19)	40 (15)	44 (16)
	Degrees of full extension[4]	50 (20)	49 (20)	53 (15)	50 (16)
	Degrees of full flexion[4]	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 degrees of full extension		39%	39%	50%	36%
% of PIP joints > 40 degrees of full extension		70%	74%	80%	80%
Little (5th) finger/MP joint - primary joint		34%	31%	27%	29%
Little (5th) finger/PIP joint - primary joint		27%	24%	42%	38%
Ring (4th) finger/MP joint - primary joint		28%	31%	16%	19%
Ring (4th) finger/PIP joint - primary joint		5%	4%	7%	5%
Another MP or PIP was the primary joint		7%	11%	8%	10%

1 ITT population (all randomized patients who received at least one dose of study medication)
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 the final study reports of Studies 57 and 59.

2.3 Patient Disposition in the Pivotal Trials

Table 4 below summarizes the disposition of the patients in the 2 pivotal trials. Overall, very few patients discontinued during the 90-day double-blind phase of the studies. Those who did discontinue withdrew for a variety of reasons, with no category predominating.

Table 4: Disposition in the pivotal trials

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

1 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.
2 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.
3 DAEs are adverse events leading to discontinuation. See Table A12 in the Appendix for a listing of the DAEs.
Reference: Adapted from the final study reports of Studies 57 and 59.

3.0 Efficacy Results

3.1 Primary Efficacy Results

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 Studies 57, 59, 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 Studies 02 and 51, only 1 intra-cord injection of study medication was administered on Day 0.

Table 5 shows the results of the primary efficacy endpoint for the pivotal trials (Studies 57 and 59). A numerical and statistically significantly greater proportion of CCH-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 CCH-treated patients, the mean (SD) number of injections required for clinical success was 1.7 (0.8) in the two trials. The proportion of patients in the CCH 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 (see Table A3 in the Appendix for the proportion of patients who achieved clinical success after the first, second, or third injection in Studies 57 and 59). For the subgroup efficacy analyses by primary joint type (MP or PIP), CCH-treated patients had a greater proportion of clinical success compared to placebo-treated patients for each of these joint types (see Table A4 in the Appendix).

The results of the primary efficacy endpoint (clinical success) in the supportive trials (Studies 03, 53, 51, and 02) demonstrated numerically greater responses in CCH-treated patients compared to placebo-treated patients (see Table A5 in the Appendix). In Study 02, the single-dose-ranging trial, patients treated with the 0.58 mg CCH dose demonstrated a numerical improvement in clinical success compared to patients treated with lower CCH doses.

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

	Study 57[1] (U.S.)		Study 59[2] (Australian)	
	CCH 0.58 mg (n=203)	Placebo (n=103)	CCH 0.58 mg(n=45)	Placebo (n=21)
Proportion of patients with clinical success	**64%**	**7%**	**44%**	**5%**
Difference	**57%**	–	**39%**	–
95% CIs for the Difference	**(48%, 65%)**	–	**(18%, 57%)**	–

CIs = confidence intervals (using an exact method)
1 MITT population was the primary statistical population for the efficacy analyses in Study 57. The MITT population included all treated patients who had at least one post-treatment contracture measurement and had baseline contracture > 5 degrees. There was 1 patient in each of the CCH and placebo groups who were included in the treated population (ITT) and excluded from the MITT population.
2 ITT population (all treated patients) was the primary statistical population for the efficacy analyses in Study 59.
Reference: Adapted from the final study reports from Studies 57 and 59.

3.2 Secondary Endpoint Efficacy Results

Results of the secondary efficacy endpoints in Studies 57 and 59 were consistent with the results of the primary efficacy endpoint in demonstrating a treatment benefit with CCH.

<u>Mean percent change from baseline in the contracture degree</u>
As shown in Table 6, **after up to 3 injections**, CCH treatment resulted in a greater decrease in the mean percent change from baseline in the contracture degree of the primary joint (MP and PIP). Results for this endpoint when subgrouped by primary joint type (MP or PIP) were consistent with the overall results supporting a treatment benefit of CCH treatment in the change in degree of contracture (see Table A6 in the Appendix).

After the first injection, the mean percentage decrease from baseline in contracture degree for CCH-treated patients was 65% in Study 57 and 59% in Study 59.

Table 6: Mean percent change from baseline in contracture degree after up to 3 injections of the primary joint (MP or PIP) in the pivotal trials

	Study 57[1]		Study 59[2]	
	CCH	Placebo	CCH	Placebo
	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)
Mean % decrease from baseline in degree of contracture, 30 days after last injection	79%	9%	71%	14%

1 MITT was the primary statistical population 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).
2 ITT population (all treated patients) was the primary statistical population in Study 59.
Reference: Adapted from the final study reports for Studies 57 and 59.

Mean increase in ROM from baseline (in degrees)

As shown in Table 7, **after up to 3 injections**, CCH treatment resulted in a greater increase in the range of motion (ROM) from baseline for the primary joint (MP and PIP). When subgrouped by primary joint type (MP or PIP), results for this endpoint were consistent (See Table A7 in the Appendix) in showing a treatment benefit in favor of CCH.

After the first injection, the mean (SD) increase from baseline in ROM for CCH-treated patients was 28 (±20) degrees in Study 57 and 29 (±17) degrees in Study 59.

Table 7: Mean (±SD) change from baseline in ROM (in degrees) after up to 3 injections of the primary joint (MP or PIP) in the pivotal trials[1]

	Study 57[2]		Study 59[3]	
	CCH	Placebo	CCH	Placebo
	n=197	n=102	n=45	n=21
ROM at baseline	44 (±20)	45 (±19)	40 (±15)	44 (±16)
ROM 30 days after injection	80 (±20)	50 (±22)	76 (±18)	52 (±20)
Change from baseline in ROM 30 days after injection	36 (±21)	4 (±15)	35 (±18)	8 (±15)

1 The numbers of patients at each time point with a ROM value differed.
2 MITT population was the primary statistical population in Study 57 (all treated patients who had at least one post-treatment contracture measurement and had baseline contracture > 5 degrees).
3 ITT population (all treated patients) was the primary statistical population in Study 59.
Reference: Adapted from the July 15, 2009 response to a statistical information request and from the final study report for Study 59.

Proportion of Patients with ≥ 50% Reduction in Contracture from Baseline

In Study 57, after up to 3 injections, CCH-treated patients showed a significantly greater increase in the proportion of patients with ≥ 50% reduction in contracture from baseline compared to placebo-treated patients (85% vs. 12%). In Study 59, after up to 3 injections, CCH-treated patients showed a significantly greater increase in the proportion of patients with ≥ 50% reduction in contracture from baseline compared to placebo-treated patients (78% vs. 14%).

3.3 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 defined as an increase in contracture of ≥ 20° associated with the presence of a palpable cord. In the pooled controlled and uncontrolled portions of these studies, of the 830 CCH-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.

Because no non-surgical treatments are currently available, the incidence of contracture recurrence in the CCH studies was assessed in light of the reported incidence of contracture recurrence following fasciectomy and/or fasciotomy for DC (see Table 8) in the literature. 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 CCH-treated patients is shorter and still accruing, the incidence of recurrence following CCH-treatment thus far does not appear to be greater than literature reports of recurrence following surgery.

Table 8: 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[1]	# of Surgeons	Recurrence Definition
Fasciectomy					
Foucher 1992	23% (n=107)	5.6 years	Retrospective	1	Severe enough to require another operation. Extension of disease at and outside surgical site
	6% (n=107)				Severe enough to require another operation. Only disease at surgical site
Skoff 2004	3% (n=30)	2.7-3.5 years	Prospective cohort	1	Required a second operation
Searle[2] 1992	0% (n=32)	3.2 years	Retrospective	N/A	Recurrent cord formation
Hall[2] 1997	0% (n=67)	4 years	Retrospective	N/A	Recurrent flexion contracture
Fasciectomy or Fasciotomy					
Dias 2006	15% (n=1037)	2.3 years	Retrospective	Many	Any deformity more than a mild MP joint contracture (severe enough to require another operation)
McFarlane 1990	6%-8% (n=434)	At 2 years[3]	Retrospective	Many	Appearance of disease within the area of operation that required reoperation
	6%-8% (n=48)	At 10 years[3]			
Fasciotomy					
Van Rijssen 2006	42% (n=55)	2.8 years	Retrospective	Many	Severe enough to require another operation
Duthie 1997	66% (n=82)	10 years	Retrospective	1	Required a second operation
Foucher 2003	19% (n=100)	3.2 years	Retrospective	Many	Required a second operation

1 All these studies were observational; 2 Patients in the Hall 1997 and Searle 1992 articles had radical dermofasciectomy.
3 These are not mean follow-up times; rather, they are incidences of recurrence at 2 and 10 years.

4.0 Safety Results

4.1 Clinical Studies Used to Evaluate Safety and CCH Exposure

The safety of CCH was evaluated in the randomized, double-blind, placebo-controlled portions of the 2 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. In this pooled safety database, 249 patients received at least one injection of 0.58 mg of CCH and 125 patients received placebo injections into the cord affecting the primary joint.

The safety of CCH was also evaluated in the controlled and uncontrolled portions of all 12 submitted CCH studies through the last safety cut-off date (Studies 02, 03, 04, 51, 52, 53, 54, 55, 56, 57, 58, and 59). In this pooled safety database, 1082 patients with 1780 Dupuytren's cords received at least one dose of 0.58 mg of CCH (2630 CCH injections). See Table 9 for the number of CCH injections that patients received in the 12 studies. The mean (SD) duration of safety follow-up for these 1082 patients was 9.5 (4.6) months.

Table 9: CCH exposure in the controlled and uncontrolled portions of the 12 CCH studies

# of CCH 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%)

Source: Integrated Summary of Safety, BLA 125338.

4.2 Safety overview

Table 10 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 CCH studies. Almost all CCH-treated patients had an adverse event (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 CCH-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 CCH exposure after single intra-cord injections of 0.58 mg of CCH—AUX-I and AUX-II enzyme levels were not detected 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. (See Table A2 in the Appendix for the timing and assay sensitivity of PK assessments, and number of patients with PK samples.)

A slightly greater proportion of CCH-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 CCH clinical program appear to be consistent with what might be expected for the underlying patient population.

Table 10: Major safety results

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

1 Includes all patients who received ≥ 1 injection of study medication in the pooled Studies 57 and 59 through Day 90
2 Includes all patient who received at least one injection of 0.58 mg of CCH in the pooled submitted studies (Studies 02, 03, 04, 51, 52, 53, 54, 55, 56, 57, 58, and 59).
3 Two CCH-associated deaths from an academic study in the literature are not included in this incidence (see Table 11 for the listing of the causes of death and Table A9 in the Appendix for the detailed narratives of the 5 deaths in the 12 submitted CCH studies and the 2 deaths from the academic study).
4 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 CCH; therefore, this incidence likely represents an upper bound of related SAEs involving the treated extremity.
Reference: Adapted from the final study reports from Studies 57 and 59.

4.3 Deaths

As shown in Table 11, in the complete clinical development program for CCH, there were a total of 7 deaths in patients who received intra-cord injections of 0.58 mg of CCH. Two deaths occurred in extended follow up from an earlier, academic pilot study of CCH. In an early phase dose-ranging clinical study, there were no deaths in placebo-treated patients or the CCH-treated patients who received either 0.145 or 0.29 mg of CCH, but exposure periods for patients in the placebo and lower-dose groups were brief. The reported causes of death were consistent with the underlying patient population and their comorbidities. See Table A9 in the Appendix for

detailed narratives of these 7 deaths. There was no evidence of an increase in the incidence of death with a greater number of CCH doses.

Table 11: Deaths in the controlled and uncontrolled portions of all the CCH studies in DC[1]

	Patient #	Study	Age in years (Gender)	Past Medical History	Cause of Death	Time Between Last CCH Injection & Death Date	# of CCH Injections
Auxilium's Submitted Studies of CCH[2]							
1	101-CMP	02	68 (male)	COPD	COPD	208 days	2
2	004-CMP	02	63 (male)	–	Liver cancer	≥ 76 days	3
3	1168-7010	56	77 (male)	CAD	MI	157 days	1
4	1178-7704	56	79 (male)	DM type II	MI	180 days	1
5	6002-4242	54	76 (male)	CAD	MI	267 days	1
Pilot Academic Study of CCH[3]							
6	1008[2]		75 (male)	COPD	Pulmonary fibrosis	About 365 days	1
7	100028[2]		68 (male)	Cardiac disease	Rupture of aortic aneurysm.	About 60 days	1

1 All of the patients who died received 0.58 mg of CCH. See Table A9 in the Appendix for the detailed narratives.
2 These 5 deaths were from 12 submitted CCH studies (Studies 02, 03, 04, 51, 52, 53, 54, 55, 56, 57, 58, and 59).
3 These 2 deaths, reported by Auxilium, were from an academic pilot study.
Reference: Adapted from the case report forms and narratives from Studies 02, 54, and 56.

4.4 Serious Adverse Events (SAEs)

In the double-blind, controlled portions of the pivotal trials through Day 90, 3% and 1% of the CCH-treated and placebo-treated patients had a SAE (see Table 12). Of these SAEs, a similar proportion of CCH-treated and placebo-treated patients had SAEs that did not involve the injected extremity; however, a greater proportion of CCH-treated patients, compared to placebo-treated patients, had SAEs involving the injected extremity (2% vs. 0%). All of SAEs that involved the treated extremity occurred in CCH-treated patients.

Table 12: SAEs during placebo-controlled portion of the pooled pivotal trials through Day 90

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

Reference: Adapted from the final study reports from Studies 57 and 59.

As shown in Table 13, in the controlled and uncontrolled portions of the 12 submitted CCH studies, out of 1082 patients treated with 0.58 mg of CCH (with a total of 2630 CCH injections), 11 (1.0%) patients had SAEs that involved the injected extremity. Of the 11 SAEs, 7 (64%) occurred within 2 weeks of the last CCH injection. Many of these patients required surgery or additional medical treatment to correct the SAE. See Tables A10 and A11 in the Appendix for detailed narratives regarding these SAEs involving the injected extremity that occurred in the controlled and uncontrolled portions of the trials, respectively.

Of these 11 SAEs, 3 were tendon ruptures, which occurred within 7 days of CCH injection of the cord of the affected digit, and 1 was a flexor pulley rupture occurring 43 days after CCH injection of the cord of the affected digit. These events appeared to be related to study treatment. The patient who underwent an elective amputation of the right 5th finger had received CCH-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.

Table 13: SAEs that involved the injected extremity in the controlled and uncontrolled portions of all the CCH studies[1]

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

1 CCH Studies include Studies 02, 03, 04, 51, 52, 53, 54, 55, 56, 57, 58, and 59. See Tables A10 and A11 in the Appendix for detailed narratives of these SAEs that involved the injected extremity.
2 Number of CCH injections into the relevant cord prior to the SAE. CCH may have been injected at other sites.
Reference: Narratives and case reports forms 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 14, the incidence of SAEs of the treated extremity observed in the CCH 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 14: Intraoperative and postoperative complications after fasciectomy or fasciotomy for DC compared to CCH-associated SAEs involving the treated extremity in the CCH studies

Surgical Complications in the Literature[1]	
Intra-operative complications	**Proportion**
Nerve injuries	**0-8%**
Arterial injury/transection	**0-10%**
Post-operative complications	**Proportion**
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%**
Local Extremity SAEs[2] in the 12 Submitted Studies	
SAEs involving the treated extremity[2]	**0.3%**
Tendon Ruptures[2]	**0.1%**

1 Data are from retrospective and prospective observational studies.
2 SAEs are reported as events per CCH injection. These data are from the controlled and uncontrolled portions of the 12 submitted CCH studies.
Reference: Bulstrode 2005, McFarlane 1990, Foucher 1992, Foucher 2003, Gelberman 1982, Moermans 1991, Rodrigo 1976, Sennwald 1990, Skoff 2004, Van Rijssen.

4.5 Adverse Events Leading to Discontinuation (DAEs)

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 CCH-treated and placebo-treated patients had DAEs, respectively). See Table A12 in the Appendix for a listing of these DAEs. All 3 DAES were associated with CCH treatment. Of the 3 CCH-associated DAEs, 2 involved the treated extremity (severe injection site pain and exacerbation of a regional pain syndrome.

4.6 Common Adverse Events

As shown in Table 15, 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 CCH-treated patients than placebo-treated patients had an AE (98% vs. 49%). The overwhelming majority of CCH-associated AEs were local reactions. The most commonly reported CCH-associated AEs were

edema, contusion, hemorrhage, and pain involving the extremity and were likely related to CCH injection. For CCH-treated patients, the types and proportion of AEs were similar after 1 CCH injection to after up to 3 CCH injections, although fewer placebo-treated patients experienced an AE after a single injection (26%, see Table A13 in appendix).

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 CCH-treated compared to placebo-treated patients had pain in the extremity (35% vs. 5%) or injection site pain (33% vs. 6%).

Table 15: AEs (≥ 5% in either treatment group) during placebo-controlled portion of the pooled pivotal trials through Day 90[1]

	0.58 mg of CCH (n=249)	Placebo (n=125)
Patients with ≥ 1 AE	**243 (98%)**	**61 (49%)**
Edema (involving the extremity)	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%)

1 Includes all patients who received at least one injection of study medication. Preferred terms were coded using MedDRA dictionary (Version 8.0). If multiple AEs were reported for a given preferred term, only 1 event was counted per patient.
Reference: Adapted from the final study reports from Studies 57 and 59.

4.7 Immunogenicity

Immunogenicity data were collected in almost all of the Auxilium-sponsored multiple-dose CCH 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 CCH-treated patients had anti-AUX-I (89% to 95%) or anti-AUX-II (82% to 88%) after the first injection (see Table A14 in the Appendix). All CCH-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.

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 CCH-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 CCH-treated patients with positive or negative neutralizing antibody status to AUX-I who achieved the primary endpoint of clinical success (See Table A8 in the Appendix). A slightly lower proportion of CCH-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.

4.8 Allergic Reactions

CCH contains foreign proteins, so immunogenicity and allergic reactions would not be unexpected, particularly with repeated exposures. Data from the CCH 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 16, a greater proportion of CCH-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 CCH doses were administered. Overall, these data suggest CCH 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 16: Pruritus AEs after up to 1, 2, or 3 injections in the placebo-controlled pivotal trials through Day 90[1]

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

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

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 stratified by professional specialization. Study 59 allowed for an assessment by surgical vs. non-surgical background due to participation by rheumatologists as investigators.

5.1 Efficacy subgroup analysis by specialty

In Study 57, all investigators injecting study medication were surgeons. As shown in Table 17, orthopedic surgeons and hand surgeons who performed the injections obtained similar results for the primary efficacy endpoint (73% vs. 63%).

Table 17: Efficacy by specialty analysis in Study 57[1]

Site #		Total # (%) of patients at site	Proportion of Patients with Clinical Success (Primary Efficacy Endpoint)[1]	
			CCH	Placebo
All Sites		306 (100%)	130/203 (64%)	7/103 (7%)
Hand Surgeons[2]		273 (89%)	114/181 (63%)	7/92 (8%)
1	1158	11%	61%	20%
2	1160	9%	85%	0%
3	1154	8%	88%	11%
4	1164	7%	50%	14%
5	1159	6%	62%	0%
6	1175	5%	36%	0%
7	1166	5%	64%	0%
8	1161	5%	67%	0%
9	1165	4%	50%	20%
10	1170	4%	50%	0%
11	1152	3%	83%	0%
12	1182	3%	67%	50%
13	1153	6%	64%	0%
14	1157	12%	52%	0%
Orthopedic Surgeons[3]		33 (11%)	16/22 (73%)	0/11 (0%)
15	1155	6%	69%	0%
16	1172	5%	78%	0%

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 up to 3 injections, using the MITT population.
2 Of these 26 investigators who performed injections, 25 were hand surgeons except 1 plastic surgery fellow
3 Of these 7 investigators who performed injections, 6 were orthopedic surgeons except 1 hand surgeon.
Reference: Adapted from the final study report for Study 57.

Study 59 included a subgroup of rheumatologists who injected study medication. Table 18 displays the results of a subgroup efficacy analysis, using the primary efficacy endpoint, subgrouped by medical specialist who performed the injections (hand 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 (45% vs. 44%).

Table 18: Efficacy by specialty analysis in Study 59[1]

Site #		Total # (%) of patients at site	Proportion of Patients with Clinical Success (Primary Efficacy Endpoint)[1]	
			CCH	Placebo
All Sites		66 (100%)	20/45 (44%)	1/21 (5%)
Hand Surgeons[2]		50 (76%)	15/34 (44%)	1/16 (6%)
1 & 2	6003 and 6007	23 (35%)	6/15 (40%)	1/8 (13%)
3	6005	15 (23%)	6/10 (60%)	0/5 (0%)
4	6006	12 (18%)	3/9 (33%)	0/3 (0%)
Rheumatologists[3]		16 (24%)	5/11 (45%)	0/5 (0%)
5	6002[3]	16 (24%)	5/11 (45%)	0/5 (0%)

1 Primary efficacy endpoint was the proportion of patients that achieved a contracture reduction to 0 to 5 degrees of the primary joint (up to 3 injections), using the ITT population (all treated patients).
2 All of the investigators who performed the injections were hand surgeons.
3 At Site 6002, the 4 injectors were rheumatologists.
Reference: Adapted from the final study report from Study 59 and from the June 23, 2009 response to information requests.

5.2 Investigator Training

In the pivotal trials, principal investigators received injection technique manuals and DVDs, attended workshops and investigator meetings, and had a teleconference about the proper injection and finger extension technique (see Table 19). No simulations were performed in these training sessions. Principal investigators were responsible for training all sub-investigators in injection and finger manipulation procedures and other types of study procedures.

Table 19: Investigator training in the pivotal trials

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

PIs = principal investigators. Reference: Adapted from the June 23, 2009 response to information request.

6.0 Auxilium's Proposed Risk Management Plan

Auxilium proposes routine pharmacoviligence for risk assessment of CCH-associated AEs, with labeling, physician education, and a requirement for self-attestation of completion of training as measures intended to minimize the risk of procedure-related complications (see Table 20).

Table 20: Auxilium's proposed risk management plan for SAEs involving the treated extremity

Risk Assessment
Routine Pharmacoviligence
Includes standard follow-up questionnaire to obtain safety information about tendon or ligament ruptures.
Aggregate review of AEs monthly for first year then quarterly
Risk Minimization
Labeling
Section 2.0 Dose & Administration: CCH "should be administered by a healthcare professional experienced in the treatment" of DC.
Section 5.0 Warnings & Precautions: Injection of CCH "into collagen containing structures may result in damage to those structures, & possible permanent injury such as tendon rupture or ligament damage."
Section 17.0 Patient Information: "Rarely, damage or rupture of the tendon in the treated finger can occur. This may result in trouble bending your finger fully and may require surgical repair."
Education to healthcare professionals
CD-ROM & Manual for Proper Injection Technique & Finger Extension Procedure.
Auxilium's restricted distribution program (self-attestation prior to receiving CCH)
Physicians must sign a form that states that they understand the injection procedures, CCH risks including tendon rupture, and they have viewed a CCH video.
If physicians do not sign this form, CCH will not be provided

Reference: Adapted from the Risk Management Plan also from the July 8, 2009 response to clinical information request.

7.0 Risk-Benefit Summary

Table 21 contains an estimate of the potential benefits versus risks of CCH-treatment based on selected efficacy and safety outcomes observed during the controlled periods of pooled pivotal trials (Studies 57 and 59). Note that the number-needed-to-harm (NNH) calculation utilizes the total number of AEs for each category and does not incorporate a definitive causality assessment. The risk:benefit assessment of CCH is also not complete without consideration of the relative risk:benefit of currently available surgical options.

This summary likely represents a "best-case" scenario of CCH use, where the healthcare professionals administering the treatment were highly trained, and patients were carefully selected and monitored. Nonetheless, these results may be useful as a starting point for an evaluation of how the risk:benefit ratio may differ if CCH is approved and used in the clinical practice setting. In the optimized setting of these clinical trials, very few patients were treated for each patient who experienced benefit, whereas a much greater number of patients were treated for each patient who experienced an SAE involving the treated extremity, or a tendon rupture.

Table 21: Benefit-Risk overview after up to 3 intra-cord injections[1]

Possible Benefit			
	CCH[1]	**Placebo**	**Number Needed to Treat**
Proportion of patients who had a contracture reduction to 0 to 5 degrees after up to 3 injections	**150/248 (60%)**	**8/124 (6%)**	**~ 2**
Proportion of patients who had a contracture reduction from baseline ≥ 50% after up to 3 injections	**207/248 (83%)**	**15/124 (12%)**	**~ 1**
Possible Risk			
	CCH	**Placebo**	**Number Needed to Harm**
Local AEs[2]	**236/249 (95%)**	**32/125 (26%)**	**~ 1**
SAE involving the treated extremity[3]	**5/249 (2%)**	**0/125 (0%)**	**~ 50**
Tendon Rupture[3]	**2/249 (1%)**	**0/125 (0%)**	**~ 125**

1 The benefit and risk calculations were based on the efficacy and safety results of the pooled pivotal trials through Day 90 (Studies 57 and 59). The CCH denominator for the benefits was based on the number of patients in the primary efficacy population (n=248) and the CCH denominator for the risks was based on the number of patients in the primary safety population (n=249). The mean (±SD) number of injections given in the pivotal trials through Day 90 was 1.7 (±0.8) injections.
2 Local AEs were the most common AEs (e.g., edema, contusion, injection site hemorrhage, pain in extremity, injection site pain, injection site swelling, and tenderness).
3 The 5 CCH-associated SAEs involving the treated extremity in the controlled portions of the pivotal trials through Day 90 included 2 tendon ruptures.

The Agency is asking the Committee to review the safety and efficacy data for CCH, and to provide your assessment of the risks and benefits of CCH-treatment, and your recommendations regarding how the risk:benefit profile of this treatment might be optimized in the clinical practice setting.

8.0 Items for Discussion for the AC

1. Auxilium proposes that their clostridial collagenase product should be administered by "healthcare professionals experienced in the treatment of Dupuytren's Disease." This would likely include a broader range of healthcare professionals than was represented in the clinical development program, which was primarily comprised of hand surgeons and orthopedic surgeons. Please discuss whether the intended healthcare professionals could be reasonably expected to adequately perform collagenase injections of Dupuytren's cords, or whether expertise in hand surgery or in injections of the hand should be specified.

2. Investigator training in the clinical studies included injection technique instruction via manuals and DVDs, workshops, and investigator meetings, and may be more extensive than the training proposed for the education of healthcare professionals in clinical practice if the product is approved. Please discuss whether the training, as proposed by Auxilium for the education of healthcare professionals in clinical practice, is adequate.

3. In view of the data available for safety and efficacy, please discuss whether Auxilium's clostridial collagenase should be approved for the treatment of patients with advanced Dupuytren's Disease.

4. Depending on results of the discussion of item 3, please address the following:

    a. If you recommend approval, discuss what additional studies, if any, should be conducted post-approval to further assess the safety of the product.

    b. If you do not recommend approval, discuss what additional data are needed to support approval.

9.0 References

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10.0 Appendices

10.1 Appendix – Proposed Dosage and Administration

Table A1: Auxilium's proposed dosage and administration of CCH (reconstitution, preparing for injection, injection and finger extension procedures)

General Considerations for Administration: Should be administered by a healthcare professional experienced in the treatment of DD

Reconstitution of the Lyophilized Powder:

- **Before use, the vial containing CCH and the vial containing the diluent for reconstitution should be removed from the refrigerator and allowed to stand at room temperature for at least 15 minutes and no longer than 60 minutes.**
- **Using a syringe that contains 0.01 mL graduations, withdraw 0.39 mL of diluent for cords affecting the MP joint or 0.31 mL of diluent for cords affecting the PIP joint. Inject the diluent slowly into the vial containing the lyophilized powder of CCH. Slowly swirl the solution in the vial containing CCH to ensure that the entire contents of the vial have gone into solution.**
- **The reconstituted CCH solution can be kept at room temperature (25ºC/77ºF) for up to one hour or refrigerated at 2º to 8°C (36º to 46°F) for up to 8 hours prior to administration. If refrigerated, the reconstituted CCH solution should be allowed to return to room temperature for approximately 15 minutes before use.**

Preparing for Injection:

- **Administration of a local anesthetic agent prior to injection is not recommended (may interfere with placement of the injection).**
- **The site chosen for injection should be 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.**
- **If injecting into a cord affecting the PIP joint of the fifth (little) finger, care should be taken to inject as close to the palmar digital crease as possible.**

Injection Procedure:

- **Using a syringe with 0.01 mL graduations and a permanently fixed, ½-inch needle (26 or 27 gauge), withdraw 0.25 mL of reconstituted solution (containing 0.58 mg of CCH) for cords affecting a MP joint or 0.20 mL of reconstituted solution (containing 0.58 mg of CCH) for cords affecting a PIP. Discard the unused portion of the reconstituted solution after injection. Do not store, pool, or use any vials containing unused reconstituted CCH solution.**
- **Place the needle into the cord, using caution to keep the needle within the cord. Avoid having the needle tip pass completely through the cord to help minimize the potential for injection of CCH into tissues other than the cord. If insertion of the needle into a tendon is suspected or paresthesia is noted by the patient, withdraw the needle and reposition it into the cord.**
- **After confirming that the needle is correctly placed in the cord, inject approximately one-third of the dose. Next, withdraw the needle tip from the cord and reposition it in a slightly more distal location (approximately 2-3 mm) to the initial injection in the cord and inject another one-third of the dose. Again withdraw the needle tip from the cord and reposition it a third time proximal to the initial injection (approximately 2-3 mm) and inject the final portion of the dose into the cord.**

Post-Injection Procedures: Place a bulky dressing over the palm of the patient's treated hand and instruct the patient to limit motion of the injected finger until the day after the injection. The patient should be instructed to return to the physician's office the next day after the injection procedure.

Finger Extension Procedure (about 24 hours after the Injection Procedure):

- **If a clinically significant cord contracture remains, a passive finger extension procedure should be undertaken to facilitate cord disruption. Local anesthesia may be used. Apply moderate stretching pressure to the injected cord for approximately 10 to 20 seconds.**
- **If the first finger extension procedure does not result in disruption of the cord, a second and third attempt can be performed at 5 to 10 minute intervals. However, no more than 3 attempts are recommended to disrupt a cord. If the cord has not disrupted after 3 attempts of the finger extension procedure, a follow-up visit should be scheduled about 4 weeks after the injection.**

Additional Injections:

- **At the 4 week follow-up visit, if the contracture persists, the cord may be re-injected with a single dose of CCH and the finger extension procedure repeated approximately 24 hours after injection.**
- **Injections and finger extension procedures may be administered up to 3 times per cord at approximately 4-week intervals.**
- **Only one cord should be treated at a time. If there are multiple contractures, treatment of each cord should be undertaken in a sequential order.**

How Supplied:
CCH is supplied as a lyophilized powder in a single-use glass vial to deliver a 0.58 mg dose after reconstitution (3 mL of sterile diluent for reconstitution is supplied). Prior to reconstitution, the vials of CCH and diluent should be stored in a refrigerator at 2º to 8ºC (36º to 46ºF).

Reference: Adapted from Auxilium's most recent proposed CCH label.

10.2 Appendix – PK

Table A2: 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
Study 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**
Study 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.

10.3 Appendix – Efficacy

Table A3: 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[1] (U.S.)		Study 59[2] (Australian)	
	CCH	Placebo	CCH	Placebo
Last injection (up to 3 injections)[3]	n=203 64%	n=103 7%	n=45 44%	n=21 5%
First injection[4]	n=203 39%	n=103 1%	n=45 27%	n=21 5%
Second injection[4]	n=99 35%	n=100 1%	n=22 27%	n=19 0%
Third injection[4]	n=45 36%	n=91 6%	n=8 25%	n=18 0%

1 MITT population in Study 57.
2 ITT population (all treated patients) in Study 59.
3 Clinical success after the last injection (up to 3 injections) was the primary efficacy endpoint (see Table 5).
4 The proportion of patients that achieved clinical success after the 1st injection was a secondary endpoint included in the statistical hierarchy. The proportion of patients that achieved clinical success after the 2nd and 3rd injections were not pre-specified endpoints.
Reference: Adapted from the final study reports for Studies 57 and 59.

Table A4: Proportion of patients that achieved a contracture reduction of the primary joint to 0 to 5 degrees, 30 days after up to 3 injections by joint subtype (MP or PIP) in the pivotal trials

Treatment Groups	Primary Efficacy Endpoint		Subgroup Efficacy Analyses by Joint Type			
	Primary Joint (MP & PIP)		Primary MP Joint		Primary PIP Joint	
	n		n		n	
Study 57 (up to 3 injections on Days 0, 30, and 60)[1]						
CCH 0.58 mg	203	64%	133	77%	70	40%
Placebo	103	7%	69	7%	34	6%
Study 59 (up to 3 injections on Days 0, 30, and 60)[2]						
CCH 0.58 mg	45	44%	20	65%	25	28%
Placebo	21	5%	11	9%	10	0%

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.
2 ITT population (all treated patients) was the primary statistical population for the efficacy analyses in Study 59.
Reference: Adapted from the final study reports for Studies 57 and 59.

Table A5: Proportion of patients that achieved a contracture reduction of the primary joint to 0 to 5 degrees, 30 days after the last injection in the supportive trials[1]

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

1 The supportive trials were Studies 03, 53, 51, and 02.
2 Randomized population was the primary statistical population for the efficacy analyses in Studies 02 and 03.
3 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.

Table A6: 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		Study 59	
	CCH	Placebo	CCH	Placebo
All Primary Joints (MP or PIP)	n=203[1]	n=103[1]	n=45[2]	n=21[2]
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)
Mean % decrease from baseline in degree of contracture, 30 days after injection	79%	9%	71%	14%
Primary MP Joints	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%
Primary PIP Joints	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%

1 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.
2 ITT population (all treated patients) was the primary statistical population in Study 59.
Reference: Adapted from the final study reports for Studies 57 and 59.

Table A7: 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

	Study 57[1]		Study 59[2]	
	CCH	Placebo	CCH	Placebo
All Primary Joints (MP or PIP)	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)
Change from baseline in ROM 30 days after injection	36 (±21)	4 (±15)	35 (±18)	8 (±15)
Primary MP Joints	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)
Primary PIP Joints	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)

1 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.
2 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 and from the final study report for Study 59.

Table A8: Proportion of CCH-treated patients with contracture reduction to 0 to 5 degrees after up to 3 injections by neutralizing antibody status in Study 57[1]

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

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

10.4 Appendix – Safety

Table A9: Narratives of the 7 deaths in the controlled and uncontrolled portions of all the studies and literature reports of CCH in DC[1]

	Patient # (Study)	Narrative	Time between last CCH injection & Death Date [# of Injections][2]
Auxilium's Submitted Studies of CCH[3]			
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 CCH 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 2001).	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 CCH on Day 1 and subsequently received 2 injections of 0.58 mg of CCH 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 CCH injection on Day 1 and had symptoms of an MI and died of an MI on Day 157 (second quarter of 2008).	157 days [1]
4	1178-7704 (Study 56)	79 year old male with DM type II, HTN, hyperlipidemia, GERD, and hypothyroidism. Received 1 CCH injection on Day 1 and died on Day 180 due to a MI (second quarter of 2008).	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 CCH injection on Day 1 and had an MI on Day 261 and died on Day 267 (fourth quarter of 2008).	267 days [1]
Pilot Academic Study[4]			
6	1008[2]	75 year old male with COPD over 20 years died from complications of pulmonary fibrosis about one year after his last injection of CCH.	About 365 days [1]
7	100028[2]	68 year old male with history of cardiac disease died 2 months after his last injection of CCH from a rupture of aortic aneurysm.	About 60 days [1]

1 All of the patients who died received 0.58 mg of CCH.
2 Number of CCH injections received prior to death.
3 These 5 deaths were from 12 submitted CCH 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.

Table A10: Narratives of the 5 SAEs that involved the injected extremity in the 90-day, controlled portions of all the CCH studies[1]

Patient # (Study)	Narrative	Time Between Last CCH Injection & AE (# of Injections)[2]
1157-4203 (Study 57)	76-year-old male with prior fasciotomy for DC (left 3rd and 5th fingers), HTN, received 1 CCH injection into the cord affecting the left 5th MP joint on Day 1 and on Day 2 had 3 finger extensions. On Day 28, had a second CCH injection into the cord affecting the left 5th MP joint and on Day 29 had 3 finger extension procedures. On Day 54, had a first CCH injection into the cord affecting the left 5th 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, surgery 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 CCH on Day 1 into the cord 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. Surgical procedures: 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, CCH 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 treated with oral steroids, pregabalin, and hand therapy.	13 days (1)
1170-3801 (Study 57)	73-year-old female with HTN, hyperlipidemia, gastritis, and hypothyroidism. Received CCH 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 5th right finger was deficient. An examination showed sagittal band disruption with nonreducer tendon. The investigator considered this ligament disorder to be a chronic deformity, 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 CCH). Event ongoing.	20 days (3)
6003-1601 (Study 59)	61 year old male. On Day 1 received CCH into the cord associated with the left 5th PIP and then had a second CCH injection on Day 28. On Day 71, had worsening of his left 5th finger contracture. On examination on Day 84, left 5th 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 surgery: a left 5th 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 CCH injections.
2 Number of CCH injections into the relevant cord prior to the SAE. CCH 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 A11: Narratives of the 6 SAEs that involved the injected extremity in the uncontrolled, open-label portions of all the CCH studies[1]

Patient # (Study)	Narrative	Days Between Last CCH Injection & AE [# of Injections][2]
1167-1011 (Study 55)	62 year old male with HTN, asthma, GERD, BPH, hyperlipidemia, back pain, and a Boutonnière deformity of the 5th finger. Received CCH 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 5th (right) flexor digitorum superficialis tendon and a significant attenuation of the size of the flexor digitorum profundus tendon. Had surgical fusion of DIP, event resolving.	≤ 7 days [1]
6002-1502 (Study 59)	51 year old male with hyperlipidemia. On Day 1, given CCH and on Day 29 given a second CCH injection in the cord associated with the left 2nd 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 2nd finger. Post-surgery the patient had full ROM. Event resolved.	13 days [2]
6006-4528 (Study 54)	67 year old male with history of hyperlipidemia. On Day 1 received 1 CCH injection into the cord associated with right 2nd MP joint. On Day 14, had a farming accident and his right 2nd finger was caught in a cattle crush. On Day 29, diagnosed with a fracture of the tip of right 2nd finger with a ligament tear. Patient recovered without surgery.	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 CCH 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 CCH injection into the cord involving the right 5th PIP joint and on Day 2 required 2 finger extensions. On Day 30, received 1 CCH injection into the cord involving the left 5th MP joint. On Day 133, received his fourth CCH injection into the cord involving the right 3rd 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 3rd finger. MRI showed hypertrophic tendonitis and intrasubstance but not complete tear. Managed conservatively, outcome unknown.	14 days [4]
1170-3816 (Study 58)	67 year old female with anxiety, hyperlipidemia, GERD, HTN. Received CCH injection in the cord affecting the left 5th PIP on Day 1 and on Day 28 developed a Boutonniere deformity of the left 5th DIP and a splint was placed to correct the deformity. Event ongoing.	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 CCH on Day 0 to the cord affecting the right fifth MP joint (the cord affecting the right 5th PIP was untreated) and on Day 0 had right hand bruising, swelling, injection site tenderness, 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 right 5th finger were 105, 105, and 100 degrees, respectively. On Day 103, injured her right 5th 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 5th 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]

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 CCH injections.
2 Number of CCH injections into the relevant cord prior to the SAE. CCH 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 A12: DAEs during the 90-day DB treatment period in Studies 57 and 59

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

DAEs are AEs leading to discontinuation
Reference: Adapted from the final study report of Study 57 and the Safety Update.

Table A13: AEs (≥ 5% in either treatment group) after 1 injection in pooled Studies 57 and 59

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

1 Includes all patients who received at least 1 injection of study medication. 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.
Reference: Reviewer's analysis from ADAE JMP datasets from Studies 57 and 59.

Table A14: Antibodies to AUX-I or AUX-II after the first CCH injection in the pivotal trials

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

1 CCH-treated patients
2 CCH-treated patients who had an anti-product sample
Reference: Adapted from the final study reports from Studies 57 and 59.