



**Briefing Document for Collagenase Clostridium
Histolyticum (AA4500) in the Treatment of Advanced
Dupuytren's Disease**

Arthritis Advisory Committee Meeting: 16 September 2009

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ASSH	American Society for Surgery of the Hand
AST	Aspartate aminotransferase;
AUX-I	Clostridial type I collagenase
AUX-II	clostridial type II collagenase
BLA	Biologics License Application
BMI	Body mass index
BPM	Beat per minute
BSSH	British Society for Surgery of the Hand
BTC	BioSpecifics Technologies Corp.
BUN	Blood urea nitrogen
CRPS	Complex regional pain syndrome
CS	Clinically significant
DIP	Distal interphalangeal
ELISA	Enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
IV	Intravenous
kDA	kilodalton
MedDRA	Medical Dictionary for Regulatory Activities
MMP	Matrix metalloproteinase
MP (or MCP)	Metacarpophalangeal
MSS	Musculoskeletal syndrome
PIP	Proximal interphalangeal
PMN	Neutrophil
ROM	Range of motion
RPM	Respirations per minute
SAE	Serious adverse event
TEAE	Treatment-emergent adverse events were events with a start date equal to or after the first injection of study drug.
ULN	Upper limit of normal

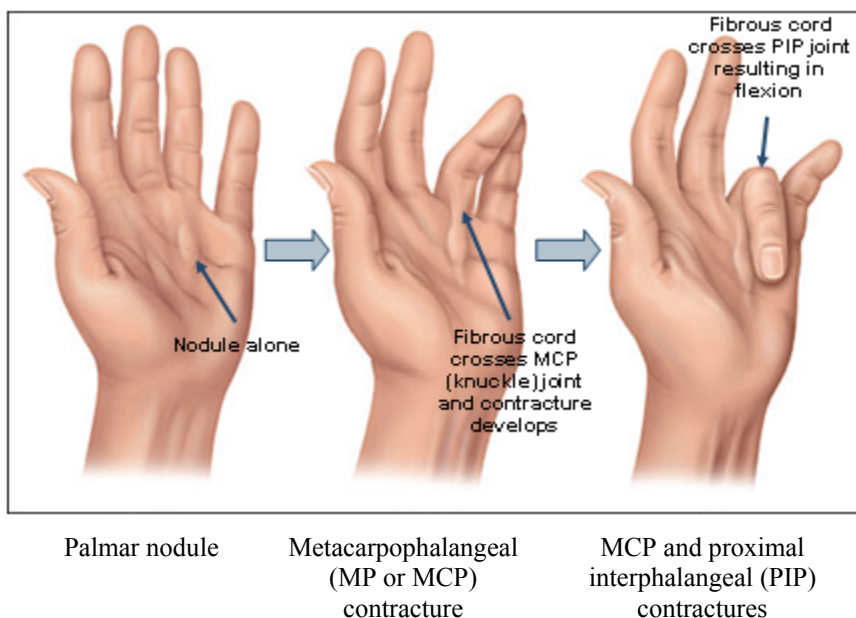
1. EXECUTIVE SUMMARY

1.1. Background

Dupuytren's disease is a slowly progressive fibroproliferative disease of the palmar fascia in the hand. The etiology and pathogenesis of Dupuytren's disease are not well understood. However, the abnormal collagen deposition, which results in nodule and cord formation, may eventually limit hand movement by causing the affected finger(s) to bend or flex (contract) toward the palm of the hand with loss of the ability to straighten (extend) the finger(s). When the fibrous cord retracts the finger toward the palm, the resulting pathology is known as Dupuytren's contracture.

Progression of disease is not absolute and in many cases contractures remain confined to palmar involvement. Progression is unpredictable and it is not possible to identify individuals in whom the disease will progress rapidly, if at all. Some individuals will have only small lumps or cords while others will develop severely bent fingers. More than 50% of patients will have bilateral disease or more than one affected finger (McFarlane, 1983 and American Society for Surgery of the Hand [ASSH]). When progression of Dupuytren's disease occurs, contractures become irreversible without treatment (Luck, 1959). The natural progression of Dupuytren's contracture is illustrated in Figure 1.

Figure 1: Illustration of the Natural History of Dupuytren's Contracture



As the disease progresses and contracture develops, many activities of daily living, such as face washing (poking the eye and the face with affected digit), combing hair, putting hand in a pocket or glove, shaking hands, turning door knobs, driving, playing sports (eg, golf), and playing instruments (eg, piano, trumpet) may become difficult or impossible (Bayat and McGrouther, 2006). Employment related tasks such as typing and gripping tools or instruments also can become more difficult or impossible if they require full range of motion of the fingers. Functional disability worsens with increasing deformity. Subjects may also feel considerable

embarrassment regarding the visible deformity of the contracture and aspire to have straight and supple fingers that do not impede activities of daily living (Dias, 2006).

There is no cure for Dupuytren's disease. Available treatments to address the resultant contracture include invasive surgical procedures to divide or excise the diseased fascia. These surgical procedures can be challenging and may result in both intraoperative and postoperative complications, such as nerve injury, arterial injury, wound infection, scar contracture, loss of function, and rarely flexor tendon injury. Recurrence of the contracture may also occur. Not all subjects may be suitable for surgery, and diabetic subjects respond to surgery less favorably (Leclercq, 2000). Moreover, surgery often requires a prolonged recovery (Bulstrode et al., 2005; Skoff, 2004). Due to variable disease severity and surgical techniques, immediate postoperative recovery time can range from 21 days to 58 days (Rodrigo et al., 1976; Tubiana, 1999). Physical therapy and splinting for at least one month is usually required after surgery for good results to be maintained (Mackin and Byron, 1990; Mackin and Skirven, 2000).

1.2. Collagenase Clostridium Histolyticum (AA4500)

Collagenase clostridium histolyticum (hereafter referred to as AA4500) is a novel non-surgical treatment targeting Dupuytren's contractures through the injection of enzymes into the pathologic diseased cords. AA4500 is a new molecular entity, comprising a fixed-ratio mixture of two purified collagenolytic enzymes (AUX-I [clostridial type I collagenase] and AUX-II [clostridial type II collagenase]) isolated from the culture medium of *Clostridium histolyticum*. AUX-I is a single polypeptide chain containing approximately 1,000 amino acids of known sequence and with a molecular weight of 114 kilodaltons (kDa). AUX-II is also approximately 1,000 amino acids long and has a molecular weight of 113 kDa. These enzymes have been shown by substrate activity patterns to be representative of the Class I and Class II collagenases, respectively. The Class I and Class II collagenases are generated by the homologous expression of their respective separate chromosomal genes, *colG* and *colH*; both are metalloproteinases, requiring the metal cofactors zinc and calcium for full activity and both have selective activity against collagen. They differ from each other in terms of domain structure, substrate affinity, catalytic efficiency and preferred cleavage site on the collagen molecule.

The differences between the two collagenase classes result in improved activity against collagen when the two are combined, compared to the activity seen with either class acting alone. The fixed-ratio of AUX-I and AUX-II represented in AA4500 drug product falls within the range of effective ratios for which improved speed and completeness of digestion of either soluble (Mandl et al., 1964; Kono, 1968) or intact interstitial collagen (Wolters et al., 1995; Vos-Scheperkeuter et al., 1997) has been reported in the literature.

1.3. Benefits

The use of AA4500 for the treatment of advanced Dupuytren's disease constitutes the first use of this novel biologic as an alternative to surgery for this debilitating condition.

AA4500 administered at the proposed commercial dose of 0.58mg was statistically superior to placebo ($p < 0.001$) with respect to the percentage of subjects who achieved a reduction in contracture to 5° or less in each of the three double-blind, placebo-controlled studies (AUX-CC-857 [Study 1], 64.0% versus 6.8%; AUX-CC-859 [Study 2], 44.4% versus 4.8%; and DUPY-303 [Study 3]), 91.3% versus 0%.

In each study, subjects treated with AA4500 had a greater reduction in baseline contracture, a greater increase in range of motion (ROM) without negative impact on grip strength, and a shorter time to achieve this reduction compared with subjects who received placebo.

The inability for a subject to flex a finger to the distal palmar crease (ie, full flexion) has been reported in 4.6% of subjects after surgical correction of Dupuytren's contracture (McFarlane and McGrouther, 1990). In the three double blind, placebo-controlled studies, full flexion was virtually unaffected by AA4500. Furthermore, loss of finger joint mobility has been reported to occur after surgery (Tubiana, 2000). In the three double-blind, placebo-controlled studies, AA4500 produced no detrimental effect on joint mobility or joint flexion.

Since there is no curative treatment for Dupuytren's disease, recurrence of the cord and contracture may occur. Depending on the type of surgery performed, recurrence rates of up to 60% have been observed after surgical correction (Rodrigo et al., 1976). Following treatment with AA4500, duration of correction was evaluated in subjects with up to 12 months of follow-up and who had a reduction in contracture to 5° or less. Recurrence was defined as an increase in joint contracture to at least 20° in the presence of a palpable cord. During the 12-month follow-up period for each subject, 30 of the 830 successfully treated Dupuytren's cords were recurrent (nominal rate of 3.6%) with an estimated rate of recurrence at 12 months of 6.7% ($\pm 1.7\%$), based on the Kaplan-Meier estimate.

No differences in the efficacy of AA4500 were observed with regard to age, gender, body weight, body mass index (BMI), or history of diabetes. It is of note that AA4500 showed no differences in efficacy in subjects with diabetes, as this group is reported to have a less robust outcome after surgery (Leclercq, 2000).

AA4500 also has been shown to be well tolerated in clinical studies, with the majority of reported adverse events occurring locally and of mild to moderate severity. Following resolution of the local events, usually within 2 to 4 weeks after injection, most subjects are able to fully extend their previously contracted finger and return to most activities of daily living, without the requirement for adjunctive therapy, such as physical therapy of the hand. These findings, along with the high degree of overall subject satisfaction with AA4500 treatment, indicate the clinically relevant benefits of this potential new treatment option that can be administered in an office setting to individuals suffering from advanced Dupuytren's disease.

2. DISEASE OVERVIEW AND CURRENT THERAPY

2.1. Epidemiology

Dupuytren's disease, the etiology of which is unknown, occurs in all races, but has a genetic predisposition to occur in men of Northern European ancestry (Brown et al., 2008; Leclercq, 2000; McFarlane and McGrouther, 1990). Dupuytren's disease is thought to be a genetic disease of autosomal dominant transmission with variable penetrance (Burge, 1999; Ling, 1963) and with an origin in the Celtic races of northern Europe (Hueston, 1985). Migration is believed to have disseminated the disease throughout the world and while the disease is most common in Scandinavia and the British Isles, it is also common in Australia and the eastern coast of North America. Results from an epidemiology survey comparing subject profiles (N=1150) across countries (McFarlane et al., 1990) is shown Table 1. In this survey, subjects were mostly of northern European descent and male. Fewer women had surgery and those who did tended to be older, indicating either that they were more inclined to accept contracture rather than have surgery or that contracture was not as severe as in men.

Table 1: Subject Profile by Country (McFarlane, 1990)

	United Kingdom	France	West Germany	United States	Australia	Canada	Japan
Northern European Ancestry (%)	98	95	100	89	100	98	0
Male (%)	84	89	89	78	76	84	95
Family History (%)	27	11	39	25	57	34	5
Other Areas (%)	30	32	35	22	22	32	16
Manual Work (%)	54	34	33	47	40	62	63
Epilepsy (%)	2	6	1	3	0	3	2
Diabetes (%)	4	3	6	3	3	7	14
Alcoholism (%)	6	12	6	8	5	15	2
Trauma (%)	14	10	10	17	27	9	15
Age at Onset (yrs)							
Male	50.3	44.1	39.3	54.4	42.3	47.4	53.1
Female	54.0	54.6	54.3	60.2	52.0	54.3	NA
Age at Surgery (yrs)							
Male	56.2	56.0	53.4	60.2	56.0	57.0	60.3
Female	68.5	62.8	64.3	63.3	59.4	61.4	63.0
Hand Profile (%)							
Bilateral	48	72	82	45	78	78	73
Palm Only	4	5	0	6	9	5	6
No Palm	4	0	16	9	7	4	3
One Ray	50	36	36	33	40	30	29
Three or More Rays	16	33	29	26	25	37	30
Little Finger	70	73	70	70	67	69	75
Ring Finger	36	56	62	67	51	63	72
Middle Finger	22	31	41	30	21	34	31
Index Finger	2	20	13	9	12	13	11
Thumb	12	26	19	18	35	36	12

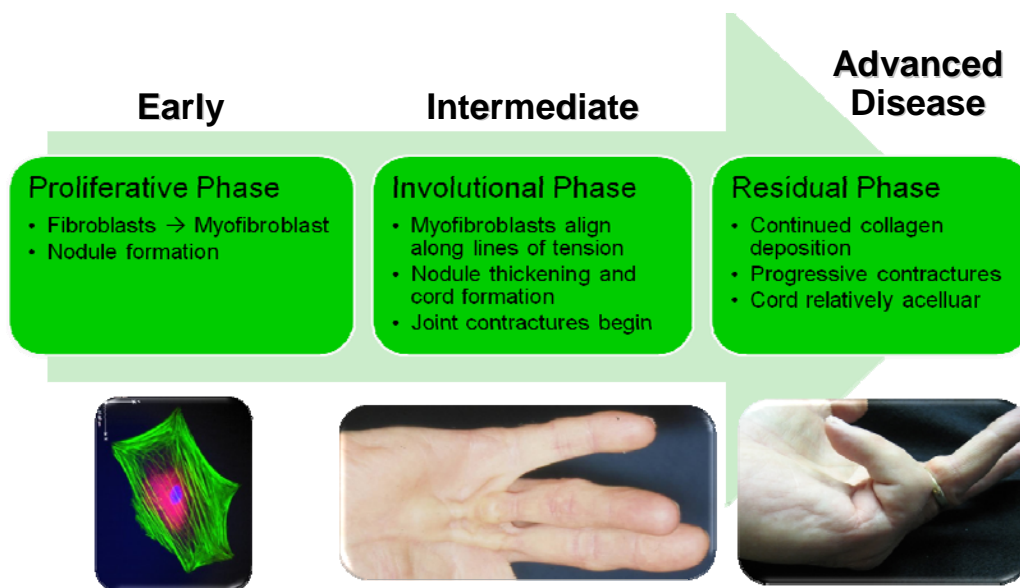
NA=not available

In a recent large, single-center retrospective analysis of 558 partial fasciectomy in 261 Dutch subjects, Coert et al., 2006 confirmed the earlier epidemiology data reported by McFarlane et al., 1990. The majority of subjects were men between 50 and 70 years. Twenty-seven percent of the subjects had a family predisposition for Dupuytren's disease. Subjects underwent on average 2.5 surgical operations for Dupuytren's disease and young age was a risk factor for a significantly higher number of surgical interventions.

2.2. Pathophysiology

Dupuytren's disease is a slowly progressive fibroproliferative disease of the palmar fascia defined by early, intermediate, and advanced phases (Figure 2).

Figure 2: Clinical Stages of Dupuytren's Disease



The early phase is characterized by skin changes with loss of normal architecture, the presence of nodules and formation of skin pits (Leclercq, 2000). A Dupuytren's nodule is a firm, soft-tissue mass that seems to originate in the superficial components of the palmar or digital fascia. Nodules are usually well defined, localized and raised above the surface, but can be a diffuse thickening of the deeper fascia. Nodules have an abundance of myofibroblasts, limited collagen content and a rich vascular supply. Nodules tend to regress spontaneously and are replaced by a fibrotic cord during the intermediate phase. Cords can develop and mature without nodule regression. A mature cord contains only sparse myofibroblasts, but abundant type I and III collagen. Cords are located in the palm, the palmodigital area, or the digits and are palpable like thick strings beneath the skin. Cords are responsible for the tethering that results in a fixed-flexion contracture of the digit. Contraction of the joint capsule or ligamentous components can also occur as a secondary phenomenon. When an affected joint cannot be fully straightened in any hand position, the result is called a "fixed-flexion contracture." A fixed-flexion contracture can develop in single or multiple joints; including metacarpophalangeal (MP) joints, proximal interphalangeal (PIP) joints, and distal interphalangeal joints (DIP), and often spans several adjacent joints. In advanced Dupuytren's disease, progressive fixed-flexion contracture leads to

finger deformity and loss of finger ROM, which ultimately leads to loss of hand function. The clinical deformities caused by contracture become irreversible without treatment (Luck, 1959).

2.3. Clinical Presentation

The diagnosis of Dupuytren's disease relies on clinical findings. The earliest sign of Dupuytren's disease is most commonly found in the palm. The disease begins as a small, dome-shaped nodule, arising at the distal palmar transverse crease, and in line with the corresponding finger (Mawhinney et al., 1999). Nodules are usually painless but can be tender under pressure. There can be temporary pain and swelling associated with the inflammatory reaction to the formation of a Dupuytren's cord.

There are no associated blood test abnormalities that aid in the diagnosis of Dupuytren's disease, and radiological evaluations are not specific. The ring finger is the most commonly involved digit, followed by the little, long, index fingers, and lastly, the thumb. Disease progression is unpredictable and it is not possible to identify the individual in whom the disease will progress rapidly, or not at all. Some individuals will have only small lumps or cords while others will develop severely contracted fingers (American Society for Surgery of the Hand [ASSH¹]; McFarlane, 1983).

Functional disability associated with Dupuytren's contracture can manifest at various stages depending on how critical the use of the hand may be for a subject. The disease may first be noticed because of difficulty placing the hand flat on an even surface, such as a tabletop (ASSH). As the disease progresses and contracture develops, many activities of daily living, such as face washing (resulting in poking the eye and the face with affected digit), combing hair, putting hand in a pocket or glove, shaking hands, turning door knobs, driving, playing sports (eg, golf), and playing instruments (eg, piano, trumpet) may become difficult or impossible (Bayat and McGrouther, 2006). Employment related tasks such as typing and gripping tools or instruments also can become more difficult or impossible if they require full range of motion of the fingers.

Subjects may feel considerable embarrassment regarding the visible deformity of the contracture and aspire to have a straight and supple finger that does not impede activities of daily living (Dias, 2006).

Functional disability has been shown to be worse in subjects with greater Dupuytren's contractures and finger deformities (Dias, 2006). A strong correlation has been reported between pre- and post-surgical deformities; the greater the deformity before surgery, the greater the residual deformity after surgery (Sinha, 2002). A greater degree of deformity is associated with poorer function suggesting that treatment at an earlier stage should be considered. Allowing the deformity to worsen may not only result in a poorer correction of Dupuytren's contractures but also a poorer functional outcome.

¹ Available at: <http://www.assh.org/Public/HandConditions/Pages/Dupuytren'sDisease.aspx>

2.4. Treatment

2.4.1. Surgery

There is no cure for Dupuytren's disease. Currently there are no approved non-surgical options for the management of the cord and contractures caused by Dupuytren's disease. Many non-surgical treatments have been attempted, including physiotherapy (ie, ultrasound therapy and ionization, splints), radiotherapy, vitamin E, steroid injections, and enzymatic fasciotomy (eg, pepsin, trypsin, hyaluronidase) (Naylor et al., 1994). Most of these treatments have been abandoned due to their ineffectiveness or potential to harm to other structures of the hand. A major limitation of non-surgical treatments is the lack of objective, multicenter controlled trials to test the safety and efficacy of potentially effective drugs.

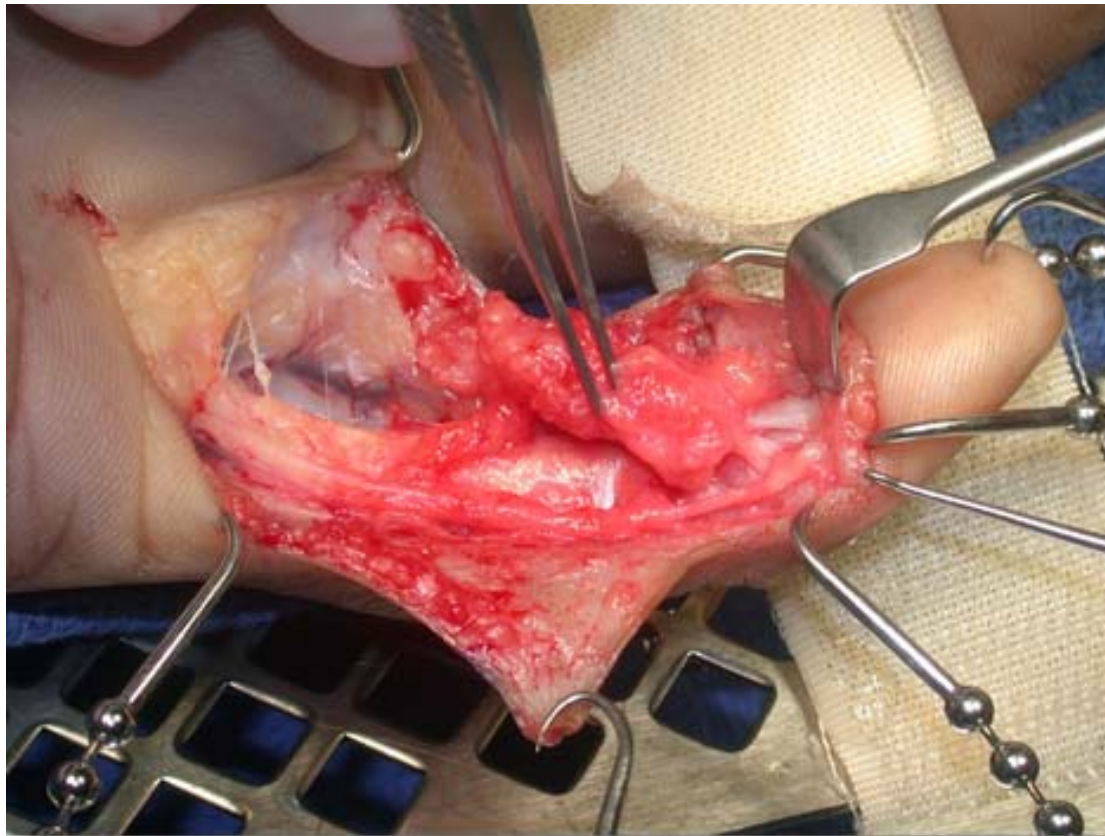
The only treatment previously demonstrated to be effective at correcting Dupuytren's contracture is surgery. Because surgical treatment is not a cure (ie, recurrence of Dupuytren's contracture is common) and major complications can be associated with surgical procedures, observation or watchful waiting is indicated for a subject who has non-progressive Dupuytren's disease with minimal contracture and without functional disability.

The typical Dupuytren's subject presenting for surgery is a white male, about 57 years of age and of northern European decent. Classically he would have had Dupuytren's disease for about 10 years (McFarlane, 1983). The disease is often bilateral with one hand being more severely involved. He is equally likely to have one, two, or three digits involved in the hand considered for surgery. Surgery is usually recommended for functionally impaired subjects with MP joint contractures $\geq 30^\circ$ or PIP joint contractures $\geq 20^\circ$ with disease progression (Tubiana et al., 2000). McGrouther (2005) asserts that it is better to "rely on functional difficulty and the rate of progression when deciding on surgery, rather than choosing a set amount of joint contracture".

The four objectives of surgically treating Dupuytren's contracture are (1) to correct the finger deformity and gain improvement in hand function (Tubiana, 1999); (2) to avoid complications that are solely due to the surgery; (3) to shorten the postoperative recovery; and (4) prophylactic prevention of recurrences where possible. Satisfactory surgical outcome depends not only on the degree of finger extension achieved, but also on whether there is return of a functionally useful hand rather than a stiff, straight digit or a vascularly compromised finger requiring amputation.

Several surgical options are available. The most common surgical approach is limited fasciectomy to excise the diseased fascia (Figure 3).

Figure 3: Fasciectomy



For less advanced cases, fasciotomy (simple division) of contracted fascia may be performed by either an open operation (Figure 4) or a closed technique using a blade or a needle (percutaneous needle fasciotomy) (Figure 5).

Figure 4: Fasciotomy - Open

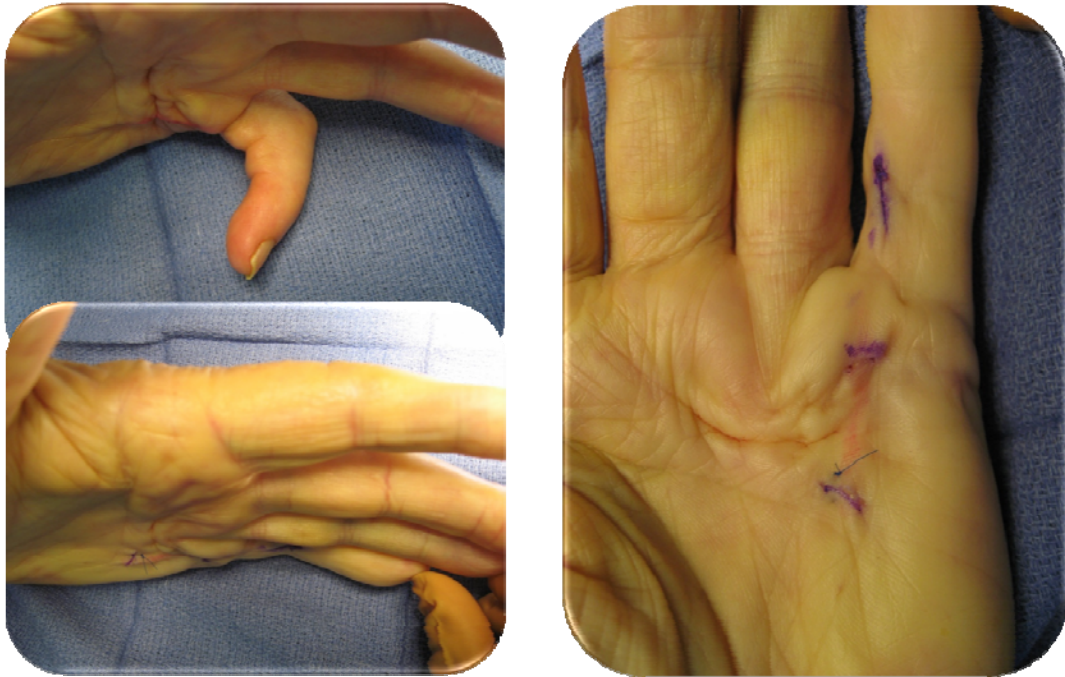


Figure 5: Percutaneous Fasciotomy (Needle Aponeurotomy)



For more advanced cases or for recurrent disease, both skin and fascia may be removed (dermofasciectomy) and a skin graft used to cover the wound.

Given the risk of recurrence, extensive operations are believed by some to be more appropriate in an attempt to control the disease. However, the morbidity associated with more extensive surgical procedures may outweigh the potential benefits. In a recent randomized, controlled trial comparing dermofasciectomy to fasciectomy, no improvement in correction or recurrence of contracture after dermofasciectomy was identified up to three years after surgery (Ullah et al., 2009). In an attempt to restore function in subjects with very severe Dupuytren's contractures, arthroplasty and arthrodesis can be alternatives to the last resort of finger amputation. There are no routine procedures and the choice of these various techniques are tailored to the needs of the individual subject and depend on the subject's age, general health, the extent of the disease, and the rate of progression (Rayan, 2007).

Surgery often requires a prolonged recovery (Bulstrode et al., 2005; Skoff, 2004). Due to variable disease severity and surgical techniques, immediate postoperative recovery time can range from 21 to 58 days (Rodrigo et al., 1976; Tubiana, 1999.). Additionally, at least one month of postoperative physical therapy is usually required for good results to be maintained (Mackin and Byron, 1990; Mackin and Skirven, 2000).

2.4.2. Surgical Outcomes

As reported in the literature, surgical outcomes including complications, recurrence, and function after surgical correction of Dupuytren's contracture are highly variable. Good finger correction can be achieved by surgery; however, significant rates of both complications and recurrent contracture occur, especially with more severe initial Dupuytren's contractures.

Dupuytren's contracture correction data from McFarlane et al., 1990 are presented in Table 2 and Table 3. These data represent the largest published series of 1150 subjects with Dupuytren's contracture reporting on the surgical outcome from various surgical procedures (ie, local fasciotomy/fasciectomy, regional fasciectomy, extensive fasciectomy and dermofasciectomy) from investigators in 20 different countries including Australia, Europe, and North America. The comparison of the results of treatment by type of operation indicates that full correction of joint contracture was readily achieved for MP joints (perfect outcome achieved in 70% to 89% of cases). Treatment of PIP joints, however, was less successful. While a significant improvement in fixed-flexion contracture was achieved in PIP joints, full correction of joint contracture was achieved in only 13% to 29% of the cases, with residual contractures of 22° to 35° angles reported (Table 3). It has also been reported that surgical correction of low severity PIP contractures may result in worsening of the contracture (McFarlane, 1990).

Table 2: Outcomes of Surgical Correction of Dupuytren's Contracture Angles in the Little and Ring Finger (McFarlane, 1990)

	Little Finger			Ring Finger		
		Pre degrees	Post degrees		Pre degrees	Post degrees
MP Joint (n)	258	44.1±24.8	3.2±11.1	251	36.3±20.0	2.5±8.4
Outcome (%)						
Perfect	84%	42.8±24.1	0	86%	34.3±18.9	0
Improved	13%	54.9±25.3	14.3±11.2	12%	52.5±20.4	15.3±14.0
Same/Worse	3%	31.4±31.5	46.4±35.9	2%	22.0±16.8	29.0±21.3
PIP Joint (n)	263	52.9±25.2	27.2±23.0	138	49.5±26.5	16.9±21.0
Outcome (%)						
Perfect	19%	46.5±23.8	0	45%	41.7±24.1	0
Improved	56%	63.2±21.3	28.8±17.4	42%	64.3±22.8	29.0±18.2
Same/Worse	25%	34.9±22.7	44.9±23.3	13%	28.2±19.8	36.2±22.7

Mean ± standard deviation

Perfect = the flexion contracture was completely corrected; improved = the flexion contracture was less, but not completely corrected; same/worse = there was no correction or the flexion contracture was worse

Table 3: Outcomes of Surgical Correction of Dupuytren's Contracture Angles in the Little Finger (McFarlane, 1990)

	Angles at MP				Angles at PIP				Perfect Outcome (%)	
	N	Pre	Post	Δ	N	Pre	Post	Δ	MP	PIP
Palm Operation										
Local	20	59.3±26.5 ¹	9.3±18.9	50.0 ⁴	21	47.5±21.5	22.9±22.9	26.0	70	29 ⁶
Regional	146	43.9±25.3 ²	2.9±11.4	41.0	141	54.1±27.3	28.8±23.9	25.3	84	18
Extensive	19	48.3±20.8	1.8±6.1	46.5	20	53.6±19.5	22.2±19.7	31.4	89	25
Dermofasciectomy	58	39.8±22.5 ³	2.4±8.6	37.4 ⁵	49	50.2±24.0	24.5±19.4	25.7	89	16 ⁷
Finger Operation										
Local	18	48.2±36.4	4.7±14.4	43.5	28	50.0±22.1	23.2±22.7	26.9	83	28
Regional	90	47.6±25.0	3.2±13.8	44.4	94	54.8±28.3	25.0±25.7	29.8	84	23
Extensive	101	43.5±22.9	1.4±4.5	42.1	134	51.6±23.1	30.1±20.6	28.5	89	13
Dermofasciectomy	1	50.0			2	50.0±28.3	35.0±7.1	15.0		

Blanks indicate insufficient data (less than 10 observations).

Significant differences between groups: 1-2 p<0.02; 1-3 p<0.005; 4-5 p<0.05; 6-7 p<0.05

In more recent studies, Coert et al. (2006) and Denkler (2005) confirmed that Dupuytren's contracture correction after fasciectomy was better for MP and DIP joints than for the PIP joints and that results for the ring finger are better than for the little finger.

2.4.3. Surgical Complications

Each of the surgical techniques can result in a variety of significant intraoperative and postoperative complications. The reported overall rate of complications varies between 17% and 30% (McFarlane, 1990; Van Rijssen, 2006; Coert, 2006). Complications include inflammation, hematoma, ischemic skin necrosis, wound infection, granuloma formation, neuropraxia, neurovascular injury, flexor tendon/ligament injury, scar contracture, persistent PIP flexion contracture, DIP hyperextension deformity, joint stiffness, poor flexion and grip strength, pain, circulatory disturbance and complex regional pain syndrome (CRPS) (Table 4). A higher incidence of surgical complications has been reported in diabetic subjects (Leclercq, 2000) including the typical diabetic stiff hand (Fournier K et al., 2008). Repeat surgery for recurrences becomes significantly complex as separating diseased tissue from adherent skin and/or nerve tissue is rendered difficult by post-surgical fibrosis.

CRPS, also called reflex sympathetic dystrophy or algodystrophy, may occur after surgery. CRPS is a complex of symptoms that includes severe pain, swelling, autonomic vasomotor dysfunction, and impaired mobility of the affected extremities out of proportion to that which is expected. Direct trauma to the nerves and excessive dissection are thought to be predisposing factors. The release of a carpal tunnel syndrome with the surgery for Dupuytren's disease is a predisposing factor, especially in women.

Table 4: Rates of Most Common Surgical Complications

Reference	N	Type of Surgery	Neuropraxia (%)	Nerve Injury (%)	Artery Injury (%)	Infection (%)	Hematoma (%)	CRPS (%)	Skin Comp. (%)
Coert 2006	558	F	NA	7.7	1.9	3.6	NA	4.5	6.9
Van Rijssen 2006	78	F	16.7	1.2	NA	1.2	1.2	0	0
Van Rijssen 2006	88	A	4.5	0	NA	0	0	0	33
Denkler 2005	102	F	NA	2.9	1.9	7	1.0	0	5
Bulstrode 2005	253	F	0.4	2.0	0.8	9.6	2.0	2.4	2.4
Shaw 1996	26	F	NA	3.8	NA	NA	NA	3.8	NA
Foucher 2003	211	A	2.4	NA	NA	NA	0.5	0.5	9.0
Foucher 1995	54	F	3.7	1.9	NA	NA	0	9.3	0
Foucher 1992	140	F	NA	3.2	NA	NA	0.7	7.0	NA
Makela 1991	153	F	NA	1.0	NA	7.4	3.5	1.5	NA
Sennwald 1990	98	F	1	7.8	9.7	1	2.9	18.5	NA
McFarlane 1990	1150	DF/F/A	2.7	1.5	0.8	1.3	2.2	4.2	4.7
Rodrigo 1976	230	F/A	NA	0.4	NA	1.3	4	10	0.4

DF = Dermofasciectomy; F = fasciectomy; A = needle aponeurotomy/fasciotomy; NA = not applicable

In a recent study of 261 subjects with partial fasciectomy, Coert et al., 2006 reported an overall complication rate of 26%. The overall incidence of nerve lesions was 7.7%, significantly higher (12%) in recurrent surgery compared with primary surgery (5%). The incidence of CRPS was 4.5%. The risk for nerve lesion, necrosis and infection were higher in recurrent surgery.

In a recent survey of hand surgeons, the quoted complication rates included stiffness: 10%, 20%; CRPS: 5%, 10%; infections: 5%, 10%; nerve damage: 2%, 5%; and finger loss: <1% (Au-Yong et al., 2005).

In a British Society for Surgery of the Hand (BSSH) study (Dias and Braybrooke, 2006), subjects reported a surgical complication rate of 46%. The most common complications included neurapraxia for more than 2 days, which affected 36% of subjects, followed by wound infection (19%) and circulatory disturbance (12%). The incidence of complications was related to the initial severity of the deformity, possibly due to increasing complexity of surgery.

In a study published by Symes and Stothard (2006), complication rates after percutaneous needle fasciotomy included: skin fissure (15% - 50%), infection (2%), nerve injury (0.05% - 2%), and flexor tendon rupture (0.05%). However, the true incidence rate of tendon injury following percutaneous needle fasciotomy is not well established. While Leclercq (1997) reported a high number of flexor tendon ruptures; others have reported no cases of tendon injury following percutaneous needle fasciotomy (Foucher, 2003; Van Rijssen, 2006).

2.5. Recurrence of Contracture

Recurrence following surgical correction is not uniformly defined and varies between reports. Depending on the type of surgery performed and the length of follow-up, recurrence rates range from 2% to 60%, with an average of 33% (Rayan, 2007). For example, Anwar et al., (2007) reported recurrence rates of 22% in women and 19% in men on average 12 months following fasciectomy. Leclercq examined 38 subjects 8 to 14 years after surgery, and found a 66% rate of recurrence; 34% was reported within the first 2 years following surgery (Leclercq, 2000). A 50% or greater recurrence rate has been published in three separate studies following percutaneous needle fasciotomy: 50% at 5 years (Badois, 1993); 58% at 3.2 years (Foucher, 2001); and 65% at 33 months (Van Rijssen, 2006). Recurrence may be due to appearance of new Dupuytren's tissue within the area cleared at operation site or disease extension (appearance of new Dupuytren's tissue beyond the area cleared at operation).

Recurrence is more common in subjects with PIP joint involvement, little finger involvement, and more than one digit affected, as well as in those subjects who present a longer time after surgery or after a secondary fasciectomy. In a large series of 224 subjects with surgically treated Dupuytren's contractures, Hueston reported a 28% rate of recurrence. If recurrence occurred, it occurred early (~90% within 2 years) (Hueston, 1963).

In a BSSH study (Dias and Braybrooke, 2006); recurrence was defined as any deformity that was more than a mild MP joint contracture, an equivalent to a positive Hueston table-top test. The recurrence rate was 15% over a mean follow-up period of 27 months. Recurrence was more common in those with greater initial deformity, even after good surgical correction. In the group with severe contractures of both joints, the recurrence rate was 14% after a full surgical correction and 100% after a poor surgical correction. These data suggest that there is residual disease after incomplete surgical correction or the disease is more aggressive in these subjects. Thus, good initial correction is a favorable prognostic sign for a lower recurrence rate.

Of note, digital artery injury and digital nerve injury were more commonly observed in patients with recurrent disease than those with primary disease. The incidence of digital artery injury and digital nerve injury in patients with primary disease was approximately 1% for each; in patients with recurrent disease the incidence was 11.1% for digital artery injury and 22.2% for digital nerve injury (Denkler, 2005, Ebskov et al., 1997, Sennwald, 1990).

3. PRODUCT DEVELOPMENT AND REGULATORY HISTORY OF AA4500

3.1. AA4500 Product Development

Auxilium Pharmaceuticals, Inc. acquired the global development rights for AA4500 from BioSpecifics Technologies Corp. (hereafter, referred to as BTC) in June 2004.

AA4500 (collagenase *clostridium histolyticum*) is a novel non-surgical treatment targeting Dupuytren's disease contractures through the injection of purified clostridial collagenase into the pathologic Dupuytren's cord. Auxilium has investigated the use of the localized injection of AA4500 as a non-surgical option for the treatment of subjects with advanced Dupuytren's disease.

AA4500 is a lyophilized product comprised of two collagenases (proteinases that can hydrolyze the triple-helical region of collagen under physiological conditions) in a fixed-ratio, Collagenase I (AUX-I, Clostridial type I collagenase) and Collagenase II (AUX-II; Clostridial type II collagenase). These collagenases are isolated and purified from the culture medium of *Clostridium histolyticum*. Collagenase AUX-I is a single polypeptide chain containing approximately 1,000 amino acids of known sequence and with a molecular weight of 114 kDa. Collagenase AUX-II is also approximately 1,000 amino acids long and has a molecular weight of 113 kDa. These two collagenases are not immunologically cross-reactive and they also differ from each other in terms of domain structure, substrate affinity, catalytic efficiency and preferred cleavage site on the collagen molecule.

The differences between the two collagenase classes result in improved activity against collagen when the two are combined, compared to the activity seen with either class acting alone. The fixed-ratio of AUX-I and AUX-II represented in AA4500 drug product falls within the range of effective ratios for which improved speed and completeness of digestion of either soluble (Mandl et al., 1964; Kono, 1968) or intact interstitial collagen (Wolters et al., 1995; Vos-Scheperkeuter et al., 1997) has been reported in the literature.

The pharmacologic activity of AA4500 involves selective lysis of collagen at the site of injection (ie, the Dupuytren's cord). AA4500's therapeutic activity is thus localized and AA4500 does not require systemic exposure to be effective.

The proposed dose of AA4500 is 0.58 mg which is administered by a single local injection into a Dupuytren's cord. This is followed approximately 24 hours after injection by a finger extension procedure to facilitate cord disruption in those subjects who did not have spontaneous disruption of the cord. If the contracture caused by the Dupuytren's cord has not adequately responded within approximately 4 weeks of the first injection and finger extension procedure, the cord may be re-injected with a single dose of AA4500 0.58 mg 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. The dosing regime for AA4500 thus constitutes acute, intermittent, non-systemic therapy.

Following acquisition by Auxilium, the manufacturing process was optimized (Process 3) and the investigational drug was then referred to as AA4500. Material produced by both BTC and

Auxilium has been evaluated in the development program for AA4500. To distinguish the different materials, early process BTC material is designated “AA4500 (early BTC process),” material produced by BTC Process 1 is designated “AA4500 (Process 1),” and material produced by Auxilium’s Process 3 is designated “AA4500.”

Process optimization was undertaken both by BTC and by Auxilium in order to improve the quality (impurity profile) and scalability of the resultant drug substance and drug product for future commercial purposes, while ensuring appropriate activity was maintained. Analytical comparability data were generated during process optimization to ensure that the materials manufactured by different processes were comparable in terms of the identity and potency of the two enzymes and the resultant drug product. These data confirm that AA4500 produced by Process 1 is of superior quality to AA4500 produced by the early BTC process. The data also confirm that the identity and potency of AA4500 produced by BTC (Process 1) and AA4500 produced by Process 3 are comparable; however, Auxilium’s optimized process is superior for several attributes (such as purity, aggregation, etc.). Because AA4500 manufactured by both Process 1 and Process 3 is comparable in terms of identity and potency, the results of both clinical and nonclinical studies performed with AA4500 manufactured by either process are relevant for evaluation of the safety and efficacy of AA4500

The proposed commercial drug product, which was utilized in clinical trials and nonclinical studies conducted by Auxilium, contains 0.9 mg AA4500 as a lyophilized presentation formulated in sucrose (18.5 mg/vial), trimethomine (1.1 mg/vial) and hydrochloric acid (0.5 mg/vial). Clinical trial material manufactured by BTC (AA4500 early BTC process and Process 1) and used for early nonclinical and/or clinical development studies was formulated as a final lyophilized presentation containing active pharmaceutical product with 1.5 mg lactose/vial. As AA4500 acts locally following injection into a Dupuytren’s cord, bioequivalence studies comparing the 2 drug substance formulations have not been undertaken and are not relevant.

3.1.1. Overview of Nonclinical Studies

To support single-dose intermittent use by local injection, Good Laboratory Practice (GLP) single dose, local tolerance studies were performed with AA4500 (BTC early process) in Zucker rats and single- and repeat-dose toxicity/local tolerance studies with AA4500 in dogs. In order to characterize any systemic toxicity that might result from the inadvertent systemic exposure to AA4500 in subjects, single- and repeat-dose rat intravenous (IV) toxicity studies were performed; these also served as bridging studies to demonstrate the comparability of AA4500 Process 1 and two different lots of AA4500 Process 3. Although the lack of systemic exposure following local administration indicates minimal to no risk to human reproduction, studies were performed in rats using the IV route of administration to rule out any potential effects on fertility or early embryonic development due to either AA4500 or anti-AA4500 antibodies.

The nonclinical studies were supplemented with published literature reports that utilized AA4500 (early BTC process) and were considered to have been described in adequate detail to judge their scientific merit and applicability to AA4500 use in advanced Dupuytren’s disease in humans.

As a foreign (bacterial) protein, the generation of anti-AA4500 antibodies was expected. In order to both characterize the antibody responses and evaluate any potential adverse effects resulting from their generation, antibody formation against AUX-I and AUX-II was evaluated in

all repeat-dose toxicity studies (by any route of administration) and the fertility and general reproduction toxicity study performed with either AA4500 (Process 1) or AA4500.

Because no systemic exposure was detected in definitive and supportive pharmacokinetic studies in subjects with Dupuytren's disease, safety pharmacology, tissue distribution and excretion studies were not performed with AA4500. Chronic toxicity and carcinogenicity studies were also not conducted, because of the intended clinical use (intermittent local administration of single doses at monthly intervals with a limit to the total number of doses that may be administered to each cord), nature of the drug product (nonendogenous protein with no known growth factor activity relevant to carcinogenesis), and negative genetic toxicity study results. In agreement with the Food and Drug Administration (FDA), these studies were waived as registration requirements.

No systemic toxicity following administration of AA4500 by local injection has been reported in published studies (Friedman et al., 1986; Bromley et al., 1980; Miyabayashi et al., 1992) or following single or repeat dose local injection in rats, guinea pigs and dogs. Additionally, only limited systemic exposure was detected following local injection in dogs, and then only when AA4500 was administered into highly vascular locations.

Tissue responses at the site of application are essentially identical in all studies utilizing locally-applied AA4500 in all species and consist of swelling and/or bruising at or surrounding the injection site, with corresponding gross necropsy observations and histologic findings (hemorrhage, acute (neutrophilic) or subacute inflammation progressing to chronic (lymphocytic) inflammation, and neovascular proliferation). No effects on adjacent nerves, blood vessels with smooth muscle-containing walls, or epithelial or mesenchymal cells have been detected. These local effects are seen across a wide range of doses with either low or inapparent dose-responses for incidence or severity, and the injection site findings reverse (partially to completely) within 30 days following cessation of dosing.

AA4500 is not a reproductive toxicant in male and female rats and is without effect on the development of rat embryos or fetuses (not teratogenic). Systemic toxicity in rats (reversible liver pathology) required repeated IV administration of AA4500 by IV bolus, which should not occur under conditions of clinical use. In the unlikely event of a single dose being inadvertently administered by intravenous bolus, adequate safety margins exist based on the rat study findings. These systemic effects on the liver are not considered to represent safety concerns for the clinical use of AA4500.

Although AUX-I and AUX-II were detected in the plasma following IV administration in rats, both components were cleared rapidly from the systemic circulation. At the highest dose level tested (0.29 mg/animal, equivalent to ~22X the clinical dose of 0.58 mg), AUX-I was not detectable by 30 minutes and AUX-II was undetectable by 2 hours following administration. No accumulation of either AUX-I or AUX-II was detected with frequent (q48h) repeated dosing.

Antibodies to AA4500 components (AUX-I and AUX-II) occurred in the majority of animals treated with repeated doses of AA4500 by either IV or local injection. Titers above background levels were apparent after 7-8 days, following 2-3 doses, and persisted for at least 30 days after the last injection. Dose responses were either minimal or not apparent, especially following administration by local injection, indicating that evaluation of any dose of AA4500 by local injection is adequate to characterize local and systemic adverse effects mediated by antibodies

(provided at least three doses have been administered). These antibodies do not appear to affect the pharmacologic activity of locally administered AA4500. There is also no evidence that they mediate any adverse effects, either directly or as the result of cross-reactivity with endogenous collagenases (MMPs). Systemic inhibition of MMPs results in a spectrum of well-characterized clinical signs (gait abnormalities, reluctance or inability to move, and hind paw swelling), histologic changes (thickening of the epiphyseal growth plate with disorganization and thickening of the underlying metaphyseal trabecular bone, synovial hyperplasia with fibrosis of the underlying adipose tissues, and increased proliferation of fibroblasts in the joint capsule and extracapsular ligaments) and effects on reproduction and development (impaired implantation, abnormal placental development and soft tissue and skeletal anomalies in fetuses) (Alexander et al, 1996; Drummond et al, 1999; Close, 2001; Renkiewicz et al, 2003; Younis et al, 2006). None of these findings have been described in either dogs or rats that have prolonged high titers of anti-AA4500 antibodies.

3.1.2. Overview of Clinical Studies

A total of 13 (one Phase 1, three Phase 2, and nine Phase 3) clinical studies were conducted in subjects with advanced Dupuytren's disease in the United States, Europe, and Australia. To be eligible for treatment, subjects had to have a diagnosis of advanced Dupuytren's disease with a fixed-flexion (ie, $\geq 20^\circ$ but $\leq 80^\circ$ for PIP joint; $\geq 20^\circ$ but $\leq 100^\circ$ for MP joint) deformity of at least one finger, other than the thumb, which was caused by a palpable cord and a positive "table top test," defined as the inability to simultaneously place the affected finger(s) and palm flat against a table top. Overall, a total of 1082 subjects have received at least one injection of AA4500 0.58 mg, the proposed commercial dose, across the 11 studies with formal databases; data from two supportive studies (Open-label study and DUPY-101) were not pooled in the integrated database but were reported separately. The design of each study included in the Biologics License Application (BLA) submission is shown in Table 5.

Efficacy data demonstrating the treatment of subjects with advanced Dupuytren's disease are primarily derived from three adequate and well-controlled, double-blind studies: AUX-CC-857 (Study 1), AUX-CC-859 (Study 2), and DUPY-303 (Study 3). Studies AUX-CC-854, AUX-CC-856, and AUX-CC-858 were primarily conducted to obtain long-term safety information, although efficacy data were also collected. Efficacy data from these open-label studies are considered supportive.

Two of the Phase 3 studies (AUX-CC-851/852 and AUX-CC-853) were terminated early due to a manufacturing issue. Consequently, subjects in AUX-CC-851/852 received only one injection of AA4500 and subjects in AUX-CC-853 received one or two injections of AA4500 (per protocol, up to eight injections of AA4500 were allowed per subject across the double-blind and open-label phases of these studies). Both efficacy and safety data from these two studies are included in the BLA and are considered supportive.

Table 5: Overview of Clinical Program for AA4500 in the Treatment of Contractures Caused by Advanced Dupuytren's Disease

Study	Design	Status
AUX-CC-855	Phase 1, single dose, definitive pharmacokinetic study	Completed
Open-label Study	Phase 2, open-label single dose response study	Completed, results based on a publication (Badalamente and Hurst, 2000).
DUPY-101	Phase 2, double-blind, placebo-controlled single-dose study followed by an open-label extension	Completed; results based on data on file for the MP joint, and a publication for MP and PIP joints (Badalamente et al., 2002)
DUPY-202	Phase 2, double-blind, placebo-controlled, dose response study followed by an open-label extension	Completed
DUPY-303 (Study 3)	Phase 3, double-blind, placebo controlled study	Completed
DUPY-404	Phase 3, open-label extension of DUPY-303	Completed
AUX-CC-851/852	Phase 3, double-blind, placebo-controlled followed by open-label extension	Completed (study prematurely terminated due to a manufacturing issue)
AUX-CC-853	Phase 3, double-blind, placebo-controlled followed by open-label extension	Completed (study prematurely terminated due to a manufacturing issue)
AUX-CC-854	Phase 3, open-label study	Completed
AUX-CC-856	Phase 3, open-label study	Completed
AUX-CC-857 (Study 1)	Phase 3, double-blind, placebo controlled study	Completed
AUX-CC-858	Phase 3, open-label extension of AUX-CC-857	Completed
AUX-CC-859 (Study 2)	Phase 3, double-blind, placebo-controlled followed by open-label extension	Completed

One additional study is ongoing. Study AUX-CC-860 is a Phase 3, non-treatment 2 to 5 year follow-up to the 9-month open-label studies (AUX-CC-854 and AUX-CC-856) and the 12-month double-blind with open-label extension studies (AUX-CC-857/AUX-CC-858 and AUX-CC-859) in subjects who received at least one dose of AA4500. The objectives of this study are:

- To assess the durability of response (ie, recurrence of contracture) in joints with measurable improvement ($\geq 20^\circ$) in contracture after treatment with AA4500 in one of the Auxilium sponsored studies (AUX CC-854, AUX-CC-856, AUX-CC-857/AUX-CC-858, or AUX-CC-859)
- To assess the progression of disease in joints that either were not treated with AA4500 or did not have measurable improvement ($< 20^\circ$) in contracture after treatment with AA4500 in one of the Auxilium sponsored studies (AUX CC-854, AUX-CC-856, AUX-CC-857/AUX-CC-858, or AUX-CC-859)
- To assess the long-term safety of AA4500

3.2. Clinical Regulatory Guidance and Advice

An end of Phase 2/pre-Phase 3 teleconference was held on August 22, 2001 between BTC and Center for Biologics Evaluation Research (CBER) at which it was confirmed that a dose of 10,000 Units (equivalent to 0.58 mg) was appropriate for evaluation in the Phase 3 clinical program for the treatment of advanced Dupuytren's disease. Following product licensing by

Auxilium Pharmaceuticals, Inc., two further regulatory guidance meetings were subsequently held by Auxilium with representatives from the Division of Anesthesia, Analgesia and Rheumatology Products and Auxilium on 04 April 2006 (Type C) and 15 September 2008 (Type B) to discuss Auxilium's plans for completion of the development program and the filing plans for the product. The Type C meeting was held to discuss the Phase 3 development plans for AA4500 for the treatment of advanced Dupuytren's disease and the Type B meeting to present the approach for the BLA. Key outcomes of these meetings (and subsequent clarification requests by Auxilium) from a clinical perspective are discussed below.

Outcome of clinical discussion from Type C meeting:

- The proposed design of a pivotal Phase 3 study was considered acceptable by the Division. The original study presented, AUX-CC-851, was subsequently superseded by studies AUX-CC-857 and AUX-CC-859, both of which have comparable designs.
- A method for imputation of missing data of the primary endpoint was recommended by FDA and implemented by Auxilium.
- FDA concurred with the proposed primary and secondary endpoints. Secondary endpoints were requested to be ranked. Simultaneous hypothesis testing for all efficacy analyses for the two adequate and placebo-controlled studies conducted by Auxilium (AUX-CC-857 and AUX-CC-859) was accomplished by applying a closed hierarchical testing procedure with a family-wise 5% significance level.
- FDA requested that substantial efficacy should consist of at least two adequate and well-controlled trials. FDA further advised that DUPY-303 may be considered as one of the two trials demonstrating efficacy of AA4500.

Outcome of clinical discussions from Type B meeting:

- The proposals for safety and efficacy data to be provided in the BLA, as summarized below, were considered consistent with expectations set forth in previous discussions with the Division and adequate to support the BLA.
 - For the purpose of demonstrating primary efficacy, it was proposed that the BLA submission would include data from 409 subjects who received up to three injections of AA4500 (0.58mg) into the primary joint in three double-blind, placebo controlled studies: DUPY-303, AUX-CC-857, and AUX-CC-859. These three studies met the primary endpoint of a higher proportion of subjects achieving contracture reduction to within 5° of normal at a pre-identified target joint compared with placebo, 30 days after the last injection of study drug. It was further proposed that supportive efficacy data would include results from three, open-label, Phase 3 clinical studies which were ongoing at the time of the BLA and would include data from subjects in these studies.
 - It was proposed that the safety database for the BLA submission would include data from three controlled studies and their long term extensions, and supportive data from the remaining six clinical studies in the clinical development program, comprising greater than 1000 subjects treated for advanced Dupuytren's disease who had received at least one injection at the proposed dose. It was further indicated that in total, these subjects would have received over 2500 injections of

AA4500. Further, the safety data would include over 100 subjects who had been followed for 12 months following their first AA4500 injection.

- FDA indicated that the results of Study AUX-CC-855, conducted to assess systemic exposure to AA4500, appeared to demonstrate a lack of systemic exposure with intralesional administration of AA4500 0.58mg into the Dupuytren's cord.
- FDA confirmed that a neutralizing antibody assay need not be developed prior to submitting the BLA, although efforts to develop an appropriate method were requested to continue. Auxilium presented details of a neutralizing antibody assay and its validation in the BLA. Data on neutralizing antibody levels from Study AUX-CC-857 were presented in the safety update.

In an additional correspondence dated May 23, 1996, the FDA determined that clostridial collagenase qualified for orphan designation for the treatment of advanced Dupuytren's disease.

4. PHARMACOLOGY OF AA4500

4.1. Primary Pharmacodynamics

Collagenase activity was discovered in the medium of cultures of *Clostridium histolyticum* over fifty years ago (MacLennon et al., 1953), and an extensive published literature base exists on its purification, characterization and potential therapeutic and research uses. AA4500 is composed of a mixture of two antigenically and functionally distinct collagenases, AUX-I and AUX-II, which have been shown by substrate activity patterns and enzyme kinetic parameters to be representative of the Class I and Class II collagenases, respectively.

Clostridium histolyticum collagenases are metalloprotease enzymes of the matrixin subfamily generated by the homologous expression of two separate chromosomal genes, *colG* and *colH*. A total of seven different proteolytic enzymes (collagenases and gelatinases) are generated by proteolytic cleavage of COOH terminus of the *colG* and *colH* full length gene products (Van Wart and Steinbrink, 1985; Matsushita et al., 1999). The collagenases are placed into one of two classes, based on substrate specificity, protein domain arrangement and the gene of origin. Relevant features of each collagenase class are summarized in Table 6.

Table 6: Characteristics of Class I and Class II Clostridial Collagenases

Attribute	Class I Characteristic	Class II Characteristic
Gene of Origin	<i>colG</i>	<i>colH</i>
Subtypes in class	α , β , γ and η	δ , ϵ and ζ
Affinity for Intact Collagen	High	Low
Collagen Binding Domain Structure	Tandem domains (S3a & S3b)	Single domain (S3)
Preferred cleavage sites	N and C termini	Internal peptide sequences
Preferred substrate(s)	Triple helical (intact) collagen	Small peptides > Denatured collagen (gelatin) > Triple helical (intact) collagen

Information from: Seifter et al., 1959; Bond and van Wart, 1984; Steinbrink et al., 1985; French et al 1987; Mookhtiar and van Wart, 1992; Matsushita et al., 2001 and Toyoshima et al., 2001

Catalytic activity against intact collagen by either collagenase class requires an intact enzyme molecule containing both active catalytic and collagen-binding domains, and adequate amounts of the metal cofactors, calcium and zinc. Binding of zinc to the catalytic site is essential for its activity, whereas calcium is required to maintain the conformation of the collagen binding sites in a state that allows them to bind to native (triple helical) collagen fibrils (Jung et al., 1999; Wilson et al 2003). For both classes, levels of zinc present in the extracellular fluid of mammals are more than adequate for optimal enzyme activity without being inhibitory (Yagisawa et al., 1965). While normal extracellular calcium levels (~1.0 mM) are in the range required for stabilization of calcium binding domain and optimal collagen binding in class I collagenase (0.1-10 mM) (Wilson et al., 2003), local levels of extracellular calcium can be extremely variable and are particularly low in the deepest layers of the epidermis (Brown et al., 1995; Momose et al., 2004). For this reason, the diluent used to reconstitute AA4500 contains 2 mM calcium, a

level within this optimum concentration range, to safeguard against potential suboptimal local levels.

AA4500's primary *in vivo* activity is to selectively degrade the relevant pathologic collagen subtypes (I and III) that comprise Dupuytren's cords (Hanyu et al., 1984; Melling et al., 2000). This is due to the highly potent binding affinity of the collagen binding domains of the Class I and Class II collagenases for these fibrillar collagen subtypes in their native (*in vivo*) conformation (Matsushita et al., 1998, 2001; Toyoshima et al., 2001), which has been shown to be a more relevant predictor of the potential for *in vivo* activity than the intrinsic catalytic activity of the enzyme against soluble collagen (McCarthy et al., 2008). However, despite the ability of the collagen binding domain from Class I collagenase to recognize type IV collagen (the primary component of basement membranes and the perineurium of peripheral nerves) in its native conformation in tissues (Toyoshima et al. 2001), clostridial collagenase is not effective at degrading type IV collagen *in vivo*. Purified clostridial collagenase had no significant activity against type IV collagen in a synthetic basement membrane model. More importantly, no degradation of blood vessel basement membranes was detected following subcutaneous injection in rats (Miyoshi et al., 1998), nor were any effects on blood vessels, nerves and epithelia noted following local injection in the non-clinical studies. The lack of activity against type IV collagen translates into preservation of the integrity of normal tissue elements (blood vessels, nerves, and epithelia) that may be within or adjacent to the site of injection for AA4500.

4.2. Drug Interactions and Secondary Pharmacodynamics

Because AA4500 is not intended for systemic administration and has not been detected in the systemic circulation following local injection in subjects, drug interactions and systemic secondary pharmacodynamic effects (including specific safety pharmacology studies) have not been evaluated. No systemic effects indicative of potential secondary or safety pharmacology concerns have been noted either in subjects in the clinical studies or any animal studies, even following intravenous administration of AA4500.

Inactivation of clostridial collagenase by some antibiotics has been described in the published literature. Tetracycline derivatives have been shown to inhibit matrix metalloproteinase-mediated collagen degradation at pharmacologically relevant concentrations (Suomalainen et al., 1992; Golub et al., 1998; and Smith et al., 1999). This phenomenon has not been specifically described for clostridial collagenase, but because at least part of the inactivation results from local chelation of metal cofactors (calcium and zinc) essential to the activity of all metalloproteinases (Golub et al., 1998), such an interaction should be considered possible for AA4500. Selective inhibition of clostridial collagenase by a number of members of the anthracycline class of antibiotics has been reported (Tanaka et al., 1991; Bols et al., 1992). These include the antimetabolic agents daunomycin and adriamycin, with reported IC_{50} values in the range of 1.1 - 30 μ M.

Local secondary pharmacodynamic effects attributable to AA4500 administration may result from its primary pharmacologic activity, collagen lysis. Degradation of extracellular matrix components has been shown to expose biologically active sites that are not normally exposed in the mature secreted matrix protein ("matricryptic sites") and/or release bound (inactive) forms of growth factors which initiate a number of physiologic responses that are important in

regeneration and repair processes (Davis et al., 2000). Secondary pharmacodynamic effects considered related to AA4500-mediated collagen lysis met the following criteria:

- They were evident only after the administration of fully active collagenase
- They were described following local administration of any form of AA4500
- They were temporally correlated to the time of collagenase activity in tissue explants (2-24h following injection)
- They were documented by the peer reviewed literature to be plausibly attributable to products resulting from the activity of clostridial collagenase on collagen.

Three such secondary effects have been identified as indirect biomarkers for collagenase activity *in vivo*: vascular leakage, neutrophil (PMN) chemotaxis and wound healing responses.

Vascular leakage. Edema and hemorrhage at the site of application has been described following local administration of purified commercial collagenase (Vargaftig et al., 1976; Legat et al., 1994; Sousa Pinto et al., 1995; Damas et al 1996, 1997), AA4500 (early BTC process) (Rydevik et al., 1985, 1989) and in clinical and animal studies with AA4500. These effects appear to be mediated by bradykinin, serotonin and/or substance P. Because they were also detected at equal or greater severity in kininogen-deficient rats, the conclusion from the investigations is that the injection site effects result primarily from locally released serotonin, with the most likely source considered to be degranulation of local tissue mast cells (Sousa Pinto et al., 1995). However, products released from collagen by purified clostridial collagenase have been shown to have potent bradykinin-like effects on skin capillaries and small intestine (Buczko et al., 1980), and have 50X greater ability to cause mast cell degranulation than bradykinin (Wize et al., 1986). Thus, these products alone may account for the bradykinin-mediated effects, without the need for kininogen activation. This is especially likely since clostridial collagenase cannot directly activate kininogens in rat plasma (Sousa Pinto et al., 1995) or degranulate mast cells (Vargaftig et al., 1976).

Neutrophil (PMN) chemotaxis. Margination of PMNs in capillaries directly adjacent to the site of injection was noted in the blood vessels of hamster cheek pouch within 60 minutes of the injection of AA4500 (early BTC process) (Rydevik et al., 1989), evidence of the presence of chemotactic mediators in the underlying tissue. This finding was noted before the onset of vascular leakage. Products liberated from collagen by the digestion of collagen types I, II or III by purified clostridial collagenase have been shown to be chemotactic to PMNs and macrophages, both *in vivo* (Bagdy et al., 1992; Radice et al., 1999) and *in vitro* (Postlethwaite and Kang, 1976; Laskin et al., 1986; Weinberger et al., 2005) in all species examined. In addition, these products prevented apoptosis in cultured PMNs, indicating the potential for enhanced survival at sites of inflammation (Weinberger et al., 2005). Prolonged digestion of type I collagen with clostridial collagenase results in inactivation of these products (Houck and Chang, 1971), which is consistent with the transient nature of the neutrophilic inflammatory changes *in vivo*.

Wound healing responses. A consistent early change (within 24 hours after injection) noted at the injection sites in animals treated with either AA4500 (BTC early process) (Rydevik et al., 1985; Friedman et al., 1986) or AA4500 (Process 3 following local injection in dogs) was increased numbers of fibroblasts and neocapillary formation, characteristics of a wound healing

(granulation tissue) response. The digestion of Type I collagen by purified clostridial collagenase results in a granulation tissue response in adjacent subcutaneous tissue (Radice et al., 1999), and products liberated by collagen digestion are directly chemotactic for fibroblasts in culture (Postlethwaite et al., 1978; Radice et al., 1999) and induce decreases in focal adhesion complexes and morphologic changes indicative of increased motility in cultured smooth muscle cells (Carragher et al., 1999). Collectively, these effects are indicative of an enhanced wound healing response, which is postulated to be initiated by the exposure of integrin receptor sites on collagen as the result of collagen cleavage. Prolonged collagen digestion by purified clostridial collagenase denatures these integrin binding sites, which eliminates the binding of integrins to collagen and reduces the cellular chemotactic and proliferative healing responses (Davis et al., 2000). This indicates that fibroproliferative responses resulting from AA4500 administration will be self-limiting and reversible.

4.3. Pharmacokinetics

Absorption: Data from the definitive Phase 1 single-dose study (AUX-CC-855) confirm that there is no detectable systemic exposure following a single injection of AA4500 0.58 mg into the cord of the affected finger in subjects with advanced Dupuytren's disease or following the subsequent procedure to disrupt the cord (Lower limit of quantification for AUX I and AUX II in human plasma is 5 ng/mL and 25 ng/mL, respectively). These findings are further supported by the results from an earlier single-dose pharmacokinetic study (DUPY-202).

Distribution: No tissue distribution studies have been performed with AA4500, as the absence of significant systemic exposure in human subjects following local administration of AA4500 indicates that AA4500 primarily remains confined to the tissues near the injection site and/or is rapidly degraded either before or upon reaching the systemic circulation.

Metabolism: AA4500 is not a substrate for cytochrome P450 or other drug metabolizing enzyme pathways. Therefore, no metabolism studies have been performed with AA4500.

Elimination: Excretion was not directly evaluated after treatment with AA4500 because there was no detectable systemic exposure following injection of AA4500 into Dupuytren's cords. However, the mechanism of elimination of a number of activated proteases (including collagenases such as MMP's as well as clostridial collagenase) from the systemic circulation has been described. The published studies indicate that the elimination of these enzymes results from their inactivation by endogenous serum components, primarily as the result of complex formation with α -2-macroglobulin (α 2M), a serum protein that serves as a substrate/inhibitor for proteases of a variety of types. Inactivation of the enzyme activity results from steric inhibition (which prevents access of macromolecular substrates to the active site of the enzyme) followed by removal of circulating α 2M-protease complexes primarily in the liver (both by hepatocytes and Kupffer cells) (Bergsma et al., 1985; Sottrup-Jensen, 1989; Borth, 1992; Feinman, 1994). Inactivation of AA4500 at the site of injection may also occur due to the local synthesis and release of α 2M by fibroblasts and tissue macrophages (Willingham et al., 1979; Gliemann et al., 1994), followed by endocytosis and lysosomal proteolysis of the resulting complexes by fibroblasts, tissue macrophages and other inflammatory cells adjacent to the site of injection (Sottrup-Jensen, 1989; Roberts et al., 1995).

Pharmacokinetics of Active Metabolites: AA4500 is a protein that is active in its native form, and does not require proteolytic cleavage for activity.

Plasma Concentration-Effect Relationship: AA4500 is not intended to be systemically active, and has not been shown to access the systemic circulation following local administration via a clinically relevant route. Therefore, plasma concentration-effect relationships are not relevant and have not been examined.

Dose and Time Dependencies: Because pharmacodynamic activity cannot be evaluated directly or by surrogate biomarkers in subjects and is not a function of systemic exposure, dose and time dependencies have only been evaluated in in-vitro model systems (Gelbard et al., 1982; Starkweather et al., 1996). Collectively, these studies indicated that collagen digestion in injected tissues was nearly complete in 24 hours, and that doses of at least 3600 U were required to result in adequate collagen lysis to cause disruption of isolated Dupuytren's cords.

Special Subject Groups: The Phase 3 clinical studies evaluated the safety and efficacy of AA4500 in a subject population that is representative in terms of age, gender, and race, of the intended target population. As systemic exposure to AA4500 after intralesional injection into Dupuytren's cords is below quantifiable level, no studies are deemed necessary to evaluate the effects of AA4500 in subjects with impaired hepatic or renal function.

Interactions: Pharmacokinetic drug interactions have not been evaluated. AA4500 is not a substrate for cytochrome P450 or other drug metabolizing enzyme pathways and data from the pharmacokinetic Study AUX-CC-855 have confirmed that systemic exposure to AA4500 does not occur following local administration. Thus, AA4500 is not expected to compete for protein binding sites and/or clearance of other protein therapeutics by receptor-mediated endocytotic pathways.

5. CLINICAL INFORMATION RELEVANT TO DOSING RECOMMENDATIONS

In a Phase 2 dose-response study, single injections of AA4500 2500 U, 5000 U, and 10,000 U (equivalent to 0.58 mg), followed after approximately 24 hours by a finger extension procedure to facilitate cord disruption, were all statistically superior ($p \leq 0.002$) to placebo in reducing baseline contracture to 5° or less in the primary joint (2500 U, 50.0%; 5000 U, 45.5%, 10,000 U [equivalent to 0.58 mg], 78.3%; placebo, 0%). However, when the primary joint was analyzed separately by joint type (MP or PIP), the 10,000 U (0.58 mg) dose was the only dose effective in reducing baseline contracture to 5° or less in both MP (81.3%) and PIP (71.4%) joints as compared with placebo.

In an early open-label study (Badalamente and Hurst, 2000), no clinical effects were observed at dose levels < 10,000 U (equivalent to 0.58 mg).

Evaluation of the safety of AA4500 was performed at 2500 U, 5000 U, and 10,000 U (0.58 mg) in Study DUPY-202. Compared with placebo, all three doses of AA4500 showed a significant increase in TEAEs and treatment-related AEs compared with placebo. However, no significant difference across AA4500 treatment groups was observed for any TEAE, indicating no dose-response relationship. All TEAEs were mild or moderate in intensity, non-serious, and resolved within a relatively short period without sequelae.

Therefore, based on the efficacy and safety results from these two studies, and as agreed to by CBER for evaluation in the Phase 3 program, the recommended dose of AA4500 is 0.58 mg per injection into the Dupuytren's cord. This may be followed after approximately 24 hours by a finger extension procedure to facilitate cord disruption. If the contracture caused by the Dupuytren's cord has not adequately responded within approximately four weeks of the first injection and finger extension procedure, the cord may be re-injected with a single dose of AA4500 0.58 mg and the finger extension procedure repeated. Injection and finger extension procedure may be performed up to three times per cord.

Clinical studies have shown that the 4-week interval between injections allows adequate time for the local effects of AA4500 to resolve.

It is recommended that one cord should be treated at a time. If multiple contractures are present, treatment of each cord should be undertaken in a sequential order.

6. CLINICAL PROGRAM

The Division of Anesthesia, Analgesia and Rheumatology Products advised the sponsor that the efficacy of the AA4500 product should be based on at least two, adequate and well-controlled, double-blind Phase 3 studies and the safety database should include at least 1000 subjects who had received at least one injection of AA4500 0.58 mg (10,000 U). To demonstrate the efficacy of AA4500, the sponsor's BLA submission examines the data from three, double-blind, placebo-controlled studies (AUX-CC-857 [Study 1], AUX-CC-859 [Study 2], and DUPY-303 [Study 3]) in which 409 subjects with advanced Dupuytren's disease received up to three injections of AA4500 0.58 mg (N=271) or placebo (N=136) in the treatment of the cord affecting their primary joint.

A total of 1082 subjects who received at least 1 dose of AA4500 0.58 mg in the 11 studies with formal databases were analyzed for the safety of AA4500 in the treatment of advanced Dupuytren's disease; 266 of these subjects were followed for 12 months.

6.1. Overview of Efficacy

No established medical guidelines exist for evaluating the effectiveness of treatment for Dupuytren's disease. In the AA4500 clinical program, the primary endpoint was reduction in contracture of the primary joint to 5° or less after the last injection of study drug, an objective and stringent outcome measure. AA4500 0.58 mg was consistently statistically superior to placebo ($p < 0.001$) with respect to the primary endpoint (ie, reduction in contracture to 5° or less) and gave consistent and reproducible clinically relevant responses of a similar magnitude to the responses achieved by surgical procedures as described in Section 2.4.2. The primary endpoint results observed on primary joints were observed for both MP joints and PIP joints. In addition, AA4500 0.58 mg was effective in the treatment of both high and low severity contractures; the treatment response tended to be greater in joints with lower severity of contracture than in those with higher severity, consistent with that observed after surgical intervention for Dupuytren's contracture as described in Section 2.4.2.

The efficacy on the objective stringent primary endpoint translated into a clinically meaningful functional benefit to subjects as demonstrated by improvements in both range of motion (ROM) without negative impact on grip strength, and the high degree of overall subject satisfaction with AA4500 treatment. ROM, the active full flexion and extension of a finger, is commonly used as a functional measure to evaluate the efficacy of therapeutic interventions (Ellis and Burton, 2002). In clinical practice, hand surgeons and specialists, commonly use ROM as a surrogate for functional outcome of surgical procedures. Normal ROM varies with body habitus, age and genetic background; however, ROMs of 90 degrees for MP joints and 100 degrees for PIP joints are considered normal.

In the Phase 3 double-blind, placebo-controlled studies, treatment with AA4500 0.58 mg restored near normal ROM. In studies AUX-CC-857 (Study 1), AUX-CC-859 (Study 2), and DUPY-303 (Study 3), mean ROM after the last injection improved to 83.7 degrees, 79.5 degrees, and 87.9 degrees in MP joints and to 74.9 degrees, 72.8 degrees, and 101.1 degrees in PIP joints respectively, (p -values for change in ROM < 0.001). This highly significant improvement in ROM was correlated with subject global assessment of treatment satisfaction (Spearman rho = 0.51, $p < 0.001$). Eighty-seven percent of subjects evaluated were very or quite satisfied with AA4500 treatment. This high level of satisfaction was maintained over 1 year as demonstrated in the open-label extension studies. Taken together, these data indicate the clinical benefit of AA4500 treatment to subjects with restoration of hand functionality.

Duration of correction was evaluated in subjects with up to 12 months of follow-up and who had a reduction in contracture to 5° or less after treatment with AA4500. Recurrence was defined as an increase in joint contracture to at least 20° in the presence of a palpable cord. During the 12-month follow-up period for each subject, 30 of the 830 successfully treated Dupuytren's cords were recurrent (nominal rate of 3.6%) with an estimated rate of recurrence at 12 months of 6.7% ($\pm 1.7\%$), based on the Kaplan-Meier estimate.

AA4500 is a novel non-surgical treatment for Dupuytren's contracture that consistently demonstrated efficacy in reducing contractures in both MP and PIP joints and in contractures of low or high degrees of severity. The safety profile of AA4500 0.58 mg from clinical studies indicated that the most commonly reported events were local AEs, confined to the treated extremity, and generally resolved prior to the next injection.

6.2. Demographics and Other Baseline Characteristics

The subject population studied was typical of subjects with advanced Dupuytren's disease with regard to age, gender, and race (Brown et al., 2008). In the three Phase 3 double-blind, placebo-controlled studies, demographics were as follows:

- Most (80.6%) subjects were men
- All subjects were white except for one who was Hispanic
- Most (71.9%) subjects were between the ages of 55 and 74 years

In the three double-blind, placebo-controlled studies, 271 cords affecting primary joints were treated with 455 injections of AA4500 0.58 mg and 136 cords were treated with 388 injections of placebo.

Primary joint distribution by joint type and severity at baseline is presented in Table 7. Of note, 25 primary PIP joints treated with AA4500 in Study AUX-CC-859, 44.4% (20/45) had a baseline contracture $>40^\circ$ (high severity); while in Study AUX-CC-857 only 24.1% (49/203) of the primary PIP joints treated with AA4500 had a baseline contracture $>40^\circ$.

Table 7: Primary Joint Distribution by Joint Type and Severity

	AUX-CC-857 (Study 1)		AUX-CC-859 (Study 2)		DUPY-303 (Study 3)	
	AA4500 N=203	Placebo N=103	AA4500 N=45	Placebo N=21	AA4500 N=23	Placebo N=12
MP low severity	81 (39.9%)	43 (41.7%)	10 (22.2%)	7 (33.3%)	7 (30.4%)	6 (50.0%)
PIP low severity	21 (10.3%)	9 (8.7%)	5 (11.1%)	2 (9.5%)	3 (13.0%)	4 (33.3%)
MP high severity	52 (25.6%)	26 (25.2%)	10 (22.2%)	4 (19.0%)	7 (30.4%)	1 (8.3%)
PIP high severity	49 (24.1%)	25 (24.3%)	20 (44.4%)	8 (38.1%)	6 (26.1%)	1 (8.3%)

MP low severity= $\leq 50^\circ$; MP high severity= $>50^\circ$

PIP low severity= $\leq 40^\circ$; PIP high severity= $> 40^\circ$

Risk factors for Dupuytren's disease were similar between the placebo and AA4500 0.58 mg treatment groups. Overall, 45.5% of subjects had a family history of Dupuytren's disease. More than half (56.3%) of all subjects had not previously sought any treatment for Dupuytren's disease, while 40.5% had undergone surgery before enrolling in the studies.

Demographics and other baseline characteristics of subjects who participated in the open-label studies (DUPY-404, AUX-CC-854, AUX-CC-856, AUX-CC-858, and AUX-CC-859 [open-label phase]) and the Phase 2 studies (DUPY-202 and DUPY-101) were similar to those of the three Phase 3, double-blind, placebo-controlled studies.

6.3. Primary Endpoint: Reduction of Contracture to 5° or Less in the Primary Joint

The primary endpoint was achieved in all three Phase 3 double-blind, placebo-controlled studies; that is, AA4500 0.58 mg was consistently superior to placebo with respect to the percentage of subjects who achieved a reduction in contracture of their primary joint to 5° or less after the last injection ($p < 0.001$; Table 8). Most subjects required one or two injections of AA4500 for a reduction in contracture of the primary joint to 5° or less.

Table 8: Reduction of Contracture to 5° or Less in the Primary Joint After the Last Injection – Studies AUX-CC-857, AUX-CC-859, and DUPY-303

	AUX-CC-857 (Study 1)		AUX-CC-859 (Study 2)		DUPY-303 (Study 3)	
	AA4500 N=203	Placebo N=103	AA4500 N=45	Placebo N=21	AA4500 N=23	Placebo N=12
Number (%) of subjects with a reduction in contracture to $\leq 5^\circ$ p-value ^a	130 (64.0%) <0.001	7 (6.8%) -	20 (44.4%) <0.001	1 (4.8%) -	21 (91.3%) <0.001	0 -
Mean (SD) number of injections to achieve reduction in contracture to $\leq 5^\circ$	1.5 (0.7)	2.6 (0.8)	1.5 (0.7)	1.0	1.4 (0.7)	NA

NA= not applicable due to ineligibility for statistical analysis

Note: Stratification for MP:PIP was 2:1 in Study 1 and Study 3, and 1:1 in Study 2.

In Study 1 and Study 3, 50.4% of primary joints were of high severity at baseline, while 66.7% of the primary joints in Study 2 were of high severity.

Last injection=final injection of AA4500 into the cord. Individual cords could receive up to three injections of AA4500.

^a p-value based on Cochran-Mantel-Haenszel test comparing treatment groups, stratified by baseline severity group and joint type.

6.4. Secondary Endpoints

The secondary endpoints evaluated in the Phase 3 double-blind, placebo-controlled studies were in accordance with those used by hand surgeons as outcome measures for the surgical correction of Dupuytren's contracture. Evaluation of these endpoints was robust, with a hierarchical testing procedure prospectively defined in Studies AUX-CC-857 and AUX-CC-859. With this approach, the first test in the hierarchy that failed to reject its individual hypothesis at the 5% level meant that all hypotheses following the first non-significant hypothesis could not be tested. If similar hierarchical testing had been carried out for Study DUPY-303, all primary and secondary hypotheses stated in the DUPY-303 analyses plan would have been accepted because all observed p-values were significant.

In all three Phase 3 double-blind, placebo-controlled studies, subjects treated with AA4500 had a greater percent reduction in baseline contracture ($p < 0.001$), a greater increase in ROM ($p < 0.001$), and a shorter time to achieve clinical success ($p < 0.001$) of their primary joint compared with subjects who were treated with placebo. A higher percentage ($p < 0.001$) of subjects treated with AA4500 in Studies AUX-CC-857 and AUX-CC-859 had 50% or greater reduction in baseline contracture of their primary joint compared with subjects who were treated with placebo (this endpoint was not analyzed in Study DUPY-303).

Results for efficacy by joint type, clinical improvement, change in degree of contracture, and ROM are detailed below.

6.4.1. Efficacy by Joint Type

In the three double-blind, placebo-controlled studies, AA4500 was also consistently superior to placebo with respect to the percentage of subjects who achieved a reduction in contracture of their primary MP joint to 5° or less after the last injection ($p \leq 0.003$). In Studies AUX-CC-857 and DUPY-303, AA4500 was superior to placebo with respect to the percentage of subjects who achieved a reduction in contracture of their primary PIP joint to 5° or less after the last injection ($p \leq 0.003$) (Table 9).

In Study AUX-CC-859, 28% of subjects with a primary PIP joint had a reduction in contracture to 5° or less compared with no subject in the placebo group; however, the difference between the groups was not statistically significant ($p=0.069$). In this study, almost three-quarters (72.2%, 13/18) of the subjects in the AA4500 group who did not have a reduction in contracture to 5° or less in their primary PIP joint also did not receive the full treatment regimen of up to three injections. Twenty-eight percent of these subjects had no palpable cord to inject after only one or two injections of AA4500 and another 12% were satisfied with the correction and requested no further treatment of their primary joint.

Table 9: Reduction of Contracture to 5° or Less in the Primary Joint After the Last Injection Subset by Joint Type – Studies AUX-CC-857, AUX-CC-859, and DUPY-303

	AUX-CC-857 (Study 1)		AUX-CC-859 (Study 2)		DUPY-303 (Study 3)	
	AA4500	Placebo	AA4500	Placebo	AA4500	Placebo
Primary MP	N=133	N=69	N=20	N=11	N=14	N=7
Number (%) of subjects who achieved reduction in contracture to $\leq 5^\circ$ p-value ^a	102 (76.7%) <0.001	5 (7.2%) ^b -	13 (65.0%) 0.003	1 (9.1%) -	12 (85.7%) <0.001	0 -
Mean (SD) number of injections to achieve reduction in contracture to $\leq 5^\circ$	1.6 (0.8)	2.8 (0.5)	1.4 (0.7)	1.0	1.3 (0.6)	NA
Primary PIP	N=70	N=34	N=25	N=10	N=9	N=5
Number (%) of subjects who achieved reduction in contracture to $\leq 5^\circ$ p-value ^a	28 (40.0%) <0.001	2 (5.9%) ^b -	7 (28.0%) 0.069	0 -	9 (100.0%) <0.001	0 -
Mean (SD) number of injections to achieve reduction in contracture to $\leq 5^\circ$	1.3 (0.5)	2.0 (1.4)	1.7 (0.8)	NA	1.6 (0.9)	NA

NA=not applicable due to ineligibility for statistical analysis.

Last injection=final injection of AA4500 into the cord. Individual cords could receive up to 3 injections of AA4500.

^a p-value based on Cochran-Mantel-Haenszel test comparing treatment group, stratified by baseline severity group and joint type.

^b Subjects 1154-2715 and 1182-4309 were inadvertently administered AA4500 at the 2nd and 3rd injection, respectively.

6.4.2. Clinical Improvement

Clinical improvement was defined as a $\geq 50\%$ reduction from baseline in degree of contracture after an injection. Clinical improvement was not a secondary endpoint in Study DUPY-303.

A significantly higher proportion of subjects who were treated with AA4500 in Studies AUX-CC-857 and AUX-CC-859 had a 50% or greater improvement in the baseline contracture of their primary joint compared with subjects treated with placebo ($p < 0.001$) (Table 10).

Table 10: Clinical Improvement^a of the Primary Joint After the Last Injection Primary Joint Overall and by Joint Type – Studies AUX-CC-857 and AUX-CC-859

	AUX-CC-857 (Study 1)		AUX-CC-859 (Study 2)	
	AA4500	Placebo	AA4500	Placebo
All Primary	N=203	N=103	N=45	N=21
% subjects with $\geq 50\%$ reduction in degree of contracture	84.7%	11.7%	77.8%	14.3%
p-value ^b	<0.001	-	<0.001	-
Primary MP	N=133	N=69	N=20	N=11
% subjects with $\geq 50\%$ reduction in degree of contracture	94.0%	11.6%	95.0%	18.2%
p-value ^c	<0.001	-	<0.001	-
Primary PIP	N=70	N=34	N=25	N=10
% subjects with $\geq 50\%$ reduction in degree of contracture	67.1%	11.8%	64.0%	10.0%
p-value ^c	<0.001	-	NA	-

MP=metacarpophalangeal; PIP=proximal interphalangeal; NA=not applicable due to ineligibility for statistical analysis.

^a Clinical improvement: reduction of contracture to $\geq 50\%$ of baseline after the last injection.

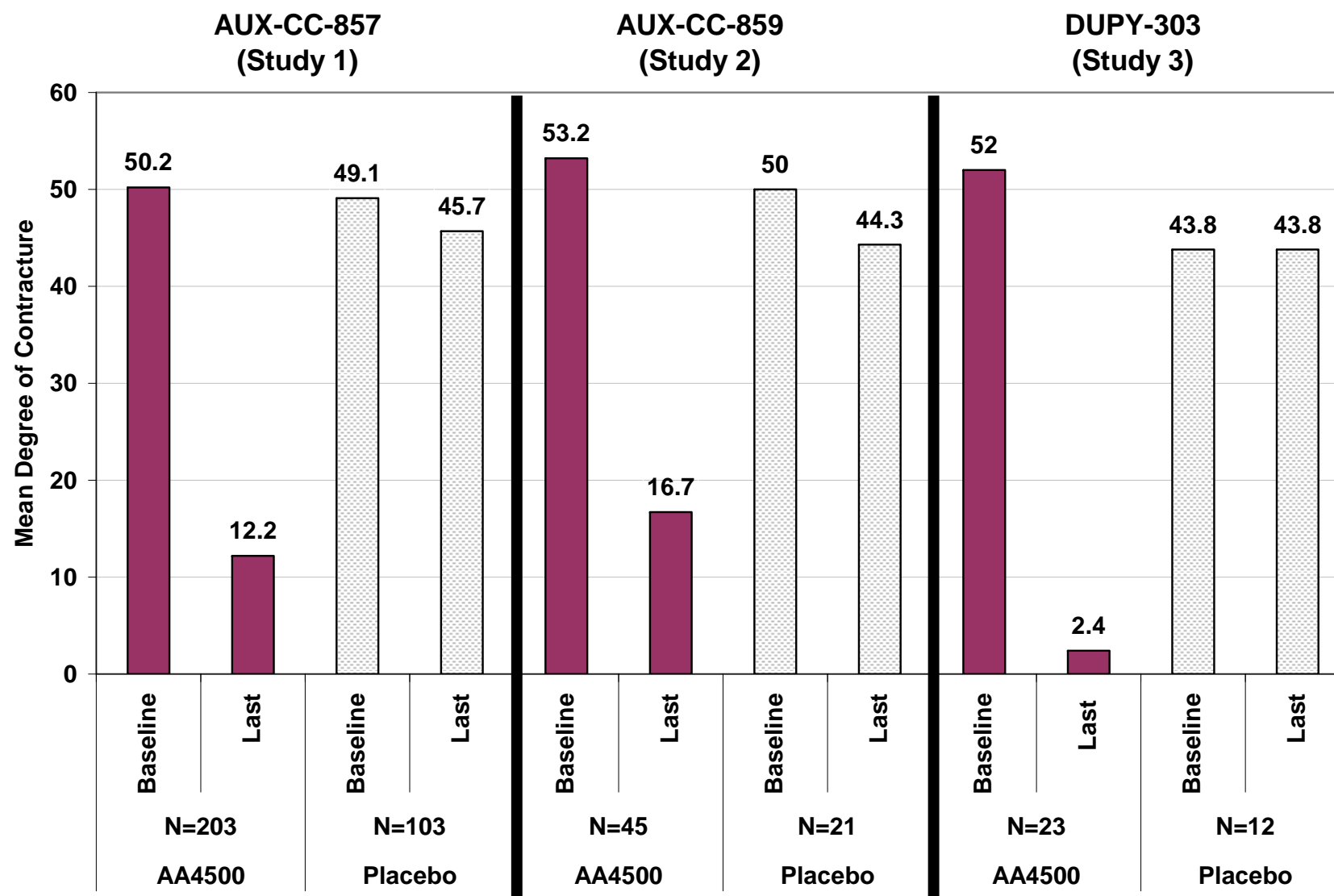
^b p-value based on Cochran-Mantel-Haenszel test comparing treatment group, stratified by baseline severity group and joint type.

^c p-value based on Cochran-Mantel-Haenszel test comparing treatment group, stratified by baseline severity group.

6.4.3. Degree of Contracture After the Last Injection, All Primary Joints

After the last injection of AA4500, there was a notable reduction from baseline in the degree of contracture of the primary joint in Studies AUX-CC-857, AUX-CC-859, and DUPY-303 compared with little or no reduction in contracture after the last injection of placebo (Figure 6).

Figure 6: Mean Degree of Contracture in the Primary Joint at Baseline and After the Last Injection – Studies AUX-CC-857, AUX-CC-859, and DUPY-303

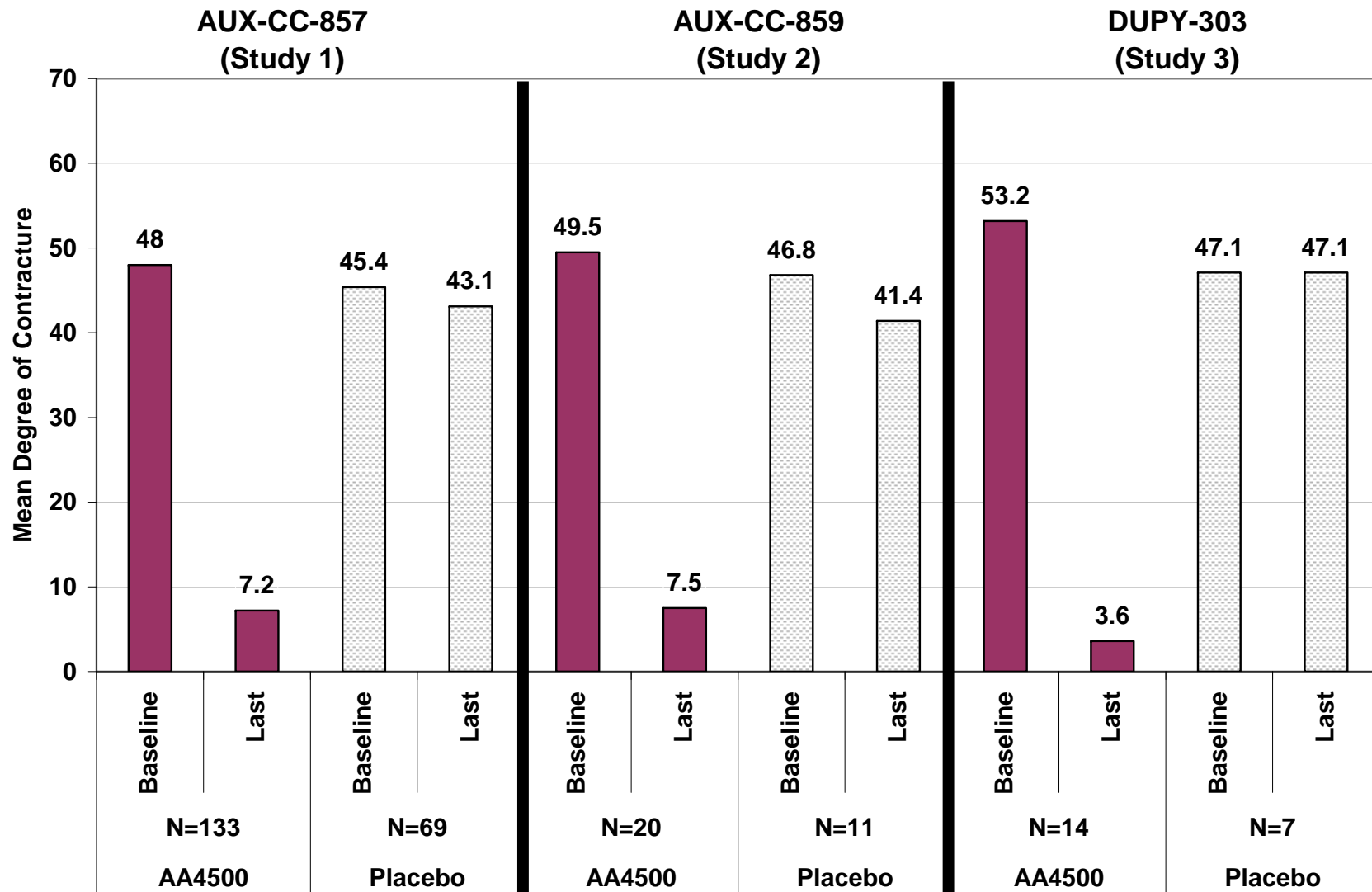


Last injection=final injection of study drug into the cord. Individual cords could receive up to 3 injections of AA4500.

6.4.4. Degree of Contracture After the Last Injection by Joint Type

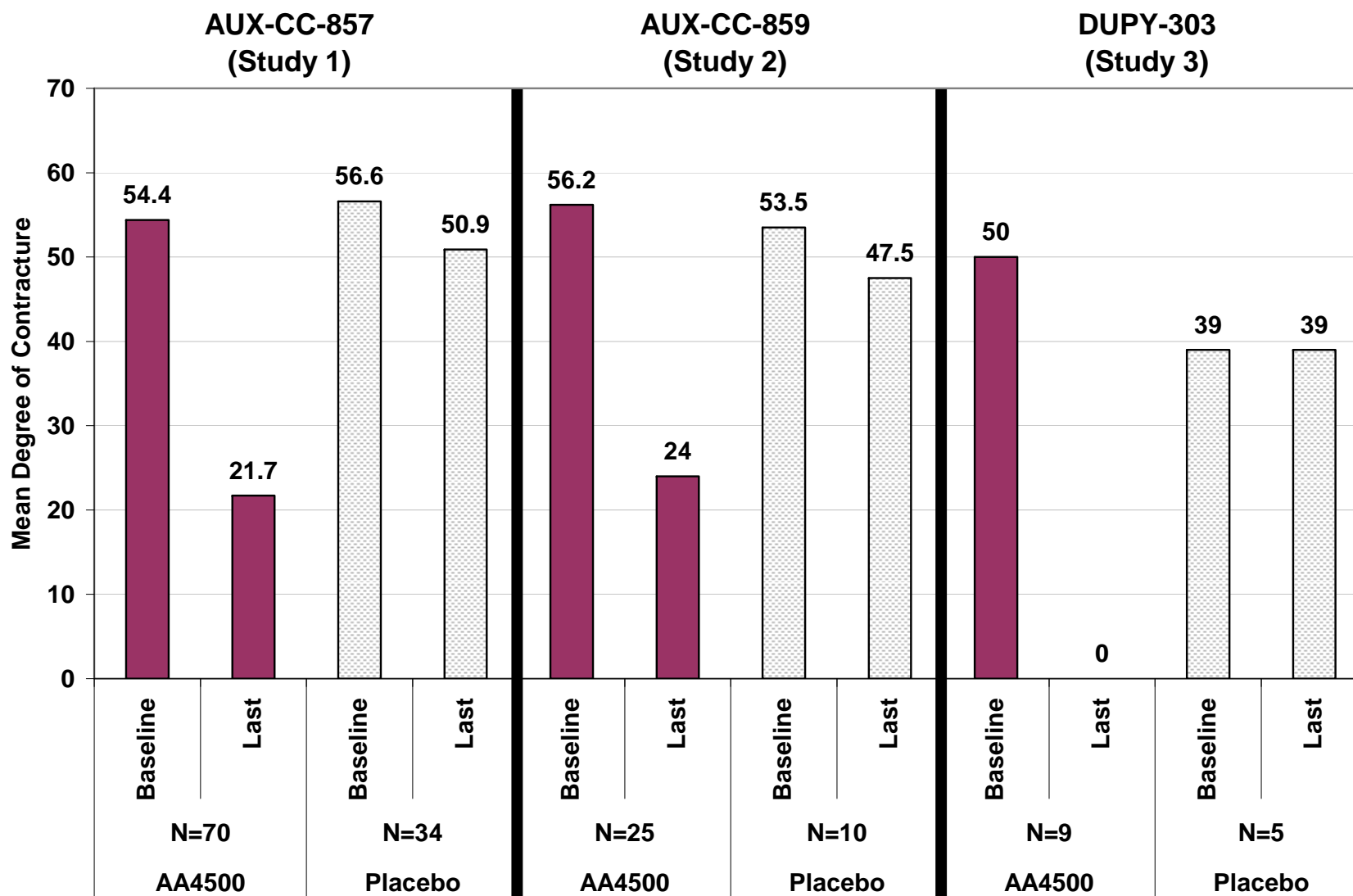
After the last injection of AA4500, there were notable reductions from baseline in the degree of contracture in primary MP and primary PIP joints in each of the three studies (Figure 7 and Figure 8). Primary MP and PIP joints showed little or no reduction in the degree of contracture after the last injection of placebo. The reduction in contracture in Studies AUX-CC-857 and AUX-CC-859 tended to be greater in MP joints (final mean contracture $<10^{\circ}$) than in PIP joints (final mean contracture $<25^{\circ}$).

Figure 7: Mean Degree of Contracture in Primary MP Joints at Baseline and After the Last Injection – Studies AUX-CC-857, AUX-CC-859, and DUPY-303



Last injection=final injection of study drug into the cord. Individual cords could receive up to 3 injections of AA4500.

Figure 8: Mean (°) Contracture of the Primary PIP Joints at Baseline and After the Last Injection – Studies AUX-CC-857, AUX-CC-859, and DUPY-303



Last injection=final injection of study drug into the cord. Individual cords could receive up to 3 injections of AA4500.

6.4.5. Change in Range of Motion

Range of motion, the active full flexion and extension of a finger, is commonly used as a functional measure to evaluate the efficacy of therapeutic interventions (Ellis and Burton, 2002). In clinical practice, hand surgeons and specialists commonly use ROM as a surrogate for functional outcome of surgical procedures. Normal ROM varies with body habitus, age and genetic background; however, ROMs of 90 degrees for MP joints and 100 degrees for PIP joints are considered normal.

Range of motion in the three studies was defined as the difference between the full flexion angle (ie, the ability to make a fist) and full extension angle (ie, the ability to straighten the finger), expressed in degrees. In all three studies, there was a significant increase ($p < 0.001$) from baseline in ROM in the primary joint after the last injection of AA4500 (Table 11 and Table 12). Similar results were observed for primary MP joints treated with AA4500 in the three studies and for primary PIP joints in Studies DUPY-303 and AUX-CC-857.

In the three studies, up to three injections of AA4500 into the cord affecting MP joints and PIP joints did not adversely affect the full flexion angle; that is joints that had full flexion at baseline continued to have full flexion after treatment with AA4500. The change in ROM resulted from improvement in the full extension angle; subjects were able to further extend their affected finger after treatment with AA4500.

Table 11: Mean Change in Range of Motion From Baseline to After the Last Injection Overall and by Joint Type – Studies AUX-CC-857 and AUX-CC-859

Range of Motion (°)	AUX-CC-857 (Study 1)		AUX-CC-859 (Study 2)	
	AA4500	Placebo	AA4500	Placebo
All Primary	N=197	N=102	N=45	N=21
Baseline ROM Mean (SD)	43.9° (20.1)	45.3° (18.7)	40.3° (15.2)	44.0° (16.5)
Day 30 ROM Mean (SD)	80.7° (19.0)	49.5° (22.1)	75.8° (17.7)	51.7° (19.6)
Mean increase in ROM	36.7°	4.0°	35.4°	7.6°
p-value ^a	<0.001	-	<0.001	-
Primary MP	130	68	N=20	N=11
Baseline ROM Mean (SD)	42.6° (20.0)	45.7° (19.2)	39.5° (11.8)	41.4° (20.8)
Day 30 ROM Mean (SD)	83.7° (15.7)	49.7° (21.1)	79.5° (11.1)	50.0° (21.5)
Mean increase in ROM	40.6°	3.7°	40.0°	8.6°
p-value ^a	<0.001	-	<0.001	-
Primary PIP	N=67	N=34	N=25	N=10
Baseline ROM Mean (SD)	46.4° (20.4)	44.4° (17.9)	41.0° (17.7)	47.0° (10.3)
Day 30 ROM Mean (SD)	74.9° (23.1)	49.1° (24.4)	72.8 (21.3)	53.5° (18.3)
Mean increase in ROM	29.0°	4.7°	31.8°	6.5°
p-value ^a	<0.001	-	NA	-

MP=metacarpophalangeal; PIP=proximal interphalangeal; ROM=range of motion. NA=not applicable due to ineligibility for statistical analysis.

^a p-value based on full factorial model analysis of variance (ANOVA) with treatment group, joint type, and baseline severity as factors.

Table 12: Mean (%) Change in Range of Motion From Baseline to After the Last Injection Overall and by Joint Type – DUPY-303

	DUPY-303 (Study 3)	
Range of Motion (%)	AA4500	Placebo
All Primary Joints	N=23	N=12
Baseline ROM Mean (SD)	41.7 (15.0)	50.8 (12.8)
Day 30 ROM Mean (SD)	93.0 (10.3)	52.5 (12.5)
Mean % increase in ROM	150.4%	4.2%
p-value ^a	<0.001	-
Primary MP Joints	N=14	N=7
Baseline ROM Mean (SD)	37.5 (13.6)	43.6 (11.4)
Day 30 ROM Mean (SD)	87.9 (9.6)	45.0 (10.0)
Mean % increase in ROM	163.5%	4.8%
p-value ^b	<0.001	-
Primary PIP Joints	N=9	N=5
Baseline ROM Mean (SD)	48.3 (15.4)	61.0 (5.5)
Day 30 ROM Mean (SD)	101.1 (4.9)	63.0 (6.7)
Mean % increase in ROM	130.0%	0.0%
p-value ^b	<0.001	-

MP=metacarpophalangeal; PIP=proximal interphalangeal; ROM=range of motion

^a p-value is from an analysis of covariance (ANCOVA) with terms for joint type, treatment, and baseline value as covariates.

^b p-value is from an ANCOVA with terms for treatment and baseline value as covariates.

6.4.6. Category of Final Contracture (°) After the Last Injection

Among subjects treated with AA4500 in Studies AUX-CC-857 and AUX-CC-859, 91.7% and 95.0%, respectively, had a reduction in contracture of their MP joint to $\leq 25^\circ$ after the last injection, which would make the contracture ineligible for surgery (ie, $\leq 30^\circ$ [Townley et al., 2006]) (Table 13). Additionally in Studies AUX-CC-857 and AUX-CC-859, 64.3% and 60.0% of subjects, respectively, achieved a reduction in contracture of their PIP joint to $\leq 25^\circ$ after their last injection of AA4500.

Table 13: Category of Final Contracture (°) After the Last Injection of AA4500 – Studies AUX-CC-857 and AUX-CC-859

	Degree of Final Contracture		
	0-5°	0-15°	0-25°
	AUX-CC-857 (Study 1)		
All primary joints (N=203)	64.0%	74.4%	82.3%
Primary MP joints (N=133)	76.7%	85.7%	91.7%
Primary PIP joints (N=70)	40.0%	52.9%	64.3%
	AUX-CC-859 (Study 2)		
All primary joints (N=45)	44.4%	66.7%	75.6%
Primary MP joints (N=20)	65.0%	85.0%	95.0%
Primary PIP joints (N=25)	28.0%	52.0%	60.0%

6.5. Other Efficacy Endpoints

6.5.1. Subject Global Assessment of Treatment

Subjects in Studies AUX-CC-857 and AUX-CC-859 were asked to rate their satisfaction with treatment as very satisfied, quite satisfied, neither satisfied nor dissatisfied, quite dissatisfied, or very dissatisfied. Overall in each of the studies, more subjects who received AA4500 were satisfied with their treatment compared with subjects who received placebo ($p < 0.001$).

Approximately 87% of subjects who received AA4500 in each of the studies were very or quite satisfied with their treatment (Figure 9 and Figure 10).

Figure 9: Subject Treatment Satisfaction at Day 90 – AUX-CC-857 (Study 1)

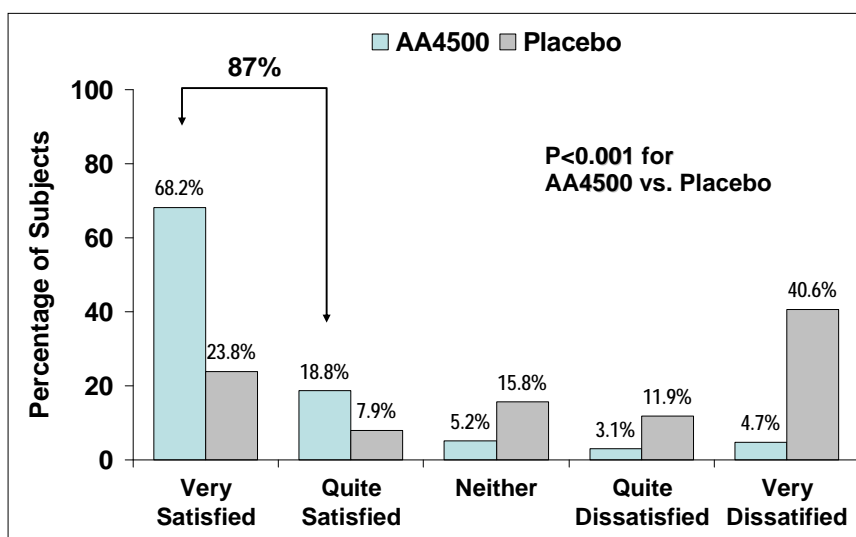
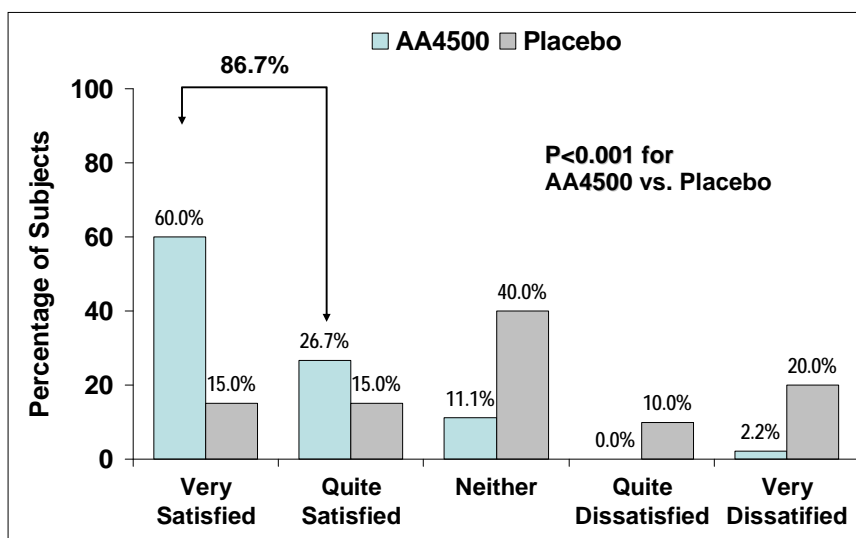


Figure 10: Subject Treatment Satisfaction at Day 90 – AUX-CC-859 (Study 2)



6.6. Combined Analyses

6.6.1. Efficacy in Subpopulations

In the combined analysis of data from all three double-blind, placebo-controlled studies, no notable differences in efficacy were observed by age category (< 45, 45-54, 55-64, 65-74, ≥ 75 years), gender, weight quartile (first, second, third, fourth quartile), BMI category (normal, overweight, obese), and history of diabetes (yes, no).

The only exception was country location. When all primary joints were analyzed by country location, a higher percentage of subjects treated in the United States had a reduction in contracture of the primary joint to 5° or less compared with subjects treated in Australia (66.8% versus 44.4%). It may be noteworthy that the distribution of baseline severity and joint type was different between Studies AUX-CC-857 and AUX-CC-859 (see Table 7). In Study AUX-CC-857, 39.9% of primary MP joints treated with AA4500 were of low severity ($\leq 50^\circ$) compared with 22.2% in Study AUX-CC-859. In Study AUX-CC-859, 44.4% of the primary PIP joints treated with AA4500 were of high severity ($>40^\circ$) compared with 24.1% in Study AUX-CC-857.

Of the PIP joints that did not achieve the primary endpoint, 72.2% (13/18) in Australia did not receive the full AA4500 treatment regimen compared with 50.0% (21/42) in the United States. In both countries, the reason most commonly cited for not receiving the full treatment regimen of up to three injections was “no palpable cord to inject.”

No conclusions could be drawn about race, as only one of the 407 subjects who were treated in the three studies was non-white. The low number of non-white subjects was to be expected as Dupuytren’s disease has a genetic predisposition to occur in men of Northern European ancestry (Brown et al., 2008; Leclercq, 2000; McFarlane and McGrouther, 1990).

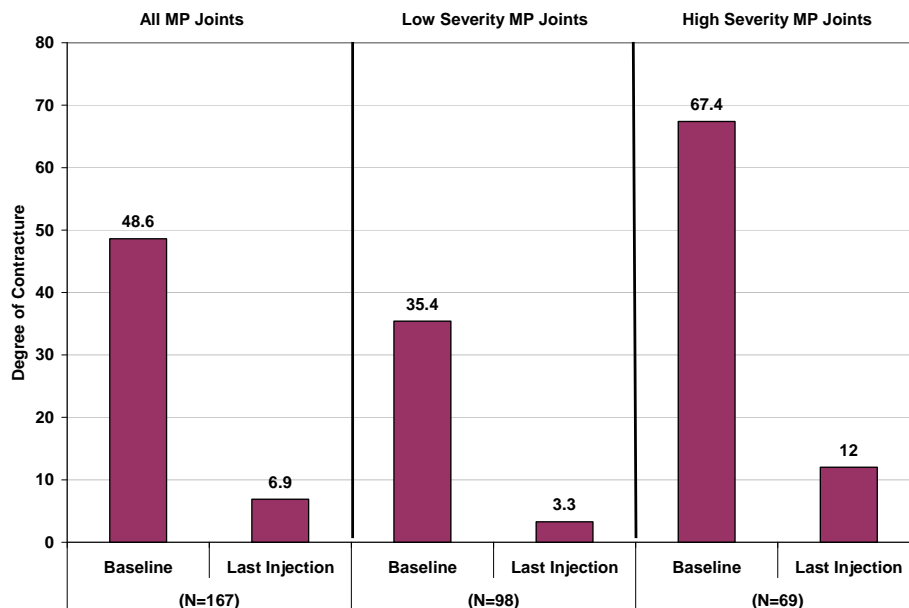
6.6.2. Efficacy by Joint Type and Baseline Disease Severity

In the combined analysis of data from all three double-blind, placebo-controlled studies, the majority of MP joints (86.7%) and PIP joints (75.9%) of low severity ($\leq 50^\circ$ for MP, $\leq 40^\circ$ for PIP) achieved the primary endpoint of reduction in contracture to 5° or less after the last injection of AA4500.

Severely contracted MP and PIP joints also responded to treatment with AA4500.

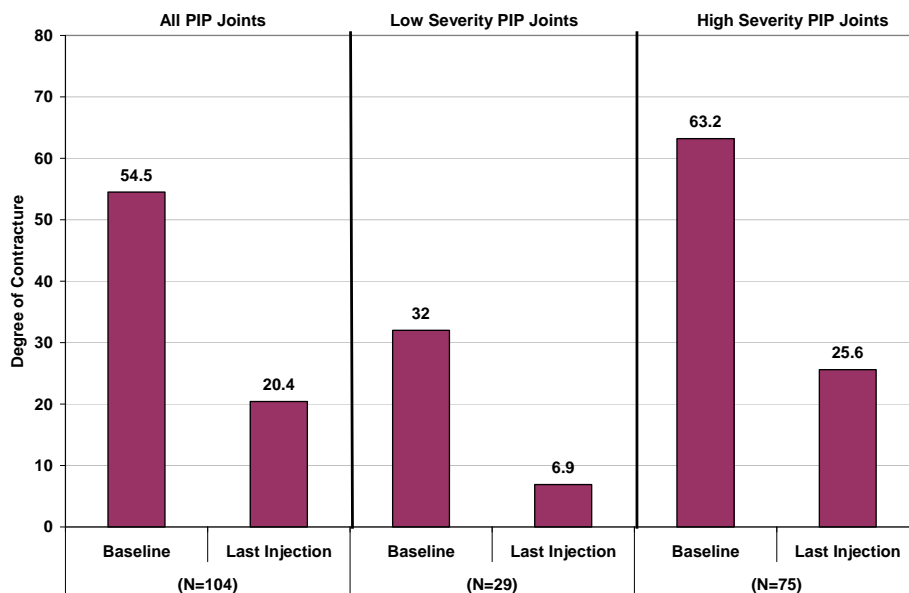
Approximately 61% of MP joints and 29% of PIP joints of high severity achieved the primary endpoint of reduction in contracture to 5° or less after treatment with AA4500. MP joints of high severity had a reduction from 67.4° at baseline to 12° after the last injection of AA4500 (Figure 11). Although fewer PIP joints of high severity achieved the primary endpoint, AA4500 was efficacious in the treatment of these joints. PIP joints of high severity had a reduction from 63.2° at baseline to 25.6° after the last injection of AA4500 (Figure 12).

Figure 11: Degree of Contracture in the Primary MP Joint at Baseline and After the Last Injection by Baseline Joint Severity – All Subjects Who Received AA4500 in Studies AUX-CC-857 (Study 1), AUX-CC-859 (Study 2), and DUPY-303 (Study 3)



Last injection=final injection of study drug into the cord. Individual cords could receive up to three injections of AA4500
MP low severity= ≤ 50 ; MP high severity= >50

Figure 12: Degree of Contracture in the Primary PIP Joint at Baseline and After the Last Injection by Baseline Joint Severity – All Subjects Who Received AA4500 in Studies AUX-CC-857 (Study 1), AUX-CC-859 (Study 2), and DUPY-303 (Study 3)



Last injection=final injection of study drug into the cord. Individual cords could receive up to three injections of AA4500.
PIP low severity= ≤ 40 ; PIP high severity= >40

The vast majority (> 91%) of MP joints of high or low severity showed clinical improvement (ie, a 50% or greater reduction in contracture from baseline). Approximately 83% of PIP joints of low severity, and 64% of PIP joints of high severity showed clinical improvement.

6.7. Recurrence of Contracture

Dupuytren's disease is a fibroproliferative condition that cannot be cured with AA4500 or surgery. Therefore, recurrence of contracture is an inevitable consequence of Dupuytren's disease if the subject lives long enough (Bulstrode, 2005).

Recurrence of contracture was evaluated for up to 12 months after the first injection of AA4500. Recurrence of contracture was evaluated in joints that achieved a reduction in contracture to 5° or less as measured by finger goniometry after an injection. The investigator determined there was recurrence when the joint contracture increased to at least 20° and there was a palpable cord at any time during the study.

During the 12-month follow-up period for each subject, 30 of the 830 successfully treated Dupuytren's cords (ie, reduction in contracture to 5° or less) were recurrent (nominal rate of 3.6%) with an estimated rate of recurrence at 12 months of 6.7% ($\pm 1.7\%$), based on the Kaplan-Meier estimate. Depending on the type of surgery performed and the length of follow-up, contracture recurrence rates range from 2% to 60%, with an average of 33% (Rayan, 2007).

6.8. Efficacy Findings and Conclusions

Results from the three double-blind placebo-controlled studies independently demonstrate the effectiveness of AA4500 for the treatment of contractures caused by advanced Dupuytren's disease and together demonstrate the reproducibility of the treatment effects.

6.8.1. Primary Endpoint

AA4500 0.58 mg was statistically superior to placebo with respect to the proportion of subjects who achieved a reduction in contracture to 5° or less of their primary joint after the last injection ($p < 0.001$). The primary endpoint was achieved in each of the three double-blind, placebo-controlled studies.

6.8.2. Secondary and Other Endpoints

In each of the three double-blind, placebo-controlled studies, subjects treated with AA4500 0.58 mg had a greater reduction in baseline contracture, a greater increase in ROM, and a shorter time to achieve this reduction compared with subjects who received placebo. In the two studies where clinical improvement was evaluated, a higher proportion of subjects treated with AA4500 0.58 mg had a 50% or greater reduction in baseline contracture of their primary joint compared with subjects who were treated with placebo. Similar results were observed for primary MP joints in each of the three studies and for primary PIP joints in two of the three studies (AUX-CC-857 [Study 1] and DUPY-303 [Study 3]).

In Study AUX-CC-859 (Study 2), more primary PIP joints treated with up to three injections of AA4500 0.58 mg had a reduction in contracture to 5° or less compared with placebo (7 joints versus 0 joints); however, the difference between the groups was not statistically significant ($p = 0.069$). Among those joints in Study 2 with the final contracture measurement greater than 5°

after treatment with AA4500 0.58 mg, 72.2% (13/18) of PIP joints did not receive the full AA4500 treatment regimen, most commonly because there was “no palpable cord to inject” after only one or two injections of AA4500 0.58 mg. The residual contracture observed in these joints was thought to be due to intrinsic or extrinsic factors such as joint stiffness or the presence of adjunct cords. PIP joints that could not be treated further because there was “no palpable cord to inject”, taken together with those that reached the primary endpoint resulted in 56.0% of PIP joints achieving the maximum correction possible with AA4500 0.58 mg. Three additional subjects in this study, who were satisfied with the improvement achieved after one or two injections of AA4500 0.58 mg, declined further treatment even though the contracture in their PIP joint had not been reduced to 5° or less. Approximately 87% of subjects who received AA4500 in Studies AUX-CC-857 and AUX-CC-859 were very or quite satisfied with their treatment.

During the 12-month follow-up period for each subject, 30 of the 830 successfully treated Dupuytren’s cords were recurrent (nominal rate of 3.6%) with an estimated rate of recurrence at 12 months of 6.7% ($\pm 1.7\%$), based on the Kaplan-Meier estimate.

6.8.3. AA4500 0.58 mg and Surgery

In the surgical correction of Dupuytren’s contractures, two observations stand out clearly: MP joints respond to surgery considerably better than PIP joints, and the results following surgery of the PIP joint in the little finger are often poor (McFarlane et al., 1990). In the three double-blind, placebo-controlled studies, AA4500 0.58 mg was effective in reducing the degree of contracture in both MP and PIP joints. After the last injection of AA4500, baseline contracture was reduced on average from 48.6° to 6.9° in MP joints, and from 54.5° to 20.4° in PIP joints.

In the three double-blind, placebo-controlled studies, there was no evidence that PIP contractures were made worse after treatment with AA4500. Most MP (86.7%) and PIP joints (75.9%) of low severity ($\leq 50^\circ$ for MP; $\leq 40^\circ$ for PIP) had a reduction in contracture to 5° or less after the last injection of AA4500.

Joints with more severe contractures also responded to treatment with AA4500. Approximately 61% of MP joints and 29.3% of PIP joints of high severity had a reduction in contracture to 5° or less after treatment with AA4500. Although fewer PIP joints of high severity achieved the primary endpoint, AA4500 was efficacious in the treatment of these joints. On average following the last injection of AA4500, contracture in PIP joints of high severity was reduced from 63.2° at baseline to 25.6°. Although AA4500 has been shown to be effective in the treatment of both high and low severity contractures, the treatment response tended to be greater in joints with lower severity of contracture than in those with higher severity, consistent with that observed after surgical intervention for Dupuytren’s contracture (Misra et al., 2007; Dias and Braybrooke, 2006).

The inability for a subject to flex a finger to the distal palmar crease (ie, full flexion) has been reported in 4.6% of subjects after surgical correction of Dupuytren’s contracture (McFarlane and McGrouther, 1990). Furthermore, loss of finger joint mobility has also been reported to occur after surgery (Tubiana, 2000; Bulstrode et al., 2005). In the three double-blind, placebo-controlled studies, full flexion was virtually unaffected by AA4500.

6.8.4. Efficacy Conclusions

- In all three double-blind, placebo-controlled Phase 3 studies, AA4500 0.58 mg was demonstrated to be effective in the treatment of joint contractures caused by advanced Dupuytren's disease.
- AA4500 0.58 mg could fulfill the unmet need for a non-surgical, pharmacologic agent that is effective in the treatment of this debilitating disease.

6.9. Overview of Safety

The safety of AA4500 was assessed in Phase 1, 2, and 3 clinical studies conducted in subjects with advanced Dupuytren's disease.

Two integrated analysis populations demonstrate the clinical safety of AA4500 0.58 mg in the treatment of advanced Dupuytren's disease:

- The *Phase 3 Double-Blind, Placebo-Controlled* analysis population comprised subjects who received at least one injection of double-blind study medication in Study AUX-CC-857 (Study 1), the double-blind phase of Study AUX-CC-859 (Study 2), and in Study DUPY-303 (Study 3). Subjects in this analysis population could have received up to three injections of either AA4500 0.58 mg (N=272) or placebo (N=137).
- The *All Subjects With At Least One Dose of AA4500 0.58 mg* analysis population included subjects who received at least one dose of AA4500 0.58 mg across Phase 2 and Phase 3 studies (Studies DUPY-202, DUPY-303, DUPY-404, AUX-CC-851/852, AUX-CC-853, AUX-CC-854, AUX-CC-855, AUX-CC-856, AUX-CC-857, AUX-CC-858, and AUX-CC-859). A total of 1082 subjects were included in this population. Subjects in this analysis population could have received up to eight injections of AA4500 0.58 mg.

6.9.1. Disposition

6.9.1.1. Phase 3 Double-Blind, Placebo-Controlled Studies

Subject disposition for the *Phase 3 Double-Blind, Placebo-Controlled* analysis population is summarized in Table 14. Four hundred nine (409) subjects (272 subjects in the AA4500 0.58 mg group and 137 subjects in the placebo group) entered the double-blind Phase 3 studies and received at least 1 injection of study drug. Similar percentages (94.5% AA4500 0.58 mg and 95.6% placebo) of subjects completed the double-blind, Phase 3 studies.

Few subjects discontinued these studies prematurely for any reason (5.5% AA4500 0.58 mg and 4.4% placebo). Of the 21 subjects (15 AA4500 0.58 mg and 6 placebo) who discontinued, the most common reason was withdrawal of consent; the percentage of subjects who withdrew consent was higher in the placebo group (3.6%) than in the AA4500 0.58 mg group (1.5%).

Table 14: Subject Disposition - Phase 3 Double-Blind, Placebo-Controlled Studies^a

	AA4500 0.58 mg (N=272)	Placebo (N=137)
Double-blind Phase 3 study, n (%)		
303 ^b	23 (8.5)	12 (8.8)
857	204 (75.0)	104 (75.9)
859 (double-blind phase only)	45 (16.5)	21 (15.3)
Completion status, n (%)		
Completed ^c	257 (94.5)	131 (95.6)
Discontinued	15 (5.5)	6 (4.4)
Withdrew consent	4 (1.5)	5 (3.6)
Lost to follow-up	4 (1.5)	1 (0.7)
AEs	3 (1.1)	0 (0.0)
Protocol violation	1 (0.4)	0 (0.0)
Other	3 (1.1)	0 (0.0)

a Includes all subjects who received at least 1 injection of double-blind study medication (placebo or AA4500 0.58 mg).

b Three subjects received AA4500 0.58 mg (1 injection) and placebo (2 injections) as part of randomization scheme and are summarized with AA4500 only.

c Completed the study is defined as completing the final double-blind planned evaluation.

6.9.1.2. All Subjects With At Least 1 Dose of AA4500 0.58 mg

Subject disposition is summarized in Table 15. Of the 1082 subjects who received at least 1 injection of AA4500 0.58 mg, 948 subjects (87.6%) completed the study and 134 subjects (12.4%) prematurely discontinued. The primary reasons for discontinuation were lost to follow-up and withdrawal of consent; as was seen in the double-blind, placebo controlled studies, few (<1%) subjects discontinued due to AEs.

Table 15: Subject Disposition - All Subjects With At Least 1 Dose of AA4500 0.58 mg^a

	AA4500 (N=1082)
Study number, ^b n (%)	
202	73 (6.7)
303	23 (2.1)
404	12 (1.1)
851/852	5 (0.5)
853	17 (1.6)
854	379 (35.0)
855	16 (1.5)
856	195 (18.0)
857	204 (18.9)
858	95 (8.8)
859	63 (5.8)
Completion status, n (%)	
Completed ^c	948 (87.6)
Ongoing	0
Discontinued	134 (12.4)
Withdrew consent	33 (3.0)
Lost to follow-up	53 (4.9)
AEs	7 (0.6)
Administrative reasons	4 (0.4)
Protocol violation	11 (1.0)
Lack of efficacy	3 (0.3)
Died ^d	4 (0.4)
Other	19 (1.8)

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

b Subjects enrolled in more than 1 study were counted in the study in which they received their first injection of AA4500 0.58 mg.

c Completed the study was defined as completing the final planned evaluation. For subjects enrolled in multiple studies, completion status was based on the final study enrolled.

d Determination of death was based on either the end of study page or the AE page.

6.9.2. Extent of Exposure

6.9.2.1. Phase 3 Double-Blind, Placebo-Controlled Studies

The extent of exposure for the *Phase 3 Double-Blind, Placebo-Controlled* analysis population is summarized in Table 16. Four hundred nine (409) subjects (272 AA4500 0.58 mg and 137 placebo) had 532 (392 AA4500 0.58 mg and 140 placebo) Dupuytren's cords treated with 990 (597 AA4500 0.58 mg and 393 placebo) injections of study drug. The median duration of subject participation in the double-blind phase of the study was 92.0 days.

Table 16: Extent of Exposure - Phase 3 Double-Blind, Placebo-Controlled Studies^a

Statistic	AA4500 0.58 mg (N=272)	Placebo (N=137)
Number of injections received, n (%)		
1	80 (29.4)	5 (3.6)
2	59 (21.7)	8 (5.8)
3	133 (48.9)	124 (90.5)
Total Number of Injections Received	597	393
Number of cords injected, n (%)		
1	175 (64.3)	134 (97.8)
2	74 (27.2)	3 (2.2)
3	23 (8.5)	0 (0.0)
Total cords injected	392	140
Number of MP cords injected, n (%)		
0	85 (31.3)	49 (35.8)
1	158 (58.1)	88 (64.2)
2	28 (10.3)	0 (0.0)
3	1 (0.4)	0 (0.0)
Total MP cords injected	217	88
Number of PIP cords injected, n (%)		
0	122 (44.9)	86 (62.8)
1	130 (47.8)	50 (36.5)
2	15 (5.5)	1 (0.7)
3	5 (1.8)	0 (0.0)
Total PIP cords injected	175	52
Duration in study (days) ^b		
Mean (SD)	112.5 (78.91)	97.1 (31.75)
Median	92.0	92.0
Min, Max	2, 597	2, 288

a Includes all subjects who received at least 1 injection of double-blind study medication (placebo or AA4500 0.58 mg).

b From day of first injection of double-blind study medication to last double-blind visit (AUX-CC-857 or AUX-CC-859) or the last clinical visit (DUPY-303).

6.9.2.2. All Subjects With At Least 1 Dose of AA4500 0.58 mg

The extent of exposure for the *All Subjects With At Least 1 Dose of AA4500 0.58 mg* analysis population is summarized in Table 17. One thousand eighty-two (1082) subjects had 1780 Dupuytren's cords treated with 2630 injections of study drug. Most (61.2%) subjects received 1 or 2 injections of study drug.

Table 17: Extent of Exposure - All Subjects With At Least 1 Dose of AA4500 0.58 mg^a

Statistic	AA4500 0.58 mg (N=1082)
Number of AA4500 injections received, n (%)	
1	443 (40.9)
2	219 (20.2)
3	170 (15.7)
4	93 (8.6)
5	116 (10.7)
6	14 (1.3)
7	13 (1.2)
8	14 (1.3)
Total Number of Injections –Received	2630
Number of cords injected, n (%)	
1	615 (56.8)
2	295 (27.3)
3	127 (11.7)
4	34 (3.1)
5	8 (0.7)
6	3 (0.3)
Total cords injected	1780
Number of MP cords injected, n (%)	
0	291 (26.9)
1	583 (53.9)
2	175 (16.2)
3	29 (2.7)
4	4 (0.4)
Total MP cords injected	1036
Number of PIP cords injected, n (%)	
0	502 (46.4)
1	455 (42.1)
2	91 (8.4)
3	30 (2.8)
4	4 (0.4)
Total PIP cords injected	743 ^b

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

b A single DIP joint was treated in DUPY-202 (Total IP = 744)

The duration of exposure for the all subjects who received at least 1 dose of AA4500 0.58 mg is summarized in Table 18. The median duration of subject participation overall was 275.0 days.

Table 18: Duration of Exposure - All Subjects With At Least 1 Dose of AA4500 0.58 mg^a

Duration (Days)	AA4500 0.58 mg (N=1082)
Overall duration ^b	
Mean (SD)	289.1 (139.09)
Median	275.0
Min, Max	2, 2446
Treatment phase ^c	
Mean (SD)	98.5 (113.11)
Median	64.0
Min, Max	2, 2039
Posttreatment phase ^d	
Mean (SD)	190.6 (100.4)
Median	212.0
Min, Max	0, 658

- a Includes all subjects who received at least 1 injection of AA4500 0.58 mg.
- b From day of first injection of AA4500 0.58 mg to the end of study visit. For subjects enrolled in more than 1 study, duration was the sum overall duration from each study.
- c From day of first injection of AA4500 0.58 mg to Day 30 visit after the last injection of AA4500. For subjects enrolled in more than 1 study, duration was the sum treatment phase duration from each study.
- d From Day 30 visit after the last injection of AA4500 0.58 mg + 1 to the end of study visit. For subjects enrolled in more than 1 study, duration was the sum posttreatment phase duration from each study.

6.9.3. Analysis of Adverse Events

6.9.3.1. Phase 3 Double-Blind, Placebo-Controlled Studies

The overall percentage of subjects with TEAEs and treatment-related AEs from the first dose of AA4500 0.58 mg to the end of the study in the *Phase 3 Double-Blind, Placebo-Controlled* analysis population is presented in Table 19. Overall, 97.8% of subjects treated with AA4500 0.58 mg reported at least 1 TEAE during the double-blind study compared with 54.0% of subjects treated with placebo.

Table 19: First Dose to End of Double-Blind Study:^a Overall Summary of Treatment-Emergent and Treatment-Related Adverse Events - Phase 3 Double-Blind, Placebo-Controlled Studies^b

	AA4500 (N=272) n (%)	Placebo (N=137) n (%)
Total number of injections	597	393
Total number of TEAEs reported ^c	1999	143
Total number of treatment-related AEs reported ^d	1871	68
Number of subjects reporting:		
At least 1 TEAE	266 (97.8)	74 (54.0)
At least 1 treatment-related AE	265 (97.4)	36 (26.3)
At least 1 treatment-emergent SAE	10 (3.7)	2 (1.5)
At least 1 treatment-related SAE	4 (1.5)	0 (0.0)
At least 1 moderate/severe TEAE	178 (65.4)	25 (18.2)
At least 1 TEAE leading to discontinuation	3 (1.1)	0 (0.0)

a Includes all AEs with a start date on or after the date of the first double-blind injection to last double-blind visit.

b Includes all subjects who received at least 1 injection of double-blind study medication (placebo or AA4500 0.58 mg).

c Total number of AEs reported included the same AE occurring multiple times for a subject being counted at each occurrence.

d Includes all AEs with a start date on or after the date of the first double-blind injection to last double-blind visit and with a relationship to study medication of possible or probable.

6.9.3.2. All Subjects With At Least 1 Dose of AA4500 0.58 mg

The overall percentage of subjects with at least one TEAE reported overall (ie, first injection of AA4500 0.58 mg to the end of the study) is presented in Table 20.

Table 20: First Dose of AA4500 0.58 mg to End of Study^a: Overall Summary of Treatment-Emergent Adverse Events - All Subjects With At Least 1 Dose of AA4500 0.58 mg^b

	AA4500 0.58 mg (N=1082) n (%)
Total number of injections	2630
Total number of TEAEs reported ^c	9907
Total number of treatment-related AEs reported ^d	8697
Number of subjects reporting:	
At least 1 TEAE	1064 (98.3)
At least 1 treatment-related AE	1051 (97.1)
At least 1 treatment-emergent SAE	92 (8.5)
At least 1 treatment-related SAE	9 (0.8)
At least 1 moderate/severe TEAE	784 (72.5)
At least 1 TEAE leading to discontinuation	9 (0.8)
Number of deaths	7 (0.6)

a Included all AEs with a start date on or after the date of the first injection of AA4500 0.58 mg.

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

c Total number of AEs reported included the same AE occurring multiple times for a subject being counted at each occurrence.

d Included all AEs with a start date on or after the date of the first injection of AA4500 0.58 mg and with a relationship to study drug of either possible or probable.

6.9.4. Common Adverse Events

6.9.4.1. Phase 3 Double-Blind, Placebo-Controlled Studies

Treatment-emergent adverse events (TEAEs) occurring in $\geq 2.0\%$ of subjects from the first dose to the end of the double-blind studies for the *Phase 3 Double-Blind, Placebo-Controlled* analysis population is presented in Table 21.

The majority of subjects treated with AA4500 0.58 mg had higher rates of TEAEs and treatment-related AEs compared with subjects treated with placebo. The most frequently reported ($\geq 25.0\%$ in either treatment group) TEAEs were edema peripheral, contusion, injection site pain, injection site hemorrhage, and pain in extremity.

Table 21: Percentage of Subjects With Treatment-Emergent Adverse Events ($\geq 2.0\%$ of Subjects in Either Treatment Group) - First Dose to End of Double-Blind Study - Phase 3 Double-Blind, Placebo-Controlled Studies^a

Preferred Term^b	AA4500 0.58 mg (N=272) n (%)	Placebo (N=137) n (%)
Number (%) of subjects with ≥ 1 AE	266 (97.8)	74 (54.0)
Edema peripheral	206 (75.7)	7 (5.1)
Contusion ^c	138 (50.7)	4 (2.9)
Injection site pain	106 (39.0)	13 (9.5)
Injection site hemorrhage	95 (34.9)	4 (2.9)
Pain in extremity	90 (33.1)	5 (3.6)
Injection site swelling	59 (21.7)	7 (5.1)
Tenderness	63 (23.2)	0 (0.0)
Ecchymosis	63 (23.2)	0 (0.0)
Lymphadenopathy	41 (15.1)	0 (0.0)
Pruritus	33 (12.1)	1 (0.7)
Skin laceration	25 (9.2)	0 (0.0)
Lymph node pain	21 (7.7)	0 (0.0)
Blood blister	20 (7.4)	0 (0.0)
Nasopharyngitis	9 (3.3)	10 (7.3)
Axillary pain	15 (5.5)	0 (0.0)
Erythema	15 (5.5)	0 (0.0)
Injection site pruritus	14 (5.1)	0 (0.0)
Arthralgia	11 (4.0)	2 (1.5)
Blister	11 (4.0)	0 (0.0)
Headache	8 (2.9)	5 (3.6)
Inflammation	8 (2.9)	0 (0.0)
Paresthesia	7 (2.6)	2 (1.5)
Hypoesthesia	6 (2.2)	0 (0.0)
Injection site vesicles	6 (2.2)	1 (0.7)
Joint swelling	6 (2.2)	0 (0.0)
Swelling	6 (2.2)	0 (0.0)
Hypertension	4 (1.5)	4 (2.9)
Sinusitis	4 (1.5)	3 (2.2)
Upper respiratory tract infection	4 (1.5)	6 (4.4)
Hypercholesterolemia	0 (0.0)	3 (2.2)

Note: Table includes TEAEs occurring in $\geq 2.0\%$ of subjects in either treatment group. The corresponding treatment-related AE incidence rates are also displayed.

- a Includes all subjects who received at least 1 injection of double-blind study medication (placebo or AA4500 0.58 mg).
- b Preferred term was coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary (Version 8.0). If multiple AEs were reported for a given preferred term, only 1 event was counted per subject.
- c 1 subject's report of contusion (considered treatment related) was mapped to musculoskeletal and connective tissue disorders system organ class (SOC); the remainder were mapped to injury, poisoning and procedural complications SOC.

6.9.4.2. All Subjects With At Least 1 Dose of AA4500 0.58 mg

6.9.4.2.1. First Dose to the End of the Study

Treatment-emergent AEs occurring in $\geq 2.0\%$ of subjects overall (ie, first injection of AA4500 0.58 mg to the end of the study) are presented in Table 22. The most frequently reported TEAEs ($\geq 25.0\%$) were: edema peripheral, contusion, injection site pain, pain in extremity, injection site hemorrhage, and tenderness.

Table 22: Percentage of Subjects With Treatment-Emergent Adverse Events ($\geq 2.0\%$ of Subjects) and Treatment-Related Adverse Events – First Dose AA4500 to End of Study - All Subjects With At Least 1 Dose of AA4500 0.58 mg^a

Preferred Term ^b	AA4500 0.58 mg (N=1082) n (%)	
	All Adverse Events ^c	Treatment-Related Adverse Events ^d
Number (%) of subjects with ≥ 1 AE	1062 (98.2)	1051 (97.1)
Edema peripheral	833 (77.0)	830 (76.7)
Contusion ^e	590 (54.5)	586 (54.2)
Injection site pain	442 (40.9)	439 (40.6)
Pain in extremity	405 (37.4)	387 (35.8)
Injection site hemorrhage	373 (34.5)	368 (34.0)
Tenderness	317 (29.3)	308 (28.5)
Injection site swelling	267 (24.7)	265 (24.5)
Ecchymosis	196 (18.1)	194 (17.9)
Pruritus	137 (12.7)	135 (12.5)
Skin laceration	137 (12.7)	118 (10.9)
Lymphadenopathy	119 (11.0)	118 (10.9)
Blood blister	97 (9.0)	97 (9.0)
Axillary pain	73 (6.7)	72 (6.7)
Hematoma	60 (5.5)	56 (5.2)
Injection site pruritus	57 (5.3)	57 (5.3)
Arthralgia	53 (4.9)	37 (3.4)
Erythema	50 (4.6)	39 (3.6)
Injection site vesicles	48 (4.4)	48 (4.4)
Lymph node pain	41 (3.8)	40 (3.7)
Nasopharyngitis	41 (3.8)	3 (0.3)
Pain	40 (3.7)	37 (3.4)
Joint swelling	37 (3.4)	31 (2.9)
Swelling	34 (3.1)	32 (3.0)
Headache	32 (3.0)	21 (1.9)
Dizziness	30 (2.8)	17 (1.6)
Paresthesia	27 (2.5)	23 (2.1)
Edema	26 (2.4)	25 (2.3)
Blister	26 (2.4)	25 (2.3)
Upper respiratory tract infection	26 (2.4)	2 (0.2)
Hypoesthesia	22 (2.0)	18 (1.7)

Note: Table includes TEAEs occurring in $\geq 2.0\%$ of subjects. The corresponding treatment-related AE incidence rates are also displayed.

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

b Preferred term was coded using MedDRA dictionary (Version 8.0). If multiple AEs were reported for a given preferred term, only 1 event was counted per subject.

c Includes AEs with a start date on or after the date of the first injection of AA4500 0.58 mg.

d Includes AEs with a start date on or after the date of the first double-blind injection to last double-blind visit and have a relationship to study medication of possible, probable, or missing.

e 1 subject's report of contusion (considered treatment related) was mapped to musculoskeletal and connective tissue disorders SOC; the remainder were mapped to injury, poisoning and procedural complications SOC.

6.9.4.2.2. Treatment Period (First Dose to 30 Days Post Last Dose)

Treatment-emergent AEs occurring in $\geq 2.0\%$ of subjects during the treatment period (ie, first dose of AA4500 0.58 mg to 30 days after the last injection) are presented in Table 23. The most frequently reported TEAEs ($\geq 25.0\%$) during the treatment period were: edema peripheral, contusion, injection site pain, pain in extremity, injection site hemorrhage, and tenderness.

Table 23: Percentage of Subjects With Treatment-Emergent Adverse Events ($\geq 2.0\%$ of Subjects) and Treatment-Related Adverse Events - First Dose AA4500 0.58 mg to 30 Days Post-Last Dose - All Subjects With At Least 1 Dose of AA4500 0.58 mg^a

Preferred Term ^b	AA4500 0.58 mg (N=1082) n (%)	
	All Adverse Events ^c	Treatment-Related Adverse Events ^d
Number (%) of subjects with ≥ 1 AE	1061 (98.1)	1050 (97.0)
Edema peripheral	833 (77.0)	830 (76.7)
Contusion ^e	590 (54.6)	586 (54.2)
Injection site pain	440 (40.7)	437 (40.4)
Pain in extremity	394 (36.4)	381 (35.2)
Injection site hemorrhage	373 (34.5)	368 (34.0)
Tenderness	309 (28.6)	301 (27.8)
Injection site swelling	266 (24.6)	264 (24.4)
Ecchymosis	196 (18.1)	194 (17.9)
Pruritus	135 (12.5)	135 (12.5)
Skin laceration	131 (12.1)	118 (10.9)
Lymphadenopathy	119 (11.0)	118 (10.9)
Blood blister	97 (9.0)	97 (9.0)
Axillary pain	73 (6.7)	72 (6.7)
Hematoma	60 (5.5)	56 (5.2)
Injection site pruritus	56 (5.2)	56 (5.2)
Erythema	48 (4.4)	39 (3.6)
Injection site vesicles	48 (4.4)	48 (4.4)
Arthralgia	43 (4.0)	33 (3.0)
Lymph node pain	40 (3.7)	40 (3.7)
Pain	40 (3.7)	37 (3.4)
Joint swelling	37 (3.4)	31 (2.9)
Nasopharyngitis	36 (3.3)	1 (0.1)
Swelling	34 (3.1)	32 (3.0)
Headache	30 (2.8)	21 (1.9)
Dizziness	24 (2.2)	17 (1.6)
Edema	26 (2.4)	25 (2.3)
Blister	26 (2.4)	25 (2.3)

Note: Table includes TEAEs occurring in $\geq 2.0\%$ of subjects. The corresponding treatment-related AE incidence rates are also displayed.

- a Includes all subjects who received at least 1 injection of AA4500 0.58 mg.
- b Preferred term was coded using MedDRA dictionary (Version 8.0). If multiple AEs were reported for a given preferred term, only 1 event was counted per subject.
- c Includes all AEs with a start date on or after the date of the first injection of AA4500 0.58 mg to the Day 30 visit after the last injection of AA4500. If the Day 30 visit was missing then the next available visit after the Day 7 visit after the last injection was used.
- d Includes all AEs with a start date on or after the date of the first injection AA4500 0.58 mg to the Day 30 visit after the last injection of AA4500 and have a relationship to study drug of either possible, probable, or missing. If the Day 30 visit was missing then the next available visit after the Day 7 visit after the last injection was used.
- e 1 subject's report of contusion (considered treatment related) was mapped to musculoskeletal and connective tissue disorders SOC; the remainder were mapped to injury, poisoning and procedural complications SOC.

6.9.4.2.3. Posttreatment Period (From Day 31 After Last Injection Through End of Study)

Of 1082 subjects who received at least 1 dose of AA4500 0.58 mg, only recurrence of contracture or other findings related to Dupuytren's disease that did not meet the definition of recurrence (preferred term: Dupuytren's contracture) and pain in the extremity occurred in $\geq 2.0\%$ of subjects during the posttreatment period (ie, Day 31 after the last injection of AA4500 0.58 mg through the end of study). The relatively low overall rate of TEAEs reported during the posttreatment period compared with the treatment period (32.3% versus 98.1%) support a temporal relationship between the AA4500 injection or subsequent manipulation and the TEAEs observed in the clinical program.

Table 24: Percentage of Subjects With Treatment-Emergent Adverse Events ($\geq 2.0\%$ of Subjects) - First Dose AA4500 0.58 mg to 30 Days Post-Last Dose - All Subjects With At Least 1 Dose of AA4500 0.58 mg^a

Preferred Term ^b	AA4500 0.58 mg (N=1082) n (%)
Number (%) of subjects with ≥ 1 AE	350 (32.3)
Dupuytren's contracture	33 (3.0)
Pain in extremity	25 (2.3)

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

b Preferred term was coded using MedDRA dictionary (Version 8.0). If multiple AEs were reported for a given preferred term, only 1 event was counted per subject.

6.9.4.3. Deaths, Other Serious, and Other Significant Adverse Events

6.9.4.3.1. Deaths

A total of seven subjects died during the course of a study. None of these deaths were considered by the investigator to be related to study drug. The estimated mortality rate in the US population is 1564.6/100,000 people aged 55 years to 74 years. Based on this rate, one might have expected 17 deaths to occur in our clinical program of 1082 subjects.

DUPY-101:

- Subject 10008, a 75-year old male with a 20 year history of emphysema (pulmonary fibrosis) and atherosclerosis, died on (b) (6) from cardiopulmonary arrest, acute and chronic respiratory failure, idiopathic pulmonary fibrosis, bilateral pneumocystis, and coronary artery disease approximately 1 year (b) (6) after his second injection of AA4500 10,000 units (equivalent to 0.58 mg) in Study DUPY-101. The death was considered by the investigator to be unrelated to study medication.
- Subject 100028, a 68-year old male with a history of hypertension, cardiac disease (placement of 3 pacemakers), diabetes, high cholesterol, and rheumatoid arthritis died on (b) (6) from rupture of an aortic aneurysm approximately 2 months (b) (6) after his second injection of AA4500 10,000 units (equivalent to 0.58 mg) in Study DUPY-101. The death was considered by the investigator to be unrelated to study medication.

DUPY-202:

- Subject 004.CMP was a 63-year-old white man with a history of hearing loss in his left ear, hypertension, insulin dependent diabetes mellitus, and hemicolectomy for colon cancer, which was performed approximately 9 years before he entered the study. The subject received three injections of AA4500 (2500 U on (b) (6); 10,000 U (equivalent to 0.58 mg) on (b) (6) and (b) (6)). On (b) (6) the subject reported cough, pain, pyrexia, and weight decreased, all of which were considered by the investigator to be mild in intensity, except for weight decreased, which was moderate. All were considered by the investigator to be possibly related to study drug. The subject was last examined in the clinic on (b) (6). Subsequent to this clinic visit (b) (6) the subject's wife called the investigator and reported that he had been diagnosed with liver cancer and needed to discontinue the study to undergo chemotherapy. The sponsor subsequently contacted the investigative site for details and on (b) (6) the investigator confirmed that the liver cancer was a serious adverse event, which was unrelated to study drug. The investigator noted in the serious adverse event reporting form that the subject had subsequently died but the date of death was not listed. Additionally, there were no pathology results describing the tumor.
- Subject 101.CMP, a 68-year old male with a history of emphysema, cluster headaches, and prostate cancer that was treated with radioactive seed implants received one placebo injection on (b) (6) and two injections of AA4500 10,000 U (equivalent to 0.58 mg) on (b) (6) and (b) (6) respectively. Approximately 5 months after his last injection (b) (6) the subject was hospitalized for severe iliac artery stenosis. He died on (b) (6) from end-stage chronic obstructive pulmonary disease. The death was considered unrelated to study drug.

AUX-CC-854

- Subject 6002-4242 was a 76-year-old white male with a history of emphysema, coronary disease, hypertension, high cholesterol, epilepsy, prostate cancer, and acute myocardial infarctions in 1997 and 2006. Concomitant medications included acetylsalicylic acid, budesonide, ramipril, inegy, metoprolol, and levetiracetam. AA4500 was administered (b) (6). On (b) (6) (Day 261), the subject experienced a myocardial infarction that was considered by the investigator to be not related to study drug. The subject died six days later.

AUX-CC-856

- Subject 1168-7010 was a 77-year-old white male with a history of glaucoma, arthritis, arteriosclerotic heart disease, and hyperlipidemia. Concomitant medications included dorzolamide hydrochloride/timolol maleate, travoprost, vitamin D, calcium, saw palmetto, vitamin E, magnesium, cold liver oil, fish oil, iodine, vitamin C, glucosamine hydrochloride/chondroitin sulfate, grape seed extract, multivitamin with lycopene, sustained release niacin, riboflavin, niacin, thymine, folate, vitamin B, vitamin B6, garlic, coenzyme Q10, selenium, and lycopene. AA4500 was administered (b) (6). On (b) (6) (Day 157), the subject experienced a myocardial infarction, resulting in death that was considered by the investigator to be not related to study drug.
- Subject 1178-7704 was a 79-year-old white male with a history of allergies, nasal congestion, seasonal rhinitis, cough, heartburn, decreased uric acid, hyperlipidemia, diabetes, hypothyroidism, diuresis, hypertension, and periungual infection. Concomitant medications included fexofenadine, mometasone furoate, loratadine, guaifenesin, ranitidine, acetylsalicylic acid, allopurinol, fenofibrate, nicotinic acid, glipizide, levothyroxine sodium, indapamide, captopril, multivitamin, calcium, vitamin D, and cephalexin. AA4500 was administered (b) (6). On (b) (6) (Day 180), the subject experienced an acute myocardial infarction (preferred term: acute myocardial infarction), resulting in death that was considered by the investigator to be not related to study drug.

6.9.4.3.2. Other Serious Adverse Events

A total of 92 subjects who received at least one dose of AA4500 0.58 mg experienced at least one nonfatal serious AE (SAE) across the 13 studies. Nine of these subjects had at least one SAE that was possibly or probably related to study drug. The majority of treatment-related SAEs were related to events of the hand. Four of these were related to effect of AA4500 on collagen (three tendon ruptures and one ligament injury [pulley injury]). Other SAEs related to events of the hand included tendonitis, finger deformity, and Dupuytren's contracture (Table 25).

Table 25: Serious Adverse Events At Least Possibly Related to Study Drug by the Investigator

Subject Number	Age/ Gender	Total # of Injections Received	Preferred Term/ Verbatim Term	Onset Day (days since last injection)/ Stop Day	Severity/ Relationship	Action Taken	SAE Code	Relevant History
AUX-CC-854								
6003-4314	62/M	1	Deep vein thrombosis/ Left leg deep vein thrombosis	2 (2)/resolving	Moderate/ Possible	Dose not changed/ medication given	Other medically important event	Subject reported extended period of automobile driving at the time of the event.
6008-4705	47/M	4	Tendonitis/Hypertrophic tendonitis and intrasubstance but not complete tear	147 (14)/the subject was managed conservatively and chose to decline further follow-up; therefore, the final outcome is unknown.	Moderate/ Probable	Dose not changed	Other medically important event	1 day after 3 rd injection subject performed self manipulation of cord.
AUX-CC-855								
1167-1011	62/M	1	Tendon rupture/Rupture of 5 th (right) digit flexor digitorum profundus	1 (1)/the subject underwent fusion of the DIP of the affected 5 th digit due to preexisting Boutonniere deformity. The subject tolerated the procedure well and at the time of the report the event was resolving.	Severe/ Probable	Dose not changed	Other medically important event	Boutonniere deformity pre-injection
AUX-CC-857								
1154-2710	61/M	1	Tendon rupture/ Left small finger flexor tendon rupture	8 (8)/276	Moderate/ Probable	Dose not changed	Persistent or significant disability incapacity	Occurred while the subject was pulling a several hundred pound palette at work.

F=female; M=male

Table 25: Serious Adverse Events At Least Possibly Related to Study Drug by the Investigator (continued)

Subject Number	Age/ Gender	Total # of Injections Received	Preferred Term/ Verbatim Term	Onset Day (days since last injection)/ Stop Day	Severity/ Relationship	Action Taken	SAE Code	Relevant History
AUX-CC-857								
1157-4201	66/F	1	Complex regional pain syndrome/Complex regional pain syndrome	13 (13)/at the time of the last report the event was resolving.	Moderate/ Probable	Medication given/drug withdrawn	Persistent or significant disability incapacity	Previous history of complex regional pain syndrome after surgery.
1157-4203	76/M	3	Tendon rupture/Left 5 th tendon rupture FDS and FDP	61 (7)/279	Severe/ Probable	Dose not changed	Persistent or significant disability incapacity	No relevant history
AUX-CC-858								
1170-3816	66/F	1	Finger deformity/ Boutonniere deformity L little dip	208 (27)/ongoing	Mild/ Probable	Dose not changed	Other medically important event	No relevant history
AUX-CC-859 (double-blind)								
6003-1601	61/M	2	Ligament injury/ Flexion pulley rupture of left little finger	71 (43)/238	Severe/ Probable	Dose not changed	Other medically important event	History of osteoarthritis
AUX-CC-859 (open-label)								
6002-1502	51/M	2	Dupuytren's contracture/ Proliferation of Dupuytren's cord (left hand)	182 (153)/resolved 10FEB09	Moderate/ Probable	Dose not changed	Other medically important event	5 months after 2 nd injection subject thought cord was thicker and that there was decreased sensation.
			Sensory disturbance/Sensory abnormality of left hand	182 (153)/resolved 10FEB09	Moderate/ Probable	Dose not changed	Other medically important event	

F=female; M=male

6.9.4.3.3. Adverse Events Leading to Discontinuation

Across the 13 studies, 9 subjects had a nonfatal AE recorded as a primary or secondary reason for premature discontinuation (Table 26). Only 3 events (injection site pain, dizziness, complex regional pain syndrome) were considered by the investigator to be at least possibly related to study drug.

Table 26: Subjects With Nonfatal Adverse Events Leading to Discontinuation

Subject Number	Age/ Gender	Total # Inj. Rec'd	Preferred Term/ Verbatim Term	Onset Day (days since last injection)/ Stop Day	Severity/ Relationship	Action Taken
DUPY-202						
202-004-C-MP	63/M	3	Liver cancer (was not coded for preferred term)	455/ unknown	Unknown/ Not related	Discontinued
AUX-CC-851/852						
1154-2001	66/M	1	Prostate cancer metastatic/ Metastatic prostate cancer	42 (42)/ongoing	Severe/ Not related	Drug Withdrawn/ Medication given
			Prostate cancer/ Prostate cancer	42 (42)/ongoing	Severe/ Not related	Drug Withdrawn/ Medication given
AUX-CC-854						
6005-4403	61/M	1	Gastrointestinal carcinoma/ Bowel cancer	27 (27)/91	Severe/ Not related	Drug Withdrawn
6003-4305	76/M	2	Pancreatic carcinoma/Pancreatic cancer	252 (70)/ ongoing	Severe/ Not related	Drug Withdrawn
AUX-CC-856						
1176-7408	60/M	2	Lung neoplasm malignant/Lung cancer	52 (22)/ongoing	Severe/ Not related	Drug withdrawn
AUX-CC-857						
1153-2921	64/M	1	Injection site pain/ Pain at injection site	0/60	Severe/ Probable	Drug withdrawn/ Medication given
1155-3105	68/M	1	Dizziness/Feeling faint	28 (28)/ 28	Mild/ Probable	Drug withdrawn
1157-4201	66/F	1	Complex regional pain syndrome/Complex regional pain syndrome	13 (13)/ ongoing	Moderate/ Probable	Drug withdrawn/ Medication given
1158-2602	75/M	1	Myocardial infarction/ Myocardial infarction	98 (38)/ 110	Severe/ Not related	Drug withdrawn

F=female; M=male

6.9.4.4. Analysis of Treatment-Related Adverse Events

Further analysis of treatment-related AEs that occurred during the treatment period (first dose to 30 days post last dose) in the all subjects who received at least 1 dose of AA4500 0.58 mg demonstrated that the majority of treatment-related AEs either began on the day of injection or on the day of the finger extension procedure. Most treatment-related AEs resolved without intervention before the next scheduled injection of AA4500 0.58 mg.

6.9.5. Clinical Laboratory Parameters: Individual Clinically Significant Abnormalities

6.9.5.1. Phase 3 Double-Blind, Placebo-Controlled Studies

The number and percentage of subjects with Sponsor-defined potentially clinically significant laboratory values in the *Phase 3 Double-Blind, Placebo-Controlled* analysis population are presented in Table 27. The percentage of subjects with clinically significant laboratory values was low and similar between the treatment groups.

Table 27: Summary of Sponsor-Defined Clinically Significant Laboratory Values: Phase 3 Double-Blind, Placebo-Controlled Studies^a

Laboratory Parameter	SI Criteria	AA4500 0.58 mg (N=249)		Placebo (N=125)	
		n ^b	n (%)	n ^b	n (%)
Hematology					
Hematocrit	CS+: ≥ 0.6 L/L	239	0 (0.0)	120	0 (0.0)
	CS-: ≤ 0.3 L/L	239	0 (0.0)	120	0 (0.0)
Hemoglobin	CS+: ≥ 190 g/L (female), ≥ 200 g/L (male)	239	0 (0.0)	120	0 (0.0)
	CS-: ≤ 100 g/L (female), ≤ 110 g/L (male)	239	2 (0.8)	120	0 (0.0)
Platelets	CS+: $\geq 650 \times 10^9$ /L	238	0 (0.0)	120	0 (0.0)
	CS-: $\leq 100 \times 10^9$ /L	238	2 (0.8)	120	0 (0.0)
Chemistry					
BUN	CS+: ≥ 12 mmol/L	237	3 (1.3)	120	1 (0.8)
Creatinine	CS+: ≥ 300 mmol/L	237	0 (0.0)	120	0 (0.0)
ALT (U/L)	CS+: 3xULN	235	0 (0.0)	120	1 (0.8)
AST (U/L)	CS+: 3xULN	235	2 (0.9)	120	1 (0.8)

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

a Includes all subjects who received at least 1 injection of double-blind study medication (placebo or AA4500 0.58 mg).

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

6.9.5.2. All Subjects With At Least 1 Dose of AA4500 0.58 mg

The number and percentage of subjects with potentially clinically significant laboratory values among subjects who received at least 1 dose of AA4500 0.58 mg are presented in Table 28. The percentage of subjects with clinically significant laboratory values was low and similar to that observed among subjects treated with placebo. Of subjects who had a clinically significant laboratory value, 7 subjects had their findings reported as non-serious AEs

Table 28: Sponsor-Defined Clinically Significant Laboratory Values: All Subjects With At Least 1 Dose of AA4500 0.58 mg^a

		AA4500 0.58 mg N=974	
Laboratory Parameter	SI Criteria	n ^b	N (%)
Hematology			
Hematocrit	CS+: ≥ 0.6 L/L	924	0 (0.0)
	CS-: ≤ 0.3 L/L	924	1 (0.1)
Hemoglobin	CS+: ≥ 190 g/L (female), ≥ 200 g/L (male)	927	0 (0.0)
	CS-: ≤ 100 g/L (female), ≤ 110 g/L (male)	927	4 (0.4)
Platelets	CS+: ≥ 650 GI/L	923	1 (0.1)
	CS-: ≤ 100 GI/L	923	4 (0.4)
Chemistry			
BUN	CS+: ≥ 12 mmol/L	925	9 (1.0)
Creatinine	CS+: ≥ 300 μ mol/L	925	0 (0.0)
ALT (U/L)	CS+: > 3 xULN	924	6 (0.7)
AST (U/L)	CS+: > 3 xULN	923	6 (0.7)

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

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

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

6.9.6. Vital Signs: Individual Clinically Significant Abnormalities

6.9.6.1. Phase 3 Double-Blind, Placebo-Controlled Studies

The number and percentage of subjects with Sponsor-defined potentially clinically significant vital sign values in the *Phase 3 Double-Blind, Placebo-Controlled* analysis population are presented in Table 29. Similar percentages of subjects with clinically significant vital sign values were observed between AA4500 0.58 mg and placebo.

Table 29: Summary of Sponsor-Defined Clinically Significant Vital Sign Values: Change From Baseline to Final Assessment - Phase 3 Double-Blind, Placebo-Controlled Studies^a

Vital Sign	Criteria	AA4500 0.58 mg (N=272) n (%)	Placebo (N=137) n (%)
Systolic blood pressure	CS+: ≥ 180 mmHg and increase ≥ 20 mmHg from baseline	24 (8.8)	12 (8.8)
	CS-: ≤ 90 mmHg and decrease ≥ 20 mmHg from baseline	6 (2.2)	5 (3.6)
Diastolic blood pressure	CS+: ≥ 105 mmHg and increase ≥ 15 mmHg from baseline	26 (9.6)	8 (5.8)
	CS-: ≤ 50 mmHg and decrease ≥ 15 mmHg from baseline	9 (3.3)	10 (7.3)
Heart rate	CS+: ≥ 120 bpm and increase ≥ 15 bpm from baseline	3 (1.1)	2 (1.5)
	CS-: ≤ 50 bpm and decrease ≥ 15 bpm from baseline	10 (3.7)	4 (2.9)
Respiratory rate	CS+: ≥ 25 rpm and increase ≥ 7 rpm from baseline	3 (1.1)	2 (1.5)
	CS-: ≤ 8 rpm and decrease ≥ 7 rpm from baseline	5 (1.8)	2 (1.5)
Temperature	CS+: ≥ 38.3 °C and increase ≥ 1.1 °C from baseline	0 (0.0)	0 (0.0)

Note: Baseline is last available vital sign measurement prior to the first injection of double-blind study medication.

CS+ = clinically significant high, CS- = clinically significant low, bpm=beats per minute, rpm=respirations per minute

a Includes all subjects who received at least 1 injection of double-blind study medication (placebo or AA4500 0.58 mg).

6.9.6.2. All Subjects With At Least 1 Dose of AA4500 0.58 mg

The number and percentage of subjects with sponsor-defined potentially clinically significant vital sign values among subjects who received at least 1 dose of AA4500 0.58 mg are presented Table 30. The percentage of subjects with clinically significant vital sign values was low and similar to that observed among subjects treatment with placebo.

Table 30: Sponsor-Defined Clinically Significant Vital Sign Values: Change From Baseline to Final Assessment - All Subjects With At Least 1 Dose of AA4500 0.58 mg^a

Vital Sign	Criteria	AA4500 0.58 mg (N=1082) n (%)
Systolic blood pressure	CS+: ≥ 180 mmHg and increase ≥ 20 mmHg from baseline	118 (10.9)
	CS-: ≤ 90 mmHg and decrease ≥ 20 mmHg from baseline	31 (2.9)
Diastolic blood pressure	CS+: ≥ 105 mmHg and increase ≥ 15 mmHg from baseline	99 (9.1)
	CS-: ≤ 50 mmHg and decrease ≥ 15 mmHg from baseline	36 (3.3)
Heart rate	CS+: ≥ 120 bpm and increase ≥ 15 bpm from baseline	9 (0.8)
	CS-: ≤ 50 bpm and decrease ≥ 15 bpm from baseline	43 (4.0)
Respiratory rate	CS+: ≥ 25 rpm and increase ≥ 7 rpm from baseline	13 (1.2)
	CS-: ≤ 8 rpm and decrease ≥ 7 rpm from baseline	6 (0.6)
Temperature	CS+: ≥ 38.3 °C and increase ≥ 1.1 °C from baseline	3 (0.3)

Note: Baseline is last available vital sign measurement prior to the first injection of double-blind study medication.

CS+ = clinically significant high, CS- = clinically significant low, bpm=beats per minute, rpm=respirations per minute

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

6.9.6.3. Grip Strength

In an effort to determine whether AA4500 adversely affected grip strength, grip strength was assessed using hand-held dynamometry (in kg) on the treated hand(s) throughout each study. Mean changes in hand grip strength from baseline to the final assessment hands treated with AA4500 were not considered clinically significant. None of the 1082 subjects who received at least one dose of AA4500 reported loss of grip strength as an adverse event. Treatment with AA4500 did not appear to adversely affect grip strength.

6.10. Immunogenicity

6.10.1. Anti-Drug Antibody (ADA) Responses

In Studies AUX-CC-851/852, AUX-CC-853, AUX-CC-854, AUX-CC-856, AUX-CC-857, AUX-CC-858, and AUX-CC-859, serum samples were collected from all subjects at screening and 30 days after each injection and at the 6 month, 9 month, and 12 month follow-up visits, as applicable. Validated sandwich enzyme-linked immunosorbent assay (ELISA) methods were used to determine the presence of anti-AUX-I and anti-AUX-II antibodies in serum samples. Antibody levels in positive samples were semi-quantified by the determination of antibody titers. Four subjects had positive AUX-I and AUX-II titers at baseline due to receiving an injection of

collagenase in a previous clinical study. The adverse event profiles for each of these four subjects was similar in both studies.

Most subjects ($\geq 85.7\%$) were confirmed positive for the presence of antibodies to AUX-I and/or AUX-II 30 days after the first injection of AA4500 (Figure 13 and Figure 14, respectively). All subjects were confirmed positive for the presence of antibodies to both AUX-I and AUX-II after the third or fourth injection of AA4500 0.58 mg.

Figure 13: Percentage of Subjects With Positive Anti-AUX-I Titers and Log Mean Titer Levels Across Injections 1 through 8 - AA4500 0.58 mg Intent-to-Treat Population

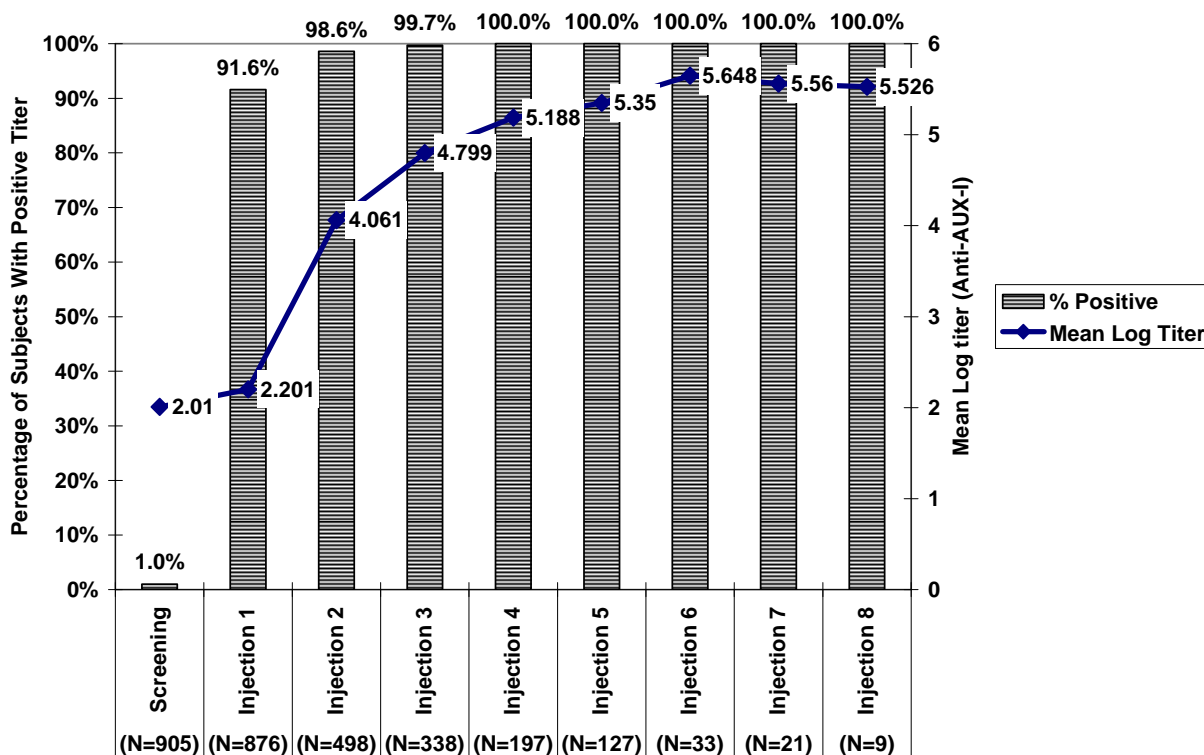
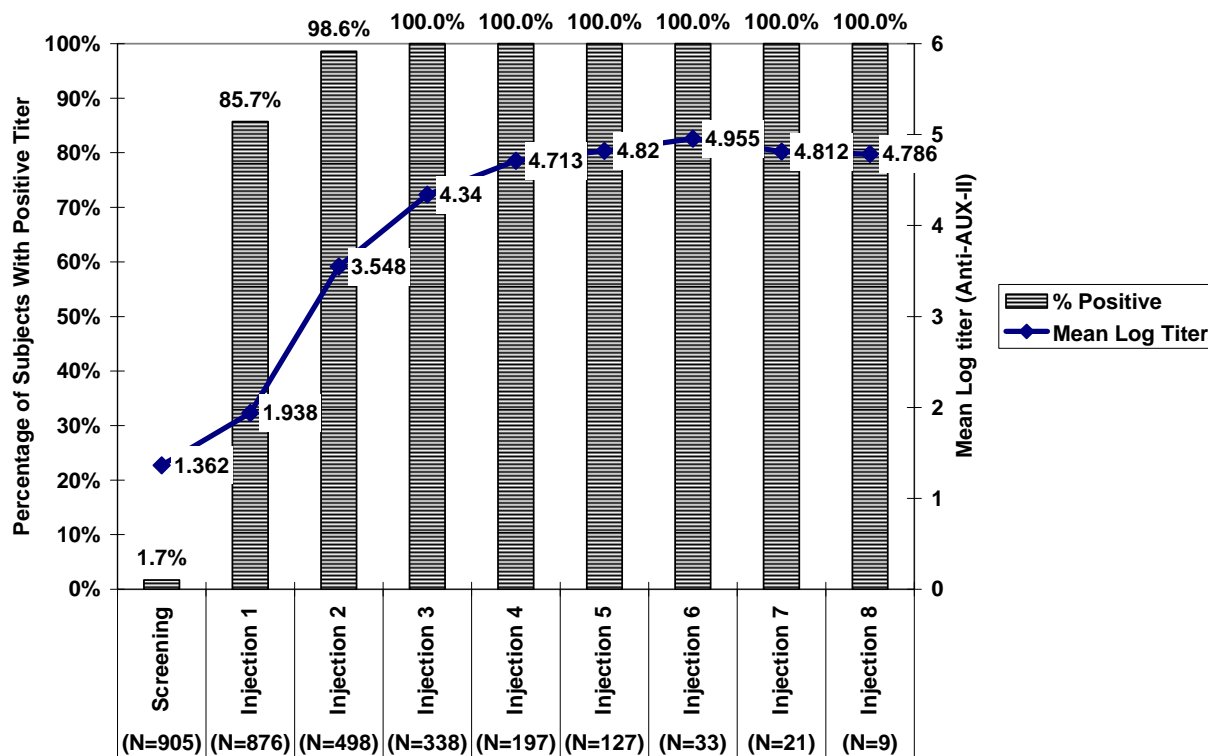
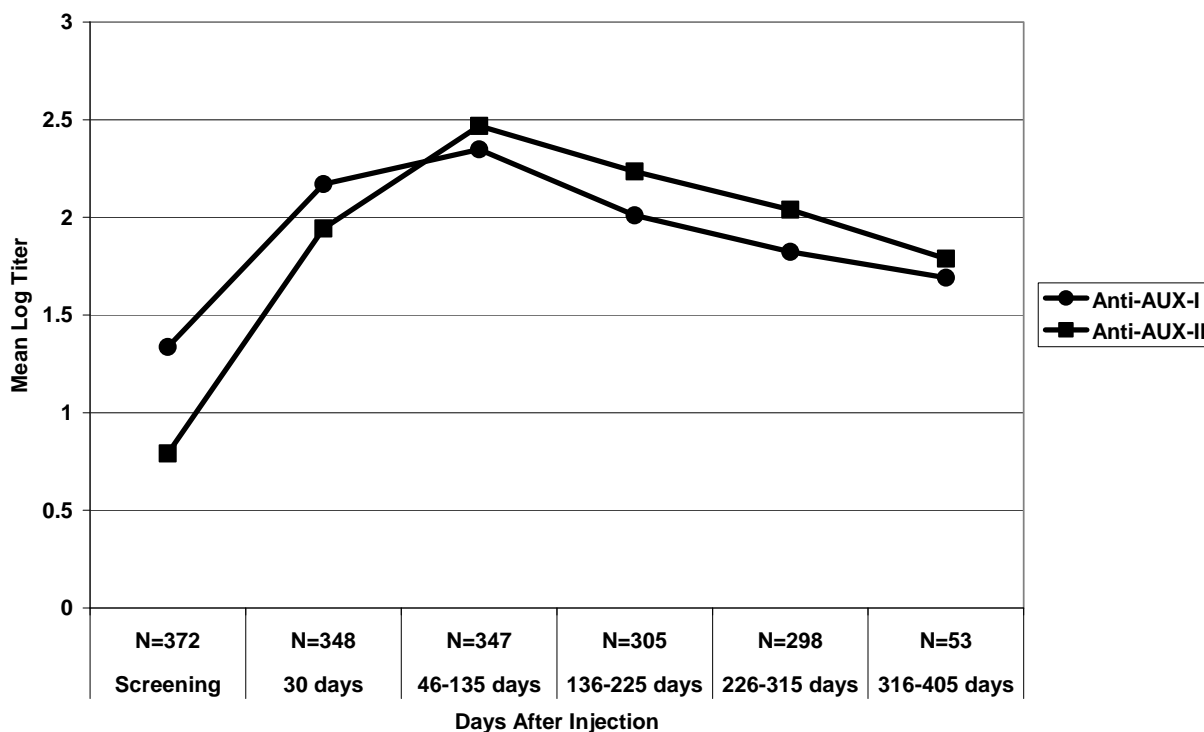


Figure 14: Percentage of Subjects With Positive Anti-AUX-II Titers and Log Mean Titer Levels Across Injections 1 through 8 - AA4500 0.58 mg Intent to Treat Population



When titers levels were examined by the total number of AA4500 injections received, anti-AUX-I and anti-AUX-II titers decreased during the follow-up period after the last injection. This trend (ie, diminution of titer levels after the last injection) is clearly demonstrated over the approximately 1 year follow-up in subjects who received a single injection of AA4500 (Figure 15).

Figure 15: Anti-AUX-I and Anti-AUX-II Titers Over Time – Subjects Who Received a Single Injection of AA4500 0.58 mg



6.10.2. Neutralizing Antibodies to AUX-I and AUX-II

Two assays were developed and validated to measure the capacity of ADAs to inhibit the enzymatic activity of AUX-I and AUX-II, respectively.

The limited volume of a human positive control serum precluded estimation of the sensitivity of the neutralizing antibody assays in terms of mass units of IgG. Thus, at the present time, this assay can be used only in the qualitative sense to investigate whether serum samples confirmed as positive in the ADA bridging ELISAs have the capacity to inhibit the enzymatic activity of AUX-I or AUX-II. Nevertheless, percentage of inhibition values are available from the neutralizing assay and have been assessed for possible correlation with the magnitude or the ADA response measured in the ELISA format.

6.10.3. Neutralizing Potential of ADAs

Serum samples were collected from each subject treated with AA4500 0.58 mg in Study AUX-CC-857 and assayed to determine the ability of ADAs present in human serum to inhibit the activity of AUX-I and AUX-II.

Despite the high rate (100%) of seroconversion and ADA titers, only 22 of 200 samples among subjects who received AA4500 had neutralizing activity against AUX-I and 44 of 204 samples had neutralizing activity against AUX-II. The distribution of positive samples for the neutralizing assay by quartile of ADA titer is summarized in Table 31.

Table 31: Comparison of ADA Titer vs. Positive Result in Enzyme Activity Neutralization Assay by ADA Titer Quartile – Subjects Who Received AA4500 in Study AUX-CC-857

ADA Titer by Quartile	Proportion Positive in Neutralization Assay	
	AUX-I	AUX-II
Upper quartile	13/50 (26%)	24/51 (47%)
2 nd quartile	5/50 (10%)	16/51 (31%)
3 rd quartile	1/50 (2%)	3/51 (6%)
Lower quartile	3/50 (6%)	1/51 (2%)
Negative	8/175 (5%)	9/171 (5%)

While these data show a trend toward an association between the magnitude of ADA titer detected in the ELISA and a positive result in the neutralizing assay, there was not a consistent correlation between presence of ADA titer and positive classification in the neutralization assays. A number of samples exhibiting very high ADA titers did not inhibit AUX-I or AUX-II enzyme activity, while others that were negative for the presence of ADA by ELISA were positive in the neutralizing assay.

6.10.4. Antibody-Mediated Effects on Subject Safety

6.10.4.1. Analyses Performed

In order to evaluate the potential impact of anti-AUX-I and anti-AUX-II antibodies on the safety profile of AA4500, multiple analyses were performed.

1. Medical review of safety database for adverse events coded as hypersensitivity.
2. Analysis of the rate of the adverse events in subjects with up to 8 injections of AA4500.
3. Analysis of the severity of adverse events and anti-AUX-I and anti-AUX-II antibody titers.
4. Analysis of the duration of adverse events by injection cohort in subjects receiving up to 8 injections of AA4500.
5. Analysis of the safety database for other adverse events possibly consistent with immunologic events.
6. Analysis of the safety database for adverse events consistent with inhibition of MMPs.
7. Analysis of the safety database for evidence of systemic anaphylactic reactions.

6.10.4.2. Adverse Events Coded as Hypersensitivity

Eight adverse events were coded as hypersensitivity reactions. According to the investigator, 5 of these events were non-related (rash behind knee, nasal allergy, allergic symptoms, allergic cough, and swollen lip from possible bee sting [reported after the BLA]) and 3 were considered related (local allergic reactions of redness itch, heat, and swelling of the treated hand). None of the events coded as hypersensitivity were consistent with a clinically meaningful systemic hypersensitivity event.

6.10.4.3. Rate of Adverse Events in Subjects With up to Eight Doses of AA4500

The rates of the four most frequently reported adverse events and the four events possibly consistent with an immunologic event were examined in the safety population of 1082 subjects who received at least one dose of AA4500 (0.58 mg). If anti-drug antibodies were to negatively affect subject safety, it could be expected that adverse event rates would increase as antibody titers increase (ie, with increasing numbers of injections). Among subjects who received up to eight injections of AA4500, there was no consistent pattern of increasing adverse event rates with increasing numbers of injections of AA4500 (and therefore increasing antibody titers) (Table 32). It is also important to note that the frequency of reported adverse events was consistent between the first and subsequent injections.

Table 32: Most Frequently Reported Treatment-Related Adverse Events and Those Possibly Consistent With an Immunologic Event by Injection Number - First Dose AA4500 0.58 mg to 30 Days Post-Last Dose - All Subjects With At Least 1 Dose of AA4500 0.58 mg^a

Preferred Term ^b	AA4500 0.58 mg							
	Injection 1 (N=1082)	Injection 2 (N=639)	Injection 3 (N=420)	Injection 4 (N=250)	Injection 5 (N=157)	Injection 6 (N=41)	Injection 7 (N=27)	Injection 8 (N=14)
Number (%) of subjects with ≥ 1 treatment-related AE	1028 (95.0)	603 (94.4)	381 (90.7)	230 (92.0)	139 (88.5)	36 (87.8)	25 (92.6)	13 (92.9)
Peripheral edema	727 (67.2)	406 (63.5)	256 (61.0)	165 (66.0)	110 (70.1)	30 (73.2)	21 (77.8)	11 (78.6)
Contusion ^c	514 (47.5)	238 (37.2)	125 (29.8)	71 (28.4)	48 (30.6)	12 (19.3)	10 (37.0)	4 (28.6)
Injection site pain	346 (32.0)	171 (26.8)	112 (26.7)	55 (22.0)	39 (24.8)	11 (26.8)	7 (25.9)	4 (28.6)
Pain in extremity	278 (25.7)	142 (22.2)	78 (18.6)	42 (16.8)	21 (13.4)	7 (17.1)	6 (22.2)	2 (14.3)
Injection site swelling	179 (16.5)	117 (18.3)	84 (20.0)	49 (19.6)	26 (16.6)	6 (14.6)	2 (7.4)	2 (14.3)
Pruritus	40 (3.7)	50 (7.8)	50 (11.9)	25 (10.0)	25 (15.9)	9 (22.0)	3 (11.1)	2 (14.3)
Lymphadenopathy	91 (8.4)	29 (4.5)	15 (3.6)	7 (2.8)	2 (1.3)	0 (0.0)	1 (3.7)	0 (0.0)
Injection site pruritus	17 (1.6)	15 (2.3)	19 (4.5)	15 (6.0)	9 (5.7)	1 (2.4)	2 (7.4)	0 (0.0)

Note: Includes the four most frequently reported treatment-related TEAEs, and four possibly consistent with an immunologic event and have a relationship to study drug of either possible, probable, or missing.

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

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

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

6.10.4.4. Adverse Event Severity and Anti-AUX-I and Anti-AUX-II Antibody Titers

The severity of adverse events was examined in relation to anti-AUX-I and anti-AUX-II antibody titers in subjects who received AA4500 in Studies AUX-CC-851/852, -853, -854, -856, -857, -858, and -859. If anti-drug antibodies were to negatively affect safety, it could be expected that adverse event severity would correlate with antibody titers (severe adverse events would have higher mean log antibody titers than moderate, mild, or no adverse events). In these studies, the data demonstrate there was no correlation between the absence or presence of an adverse event, or the severity of that adverse event and anti-AUX-I or anti-AUX-II antibody titers. Figure 16 through Figure 23 compare the AA4500 antibody titers to the absence / degree of severity of the four most frequently reported treatment-related adverse events and the four events possibly consistent with an immunologic event.

Figure 16: Edema Peripheral: Anti-AUX-I and Anti-AUX-II Antibody Titer and Adverse Event Severity

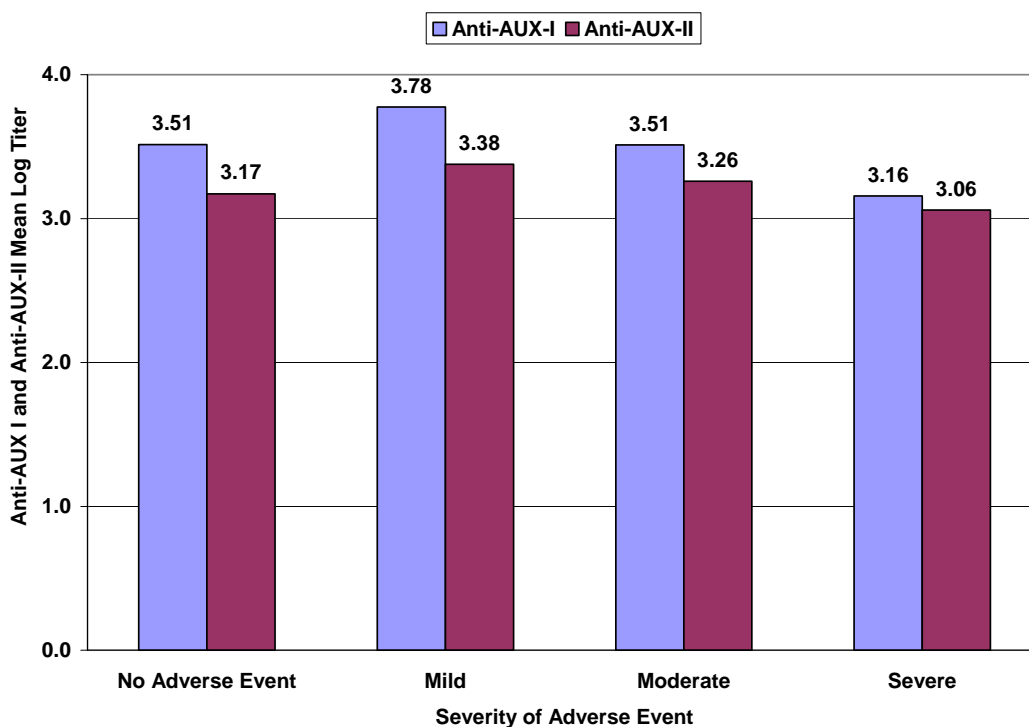


Figure 17: Contusion: Anti-AUX-I and Anti-AUX-II Antibody Titer and Adverse Event Severity

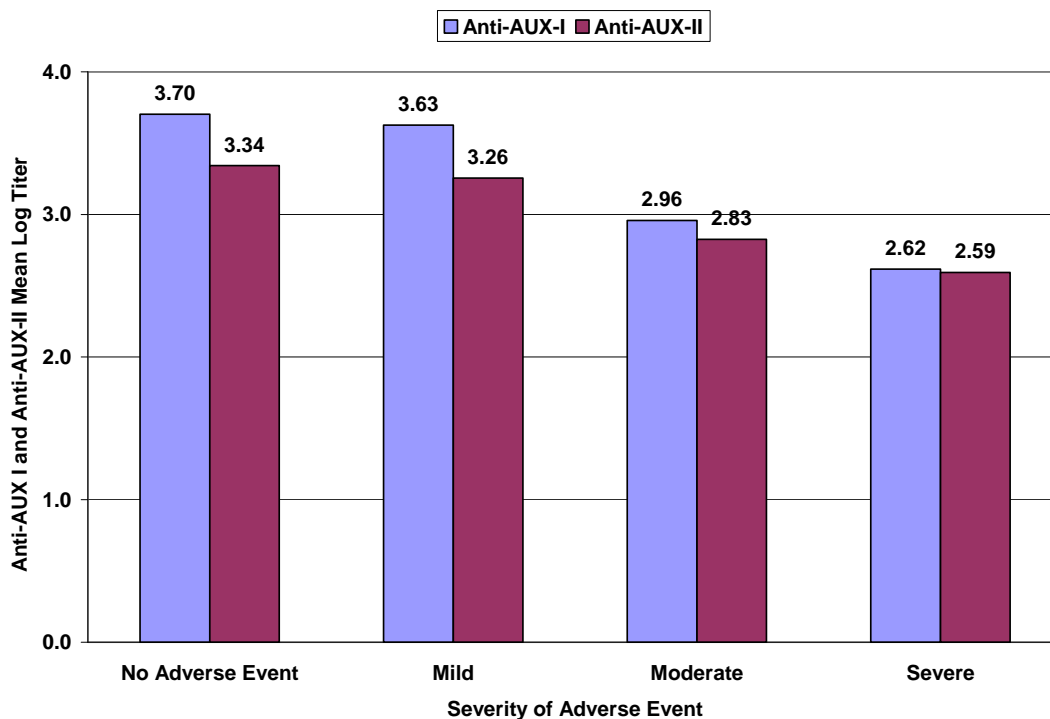


Figure 18: Injection Site Pain: Anti-AUX-I and Anti-AUX-II Antibody Titer and Adverse Event Severity

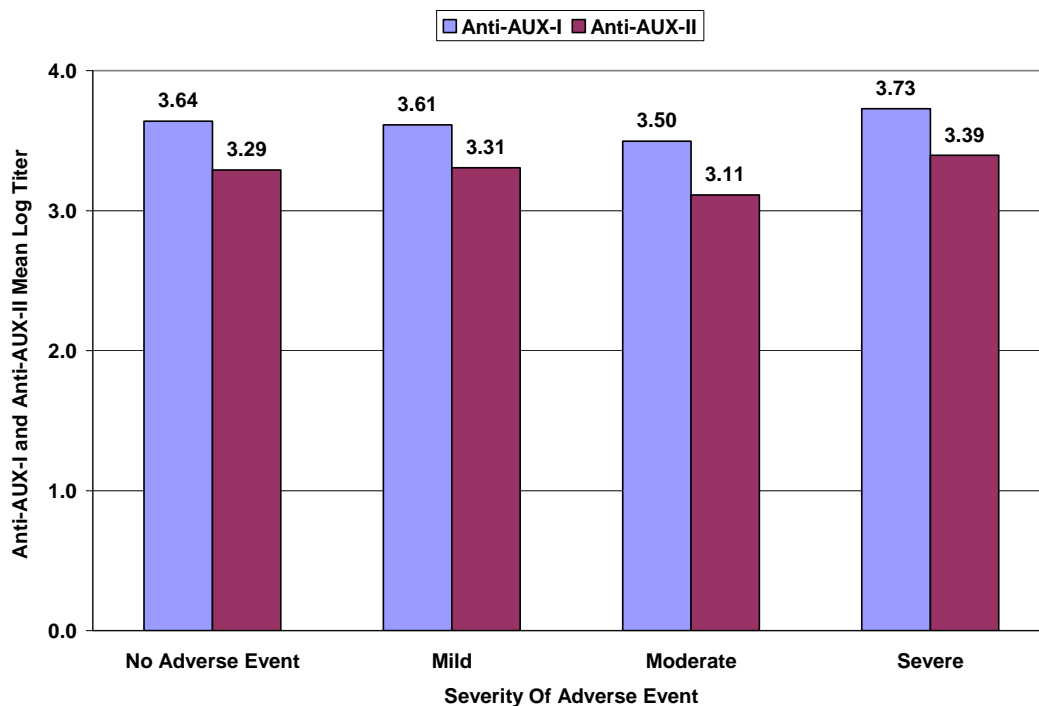


Figure 19: Extremity Pain: Anti-AUX-I and Anti-AUX-II Antibody Titer and Adverse Event Severity

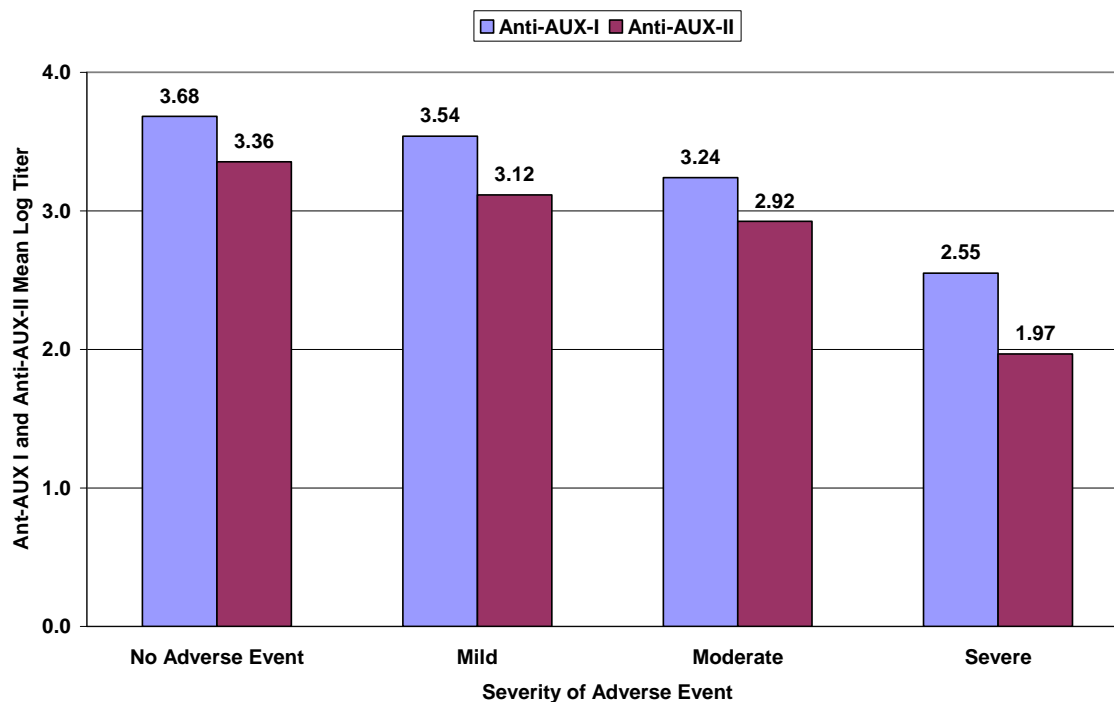


Figure 20: Injection Site Swelling: Anti-AUX-I and Anti-AUX-II Antibody Titer and Adverse Event Severity

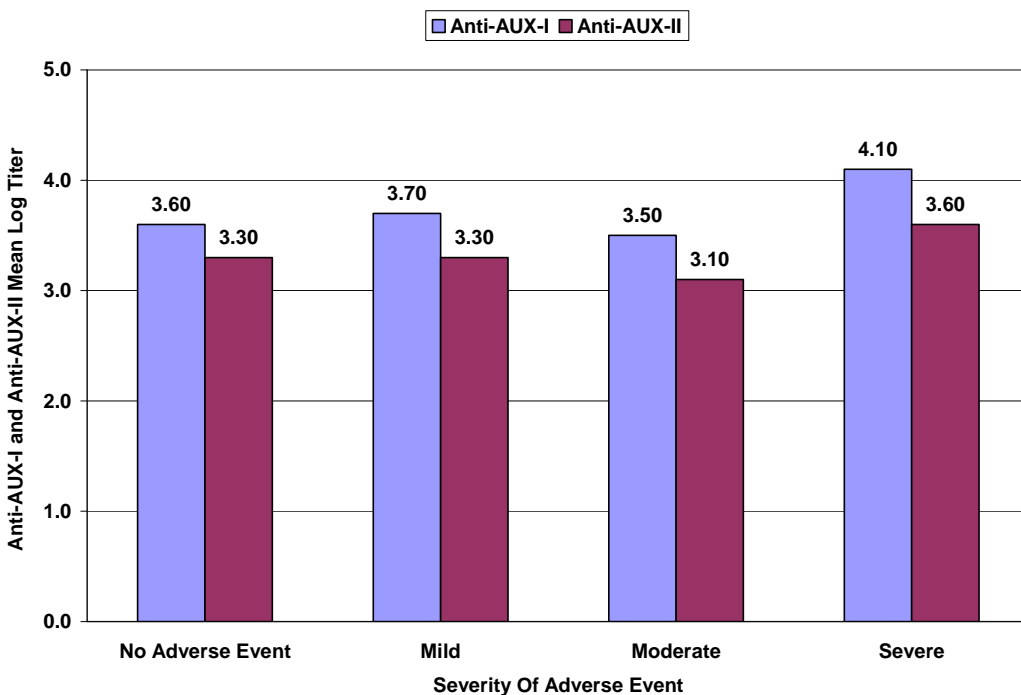


Figure 21: Pruritus: Anti-AUX-I and Anti-AUX-II Antibody Titer and Adverse Event Severity

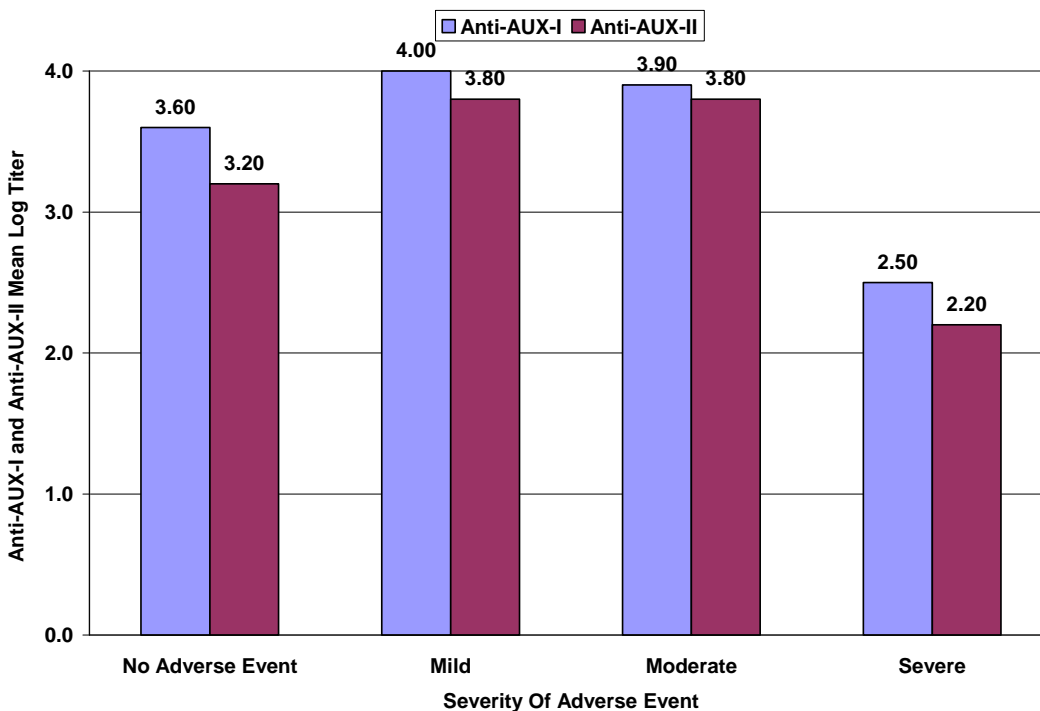


Figure 22: Lymphadenopathy: Anti-AUX-I and Anti-AUX-II Antibody Titer and Adverse Event Severity

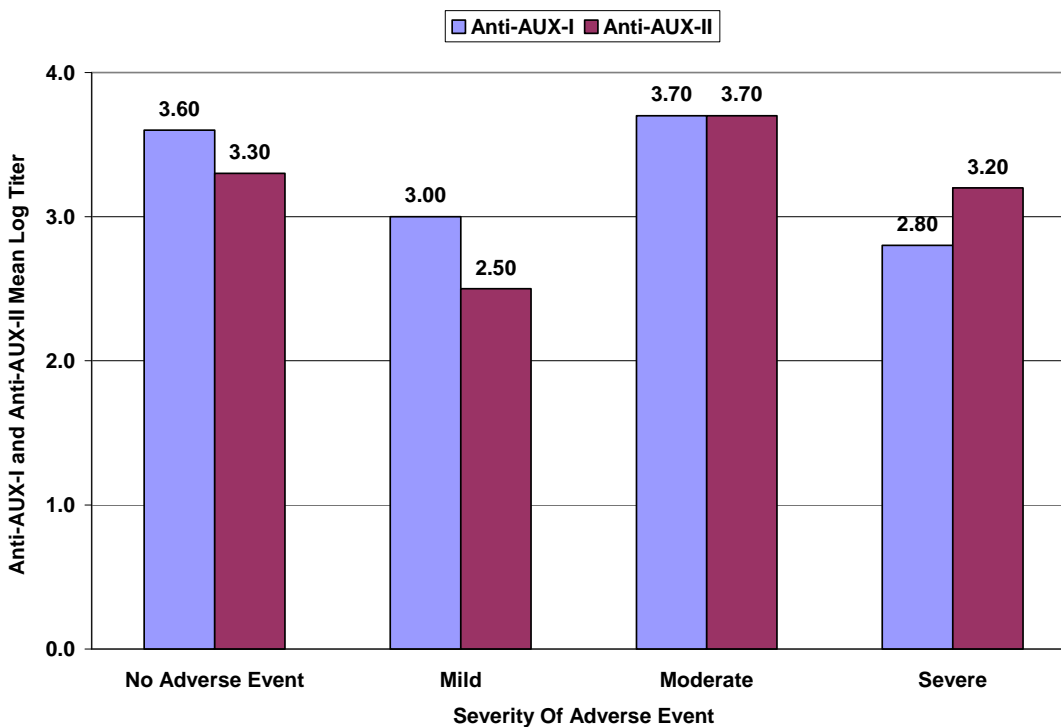
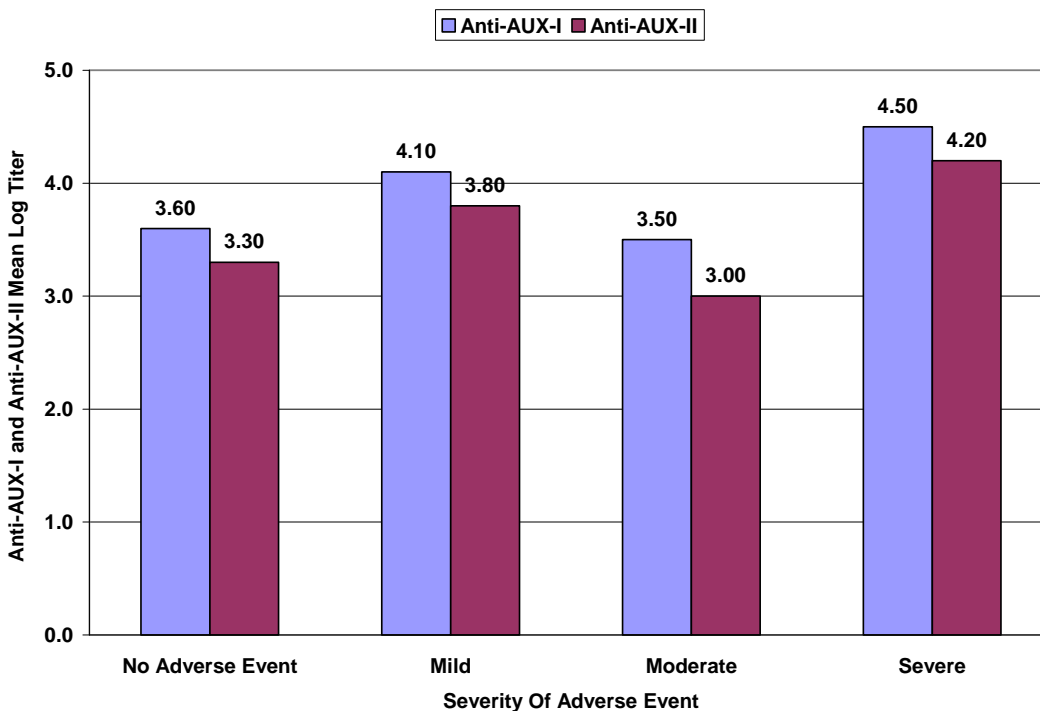


Figure 23: Injection Site Pruritus: Anti-AUX-I and Anti-AUX-II Antibody Titer and Adverse Event Severity



6.10.4.5. Duration of Adverse Events and Anti-AUX-I and Anti-AUX-II Antibody Titers

The durations of the four most frequently reported adverse events and the four events possibly consistent with an immunologic event were examined in the safety population of 1082 subjects who received at least one dose of AA4500 (0.58 mg). If anti-drug antibodies negatively affected safety, it could be expected that the duration of adverse events would increase as antibody titers increase. As demonstrated in Table 33, the median duration of adverse events did not increase with increasing numbers of injections of AA4500 (and therefore increasing antibody titers). It is also important to note that adverse event duration was consistent between the first and subsequent injections.

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Table 33: Most Frequently Reported Treatment-Related Adverse Events and Those Possibly Consistent With an Immunologic Event by Median Duration (Days) and Injection Number - All Subjects With At Least 1 Dose of AA4500 0.58 mg

Preferred Term	AA4500 0.58 mg							
	Injection 1 (N=1082)	Injection 2 (N=639)	Injection 3 (N=420)	Injection 4 (N=250)	Injection 5 (N=157)	Injection 6 (N=41)	Injection 7 (N=27)	Injection 8 (N=14)
Peripheral edema								
N	712	399	250	162	107	30	21	10
Median	11.0	9.0	8.0	8.0	7.0	5.0	5.0	6.0
Contusion ^a								
N	500	231	117	68	45	11	10	3
Median	15.0	14.0	14.0	10.5	7.0	11.0	4.5	8.0
Injection site pain								
N	335	160	111	54	37	11	7	4
Median	15.0	13.0	8.0	10.5	11.0	10.0	15.0	8.5
Pain in extremity								
N	269	135	73	41	21	7	6	2
Median	9.0	8.0	8.0	8.0	5.0	6.0	14.0	3.0
Injection site swelling								
N	172	111	82	48	25	6	2	2
Median	14.0	10.0	8.0	8.0	9.0	17.5	25.5	17.0
Pruritus								
N	40	50	49	25	25	9	3	2
Median	4.0	4.0	3.0	2.0	2.0	2.0	1.0	1.5
Lymphadenopathy								
N	90	29	14	7	2	0	1	0
Median	7.0	6.0	8.5	6.0	47.5		5.0	
Injection site pruritus								
N	17	15	19	15	9	1	2	0
Median	3.0	4.0	2.0	2.0	1.0	1.0	2.0	

Note: Includes four most frequently reported treatment-related TEAEs, and four possibly consistent with an immunologic event and have a relationship to study drug of either possible, probable, or missing.

Note: Duration of treatment-related AEs was the date resolved - the onset date + 1. If the AE occurred more than once within an injection cycle for a given subject, the duration was the sum duration from all the AEs minus the number of overlapping days.

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

NA = not applicable

a One additional event of contusion was mapped to musculoskeletal and connective tissue disorders SOC.

6.10.4.6. Other Adverse Events Possibly Consistent With Immunologic Events

There was no evidence of any clinically meaningful systemic hypersensitivity events in the AA4500 clinical program. The safety database was reviewed for terms in addition to “hypersensitivity” possibly suggestive of/or consistent with localized or systemic hypersensitivity events. These included the most common adverse events identified previously (edema peripheral, lymphadenopathy, pruritus) as well as others which could be suggestive of an immunologic event. These included urticaria (hives), generalized rash, and allergy.

There were three cases of urticaria (hives) identified in the AA4500 clinical program as follows:

- Subject DUPY 101 – 10033C-MP – 55 year old male subject experienced hives on his right forearm following injection number six to his left hand. This was managed with diphenhydramine with resolution. There is no further information available for this subject.
- Subject AUX-CC-856 – 1178-7711 – 64 year old male complained of hives on his lower back and hips four days after his second injection with AA4500. He was managed with a medrol dose pack and the complaint resolved without sequelae. He was later retreated with AA4500 approximately 30 days later without premedication and without the re-appearance of hives.
- Subject AUX-CC-856 – 1166-7902 – 72 year old male subject reported hives on his trunk and axilla three weeks after his third injection of AA4500. He was treated with levocetirizine for 4 days and the hives resolved. He later received a 4th and 5th injection of AA4500 without premedication and without the re-appearance of hives.

6.10.4.7. Adverse Events Possibly Consistent With Inhibition of MMPs

The potential for anti-AUX-I or anti-AUX-II antibodies to cross react with and neutralize (inhibit) mammalian MMPs was evaluated by comparison of the adverse events noted in seropositive patients with those described in the published literature following the use of broad-spectrum MMP inhibitors in clinical trials. These products have been studied in clinical trial settings for potential therapeutic indications including oncology uses and osteoarthritis. In these clinical programs, dosing was limited or discontinued due to the appearance of a characteristic set of side effects mediated by broad spectrum MMP inhibition. In one such program (PG116800) a definition of MMP inhibitor-associated musculoskeletal syndrome (MSS) was used to describe these effects, which included painless loss of range of motion (ROM) in large joints (particularly in the shoulders), joint stiffness and joint swelling, soft tissue pain, and fibrosis of palmar tendons (Dupuytren’s contracture) (Krzieski et al., 2007; Bramhall et al., 2002).

In the AA4500 clinical program, medical review of all treatment-emergent adverse events across the clinical studies revealed no safety signals related to the inhibition of endogenous collagenases (MMPs). Specifically, there were no reports of musculoskeletal events such as polyarthritis, osteolysis, and shoulder girdle pain or reduction of ROM that would be indicative of cross reactivity resulting in inhibition of endogenous collagenases among subjects who received up to eight injections of AA4500. Joint stiffness and swelling was found in the treated hand following the first dose (in the absence of anti-drug antibodies) as well as following subsequent doses. It is important to note there was no evidence of worsening of Dupuytren’s

disease as a result of treatment with AA4500, as would be anticipated with significant inhibition of MMPs by anti-AUX-I or anti-AUX-II in this patient population.

6.10.4.8. Systemic Anaphylactic Events

Medical review of the clinical safety database revealed no events indicative of systemic anaphylaxis in any subject who received AA4500.

6.11. Safety Conclusions

The safety of AA4500 was assessed in Phase 1, 2, and 3 clinical studies conducted in 1082 subjects with Dupuytren's disease. This represents 2630 injections and treatment of 1780 Dupuytren's cords. The safety results of these studies demonstrate that:

- The most frequently reported TEAEs ($\geq 25.0\%$) among subjects who received at least 1 injection of AA4500 0.58 mg were local events of edema peripheral, contusion, injection site pain, pain in extremity, injection site hemorrhage, and tenderness. These events tended to be of mild or moderate severity and resolved prior to the next dose of AA4500.
- Eleven subjects, all of whom received at least 1 injection of AA4500 0.58 mg, had at least 1 treatment-related SAE. The majority of treatment-related SAEs were related to events of the hand (3 subjects had tendon ruptures and 1 subject each had tendonitis, finger deformity, ligament injury [pulley injury], and Dupuytren's contracture). To further minimize the risk of tendon rupture and other potential adverse events following approval, Auxilium has designed a comprehensive risk management plan to mitigate this risk.
- There were seven deaths in the clinical program. None were considered related to the study drug by the investigator.
- The percentage of subjects with clinically significant laboratory or vital sign values was similar between the AA4500 and the placebo groups.
- Mean changes in hand grip strength from baseline to the final assessment for the primary and secondary hand were not considered clinically significant. None of the 1082 subjects who received at least one dose of AA4500 reported loss of grip strength as an adverse event.
- Most subjects ($\geq 85.8\%$) developed antibodies to AUX-I and/or AUX-II 30 days after the first injection of AA4500. All subjects developed positive antibodies to both AUX-I and AUX-II after the third or fourth injection of AA4500. When titers levels were examined by the total number of AA4500 injections received, anti-AUX-I and anti-AUX-II titers decreased during the follow-up period after the last injection.
- There was a trend toward an association between the magnitude of ADA titer detected in the ELISA and a positive result in the neutralizing assay; however, there was not a consistent correlation between the presence of ADA titers and positive classification in the neutralization assays.

- Anti-drug antibody titers were not predictive of the rate, severity, or duration of adverse events. This suggests that anti-drug antibodies, while present in virtually all subjects, did not affect the safety profile of AA4500.
- The AA4500 clinical safety database did not show a treatment associated risk of immune-mediated adverse events. Adverse events observed in the clinical program did not suggest any clinical findings due to cross reactivity with MMPs.
- There were no systemic anaphylactic events in the clinical program.

7. BENEFITS AND RISKS CONCLUSIONS

7.1. Benefits

AA4500, collagenase clostridium histolyticum, administered by intralesional injection into the Dupuytren's cord, provides a novel, non-surgical treatment for Dupuytren's contracture. This acute, intermittent non-systemic treatment may be administered in an office setting. The injection of the clostridial collagenase into the pathologic structure, which is composed predominantly of collagen, followed by a finger extension procedure, allows for the local disruption of the cord. This cord disruption produces correction of the offending contracture and may preclude the resultant morbidity and extensive recovery time and rehabilitation associated with invasive surgical procedures. After successful treatment with AA4500, most subjects should be able to return to most activities of daily living almost immediately, and without the requirement for adjunctive therapy, such as physical therapy of the hand.

The data presented in this application demonstrate that AA4500 significantly reduces contracture caused by advanced Dupuytren's disease, which would have otherwise required surgical intervention. In each of the three double-blind, placebo-controlled studies, AA4500 0.58 mg was significantly superior to placebo with respect to the percentage of subjects who achieved a reduction in contracture to 5° or less of their primary joint 30 days after the last injection ($p < 0.001$). In each study, subjects treated with AA4500 0.58 mg had a greater reduction in baseline contracture, a greater increase in ROM, and a shorter time to achieve this reduction compared with subjects who received placebo.

The majority of MP joints (86.7%) and PIP joints (75.9%) of low severity ($\leq 50^\circ$ for MP, $\leq 40^\circ$ for PIP) achieved the primary endpoint of reduction in contracture to 5° or less after the last injection of AA4500. Joints with more severe contractures also responded well to treatment with AA4500. Approximately 61% of MP joints and 29% of PIP joints of high severity (MP $> 50^\circ$, PIP $> 40^\circ$) met the primary efficacy of reduction in contracture to 5° or less after treatment with AA4500. Although severely contracted joints and PIP joints were less responsive to treatment with AA4500 than were less severely contracted joints and MP joints, this finding is consistent with outcomes of surgery (Misra et al., 2007; Dias and Braybrooke, 2006; Bulstrode et al., 2005). Approximately 87% of subjects who received AA4500 in Studies AUX-CC-857 and AUX-CC-859 were very or quite satisfied with their treatment.

7.1.1. AA4500 0.58 mg and Surgery

In the three double-blind, placebo-controlled studies, AA4500 0.58 mg was effective in reducing the degree of contracture in both MP and PIP joints. After the last injection of AA4500, baseline contracture was reduced on average from 48.6° to 6.9° in MP joints, and from 54.5° to 20.4° in PIP joints. In the surgical correction of Dupuytren's contractures, two observations stand out clearly: MP joints respond to surgery much better than PIP joints, and the results following surgery of the PIP joint in the little finger are often poor (McFarlane et al., 1990).

In the three double-blind, placebo-controlled studies, most MP (86.7%) and PIP joints (75.9%) of low severity ($\leq 50^\circ$ for MP; $\leq 40^\circ$ for PIP) had a reduction in contracture to 5° or less after the last injection of AA4500, thereby demonstrating that AA4500 is a viable non-surgical,

pharmacologic treatment option for joint contractures of lesser severity that do not qualify for surgery, as well as those contractures that do qualify for surgery. It has been reported that surgical correction of low severity PIP contractures may result in worsening of the contracture (McFarlane, 1990). There was no evidence that PIP contractures were made worse after treatment with AA4500.

Joints with more severe contractures also responded to treatment with AA4500. Approximately 61% of MP joints and 29% of PIP joints of high severity had a reduction in contracture to 5° or less after treatment with AA4500. Although fewer PIP joints of high severity achieved the primary endpoint, AA4500 was efficacious in the treatment of these joints. On average following the last injection of AA4500, contracture in PIP joints of high severity was reduced from 63.2° at baseline to 25.6°. Although AA4500 has been shown to be effective in the treatment of both high and low severity contractures, the treatment response tended to be greater in joints with lower severity of contracture than in those with higher severity, consistent with that observed after surgical intervention for Dupuytren's contracture (Misra et al., 2007; Dias and Braybrooke, 2006).

The inability for a subject to flex a finger to the distal palmar crease (ie, full flexion) has been reported in 4.6% of subjects after surgical correction of Dupuytren's contracture (McFarlane and McGrouther, 1990). Furthermore, loss of finger joint mobility has also been reported to occur after surgery (Tubiana, 2000; Bulstrode et al., 2005). In the three double-blind, placebo-controlled studies, full flexion was virtually unaffected by AA4500. Treatment with AA4500 produced no detrimental effect on nerves or arteries.

Since there is no curative treatment for Dupuytren's disease, recurrence of the cord and contracture may occur. Therefore, duration of correction was evaluated in subjects with up to 12 months of follow-up and who had a reduction in contracture to 5° or less after treatment with AA4500. Recurrence was defined as an increase in joint contracture to at least 20° in the presence of a palpable cord. During the 12-month follow-up period for each subject, 30 of the 830 successfully treated Dupuytren's cords were recurrent (nominal rate of 3.6%) with an estimated rate of recurrence at 12 months of 6.7% ($\pm 1.7\%$), based on the Kaplan-Meier estimate. In contrast, depending on the type of surgery performed and the length of follow-up, contracture recurrence rates for surgery range from 2% to 60%, with an average of 33% (Rayan, 2007). Leclercq examined 38 subjects 8 to 14 years after surgery, and found a 66% rate of recurrence; 34% was reported within the first 2 years following surgery (Leclercq, 2000).

No differences in the efficacy of AA4500 were observed with regard to age, gender, body weight, BMI, or history of diabetes. It is of note that AA4500 showed no differences in efficacy in subjects with diabetes, as this group is reported to have a less robust outcome after surgery (Leclercq, 2000). Since Dupuytren's disease has a genetic component that results in its being almost exclusively present in men of Northern European ancestry (ie, Caucasian) (Brown et al., 2008; Leclercq, 2000; McFarlane et al., 1990), the majority of the subjects in the clinical trials were Caucasian. As such, there were too few non-Caucasian subjects in the studies to allow comparisons of efficacy with regard to race.

7.2. Risks

7.2.1. Risks of No Treatment and Surgical Treatment

Over time, the biochemical remodeling process of the collagen in the untreated Dupuytren's cord results in advancing degree of flexion contraction and the resultant increase in disability to the affected finger. This results in loss of function and a deformity of the finger(s). The deformities (contractures) progress slowly and become irreversible without treatment (Luck, 1959).

Currently, there are no approved non-surgical treatments for advanced Dupuytren's disease. The only treatments available are a number of invasive surgical procedures to excise or divide the diseased fascia. These types of surgical procedures may be complicated and can result in both intraoperative and postoperative complications, such as nerve injury, arterial injury, wound infection, scar contracture, and rarely flexor tendon injury. Not all subjects may be suitable for surgery, and diabetic subjects respond to surgery less favorably (Leclercq, 2000). Moreover, surgery often requires a prolonged recovery (Bulstrode et al., 2005; Skoff, 2004). Due to variable disease severity and surgical techniques, immediate postoperative recovery time can range from 21 to 58 days (Rodrigo et al., 1976; Tubiana, 1999.). Physical therapy for at least one month is usually required for good results after surgery to be maintained (Mackin and Byron, 1990; Mackin and Skirven, 2000).

7.2.2. Risks of AA4500 Treatment

AA4500 acts locally at the site of injection and does not require systemic exposure to be effective; in fact, systemic exposure to AA4500 is not quantifiable in Dupuytren's patients under conditions of clinical use. Results from nonclinical toxicity studies indicate that AA4500 disappears rapidly (within 2 hours) from the systemic circulation following IV administration and that significant systemic toxicity requires repeated and frequent (q48h) IV dosing. The systemic risks associated with AA4500 treatment are thus considered extremely low.

The safety population for AA4500 includes data from 1082 subjects with advanced Dupuytren's disease who received at least one injection of AA4500 at the proposed commercial dose of 0.58 mg, including 266 subjects with 12 months' data after the first injection of AA4500. Most (61%) subjects received one or two injections of study drug; 39% received between three and eight injections.

The majority of the TEAEs occurring with AA4500 injection were mild or moderate in intensity, generally confined to the extremity treated, and generally resolved by the 30-day follow-up visit. Considering those AEs occurring greater than 25% in the safety database of 1082 subjects, edema peripheral was the most frequently occurring related event (76.7%), followed by contusion (54.2%), injection site pain (40.6%), pain in extremity (35.8%), injection site hemorrhage (34.0%), and tenderness (28.5%). Additional events occurring at greater than 5.0% frequency included injection site swelling, ecchymosis, pruritus, skin laceration, lymphadenopathy, injection site pruritus, axillary mass, lymph node pain, blood blister, axillary pain, and erythema were also generally limited to local reactions confined to the treated extremity.

Long-term data from subjects who were followed for 12 months after the first injection of AA4500 show that most TEAEs started on the day of injection or the day of the finger extension

procedure and resolved without intervention before the next scheduled injection. No clinically meaningful differences in the incidence of TEAEs were observed between or among subgroups (age, gender, weight quartile, BMI category, diabetes history, or location). Of note is the lack of an increase in AEs in the diabetic population studied, a population reported to have a higher rate of complications after surgical correction (Leclercq, 2000).

AA4500 provides therapy of the contracting cord by the action of AA4500 on the cord collagen. In the clinical studies, SAEs related to effect of AA4500 on collagen occurred. Three subjects experienced tendon ruptures in the treated finger and one subject experienced ligament damage (pulley injury) in the treated finger. Proposed activities to mitigate the risk associated with tendon rupture or ligament damage as well as other potential risks of treatment with AA4500 are described in Section 8.

In contrast to surgical correction, there were no reports of nerve division or artery damage in the treated finger following treatment with AA4500. Nonclinical studies examining the effects of direct injection adjacent to nerve tissue and blood vessels or intravenously did not demonstrate any adverse effects on these tissues.

There is no quantifiable systemic exposure following a single injection of AA4500 0.58 mg into the cord of the affected finger or following the subsequent procedure to disrupt the cord, thus there were no systemic events related to AA4500 that were considered to reach clinical significance. There were no deaths attributed to treatment with AA4500.

Evaluation of routine clinical laboratory safety tests and vital signs in the clinical trials revealed no clinically meaningful differences between the AA4500-treated subjects and placebo-treated subjects. Additionally, grip strength was systematically measured and was not found to be adversely affected by treatment with AA4500.

After one or more injections, AA4500 was found to induce antibody formation in the majority of subjects tested. However, during the clinical trials there were no clinically meaningful immunologically mediated events. Events that were considered at least possibly immunologically mediated (eg, pruritus, erythema, edema peripheral) were local and confined to the treated extremity. Specifically, there were no events of systemic anaphylaxis, hyperpyrexia, respiratory distress, or circulatory failure associated with administration.

8. RISK ASSESSMENT AND MANAGEMENT

The Sponsor has a comprehensive pharmacovigilance system for collection, verification, evaluation and reporting of adverse reactions it receives in accordance with worldwide regulatory reporting requirements for drug safety. New safety information is collected, reviewed and analyzed on an ongoing basis from multiple sources, including spontaneous and clinical reports, reports from health authorities and from published literature. Auxilium proactively monitors the benefit/risk of its products.

In addition to routine pharmacovigilance, the Sponsor has specifically designed a comprehensive risk management plan for AA4500. Components of this plan include:

- Detailed product labeling, including a patient package insert, which will include information regarding the product profile including detailed usage instructions as well as specific detailed cautions regarding potential or identified product risks.
- A product targeted at physicians experienced in the diagnosis and management of Dupuytren's disease. Intended physicians will include hand surgeons, orthopedic surgeons, plastic surgeons, general surgeons (with a hand focus), and rheumatologists.
- Physician training program based on the clinical program which includes an injection training video and/or injection training manual. Attestation of training will be required in order to receive access to AA4500.
- Training will include detailed information regarding identified and potential adverse events with information to facilitate case reporting.
- Limited access to AA4500; only those physicians who attest to training will be provided access.
- Establishment of a safety hotline to ease case reporting of any potential adverse events associated with AA4500 use.
- Comprehensive follow-up information will be obtained utilizing an adverse event questionnaire designed for targeted follow-up of any reports of tendon/ligament rupture or other serious adverse events.
- Aggregate safety review by an Auxilium safety physician with monthly reviews for the first year followed by quarterly reviews for years 2 through 5.
- Safety reviews will be undertaken by appropriately qualified personnel such that any new trends or signals can be readily identified, assessed and action taken, as appropriate, to amend the product labeling and inform users.
- The ongoing conduct of a long-term (2 to 5 year) follow-up study (AUX-CC-860) of subjects treated with AA4500. The study objective is to monitor disease recurrence, progression, and product safety.

9. CONCLUSIONS

AA4500 will be the first effective, well tolerated non-surgical treatment of the fixed-flexion contractures caused by advanced Dupuytren's disease. AA4500 is intended to be administered in the physician's office and to allow the successfully treated subject to return to most activities of daily living almost immediately. No adjunctive therapy, such as physical therapy of the hand, is necessary for successful outcome. AA4500 acts by enzymatically disrupting the contracting cord, thus reducing the fixed-flexion contracture while having no deleterious effect on grip strength or degree of flexion. AA4500 is effective in reducing contracture of both MP and PIP joints and in contractures of high or low severity. The efficacy of AA4500 has been consistently demonstrated regardless of age, gender, body weight, BMI, or history of diabetes. During the 12-month follow-up period for each subject, 30 of the 830 successfully treated Dupuytren's cords were recurrent (nominal rate of 3.6%) with an estimated rate of recurrence at 12 months of 6.7% ($\pm 1.7\%$), based on the Kaplan-Meier estimate.

AA4500 has been shown to be well tolerated in treating contractures caused by advanced Dupuytren's disease. The vast majority of AEs were local, mild to moderate in severity, confined to the treated extremity, and generally resolved prior to the next injection.

Based on the safety and efficacy data presented, the overall benefit of the non-surgical reduction of symptomatic contractures caused by advanced Dupuytren's disease following treatment with AA4500 is considered to outweigh any risks associated with treatment.

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