Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Collagenase clostridium histolyticum

Proprietary Product Name: Xiaflex

Sponsor: Actelion Pharmaceuticals Australia Pty Ltd

17 April 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations 4

1. Clinical rationale 6

2. Contents of the clinical dossier 6

2.1. Scope of the clinical dossier 6

2.2. Paediatric data 7

2.3. Good clinical practice 7

3. Pharmacokinetics 7

3.1. Summary of pharmacokinetics 8

3.2. Evaluator's overall conclusions on pharmacokinetics 9

4. Pharmacodynamics 9

4.1. Studies providing pharmacodynamic data 9

4.2. Summary of pharmacodynamics 9

4.3. Evaluator's overall conclusions on pharmacodynamics 13

5. Dosage selection for the pivotal studies 13

6. Clinical efficacy 16

6.1. Dupuytren's contracture 16

6.2. Evaluator's conclusions on clinical efficacy for Dupuytren's disease 40

7. Clinical safety 41

7.1. Studies providing evaluable safety data 41

7.2. Pivotal studies that assessed safety as a primary outcome 42

7.3. Patient exposure 43

7.4. Adverse events 43

7.5. Postmarketing experience 51

7.6. Safety issues with the potential for major regulatory impact 52

7.7. Other safety issues 53

7.8. Safety related to drug-drug interactions and other interactions 53

7.9. Evaluator's overall conclusions on clinical safety 53

8. First round benefit-risk assessment 55

8.1. First round assessment of benefits 55

8.2. First round assessment of risks 55

8.3. First round assessment of benefit-risk balance 56

8.4. First round recommendation regarding authorisation 59

9. Clinical questions 59

9.1. Pharmacokinetics 59

9.2. Pharmacodynamics 59
9.3. Efficacy 59
9.4. Safety 60
10. Second round evaluation of clinical data submitted in response to questions 60
10.1. Efficacy 60
10.2. Safety 63
10.3. PI and CMI 67
11. Second round benefit-risk assessment 67
11.1. Second round assessment of benefits 67
11.2. Second round assessment of risks 67
11.3. Second round assessment of benefit-risk balance 67
11.4. Second round recommendation regarding authorisation 68
12. References 68

List of abbreviations

Abbreviation	Meaning
AA4500	Collagenase clostridium histolyticum
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUX-I	Clostridial type I collagenase
AUX-II	Clostridial type II collagenase
BMI	Body mass index
BTC	Biospecifics Technology Corporation
BUN	Blood urea nitrogen
CHMP	Committee for Medicinal Products for Human Use
CSR	Clinical study report
CRF	Case report form

Abbreviation	Meaning
DB PC	Double-blind placebo-controlled
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
EU	European union
Fixed-flexion deformity/ contracture (degree of flexion)	The angle of the joint when the finger is passively extended (that is, straightened) as far as possible toward the neutral position of zero degrees (that is, full extension or normal extension)
Full extension angle (extended) as far as possible toward the neutral position of joint	The angle of a joint when the finger is straightened zero degrees (expressed in degrees)
Full flexion angle as close to the palm as possible (expressed in degrees)	The maximum angle of a joint when the finger is bent (flexed)
GCP	Good clinical practice
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IRB	Institutional review board
ISE	Integrated Summary of Efficacy
ISI	Integrated Summary of Immunogenicity
ISS	Integrated Summary of Safety
ITT	Intent-to-Treat
LOCF	Last observation carried forward
MAA	Marketing Authorisation Application
MAH	Marketing Authorization Holder
MPP	Mammalian matrix metalloproteinase
mg	Milligram
mL	Milliliter
MP	Metacarpophalangeal
Neutral Zero Method	All motions of a joint are measured from a defined zero starting point position. The degree of motion of a joint are added in the direction the joint

Abbreviation	Meaning
	moves from the zero starting position
PIP	Proximal interphalangeal
ROM	Range of motion
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	standard deviation
SOC	System organ class
TEAE	Treatment-emergent adverse events were events with a start date equal to or after the first injection of study drug
UK	United Kingdom
ULN	Upper limit of normal

1. Clinical rationale

Dupuytren's contracture is a relatively common disorder in which there is benign, slowly progressive fibrosis of the palmar fascia. This results in tendon thickening, joint stiffness and an insidious loss of full extension over decades. Typically, contractures that flex one or more fingers at the metacarpophalangeal (MP) joint develop.

Collagenase is a proteinase that can hydrolyse the triple-helical region of collagen under physiological conditions. The proposed product, AA4500, contains two collagenases: collagenase AUX-I (clostridial type I collagenase) and collagenase AUX-II (clostridial type II collagenase). The sponsor stated that these two collagenases are not immunologically cross-reactive and have different specificities such that together they become synergistic, providing a very broad hydrolysing reactivity toward collagen. The clinical rationale is that after local injection at the site of the Dupuyetren's cord there will be selective lysis of collagen at this injection site which will result in reduction of the finger contracture.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The submission contained the following clinical information:

- 45 reports of bioanalytical and analytical methods including determination of anti-drug antibodies and validation reports for the assay methods.
- Two clinical pharmacology studies (AUX-CC-855, and DUPY-202) providing pharmacokinetic data and the latter also providing dose-finding data.
- Three controlled efficacy/safety studies (DUPY-303, AUX-CC-857, AUX-CC-859).

- Four uncontrolled, open label studies (DUPY-404, AUX-CC-854, AUX-CC-856, AUX-CC-858).
- Four other efficacy/safety studies (AUX-CC-851-852, AUX-CC-853, DUPY-101, AUX-CC-860)
- Three Integrated Summaries; Efficacy (tables only), Safety (tables only) and Immunogenicity.
- Four reports of postmarketing experience (February 2010 to February 2011), case report forms and literature references

2.2. Paediatric data

The submission did not include paediatric data.

2.3. Good clinical practice

The sponsor provided statements in each clinical study report that the studies had been conducted according to Good Clinical Practice guidelines and appropriate ethical and regulatory approval.

3. Pharmacokinetics

Studies providing pharmacokinetic data

Table 1 below shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 1. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK in healthy adults	General PK Single dose Multi-dose	- -
	Bioequivalence† Single dose Multi-dose	- -
	Food effect	-
PK in special populations	Target population§ Single dose Multi-dose	AUX-CC-855 DUPY-202
	Hepatic impairment	-
	Renal impairment	-
	Neonates/infants/children/ adolescents	-
	Elderly	-
Genetic/gender-related PK	Males versus females	-

PK topic	Subtopic	Study ID
PK interactions	-	-
Population PK analyses	Healthy Subjects	-
	Target Population	-
	Other	-

† Bioequivalence of different formulations.
§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

Table 2 below, lists pharmacokinetic results that were excluded from consideration due to study deficiencies.

Table 2. Pharmacokinetic results excluded from consideration.

Study ID	Subtopic(s)	PK results excluded
DUPY-202	Urinary excretion	Urine PK results

3.1. Summary of pharmacokinetics

3.1.1. Physicochemical characteristics of the active substance

The following information is derived from the summaries the sponsor's submitted with the their application. Collagenase clostridium histolyticum (AA4500) is a parenteral lyophilised product comprised of two collagenases in an approximate 1:1 mass ratio, Collagenase I (AUX-I, Clostridial type I collagenase, formerly known as ABC-I) and Collagenase II (AUX-II; Clostridial type II collagenase, formerly known as ABC-II). These collagenases are isolated and purified from the fermentation 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 kiloDaltons (kDa). Collagenase AUX-II is also approximately 1,000 amino acids long and has a molecular weight of 113 kDa.

3.1.2. Pharmacokinetics in the target population

3.1.2.1. Absorption

The data from Study AUX-CC-855 indicate that there is no quantifiable systemic absorption of AA4500 (that is, ≤ 5 ng/mL for AUX-I and ≤ 25 ng/mL for AUX-II) following a single local injection of 0.58 mg (10,000 U) into the affected Dupuytren's cord. This was supported by limited data from DUPY-202.

In Study DUPY-202 one subject had 0.25 mL of methylene blue 1% solution injected into the affected cord to assess possible diffusion of collagenase from the cord. The blue colour was seen to immediately diffuse from the site, however it was not possible to determine the amount that diffused. The sponsor stated that collagenase could be expected to diffuse from the site and this was supported by clinical observation of short term wrist and hand swelling soon after injection.

Comment: It was not possible to draw conclusions from this single case which used a molecule smaller than the collagenase product.

3.1.2.2. Distribution

No tissue distribution studies have been performed.

3.1.2.3. Metabolism

AA4500 is not a substrate for CYP450 or other drug metabolising pathways and no metabolism studies have been performed. The protein is active in its native form and does not require cleavage.

3.1.2.4. Excretion

Excretion has not been assessed due to the lack of systemic absorption. There were no urinary samples collected in Study AUX-CC-855 and a urinary assay was not developed or validated.

The sponsor states that AA4500 is inactivated locally, most likely as a result of complex formation with α-2-macroglobulin (α2M) which is a serum protein that is a substrate for proteases of varying types. This reaction limits the systemic circulation of AUX-I and AUX-II. This is supported by data showing inhibition of AUX-I and AUX-II enzyme activity by α2M when pre-incubated at room temperature in the absence of collagen substrate (90% for AUX-I at 24 hours and 80% for AUX-II at 2 hours, Report MBR 10-112).

3.1.3. Pharmacokinetics in other special populations

This has not been assessed due to the lack of systemic absorption.

3.1.4. Pharmacokinetic interactions

Pharmacokinetic drug interaction studies have not been conducted due to the lack of systemic exposure.

3.2. Evaluator's overall conclusions on pharmacokinetics

After a single injection of AA4500 at a dose of 0.58 mg into the Dupuytren's cord on an affected finger and then a subsequent finger extension procedure there was no quantifiable systemic exposure.

No multiple dose pharmacokinetic study was conducted as no exposure was expected with a dosing regimen of up to one injection each four weeks. The sponsor is however conducting a multiple cord treatment study, AUX-CC-861, in which the safety, tolerability and pharmacokinetics will be assessed when two different cords are treated at the same time.

4. Pharmacodynamics

4.1. Studies providing pharmacodynamic data

There is no reported systemic exposure and no specific clinical pharmacodynamic studies were conducted. The sponsor states the primary pharmacodynamic activity data were obtained from *in vitro* studies using exised Dupuytren's cords and Peyronie's plaques.

4.2. Summary of pharmacodynamics

4.2.1. Mechanism of action

The activity of AA4500 collagenases is via the hydrolysis of collagen at the injection site.

4.2.2. Pharmacodynamic effects

4.2.2.1. Primary pharmacodynamic effects

Primary PD effects were assessed using *in vitro* models. After injection into the abnormal collagen deposits in the Dupuytren's cord, the lysis of the collagen results in disruption of the cord and therefore improved finger range of motion.

4.2.2.2. Secondary pharmacodynamic effects

Due to the lack of systemic exposure, no systemic secondary pharmacodynamic effects have been assessed. The sponsor describes literature reports of the collagen fragments generated by the collagenase having bradykinin-like effects and are consequently associated with development of local oedema and haemorrhage from increased vascular permeability. It was stated that nonclinical studies did not find these effects on tissues other than those adjacent to the injection site.

4.2.3. Immunogenicity

AA4500 is a product of bacterial origin and immunogenicity assessment was an important part of the development program. In Studies AUX-CC-854, AUX-CC-856, AUX-CC-857, AUX-CC-858 and AUX-CC-859, serum samples were collected at screening, before each injection and at predetermined time points after each injection to determine if antibodies had formed against AUX-I and AUX-II. These studies used the commercial manufacturing process.

The analysis of ADAs in human serum used bridging enzyme-linked immunosorbent assay (ELISA) assays for detection of either anti-AUX-I or anti-AUX-II. For anti-AUX-I the lower limit of detection was 0.8 ng/mL with stability confirmed to 26 months at -20°C and -80°C (AA33061-01 and AA33061-02). For anti-AUX-II the lower limit of detection was 1.9 ng/mL with stability confirmed to 23 months at -20°C and 26 months at -80°C (AA33062-01 and AA33062-02).

Pooled data from the clinical trials listed above, found that over 85.7% of subjects were positive for antibodies to AUX-I and/or AUX-II at 30 days post injection of 0.58 mg AA4500. After 3 or 4 injections all subjects were positive (Figures 1 and 2). Mean log titres were almost two-fold higher after the second injection, increasing with each injection until about the fourth injection. Antibody titres were found to decline over time though the majority (>82%) still remained positive after 2 years (Figures 3 and 4).

Figure 1. 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

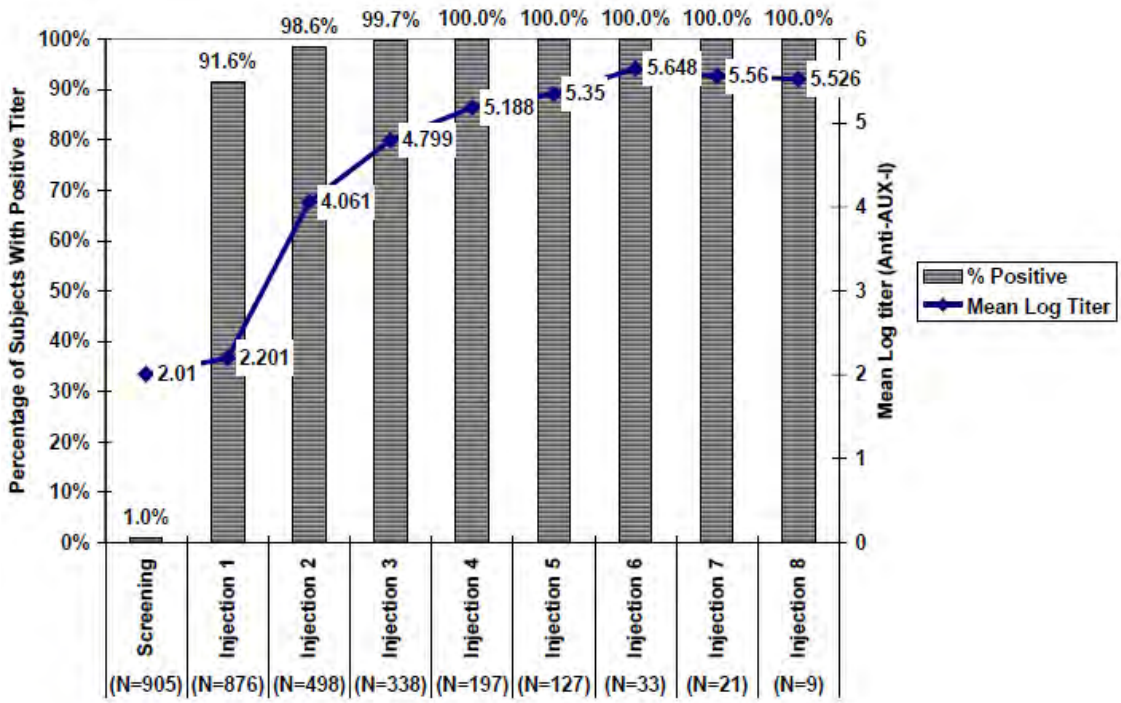


Figure 2. Figure 1. Percentage of subjects with positive Anti-AUX-II titers and log mean titer levels across Injections 1 through 8. AA4500 0.58 mg Intent to Treat Population

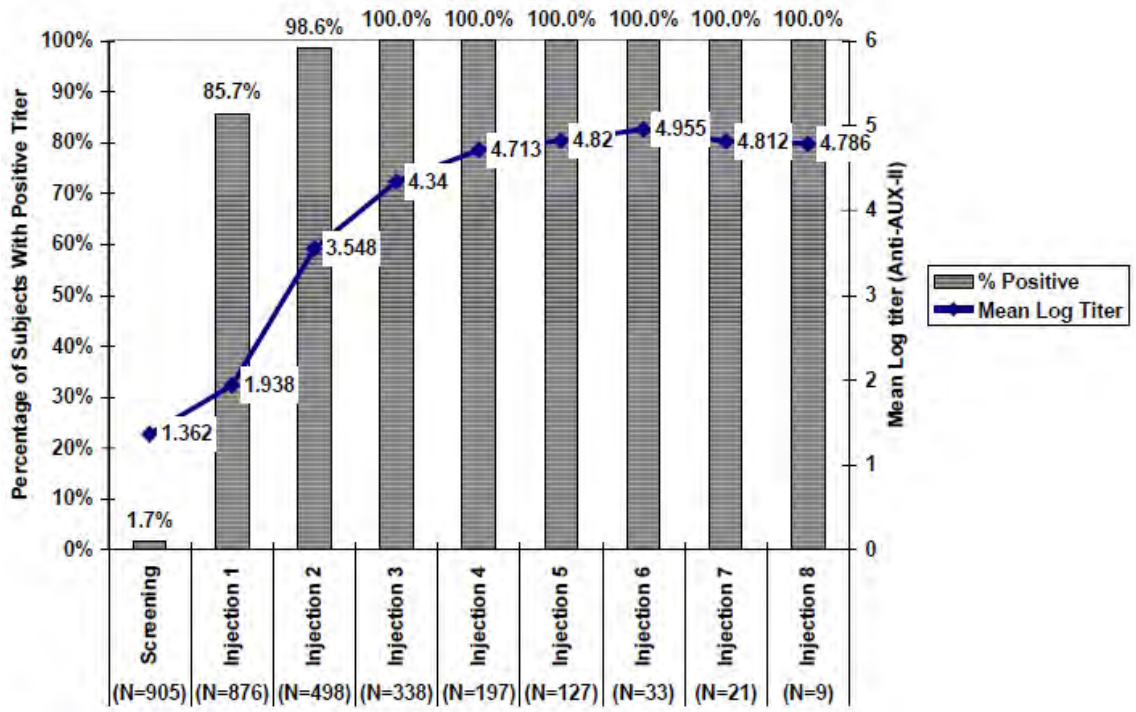


Figure 3. Log mean Anti-AUX-1 titers at the first positive sample, the maximum sample and Year 2 sample relative to the last injection (Day 0) by Injection Cohort; Study AUX-CC-860.

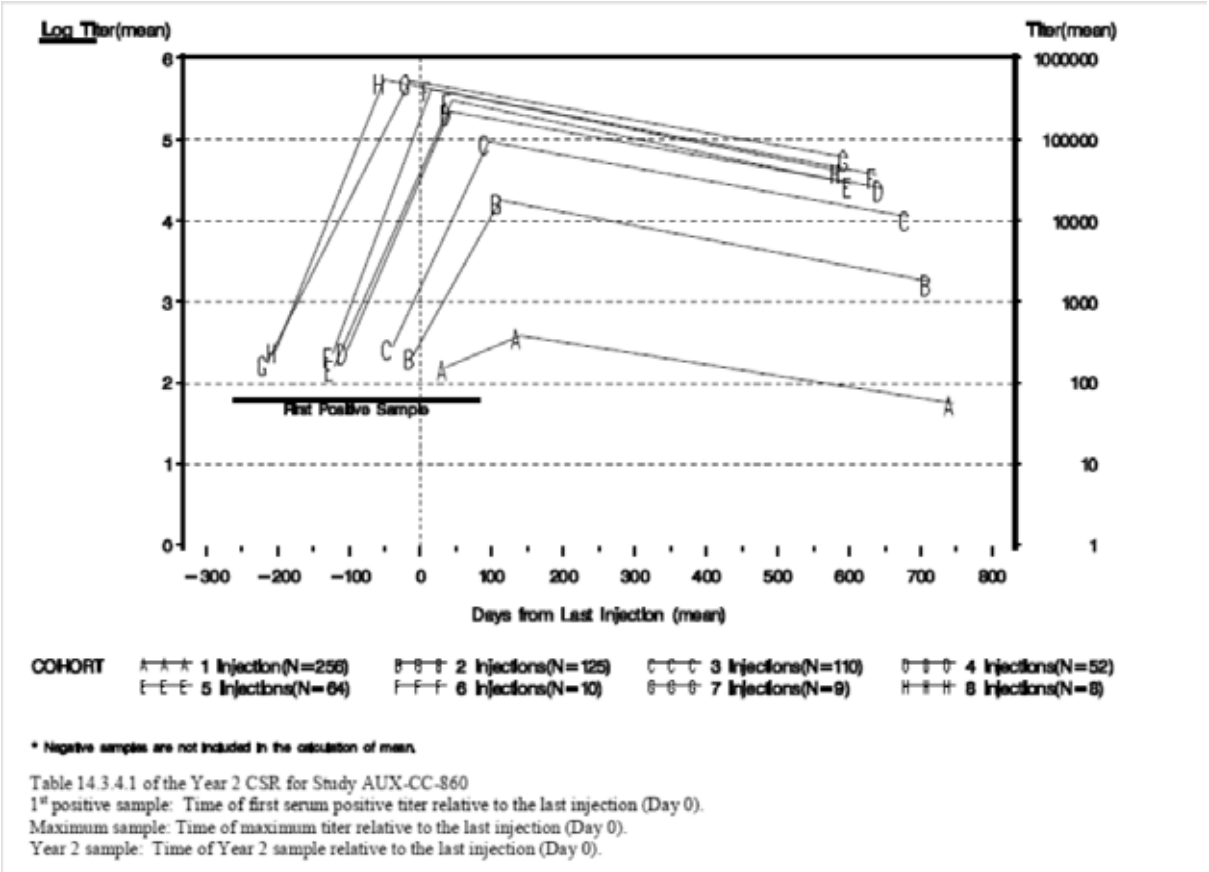
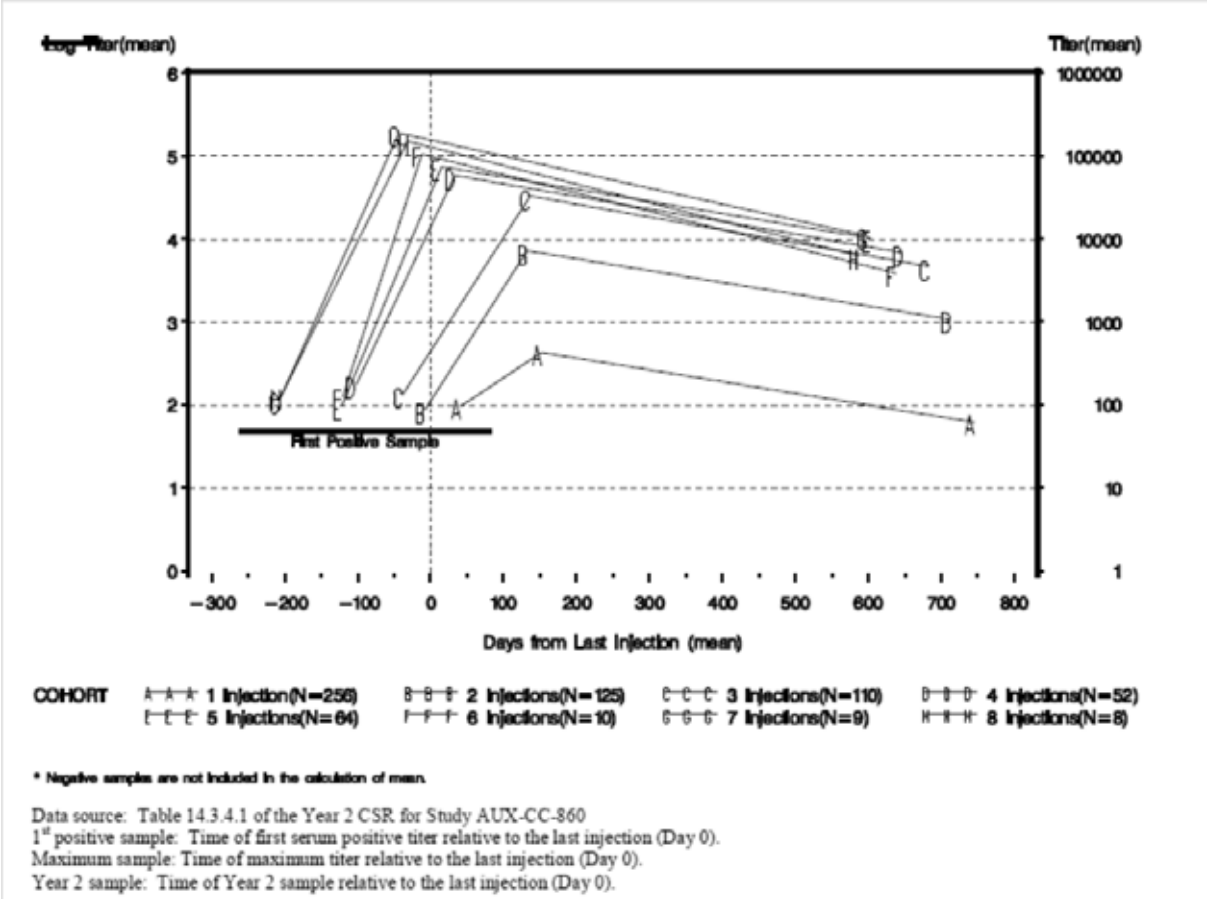


Table 14.3.4.1 of the Year 2 CSR for Study AUX-CC-860
1st positive sample: Time of first serum positive titer relative to the last injection (Day 0).
Maximum sample: Time of maximum titer relative to the last injection (Day 0).
Year 2 sample: Time of Year 2 sample relative to the last injection (Day 0).

Figure 4. Mean Log Anti-AUX-II titers at the first positive sample, maximum sample and Year 2 sample relative to the last injection (Day 0), by Injection Cohort; Study AUX-CC-860.



Data source: Table 14.3.4.1 of the Year 2 CSR for Study AUX-CC-860
1st positive sample: Time of first serum positive titer relative to the last injection (Day 0).
Maximum sample: Time of maximum titer relative to the last injection (Day 0).
Year 2 sample: Time of Year 2 sample relative to the last injection (Day 0).

Given the intrinsic immunogenicity of the product, an assessment of whether these anti-drug antibodies (ADAs) could have cross reactivity or neutralising ability of endogenous collagenases, or affect the drug's efficacy and safety, was evaluated *in vitro* as well as in the clinical program.

The closest mammalian homologs to clostridium hystoliticum are the matrix metalloproteinases (MMP). The sponsor undertook an evaluation of these to determine homology with seven such MMPs (1, 2, 3, 8, 9, 13 and 14) and found low sequence homology (24 to 53%). In addition, there were differences in chain length. As such, the product of bacterial origin is expected to have a different conformation structure to the human enzymes. Nevertheless, two competitive ELISAs to measure cross-reactivity of the ADAs with human MMPs were validated using 30 samples from AUX-CC-860 and found no cross-reactivity with MMPs 1, 2, 3, 8 or 13 (VAA90736 and VAA90737). Further assessment of 41 samples from this study found no cross reactivity with these MMPs (AAA95274, AA95275). These data indicate a low risk of anti-AUX-I and anti-AUX-II antibodies cross-reacting with any of five MMPs (1, 2, 3, 8 and 13) representing endogenous human collagenases.

An assay was developed and validated to detect neutralising activity of anti-AUX-I and anti-AUX-II antibodies (MBR08-329 and MBR08-357). The assays were however only validated against one positive control pool due to limited supply. The assay cut-point (% inhibition) was 8.8 for anti-AUX-I and 11.5 for anti-AUX-II. In Study AUX-CC-857, 100% of subjects seroconverted and had ADA titres. It was found that 22/200 (11%) and 44/204 (22%) of samples had neutralising activity against AUX-I and AUX-II, respectively, on intact soluble collagen. There was a trend for increasing ADA titre and proportion positive on the neutralisation assay (Table 3) although it

was reported that some sample of very high titre did not inhibit AUX-I or AUX-II enzyme activity.

Table 3. Comparison of ADA titers versus positive result in enzyme activity neutralisation assay by ADA titre 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%)
2nd quartile	5/50 (10%)	16/51 (31%)
3rd quartile	1/50 (2%)	3/51 (6%)
Lower quartile	3/50 (6%)	1/51 (2%)
Negative	8/175 (5%)	9/171 (5%)

4.2.4. Pharmacodynamic interactions

It has been reported that tetracycline derivatives may inhibit mammalian metalloproteinases and as a consequence subjects who had received doxycycline or a doxycycline derivative within 14 days of the first study drug injection were excluded from the clinical trials.

4.3. Evaluator's overall conclusions on pharmacodynamics

As there is no reported systemic exposure no specific clinical pharmacodynamic studies were conducted. The pharmacodynamics of AA4500 have been assessed in the nonclinical program. The activity of AA4500 collagenases is via the hydrolysis of collagen at the injection site. Collagen fragments generated by this lysis are reported to have bradykinin-like effects and are associated with development of local oedema and haemorrhage.

The product, being of bacterial origin, has high intrinsic immunogenicity and while all subjects developed anti-drug antibodies, there was no evidence of cross-reactivity with five representative human collagenases (MMPs 1, 2, 3, 8 and 13) and only low levels of neutralising activity on AUX-I or AUX-II. Further discussions on immunogenicity in relation to efficacy and safety are in *Analysis performed across trials* and S*afety issues with potential for major regulatory impact, Unwanted immunological effects.*

5. Dosage selection for the pivotal studies

The dosage selection for the Phase III program was based on a single dose-ranging study, DUPY-202. This was a randomised placebo-controlled study in 80 adults with Dupuytren's disease. Doses of 2500 U, 5000 U and 10,000 U were assessed after a single injection. It is noted that this study used the early BTC process study drug.

The clinical success rates[1] were 50.0%, 45.5%, 78.3% in the 3 respective dose groups, compared to 0% in the placebo group. This result was statistically significant for all three doses ($p \leq 0.002$). Response was greatest with the 10,000U dose when the primary affected joint was the metocarpal phalangeal (MP) or the proximal interphalangeal (PIP) and this was the only dose which had a significantly greater success on the PIP joint than placebo (Table 4).

[1] Clinical success was defined as a reduction in contracture (flexion deformity) to ≤5° of normal as measure by finger goniometry 30 days after injection.

Table 4. Clinical Success of Primary Joint After a single injection of Study drug, Primary joint Overall and by Joint type. Intent to Treat population. DUPY-202

	AA4500			
	2500 U N=18	5000 U N=22	10,000 U N=23	Placebo N=17
All Primary Joints				
N	18	22	23	17
Number (%) clinical success	9 (50.0)	10 (45.5)	18 (78.3)	0
p-value[a]:				
Compared with 2500 U	NA	1.000	0.097	0.001
Compared with 5000 U	1.000	NA	0.033	0.002
Compared with 10,000 U	0.097	0.033	NA	<0.001
Compared with placebo	0.001	0.002	<0.001	NA
Primary MP Joints				
N	14	15	16	10
Number (%) clinical success	7 (50.0)	6 (40.0)	13 (81.3)	0
p-value[a]:				
Compared with 2500 U	NA	0.715	0.122	0.019
Compared with 5000 U	0.715	NA	0.029	0.051
Compared with 10,000 U	0.122	0.029	NA	<0.001
Compared with placebo	0.019	0.051	<0.001	NA
Primary PIP Joints				
N	4	7	7	7
Number (%) clinical success	2 (50.0)	4 (57.1)	5 (71.4)	0
p-value[a]:				
Compared with 2500 U	NA	1.000	0.576	0.109
Compared with 5000 U	1.000	NA	1.000	0.070
Compared with 10,000 U	0.576	1.000	NA	0.021
Compared with placebo	0.109	0.070	0.021	NA

Data source: Section 14; Tables 10, 10.1, and 10.2

NA=not applicable; MP = metacarpophalangeal; PIP = proximal interphalangeal.

[a] A Fisher's exact test was used for the pairwise comparisons between treatment groups.

For the more severely affected joints (>50° MP and >40° PIP), the response was notably greater with the 10,000 U dose (Table 5). The improvement from baseline in degree of contracture was significantly better with AA4500 than placebo ($p \leq 0.012$), with a mean percentage change of -25.6%, -30.2%, -40.0% and -0.6% for the 2500 U, 5000 U, 10,000 U and placebo groups, respectively. There was, however, no significant difference found between the active dose groups on this parameter (Table 6). Primary joints treated with AA4500 had a significantly greater improvement from baseline in the range of motion compared to those treated with placebo ($p<0.001$). There were 37 primary joints that did not achieve success after a single injection that had further injections in the open label phase. Of these, 62% (23/37) achieved clinical success after retreatment with up to three 10,000 U injections.

Table 5. DUPY-202. Clinical success by Primary joint type, Baseline joint severity and Dose of AA4500.

Dose Level	MP Joints ≤ 50°	MP Joints >50°
2500 U	6/7 (85.7%)	1/7 (14.3%)
5000 U	4/9 (44.4%)	2/6 (33.3%)
10,000 U	9/10 (90.0%)	4/6 (66.7%)
Dose Level	**PIP Joints ≤ 40°**	**PIP Joints >40°**
2500 U	2/3 (66.7%)	0/1 (0.0%)
5000 U	3/3 (100.0%)	1/4 (25.0%)
10,000 U	2/2 (100.0%)	3/5 (60%)

Data source: Appendix 16.2; Listings 8 and 8.1

MP = metacarpophalangeal; PIP = proximal interphalangeal.

Table 6. DUPY-202. Mean change (%) in Degree of contracture (Flexion deformity) from baseline after a single injection of study drug, Primary joint overall and by Joint type. Intent to Treat Population.

	AA4500			
	2500 U N=18	5000 U N=22	10,000 U N=23	Placebo N=17
All Primary Joints				
Baseline				
N	18	22	23	17
Mean (SD)	46.8 (18.6)	47.1 (21.9)	49.0 (22.3)	55.6 (18.5)
Median	45.0	45.0	43.0	60.0
Min, Max	20.0, 85.0	20.0, 92.0	20.0, 90.0	25.0, 80.0
30 days after the injection				
N	18	22	23	17
Mean percent change (SD)	-25.6 (18.5)	-30.2 (17.0)	-40.0 (22.6)	-0.6 (4.3)
p-value[a]				
Compared with 2500 U	NA	0.405	0.011	<0.001
Compared with 5000 U	0.405	NA	0.065	<0.001
Compared with 10,000 U	0.011	0.065	NA	<0.001
Compared with placebo	<0.001	<0.001	<0.001	NA
Primary MP Joints				
Baseline				
N	14	15	16	10
Mean (SD)	49.8 (18.5)	48.1 (23.9)	44.9 (24.0)	56.5 (16.5)
Median	51.0	45.0	32.5	60.0
Min, Max	20.0, 85.0	20.0, 92.0	20.0, 90.0	25.0, 80.0
30 days after the injection				
N	14	15	16	10
Mean percent change (SD)	-26.4 (20.7)	-28.5 (20.2)	-37.1 (23.3)	0.0 (4.7)
p-value[a]				
Compared with 2500 U	NA	0.774	0.145	0.002
Compared with 5000 U	0.774	NA	0.232	<0.001
Compared with 10,000 U	0.145	0.232	NA	<0.001
Compared with placebo	0.002	<0.001	<0.001	NA
Primary PIP Joints				
Baseline				
N	4	7	7	7
Mean (SD)	36.3 (17.0)	45.0 (18.5)	58.3 (15.2)	54.4 (22.4)
Median	32.5	45.0	65.0	60.0
Min, Max	20.0, 60.0	25.0, 80.0	35.0, 75.0	25.0, 76.0
30 days after the injection				
N	4	7	7	7
Mean percent change (SD)	-22.5 (8.7)	-33.9 (6.1)	-46.9 (20.7)	-1.6 (3.7)
p-value[a]				
Compared with 2500 U	NA	0.151	0.004	0.012
Compared with 5000 U	0.151	NA	0.059	<0.001
Compared with 10,000 U	0.004	0.059	NA	<0.001
Compared with placebo	0.012	<0.001	<0.001	NA

Data source: Section 14; Tables 15, 15.1, and 15.2

NA=not applicable; MP = metacarpophalangeal; PIP = proximal interphalangeal.

[a] p-values are from one-way ANOVA with treatment as a factor.

In this study, the rate of treatment emergent AEs increased with increasing dose of AA4500 (77.8%, 81.8% and 91.3% versus 64.7% in the placebo group), however there was no statistically significant difference found between the active groups. Adverse events were mainly associated with the injection or post-injection finger manipulation (peripheral oedema, tenderness, ecchymosis) and were mild or moderate in severity.

The sponsor also included in the dossier a literature report of an early open label, dose-ranging study of the product in 35 subjects (DUPY-101). This reported that no beneficial effects were found with injections of <10,000 U. [2]

Comment: No clinical study report or data were supplied for this study so evaluation was not possible.

In Study DUPY-202, all AA4500 doses were found to be better than placebo with regard to effects on clinical success rates, improvement in range of motion and reduction in flexion deformity. There was an evident dose response and the highest dose of 10,000 U (equivalent to 0.58 mg) had a response irrespective of joint type (MP or PIP) and was more effective on the more severely contracted joints. Given these efficacy findings and the lack of a significant difference in AE rates between the dose groups, the sponsor selected the 10,000 U dose for the Phase III trials.

Comments: The high efficacy response of the 0.58 mg dose supported not assessing an even higher dose.

The use of study drug from an early manufacturing process mean the efficacy data are only considered supportive as there are no bioequivalence bridging data between this early process and the proposed commercial manufacturing process which was used in the Phase III clinical trials.

Given the proposed dosage of 0.58 mg, it is unclear why the single use product vial is 0.9 mg and a question on this has been included (see *List of Questions*).

6. Clinical efficacy

6.1. Dupuytren's contracture

6.1.1. Pivotal efficacy studies

6.1.1.1. Study AUX-CC-857 and AUX-CC-859

6.1.1.1.1. Study design, objectives, locations and dates

AUX-CC-857 and AUX-CC-859 were Phase III, double-blind, randomised, placebo-controlled safety and efficacy studies in patients with Dupuytren's contracture. The design included a 90 days randomised period which was followed by a nine month open label extension period. For Study 857 this open label extension was a separate protocol (AUX-CC-858) while for Study 859 it was part of the main protocol. Study 857 was conducted in the US at 16 sites between August 2007 and October 2008. Study 859 was conducted in Australia at six sites (five of which enrolled subjects) between August 2007 and September 2008.

The primary objective was to evaluate the efficacy and safety of up to three injections of AA4500 as compared to placebo in reducing the degree of contracture (fixed flexion deformity) in the primary joint (either MP or PIP). Efficacy evaluation at multiple joints (MP and PIP) was a secondary objective and in Study 859 a tertiary objective was an evaluation of contracture recurrence during the 12 month period.

Both protocols had amendments, the first clarified inclusion and exclusion criteria and the second changed wrist position during manipulation, updated guidance for fifth finger injection and clarified use of doxycycline. Study 859 also had a third administrative amendment.

[2] Badalamente MA and Hurst LC. Enzyme injection as nonsurgical treatment of Dupuytren's disease. *J Hand Surg*. 2000; 25A: 629-636.

6.1.1.1.2. Inclusion and exclusion criteria

Inclusion criteria were: ≥18 years of age; diagnosis of Dupuytren's disease with a fixed flexion deformity of at least one finger (other than the thumb) that was ≥20° and ≤100° for MP (≤80° for PIP) contracture caused by a palpable cord that had never been treated with AA4500; a positive "table top test"[3]; in good health; and using birth control, sterilised or post-menopausal.

Exclusion criteria were: pregnancy or lactation or planning pregnancy; chronic muscular, neurological or neuromuscular disorder affecting the hands; treatment for Dupuytren's disease at the selected joint within 90 days; allergy to collagenase; received of doxycycline or a derivative within 14 days; collagenase treatment within 30 days; anticoagulant medication (except low dose aspirin) within 7 days; and recent history of stroke, bleeding or a disease affecting the hands.

6.1.1.1.3. Study treatments

AA4500 0.58 mg or placebo was administered after reconstitution with diluent (0.9% sodium chloride containing 2 mM calcium chloride) in a volume of 0.25 mL of the reconstituted solution for cords affecting MP joints and 0.20 mL for cords affecting PIP joints. Reconstitution of the study drug was performed by designated staff. Injection was directly into the cord using a hubless syringe with attached 27 gauge ½ inch needle.

Comment: It was not clear what level of training in the correct injection technique had been undertaken for the investigators. A question on this issue has been raised with the sponsor (*List of Questions*).

There was a 60 minute observation period post injection to monitor local and systemic adverse events and vital signs. Subjects were to rest the hand until the next visit. About 24 hours post injection, if thought warranted, investigators manipulated the contracted cord by extending the finger using force according to the subject's pain tolerance. Three attempts at cord disruption were permitted. Following this, the hand was splinted each night for four months and subjects instructed to perform daily finger exercises.

Up to 3 injections could be given (one a month) during the double-blind phase. Subjects not achieving clinical success with the treated cord or who had other affected joints could receive up to 5 additional injections in the open label period however a cord affecting a joint could receive a maximum of 3 injections only.

Prohibited medications included doxycycline and its derivatives for 14 days prior and 7 days post each injection and anticoagulant medications for 7 days prior and post each injection.

6.1.1.1.4. Efficacy variables and outcomes

The main efficacy variable was the reduction in fixed flexion contracture (finger deformity) as measured by finger goniometry 30 days after an injection using the Neutral Zero Method[4]. The primary efficacy outcome was the rate of clinical success of the primary joint after the last injection. Clinical success was defined as a reduction in contracture (flexion deformity) to ≤5°.

Before treatment initiation the investigator prioritised the affected cords on the selected hand as primary, secondary and tertiary. The primary cord could be either at the MP or the PIP joint, although if they were on the same finger the MP joint was selected as primary. Once clinical success was achieved at the primary joint, the secondary and tertiary joints were treated.

[3] A positive "table top test" was defined as the inability to simultaneously place the affected finger(s) and palm flat against a table top.

[4] In the Neutral Zero Method to determine full extension and flexion all joint motions are measured with a gonimeter from a defining zero starting point. The degree of motion of a joint is added in the direction the joint moved from the zero starting position. The extended "anatomical position" of an extremity is accepted as zero degrees rather than as 180 degrees.

Other efficacy outcomes included:

- Clinical improvement which was defined as at least a 50% reduction from baseline in contracture after an injection.
- The percentage change from baseline to Day 30 in degree of contracture.
- Change from baseline to Day 30 in range of motion which was the difference between finger extension and flexion angles in degrees.
- Time to reach clinical success. This used the visit day for which reduction in contraction to 5° or less was achieved and maintained to 30 days post injection.
- Recurrence for joints which achieved clinical success. This was deemed when the joint contracture increased by at least 20° and had a palpable cord.
- Physician global assessment of the contracture and degree of improvement, subject global assessment of severity, percent improvement and treatment satisfaction.

6.1.1.1.5. Randomisation and blinding methods

Subjects were stratified by primary joint type (MP or PIP) and by baseline joint contracture severity (≤50° or >50°for MP and ≤40° or >40° for PIP joing). Randomisation was in a 2:1 ratio to AA4500 or placebo using an IVRS. Study personnel were blinded to treatment allocation.

6.1.1.1.6. Analysis populations

Efficacy analysis was based on the intention to treat (ITT) population which was defined as all subjects who had received at least one injection of study drug. The per protocol (PP) population excluded subjects with no contracture measurements after the first injection, who had a primary joint not meeting the minimum or maximum fixed flexion measurements at baseline, received the wrong treatment, did not have the day 30 evaluation or received a reduced number of injections.

6.1.1.1.7. Sample size

It was estimated that the clinical success rate (contracture reduction to ≤5°) would be 80% for those with affected MP joints and 70% for PIP joints and 10% for placebo treated joints. For the study to have 80% power at a two sided significance level of 0.05, a sample size of 54 subjects (active:placebo of 16:8 for MP and 20:10 for PIP joints) would be required. In order to adequately assess safety and allow for dropouts a sample of 216 subjects (144 MP and 72 PIP) was selected for Study AUX-CC-857 and 60 for AUX-CC-259.

6.1.1.1.8. Statistical methods

Comparison of success rate was analysed using a Cochran Mantel Haenszel (CMH) test stratified by baseline severity and joint type for all joints, and baseline severity for analysis of the MP and PIP joints separately. The percentage change from baseline in contracture and in range of motion were analysed using an analysis of variance (ANOVA) model with treatment group, baseline severity and joint type as factors. For a sensitivity analysis, subjects without Day 30 evaluations post their final injection or not post-injection evaluation were defined as not having achieved clinical success. A closed hierarchical testing procedure was used for the efficacy analysis of the primary joint meaning that if a test failed to reject the individual hypothesis at the 5% significance level then all following hypotheses could not be tested.

6.1.1.1.9. Participant flow

In AUX-CC-857 there were 352 subjects screened, 308 enrolled and 204 and 104 randomised to AA4500 and placebo, respectively. The double-blind phase, completion rates were 93.6% and 96.2%, respectively. In the PP population there were 182 (89.2%) and 91 (87.5%) in the AA4500 and placebo groups, respectively. Discontinuation rates from the double-blind phase were higher with AA4500 (6.4% versus 3.8%) and were mainly consent withdrawal and loss to

follow up. Three (1.5%) were due to adverse events and all were in the AA4500 group. The placebo group was much more likely to receive three injections (89.4% versus 47.5%) and had fewer joints treated (106 versus 287).

In the smaller AUX-CC-859, there were 66 subjects enrolled (45 in the AA4500 and 21 in the placebo group) with completion rates of 100% and 90.5%, respectively. The PP population consisted of 95.6% and 100% of the respectively groups. As with Study 857, the placebo group had more patients receiving three injections and less number of joints treated. There were only two premature discontinuations from the double-blind period, both from withdrawal of consent and both in the placebo group. There were 64 subjects in the open label period (45 AA4500 and 19 placebo) with six discontinuations (3 per original group) all due to loss to follow up. The number of injections and joints treated in this phase is in Table 7.

Table 7. AUX-CC-859. Subject disposition. Open Label Phase. ITT Population.

	AA4500 0.58 mg/ AA4500 0.58 mg[a] (N=45)	Placebo/ AA4500 0.58 mg[b] (N=19)	Total (N=64)
Intent-to-treat	45 (100.0)	19 (100.0)	64 (100.0)
Received ≥ 1 open-label injection	24 (53.3)	18 (94.7)	42 (65.6)
Did not receive any open-label injection but had ≥ 1 open-label efficacy or safety evaluation	21 (46.7)	1 (5.3)	22 (34.4)
Completed open-label phase[c], n/N (%)	42 (93.3)	16 (84.2)	58 (90.6)
Discontinued open-label phase, n/N (%):	3 (6.7)	3 (15.8)	6 (9.4)
Lost to follow-up	3 (6.7)	3 (15.8)	6 (9.4)
Time in open-label phase (days)[d]			
N	45	19	64
Mean (SD)	261.2 (47.78)	253.1 (58.46)	258.8 (50.84)
Median	273.0	274.0	274.0
Min, Max	71, 295	56, 283	56, 295
Distribution of time in open-label phase, n (%):			
1 to 84 days	1 (2.2)	1 (5.3)	2 (3.1)
85 to 168 days	2 (4.4)	1 (5.3)	3 (4.7)
169 to 252 days	2 (4.4)	1 (5.3)	3 (4.7)
> 252 days	40 (88.9)	16 (84.2)	56 (87.5)
Time in open-label treatment phase (days)[e]			
N	24	18	42
Mean (SD)	96.6 (46.91)	96.5 (62.38)	96.5 (53.37)
Median	92.5	79.5	90.0
Min, Max	22, 192	29, 220	22, 220
Time in open-label posttreatment phase (days)[f]			
N	45	19	64
Mean (SD)	206.0 (83.48)	123.7 (76.77)	181.6 (89.37)
Median	237.0	113.0	202.5
Min, Max	0, 295	0, 267	0, 295
Total number of open-label injections received, n (%):			
0[g]	21 (46.7)	1 (5.3)	22 (34.4)
1	5 (11.1)	6 (31.6)	11 (17.2)
2	7 (15.6)	5 (26.3)	12 (18.8)
3	3 (6.7)	3 (15.8)	6 (9.4)
4	4 (8.9)	0 (0.0)	4 (6.3)
5	5 (11.1)	3 (15.8)	8 (12.5)
6	0 (0.0)	1 (5.3)	1 (1.6)
Total number of open-label injections, n	69	46	115
Total number of joints treated in open-label, n (%):			
0	21 (46.7)	1 (5.3)	22 (34.4)
1	11 (24.4)	8 (42.1)	19 (29.7)
2	7 (15.6)	9 (47.4)	16 (25.0)
3	4 (8.9)	0 (0.0)	4 (6.3)
4	1 (2.2)	1 (5.3)	2 (3.1)
5	1 (2.2)	0 (0.0)	1 (1.6)
Total number of joints treated in open-label, n	46	30	76
Joints treated in double-blind + open-label	14	15	29
Joints treated in open-label only	32	15	47

Data source: Table 14.1.1b

[a] Subjects received AA4500 0.58 mg in both the double-blind and open-label phases.

[b] Subjects received placebo in the double-blind phase and AA4500 0.58 mg in the open-label phase.

[c] Completed the 12-month visit.

[d] Date last seen – (date of double-blind Day 90 visit + 1).

[e] Date of Day 30 visit after the last injection – (date of double-blind Day 90 visit) + 1. Subjects who did not receive open-label injections are not included in this summary.

[f] Date last seen – (Day 30 visit after the last injection + 1) + 1. For subjects who did not receive open-label injections, posttreatment duration is date last seen - date of double-blind Day 90 visit + 1.

[g] Subjects who completed the double-blind phase but did not receive any injections in the open-label phase.

6.1.1.1.10. Major protocol violations/deviations

In AUX-CC-857, the major deviation rate was 10.7% and 12.5% in the AA4500 and placebo groups respectively. The most common deviation was failure to receive the full treatment regimen of up to 3 injections when still eligible.

In AUX-CC-859, the protocol deviation rate was high (77.8% and 71.4%, respectively), however only two deviations were deemed major and led to exclusion from the PP population. There were six subjects with major deviations in the open label period.

6.1.1.1.11. Baseline data

Demographics were similar between treatment groups in both studies. Subjects had a mean age of 62-66 years, were male (70-87%) and White (>99%). There were on average three joints affected (range 1 to 13) with slightly more MP than PIP joints. The baseline characteristics were balanced in AUX-CC-857, while in the smaller study, the AA4500 group had a slightly higher mean number of affected joints (3.4 versus 3.0) which were PIP joints (2.0 versus 1.4). Other disease characteristics and risk factors were also balanced between the treatment groups. About half the subjects had a family history of Dupuytren's disease and 20-28% had a history of hand trauma. Alcohol use was frequent (>76%). The mean age at diagnosis was around 51-54 years. In Study 857, there was as slightly lower rate of prior surgery in the AA4500 compared to placebo group (35.8% versus 42.3%) and the rate of surgery was higher in both groups in Study 859 (53.3% versus 52.4%).

6.1.1.1.12. Results for the primary efficacy outcome

The rate of clinical success (a reduction in contracture to ≤5° by finger goniometry 30 days after injection) was significantly greater in the AA4500 treated primary joints than in those treated with placebo after the last injection in both studies (64.0% versus 6.8%, p<0.001 in AUX-CC-857 and 44.4% versus 4.8%, p<0.001 in AUX-CC-859) (Tables 8 and 9). After the first injection, the response rates were 38.9% versus 1.0% in Study 857 and 26.7% versus 4.8% in Study 859. The average number of injections at the primary joint was less in the AA4500 than the placebo group (1.7 versus 2.9 in Study 857 and 1.7 versus 2.8 in Study 859).

Table 8. AUX-CC-857. Reduction in contracture to 5 degrees or less of the Primary joint. ITT population.

	AA4500 N=203	Placebo N=103
All Primary Joints		
First injection		
N	203	103
Number (%) clinical success	79 (38.9)	1 (1.0)
p-value[b]	<0.001	-
Last injection		
N	203	103
Number (%) clinical success	130 (64.0)	7 (6.8)[c]
p-value[b]	<0.001	-
Average number of injections administered		
N	203	103
Mean (SD)	1.7 (0.8)	2.9 (0.4)
Min, Max	1, 3	1, 3
Average number of injections for success		
N	130	7
Mean (SD)	1.5 (0.7)	2.6 (0.8)
Min, Max	1, 3	1, 3

Data source: Table 14.2.2.1

[a] Clinical success: reduction of contracture to 5 degrees or less within 30 days of an injection.

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

[c] Two placebo subjects (1154-2715 and 1182-4309) had a reduction in contracture to within 0-5° after receiving AA4500 in error at their second injection (Appendix 16.2; Listing 16.2.6.1).

Table 9. AUX-CC-859. Reduction in contracture to 5 degrees or less of the Primary joint. ITT population.

	AA4500 0.58 mg (N=45)	Placebo (N=21)
All Primary Joints		
First injection		
N	45	21
Number (%) reduction in contracture to 5° or less	12 (26.7)	1 (4.8)
p-value[a]	NA	-
Last injection		
N	45	21
Number (%) reduction in contracture to 5° or less	20 (44.4)	1 (4.8)
p-value[a]	<0.001	-
Average number of injections administered		
N	45	21
Mean (SD)	1.7 (0.8)	2.8 (0.6)
Min, Max	1, 3	1, 3
Average number of injections for reduction in contracture to 5° or less		
N	20	1
Mean (SD)	1.5 (0.7)	1.0
Min, Max	1, 3	1,1

Data source: Table 14.2.2.1
NA=not applicable
[a] p-value based on Cochran-Mantel-Haenszel test comparing treatment group, stratified by baseline severity group and joint type.

Comment: No confidence intervals were reported for the primary efficacy outcome or for any of the other efficacy outcomes

6.1.1.1.13. Results for other efficacy outcomes

When assessed by joint type, a statistically significantly improved response over placebo was found at the MP joints in both studies (Study 857: 76.7% versus 7.2%, Study 859: 65.0% versus 9.1%). The response at the PIP joint was less than at the MP joint and was statistically significant in Study 857 (40.0% versus 5.9%, p<0.001) although was not significant in Study 859 (28.0% versus 0%, p=0.069) (Tables 10 and 11).

Table 10.AUX-CC-857. Reduction in contracture to 5 degrees or less of the Primary Joint by Joint type. ITT population.

	AA4500 N=133	Placebo N=69
Primary MP Joints		
First injection		
N	133	69
Number (%) clinical success	60 (45.1)	0
p-value[b]	<0.001	-
Last injection		
N	133	69
Number (%) clinical success	102 (76.7)	5 (7.2)
p-value[b]	<0.001	-
Average number of injections administered		
N	133	69
Mean (SD)	1.7 (0.8)	2.9 (0.4)
Min, Max	1, 3	1, 3
Average number of injections for success		
N	102	5
Mean (SD)	1.6 (0.8)	2.8 (0.5)
Min, Max	1, 3	2, 3
Primary PIP Joints		
First injection		
N	70	34
Number (%) clinical success	19 (27.1)	1 (2.9)
p-value[b]	0.002	-
Last injection		
N	70	34
Number (%) clinical success	28 (40.0)	2 (5.9)
p-value[b]	<0.001	-
Average number of injections administered		
N	70	34
Mean (SD)	1.8 (0.8)	2.8 (0.6)
Min, Max	1, 3	1, 3
Average number of injections for success		
N	28	2
Mean (SD)	1.3 (0.5)	2.0 (1.4)
Min, Max	1, 2	1, 3

Data source: Tables 14.2.2.2 and 14.2.2.3

MP=metacarpophalangeal; PIP=proximal interphalangeal

[a] Clinical success: reduction of contracture to 5 degrees or less within 30 days of an injection.

[b] p-value based on Cochran-Mantel-Haenszel test comparing treatment group, stratified by baseline severity group.

Table 11.AUX-CC-859. Reduction in contracture to 5 degrees or less of the Primary Joint by Joint type. ITT population.

	AA4500 0.58 mg	Placebo
Primary MP Joints		
First injection		
N	20	11
Number (%) reduction in contracture to 5° or less	9 (45.0)	1 (9.1)
p-value[a]	NA	-
Last injection		
N	20	11
Number (%) reduction in contracture to 5° or less	13 (65.0)	1 (9.1)
p-value[a]	0.003	-
Average number of injections administered		
N	20	11
Mean (SD)	1.5 (0.7)	2.7 (0.7)
Min, Max	1, 3	1, 3
Average number of injections for success		
N	13	1
Mean (SD)	1.4 (0.7)	1.0
Min, Max	1, 3	1,1
Primary PIP Joints		
First injection		
N	25	10
Number (%) reduction in contracture to 5° or less	3 (12.0)	0
p-value[a]	NA	-
Last injection		
N	25	10
Number (%) reduction in contracture to 5° or less	7 (28.0)	0
p-value[a]	0.069	-
Average number of injections administered		
N	25	10
Mean (SD)	1.8 (0.8)	2.8 (0.6)
Min, Max	1, 3	1, 3
Average number of injections for success		
N	7	NA
Mean (SD)	1.7 (0.8)	
Min, Max	1, 3	

Data source: Tables 14.2.2.2 and 14.2.2.3

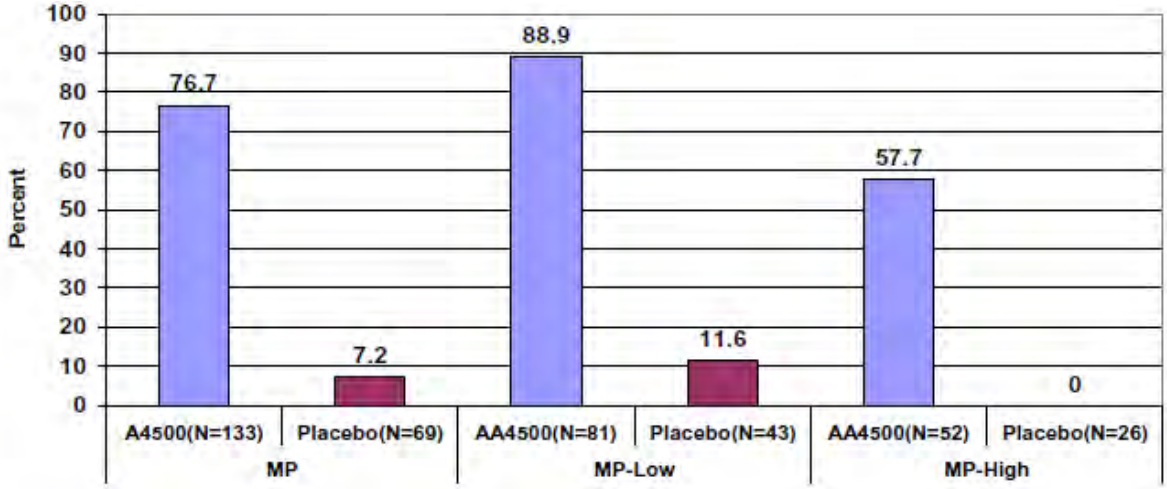
MP=metacarpophalangeal; NA=not applicable; PIP=proximal interphalangeal

[a] p-value based on Cochran-Mantel-Haenszel test comparing treatment group, stratified by baseline severity group.

In a sensitivity analysis, where subjects with missing day 30 evaluations were considered as not having reached clinical success, the results were similar for both studies. The median time to clinical success was significantly shorter in the AA4500 groups ($p<0.001$ both studies).

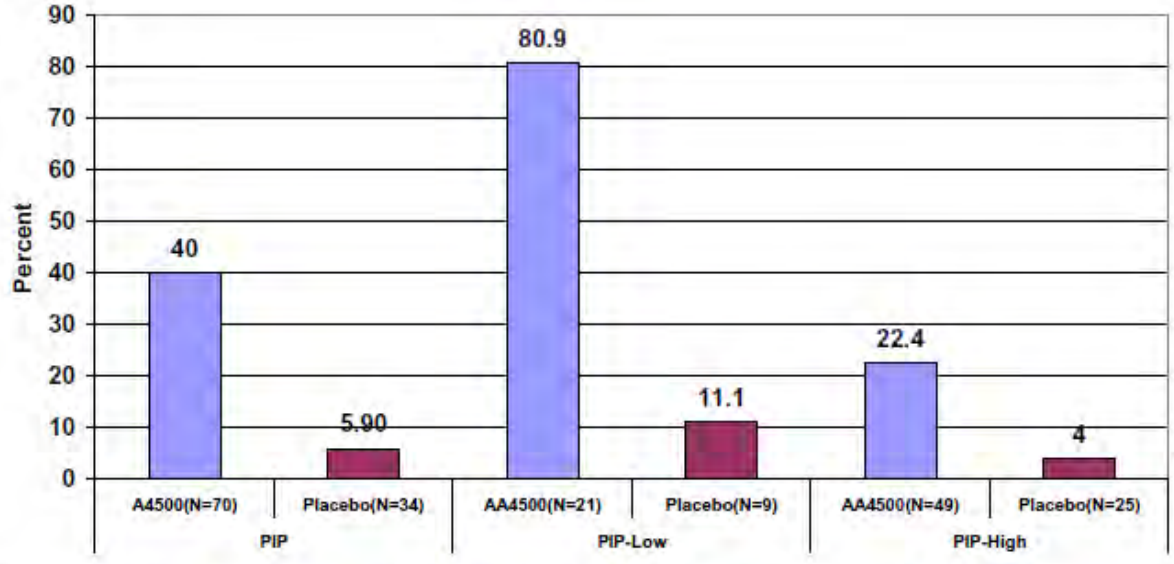
The rate of clinical success was higher for those with less severe degree of contracture (≤50° for MP and ≤40° for PIP joints) at both the MP and PIP joints. The severely contracted joints, however, still responded to treatment (MP: 57.7% versus 0% in Study 857 and 60.0% versus 0% in Study 859) (Figures 5-8).

Figure 5. AUX-CC-857. Clinical success of the Primary MP Joint Overall and by Baseline Severity. Modified ITT Population.



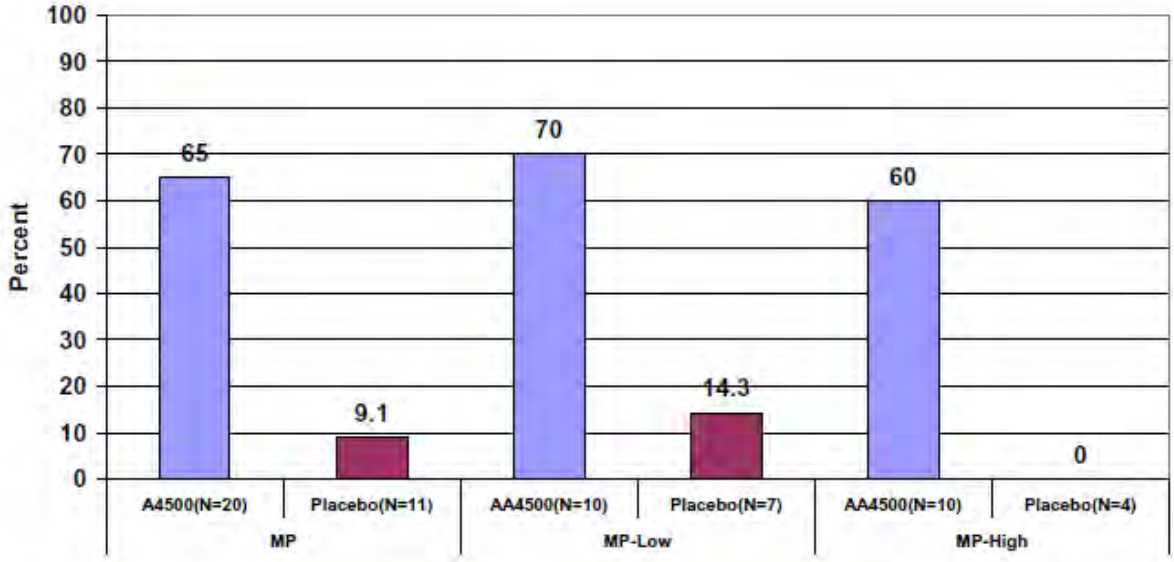
Data source: Table 14.2.2.2. and Appendix 16.2; Table 16.2.9 Statistical output supporting Table 14.2.2.2
Low severity fixed-flexion MP contracture: ≤ 50°; High severity fixed-flexion MP contracture: > 50°
Last injection=final injection of study drug into the cord. Individual cords could receive up to 3 injections of AA4500.

Figure 6. AUX-CC-857. Clinical success of the Primary PIP Joint Overall and by Baseline Severity. Modified ITT Population.



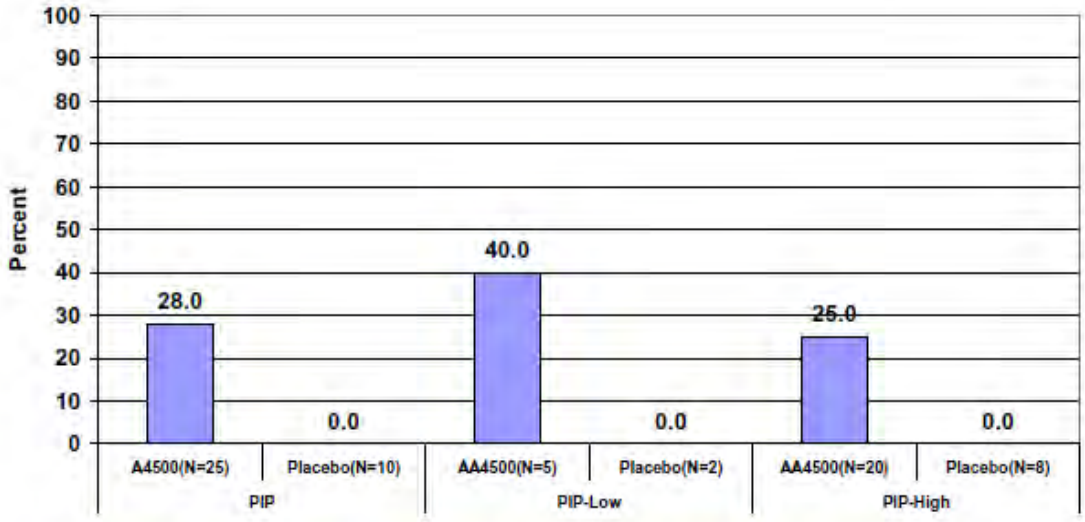
Data source: Table 14.2.2.3 and Appendix 16.2; Table 16.2.9 Statistical output supporting Table 14.2.2.3
Low severity fixed-flexion PIP contracture: ≤ 40°; High severity fixed-flexion PIP contracture: > 40°
Last injection=final injection of study drug into the cord. Individual cords could receive up to 3 injections of AA4500.

Figure 7. AUX-CC-859. Reduction in contracture to 5 degrees or less of the Primary MP Joint Overall and Baseline Severity following the last injection of study drug in Study AUX-CC-859.



Data Source: Table 14.2.2.2 and Appendix 16.2; Table 16.2.9 Statistical output supporting Table 14.2.2.2
MP-Low=≤ 50°; MP-High->50°
Last injection=final injection of study drug into the cord. Individual cords could receive up to 3 injections of AA4500 0.58 mg.

Figure 8. AUX-CC-859. Reduction in contracture to 5 degrees or less of the Primary PIP Joint Overall and Baseline Severity following the last injection of study drug in Study AUX-CC-859.



Data Source: Table 14.2.2.3 and Appendix 16.2; Table 16.2.9 Statistical output supporting Table 14.2.2.3
PIP-Low=≤ 40°; MP-High->40°
Last injection=final injection of study drug into the cord. Individual cords could receive up to 3 injections of AA4500 0.58 mg.

After the last injection of AA4500, 91.7% of MP and 64.3% of PIP joints in Study 857, and 95.0% and 60.0% respectively in Study 859, had achieved a reduction in contracture to ≤25°.

For joints that did not reach clinical success, about half did not receive the full treatment regimen. The main reason for this in both studies (as stated by the investigator) was that there was no palpable cord to inject.

The rate of clinical improvement (defined as ≥ 50% reduction from baseline in contracture) at the primary joint was significantly higher with AA4500 in both studies (Study 857: 84.7% versus 11.7%, Study 859: 77.8% versus 14.3%, p<0.001 for both).

In Study 857 the mean baseline contracture degree at the primary joint was 50.2° and 49.1° in the AA4500 and placebo groups, respectively. After the last injection the mean degree of contracture was 12.2° compared to 45.7° which represents a 79% and 8.6% decrease in the AA4500 and placebo groups, respectively. In Study 859, from a mean baseline of 53.2° and 50.0°, the mean degree of contracture after the last injection was 16.7° and 44.3° in the AA4500 and placebo groups, respectively. In both studies a similar trend was seen when assessed by MP joints and PIP joints although response was less at the PIP joint with a mean degree of contracture after AA4500 treatment of 21.7-24.0°. Similarly, the mean change in the range of motion was significantly improved in the AA4500 treatment compared to placebo at the primary joint and at both the MP and PIP joint assessments, although there was a significantly greater response at the MP than the PIP joints noted in Study 857 (p<0.001) (Table 12).

Table 12. AUX-CC-857 and 859. Mean change in Range of Motion from baseline to After the Last Injection Overall and by Joint type.

Range of Motion (°)	AUX-CC-857		AUX-CC-859	
	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**	-
95% CI[b]	27.8-34.9		18.3-32.5	
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**	-
95% CI[b]	35.0-44.4		21.5-41.1	
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**	-
95% CI[b]	12.3-30.7		1.8-37.0	

Data source: Tables 14.2.5.1, 14.2.5.2, and 14.2.5.3 of the CSR for Study AUX-CC-857; Tables 14.2.5.1, 14.2.5.2, and 14.2.5.3 of the CSR for Study AUX-CC-859; ISE Tables 14.27.1.4 and 14.27.2.4.

CI=confidence interval; 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 ANOVA with treatment group, joint type, and baseline severity as factors.

[b] CI is the 95% confidence interval around the differences in adjusted means between AA4500 subjects and placebo subjects.

At the end of double blind treatment, physician global assessment found higher rates of improvement with AA4500 (86% versus 3% much/very much improved). Subject satisfaction was higher with AA4500 and 87% of this group (compared to 32% in the placebo group) were very/quite satisfied with treatment.

6.1.1.1.14. Study 859 combined periods

Study 859 assessed treatment at all joints in the double-blind and open label period and found that clinical success rate was 67.7% for MP and 36.1% for PIP joints after the last injection. The MP and PIP joints received on average 1.6 and 1.7 injections, respectively. There were 11/62 (17.7%) MP joints and 34/72 (47.2%) PIP joints which did not achieve clinical success (contracture reduction to ≤5°). Again a higher response was seen at the less severely contracted joints. The highest responses were also found at the MP joint of the little finger and the PIP joint of the middle finger.

There were 19.4% of MP and 47.2% of PIP joints which did not achieve clinical success and also did not receive full treatment (up to 3 injections), the main reason again was no palpable cord to inject. For these joints, however, there was a 40.2% mean change from baseline in degree of contracture. After the last injection, 87% of MP and 58% of PIP joints had a contracture of ≤25° and overall 73% of joints were classed as clinically improved (≥50% reduction in contracture degree). The mean percentage change from baseline in degree of contracture was 79.5% and 57.6% and the mean change from baseline in range of motion was 31.5° and 26.3° for the MP and PIP joints, respectively. There were no subjects with recurrence of contracture during the 12 month study period. On the global assessment, there were 3 subjects (5.4%) who were found by the investigator to have become "minimally worse" and 9 (15.8%) of subjects who reported being "*neither satisfied nor dissatisfied*" or "*quite/very dissatisfied*" with the AA4500 treatment.

6.1.1.1.15. Post-hoc analyses

Subgroup analyses were conducted on combined data from the two studies. For subgroups of age, gender, weight quartile and body mass index (BMI) category there were no notable differences in response. There were too few diabetics (n=8) and non-Whites (n=1) to allow comparison in these groups. The response was noted to be lower at the Australian sites compared to the US sites (44% versus 64%) with a lower response at the PIP joint in Australia compared to the US (28% versus 40%).

Comment: The sponsor proposes this was due to more severe baseline PIP contracture in the Australian subjects. Certainly there was more disease in the PIP joints in the Australian study (mean number of affected PIP joints 2.0 compared to 1.4 in Study 857) although the mean baseline contracture of the PIP joints was similar between Study 859 and 857 (56° versus 54°).

6.1.1.1.16. Summary

AUX-CC-857 and AUX-CC-859 were Phase III, double-blind, randomised, placebo-controlled safety and efficacy studies in patients with Dupuytren's contracture. After a 90 day double blind period where up to 3 injections could be given, a statistically superior response in reducing the contracture to 5° or less at the primary joint was found (64.0% versus 6.8%, p<0.001 in AUX-CC-857 and 44.4% versus 4.8%, p<0.001 in AUX-CC-859). A positive response was seen after the first injection and the mean number of injections required to achieve clinical success was 1.5 in both studies. Treatment effect was seen at both the MP and PIP joints although response was less at the PIP joint as well as in joints with more severe contraction. There was improved response on the reduction in contracture degree and the range of motion. Results were consistent across subgroups of age, gender, weight and BMI and were associated with improvement in disease severity (as assessed by physicians) and subject satisfaction. Failure to achieve success was associated with not receiving the full injection course (52%) which was typically due to the physician having "no palpable cord to inject".

6.1.2. Other efficacy studies

6.1.2.1. Study AUX-CC-858

6.1.2.1.1. Design and methods

Study AUX-CC-858 was the nine month open label extension study of AUX-CC-857. It was conducted at 16 sites in the US between December 2007 and November 2008. The primary objective was the efficacy and safety evaluation of up to five injections of AA4500 (0.58 mg) in reducing the degree of contracture in multiple joints. Recurrence rate was a secondary objective. Subjects who completed the feeder Study 857 were eligible to enrol. If joints required further treatment either due to contracture >5° and the cord had received <3 injections, or there were other eligible cords, subjects could have up to five injections (maximum of 3 per cord) separated by four weeks. This allowed up to a maximum of eight injections over the total 12 month period. Study treatment with AA4500 and post injection treatment was the same as in

Study 857. Efficacy variables were also the same and analysis was conducted on the combined data from both Study 857 and 858.

6.1.2.1.2. Results

There were 286 subjects who entered the open label study (186 from the AA4500 and 100 from the placebo group) with 34.9% and 95.0%, respectively, who received ≥1 open label injection. Study completion was high (89-90%) and the main reasons for a premature discontinuation was "lost to follow up" and "other". When combined with Study 857, there were 299 subjects who had 542 joints treated and 869 injections given (Table 13). The number of joints treated and injections given is in Table 14. Most subjects (92.3%) had ≤5 injections in the combined studies.

Table 13. Number of Subjects and Joints treated in Studies AUX-CC-857 and AUXCC-858

	AA4500	Placebo	All
Double-Blind Phase (AUX-CC-857)			
Number of subjects treated	204	104	308
Number of primary and non-primary joints treated	287	106	393
• Number of primary joints treated	204	104	308
• Number of secondary joints treated	66	2	68
• Number of tertiary joints treated	17	0	17
Number of injections	444	297	741
Open-Label Phase (AUX-CC-858)			
Number of subjects entered open-label	186	100	286
Number of subjects treated with open-label AA4500[a]	65	95	160
Number of non-primary joints[b] treated with open-label AA4500	105	178	283
Number of injections	152	273	425
Open-Label Treatment All AA4500 (AUX-CC-857 and AUX-CC-858 pooled)	**AA4500**		
Number of subjects treated with AA4500[c]	299		
Number of primary and non-primary joints treated with AA4500	542 (204 primary + 338 non-primary)		
Number of evaluable[d] primary and non-primary joints treated	523		
Number of injections of AA4500	869		

Data source: Study AUX-CC-857; Appendix 16.2, Listing 16.2.6.2 and Tables 14.1.1a, 14.1.1c, 14.1.2a, and 14.1.2b

[a] 121 AA4500 and 5 placebo subjects did not receive open-label treatment but were followed for efficacy and safety.

[b] Joints treated with placebo during the double-blind phase and treated with AA4500 during the open-label phase were counted as non-primary for AA4500 population.

[c] This includes 95 subjects who received placebo in the double-blind phase but AA4500 in the open-label phase and 204 subjects who began treatment in the double-blind phase with AA4500.

[d] Nineteen AA4500 joints (15 MP and 4 PIP) were considered unevaluable because the fixed-flexion contracture measurement prior to the first injection was 5° or less, or the joint had no postbaseline measurements.

Table 14. AUX-CC-857 and 858. Subject disposition. AA4500 Population from Double blind and Open Label studies.

	Total[a] (N=299)
Completed,[b] n/N (%)	258 (86.3)
Discontinued, n/N (%):	41 (13.7)
Withdrew consent	7 (2.3)
Lost to follow-up	18 (6.0)
Adverse event	2 (0.7)
Administrative reason	2 (0.7)
Other	12 (4.0)
Not enrolled in open-label phase	5 (1.7)
Distribution of time in study from first AA4500 injection, n (%)[c]:	
1 to 84	13 (4.3)
85 to 168	45 (15.1)
169 to 252	47 (15.7)
253 to 336	85 (28.4)
> 336	109 (36.5)
Time in treatment phase[d]	
N	299
Mean (SD)	110.2 (83.59)
Median	88.0
Min, Max	2, 373
Time in posttreatment phase[e]	
N	299
Mean (SD)	163.1 (111.02)
Median	171.0
Min, Max	0, 364
Number of AA4500 injections received, n (%):	
1	90 (30.1)
2	51 (17.1)
3	61 (20.4)
4	36 (12.0)
5	38 (12.7)
6	9 (3.0)
7	6 (2.0)
8	8 (2.7)
Total number of AA4500 injections received, n	869
Total number of primary and non-primary joints treated, n (%):	
1	153 (51.2)
2	76 (25.4)
3	51 (17.1)
4	13 (4.3)
5	4 (1.3)
6	2 (0.7)
Total number of primary and non-primary joints treated, n	542

Data source: Tables 14.1.1c and 14.1.1d

[a] Subjects who received at least one injection of AA4500 0.58 mg during either the double-blind or open-label phase.
[b] Completed the 12-month visit.
[c] Date last seen – date of first AA4500 injection + 1.
[d] Date of Day 30 visit after the last injection – date of first AA4500 injection + 1.
[e] Date last seen – (date of Day 30 visit after the last injection) + 1.

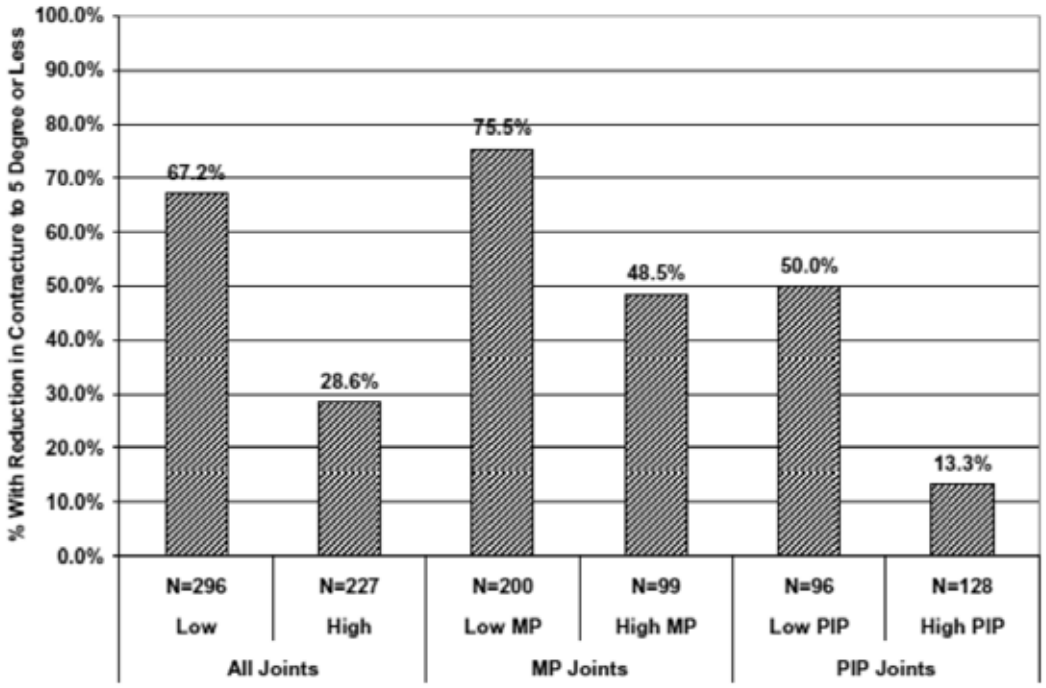
Note: There were nine subjects who never received AA4500; of these, four never had an open label evaluation and five were evaluated during the open label phase.
Note: two subjects (adverse events) and one subject (other; moved away) were reported as discontinued during the double-blind phase but had an open-label efficacy or safety measure.

In the combined study analysis of 523 joints[5], the rate of clinical success (reduction of contracture to 5° or less within 30 days after the last injection) was 50.5% with a higher response with the MP than PIP joints (66.5% versus 29.0%). On average 1.4 injections were given to achieve clinical success. The response was better in the less severely contracted joints (Figure 9) and efficacy was seen across the MP joints at all fingers (63.0% to 70.8%). Overall, there were 13.4% and 27.2% of MP and PIP joints, respectively, that did not achieve clinical success despite 3 injections of AA4500. There were a further 20.1% and 43.8% that did not achieve clinical success and did not receive 3 injections with the main reason being no palpable cord to inject. In the group of non-responders, there was still some clinical response with a

[5] There were 19 joints considered unevaluable due to contracture measurements ≤5° at first injection or there was no post-baseline measurement.

mean percentage change from baseline in contracture degree of 46.7% and 34.2% for the MP and PIP joints, respectively.

Figure 9. AUX-CC-857 and 858. Reduction in contracture to 5 degrees or less after the last injection of AA4500: by Joint Type and Baseline Severity. All Joints treated with AA4500 0.58 mg during the double-blind or open-label phases.



Data source: Table 14.2.7.2
MP=metacarpophalangeal; PIP=proximal interphalangeal
Low severity fixed-flexion MP contracture: ≤ 50°; high severity fixed-flexion MP contracture: > 50°
Low severity fixed-flexion PIP contracture: ≤ 40°; high severity fixed-flexion PIP contracture: > 40°
Last injection=final injection of study drug into the cord. Individual cords could receive up to three injections of AA4500.
Note: Nineteen AA4500 joints (15 MP and 4 PIP) were considered unevaluable because the fixed-flexion contracture measurement prior to the first injection was 5° or less, or the joint had no postbaseline measurements. These joints are included in Appendix 16.2; Listing 16.2.3 for Studies AUX-CC-857 and AUX-CC-858.

After the final injection, 90% of MP and 60% of PIP joints had reduction in contracture to ≤25°. The mean change from baseline in degree of contracture was 80.4% and 51.5% for the MP and PIP joints, respectively, and this was reflected in an improved range of motion or 33.3° and 23.1°, respectively. Physicians reported the contracture as very much/much improved (79.5%) and 82.9% of subjects were very/quite satisfied.

At the end of the 9 month open label period 12/264 (4.5%) joints had a recurrent contracture. Two cases were during placebo treatment in the double-blind phase. Nine of the 12 recurrences were at the PIP joints

6.1.2.1.3. Summary

In the combined analysis of Studies 857 and 858 there were 523 joints treated (286 subjects). The rate of clinical success over the combined 12 month period was 67% for MP joints and 29% for PIP joints with an average of 1.4 injections given to achieve this. Failure to achieve the contracture reduction to 5° or less occurred in 13% of MP and 27% of PIP joints treated with 3 injections. There were also 20% of MP and 44% of PIP joints that did not achieve the clinical success and had received <3 injections which was typically associated with lack of cord to inject. There was still some degree of clinical response in the non-responders with 60% of MP and

37% of PIP joints with ≥50% reduction in baseline contracture. Recurrence of contracture was recorded in 4.5% of responding joints.

6.1.2.2. Study AUX-CC-854 and AUX-CC-856

6.1.2.2.1. Design and methods

Study AUX-CC-854 and 856 were Phase III, nine month, open label efficacy and safety studies of up to five injections (maximum 3 per joint) of AA4500 0.58 mg in reducing the degree of contracture in multiple joints of subjects with advanced Dupuytren's disease. Study 854 was conducted between September 2007 and December 2008 at 12 sites in Europe and 8 in Australia and enrolled 386 subjects. Study 856 was conducted between October 2007 and October 2008 at 14 sites in the US and enrolled 201 subjects.

The inclusion and exclusion criteria were the same as previous studies. Subjects needed to be naive to AA4500 or could have received 1 or 2 injections in Studies AUX-CC-851, 853 or 855. Treatment and cord disruption was the same as in previously discussed studies. Efficacy analyses were on the ITT population and the primary endpoint was the reduction in contracture to 5° or less after the last injection. The sample size for both studies was chosen for the provision of safety data.

There were four protocol amendments (three dated prior to study commencement) in Study 854 and two amendments in Study 856. In these, numerous changes were made to further delineate inclusion/exclusion criteria and study assessments. These changes brought the protocols more in line with those of subsequent studies.

6.1.2.2.2. Results

There were 386 and 201 subjects included in Studies 854 and 856, respectively, with 92.7% and 83.6%, respectively, who completed the nine month study period. The main reasons for premature discontinuation were consent withdrawal (1.8% and 8.5%) and lost to follow up (3.4% and 5.0%) while adverse events were an infrequent reason (0.8% and 0.5%). There were 589 and 293 cords treated with most subjects having one or two treated (89% and 93%). The rate of significant protocol deviations was moderately high (25% in Study 854 and 33% in Study 856). This included two subjects in Study 854 and one in Study 856, who were enrolled in the study despite ineligible joints but were excluded from the efficacy analysis. Subjects were White (100%), male (87% and 82%), with a mean age of 63-65 years and, on average, 2.7-2.8 joints affected. There were 42% and 31% of subjects in Study 854 and 856, respectively, who had received prior surgical treatment.

In Study 854, 70.8% of MP joints and 41.0% of PIP joints (58.4% overall) had a reduction of contracture to 5° or less after the last injection (Table 15). The average number of injections given was 1.4. In Study 856, with the same mean injection number results were slightly lower with 67.0% of MP and 26.9% of PIP joints (52.7% overall) achieving clinical success (Table 16). As with previous studies, the clinical success was greater in the less severely contracted MP and PIP joints that the more severely contracted[6] (Study 854: 76.1% versus 31.5%, Study 856: 66.1% versus 29.2%). Efficacy was seen across all four digits, although there were few index fingers affected. Achievement of contracture reduction to ≤5° occurred after the first injection in 55-60% of MP and 19-32% of PIP joints. Failure to achieve clinical success after 3 injections occurred in 6.1-6.9% of MP and 9.8-22.1% of PIP joints in the two studies. Failure to achieve clinical success without having 3 injections occurred in 23.0-26.1% of MP and 49.2-51.2% of PIP joints. Again the main reason was not having a palpable cord to injection. In these subjects not achieving contracture reduction, the mean change from baseline in degree of contracture was 48.4% for MP and 20.5% for PIP joints in Study 854 and 55.3% for MP and 39.2% for PIP joints

[6] Low severity fixed-flexion MP contracture: ≤50°, fixed-flexion PIP contracture ≤40°; High severity fixed-flexion MP contracture: >50°, fixed-flexion PIP contracture >40°.

in Study 856. The clinical improvement rate for all joints was 78.9% and 71.6% in Study 854 and 856, respectively. This was associated with an improved range of motion of 30.7° and 28.3°, respectively, for all joints.

Table 15. AUX-CC-854. Reduction in contracture to 5 degrees or less after the First and Last injection of AA4500: Overall and by Joint Type. All Joints treated with AA4500 0.58 mg.

Injection Number	MP Joints (N=343)[a]	PIP Joints (N=244)[a]	All Joints (N=587)[a]
First			
Number (%) reduction in contracture to 5°or less	203 (59.2)	80 (32.8)	283 (48.2)
Last			
Number (%) reduction in contracture to 5°or less	243 (70.8)	100 (41.0)	343 (58.4)
Average number of injections administered			
Mean (SD)	1.3 (0.67)	1.5 (0.72)	1.4 (0.69)
Min, Max	1, 4	1, 4	1, 4
Average number of injections for reduction in contracture to 5° or less			
Mean (SD)	1.2 (0.53)	1.3 (0.56)	1.2 (0.54)
Min, Max	1, 3	1, 3	1, 3

Data source: Table 14.2.1a
MP=metacarpophalangeal; PIP=proximal interphalangeal
[a] N is the number of evaluable joints treated.
Note: Subject 5026-5211's left ring MP joint and Subject 5026-5229's right little MP joint had a baseline fixed-flexion contracture of 5°and received AA4500. These joints were considered unevaluable and were excluded from this summary.
Note: Subjects 5503-5532 and 6008-4714 received four injections to the right ring MP joint and the right ring PIP joint, respectively. The fourth injection for each subject was summarized with the last injection.
Note: Subjects 5603-5705, 6008-4701, 5026-5204, 5026-5217, 5026-5223, 5026-5224, 6006-4512, and 6008-4714 each had a joint with contracture measures between 0 and 5° at injections earlier than their last injection into the cord affecting that joint. These findings are summarized in the listing, but in this summary, a reduction in contracture to 5° or less was only counted if it occurred at the last injection.

Table 16. AUX-CC-856. Reduction in contracture to 5 degrees or less after the First and Last injection of AA4500: Overall and by Joint Type. All Joints treated with AA4500 0.58 mg.

Injection Number	MP Joints (N=188)[a]	PIP Joints (N=104)[a]	All Joints (N=292)[a]
First			
Number (%) reduction in contracture to 5° or less	104 (55.3)	20 (19.2)	124 (42.5)
Last			
Number (%) reduction in contracture to 5° or less	126 (67.0)	28 (26.9)	154 (52.7)
Average number of injections administered			
N	188	104	292
Mean (SD)	1.3 (0.62)	1.6 (0.80)	1.4 (0.70)
Min, Max	1, 3	1, 4	1, 4
Average number of injections for reduction in contracture to 5° or less			
N	126	28	154
Mean (SD)	1.2 (0.48)	1.4 (0.69)	1.2 (0.52)
Min, Max	1, 3	1, 3	1, 3

Data source: Table 14.2.1a
MP=metacarpophalangeal; PIP=proximal interphalangeal
[a] N is the number of evaluable joints treated.
Note: Subject 1158-8307's left little MP joint was injected with a baseline fixed flexion contracture of 5°. This joint was considered unevaluable and was excluded from this summary.
Note: Subject 1176-7413 received four injections to the right little PIP joint. The fourth injection was summarized with the last injection.
Note: Subjects 1168-7002 and 1179-7821 had PIP joints with contracture measures between 0° and 5° at injections earlier than their last injection to the joint. This finding was summarized in the listing but in this summary a reduction in contracture to 5° or less was only counted if it occurred at the last injection.

In Study 854, eight of 323 joints (2.3%) had a recurrence of contracture; three at the MP and five at the PIP joint. In Study 856, there were 11/154 (7.1%) recurrences; eight at the PIP joint, two at the MP joint and one at both the MP and PIP joints.

6.1.2.2.3. Summary

Studies AUX-CC-854 and 856 were nine month open label studies where subjects could receive up to five injections with a maximum of three per joint. There were 386 and 201 subjects who had 589 and 293 cords treated, respectively. Efficacy results were consistent with the pivotal trials with a reduction of contracture to 5° or less being achieved in 67-71% of MP joints and 27-41% of PIP joints with a greater response in the less severely contracted joints. Failure to achieve the defined response was again frequently associated with not having received three injections. The recurrence rate ranged from 2.3% to 7.1% and was more frequent at the PIP joint.

6.1.2.3. Study DUPY-303 and DUPY-404

6.1.2.3.1. Methods

DUPY-303 was a Phase III, double blind, randomised, placebo controlled, single-centre, study, conducted in the US between June 2003 and August 2005. Its primary objective was the assessment of efficacy and safety of AA4500 injections in reducing the degree of contracture in the primary affected joint of subjects with Dupuytren's disease, with the secondary objective being that of the secondary and tertiary affected joints. Subjects who had achieved clinical response could then be followed for up to 5 years. DUPY-404 was an open label, single-arm, five year extension study of DUPY-303 and enrolled subjects who had not achieved clinical success or who had other joints eligible for treatment.

The primary efficacy endpoint was clinical success (as previously defined) at the target MP or PIP joint. Inclusion and exclusion criteria were slightly broader than later trials. Subjects needed to have Dupuytren's disease with a fixed-flexion deformity of the finger(s) of at least 20 degrees, caused by a palpable cord, and a positive "table-top test". Exclusion criteria were surgery for Dupuytren's disease within past 30 days, allergy to doxycycline and medical conditions making them unsuitable for the trial.

Treatment was either 0.58 mg (10,000 units) of AA4500 or placebo injected into the cord of the affected joint with randomisation in a 2:1 ratio. Each joint could receive up to 3 injections. If clinical success was achieved prior to 3 injections then the secondary (or tertiary) joint could commence treatment. In the extension study, each subject was allowed up to five injections.

A sample size of 15 MP joints (10 AA4500 and 5 placebo) and 30 PIP joints (20:10) gave the study an 85% power (α=0.05) to detect a difference between active and placebo, assuming a clinical success rate of 90% for MP, 70% for PIP joints treated with AA4500 and 10% for those treated with placebo. A total of 116 subjects were initially planned to assess safety and allowing for dropouts.

The studies were initially sponsored by Advance Biofactures Corporation. With the transition of licensing of AA4500 to Auxilium in late 2004, the study enrolment was prematurely terminated. At this point, the 35 had subjects enrolled in Study 303 and a subset of 19 in Study 404. Study follow up was shorter than planned with a median follow up of 401 days (range: 246 to 597) in study 303 and 142 days (range: 128-240) in study 404.

6.1.2.3.2. Results

Of 35 subjects randomised, 33 (94.3%) completed the study and 19 entered Study 404. The groups were balanced on baseline characteristics. All of the subjects were Caucasian, with an average age of 61.3 years, predominantly male (80%) and 42.9% had previous surgery for Dupuytren's disease. Twenty-one (14:7) and 14 (9:5) subjects had primary MP and PIP joints respectively, with no significant differences between active and placebo groups for baseline characteristics of joints.

Comment: Due to the premature termination of enrolment, the number of affected joints meets the sample size requirement for MP joints but is only half the requirement for PIP joints.

Clinical success was achieved in 91.3% (21/23) of primary joints after up to 3 injections of AA4500 and 69.6% (16/23) after their first injection, compared to none in the 12 joints that received placebo (p<0.001). The mean number of injections for success was 1.4. The clinical success rate was 85.7% and 100% for primary MP and PIP joints, respectively. The median time to clinical success was 8.0 days after treatment with AA4500. For all primary joints there was a significant improvement in degree of contracture (95.6% versus 0%) and range of motion (150.4% versus 4.2) with AA4500. A secondary joint was treated in 9 subjects; 5 of 6 joints treated with AA4500 achieved clinical success after the last injection, while none of 3 treated with placebo did. One tertiary joint was randomised to AA4500 and achieved clinical success after the first injection. In Study DUPY-404, clinical success was achieved in 87.5% (14/16) of MP joints and 68.4% (13/19) of PIP joints.

Comment: There was no reporting on contracture recurrence.

6.1.2.3.3. Summary

The enrolment in Study DUPY-303 and its extension Study DUPY-404 in non-responders, was prematurely terminated due to change in licensing of AA4500. This resulted in a small sample size (35 and 19 subjects respectively). In the randomised controlled Study DUPY-303, there was a suggestion of efficacy with clinical success being achieved in 91.3% of A4500-treated subjects (compared to none in the placebo group) and similarly high rates in the MP and PIP joints (85.7% and 100%, respectively).

Comment: As the study was only conducted at one site, was terminated early, and the sample size was smaller than required to adequately power the study, the evaluator finds that the study provided only limited supportive efficacy evidence.

6.1.2.4. Study AUX-CC-851 and 852

This was a Phase III randomised double-blind, placebo-controlled study of the safety and efficacy of AA44500 in the treatment of Dupuytren's disease. Study 851 was the 90 day double-blind study and this was followed by Study 852 the nine month open label extension study. The study was conducted between November 2006 and December 2007 at three sites in the US. The planned enrolment was 216 subjects. The double-blind Study 851 was prematurely terminated in December 2006 due to a “manufacturing issue”. At this stage, 7 subjects had been randomised (2 placebo and 5 AA4500) and received the first injection of study medication. Two subjects entered the open label phase and only one completed the study. All other subjects discontinued prematurely. There was one clinical success documented.

Comment: The premature termination of the study resulted in a very small sample size and consequently no meaningful efficacy data were available.

6.1.2.5. Study AUX-CC-853

Study AUX-CC-853 was the same design as Studies 851 and 852 but with the double-blind and open label phases in the one protocol. The study was conducted at 2 sites in Australia between October 2006 and April 2007. The planned sample size was 48. Due to the above mentioned manufacturing issue, this study was also prematurely terminated in December 2006. At this stage 23 subjects (17 AA4500 and 6 placebo) had been randomised and received at least 1 injection. Of these, 21 entered the open label period. Clinical success during the double-blind period was reported at 76.5% and 0% in the AA4500 and placebo groups, respectively.

Comment: The premature termination of the study and sample size far smaller than planned mean that this study did not provide robust efficacy data.

6.1.2.6. Study DUPY-101

Study DUPY-101 was a single centre, Phase II, double-blind, randomised, placebo-controlled study of the safety and efficacy of a single injection of AA4500 in patients with Dupuytren's disease.

Comment: The dossier included a study protocol (dated 1999) and the sponsor stated that only data from a publication were available. Given the lack of a clinical study report and associated data, no evaluation was possible for this study.

6.1.2.7. Study AUX-CC-860

6.1.2.7.1. Methods

Study AUX-CC-860 was a non-treatment, long-term follow-up of subjects participating in the open label studies AUX-CC-854, 856, 857/858 and 859. It was conducted at 39 centres in the US, UK, Denmark, Finland, Sweden and Australia. The year two interim annual report, which covered visits between August 2009 and April 2010, was included in the dossier. The objectives of the study were to assess recurrence of contracture in joints which achieved clinical success, durability of response in joints with improvement, progression of disease in joints not treated or not effectively treated and long term safety. Subjects are followed once a year for 4 years (Years 2 to 5). The analysis was based primarily on investigator assessment the MP and PIP joint for recurrence[7], non-durability of response[8] or progression[9].

6.1.2.7.2. Results

There were 636 of a possible 950 subjects enrolled, with 634 having a post enrolment visit. The demographic and baseline disease characteristics were in line with the overall population from the feeder studies. Subjects had a mean age of 66 years, were predominantly male (85%) and all were White. Three quarters of subjects (74.8%) had at least one successfully treated joint and 35% at least one measurably improved[10] joint in the previous study. The successfully treated joints were typically MP joints of low baseline severity (60.4%) while the improved joints were split between MP and PIP joints and had a high baseline severity (72.9%). The joints not effectively treated were mainly PIP joints (70.9%).

By Day 730 of the study, 119/618 successfully treated joints had recurrence of contracture with a cumulative nominal rate of 19.3% and a Kaplan Meier estimate of 24.1%. The cumulative recurrence rate was higher in the PIP than the MP joints (34.1% versus 13.6%) and higher in joints with high baseline severity. For joints that had measurable improvement in the previous study, 31.5% (93/295) had a non-durable response at Day 730 with higher rates again in the PIP than the MP joints (42.9% versus 20.3%). For joints that were not effectively treated in the previous study, the rate of progression was 29.1% (44/151) with rates of 20.5% and 32.7% for the MP and PIP joints, respectively. In the untreated joints, new or worsening Dupuytren's contracture was noted in 1.9% of joints.

[7] Recurrence was assessed in successfully treated joints (i.e. reduction in contracture to 5° or less at the Day 30 evaluation after the last injection of AA4500 in a previous study) and was defined as an increase in joint contracture by at least 20° in the presence of a palpable cord, or the joint undergoes medical or surgical intervention primarily to correct a new or worsening Dupuytren's contracture in that joint.

[8] Non-durability of response was assessed in joints with measurable improvement in contracture (i.e. did not achieve clinical success but did have a reduction in baseline contracture of at least 20° at the Day 30 evaluation after the last injection or at the final evaluation) and was defined as an increase in joint contracture by at least 20° in the presence of a palpable cord, or the joint undergoes medical or surgical intervention.

[9] Disease progression was assessed in joints that either were not treated with AA4500 or not effectively treated (i.e. did not have at least a 20° reduction from baseline) and was defined as an increase in joint contracture by at least 20° in the presence of a palpable cord, or the joint undergoes medical or surgical intervention primarily to correct a new or worsening Dupuytren's contracture in that joint.

[10] Measurably improved joints were joints that did not have a reduction to 5° or less at the Day 30 evaluation after the last injection, but did have a reduction in baseline contracture of at least 20° at the Day 30 evaluation after the last injection or at the final evaluation.

Analysis based on change in degree of contracture found that for previously responsive contractures there was a worsening of contracture in 26.3% of joints (16.6% of MP and 44.5% of PIP joints). This is demonstrated in Figures 10 and 11 which show the mean change from baseline in fixed flexion contracture for all treated joints, and for the successfully treated joints, from baseline to Year 2.

Figure 10. AUX-CC-860. Mean change from baseline in Fixed Flexion Contracture. All Joints Treated with AA4500 0.58 mg.

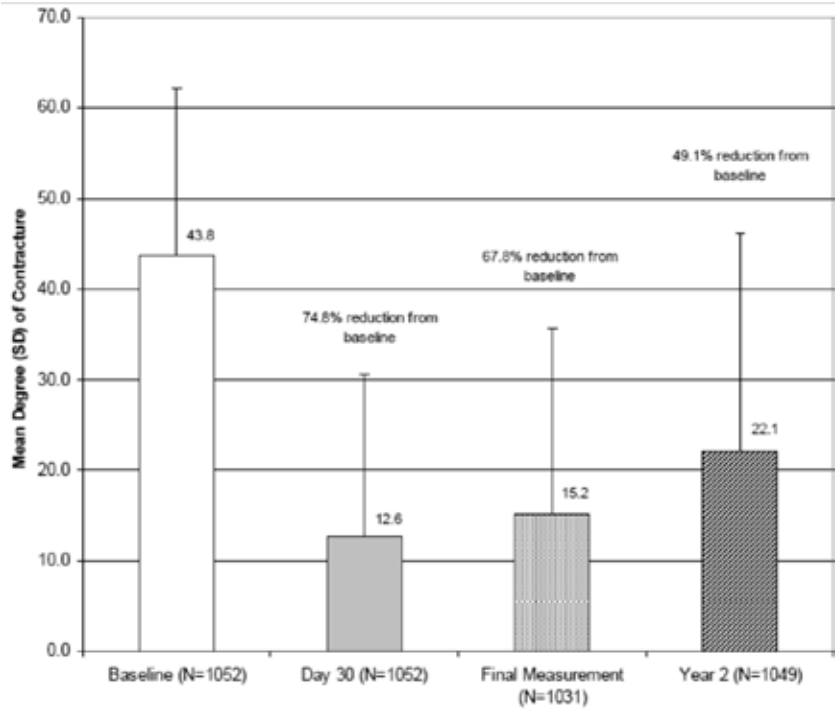
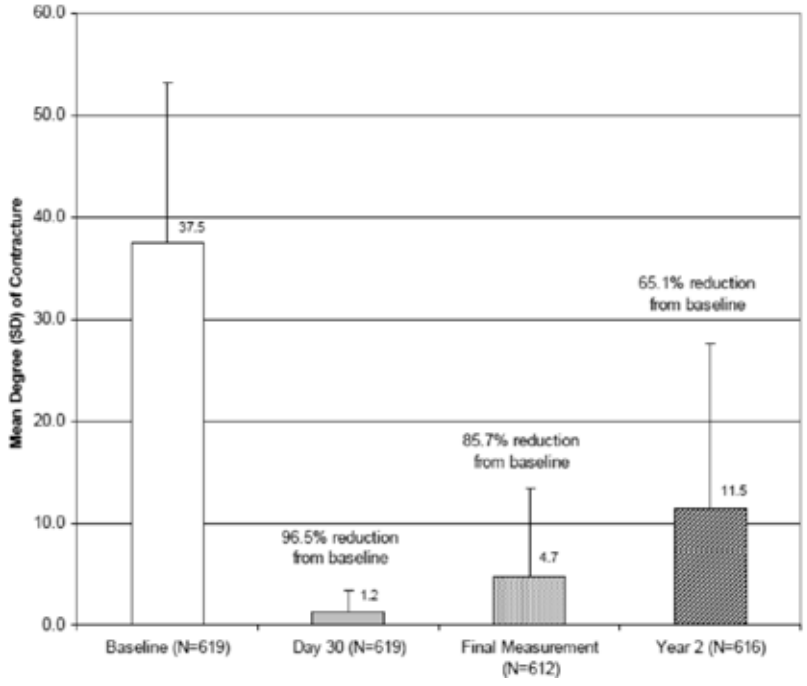


Figure 11. AUX-CC-860. Mean change from baseline in Fixed Flexion Contracture. Joints successfully Treated with AA4500 0.58 mg.



6.1.2.7.3. Summary

Study AUX-CC-860 followed up 634 subjects from a possible 950 subjects enrolled in open label extension studies. At the end for Year 2, it was found that of the 618 joints which had been successfully treated, the recurrence rate was 19% with higher recurrence in PIP than MP joints (34% versus 14%) as well as in the more severely affected joints at baseline. A non-durable response was noted in 32% of joints which had had a measurable response and progression was found in 29% of joints not effectively treated. The rate of worsening of disease in untreated joints was 1.9%.

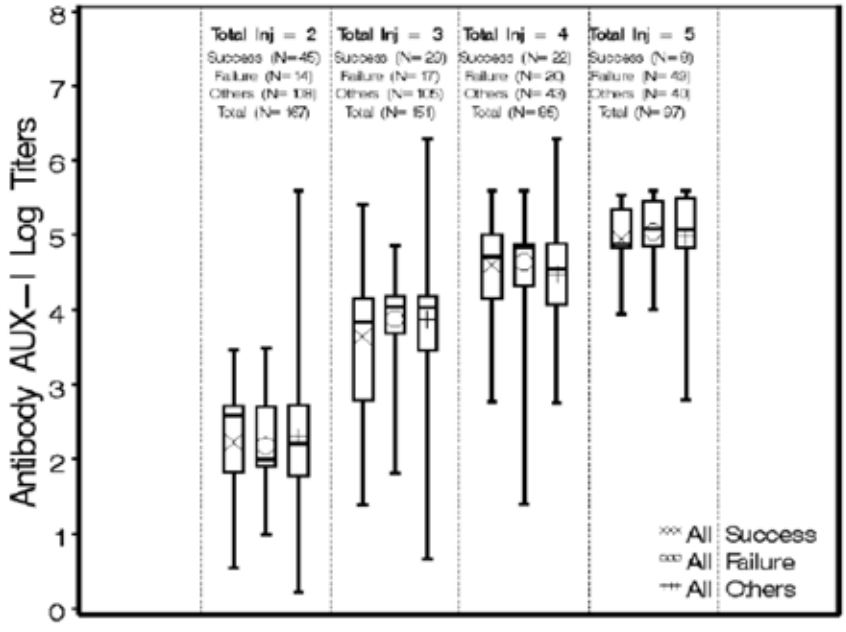
Comment: Data from the year 3 follow-up should be available and submitted for evaluation.

6.1.3. Analyses performed across trials (pooled analyses and meta-analyses)

The dossier included a Summary of Immunogenicity in which data were pooled from six clinical trials (AUX-CC-854, 856, 857, 858, 859 and 860). These studies all used AA4500 manufactured by the proposed commercial process. Antibody detection assays were validated ELISAs. Samples were collected 30 days post injection and at other predefined points. Data were pooled from 876, 498, 338, 197, 127, 33, 21 and 9 subjects who received 1, 2, 3, 4, 5, 6, 7 and 8 injections, respectively.

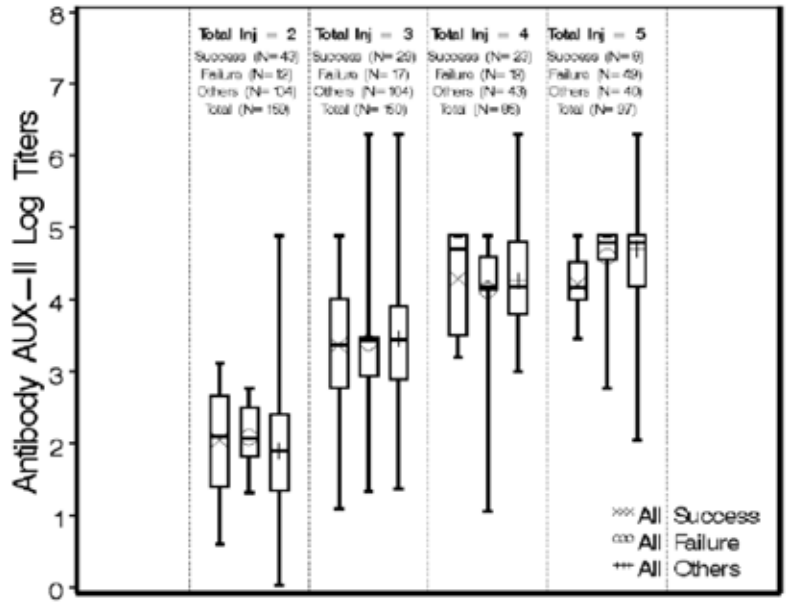
As discussed in *Secondary pharmacodynamic effects*, development of anti-drug antibodies was universal after 3 to 4 injections. The potential for antibody mediated effects on efficacy were assessed through a post-hoc analysis of clinical success and improvement versus anti-AUX-I/II titre. Subjects were classed as All Success if ≥2 joints were treated and all reached clinical success, All Failure if ≥2 joints were treated and all did not reach clinical success, or All Others if there was a combination of success/failure or only one joint was treated. Antibody titres just prior to the last injection of the last joint (up to third) were used. Box plots of results against antibody titre for cohorts of subjects who received the same number of injections failed to show any correlation between clinical outcome and antibody titre. In particular, there was no trend for poorer outcome with increasing titre (Figures 12 and 13). When the data were examined for clinical improvement (≥50% reduction from baseline in contracture degree), the results were similar (Figures 14 and 15).

Figure 12. AUX-I Antibody log titre levels relationship with next injection success- by total AA4500 injection



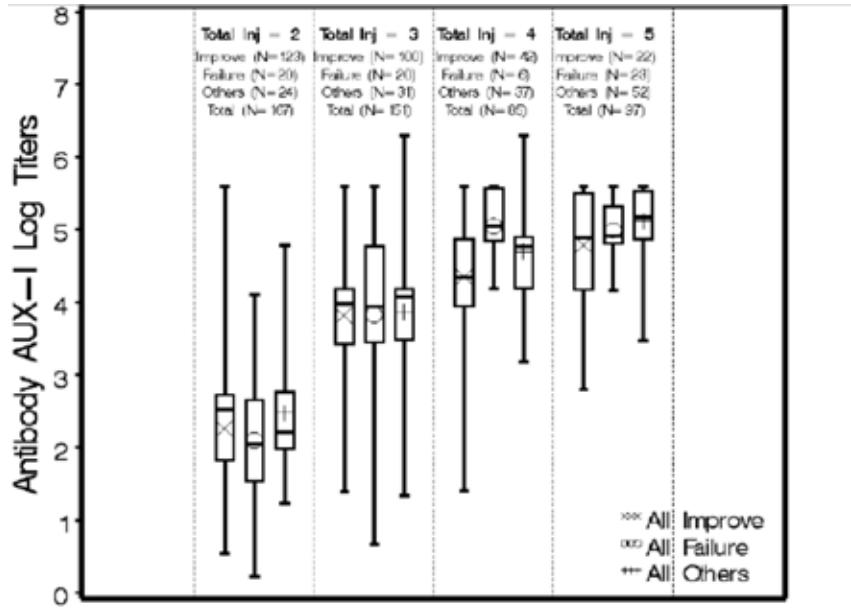
. Success=reduction in contracture to 5 degrees or less 30 days after the last injection

Figure 13. AUX-II Antibody log titre levels relationship with next injection success- by total AA4500 injection



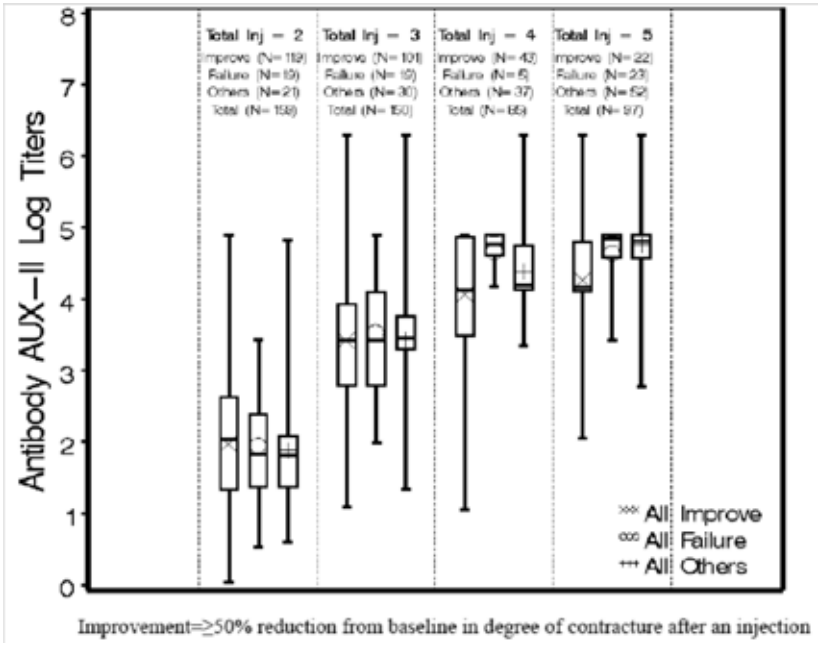
. Success=reduction in contracture to 5 degrees or less 30 days after the last injection

Figure 14. AUX-I Antibody log titre levels relationship with next injection improvement- by total AA4500 injection



. Improvement=≥50% reduction from baseline in degree of contracture after an injection

Figure 15. AUX-II Antibody log titre levels relationship with next injection improvement- by total AA4500 injection



Improvement=≥50% reduction from baseline in degree of contracture after an injection

6.2. Evaluator's conclusions on clinical efficacy for Dupuytren's disease

Dosage selection for the Phase III trials was based on Study DUPY-202 which assessed doses of 2500 U, 5000 U and 10,000U. All doses were found to be significantly better than placebo on clinical success rates, improvement in range of motion and reduction in flexion deformity. There was an evident dose response and the highest dose of 10,000 U (equivalent to 0.58 mg) had a response irrespective of joint type (MP or PIP) and was more effective on the more severely contracted joints. Given these efficacy findings and the lack of a significant difference in AE rates between the dose groups, the 10,000 U dose was selected for the Phase III trials.

Efficacy evaluation was based on two pivotal Phase III trials (AUX-CC-857 and AUX-CC-859). These had the same design with one being conducted in the US and the other in Europe and Australia. Placebo, rather than surgical treatment, was used for the comparator as this allowed blinding and safety assessment as well as not subjecting study participants to the risk of general anaesthesia. Needle fasciotomy was not considered due to high recurrence rates and lack of its routine use in clinical practice. Treatment was stratified by joint type (MP or PIP) and severity of primary joint contracture. In the double-blind phase of the studies up to 3 injections could be given, one a month, over a 90 day period. Subjects underwent a finger extension procedure on the day after the injection in attempt to disrupt the cord. Evaluation was via finger goniometry using a Neutral Zero Method at day 30 post injection. Subjects were required to have Dupuytren's disease with a fixed flexion deformity of at least one finger (other than the thumb) that was ≥20° and ≤100° for MP (≤80° for PIP) caused by a palpable cord and a positive "table top test". The primary endpoint was the proportion of subjects achieving a reduction in contracture of their primary joint to 5° or less at day 30 after the last injection.

In the two pivotal trials, subjects were invariably white (100%), male (80%) and aged between 55 and 74 years. Around 40% had previous surgery for their Dupuytren's disease. After a 90 day double-blind period where up to 3 injections could be given, a statistically superior response in reducing the contracture to 5° or less at the primary joint was found (64.0% versus 6.8%, $p<0.001$ in AUX-CC-857 and 44.4% versus 4.8%, $p<0.001$ in AUX-CC-859). A positive response was seen after the first injection and the mean number of injections required was 1.5 in both studies. Treatment effect was seen at both the MP and PIP joints although response was less at

the PIP joint and in joints with more severe contraction. Pooled efficacy data found the clinical success rate at the primary MP joint was 75.2% versus 7.5%, and at the primary PIP joint was 36.8% versus 4.5%. There was improved response on the reduction in contracture degree and the range of motion. It was noted that no confidence intervals were provided for the efficacy endpoints and this should be done.

Results were consistent across subgroups of age, gender, weight and BMI and were associated with improvement in disease severity (as assessed by physicians) and subject satisfaction. Failure to achieve success was associated with not receiving the full injection course (52%) which was typically due to the physician having "no palpable cord to inject".

There were five open label extension periods (DUPY404, AUX-CC-854, 856, 858 and 859) which included efficacy data and allowed non-primary joints to be treated. Subjects could receive up to 5 injections, maximum 3 per joint, in the 9 month period. Study 858 was the extension of 857 and 523 joints were treated. In Study AUX-CC-859, 64 subjects continued with 47 joints treated. Study AUX-CC-854 and 856 included 386 and 201 subjects who had 589 and 293 joints treated, respectively. Overall, efficacy results were consistent with the pivotal trials and confirmed that response was less with the PIP joints and more severely contracted joints.

Study AUX-CC-851, 852, 853 and DUPY-303 and 404 were all affected by premature termination of enrolment; Studies 303 and 404 due to the change in licensing of AA4500 and Studies 851, 852 and 853 due to "manufacturing issues". As a consequence the efficacy data are not sufficiently robust to draw conclusion although they do provide limited evidence which is in line with the major clinical studies.

Pooled data on immunogenicity from the clinical program found that anti-AUX-I or AUX-II antibodies were present in 100% of subjects by the third or fourth injection. Post-hoc analysis of clinical success and improvement versus anti-AUX-I/II titre indicated no relationship between titre level and treatment success or improvement, suggesting that there is likely no antibody-mediated effect on clinical efficacy.

Recurrence of contracture was assessed at 12 months through the pivotal trials and their extensions with longer term data coming from Study AUX-CC-860 which is following 634 subjects (from a possible 950) who were enrolled in open label extension studies. At 12 months the reported recurrence rate was 4.5% of responding joints in Studies 857/858 and 0% in Study 859. At the end of Year 2 (Day 730), of the 618 joints which had been successfully treated, the recurrence rate was 19%. Recurrence was higher in PIP than MP joints (34% versus 14%) and more severely affected joints at baseline. A non-durable response was noted in 32% of joints which had had a measurable response. Progression of disease was found in 29% of joints not effectively treated. The rate of worsening of disease in untreated joints was 1.9%. The data from the year three follow-up was not included, although should be available and submitted for evaluation.

7. Clinical safety

7.1. Studies providing evaluable safety data

There were 13 clinical studies in the development program of AA4500 in Dupuytren's disease. There were two early clinical studies (DUPY-101 and Badalente and Hurst [2000][11]) which were not included in the safety analyses due to the lack of clinical databases. The dose-ranging Study DUPY-202 and Studies DUPY-303 and DUPY-404 were sponsored by BTC and used an earlier formulation of AA4500. The Studies AUX-CC-851/852, AUC-CC-853 had enrolment terminated

[11] Badalamente MA and Hurst LC. Enzyme injection as nonsurgical treatment of Dupuytren's disease. *J Hand Surg*. 2000; 25A: 629-636.

early due to a manufacturing issue. There were 20 subjects included in these studies which rolled over into Studies AUX-CC-854 or 856.

In the pivotal efficacy Studies, AUX-CC-857 and AUX-CC-859, the following safety data were collected:

- General adverse events (AEs) as assessed by the investigator at each visit.
- Laboratory tests (haematology, clinical chemistry) and urinalysis.
- Electrocardiograms (ECGs), vital signs, hand grip strength by dynamometry (in kg) in the treated hand.
- Immunogenicity with bloods drawn prior to each injection and 30 days post each injection and at the Day 90 visit. Titres of anti-AUX-I and anti-AUX-II were determined.

The small early Study DUPY-303 provided some additional controlled safety data against placebo in 35 subjects. There were no pivotal safety studies however Study AUX-CC-860 was a non-treatment long-term follow-up which provided data on disease recurrence at two years.

Longer term safety data to 12 months post the first dose was provided by Studies DUPY-202, DUPY-303/404, AUX-CC-851/852, AUX-CC-853, AUX-CC-857/858, AUX-CC-859. These studies collected AEs, vital signs, grip strength, immunogenicity, and clinical laboratory tests (except in DUPY-303/404).

The pooled safety analysis populations are listed below in Table 17 below**.** The *Phase III double-blind placebo-controlled* population was used to compare AE rates to placebo. The *All subjects with at least one dose* was used to identify common events, assess subgroups and assess adverse event rates with increasing injection number. The *All subjects with 12 months post first dose* was used to assess long term safety. There was also the group of *All subjects with at least 1 dose (antibody determination)* which was used for immunogenicity analysis.

Due to the varying follow up time, in the population *All Subjects With At Least 1 Dose of AA4500,* TEAEs were analysed if they occurred from the injection to the 30 day evaluation visit post the last injection.

Table 17. Analysis Populations

Analysis Population	Studies	Subject Population
Phase 3 Double-Blind, Placebo-Controlled	DUPY-303, AUX-CC-857, AUX-CC-859 (double-blind phase only)	• AA4500 0.58 mg • Placebo
Phase 3 Double-blind, Placebo-Controlled in Support of the Prescribing Information	AUX-CC-857 and AUX-CC-859 (double-blind phase only)	• AA4500 0.58 mg • Placebo
All Subjects With At Least 1 Dose AA4500 0.58 mg	DUPY-202, DUPY-303, DUPY-404, AUX-CC-851, AUX-CC-853, AUX-CC-854, AUX-CC-855, AUX-CC-856, AUX-CC-857, AUX-CC-858, AUX-CC-859	• AA4500 0.58 mg
All Subjects With 12 Months Post First Dose AA4500 0.58 mg	DUPY-202, DUPY-303/404, AUX-CC-851/852, AUX-CC-853, AUX-CC-857/858, AUX-CC-859	• AA4500 0.58 mg
All Subjects With At Least 1 Dose AA4500 0.58 mg (Antibody Determination)	AUX-CC-851/852, AUX-CC-853, AUX-CC-854, AUX-CC-856, AUX-CC-857, AUX-CC-858, AUX-CC-859	• AA4500 0.58 mg

7.2. Pivotal studies that assessed safety as a primary outcome

None.

7.3. Patient exposure

There were 11 clinical trials providing safety data on 1,112 subjects. In this group, 13 subjects received placebo only, 17 subjects received doses of AA4500 <0.58 mg and 1,082 received at least one injection of AA4500 0.58 mg.

In the 'Phase III double-blind placebo-controlled' (DB PC) studies there were 272 AA4500 0.58 mg and 137 placebo-treated subjects with 532 cords treated (392 AA4500 and 140 placebo) with 990 injections (597 AA4500 and 393 placebo). The median participation duration was 92 days.

In the 'Subjects with at least one dose' group, there were 1082 subjects who had 1780 cords treated with 2630 injections and the median study participation duration was 275 days. In the 'All subjects with 12 months post first dose' group there 268 subjects who had 509 cords treated with 771 injections and 52% received 1 or 2 injections. For these subjects, the median study duration was 366 days.

Demographics have been discussed with the efficacy data. It is noted that there was a substantial proportion of subjects in the trials from Australia; approximately 15% in the double-blind population and 30% of subjects receiving at least one dose.

7.4. Adverse events

7.4.1. All adverse events (irrespective of relationship to study treatment)

7.4.1.1. Pivotal studies

In the pooled Phase III double-blind placebo-controlled (DB PC) studies, the rate of treatment emergent adverse events (TEAEs) was notably higher with AA4500 than placebo (97.8% versus 54.0%)(Table 18). In the AA4500 group, the rates of mild, moderate or severe TEAEs were 32.4%, 55.9% and 9.6%, while in the placebo group were 35.8%, 15.3% and 2.9%, respectively.

Table 18. First dose to end of double-blind study[a]. Overall summary of Treatment-Emergent and Treatment Related AEs. Phase III Double-blind, Placebo-controlled studies[b]. DUPY-303, AUX-CC-857 and AUX-CC-859 (double-blind phase).

	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, probable, or missing.

The most frequent TEAEs were peripheral oedema (75.7% versus 5.1%), contusion (50.7% versus 2.9%), injection site pain (39.0% versus 9.5%), injection site haemorrhage (34.9%

versus 2.9%) and pain in extremity (33.1% versus 3.6%). Other frequent (>10%) TEAEs were tenderness, ecchymosis, lymphadenopathy and pruritus.

Due to regional coding differences, the sponsor also analysed pooled data from the two pivotal studies using grouping of preferred terms. The majority of events were in the General disorders and Administration site conditions System Organ Class (SOC), the Injury/procedural complications SOC (mainly contusion 69.9% versus 3.2%) or Musculoskeletal disorders (mainly pain in extremity 34.9% versus 4.0%).

7.4.1.2. Other studies

For subjects who had at least one dose of study medication, TEAEs were virtually universal (98.3%) and 72.5% of subjects had a moderate or severe TEAE. In the 30 day period post last injection, the rate of TEAEs was 98.1%, with 68.2% of subjects having moderate/severe TEAEs. The rate of TEAEs then dropped to 32.3% in the period from Day 31 to the end of study. The data from the population of 'Subjects with 12 months post first dose' were similar to the population of subjects who received at least one dose.

The profile of TEAEs was similar to the DB PC studies when assessed in the other safety pools; subjects who had at least one dose of AA4500 (Table 19) and subjects with 12 months post first dose. The most common TEAEs were again peripheral oedema, contusion, injection site pain, pain in extremity, injection site haemorrhage and tenderness. In the post-treatment period (post Day 31), the only TEAEs occurring in ≥2% of subjects were recurrence of contracture (3.0%) and pain in extremity (2.3%). The rate of severe events in this period was 3.7%.

Table 19. Percentage of subjects with Treatment-Emergent (≥2.0% of subjects) and Treatment-related AEs. First dose AA4500 0.58 mg to End of Study. All subjects with at least 1 dose of AA4500 0.58 mg.

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	1064 (98.3)	1051 (97.1)
Peripheral edema[e]	842 (77.8)	837 (77.4)
Contusion[f]	595 (55.0)	590 (54.5)
Injection site pain	442 (40.9)	439 (40.6)
Pain in extremity	415 (38.4)	392 (36.2)
Injection site hemorrhage	374 (34.6)	369 (34.1)
Tenderness	319 (29.5)	310 (28.7)
Injection site swelling	263 (24.3)	261 (24.1)
Ecchymosis	196 (18.1)	194 (17.9)
Skin laceration	142 (13.1)	120 (11.1)
Pruritus	138 (12.8)	136 (12.6)
Lymphadenopathy	121 (11.2)	120 (11.1)
Blood blister	97 (9.0)	97 (9.0)
Axillary pain	73 (6.7)	72 (6.7)
Hematoma	60 (5.5)	56 (5.2)
Arthralgia	58 (5.4)	39 (3.6)
Injection site pruritus	57 (5.3)	57 (5.3)
Erythema	53 (4.9)	43 (4.0)
Injection site vesicles	48 (4.4)	48 (4.4)
Nasopharyngitis	44 (4.1)	3 (0.3)
Lymph node pain	41 (3.8)	40 (3.7)
Pain	41 (3.8)	37 (3.4)
Dupuytren's contracture	38 (3.5)	13 (1.2)
Swelling	35 (3.2)	33 (3.0)
Joint swelling	34 (3.1)	31 (2.9)
Headache	33 (3.0)	21 (1.9)
Upper respiratory tract infection	31 (2.9)	2 (0.2)
Dizziness	30 (2.8)	17 (1.6)
Paresthesia	30 (2.8)	24 (2.2)
Edema	28 (2.6)	26 (2.4)
Blister	26 (2.4)	25 (2.3)
Hypertension	24 (2.2)	4 (0.4)
Hypoesthesia	22 (2.0)	18 (1.7)

Note: Table includes TEAEs occurring in ≥ 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 Most involved swelling of the treated extremity.

f 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.

7.4.2. Treatment-related adverse events (adverse drug reactions)

7.4.2.1. Pivotal studies

The rate of treatment-related TEAEs in the DB PC safety pool was 97.4% and 26.3% in the AA4500 and placebo groups, respectively. Therefore, virtually all TEAEs in the AA4500 group were deemed as treatment-related and the profile of events is the same as for TEAEs overall. Data from the two pivotal studies listing TEAEs by SOC are shown in Table 20. The treatment-related TEAEs occurring in <1% of the AA4500 group but at a higher rate than the placebo group are listed in Table 21. In these two pivotal studies, the rate of severe treatment-related

TEAEs in the AA4500 group was 9.2% (none in the placebo group). The severe treatment-related TEAEs in the AA4500 group (n=23) were: injection site reaction (2%), pain in extremity (2%), peripheral oedema (1.6%), contusion (1.6%), injection site haemorrhage (1.2%), tenderness, injection site cellulitis, ligament injury, skin laceration, tendon rupture, chest wall pain and irritability (all <1%).

Table 20. All and Treatment-related AEs occurring in ≥1% of AA4500 treated subjects and at a greater incidence that Placebo. Studies AUX-CC-857 and AUX_CC-859.

	AA4500 N=249		Placebo N=125	
	All Adverse Events	Treatment-related Adverse Events[a]	All Adverse Events	Treatment-related Adverse Events
All Adverse Reactions	243 (89.3)	242 (89.0)	64 (46.7)	29 (21.2)
Blood and Lymphatic System Disorders:				
Lymph node pain	21 (8.4)	21 (8.4)	0 (0.0)	0 (0.0)
Lymphadenopathy[b]	33 (13.3)	32 (12.9)	0 (0.0)	0 (0.0)
Gastrointestinal disorders:				
Nausea	3 (1.2)	3 (1.2)	1 (0.8)	0 (0.0)
General disorders and Administration Site Conditions:				
Axillary pain	15 (6.0)	15 (6.0)	0 (0.0)	0 (0.0)
Inflammation	8 (3.2)	8 (3.2)	0 (0.0)	0 (0.0)
Injection site hemorrhage	95 (38.2)	95 (38.2)	4 (3.2)	4 (3.2)
Injection site reaction[c]	87 (34.9)	87 (34.9)	7 (5.6)	7 (5.6)
Injection site swelling[d]	61 (24.5)	61 (24.5)	8 (6.4)	8 (6.4)
Injection site vesicles	6 (2.4)	6 (2.4)	1 (0.8)	1 (0.8)
Peripheral edema[e]	183 (73.5)	183 (73.5)	6 (4.8)	6 (4.8)
Pruritus[f]	37 (14.9)	37 (14.9)	1 (0.8)	1 (0.8)
Swelling	6 (2.4)	6 (2.4)	0 (0.0)	0 (0.0)
Tenderness	60 (24.1)	60 (24.1)	0 (0.0)	0 (0.0)
Infections and Infestations:				
Lower respiratory tract infection	3 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Injury, Poisoning, and Procedural Complications:				
Contusion[g]	174 (69.9)	173 (69.5)	4 (3.2)	4 (3.2)
Skin laceration	22 (8.8)	22 (8.8)	0 (0.0)	0 (0.0)
Musculoskeletal and Connective Tissue Disorders:				
Arthralgia	11 (4.4)	10 (4.0)	1 (0.8)	1 (0.8)
Joint swelling	6 (2.4)	6 (2.4)	0 (0.0)	0 (0.0)
Myalgia	3 (1.2)	3 (1.2)	1 (0.8)	0 (0.0)
Pain in extremity	87 (34.9)	85 (34.1)	5 (4.0)	4 (3.2)
Nervous System Disorders:				
Burning sensation	3 (1.2)	3 (1.2)	0 (0.0)	0 (0.0)
Dizziness	4 (1.6)	3 (1.2)	0 (0.0)	0 (0.0)
Headache	6 (2.4)	5 (2.0)	5 (4.0)	2 (1.6)
Hypoesthesia	6 (2.4)	5 (2.0)	0 (0.0)	0 (0.0)
Paresthesia	7 (2.8)	6 (2.4)	1 (0.8)	1 (0.8)
Skin and Subcutaneous Tissue Disorders:				
Blister	11 (4.4)	11 (4.4)	0 (0.0)	0 (0.0)
Blood blister	10 (4.0)	10 (4.0)	0 (0.0)	0 (0.0)
Erythema	14 (5.6)	14 (5.6)	0 (0.0)	0 (0.0)
Hyperhidrosis	3 (1.2)	3 (1.2)	0 (0.0)	0 (0.0)
Rash	3 (1.2)	3 (1.2)	1 (0.8)	0 (0.0)

Data source: ISS Table 14.1.16.1 and 14.1.16.2

[a] Severe AEs: injection site reaction, pain in extremity (2%); peripheral edema, contusion (1.6%); injection site hemorrhage (1.2%); and tenderness, injection site cellulitis, ligament injury, skin laceration, tendon rupture, chest wall pain, irritability (<1%) (ISS Table 14.1.16.6).

[b] Includes the terms: lymphadenopathy and axillary mass

[c] Includes the terms: injection site reaction, injection site erythema, injection site inflammation, injection site irritation, injection site pain, and injection site warmth

[d] Includes the terms: injection site swelling and injection site edema

[e] Most involved swelling of the treated extremity.

[f] Includes the terms: pruritus and injection site pruritus

[g] Includes the terms: contusion (any body system) and ecchymosis

Table 21. Treatment-related AEs occurring in <1% of AA4500 treated subjects and at greater incidence than placebo. Studies AUX-CC-857 and AUX-CC-859.

- Blood and Lymphatic System Disorders: thrombocytopenia
- Eye Disorders: eyelid edema
- Gastrointestinal Disorders: abdominal pain upper, diarrhea, vomiting
- General Disorders and Administration Site Conditions: discomfort, fatigue, feeling hot, influenza like illness, injection site desquamation, injection site discoloration, injection site nodule, local swelling, malaise, edema, pain, pyrexia, therapeutic response unexpected
- Immune System Disorders: hypersensitivity
- Infections and Infestations: bronchitis, conjunctivitis infective, injection site cellulitis
- Injury, Poisoning, and Procedural Complications: ligament injury, limb injury, open wound, tendon rupture, wound dehiscence
- Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, lymph node palpable
- Musculoskeletal and Connective Tissue Disorders: chest wall pain, Dupuytren's contracture, groin pain, joint crepitation, joint stiffness, limb discomfort, muscle spasms, muscular weakness, musculoskeletral discomfort, musculoskeletal stiffness, neck pain, shoulder pain
- Nervous System Disorders: complex regional pain syndrome, monoplegia, syncope vasovagal, tremor
- Psychiatric Disorders: agitation, disorientation, insomnia, irritability, restlessness
- Reproductive System and Breast Disorders: breast tenderness, hypertrophy breast
- Respiratory, Thoracic, and Mediastinal Disorders: dyspnea, epistaxis, hyperventilation
- Skin and Subcutaneous Tissue Disorders: eczema, pain of skin, rash erythematous, rash macular, scab, skin discoloration, skin disorder, skin exfoliation, skin lesion, skin tightness, swelling face
- Vascular Disorders: hematoma, hypertension, hypotension

7.4.2.2. Other studies

For subjects with at least one dose of AA4500, the rate of treatment-related TEAEs was 97.1% with the event profile again being very similar to the overall TEAE profile (Table 19). In the subjects who had at least one injection of AA4500, most treatment-related TEAEs commenced on the injection day (80.6%) or the next day of finger manipulation (67.8%) compared to after Day 1 (33.4%). The rate of treatment-related TEAEs in the post-treatment period (Day 31 to end of study, median duration of 212 days) reduced to 7.8%. For subjects with 12 months of follow up, the rate of treatment-related TEAEs in this post-treatment period was 9.3%.

The rate of treatment-related TEAEs was relatively constant when examined by number of injections administered (1 to 8) with the exception of pruritus which increased from 3.7% after injection 1 to 22.0% after injection 6. Subjects with peripheral oedema were noted to generally have this event after each injection.

The mean duration of the treatment-related TEAEs of peripheral oedema, contusion, injection site pain and extremity pain did not appear to increase with increasing number of injections. This was also the case for other frequently reported treatment-related TEAEs. In addition, for the most frequently reported treatment-related TEAEs, the median treatment duration indicated that the event had in general resolved prior to the next scheduled injection.

7.4.3. Deaths and other serious adverse events

7.4.3.1. Deaths

There were 7 deaths (0.6%) in the clinical development program for AA4500 as follows: 2 subjects in AUX-CC-856 (myocardial infarction and acute myocardial infarction); 1 in AUX-CC-854 (acute myocardial infarction); 2 in DUPY-202 (iliac artery stenosis and liver cancer); and 2 in DUPY-101 (complications of pulmonary fibrosis and rupture of an aortic aneurysm). No death was considered treatment-related by the investigator.

7.4.3.2. Other serious adverse events

There were 92/1196 (7.7%) subjects in the 13 clinical trials with a non-fatal serious adverse event (SAE), 9 of whom had one that was deemed related to AA4500. These treatment-related non-fatal SAEs, which were typically associated with the treated hand, were: tendon rupture (n=3); ligament injury; tendonitis; finger deformity; Dupuytren's contracture and sensory disturbance of hand; DVT; and complex regional pain syndrome (Table 22). It is noted that the three tendon ruptures and one ligament injury (flexor pulley rupture) all occurred at the fifth finger PIP joint. In the DB PC studies, there were 2 SAEs in the placebo groups (acute cholecystitis and surgery for hip osteoarthritis).

Comment: The sponsor stated that after the two tendon ruptures and one ligament injury the study protocols were modified and investigators trained in a revised injection procedure particularly for the fifth finger PIP joints.

Table 22. Serious AEs Possibly or Probably related to AA4500.

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 repeated extended periods 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 3rd injection subject performed self manipulation of cord.
AUX-CC-855								
1167-1011	62/M	1	Tendon rupture/Rupture of 5th (right) digit flexor digitorum profundus	1 (1)/the subject underwent fusion of the DIP of the affected 5th 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.

Table 22 continued. Serious AEs Possibly or Probably related to AA4500.

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 5th 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 2nd 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

7.4.4. Discontinuation due to adverse events

7.4.4.1. Pivotal studies

In the three double-blind placebo-controlled studies, completion rates were high (94.5% and 95.6% in the AA4500 and placebo groups, respectively). Discontinuation due to adverse events was infrequent and only occurred in 3/272 (1.1%) subjects treated with AA4500 and there were no such cases in the placebo group. The cases were: injection site pain, dizziness and complex regional pain syndrome.

7.4.4.2. Other studies

In the group of 1082 subjects who had received at least one injection of AA4500, 87.6% completed the studies. There were 9/1082 (0.8%) subjects who discontinued due to an adverse event. In the long term population of 268 subjects the study completion rate was 95.9% and there was one (0.4%) discontinuation due to an AE (death). The events leading to discontinuation (apart from those listed above) were liver cancer, prostate cancer, gastrointestinal cancer, pancreatic cancer, lung cancer and myocardial infarction.

7.4.5. Laboratory tests

The sponsor defined clinically significant laboratory results are listed in Table 23 and clinically significant vital signs in Table 24.

Table 23. Sponsor defined clinically significant Laboratory criteria.

Analyte	Clinically Significant Low: Less than or equal to		Clinically Significant High: Greater than or equal to	
Hemoglobin	Conventional	SI	Conventional	SI
Female	≤ 10 g/dL	≤ 100 g/L	≥ 19 g/dL	≥ 190 g/L
Male	≤ 11 g/dL	≤ 110 g/L	≥ 20 g/dL	≥ 200 g/L
Hematocrit	≤ 30%	≤ 0.3 L/L	≥ 60%	≥ 0.6 L/L
Platelets	≤ 100x10^3/uL	≤ 100x10^9/L	≥ 650 x10^3/uL	≥ 650 x10^9/L
ALT (U/L)			≥ 3xULN	
AST (U/L)			≥ 3xULN	
Creatinine			≥ 3.0 mg/dL	≥ 300 mmol/L
BUN			≥ 35 mg/dL	≥ 12 mmol/L

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal.

Table 24. Sponsor defined clinically significant Vital Sign Values.

Parameter	Clinically Significant Low:	Clinically Significant High:
Systolic blood pressure	≤ 90 mmHg and decrease ≥ 20 mmHg from baseline	≥ 180 mmHg and increase ≥ 20 mmHg from baseline
Diastolic blood pressure	≤ 50 mmHg and decrease ≥ 15 mmHg from baseline	≥ 105 mmHg and increase ≥ 15 mmHg from baseline
Pulse rate	≤ 50 bpm and decrease ≥ 15 bpm from baseline	≥ 120 bpm and increase ≥ 15 bpm from baseline
Respiratory rate	≤ 8 rpm and decrease ≥ 7 rpm from baseline	≥ 25 rpm and increase ≥ 7 rpm from baseline
Temperature		≥ 38.3°C (≥ 101°F) and increase > 1.1°C (> 2°F) from injection baseline

bpm = beats per minute, rpm = respirations per minute

7.4.5.1. Pivotal studies

There were no notable mean changes between baseline and final assessment in haematology or clinical chemistry (including liver and renal function, cholesterol, triglycerides and glucose) parameters in the DB PC safety population, nor were there any notable differences between the AA4500 and placebo groups. Study DUPY-303 did not have post baseline laboratory assessments.

Clinically significant laboratory values were infrequent. There were two subjects with low haemoglobin (≤100 g/L women, ≤110 g/L men) (0.8%) and two with low platelets (≤100 x10^9/L)(0.8%) in the AA4500 group, compared to none in the placebo group. Increased blood urea nitrogen (BUN ≥12 mmol/L) was noted in three (1.3%) and one (0.8%) and increased aspartate aminotransferase (AST) (3x upper limit of normal (ULN)) in two (0.9%) and one (0.8%) subject in the AA4500 and placebo groups, respectively. There was one placebo-treated subject with elevated ALT. One case of thrombocytopaenia and one increased AST in the AA4500 group were also AEs.

7.4.5.2. Other studies

For subjects with at least one dose of AA4500, the rate of clinically significant low haemoglobin or low platelets was 0.4% each and the rate of increased BUN, increased ALT and increased AST was 1.0%, 0.6% and 0.7%, respectively. Eight of these subjects had an associated AE with an approximate rate of 0.9%.

In the long term population (subjects with 12 months post first dose) there was no meaningful change from baseline in laboratory assessments and the rates of clinically significant values were low. The highest rate was increased BUN (2.4%, n=4).

7.4.6. Vital signs

7.4.6.1. Pivotal studies

There were no clinically relevant changes in vital signs in the DB PC population. The rates of clinically significant vital signs were similar between the AA4500 and placebo groups. Adverse event rates in the respective groups for increased blood pressure (0.7% both), increased body temperature (0.7% both), hypertension (1.5% versus 2.9%) and hypotension (0.4% versus 0%) were unremarkable.

7.4.6.2. Other studies

For subjects with at least one dose of AA4500, there were no notable mean changes in vital signs and the rates of clinically significant vital signs were similar to the controlled population. The rate of TEAEs of tachycardia, blood pressure decreased and hypotension was 0.1% each, body temperature increased was 0.4%, blood pressure increased was 1.2% and hypertension was 2.2%. There were no other notable findings in the population of subjects with 12 months data.

7.4.7. Grip Strength

7.4.7.1. Pivotal studies

In the primary hand, the mean change in hand grip strength, as measured by hand-held dynamometry, from baseline to final assessment was 0.8 kg (standard deviation (SD) 9.3) and -0.7 kg (SD 8.1) in the AA4500 and placebo groups, respectively. There were insufficient numbers with final visit assessments of the secondary hand to comment on the mean change.

Comment: These changes do not indicate any adverse findings in relation to hand grip strength.

7.4.7.2. Other studies

In subjects with at least one dose of AA4500, the mean change in hand grip strength was 2.2 kg (SD 9.2) in the primary hand and 0.6 (SD 8.4) in the secondary hand. In subjects with 12 months post first dose of AA4500, the mean change in the primary hand was 2.9 kg (SD 9.1) and in the secondary hand was 0.9 kg (SD 7.3).

7.5. Postmarketing experience

The sponsor's Summary of Clinical Safety contained a review of postmarketing reports to 31 March 2011 and Module 5 contained four reports covering this period from 2 February 2010 (data of approval in the US) to 31 March 2011. The sponsor reported that in the US between launch in March 2010 to 31 March 2011 more than 7300 vials have been sold. Over this period there were 160 reports of which 146 were non-serious and 14 were serious. The majority of reports were in the SOCs of General disorders/administration site conditions (41/146 non serious and 1/14 serious) and Procedural complications (41/146 non-serious and 2/14 serious). The most frequent events were skin laceration (n=48), peripheral oedema (n=41), contusion (n=37), drug ineffective (n=19), pain in extremity (n=14), injection site haematoma (n=12) and lymphadenopathy (n=10). The serious events included: two cardiac events (one atrial fibrillation with possible allergic reaction and the other a fatal (heart attack) 5 days post injection in a 79 year old with cardiac risk factors); one pulmonary embolism one month post injection; one fatal aortic dissection 2 hours post injection; one death from a ruptured abdominal aortic aneurysm one month post injection; 2 tendon ruptures, 1 tendon damage and 5 skin tears requiring skin grafting.

Comment: The sponsor stated that the tendon damage and rupture is possibly due to inadvertent injection into collagen containing structures other than the

Dupuytren's cord and the skin tears are likely due to the finger manipulation procedure rather than the product.

7.6. Safety issues with the potential for major regulatory impact

7.6.1. Unwanted immunological events

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 at screening and 30 days post injection for determination of anti- AUX-I and anti-AUX-II antibodies. The AA4500 used in these studies were produced by the commercial manufacturing process (Process 3). As discussed in *Secondary pharmacodynamic effect*, over 85% of subjects had ADAs after one injection and all did so by the third or fourth injection.

In the clinical program there were eight TEAEs coded as hypersensitivity reactions, three of which were classed as related and these were all local reactions on the treated hand (local allergic reactions of redness itch, heat and swelling of the treated hand). The other five cases were deemed non-related (rash behind knee, nasal allergy, allergic symptoms, allergic cough, and swollen lip from possible bee sting). There were also three cases of urticaria, two of which received a subsequent AA4500 injection without premedication or reappearance of the hives. There were no identified cases of systemic anaphylaxis.

Treatment-related events possibly associated with an immunologic event were examined by injection number and no association was found between increasing number of injections (and by inference an increase in antibody titre) with increasing event rates except for pruritus and to a less extent peripheral oedema (Table 25). In addition, there was no evident increase in the median duration of these TEAEs after receipt of a higher number of injections.

Table 25. Most frequently reported treatment-related AEs 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.

	AA4500 0.58 mg							
Preferred Term[b]	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	1029 (95.1)	605 (94.7)	389 (92.6)	233 (93.2)	140 (89.2)	36 (87.8)	25 (92.6)	14 (100.0)
Peripheral edema[c]	731 (67.6)	413 (64.6)	263 (62.6)	176 (70.4)	116 (73.9)	30 (73.2)	21 (77.8)	11 (78.6)
Contusion[d]	517 (47.8)	240 (37.6)	127 (30.2)	73 (29.2)	49 (31.2)	12 (29.3)	10 (37.0)	4 (28.6)
Injection site pain	344 (31.8)	172 (26.9)	111 (26.4)	54 (21.6)	37 (23.6)	11 (26.8)	7 (25.9)	4 (28.6)
Pain in extremity	282 (26.1)	146 (22.8)	79 (18.8)	42 (16.8)	22 (14.0)	7 (17.1)	6 (22.2)	2 (14.3)
Injection site swelling	176 (16.3)	117 (18.3)	84 (20.0)	41 (16.4)	21 (13.4)	6 (14.6)	2 (7.4)	2 (14.3)
Pruritus	40 (3.7)	50 (7.8)	51 (12.1)	27 (10.8)	26 (16.6)	9 (22.0)	3 (11.1)	2 (14.3)
Lymphadenopathy	92 (8.5)	29 (4.5)	16 (3.8)	7 (2.8)	2 (1.3)	0 (0.0)	1 (3.7)	0 (0.0)
Injection site pruritus	18 (1.7)	15 (2.3)	19 (4.5)	15 (6.0)	8 (5.1)	1 (2.4)	2 (7.4)	0 (0.0)

Data source: ISS Table 14.2.19.1

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 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 Most involved swelling of the treated extremity.

d 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.

The sponsor undertook an assessment of the relationship between ADA titre and the severity of adverse events of peripheral oedema, contusion, injection site pain, extremity pain, injection site swelling, pruritus, lymphadenopathy and injection site pruritus. This showed that there was no obvious increase in ADA titre in subjects with severe events.

Comment: No formal statistical analysis of this was undertaken.

The sponsor also medically reviewed the TEAEs for events possibly related to inhibition of endogenous collagenases (MMPs) by anti-AUX-I and anti-AUX-II antibodies. There were no musculoskeletal events of polyarthritis, osteolysis or shoulder pain/reduction of range of motion. Joint stiffness and swelling was noted after the first as well as subsequent doses and

Dupuytren's disease was not noted to worsen. The sponsor reported that *in vitro* studies, using 71 samples from AUX-CC-860, found no potential for cross-reactivity of ADAs with the endogenous human MMPs (1, 2, 3, 8 and 13).

7.7. Other safety issues

7.7.1. Safety in special populations

7.7.1.1. Age

An assessment of the most frequent TEAEs by age group did not reveal any trends. The rate of severe TEAEs was slightly higher in those aged ≥75 years than those aged 45-74 years (18.5% versus 14.3-15.5%)

7.7.1.2. Gender

The rates of TEAEs were similar between males and females.

7.7.1.3. Weight/body mass index

The rate of TEAEs was similar when assessed by body weight quartiles and by body mass index category (normal, overweight, obese).

7.7.1.4. Race

There were only five non-White subjects in the clinical program so assessment by race was not possible.

7.7.1.5. Diabetes

There were 104 subjects with a history of diabetes and the rate of TEAEs in this group was similar to those with no history of diabetes. TEAE severity was also similar.

7.8. Safety related to drug-drug interactions and other interactions

Subjects were excluded from the clinical development program if they had received anticoagulants (except low dose aspirin) within 7 days of AA4500 injection. Caution is recommended in subjects receiving anticoagulants due to the risk of haemorrhage and concomitant use not advised.

Tetracycline derivatives may inhibit mammalian MMPs and therefore there exists a potential for these drugs to reduce the activity of AA4500. Subject who had received doxycycline or a doxycycline derivative within 14 days were excluded from the trials.

The sponsor reported literature cases of *in vitro* inhibition of clostridial collagenase by antimitotic agents daunomycin and adriamycin and the antimicrobial agent berberine and its derivatives.

7.9. Evaluator's overall conclusions on clinical safety

There were 13 clinical studies in the development program of AA4500 in Dupuytren's disease, although two early clinical studies were not included in the safety analyses due to the lack of clinical databases. In the 11 included clinical trials, there were 1,082 subjects who received at least one injection of AA4500 0.58 mg and 1780 cords were treated with 2630 injections.

In the two pivotal efficacy studies, AUX-CC-857 and AUX-CC-859, there were 272 subjects who had 392 cords treated with AA4500 and 137 subjects with 393 cords treated with placebo over a median participation duration of 92 days. There were also 268 subjects with at least 12 months of data post the first dose of AA4500 and half of these subjects received one or two injections.

Adverse events were virtually universal and notably higher than placebo (98% versus 54%). Nearly all TEAEs were classed as treatment-related (97% versus 26%) with most commencing on the injection day (80.6%) or the next day of finger manipulation (67.8%) rather than after Day 1 (33.4%). The duration of the TEAEs was such that, in general, they had resolved prior to the next scheduled injection one month later.

The profile of TEAEs was similar between the pivotal trials and the other safety populations and, as to be expected with a product lacking systemic exposure, the safety risks were mainly associated with the treated hand. The most frequent TEAEs were peripheral oedema (75.7% versus 5.1%), contusion (50.7% versus 2.9%), injection site pain (39.0% versus 9.5%), injection site haemorrhage (34.9% versus 2.9%) and pain in the extremity (33.1% versus 3.6%). Other frequent (>10%) TEAEs were tenderness, ecchymosis, lymphadenopathy and pruritus.

Most events were mild (32%) or moderate (56%) with severe TEAEs being less frequent (10%). All, except three cases, of the severe TEAEs were treatment-related (9% versus 0%) and these included injection site reaction, pain in extremity, peripheral oedema, contusion, injection site haemorrhage, tenderness, injection site cellulitis, ligament injury, skin laceration, tendon rupture, chest wall pain and irritability.

The rate of treatment-related TEAEs was relatively constant when examined by number of injections administered (1 to 8) with the exception of pruritus which increased from 3.7% after injection 1 to 22.0% after injection 6. Peripheral oedema was noted to occur after each injection.

There were 7 (0.6%) deaths in the clinical program with none being considered treatment-related. The rate of non-fatal SAEs was 7.7% and there were 9 (0.8%) treatment-related cases: tendon rupture (n=3, 0.3%); ligament injury; tendonitis; finger deformity; Dupuytren's contracture and sensory disturbance of hand; DVT; and complex regional pain syndrome. Post-marketing data (to March 2011) noted 160 reports with 14 serious cases including 2 tendon ruptures, 1 tendon damage and 5 skin tears requiring grafting. Discontinuation due to adverse events was infrequent (1.3% in the 13 clinical trials overall) and three cases were classed as treatment-related - injection site pain, dizziness and complex regional pain syndrome.

Laboratory assessments and vital signs were unremarkable with no meaningful changes from baseline in mean values and few cases of clinically significant values. There was no reduction in grip strength assessed by hand held dynamometry.

The product was notably immunogenic with over 85% of subjects after one injection and 100% by the third or fourth injection developing anti-drug antibodies. Assessment of unwanted immunologic events found no cases of systemic anaphylaxis although there were three cases of urticaria and three cases of local allergic type reactions on the hand. The database, however, may be too small to detect anaphylactic reactions. There was no overall association between increasing injection number, and by inference increasing antibody titre, and TEAEs except for pruritus. There was also no obvious association between the severity of events and antibody titre. In addition, there were no musculoskeletal events that may have indicated inhibition of endogenous collagenases.

Analysis of the pivotal trials found a consistent safety profile across subgroups of age, gender, weight, BMI and diabetes. Racial groups could not be assessed due to the development only being conducted in Caucasians. Subjects on anticoagulants (except low dose aspirin) or tetracyclines were excluded from the trials due to possible drug interactions. Safety has not been established in pregnancy or lactation.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

The benefits of Xiaflex 0.58 mg in the proposed usage are:

- A reduction in contracture in advanced Dupuytren's disease that was statistically significant over placebo was confirmed in the two pivotal studies. A reduction of contracture of the primary joint to five degrees or less was achieved in 64% of all treated joints in Study AUX-CC-857 and 44% of all treated joints in Study AUX-CC-859 (compared to 7% and 5% of the placebo joints, respectively).
- Efficacy was also seen in an improvement in the degree of contracture and range of motion and was consistent across subgroups of age, gender, weight and BMI. Efficacy was, however, less in PIP joints than the MP joints, as well as in the more severely contracted joints.

AA4500 offers a novel, non-surgical treatment for Dupuytren's disease and therefore avoids anaesthetic risks and possible surgical risks such as nerve or vessel injury and wound infections.

8.2. First round assessment of risks

The risks of Xiaflex 0.58 mg in the proposed usage are:

- Localised reactions at the treatment site and in the treated limb, including peripheral oedema, contusion, injection site pain, injection site haemorrhage and pain in the extremity. These events were generally mild or moderate in severity and resolved prior to the next injection.
- Tendon rupture and ligament damage, particularly in the fifth finger PIP joint (perhaps due to injection into other structures than the Dupuytren's cord). The rate of tendon rupture in the clinical program was 0.3%.
- Poor injection technique and inadvertent injection into surrounding structures and overdosing from drawing up too much reconstituted product.
- Skin tears, including rarer cases requiring skin grafting, possibly due to adherent skin and the finger manipulation post injection.
- Localised haemorrhage and the need to avoid treatment in patients on anticoagulants.
- High immunogenicity and the potential for immunogenicity-related risks. Urticaria was reported but there were no cases of systemic anaphylaxis, nor was there evidence of reduced efficacy or increasing adverse events (apart from pruritus) with increasing injection numbers or antibody titre.
- The potential cross-reactivity of anti drug antibodies with endogenous collagenases leading to musculoskeletal syndrome. There were, however, no reported cases in the safety database of musculoskeletal events of polyarthritis, osteolysis or shoulder pain/reduction of range of motion.
- The impact on subsequent surgery is unknown and there are no data on simultaneous injection of multiple cords.
- There are no studies in pregnancy or lactation and the clinical risks from anti-drug antibodies in these groups are not known.
- A reported recurrence rate of 4% at 9-12 months and 19% at two years as well as a lack of data on retreatment.

8.3. First round assessment of benefit-risk balance

Dupuytren's disease is a relatively common, slowly progressive fibroproliferative disease of the palmar fascia in which the resultant flexion contracture can cause significant disability of the hand and interference with normal daily tasks. When hand function is impaired, surgery is the mainstay of treatment and is usually a transection of cords (fasciotomy) or excision of the fascial bands (fasciectomy). Flexion deformity of >30-40° at the MP and >20° at the PIP joint had been suggested as indication for surgery. Surgery is associated with good initial response but recurrence rates are reported to be high. There are currently no pharmacological therapies for the treatment of Dupuytren's disease and as such there is an evident unmet medical need.

Xiaflex is a 1:1 ratio mix of collagenase enzymes produced by Clostridium histolyticum. It is proposed at a dose of 0.58 mg injected into the affected cord at one month intervals to a maximum of three doses. Patients undergo a finger extension procedure on the day after injection if necessary to disrupt the cord. The treatment can be given in the practice rooms. The proposed indication is *Xiaflex is indicated for the treatment of Dupuytren's contracture in adult patients with palpable cord.* The development of AA4500 commenced with Biospecifics Technologies Corporation, which conducted five trials using an early formulation. Auxilium Pharmaceuticals acquired the global development rights in 2004 and the dossier included eight trials Auxilium sponsored using the proposed formulation for marketing.

Studies have been conducted in patients with Dupuytren's disease and sufficient efficacy data were provided including from the two pivotal randomised placebo-controlled double-blind studies in 374 subjects. These pivotal trials were conducted in a population representative of the target population. In addition, the smaller of the two pivotal trials, in which 45 subjects were treated with AA4500, was conducted in Australian subjects.

The primary endpoint was proportion of subjects achieving a reduction in flexion contracture to 5 degrees or less 30 days post last injection assessed at both MP and PIP joints. This endpoint is rigorous and being close to full extension represents a clinically meaningful outcome. The primary outcome was achieved in the two pivotal trials with a statistically significant success rate at the primary joint of 64% and 44%, compared to 7% and 5% with placebo, in the two pivotal trials. Up to 3 injections were given and benefit was seen with 1 or 2 additional injections in those not achieving response after the first injection. Lower efficacy was seen at the PIP joints and the more severely contracted joints, nevertheless there was still meaningful clinical improvement seen in these types of joints which are known to be more resilient to treatment. Results of the primary efficacy endpoint were supported by significant improvements in secondary endpoints including improved range of motion, physician rating of improvement, subject satisfaction as well as subgroup analysis of age, gender, weight and BMI. Overall, the evaluator believed the efficacy data were sufficient to support the proposed wide range of severity implied by the indication.

The clinical development program did not include any trials against currently available treatment options such as surgery or percutaneous needle fasciotomy. Consequently, any comparison of outcomes between interventions can only be approximated from the literature. This was undertaken by the sponsor and a series with surgical outcomes in 1150 patients reported full correction (0°) of contracture at the MP joint in 70-89% of cases and at the PIP joint in 13-29% (McFarlane 1990). The rate of clinical success in the pivotal trials was 65-77% at the MP joint and 28-40% at the PIP joint and these data provide an indication that AA4500 efficacy may be in line with surgical therapy.

The natural history of the disease for many patients is progression and in the pivotal trials a recurrence rate of 4% was reported which increased to 19% after 2 years. The post-surgery recurrence rates from the literature, as quoted by the sponsor, range from 2% to 60% with an average of 33% (Table 26). An alternative therapy of percutaneous needle fasciotomy has been

reported to have even higher recurrence rates of 65%.[12] This implies that, on available data, recurrence is no higher with AA4500 treatment than with the main treatment alternatives. Currently, there has been insufficient follow up time to truly assess the persistence of efficacy and rates of recurrence. Therefore, the additional follow-up data from Study AUX-CC-860 should be submitted to the TGA for evaluation.

Table 26. Extension and recurrence by surgical procedure.

	Reference (Patient Number)	Follow-up	Recurrence [Time to Recurrence]
Limited Fasciectomy	Foucher G, 1995 (n=54)	6.6 yrs	38.9%
	Foucher G, 1992 (n=107)	5.6 yrs	41%; [average: 3.3 yrs]
	Citron ND, 2005 (n=79)	2+ yrs	18% (modified Bruner 33% (Z-plasty) group)
	Tonkin MA, 1984 (n=163)	3.1 yrs	54% (males) and 25% (females)
	Wilbrand S, 2003 (n=103)	4.4 yrs	47% (20% before 6 months and 27% after) [~4.4 yrs]
	Nieminen S, 1986 (n=70)	3.9 yrs	45% [~3.9 yrs]
	Bulstrode NW, 2005 (n=253)	3.6 yrs	33.3%
	Foucher G, 1985 (n=139)	1.5 yrs	2%
	Gonzalez VJ, 1998 (n=583)	0.3+ yrs	22% and 14% (2 treatment arms)
	Norotte G, 1988 (n=58)	10+ yrs	51% in first 2 yrs, 28% between 2–5 yrs and 5% after 5 yrs (primary patients) [~2 yrs]
	Ullah AS, 2009 (n=40)	3 yrs	12.5% (primary patients) [average 0.5 yrs]
Dermo-fasciectomy	Armstrong JR, 2000 (n=103)	5.8 yrs	11.6%
	Hogemann A, 2009 (n=61)	3.45 yrs	10.8%
	Tonkin MA, 1984 (n=163)	2.6 yrs	33% of primary males; 42% of recurrent males
	Roy N, 2006 (n=79)	4.4 yrs	8.9% (primary)
	Ullah AS, 2009 (n=39)	3 yrs	15.4% primary [average of 0.7 yrs]
Total Fasciectomy	Hogemann A, 2009 (n=61)	3.45 yrs	10.5% (primary); 12.5% (recurrent)
Needle Fasciotomy	Foucher G, 2003 (n=211)	3.2 yrs	58.3%
	Van Rijssen, 2006a (n=52)	2.75 yrs	65%
	Van Rijssen, 2010 (n=54)[a]	5 yrs	85%

[a] http://www.dupuytrensymposium.com/Abstracts/Van_Rijssen.pdf

The safety population consisted of 1082 subjects who received at least one dose of 0.58 mg Xiaflex and 1780 cords were treated with 2630 injections. The most frequent reactions were peripheral oedema, contusion, injection site pain, haemorrhage and tenderness. These effects may be a reaction to the actual product or a response to the collagen breakdown. These adverse events were frequent and nearly entirely related to treatment. They were, on the whole, confined to the treated extremity, the intensity generally mild to moderate and the duration such that they had resolved prior subsequent treatment if required one month later. The severe, albeit low frequency, safety risks were tendon rupture, ligament injury and skin tears requiring grafting. These risks may have in part been associated inadvertent injection into structures other than the Dupuytren's cord.

In order to address these severe risks, as well as to ensure the clinical success rates are maintained in patients with potentially varying levels of baseline severity, treating physicians must receive thorough training in the use of the product. This should include product reconstitution, dosage, injection technique and post treatment manipulation as well as adverse event information and monitoring. The evaluator assumes that in a clinical trial setting the training of physicians would have been extensive. The sponsor will need to ensure that the same level of expertise is imparted in the 'real world' to ensure maintenance of the benefit-risk balance and this should be a specific condition of registration. The evaluator also recommended that a further condition of registration be that the product is only distributed to prescribers who have undergone such training.

[12] van Rijssen AL, Werker PM. Percutaneous needle fasciotomy in dupuytren's disease.*J Hand Surg Br*. 2006; 31(5):498

The high immunogenicity of AA4500 poses the other main safety risk. Although there was no evidence of systemic absorption, all patients developed anti-drug antibodies. These antibodies did not appear to affect the efficacy (clinical success or improvement) or safety (adverse event profile, severity or duration) of AA4500. There were no severe hypersensitivity reactions or anaphylaxis reported, although there was a small number of cases of urticaria and the increasing rate of pruritus with a greater number of injections could have immunologic basis. There is also the potential for cross-reactivity of anti-drug antibodies with endogenous human matrix metalloproteinases. This was not found on assessment with five MMPs *in vitro* and the safety data did not indicate any signals for musculoskeletal syndrome.

Despite these findings, the safety database may not have been large enough to detect rarer reactions. For this reason, ongoing post-marketing surveillance of immune-mediated reactions including possible case of musculoskeletal syndrome will be critical to monitor the product risks. The evaluator also recommended that this includes monitoring of auto-immune disorders in existing patients as well as new onset of cases and this needs to be addressed satisfactorily with the context of the Risk Management Plan. The immunogenicity risks have been covered in the draft PI and it was also recommended by the evaluator that treatment should only be used in a setting able to treat anaphylaxis. This setting may be the physician's practice rooms but the ability to monitor vital signs and administer adrenalin, oxygen and intravenous fluids would need to be present. These setting requirements should also be covered in the context of the proposed Risk Management Plan.

The risk of drug interactions (anticoagulants and tetracyclines) has been adequately covered in the draft PI. Pregnancy and lactation risks have also been covered, although the evaluator recommended that as there are no studies in pregnancy or lactation and the clinical risk from anti-drug antibodies is unknown, that treatment should be deferred until after pregnancy.

The clinical development program has not addressed the administration of concurrent injections. While this is not proposed in the indication, the evaluator recommends wording the dosage section to specify this fact. The evaluator has noted that further clinical development is being conducted in this area (Studies AUX-CC-861 and AUX-CC-864), although no data were included in the dossier.

Retreatment with A4500 of previously treated cords has not been addressed in this dossier. The sponsor stated that a new Study AUX-CC-862, together with further data from AUX-CC-860, will cover this issue. Until such time as these data are evaluated, the evaluator recommended that this lack of efficacy and safety data in retreatment should be included in the product information.

In summary, Xiaflex injection has a moderate level of efficacy which appears in line with current surgical options together with a safety profile of predominantly mild to moderate adverse events which are confined to treated limb and generally resolved in under a month. While the immunogenicity-related risks have to date not been concerning, there is an evident need for these to be closely monitored. The product's safety is in part determined by the skill and knowledge of the administering physician and so it will be imperative that physicians using the product are adequately trained. Xiaflex offers a non-surgical treatment which can be administered in the clinical practice and so may offer a viable alternative to surgery which is currently the mainstay of treatment for advanced Dupuytren's disease. As such, the benefit-risk balance of Xiaflex 0.58 mg, given the proposed usage of treatment of Dupuytren's contracture in adult patients with palpable cord, was considered to be favourable. This finding is subject to no change in the benefit-risk balance after evaluation of satisfactory responses to the comments and *Clinical Questions* below.

8.4. First round recommendation regarding authorisation

The evaluator recommended approval of Xiaflex 0.58 mg injection for the treatment of Dupuytren's contracture in adult patients with palpable cord. This is subject to no change in the benefit-risk balance after review of responses to the comments and *Clinical Questions* below.

In addition to pharmacovigilance requirements as set out in the Risk Management Plan, it was recommended that authorisation be subject to:

- the sponsor ensuring that all doctors prescribing and using Xiaflex are experienced in the management of Dupuytren's disease and are appropriately trained in the product's administration. Training must cover the areas of reconstitution of the product, volumes to inject, dosing interval, injection technique, post injection finger manipulation and management, as well as information on immune-mediated reactions including anaphylaxis and its management, matrix metalloproteinase cross-reactivity and musculoskeletal syndrome, and other potential adverse events and the requirement for reporting.
- the product is only distributed to doctors who have been appropriately trained as outlined above.

9. Clinical questions

9.1. Pharmacokinetics

Nil.

9.2. Pharmacodynamics

Nil.

9.3. Efficacy

1. In the pivotal efficacy Studies AUX-CC-857 and AUX-CC-859 there were no confidence interval provided on any of the efficacy outcomes, in particular clinical success rate, clinical improvement rate, change in degree of contracture and change in range of motion. These should be provided.
2. The dossier included an interim report for Study AUX-CC-860 which summarised data for Year 2. This included data up to April 2010. Given it is now the end of 2012, data should now be available for the Year 3, and even Year 4, of the follow up. This data should be submitted to the TGA for evaluation so that further assessment of long term recurrence rates can be made. Include a discussion on these recurrence rates compared to reported rates in the literature from other treatment options.
3. The dossier included the protocol of Study B1531002 sponsored by Pfizer. It is stated to be a prospective open label Phase III study in 250 European subjects. What is the status of this study? Describe the study and comment on whether there any relevant efficacy data that are available and should be disclosed. If the study is completed, comment on why the data were not included in the dossier.
4. Provide a summary of the clinical trials in progress or planned worldwide with all sponsors and what additional data (efficacy, safety and pharmacokinetics) they are aiming to provide. Include timing for the trials and data availability.

9.4. Safety

1. The dossier included an interim report for Study AUX-CC-860 which summarised data for Year 2. This included data up to April 2010. Given it is now the end of 2012, data should now be available for the Year 3, and even Year 4, of the follow up. This data should be submitted for evaluation so that further assessment of long term safety can be made. Discuss any data and associated risks in subjects who may have had surgery on previously treated cords.
2. The dossier included the protocol of Study B1531002 sponsored by Pfizer. It is stated to be a prospective open label Phase III study in 250 European subjects. What is the status of this study? Are there any relevant safety data that are available and should be disclosed? Comment on these data in relation to the safety profile reported in this dossier.
3. The dossier also made reference to a post-approval study in the US, AUX-CC-861. The study was stated to be an open label study assessing the safety, tolerability and pharmacokinetics of two concurrent doses of AA4500 0.58 mg in the same hand of subjects with Dupuytren's contractures and a palpable cord. What is the status of this study? Are there data which should be submitted for evaluation? Again, comment on these data in relation to the safety profile reported in this dossier.
4. Why is the reconstituted dose so much greater than needed (0.9 mg for a dose of 0.58 mg)? This would appear to lead to possibility for overdosing if too much volume is drawn up and injected. Discuss the rationale behind this decision.
5. Discuss what training the investigators in the clinical development program undertook to ensure they were adequately skilled to administer the study injections. How is the sponsor proposing to ensure comparable skill levels of physicians who may use the product in Australia if registered?

10. Second round evaluation of clinical data submitted in response to questions

10.1. Efficacy

1. In the pivotal efficacy studies AUX-CC-857 and AUX-CC-859 there were no confidence intervals provided on any of the efficacy outcomes, in particular clinical success rate, clinical improvement rate, change in degree of contracture and change in range of motion. These should be provided.

Sponsor's response:

For the combined MP and PIP primary joint from Studies AUX-CC-857 and AUX-CC-859, the sponsor provided 95% confidence intervals for clinical success, clinical improvement, percentage change from baseline in contracture and change from baseline in ROM.

In the AA4500 and placebo groups, respectively, the clinical success rates were 64.0% versus 6.8% in AUX-CC-857 and 44.4% versus 4.8% in AUX-CC-859. The 95% CI for the difference in clinical success rates between AA4500 and placebo were 46.8-66.8 in Study 857 and 13.7-62.3 in Study 859.

The 95% CI for the difference in the rate of clinical improvement between the AA4500 and placebo groups were 63.7-81.7 and 40.1-81.9 for studies AUX-CC-857 and 859, respectively. The 95% CI for the adjusted mean difference in the percentage change from baseline in contracture was 62.1-74.3 and 46.4-70.8, respectively. The 95% CI for the adjusted mean difference in the change from baseline in range of motion was 27.8-34.9 and 18.3-32.5, respectively.

Evaluator's response:

The data demonstrate satisfactory response ranges. The broader intervals seen in AUX-CC-859 would be a factor of the smaller sample size.

2. ***The dossier included an interim report for Study AUX-CC-860 which summarised data for year 2. This included data up to April 2010. Given it is now the end of 2012, data should be available for the Year 3, and even Year 4, of the follow up. This data should be submitted for evaluation so that further assessment of long term recurrence rates can be made. Include a discussion on these recurrence rates compared to reported rates in the literature from other treatment options.***

Sponsor's response:

The sponsor provided the interim clinical study report for Year 4. The final report (Year 5) will be available at the end of 2013.

At July 2012, there were 645 subjects enrolled, 644 had at least one post enrolment evaluation and 539 (83.7%) completed the Year 4 visit. The mean study duration was 682.6 days and the mean days since first injection of AA4500 was 1440.8 days (range 618 to 1185 days).

In joints that had been successfully treated, the cumulative recurrence rate through to 1460 days of follow up was 42.1% (262/623) (Table 27). The recurrence rate at the PIP joint was higher than at the MP joint (61.6% versus 34.6%) (Table 28). Of the 623 joints that were successfully treated in the primary study, 12.8% had received medical or surgical intervention by the Year 4 visit.

The sponsor also reported that the recurrence definitions and rates in the literature are variable and range from 12-73% for fasciectomy/aponeurectomy and 33-100% for fasciotomy/apoenurotomy.

Evaluator's response:

Recurrence was shown to continue to increase over time, from 19% after 2 years to 42% after 4 years and remained higher at the PIP joint than the MP joint. These data indicate that for many patients treatment of this progressive condition with AA4500, as with other currently available options, is not permanent.

Table 27. Recurrence and Days of Follow-up for successfully treated joints. 860 Study Population.

Follow-Up Interval (Days)	n (%) of Joints in Each Interval[a]	n (%) of Recurrent Joints in Each Interval[b]	Number of Joints at Risk in Each Interval	Cumulative Nominal Rate (%) of Recurrence[c]	Kaplan-Meier Estimate (%) of Recurrence[d]
0-365	20 (3.2)	19 (7.0)	623	3.0	3.1
366-730	114 (18.3)	103 (37.7)	603	19.6	19.7
731-1095	128 (20.5)	96 (35.2)	489	35.0	35.8
1096-1460	216 (34.7)	44 (16.1)	361	42.1	44.9
>1460	145 (23.3)	11 (4.0)	145	43.8	--

Average follow-up after success:	1133 days
Average follow-up for recurrent joints:	836 days
Total follow-up time after success:	1932 years
Event rate per 100 joint-years of follow-up:	14.13

Data source: Table 14.2.2.1

[a] A joint is considered in an interval if the duration of assessment falls in the interval. The duration of assessment starts at the day of success (visit after the last injection where the 0° to 5° measurement was first recorded). The duration of assessment ends at the last available measurement or at the day of medical intervention for joints that do not recur and the recurrence day for recurrent joints.

[b] A recurrent joint is a joint evaluated by the investigator as having a worsening Dupuytren's contracture due to a palpable cord. The recurrence day is the visit where the recurrence was reported or the day of intervention if a joint was treated for a worsening Dupuytren's contracture. For joints reported as recurring in a previous study, the day of recurrence is the first visit with a fixed flexion contracture measurement of 20° or greater following the report of recurrence.

[c] The nominal rate of recurrence is the total number of recurrences occurring prior to the last day of the interval divided by the total number of joints (×100).

[d] The Kaplan-Meier estimate is the rate of recurrence at the final day of the interval estimated by a survival analysis with joints not recurring censored at their last measurement day or their day of medical intervention.

Table 28. Recurrence and Days of Follow-up for successfully treated joints by joint type. 860 Study Population.

Follow-Up Interval (Days)	n (%) of Joints in Each Interval[a]		n (%) of Recurrent Joints in Each Interval[b]		Number of Joints at Risk in Each Interval		Cumulative Nominal Rate (%) of Recurrence[c]		Kaplan-Meier Estimate (%) of Recurrence[d]	
	Joint Type		Joint Type		Joint Type		Joint Type		Joint Type	
	MP	PIP	MP	PIP	MP	PIP	MP	PIP	MP	PIP
0-365	8 (1.8)	12 (7.0)	8 (4.9)	11 (10.1)	451	172	1.8	6.4	1.8	6.4
366-730	64 (14.2)	50 (29.1)	56 (34.1)	47 (43.1)	443	160	14.2	33.7	14.3	34.0
731-1095	85 (18.8)	43 (25.0)	57 (34.8)	39 (35.8)	379	110	26.8	56.4	27.6	57.6
1096-1460	176 (39.0)	40 (23.3)	35 (21.3)	9 (8.3)	294	67	34.6	61.6	37.7	63.7
>1460	118 (26.2)	27 (15.7)	8 (4.9)	3 (2.8)	118	27	36.4	63.4	--	--

Joint Type	MP	PIP
Average follow-up after success:	1195 days	970 days
Average follow-up for recurrent joints:	896 days	746 days
Total follow-up time after success:	1475 years	457 years
Event rate per 100 joint-years of follow-up:	11.12	23.86

Data source: Tables 14.2.2.2 and 14.2.2.3

[a] A joint is considered in an interval if the duration of assessment falls in the interval. The duration of assessment starts at the day of success (visit after the last injection where the 0° to 5° measurement was first recorded). The duration of assessment ends at the last available measurement or at the day of medical intervention for joints that do not recur and the recurrence day for recurrent joints.

[b] A recurrent joint is a joint evaluated by the investigator as having a worsening Dupuytren's contracture due to a palpable cord. The recurrence day is the visit where the recurrence was reported or the day of intervention if a joint was treated for a worsening Dupuytren's contracture. For joint reported as recurring in a previous study, the day of recurrence is the first visit with a fixed flexion contracture measurement of 20° or greater following the report of recurrence.

[c] The nominal rate of recurrence is the total number of recurrences occurring prior to the last day of the interval divided by the total number of joints (×100).

[d] The Kaplan-Meier estimate is the rate of recurrence at the final day of the interval estimated by a survival analysis with joints not recurring censored at their last measurement day or their day of medical intervention.

3. The dossier included the protocol of study B1531002 sponsored by Pfizer. It is stated to be a prospective open label Phase III study in 250 European subjects. What is the status

of this study? Describe the study and comment on whether there any relevant efficacy data that are available and should be disclosed. If the study is completed, comment on why the data were not included in the dossier.

Sponsor's response:

This Phase IIIb study remains ongoing. This multi-centre study has 2 phases: The first is an open-label treatment phase (up to 5 months in duration) and the second is a 6 month follow-up phase. To date, a total of 254 subjects have been treated. No clinically important information has emerged from this ongoing study.

Evaluator's response:

Data should be provided when available.

4. ***Provide a summary of the clinical trials in progress or planned worldwide with all Sponsors and what additional data (efficacy, safety and pharmacokinetics) they are aiming to provide. Include timing for the trials and data availability.***

Sponsor's response:

Table 29. Ongoing studies-Xiaflex in the treatment of Dupuytren's contracture

Study Number	Design	Sponsor	Expected Completion[a]
AUX-CC-860	Phase 3, non-treatment long-term follow-up	Auxilium	Q3, 2013
AUX-CC-862	Phase 3 retreatment of recurrent contractures	Auxilium	Q1, 2014
AUX-CC-867	Phase 3b open-label concurrent treatment	Auxilium	Q1, 2014
AUX-CC-901	Non-treatment study	Auxilium	Q4, 2016
B1531002	Phase 3 open-label treatment study	Pfizer	2Q 2013
B1531005	Non-interventional study	Pfizer	2018
AK160-III-1	Phase 3 treatment study	Asahi	4Q 2013

[a] Final CSR

Q=quarter

Evaluator's response:

This information is limited. Data should be provided to the TGA for evaluation when available.

10.2. Safety

1. ***The dossier included an interim report for Study AUX-CC-860 which summarised data for Year 2. This included data up to April 2010. Given it is now the end of 2012, data should be available for the Year 3, and even Year 4, of the follow up. This data should be submitted to the TGA for evaluation so that further assessment of long term safety can be made. Discuss any data and associated risks in subjects who may have had surgery on previously treated cords.***

Sponsor's response:

The sponsor quoted three abstracts presented at conferences which reported that post Xiaflex injection there was "no significant distortion of anatomy", "a reduction in cord volume" and cords were "histologically similar" and "surgery was not found to be difficult during fascietomy performed after collagenase injections".

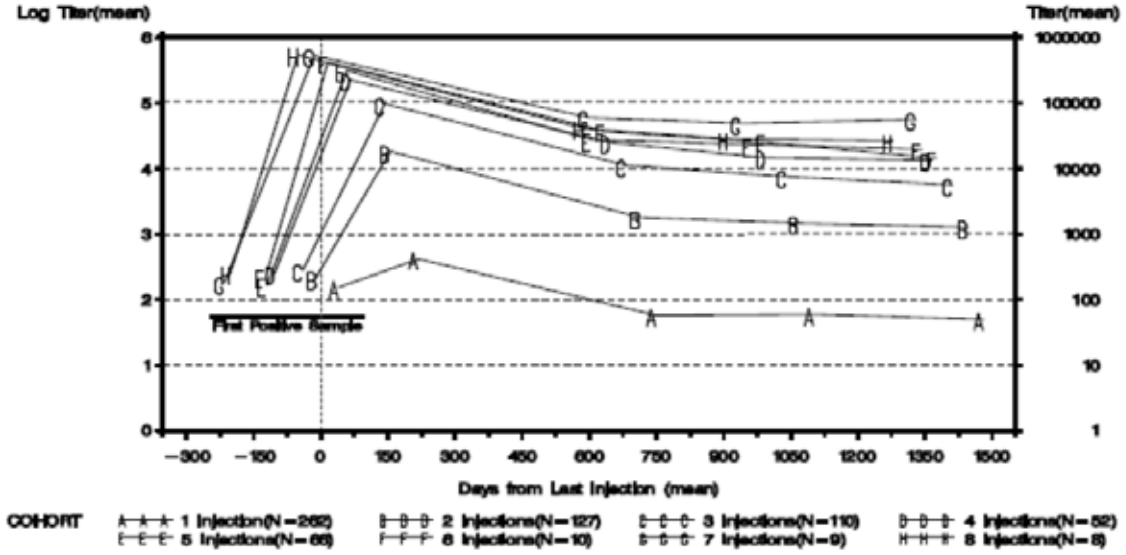
The safety data from Study AUX-CC-860 at year 4 did not report on any issues relating to surgery of previously treated cords. Of the 644 subjects enrolled in this study, 48 received at least one injection of commercially available Xiaflex. In these subjects the rate of injection site haematoma and injection site oedema was 12.5% and 10.4%, respectively. In the overall study population, there were eight deaths and 81 subjects with at least one non-fatal SAE, none of which were attributed to study drug.

Anti-drug antibodies were measured at Year 4 follow up and while the mean log titres for AUX-I and AUX-II had decreased somewhat by Year 3 the levels at Year 4 were similar to Year 3 (Figures 16 and 17). By year 4, 14.6% of subjects who had received one injection were seronegative (for AUX-I and for AUX-II) while for those who had received 2 injections only 1.9% and 1.0% were seronegative for AUX-I and AUX-II, respectively. In those who received 3 or more injections, all except one subject remained seropositive.

Evaluator's response:

Potential risks in subjects who have surgery on previously treated cords have not been defined. Anti-drug antibodies remain present 4 years after treatment in the vast majority of subjects irrespective of the number of injections received.

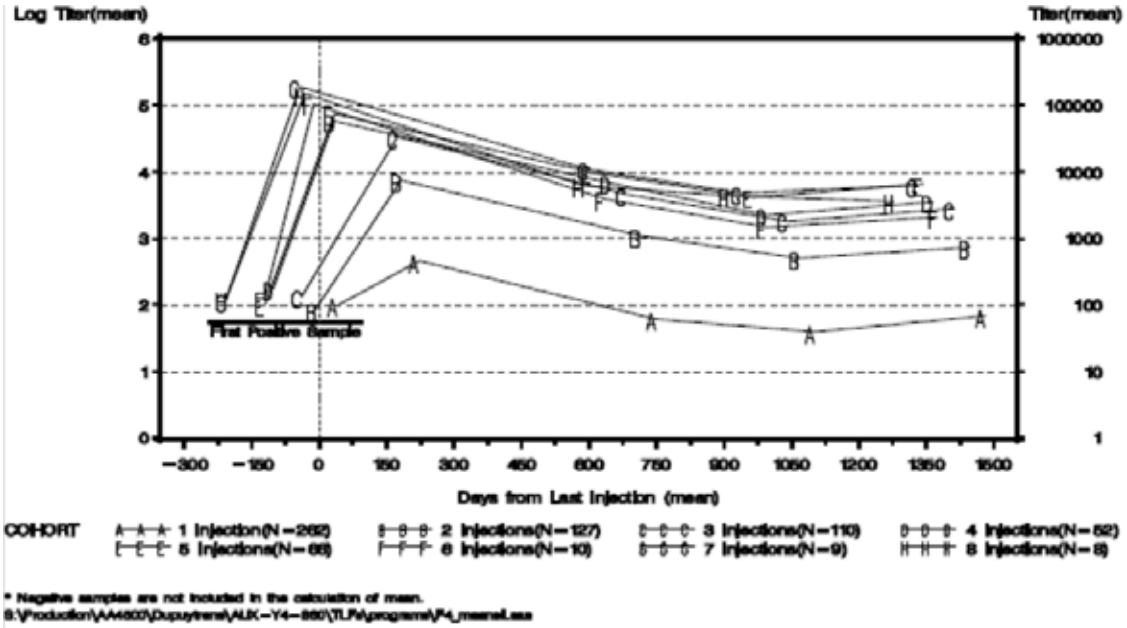
Figure 16. Mean log Anti-AUX-I titers at the First positive sample, the Maximum sample, and Year 4 sample relative to the Last injection (Day 0) by Injection cohort.



* Negative samples are not included in the calculation of mean.

Note: First positive sample was the time of first serum positive titer relative to the last injection (Day 0). The maximum sample was the time of maximum titer relative to the last injection (Day 0). The Year 4 sample was the time of the Year 4 sample relative to the last injection (Day 0).

Figure 17. Mean log Anti-AUX-II titers at the First positive sample, the Maximum sample, and Year 4 sample relative to the Last injection (Day 0) by Injection cohort.



Note: First positive sample was the time of first serum positive titer relative to the last injection (Day 0). The maximum sample was the time of maximum titer relative to the last injection (Day 0). The Year 4 sample was the time of the Year 4 sample relative to the last injection (Day 0).

2. ***The dossier included the protocol of study B1531002 sponsored by Pfizer. It is stated to be a prospective open label Phase III study in 250 European subjects. What is the status of this study? Are there any relevant safety data that are available and should be disclosed? Comment on these data in relation to the safety profile reported in this dossier.***

Sponsor's response:

This Phase IIIb study remains ongoing. This multi-center study has 2 phases: The first is an open-label treatment phase (up to 5 months in duration) and the second is a 6 month follow-up phase. To date, a total of 254 subjects have been treated. No new safety risks have been identified from this ongoing study.

Evaluator's response:

Data should be provided to the TGA when available.

3. ***The dossier also made reference to a post-approval study in the US, AUX-CC-861. The study was stated to be an open label study assessing the safety, tolerability and pharmacokinetics of two concurrent doses of AA4500 0.58 mg in the same hand of subjects with Dupuytren's contractures and a palpable cord. What is the status of this study? Are there data which should be submitted for evaluation? Again, comment on these data in relation to the safety profile reported in this dossier.***

Sponsor's response:

The sponsor provided a synopsis of this study and stated that the *study was conducted as part of an ongoing development program to evaluate the safety and efficacy of two concurrent injections of Xiaflex into multiple cords in the same hand. The safety data from this study indicate that the safety profile of Xiaflex after two concurrent injections is similar to that reported after a single injection and no new safety issues were found*.

The study enrolled 12 subjects with at least 3 Dupuytren's contractures and one cord was treated in the first period and 2 cords concurrently treated in the second period. There were no discontinuations due to AEs and no SAEs related to study drug reported.

Evaluator's response:

Without the full clinical study report, conclusions on the relative safety of concurrent treatment of two cords cannot be made.

4. Why is the reconstituted dose so much greater than needed (0.9 mg for a dose of 0.58 mg)? This would appear to lead to possibility for overdosing if too much volume is drawn up and injected. Discuss the rationale behind this decision.

Sponsor's response:

The sponsor conducted a study (reported as **50-1-0004** and **50-1-0005**) which evaluated the volume of reconstituted Xiaflex drug product that could be withdrawn from the vial by a healthcare provider (HCP) after removal of the required dosing volume. The average remaining volume withdrawn from the vial after removal of the dosage volume for an MP joint was 0.08 mL (95% CI: 0.07 to 0.1 mL). The average remaining volume withdrawn from the vial after removal of the dosage volume for a PIP joint was 0.05 mL (95% CI: 0.04 to 0.06 mL). The worst case scenarios were 0.03 mL for MP and 0 mL for PIP joints.

The sponsor stated that *these results demonstrate that the overage in the vial is necessary to allow an HCP to comfortably remove a dose from the vial and establish that 0.9 mg is the minimal amount of collagenase clostridium histolyticum per vial required to permit withdrawal of the appropriate dosage volume*.

Evaluator's response:

While the evaluator agreed with the findings, the study does not take into account the risk of healthcare providers drawing up too much reconstituted product initially. Labelling must be very clear that the entire contents of the vial should not be drawn up and that the vials are single use only and the remaining contents should not be used for treating another joint. A sentence has been included in the PI that the *entire reconstituted XIAFLEX solution contains 0.9 mg of XIAFLEX. Reconstituted XIAFLEX solution remaining in the vial after the injection should be discarded.* These issues must be covered in the doctor's training.

5. Discuss what training the investigators in the clinical development program undertook to ensure they were adequately skilled to administer the study injections. How is the sponsor proposing to ensure comparable skill levels of physicians who may use the product in Australia if registered?

Sponsor's response:

With initiation of the Auxilium clinical trial program, investigators were offered injection training in the form of a PowerPoint presentation with a video component and written material in the Investigator's Brochure. The training material covered reconstitution of the lyophilised drug powder with sterile diluent, injection of the reconstituted drug into a Dupuytren's cord and the finger extension procedure, which is carried out the day after each injection.

The sponsor outlined the Training Plan for Australia in response to a question posed in the TGA Risk Management Plan (RMP) evaluation.

The applicant's training programme is designed to comprehensively train all appropriate users of the product. Training materials, therefore, will be delivered to specialist physicians through a variety of mechanisms and media. Physicians are provided access to 3 main elements of the training programme:

1. *Training brochure and training video*
2. *Internet-based training*
3. *Peer-to-peer training meeting*

Training will be linked to a Prescriber Certification Program.

Evaluator's response:

The proposed training appears suitable. The product should only be distributed to doctors who have undergone the training.

10.3. PI and CMI

The sponsor satisfactorily responded to all comments on the PI and the Consumer Medicine Information (CMI) documents with a couple of exceptions as follows;

- Further data on contracture recurrence from Study AUX-CC-680 should be included in the PI (including recurrence rates at 2 and 4 years);
- Adverse effect data should be presented according to the referenced TGA guidelines and include a tabulation of the more frequent (≥1%) adverse events as well as data on post marketing adverse reactions.

11. Second round benefit-risk assessment

11.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Xiaflex 0.58 mg in the proposed usage are unchanged from those identified in the *First Round Assessment of benefits*.

11.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of Xiaflex 0.58 mg in the proposed usage are unchanged from those identified in *First Round Assessment of Risks* apart from the following:

- The risk of recurrence was noted to continue to increase, from 4% at 9-12 months, to 19% at two years and to 42% at 4 years.
- The nonclinical evaluation found that the role of anti-drug antibodies in potential risks had not been examined in the nonclinical studies.

11.3. Second round assessment of benefit-risk balance

After review of information provided by the sponsor, the benefit-risk balance at the end of the second round evaluation remains the same as discussed in *First Round Assessment of Benefit-Risk Balance*.

It was noted that the nonclinical evaluation found the risk of anti-drug antibodies had not been addressed in the nonclinical study program. This adds further weight to the importance of active monitoring of potential immunogenicity risks. The draft PI has adequately covered such risks and the draft RMP has been updated to ensure relevant immunogenicity-related risks are being monitored.

As previously discussed in the first round evaluation, the training of doctors using the product will be critical in ensuring maintenance of the benefit-risk balance. The sponsor provided a copy of the Training Brochure used in the US and confirms that a similar document will be used in Australia. This will need to be part of the RMP together with ensuring distribution of the product is only to doctors who have satisfactorily completed the training.

It is known that the contractures may recur following available treatments and this was also the case with Xiaflex where the recurrence rate was 42% at 4 years. The sponsor stated that the PI

will be updated with the final 5 year data from the follow-up study. Nevertheless, such data are available and prescribers should be provided with the most relevant information on which to base prescribing decisions. Therefore, the evaluator maintains that recurrence data beyond one year should be included in the current draft PI.

The recommended changes to the PI and CMI have been adopted apart from the comments relating to the presentation of data in the Adverse Effects section. These still need to be addressed as outlined by the evlautor.

Overall, the benefit-risk balance of Xiaflex 0.58 mg, given the proposed usage of treatment of Dupuytren's contracture in adult patients with palpable cord, was considered to be favourable. This finding was subject to satisfactory responses to the remaining comments on the PI.

11.4. Second round recommendation regarding authorisation

The evaluator recommends approval of Xiaflex 0.58 mg injection for the treatment of Dupuytren's contracture in adult patients with palpable cord.

The product must only be distributed to doctors who have been appropriately trained. Training must cover the areas of reconstitution of the product, volumes to inject, dosing interval, injection technique, post injection finger manipulation and management, as well as information on immune-mediated reactions including anaphylaxis and its management, matrix metalloproteinase cross-reactivity and musculoskeletal syndrome, and other potential adverse events and the requirements for reporting.

This recommendation is subject to satisfactory responses to the remaining comments on the draft PI.

12. References

Badalamente MA and Hurst LC. Enzyme injection as nonsurgical treatment of Dupuytren's disease. *J Hand Surg*. 2000; 25A: 629-636.

McFarlane R and Botz, JS. The results of treatment. In: McFarlane RM, McGrouther DA, and Flint MH, eds. *Dupuytren's Disease Biology and Treatment.* Volume 5. Edinburgh, London, Melbourne, and New York: Churchill Livingstone; 1990:387-412

van Rijssen AL, Werker PM. Percutaneous needle fasciotomy in dupuytren's disease.*J Hand Surg Br*. 2006; 31(5):498

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au