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

First round evaluation: 30 June 2015

Second round evaluation: 27 October 2015

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.
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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 <https://www.tga.gov.au/product-information-pi>.

Contents

Common abbreviations

Abbreviation	Meaning
AA4500	Collagenase clostridium histolyticum
ACPM	Advisory Committee on Prescription Medicines
ADA	Antidrug antibody
AE	Adverse event
AUX I	Clostridial type 1 collagenase
AUX II	Clostridial Type II collagenase
BTC	Biologics technology corporation
CI	Confidence interval
CMI	Consumer medicine information
ED	Erectile dysfunction
EU	European union
HED	Human Equivalent Dose
IIEF	International index of erectile function
ITT	Intention to treat
LOCF	Last observation carried forward
mITT	Modified intention to treat
MMPs	Matrix metalloproteinases
NOEL	No observable effect level
PD	Peyronie's disease
PDQ	Peyronie's disease questionnaire
PI	Product information
RMP	Risk management plan
SAE	Serious adverse event
TEAE	Treatment emergent adverse event

1. Introduction

This is a type C submission to extend the indication of Xiaflex (collagenase clostridium histolyticum) to include men with Peyronie's disease.

Note: In the clinical trials and this evaluation report, Xiaflex is also referred to as AA4500. A dose of 0.58 mg of Xiaflex is equivalent to 10,000 Units.

Xiaflex belongs to the pharmacotherapeutic group 'Other drugs for disorders of the musculoskeletal system-enzymes'.

Xiaflex is currently indicated for the treatment of Dupuytren's contracture in adult subjects with a palpable cord. There is no proposed change to this indication.

The sponsor proposed the following new indication:

> *Xiaflex is indicated for the treatment of male adults with Peyronie's disease and a palpable plaque and curvature deformity.*

The following dosage forms and strengths are currently registered:

> Xiaflex is supplied in single-use, glass vials containing 0.9 mg of collagenase clostridium histolyticum as a sterile, lyophilised powder for reconstitution.

No new dosage forms or strengths are proposed.

The sponsor proposes that Xiaflex be administered by a physician trained in the correct administration of the product and experienced in the diagnosis and treatment of male urological disease.

The recommended dose of Xiaflex is 0.58 mg per injection administered into a Peyronie's plaque. The volume of reconstituted Xiaflex to be administered into the plaque is 0.25 mL.

A treatment course consists of a maximum of four treatment cycles. Each treatment cycle consists of two Xiaflex injections and one penile modelling procedure. The second Xiaflex injection of each treatment cycle is administered 1 to 3 days after the first injection. The penile modelling procedure is performed 1-3 days after the second injection of each treatment cycle. If a satisfactory response has not been achieved after the first treatment cycle, the injection and penile modelling procedures may be repeated after approximately 6 weeks.

2. Clinical rationale

2.1. Peyronie's disease

Peyronie's disease is a disease of the localised connective tissue of the tunica albuginea. It typically affects males between the ages of 40 and 70 years. The reported incidence varies greatly (depending on age and other risk factors of the population studied and whether the cases present with symptoms or asymptomatic cases are included), but is estimated to be 1-8%. Clinical presentations include penile plaque, palpable indurations along the penile shaft, penile curvature or deformity, and penile pain. Erectile dysfunction is estimated to occur in around 20% of men with this disease. There is a large psychological burden of the disease, with up to 48% of subjects developing depression. In the early phases of disease, nodule or plaque formation can be confused for malignancy. Penile pain and deformity can impact upon the sexual and emotional health of subjects. Certain sexual positions become difficult: subjects experience concern over their body image. Men with Peyronie's disease sometimes develop a loss of hope, which causes further distancing from sexual activities.

Risk factors for Peyronie's disease include age, penile trauma, diabetes, smoking, family history and the presence of Dupuytren's contracture. Several studies have identified vascular risk factors among men with Peyronie's disease, at rates similar to men with erectile dysfunction.

Histological studies of plaque tissue demonstrate that the normal structure of the tunica albuginea is replaced by collagen fibrils in degenerative bundles. There is accumulation of fibrin, inflammation and aberrant staining of collagen. As the disease progresses there is calcification and ossification.

Two stages of Peyronie's disease are described. The first (acute or inflammatory) phase last 6-12 months and is characterised by nodule formation, pain and slight curvature deformity. The second (stable, chronic) phase is characterised by a more stable plaque and more pronounced curvature. The reported rate of spontaneous resolution (of the plaque and deformity) varies considerably in studies, with rates reported of between 13% and 80%. Resolution of these structural changes is more common in the early phases of disease. Resolution of the pain occurs in all patients with time.

2.2. Xiaflex

A collagenase is an enzyme that recognises and binds to collagen in its native conformation and cleaves the peptide bonds resulting in collagen breakdown. Clostridial collagenases selectively degrade fibrillar collagen without causing damage to normal tissue components (arteries, nerves, vessels).

It is hypothesised that injection of Xiaflex into a Peyronie's plaque will result in enzymatic disruption of the plaque and a reduction in symptoms due to the disease.

2.3. Guidance

There are no TGA adopted guidelines for the evaluation of Peyronie's disease or erectile dysfunction. The evaluator used the information in the dossier and a brief literature review for guidance.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The sponsor has submitted a comprehensive dossier.

The submission contained the following clinical information:

- An open label pharmacokinetic study (AUX-CC-805)
- A Phase IIb study (AUX-CC-801)
- Three Phase III studies
  - Two randomised, double blind placebo controlled studies (AUX-CC-803 and AUX-CC-804)
  - One open labelled study (AUX-CC-802)
  - Published references

3.2. Paediatric data

The submission did not include paediatric data. This is appropriate as Peyronie's disease does not occur in children.

3.3. Good clinical practice

The studies in the dossier were performed in accordance with good clinical practice. Local ethics approval was granted for each study site.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

Details of the pharmacokinetic AUX-CC-805 were presented. The sponsor submitted a number of other pharmacology and toxicology studies with the initial application for Dupuytren's contracture. These are not included in this evaluation.

4.1.1. Summary of pharmacokinetics

The information in the following summary is derived from the clinical trials of Xiaflex in Dupuytren's disease and Peyronie's disease.

4.1.1.1. Physicochemical characteristics of the active substance

When reconstituted, Xiaflex is a clear colourless solution, pH 7.5-8.5. It is delivered to the affected area by injection.

4.1.1.2. Pharmacokinetics in subjects with Dupuytren's contracture

There was minimal systemic exposure when subjects were exposed to a single dose of 0.58 mg injected into the collagen plaque.

4.1.1.3. Pharmacokinetics in subjects with Peyronie's disease

The anatomy of the plaque in Peyronie's disease differs from that in Dupuytren's contracture in that it is highly vascular and the connective tissue surrounding the plaque is less dense. The increased vascularity of the plaque and the need for more frequent injections increase the potential risk of systemic exposure.

The sponsor has submitted a clinical trial (AUX-CC-805) to evaluate the potential system exposure of Xiaflex after injection into the penis for Peyronie's disease. This study demonstrated that minimal amounts of AA4500 reach the systemic circulation after injection into the Peyronie's plaque. The exposure measured was low and transient. There were no systemic adverse events due to exposure. There was no evidence of accumulation after repeated doses. Most subjects developed AUX I and AUX II antibodies after two injections. It is unknown whether this is from an immune reaction to the local injection or due to systemic exposure.

Evidence from animal models suggests that systemic exposure of AA4500 is rapidly inactivated, presumable from complex formation with alpha-2-macroglobin: a serum protein that serves as a substrate or inhibitor for proteases of various types.

4.2. Evaluator's overall conclusions on pharmacokinetics

The conduct of the Study AUX-CC-805 was adequate. It confirmed that there was minimal systemic exposure after intralesional treatment of Peyronie's disease and no evidence of dose accumulation after 2 doses separated by 48 h.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

There were no human pharmacodynamic studies for clinical evaluation. Nonclinical studies in dogs and guinea pigs have been performed and will be evaluated by the toxicology section. Below is a brief summary of the pharmacodynamics data submitted.

5.1.1. Summary of pharmacodynamics

5.1.1.1. Mechanism of action

Pharmacodynamic effects

Primary pharmacodynamic effects

Clostridium histolyticum collagenases are metalloproteinase enzymes of the matrix subfamily generated by the homologous expression of two separate chromosomal genes, colG and colH. Clostridial collagenases do not have directly homologous vertebral counterparts. The closest functional (for example, extracellularly secreted, selectively collagenic) vertebrate analogues are a subset of metalloproteinases in the gluzincin subfamily referred to as metalloproteinases (MMPs). However there is only limited similarity of just 2-5 amino acids separated by gaps of around 30-150 amino acids. There was no immunogenic-related meaningful sequence homology between AUX I and AUX II and human endogenous MMPs. Clostridial collagenases are not inhibited by the tissue inhibitors of metalloproteinase (potent inhibitors of the mammalian collagenolytic MMPs). Systemic inhibition of collagenolytic MMPs results in a spectrum of clinical signals and histological changes such as thickening of the epiphyseal growth plate with disorganisation and thickening of the underlying metaphyseal trabecular bone, synovial hyperplasia with fibrosis of underlying adipose tissue, increased proliferation of fibroblasts in the joint capsule and extracapsular ligaments. The clinical signs anticipated as a result of inhibition of endogenous MMPs include exacerbation of autoimmune disease or a musculoskeletal syndrome with arthralgia, myalgia, joint stiffness, hand oedema, palmar fibrosis and thickening or nodules of the tendons.

The primary pharmacological activity of AA4500 was investigated using tissue explants from surgically harvested Peyronie's plaques. Injections of AA4500 into these explants results in well circumscribed focal lysis. Immunostaining demonstrates that AA4500 selectively lyses Type I and Type II collagen and spares Type IV collagen (which surrounds nerves and vessels). The focal lysis and high molecular weight of AUX I and AUX II were thought to be protective against systemic exposure.

The collagen lysis is more extensive in Peyronie's disease than in Dupuytren's contracture as the collagen plaque and surrounding tissues are less dense. Thus, there is the potential for more local reactions.

The safety margin was assessed using repeated injections IV injections in rats. The No observable effect level (NOEL) for systemic toxicity was 2.5 x the human equivalent dose (HED) based on surface area and 14x HED based on weight. The minimal lethal dose was 50x HED based of surface area and 50x the HED based on weight. The pathological features of the rats that died included haemorrhage into the peritoneal cavity and liver injury.

Secondary pharmacodynamic effects

Secondary pharmacodynamic effects, including inflammatory responses, may occur due to the release of small pharmacologically active peptide fragments of collagen.

5.1.1.2. Time course of pharmacodynamic effects

The lysis of collagen occurs rapidly, in less than 24 h.

5.1.1.3. Relationship between drug concentration and pharmacodynamic effect

Studies in dogs have been used to determine the response of different tissues to different doses. Local reactions were noted at > 430 U/dose. Histological findings included haemorrhage, subacute necrosis, inflammation, neovascular proliferation, focal lysis of the tunica albuginea. Reaction severity varied by injection site (corpus cavernosa/urethra> vein-artery-nerve complex> tunica albuginea).

Comment: The relationship between drug dose or concentration and effect in humans does not appear to have been systematically evaluated, or if so not clearly presented in this dossier.

5.1.1.4. Pharmacodynamic interactions

Tetracycline derivatives have been shown to inhibit MMP mediated collagen degradation at pharmacologically relevant concentrations in vitro.

5.2. Evaluator's overall conclusions on pharmacodynamics

There is a plausible pharmacodynamic mechanism for the use of Xiaflex in Peyronie's disease. Most of the pharmacodynamic studies have been using animal models, the ability to extrapolate these findings to humans in unknown. Xiaflex exerts a local effect on Type I and II collagen. Systemic effects are minimal, despite the increased vascularity of the penile tissue. Local reactions are more likely in Peyronie's disease than in Dupuytren's contracture as the connective tissue is less dense.

5.2.1. Unresolved issues:

The pharmacodynamic or histological response to the diluent or placebo was not mentioned, but the clinical studies (see Section 7) showed a significant placebo effect.

6. Dosage selection for the pivotal studies

The sponsor stated that the dosage selected for the clinical trials was based on efficacy and safety data from Phase I and II studies using different dose levels, injection volumes and treatment regimes. The dossier did not contain detailed information from the Phase I and early II clinical trials used to determine the dosage used in the Phase III clinical trials. The clinical evaluator noted two references that described earlier studies using lower doses (see descriptions of studies below).

6.1. Gelbard et al *The Journal of Urology (1985*). The use of collagenase in the treatment of Peyronie's disease

This study took place between 1982 and 1983. It was an open labelled study of several doses of collagenase in 31 men. The mean age was 55.5 years (range 22-67), and duration of Peyronie's disease was 22 months (range 2-60). Dorsal, lateral and ventral plaques were included, ranging in size from impalpable (<8 mm) to large (>15 mm). Pain and deformity were the most common symptoms. Four patients were unable to partake in sexual intercourse. The concentration of collagenase administered was much lower that than used in the more recent studies; 15 subjects received 470-620 U/ml and 16 subjects 910 U/ml. The total dose received ranged from 470-2730 units. Oral β aminopropionitrile fumarate was added to improve laxity of the collagen in 25 patients. Overall, 65% of patients had an objective improvement in symptoms. Objective relief of deformity occurred in 50% of those with small plaques, 75% of those with moderate plaques, and 65% of subjects with large plaques. Pain during election was eliminated in 93% of those with pain at the onset. Three of the 4 men who were unable to have sexual intercourse

were able to after the collagenase; the man who failed treatment had a large plaque and 180˚ curvature. Twenty one of 31 subjects had ecchymosis. One patient had a corporal rupture 2 weeks after therapy. Operations were performed in 2 patients after collagenase treatment. The surgeons noted that the collagenase made the neurovascular bundle harder to mobilise from the tunical tissue, but did not affect the patient's suitability for plaque excision and graft or plaque incision and stent.

6.2. Gelbard et al The Journal of Urology (1993). Collagenase versus placebo in the treatment of Peyronie's disease: a double blind study.

This study took place between 1987 and 1989. It included 49 men with Peyronie's disease. Patients with a coagulation abnormality or significant erectile dysfunction were excluded from the study. The patients were stratified into 3 categories, see below, and received 3 injections over 3 consecutive days.

Table 1: Study design and patient response

Category	Treatment	N 49	Response		p
			positive	negative	
overall	Collagenase: 2000units per 0.5ml of diluent	22	8 (36)	14 (64)	< 0.007
	Placebo: Diluent(0.9% NaCl and 2mM CaCl2)	27	1 (4)	26(96)	
1: bend < 30˚ and/or palpable plaque < 2cm	3 aliquots of 0.5ml	3	3 (100)	0	0.14
	0.5ml placebo	4	1 (25)	3 (75)	
2: 30-60˚ deformity and/or plaque 2-4cm	3 aliquots of 0.8ml	11	4 (36)	7 (64)	0.03
	0.8ml placebo	13	0	13 (100)	
3: > 60 ˚ deformity and plaque > 4cm	3 aliquots of 1.15ml	8	1 (13)	7 (87)	0.4
	1.15ml placebo	10	0	10 (100)	

Patients with small or moderate plaques and deformity were more likely to respond than those with large plaques and deformity. No adverse events were reported. One patient had penile popping and an ecchymosis during intercourse 3 weeks after the collagenase, this resolved spontaneously.

These studies question whether such a concentrated solution and large injected volume is required, and whether using a less concentrated solution may minimise adverse effects.

6.3. Study included in the submission

The Phase IIb Study AUX-CC-801 (described in detail in Section 7 below) used three treatment cycles of 0.58 mg (10 000 units) AA4500 separated by 42 days. Efficacy and safety was established. The 42 days between treatment cycles was maintained for the Phase III studies as this allowed sufficient time for local reactions to resolve. A further treatment cycle was added to Phase III studies with the aim of improving efficacy.

In Study AUX-CC-801, gentle penile plaque modelling was used to enhance the disruption of collagenous plaques. In this study, there was a significant difference in outcomes between the treatment group and placebo group who received modelling. There was a significant interaction between study drug and modelling indicating both factors were important in the treatment effect. Modelling was included as part of the clinical protocol for subsequent studies based on this study.

Comment: More information justifying the dose will be requested from the sponsor, particularly as the submitted clinical trials show a large placebo effect and increased rate of local reactions in the AA4500 group.

7. Clinical efficacy

7.1. Peyronie's disease

Table 2 summarises the studies included in the dossier to support the use of Xiaflex for Peyronie's disease.

Table 2: Summary of efficacy studies

	Phase	Description	Intervention	Number of subjects
AUX-CC-805	PK		Two injections of AA4500	20
AUX-CC-801	IIb	Randomised, placebo controlled	AA4500 or placebo, Penile modelling or not	145
AUX-CC-803	III	Randomised, placebo controlled	0.58 mg AA4500 up to 4 treatment cycles with modelling	417
AUX-CC-804	III	Randomised, placebo controlled	0.58 mg AA4500 up to 4 treatment cycles with modelling	415
AUX-CC-802	III	Open labelled	0.58 mg AA4500 up to 3 treatment cycles with modelling 9 months	347

7.1.1. Pivotal efficacy studies

In the clinical trials, Xiaflex is referred to as AA4500. A dose of 0.58 mg of Xiaflex is equivalent to 10,000 Units.

7.1.1.1. Outcome measures

The Peyronie's Disease Questionnaire and the International Index of Erectile Function scores were used to measure outcome in the pivotal studies.

Peyronie's disease questionnaire

Auxilium (now owned by Endo Pharmaceuticals) designed, developed and validated an instrument to assess the psychosexual consequences of Peyronie's disease -the Peyronie's Disease Questionnaire (PDQ). This is a disease specific 15 item scale that assesses the impact of Peyronie's disease following 3 domains- Peyronie's disease psychological and physical symptoms (6 items), penile pain (3 items), Peyronie's disease bother (6 items related to painful erections, the appearance of the erect penis, the impact of Peyronie's disease on intercourse and the frequency of intercourse).

The score was validated using baseline clinical data from the two Phase III clinical trials described in this submission. Confirmatory factor analysis (CFA) was used to confirm the PDQ scale structure. Internal consistency was assessed for each subscale using Cronbach α. Construct validity was assessed using convergent, discriminant and known group validity testing against investigator assessed penile curvature, self-reported penile curvature, pain upon erection, disease distress, and the 5 international index of erectile function (IIEF) domains.

The CFA showed that all 3 PDQ domains had adequate to good fit with the observed data. Inter item consistency of the 3 PDQ domains revealed a Cronbach α of greater than 0.7 for each domain. The confirmatory and discriminate validity is displayed in Table 3. The sponsor has suggested a Pearson correlation of > 0.3 suggests convergent validity and one <-0.3 suggests discriminate validity. Using these cut offs, there was minimal correlation between the measured curvature deformity and PDQ.

Self-reported distress over Peyronie's disease and the IIEF items overall satisfaction, intercourse satisfaction and erectile function had significant correlations with the PDQ Peyronie's disease symptom bother score. Only self-reported pain on erection had significant correlation with the PDQ penile pain subgroup. The PDQ Peyronie's disease psychological and physical symptom subscale had significant correlations with self-reported Peyronie's disease curvature deformity, distress over Peyronie's disease, intercourse satisfaction and overall satisfaction.

Table 3: Pearson correlation co-efficients of PDQ domain scores showing convergent and discriminant construct validity, and known groups validity tests of PDQ domain score

	PD Psychological + Physical Symptoms				Penile Pain				PD Symptom Bother			
	IMPRESS I	p Value	IMPRESS II	p Value	IMPRESS I	p Value	IMPRESS II	p Value	IMPRESS I	p Value	IMPRESS II	p Value
*Pearson correlation coefficient**												
Investigator measured curvature deformity	0.16	≤0.008	0.12	<0.05	−0.06	—	−0.04	—	0.11	<0.05	0.16	≤0.008
Self-reported PD symptoms:												
Curvature deformity	0.30	≤0.0001	0.35	≤0.0001	0.08	—	0.07	—	0.28	<0.05	0.42	≤0.0001
Pain on erection	0.23	≤0.0001	0.17	≤0.008	0.59	≤0.0001	0.65	≤0.0001	0.26	≤0.0001	0.30	≤0.0001
Distress over PD	0.42	≤0.0001	0.33	≤0.0001	0.28	≤0.0001	0.16	≤0.008	0.62	≤0.0001	0.49	≤0.0001
IIEF:												
Erectile function	−0.28	≤0.0001	−0.25	≤0.0001	−0.20	≤0.0008	−0.17	≤0.008	−0.32	≤0.0001	−0.31	≤0.0001
Orgasmic function	−0.26	≤0.0001	−0.21	≤0.0001	−0.23	≤0.0001	−0.14	≤0.008	−0.29	≤0.0001	−0.23	≤0.0001
Sexual desire	−0.09	—	−0.03	—	−0.05	—	−0.11	<0.05	−0.13	<0.05	−0.02	—
Intercourse satisfaction	−0.31	≤0.0001	−0.31	≤0.0001	−0.17	≤0.008	−0.17	≤0.008	−0.32	≤0.0001	−0.35	≤0.0001
Overall satisfaction	−0.43	≤0.0001	−0.43	≤0.0001	−0.30	≤0.0001	−0.23	≤0.0001	−0.58	≤0.0001	−0.58	≤0.0001
Known groups validity test												
Mean ± SD penile curvature difference (30–60 vs greater than 60 degrees)	−1.29 ± 5.1	—	−0.67 ± 4.9	—	0.72 ± 5.0	—	0.63 ± 5.2	—	−0.45 ± 3.6	—	−0.97 ± 3.6	<0.05
Mean ± SD disease distress difference (none/mild vs moderate/severe) (t test)	−4.67 ± 4.8	<0.0001	−3.42 ± 4.7	<0.0001	−2.32 ± 4.9	<0.0001	−1.48 ± 5.2	<0.05	−3.55 ± 3.3	<0.0001	−3.23 ± 3.4	<0.0001
Erectile function overall F value (ANOVA)†												
No vs moderate/severe	16.36	<0.001	13.58	<0.001	6.82	<0.001	3.08	<0.05	20.34	<0.001	14.85	<0.001
Mild vs moderate/severe	16.36	<0.001	13.58	<0.01	6.82	<0.05	3.08	—	20.34	<0.001	14.85	<0.001

* Correlations ≥0.30 suggest convergent validity and <0.30 suggest discriminant validity.
† Pairwise p values.

Source: Hellstrom et al , The Journal of Urology, 2013. 190, page 627-634

The International Index of Erectile Function (IIEF) is a widely used measure of erectile dysfunction that was developed by Pfizer during the development program for Sildenafil.

Comment: The use of a questionnaire to include a psychological efficacy end point is important. The sponsor used appropriate tools to develop and verify the PDQ questionnaire, with changes to some of the questions during the clinical trials to improve its validity.

The PDQ bother scale, PDQ psychological and physical symptom scale, IIEF and global assessment of Peyronie's disease scale have some items in common. In the evaluation of the clinical trials, it is important to consider that this may be multiple ways of examining a similar outcome factor rather than separate outcomes.

7.1.2. AUX-CC-803

7.1.2.1. Study design, objectives, locations and dates

This was a Phase III, double blind, randomised, placebo controlled study of the safety and efficacy of AA4500 administered twice per treatment cycle for up to 4 treatment cycles in men with Peyronie's disease.

There were 32 investigative sites in the USA and Australia.

Study period was 365 days. The first subject enrolled in September 2010, and the last subject completed April 2012.

The co-primary objectives were to evaluate the efficacy of AA4500 on the percentage improvement from baseline in curvature deformity of the penis, and the change from baseline in the Peyronie's disease bother domain of the PDQ.

The secondary objectives included a responder analysis based on a subject global assessment of Peyronie's disease scale, reduction in the severity of Peyronie's disease physical and psychological symptoms, change in overall satisfaction index of erectile function, change in penile plaque consistency, change in penile length, change in the penile domain of PDQ.

Safety was also evaluated and is discussed in Section 8.

7.1.2.2. Inclusion and exclusion criteria

The inclusion and exclusion criteria were as follows:

Inclusion criteria:

1. Healthy male subjects > 18 years
2. Diagnosis of Peyronie's disease for at least 12 months
3. Curvature deformity of at least 30 degrees
4. Stable relationship with a female partner and willing to have vaginal intercourse with that partner.

Exclusion criteria

1. A curvature deformity <30˚ or >90˚
2. Any of the following: chordee in the presence of hypospadias; thrombosis of the dorsal penile artery or vein; infiltration by a benign or malignant mass; infiltration by an infectious agent; ventral curvature; STD; Hep B or C; HIV
3. Previous surgery for Peyronie's disease
4. Unable to have an erection induced by pharmacological stimuli
5. Calcified plaque
6. Penile hourglass deformity
7. Plaque at the base of the penis
8. Use of other alternative intralesional medications for Peyronie's disease within 3 months (that is, steroids, verapamil, interferon) or alternative oral medications (vitamin E > 500U, potassium aminobenzoate, tamoxifen, colchicine, pentoxifylline, over the counter erectile dysfunction medications) or topical therapy (for example, verapamil cream) within 3 months
9. Had been treated with extracorporeal shock wave therapy within 6 months
10. Had used any mechanical device for correction of Peyronie's disease or to induce an erection within the 2 week study period before screening
11. Significant erectile dysfunction that had failed to respond to oral treatment with phosphodiesterase 5 inhibitors
12. Compromised penile haemodynamics on ultrasound
13. Uncontrolled hypertension, recent history of stroke, bleeding, other medical condition, abnormal ECG
14. Had received tetracycline, doxycycline, or other tetracycline derivatives within 5 days before the study drug.

Table 4: Screening assessment for Study AUX-CC-803 (and other studies)

Procedures	Screening Period (Day -21 to Day -1)
Informed consent	X
Medical history	X
Peyronie's disease history, including previous treatments for Peyronie's disease	X
Peyronie's disease symptomatology at baseline and severity of each symptom	X
Prior/concomitant medications/procedures	X
Peyronie's disease questionnaire	X
International Index of Erectile Function	X
Physical examination (body weight and height)	X
Penile physical examination (flaccid penis): • Identification of all plaques • Penile length measurement • Penile pain on palpation	X X X X
Penile x-ray/ultrasound	X
Vital signs	X
12-lead electrocardiogram	X
Pharmacological stimulant to induce erection: • Designation of primary plaque • Measurement of curvature deformity and identification of the maximum concavity (or focal point) of the bend and mark the point of maximum concavity (in the primary plaque)[a] • Documentation of direction of curvature • Evaluation for decreased erection beyond plaque • Evaluation for penile indentations • Penile duplex Doppler ultrasound	X X X X X X X
Clinical laboratories	X
Anti-AUX-I/anti-AUX-II antibody levels and neutralizing antibodies to AUX-I and AUX-II[b]	X
Adverse events	X

[a] Identification of the maximum concavity (or focal point) of the bend by measuring from the corona to the maximum point of curvature and marking the site for proposed injection.
[b] Blood sample for anti-AUX-I and anti-AUX-II antibody levels and neutralizing potential of antibodies to AUX-I and AUX-II.

7.1.2.3. Study treatments

The intervention was AA4500 0.58mg (10 000U) injected into the penile plaque at the point of maximum curvature. Two injections were administered 24-72 h apart. A repeat dose was given after 42 ± 5 days for up to 4 cycles.

After the second injection of each cycle, the investigator or qualified designee modelled the plaque in attempt to stretch or elongate the plaque. Subjects were instructed in home modelling for each day of the following 6 week period. Treatment was stopped if the subject's curvature deformity was reduced to < 15%, adverse events, or if the investigator determined that further treatment was not indicated.

The placebo used was 10mM tris and 60mM sucrose reconstituted with the same diluent used for AA4500 (0.03% calcium chloride dehydrate in 0.9% sodium chloride).

Option penile anaesthesia with topical anaesthesia or a dorsal/circumferential penile block was available before each procedure and modelling.

7.1.2.4. Efficacy variables and outcomes

The main efficacy variables were:

- Percent improvement from baseline in curvature deformity- assessed by investigator
- Change from baseline in Peyronie's disease bother score- assessed by subject

The primary analysis time point was 52 weeks.

Other efficacy outcomes included:

- Responder analysis based on global assessment of Peyronie's disease questionnaire
- Change from baseline in the severity of Peyronie's disease physical and psychological symptoms
- Change in overall satisfaction domain of the International Index of Erectile Function (IIEF)
- Change in penile plaque consistency- assessed by investigator
- Change in penile length- assessed by investigator
- Change in penile domain of the PDQ in subjects with a penile pain score > 4 at baseline

An investigator measured curvature deformity, plaque size, penile length, and penile pain.

Pharmacological stimulation of the penis to induce an erection was given at screening, baseline and multiple time points before treatment cycles. The stimuli included PGE1 or trimix (phentolamine, papaverine and prostaglandin) administered into one of the corpus cavernosa. If needed, phenylephrine was used for detumescence.

Each subject completed a Peyronie's Disease Questionnaire (PDQ) at screening, visit 1 and visit 2. The PDQ assesses the impact of Peyronie's disease using the following domains: Peyronie's disease bother, psychological and physical symptoms and penile pain. A global assessment of Peyronie's disease questionnaire evaluated the overall impact of Peyronie's disease on the subject's life.

Table 5: Schedule of assessments for Study AUX-CC-803 and 804

	Treatment				Follow-up (Nominal week)			
	Cycle 1	Cycle 2	Cycle 3	Cycle 4	FU 1 (week 24)	FU 2 (week 33)	FU 3 (week 42)	FU 4 (week 52)
Procedures	Day 1 (Injection 1)	Day 43 (±5 days) (Injection 1)	Day 85 (±5 days) (Injection 1)	Day 127 (±5 days) (Injection 1)	Day 169 (±7 days)	Day 232 (±7 days)	Day 295 (±7 days)	Day 365 (±7 days)
Concomitant medications/procedures	X	X	X	X	X	X	X	X
Peyronie's disease questionnaire					X			X
Dupuytren MMA			X			X		
International Index of Erectile Function					X			X
Global assessment of Peyronie's disease					X			X
Penile physical examination (flaccid penis):		X[a]	X[a]	X[a]	X	X	X	X
• Identification of all plaques								X
• Injection site reactions/local tolerability	X	X	X	X	X	X	X	X
• Penile length measurement		X[a]	X[a]	X[a]	X	X	X	X
• Penile pain on palpation		X[a]	X[a]	X[a]	X	X	X	X
• Primary plaque consistency	X[a]	X[a]	X[a]	X[a]	X	X	X	X
Vital signs	X[b]	X[b]	X[b]	X[b]	X	X	X	X
Clinical laboratories		X[c]	X[c]	X[c]				X
Anti-AUX-I anti-AUX-II antibody levels and neutralizing antibodies to AUX-I and AUX-II		X[a,f,g]	X[a,f,g]	X[a,f,g]	X			X
Pharmacological stimulant to induce erection:		X[a]	X[a]	X[a]	X		X	X
• Penile curvature measurements		X[a]	X[a]	X[a]	X		X	X
• Mark point of maximum concavity on the 1st plaque		X[a]	X[a]	X[a]				
• Direction of curvature		X[a]	X[a]	X[a]	X		X	X
Study drug administration	X[a]	X[a,d]	X[a,d]	X[a,d]				
Investigator penile plaque modeling[3]	X	X	X	X				
Subject home modeling	X[e]	X[e]	X[e]	X[e]	X			
Adverse events	X	X	X	X	X	X	X	X
Discharge from the study								X

Comments: Overall, the outcome factors measured were appropriate. The investigators used a combination of markers of the pathology of Peyronie's disease (curvature, plaque size and consistency) and functional problems faced as a result of Peyronie's disease. Lysis of the collagen plaque, an improvement in penile curvature, and softening of the plaque could be seen as evidence of pharmacodynamic effect. However, previous studies have shown little correlation between plaque size and penile curvature, and penile curvature and Peyronie's bother score or erectile function. Thus, improving the outcome of Peyronie's disease appears to require more than just an improvement in penile curvature.

Erectile dysfunction and sexual function may be due to Peyronie's disease but may also have been due to other factors. Failure of AA4500 to improve these parameters

may not necessarily be due to lack of efficacy but due to other contributing factors. Many of the risk factors for Peyronie's disease are the same as those for erectile dysfunction.

7.1.2.5. Randomisation and blinding methods

Before dosing, subjects were stratified by degree of curvature deformity (30-60˚ or 60-90˚) then randomised in a 2:1 method into 2 treatment groups. Randomisation was performed by an electronic data capture system. The investigator, study subject and other study personnel were blinded to the treatment allocation.

7.1.2.6. Analysis populations

The ITT population included all subjects who had been randomised and received at least 1 dose of study medication.

The mITT population included subjects who had both a curvature deformity measurement and PDQ response as baseline and one subsequent time point. This population was the prespecified primary population for efficacy. It excluded subjects who were not sexually active at baseline (as they could not complete the PDQ) and those who did not complete the PDQ after treatment.

7.1.2.7. Sample size

Four hundred subjects were planned (267 AA4500 and 133 placebo) and 417 were analysed.

The sample size was chosen to give a power of 95% to detect a change in curvature deformity of 19% (SD 30%) and bother of 2.2 (SD 4.5). Using these calculations, 252 subjects in the Xiaflex arm would be needed.

7.1.2.8. Statistical methods

Missing data was dealt with using the last analysis carried forward. For each co primary end point, the hypothesis of no drug effect was tested using a two-sided test with a family type 1 error of 0.05. For the secondary endpoints, multiplicity tests were used to control family wise errors. Results were compared between treatment groups using analysis of covariance for continuous efficacy parameters and Cochrane Mantel Haensel test for general association for those categorical parameters for which statistical testing was performed. Gate keeping procedures were used to control for family wise errors between primary and secondary endpoints. A combination of Bonferroni's and Hochbergs procedures was used to test multiple hypotheses of secondary endpoints.

7.1.2.9. Participant flow

A total of 418 subjects were randomised. Most subjects completed all 4 treatment cycles, 87% in the active arm and 89% in the placebo arm. The most common reason for study discontinuation was withdrawal of consent, see Table 6.

Table 6: Subject disposition Study AUX-CC-803

	AA4500	Placebo	Total
Screened subjects			512
Randomized subjects	278	140	418
ITT population[a]	277 (100.0)	140 (100.0)	417 (100.0)
PM population[b]	275 (99.3)	139 (99.3)	414 (99.3)
PDQ population[c]	199 (71.8)	104 (74.3)	303 (72.7)
mITT population[d]	199 (71.8)	104 (74.3)	303 (72.7)
PP population[e]	165 (59.6)	89 (63.6)	254 (60.9)
Completed[f]	241 (87.0)	124 (88.6)	365 (87.5)
Discontinued, n (%):	36 (13.0)	16 (11.4)	52 (12.5)
Withdrawal by subject	20 (7.2)	6 (4.3)	26 (6.2)
Lost to follow-up	6 (2.2)	5 (3.6)	11 (2.6)
Adverse event	4 (1.4)	1 (0.7)	5 (1.2)
Protocol violation	1 (0.4)	0 (0.0)	1 (0.2)
Death	2 (0.7)	0 (0.0)	2 (0.5)
Other	3 (1.1)	4 (2.9)	7 (1.7)
Days in study[g]			
Mean (SD)	338.8 (74.01)	340.6 (75.73)	339.4 (74.51)
Median	365.0	365.0	365.0
Min, Max	1, 399	5, 387	1, 399

7.1.2.10. Major protocol violations/deviations

There were 13 subjects with major protocol deviations during the study. Four of these subjects were excluded, 2 for receiving the wrong study drug and 2 for taking other medications (verapamil and pentoxifylline).

7.1.2.11. Baseline data

A total of 418 subjects were randomised, 278 to AA4500 and 140 to placebo. The majority of subjects were White (95.2%). The median age was 59 years, range 28-81 years. Approximately 11.5% were currently smoking, and 35.3% previously smoked. There was no difference in baseline demographic or Peyronie's disease characteristics between the two treatment groups.

The median duration of Peyronie's disease was 2.9 years (range 1-50.8 years). Approximately 49% had erectile dysfunction. Most subjects had penile shortening of 1.75-5cm moderate curvature deformity (52%), no pain in the erect penis (66.4%), no change in penile shape (50.8%), moderate distress in Peyronie's disease (52%). At screening, most subjects had no calcification of their penis (70.3%). No subjects had an abnormal Doppler ultrasound of the penis. These characteristics are shown in detail in Tables 7 and 8.

Table 7: Study AUX-CC-803 Baseline study characteristics Peyronie's disease history

Parameter	AA4500 (N=277)	Placebo (N=140)	Total (N=417)
Duration (years) of Peyronie's disease			
Mean (SD)	3.88 (4.044)	4.78 (6.193)	4.18 (4.883)
Median	2.70	2.90	2.90
Min, Max	1.0, 35.9	1.0, 50.8	1.0, 50.8
Erectile dysfunction, n (%)			
No	149 (53.8)	65 (46.4)	214 (51.3)
Yes	128 (46.2)	75 (53.6)	203 (48.7)
Trauma to the penis, n (%)			
No	211 (76.2)	107 (76.4)	318 (76.3)
Yes	66 (23.8)	33 (23.6)	99 (23.7)
Family history of Peyronie's disease, n (%)			
No	194 (97.0)	95 (95.0)	289 (96.3)
Yes	6 (3.0)	5 (5.0)	11 (3.7)
Unknown	77	40	117
Family history of Dupuytren's disease, n (%)			
No	213 (91.8)	106 (89.8)	319 (91.1)
Yes	19 (8.2)	12 (10.2)	31 (8.9)
Unknown	45	22	67
Family history of Ledderhose's disease, n (%)			
No	220 (100.0)	111 (91.1)	331 (99.7)
Yes	0 (0.0)	1 (0.9)	1 (0.3)
Unknown	57	28	85
Prior exposure to AA4500, n (%)			
No	275 (99.3)	140 (100.0)	415 (99.5)
Yes	2 (0.7)	0 (0.0)	2 (0.5)

Table 8: Study AUX-CC-803 Baseline study characteristics Peyronie's disease symptomatology

Parameter	AA4500 (N=277)	Placebo (N=140)	Total (N=417)
Penile shortening, n (%)			
None	43 (15.5)	28 (20.0)	71 (17.0)
>0 to ½ inch	56 (20.2)	19 (13.6)	75 (18.0)
>½ inch to 1 inch	98 (35.4)	43 (30.7)	141 (33.8)
>1 inch to 2 inches	68 (24.5)	37 (26.4)	105 (25.2)
>2 inches	12 (4.3)	13 (9.3)	25 (6.0)
Presence of plaque/lesion on the penis, n (%)			
None	42 (15.2)	17 (12.1)	59 (14.1)
Mild	69 (24.9)	29 (20.7)	98 (23.5)
Moderate	118 (42.6)	70 (50.0)	188 (45.1)
Severe	48 (17.3)	24 (17.1)	72 (17.3)
Subject-rated curvature deformity, n (%)			
Mild	36 (13.0)	13 (9.3)	49 (11.8)
Moderate	141 (50.9)	76 (54.3)	217 (52.0)
Severe	100 (36.1)	51 (36.4)	151 (36.2)
Pain in erect penis, n (%)			
None	183 (66.1)	94 (67.1)	277 (66.4)
Mild	59 (21.3)	33 (23.6)	92 (22.1)
Moderate	32 (11.6)	13 (9.3)	45 (10.8)
Severe	3 (1.1)	0 (0.0)	3 (0.7)
Change in penile shape, n (%)			
None	135 (48.7)	77 (55.0)	212 (50.8)
Mild	63 (22.7)	27 (19.3)	90 (21.6)
Moderate	49 (17.7)	23 (16.4)	72 (17.3)
Severe	30 (10.8)	13 (9.3)	43 (10.3)
Decrease in rigidity/stability with erection, n (%)			
None	93 (33.6)	42 (30.0)	135 (32.4)
Mild	68 (24.5)	50 (35.7)	118 (28.3)
Moderate	86 (31.0)	32 (22.9)	118 (28.3)
Severe	30 (10.8)	16 (11.4)	46 (11.0)
Subject-rated distress over Peyronie's disease, n (%)			
None	6 (2.2)	5 (3.6)	11 (2.6)
Mild	33 (11.9)	18 (12.9)	51 (12.2)
Moderate	151 (54.5)	66 (47.1)	217 (52.0)
Severe	87 (31.4)	51 (36.4)	138 (33.1)

Data source: Table 14.1.4
Note: 26 non-prespecified terms for Peyronie's disease symptomatology reported from 23 subjects were not summarized in this table.

Common and significant medical histories among the subjects included hypertension (36.7%), hypercholesterolaemia (23.3%), benign prostatic hypertrophy (21.6%), gastroesophagael reflux disease (19.9%), depression (15.8%), hyperlipidaemia (15.1%), anxiety (10.6%), type 2 diabetes (7.7%), hypogonadism (8.2%) and hypothyroidism (4.8%).

The CSR states that majority of subjects (91% and 87.1%) had not received any treatment for Peyronie's disease, but the majority of subjects (54.2% and 59.3%) were taking Peyronie's disease medication. The most common Peyronie's medications were tocopherol (Vitamin E) and verapamil.

Other common or significant medications included acetylsalicylic acid in 30%, testosterone derivative 6.3%, benzodiazepines 13.4%, drugs for erectile dysfunction 33.1% (sildenafil, tadalafil, vardenafil), and antidepressants 14.4%.

Comment: This was quite a select group of patients. The incidence of Peyronie's disease varies among different populations studies. There is likely to be a number of patients who have a penile deformity but do not seek treatment for it. Those who present for treatment or volunteer to be involved in a clinical trial are likely to have more severe disease or are more bothered by it. The investigators chose subjects with a mild-moderate deformity on the lateral or dorsal surface. They excluded subjects in homosexual relationships, those with severe erectile dysfunction that was unresponsive to PGE5 inhibitors , those who were unable to sustain an erection after pharmacological stimuli, and those with significant calcification on penile ultrasound. Approximately 25% of those enrolled in the RCT were not having sexual

intercourse at baseline. A large number of these patients had other co-morbidities and were taking other medications that may affect their sexual function.

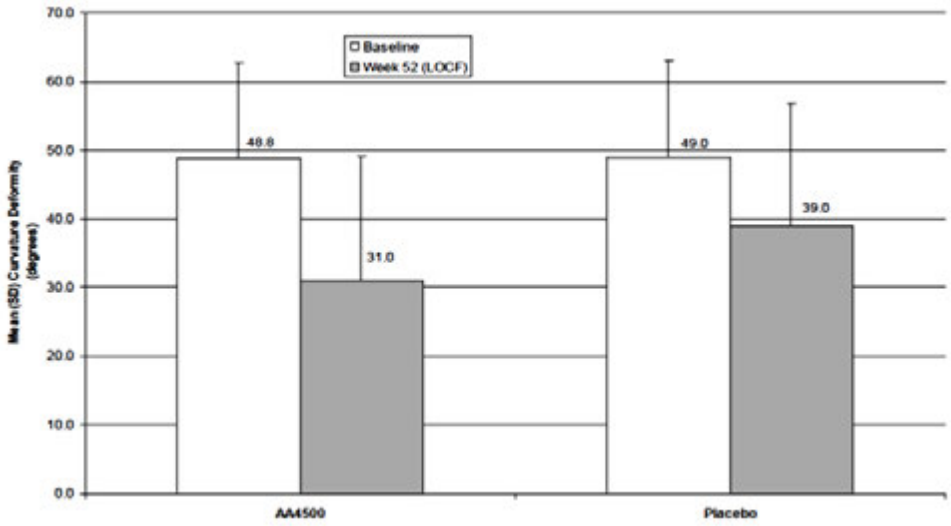
7.1.2.12. Results for the primary efficacy outcome

Percentage change from baseline in curvature deformity.

Subjects who received AA4500 demonstrated a statistically significant mean improvement of around 17˚ or 37.6% (SD 30.29%) in penile curvature from baseline to Week 52 compared to 10 ˚ or 21.3 % (SD 29.9%) in the placebo group. The response was greater in those with lower curvature at baseline, see **Error! Reference source not found.**.

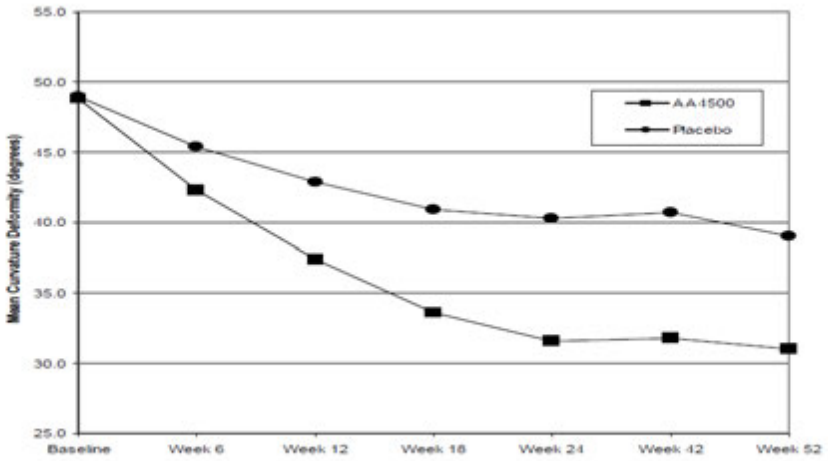
Comment: Note the large placebo effect, variability and overlapping confidence intervals.

Figure 1: Study AUX-CC-803 Change in curvature deformity of the penis at baseline and Week 52 in the mITT population



The mean curvature improvement began after the first cycle and increased with each cycle of therapy. The response was sustained for 28 weeks after the last treatment cycle, see Figure 2.

Figure 2: Study AUX-CC-803: mean penis curvature deformity over time (mITT population)

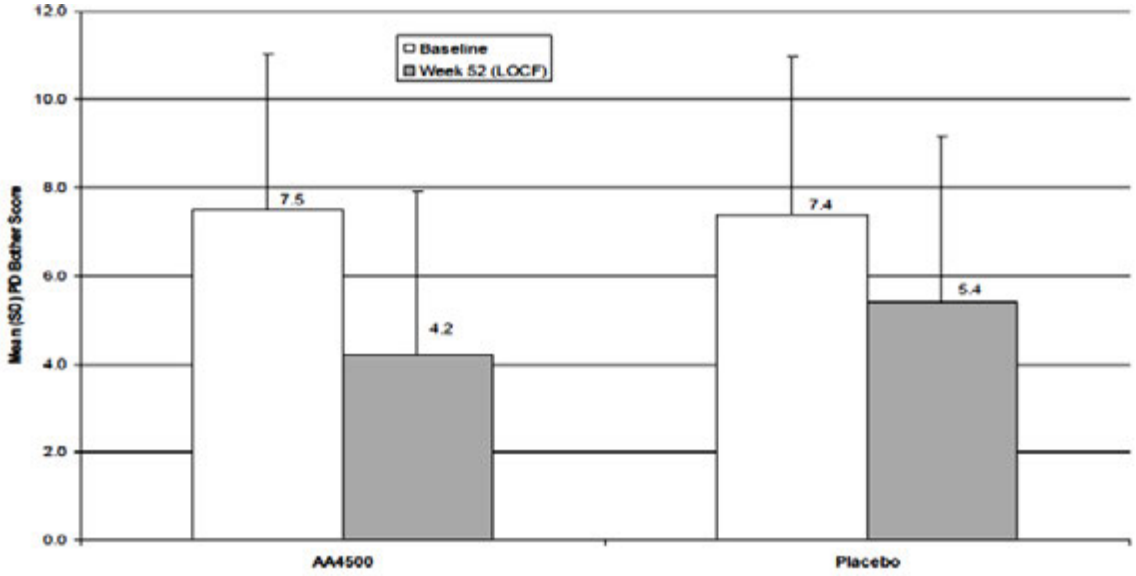


Data source: Table 14.2.3.1
Note: Week 52 value is LOCF.

Peyronie's disease bother score

Both the AA4500 and placebo group experienced an improvement in Peyronie's bother score. This was greater in the active treatment group, -3.3 (SD 3.83) versus -2.0 (SD 3.53) p=0.045, see Figure 3. The response was greater in those with lower curvature at baseline.

Figure 3: Study AUX-CC-803: mean (± SD) Peyronie's disease bother score at baseline and Week 42 (mITT population)



7.1.2.13. Results for other efficacy outcomes

Overall global assessment of Peyronie's disease

The incidence of a positive response (that is, some improvement) in the global assessment of Peyronie's disease was greater in the AA4500 group, 66.2% compared with the placebo group, 29.1% (p<000.1).

Change in Peyronie's disease physical and psychological symptom score

Subjects who received AA4500 had a greater improvement from baseline to Week 52 in Peyronie's disease physical and psychological symptom score compared to placebo, mean change -3.2 versus -1.6. However the difference was not statistically significant based on the multiple comparison algorithms.

Change from baseline in IIEF overall satisfaction

There was a greater improvement in IIEF overall satisfaction from baseline to Week 52 in the AA4500 group (1, SD 2.55) compared to the placebo group (0.5, SD2.42). This was not statistically significant.

Composite response

For this measurement, response was based on a change of curvature deformity of > 20%, change in Peyronie's bother score of > 1, change in reporting of 'no' to some sexual activity. There was a greater response in those who received AA4500 (50.6%) compared to placebo (25.4%).

Change in penile plaque consistency

There was no statistically significant pattern of change in penile plaque between the placebo and AA4500 groups. Those with a 'hard' plaque at baseline were more likely to develop more softness with treatment with AA4500. For those with a soft plaque at baseline, a similar number

of subjects had a softening of the plaque to that developed more hardening of the plaque, see Table 9.

Table 9: Study AUX-CC-803 Mean change from baseline in penile plaque consistency at Week 52 (mITT population)

Time point Treatment Consistency (score)	Penile Plaque Consistency (Score) at Baseline n (%) Hard (5)	Firm Throughout (4)	Moderate Firmness (3)	Soft (2)	Non-palpable (1)	Score difference from baseline
Week 52 (LOCF)						
AA4500						
Hard (5)	1 (3.4)	1 (1.6)	0 (0.0)	0 (0.0)	0	--
Firm throughout (4)	18 (62.1)	15 (24.2)	6 (6.5)	2 (13.3)	0	4: 0 (0.0)
Moderate firmness (3)	6 (20.7)	33 (53.2)	49 (52.7)	3 (20.0)	0	3: 0 (0.0)
Soft (2)	1 (3.4)	11 (17.7)	25 (26.9)	6 (40.0)	0	2: 2 (1.0)
Non-palpable (1)	3 (10.3)	2 (3.2)	13 (14.0)	4 (26.7)	0	1: 10 (5.0)
Score difference from baseline		-4: 3 (1.5)	-3: 3 (1.5)	-2: 30 (15.1)	-1: 80 (40.2)	0: 71 (35.7)
Mean (SD)	-0.7 (0.97)					
Week 52 (LOCF)						
Placebo						
Hard (5)	3 (27.3)	1 (3.2)	0 (0.0)	0 (0.0)	0	--
Firm throughout (4)	5 (45.5)	10 (32.3)	1 (1.9)	0 (0.0)	0	4: 0 (0.0)
Moderate firmness (3)	2 (18.2)	14 (45.2)	35 (66.0)	2 (22.2)	0	3: 0 (0.0)
Soft (2)	1 (9.1)	4 (12.9)	12 (22.6)	5 (55.6)	0	2: 0 (0.0)
Non-palpable (1)	0 (0.0)	2 (6.5)	5 (9.4)	2 (22.2)	0	1: 4 (3.8)
Score difference from baseline		-4: 0 (0.0)	-3: 3 (2.9)	-2: 11 (10.6)	-1: 33 (31.7)	0: 53 (51.0)
Mean (SD)	-0.6 (0.84)					
Observed p-value	0.3085					
Multiple comparison p-value	NS					

Data source: Table 14.2.2 and Table 14.2.9.1
NS=not significant (based on the multiple comparison algorithm).

Change in penile length

There was no significant difference in the change of penile length between treatment groups.

Change in penile pain

Both placebo and A4500 groups had an improvement in penile pain score at week 52 (-5.1 SD 5.16 compared to -4.0 SD 4.09). The difference was not statistically significant.

Additional efficacy analysis

No statistically significant difference was observed between the AA4500 groups and placebo group for IIEF scales for erectile function, orgasmic function, sexual desire or intercourse satisfaction.

A spontaneous penile event was considered a positive attribute to the study drug. These events included penile popping (plaque stretching), improved penile rigidity, penile lengthening, and improved penile sensation. More subjects in the AA4500 group experience spontaneous penile events (15.6% compared to 3.8%).

7.1.3. Study AUX-CC-804

The study design and protocol for Study AUX-CC-804 was identical to that of AUX-CC-803. In summary, this was a Phase III, double blind, randomised, placebo controlled study of the safety and efficacy of AA4500 administered twice per treatment cycle for up to four treatment cycles in men with Peyronie's disease. The study took place between 4 October 2010 and 30 March 2012 in 32 sites in the USA and Australia.

7.1.3.1. Baseline data

A total of 418 subjects were randomised, 277 to AA4500 and 141 to placebo. Most subjects completed the study, 86.1% of the AA4500 group and 90.1% of the placebo group. The most common reason for discontinuation was withdrawal of consent (6.5%).

There was no significant difference in demographics between the two treatment groups. The majority (97.3%) of subjects were White; the median age was 58 years (age 23-84). Approximately 11.6% were current smokers, 37.1% previously smoked. Common or significant co-morbidities included hypertension (35.9%), hypercholesterolaemia (25.3%), gastroesophagael reflux disease (20.2%), benign prostatic hypertrophy (20.2%), depression (12.8%), anxiety (5.8 %), type 2 diabetes (6.7%), hypogonadism (6.5%), and hypothyroidism (4.3%).

The sponsor states that the majority of subjects (89.1% and 87.2%) had not received any treatment for Peyronie's disease prior to the study, but that the majority (56.6 and 59.6%) had taken Peyronie's medication prior to the study. The most common medications were tocopherol and verapamil.

Other common or significant medications included acetylsalicylic acid in 27.2%, testosterone derivative 6.5%, benzodiazepines and related drugs 9.6%, drugs used for erectile dysfunction 35.7% (sildenafil, tadalafil, vardenafil), and antidepressants 13%.

The two groups had similar Peyronie's disease histories, except the AA4500 group had a longer mean duration of illness than the placebo group (4.24 versus 3.42 years). This would potentially bias results against finding a treatment effect, see Tables 10 and 11.

Table 10: Study AUX-CC-804 Peyronie's disease symptomatology at baseline (ITT)

Parameter	AA4500 (N=274)	Placebo (N=141)	Total (N=415)
Penile shortening, n (%)			
None	33 (12.0)	24 (17.0)	57 (13.7)
>0 to ½ inch	43 (15.7)	24 (17.0)	67 (16.1)
>½ inch to 1 inch	96 (35.0)	44 (31.2)	140 (33.7)
>1 inch to 2 inches	81 (29.6)	37 (26.2)	118 (28.4)
>2 inches	21 (7.7)	12 (8.5)	33 (8.0)
Presence of plaque/lesion on the penis, n (%)			
None	47 (17.2)	24 (17.0)	71 (17.1)
Mild	49 (17.9)	35 (24.8)	84 (20.2)
Moderate	130 (47.4)	56 (39.7)	186 (44.8)
Severe	48 (17.5)	26 (18.4)	74 (17.8)
Subject-rated curvature deformity, n (%)			
Mild	28 (10.2)	13 (9.2)	41 (9.9)
Moderate	144 (52.6)	67 (47.5)	211 (50.8)
Severe	102 (37.2)	61 (43.3)	163 (39.3)
Pain in erect penis, n (%)			
None	178 (65.0)	88 (62.4)	266 (64.1)
Mild	62 (22.6)	31 (22.0)	93 (22.4)
Moderate	28 (10.2)	18 (12.8)	46 (11.1)
Severe	6 (2.2)	4 (2.8)	10 (2.4)
Change in penile shape, n (%)			
None	108 (39.4)	66 (46.8)	174 (41.9)
Mild	66 (24.1)	26 (18.4)	92 (22.2)
Moderate	67 (24.5)	33 (23.4)	100 (24.1)
Severe	33 (12.0)	16 (11.3)	49 (11.8)
Decrease in rigidity/stability with erection, n (%)			
None	81 (29.6)	36 (25.5)	117 (28.2)
Mild	74 (27.0)	36 (25.5)	110 (26.5)
Moderate	87 (31.8)	50 (35.5)	137 (33.0)
Severe	32 (11.7)	19 (13.5)	51 (12.3)
Subject-rated distress over Peyronie's disease, n (%)			
None	8 (2.9)	4 (2.8)	12 (2.9)
Mild	48 (17.5)	21 (14.9)	69 (16.6)
Moderate	128 (46.7)	67 (47.5)	195 (47.0)
Severe	90 (32.8)	49 (34.8)	139 (33.5)

Data source: Table 14.1.4

Note: 24 non-prespecified terms for Peyronie's disease symptomatology reported from 21 subjects were not summarized in this table.

Table 11: Study AUX-CC-804 Peyronie's disease questionnaire at baseline

Parameter	AA4500 (N=274)	Placebo (N=141)	Total (N=415)
Peyronie's Disease Symptoms (Max=24)	(n=228)[a]	(n=116)[a]	(n=344)
Mean (SD)	10.7 (4.80)	11.1 (5.07)	10.8 (4.89)
Median	11.0	11.0	11.0
Min, Max	0, 23	0, 24	0, 24
Penile Pain (Max=30)	(n=228)[a]	(n=116)[a]	(n=344)
Mean (SD)	4.2 (4.80)	5.0 (5.86)	4.5 (5.19)
Median	2.5	2.0	2.0
Min, Max	0, 24	0, 25	0, 25
Peyronie's Disease Bother (Max=16)	(n=228)[a]	(n=116)[a]	(n=344)
Mean (SD)	7.4 (3.49)	8.0 (3.74)	7.6 (3.58)
Median	7.0	8.0	8.0
Min, Max	0, 15	0, 16	0, 16

Data source: Table 14.1.7

[a] Seventy (70) subjects (45 AA4500, 25 placebo) were not sexually active at baseline and could not be included in the primary population for efficacy, as they were ineligible to complete the PDQ at baseline or thereafter, as prescribed by the protocol (ie, subjects had to have vaginal intercourse within 3 months of any PDQ assessment).

7.1.3.2. Protocol deviations

There were 18 subjects who had major protocol deviations during the study, 13 in the study group and 5 in the placebo group. Two were withdrawn (due to receiving the incorrect study drug).

7.1.3.3. Efficacy results

Penile curvature

There was an improvement in penile curvature deformity in both the placebo and AA4500 groups of 8.5 ˚or -15.2% (SD 28.66%) and 16.2 ˚or -30.5% (SD 27.7%) respectively. This was statistically significant when corrections for multiple comparisons were made, see Figure 4.

Figure 4: Mean curvature deformity at baseline and after 52 weeks (mITT)

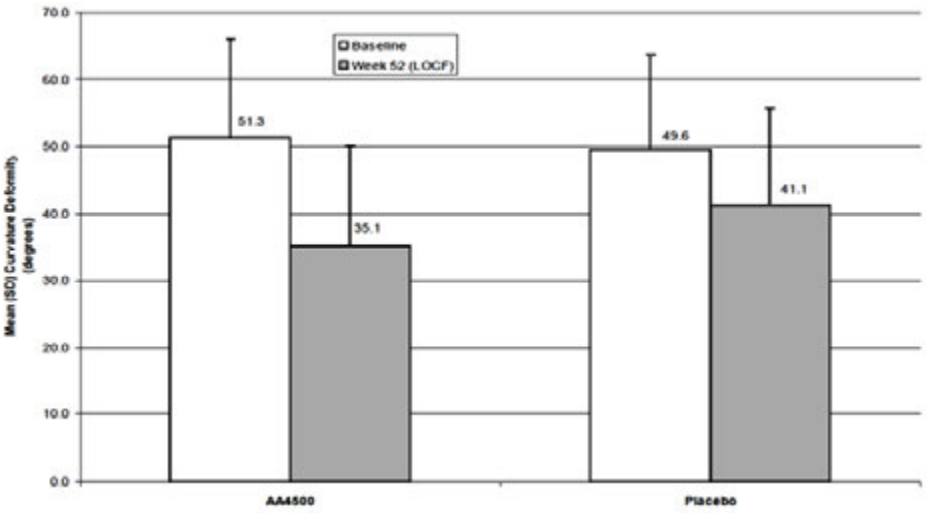
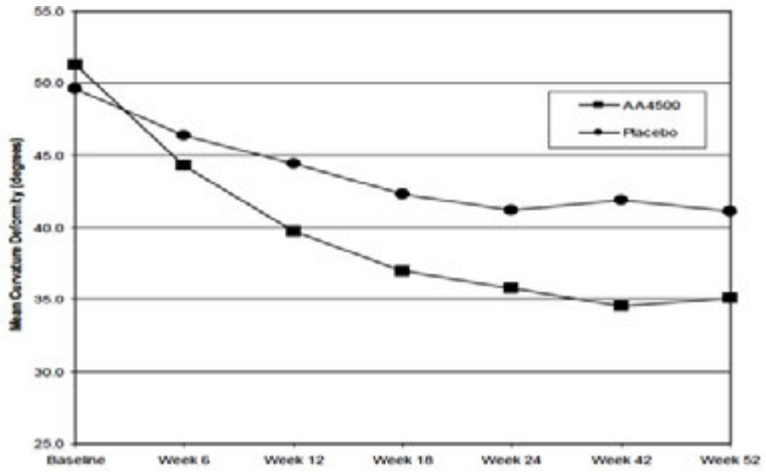


Figure 5: Study AUX-CC-804 Mean curvature deformity over time



As in Study AUX-CC-803, the improvement in curvature was seen after the 1st treatment cycle that continued until the after the fourth treatment cycle and was then maintained.

Improvements in penile curvature were similar regardless of initial penile deformity (Table 12).

Table 12: Mean percent change from baseline in curvature deformity at Week 52 by baseline curvature deformity stratum (mITT)

	Baseline Curvature Deformity Stratum			
	30° to 60° (N=242)		61° to 90° (N=67)	
	AA4500 (N=155)	Placebo (N=87)	AA4500 (N=47)	Placebo (N=20)
Baseline value				
Mean (SD)	45.0 (9.24)	44.5 (9.48)	72.3 (9.11)	71.9 (7.37)
Min, Max	30, 60	30, 60	61, 90	62, 85
Week 52 value (LOCF)				
Mean (SD)	32.3 (14.18)	39.4 (14.41)	44.2 (14.68)	48.5 (13.42)
Min, Max	0, 65	10, 80	12, 82	17, 75
% change from baseline				
Mean (SD)	-28.1 (29.06)	-11.3 (29.32)	-38.3 (21.13)	-32.4 (17.64)
Min, Max	-100, 44	-67, 67	-82, 17	-76, -9

Peyronie's disease bother score

The Peyronie's disease bother score improved in both treatment groups, but more so in the Xiaflex treatment group. This difference remained significant when statistical adjustments were made for multiple comparisons, see Table 13.

Table 13: Study AUX-CC-804: Mean change from baseline in Peyronie's disease bother score at Week 52 (mITT)

	AA4500 (N=202)	Placebo (N=107)
Baseline value		
Mean (SD)	7.4 (3.56)	8.2 (3.72)
Min, Max	0, 15	0, 16
Week 52 value (LOCF)		
Mean (SD)	5.0 (3.93)	6.5 (4.20)
Min, Max	0, 16	0, 16
Change from baseline		
Mean (SD)	-2.4 (3.62)	-1.6 (3.52)
Min, Max	-14, 9	-12, 6
Observed p-value	0.0496	
Multiple comparison p-value	*	

Data source: Table 14.2.2 and Table 14.2.4.3.1

* Represents statistical significance based on the multiple comparison algorithm.

Those with greater penile deformity had slightly higher score of the PDQ at baseline and but similar improvements with AA4500 and placebo, see Table 14.

Table 14: Study AUX-CC-804 Mean change from baseline in Peyronie's disease bother score at Week 52 by baseline curvature deformity (mITT)

	Baseline Curvature Deformity Stratum			
	30° to 60° (N=242)		61° to 90° (N=67)	
	AA4500 (N=155)	Placebo (N=87)	AA4500 (N=47)	Placebo (N=20)
Baseline value				
Mean (SD)	7.2 (3.62)	7.9 (3.80)	8.1 (3.30)	9.5 (3.09)
Min, Max	0, 15	0, 16	2, 15	3, 14
Week 52 value (LOCF)				
Mean (SD)	5.0 (3.94)	6.2 (4.21)	5.1 (3.94)	8.1 (3.85)
Min, Max	0, 16	0, 16	0, 14	2, 15
Change from baseline				
Mean (SD)	-2.2 (3.56)	-1.7 (3.42)	-3.0 (3.78)	-1.4 (4.02)
Min, Max	-14, 9	-12, 4	-9, 6	-9, 6

7.1.3.4. Secondary efficacy endpoints

Responders based on the overall global assessment of Peyronie's disease

There was a greater number of responders in the AA4500 group (55.4%) compared to the placebo group (29.9%). This was significant when statistical adjustments for multiple comparisons were made.

Responders based on the Peyronie's disease physical and psychological symptom score

There was an improvement in the PDQ physical and psychological symptom score in both placebo and treatment groups. Although this was numerically greater in the AA4500 group (-2.6 (SD 4.83) versus -1.0 (SD 4.78)), this was not statistically significant when adjustment for multiple comparisons was made.

IIEF

There was a greater improvement from baseline to Week 52 in the AA4500 group compared to the placebo group (1.0 versus 0.3) however this was not statistically significant when adjustments for multiple comparisons were made.

Composite response

For this criterion, a positive response was defined as a change in curvature deformity of > 20%, a change in Peyronie's bother score of > 1, or a change in sexual activity from no sexual activity at screening to some sexual activity. There were more responders in the AA4500 group (42.3%) compared to the placebo group (30.6%), however the difference was not statistically significant based on the multiple treatment algorithm.

Plaque consistency

There was an improvement in plaque consistency in both AA4500 and placebo groups, particularly in those where the plaque was described as hard or firm throughout. Although this was numerically greater in the AA4500 group, it was not statistically significant when corrections for multiple comparisons were made, see Table 15.

Table 15: Study AUX-804: mean change from baseline in penile plaque consistency at Week 52 (mITT)

Time point Treatment Consistency (score)	Penile Plaque Consistency (Score) at Baseline n (%) Hard (5)	Firm Throughout (4)	Moderate Firmness (3)	Soft (2)	Non-palpable (1)	Score difference from baseline
Week 52 (LOCF)						
AA4500						
Hard (5)	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	0	--
Firm throughout (4)	13 (44.8)	18 (26.5)	5 (5.9)	0 (0.0)	0	4: 0 (0.0)
Moderate firmness (3)	8 (27.6)	28 (41.2)	45 (52.9)	2 (10.0)	0	3: 0 (0.0)
Soft (2)	5 (17.2)	16 (23.5)	29 (34.1)	11 (55.0)	0	2: 0 (0.0)
Non-palpable (1)	2 (6.9)	6 (8.8)	6 (7.1)	7 (35.0)	0	1: 7 (3.5)
Score difference from baseline		-4: 2 (1.0)	-3: 11 (5.4)	-2: 30 (14.9)	-1: 77 (38.1)	0: 75 (37.1)
Mean (SD)	-0.8 (0.97)					
Week 52 (LOCF)						
Placebo						
Hard (5)	1 (9.1)	2 (5.9)	0 (0.0)	0 (0.0)	0	--
Firm throughout (4)	6 (54.5)	12 (35.3)	2 (4.7)	1 (5.3)	0	4: 0 (0.0)
Moderate firmness (3)	4 (36.4)	13 (38.2)	25 (58.1)	7 (36.8)	0	3: 0 (0.0)
Soft (2)	0 (0.0)	7 (20.6)	15 (34.9)	8 (42.1)	0	2: 1 (0.9)
Non-palpable (1)	0 (0.0)	0 (0.0)	1 (2.3)	3 (15.8)	0	1: 11 (10.3)
Score difference from baseline		-4: 0 (0.0)	-3: 0 (0.0)	-2: 12 (11.2)	-1: 37 (34.6)	0: 46 (43.0)
Mean (SD)	-0.4 (0.86)					
Observed p-value	0.0144					
Multiple comparison p-value	NS					

Data source: Table 14.2.2 and Table 14.2.9.1
NS=not significant (based on the multiple comparison algorithm).

Changes in penile length

Overall, subjects who received AA4500 had a greater improvement in penile length (0.5cm) compared to those who received placebo (0.2 cm), however the difference was not statistically significant.

Other endpoints

There was a significantly greater improvement in intercourse satisfaction (1.1 versus -0.1 of a scale of 15) in the AA4500 group compared to the placebo group. There was no significant difference between the AA4500 and placebo groups in penile pain, erectile function, orgasmic function or sexual desire. There was no significant difference in sexual activity at baseline or week 52 in the AA4500 or placebo groups.

There was a higher incidence of spontaneous penile events in the AA4500 group (15.3%) than the placebo group (5.6%).

7.1.4. Study AUX-CC-801

This has been included as a pivotal study because it assessed the efficacy of the modelling procedure.

7.1.4.1. Study design, objectives, locations and dates

This was a Phase IIb, double blind, multicentre, randomised, placebo controlled study of the safety and efficacy of AA4500 administered two times a week, with and without modelling, for up to three treatment cycles in subjects with Peyronie's disease.

This study was conducted at 12 sites in the USA. The study duration was 36 weeks. The first subject was enrolled in August 2008. The last subject completed in October 2009.

The objectives of the study were to assess the sensitivity of the Peyronie's Disease Questionnaire (PDQ); assess the effectiveness of AA4500 in improving penile curvature in men with Peyronie's disease; assess the safety of AA4500 in men with Peyronie's disease.

7.1.4.2. Inclusion and exclusion criteria

The same inclusion and exclusion criteria for Study AUX-CC-803 also applied to this study.

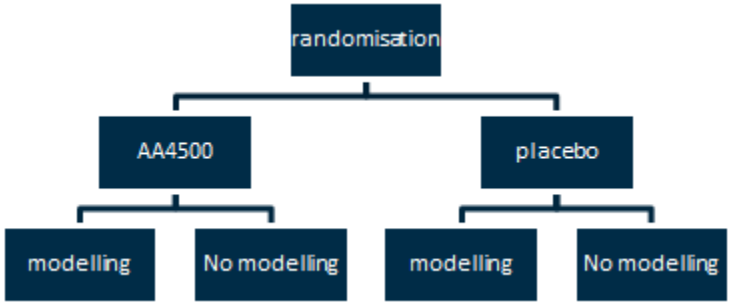
7.1.4.3. Study treatments

Subjects were stratified by the degree of penile curvature (30-60˚ or 60-90˚) then randomised into four treatment groups to receive in a 3:1 ratio to either AA4500 or placebo; and further randomised in a 1:1 ratio to receive either penile plaque modelling or no modelling. The treatment given was AA4500 at a dose of 0.58mg in a volume of 0.25ml delivered into the penile plaque. The diluent used in both the AA4500 and placebo group was 0.9% saline with 2mMCaCl2.

Each treatment cycle consisted of were 2 injections separated by 24-72 h, and followed by modelling. Each cycle was repeated every 6 weeks for a maximum of 3 cycles.

Following the maximum number of treatment cycles, subjects were followed at Weeks 18, 24 and 36.

Figure 6: Study design



7.1.4.4. Efficacy variables and outcomes

The main efficacy variables were:

- Penile curvature
- Peyronie's Disease Questionnaire
- International Index of Erectile Function (IIEF)
- Penile length
- Plaque length
- Plaque width
- Plaque area
- Peyronie's symptomatology
- Peyronie's disease global assessment

Table 16: Study AUX-CC-801 Schedule of assessments

Procedures	Screening	Week 1 (Treatment Cycle 1)	10-14 days after first injection	Week 6 ± 7 days	Week 7 (Treatment Cycle 2)	Week 12 ± 7 days	Week 13 (Treatment Cycle 3)	Week 18 ± 7 days	Week 24 ± 7 days	Week 36 ± 7 days
Informed consent	X									
Medical history including demographics/Peyronie's history	X									
Physical examination	X									X
Body weight	X									X
Height	X									
Vital signs	X	X[a]			X[a]		X[a]	X	X	X
Peyronie's disease symptomatology	X			X		X		X	X	X
Penile plaque measurement	X			X		X		X	X	X
Penile length	X			X		X		X	X	X
Penile curvature measurements[b]	X			X		X		X	X	X
Penile x-ray/ultrasound	X									
Penile duplex Doppler ultrasound[c]	X									X
PDQ	X			X		X		X	X	X
International Index of Erectile Function (IIEF) Questionnaire	X			X		X		X	X	X
Global Assessment of Peyronie's disease Questionnaire				X		X		X	X	X
Clinical laboratories	X		X		X[d]		X[d]			X
Immunogenicity	X		X		X[d,f]		X[d,f]			X
12-lead electrocardiogram	X									
Study drug administration		X[g]			X[d,h]		X[d,h]			
Penile plaque modeling[i]		X			X		X			
Adverse injection site reactions		X[j]	X		X[j]		X[j]			
Cognitive debriefing interview[k]									X	X
Adverse events		X	X	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X
Discharge from the study										X

[a] Immediately before and after injection, at 5, 10, 20, 30, and 60 minutes after injection, and before discharge. Vital signs must have been stable for a period of at least 60 minutes before the subject could have been discharged from the study unit.
[b] After pharmacological stimulation to induce a rigid erection, which, in the opinion of the investigator, was sufficient to accurately measure the subject's penile deformity.
[c] Repeated during the first, second, or third treatment cycle if the subject reported complete inability to have a spontaneous erection.
[d] Before the first injection of the treatment cycle.
[e] 10-mL blood sample for immunogenicity testing for antibodies to AA4500 was collected before the first injection of the treatment cycle.
[f] All subjects, including those not receiving treatment at either Week 7 and/or Week 13, had immunogenicity testing.
[g] Two injections separated by at least 24 hours but not more than 72 hours.
[h] If the subject's penile curvature was reduced to < 15° after the first or second cycle of injections or if further treatment was not clinically indicated, subsequent treatment cycles were not administered.
[i] For subjects randomized to penile plaque modeling, the investigator or qualified designee modeled the plaque at least 24 hours but not more than 72 hours after the last injection of the treatment cycle and after penile anesthesia had been administered.
[j] Immediately before the second injection of the cycle (all subjects), before penile plaque modeling in each treatment cycle (subjects randomized to modeling), and a telephone interview 24 to 72 hours after the second injection of the cycle (subjects who were not randomized to modeling).
[k] Between 15 and 40 subjects were interviewed at Week 24 or at Week 36.

7.1.4.5. Randomisation and blinding methods

Randomisation was via an electronic data capture system. The investigator, study subject and other study site personnel were blinded to the medication treatment allocation.

Comment: The penile modelling procedure was not blinded. Compliance with the modelling was assessed by patient's report. This has the impact of minimising any treatment difference between the two groups – as those in the placebo group may have tried modelling if they spoke with other trial participants, and those in the treatment group may not have been compliant as they were not closely supervised with home modelling.

7.1.4.6. Analysis populations

The mITT population was all ITT subjects with at least one penile curvature measurement and one PDQ questionnaire completed after the first injection of the study drug.

The ITT population included all subjects who had at least one injection of the study drug.

The PDQ population included all ITT subjects who had both a baseline set and at least one post baseline set of PDQ responses.

The PP population included all mITT subjects who had a penile curvature measured at week 36, had PDQ responses of at screening and one other visit, and had no protocol deviations that would affect the efficacy evaluations.

Sample size

One hundred and thirty subjects were planned (102 in the active arm and 34 in the placebo arm). One hundred and forty seven subjects were analysed.

Power calculations were performed using SAS software. To detect a 35% (SD 20%) change in penile curvature with AA4500 with modelling and a 25% (SD 20%) change in penile curvature without modelling, 136 patients would give a power of 0.99 for the effect of drug with modelling and 0.94 for the effect of drug without modelling.

7.1.4.7. Statistical methods

The primary analysis was at Week 36. Penile curvature, change from baseline and percent change from baseline in penile curvature were summarised with descriptive statistics at each visit window. Comparisons between treatment groups were based on Analysis of variance (ANOVA) with factors for drug and modelling and drug/modelling interaction.

Total scores and change from baseline scores for each of the four scales of the PDQ were analysed separately and with descriptive statistics for each visit window. The comparison between treatment groups was based on the change from baseline using ANOVA with factors such for drug and modelling and drug-modelling interaction.

Scores and changes from baseline scores for each plaque length, plaque width, penile length, Peyronie's disease symptomatology and IIEF questionnaire were analysed separately with descriptive statistics at each visit window. The comparison between treatment groups was based on the change from baseline using an ANOVA with factors for drug and modelling and a drug-modelling interaction.

The relationship between penile curvature and PDQ was examined using Pearson's correlations between the reduction in penile curvature and the change from baseline in scores on the four scales of the PDQ at screening and Week 36.

Participant flow

A total of 147 were randomised to the study. One hundred and eleven subjects received the study drug. Seventy four subjects received modelling, and 73 had no modelling. Over 90% of subjects completed the trial, Table 17.

Table 17: Study AUX-CC-801 subject disposition

	With Modeling (N=74)		Without Modeling (N=73)	
	AA4500 (N=54)	Placebo (N=20)	AA4500 (N=57)	Placebo (N=16)
Randomized subjects	54	20	57	16
ITT population[a]	54 (100.0)	20 (100.0)	57 (100.0)	16 (100.0)
mITT population[b]	54 (100.0)	20 (100.0)	55 (96.5)	16 (100.0)
PDQ population[c]	50 (92.6)	18 (90.0)	50 (87.7)	16 (100.0)
PP population[d]	46 (85.2)	17 (85.0)	46 (80.7)	14 (87.5)
Completed[e]	52 (96.3)	19 (95.0)	51 (89.5)	15 (93.8)
Discontinued, n (%):	2 (3.7)	1 (5.0)	6 (10.5)	1 (6.3)
Withdrew consent	1 (1.9)	1 (5.0)	3 (5.3)	1 (6.3)
Lost to follow-up	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)
Adverse event	1 (1.9)	0 (0.0)	1 (1.8)	0 (0.0)
Administrative reason	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol violation	0 (0.0)	0 (0.0)	2 (3.5)	0 (0.0)
Days in study[f]				
Mean (SD)	242.4 (34.71)	242.3 (37.88)	236.9 (49.19)	247.1 (12.28)
Median	248.0	248.0	248.0	246.5
Min, Max	66, 263	85, 281	39, 290	218, 281

Data source: Table 14.1.1

[a] All subjects who were randomized and received at least one dose of study drug. Percentages in this table are based on this population.

[b] All ITT subjects with at least one penile curvature measurement after the first injection of study drug.

[c] All ITT subjects with baseline set and at least one post-baseline set of PDQ responses. The following ITT subjects were excluded from this population: four subjects (1064-1064, 1100-1119, 1106-1305, 9146-1761) with no baseline and post-baseline PDQ responses, seven subjects (1100-1115, 1185-1016, 9141-1701, 9141-1708, 9141-1711, 9141-1712, 9269-1254) with no baseline but at least one set of post-baseline PDQ responses, and two subjects (1054-1651, 9146-1769) with baseline but no post-baseline PDQ responses.

[d] All ITT subjects who satisfied all of the following: (1) had a penile curvature measurement at Week 36, (2) had PDQ responses (at least 50%) at both screening and Week 36, and (3) had none of following protocol deviations: a) baseline penile curvature <30° or >90°, b) received at least one dose of incorrect study drug, c) received at least one incorrect modeling procedure, and d) received <6 injections without any of the following events: achieved penile curvature <15° or had no plaque, or an AE that prevented additional injections.

[e] Completed the Week 36 evaluations.

[f] Date of last visit seen or date of Week 36 visit - date of first injection + 1.

7.1.4.8. Major protocol violations/deviations

There were 23 major protocol deviations. Most of these related to not completing the PDQ or other outcome measures not being performed. No subjects were withdrawn due to protocol violations.

7.1.4.9. Baseline data

Most of the subjects were White (95.2%). The median age of subjects was 58 years.

Erectile dysfunction was reported in 44.2% of subjects, penile pain in around 50-57%. The duration of Peyronie's disease was longer in the treatment group (2.9 years) and the placebo group (2.1 years), this may potentially bias results in favour of placebo, see Tables 18 and 19.

Table 18: Study AUX-CC-802 Baseline data Peyronie's disease history

	With Modeling (N=74)		Without Modeling (N=73)	
Parameter	**AA4500 (N=54)**	**Placebo (N=20)**	**AA4500 (N=57)**	**Placebo (N=16)**
Trauma to the erect penis, n (%)				
No	40 (74.1)	19 (95.0)	44 (77.2)	11 (68.8)
Yes	14 (25.9)	1 (5.0)	13 (22.8)	5 (31.3)
Penile pain, n (%)				
None	31 (57.4)	10 (50.0)	30 (52.6)	9 (56.3)
For <3 months	8 (14.8)	2 (10.0)	9 (15.8)	2 (12.5)
For 3-6 months	4 (7.4)	5 (25.0)	4 (7.0)	2 (12.5)
For 6-9 months	2 (3.7)	0 (0.0)	6 (10.5)	1 (6.3)
For >9 months	9 (16.7)	3 (15.0)	8 (14.0)	2 (12.5)
Penile shortening, n (%)				
None	18 (33.3)	2 (10.0)	19 (33.3)	3 (18.8)
≤1 inch	24 (44.4)	13 (65.0)	23 (40.4)	6 (37.5)
>1 inch	12 (22.2)	5 (25.0)	15 (26.3)	7 (43.8)
Deformity, n (%)				
Dorsal	44 (81.5)	17 (85.0)	47 (82.5)	15 (93.8)
Lateral right	8 (14.8)	3 (15.0)	7 (12.3)	6 (37.5)
Lateral left	22 (40.7)	6 (30.0)	18 (31.6)	2 (12.5)
Ventral	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Erectile dysfunction, n (%)				
No	28 (51.9)	13 (65.0)	32 (56.1)	9 (56.3)
Yes	26 (48.1)	7 (35.0)	25 (43.9)	7 (43.8)
Duration (years) of Peyronie's disease				
Mean (SD)	2.952 (2.6228)	2.100 (1.3163)	2.958 (3.4717)	2.150 (2.6369)
Median	2.250	2.000	1.700	1.200
Min, Max	0.50, 14.80	0.60, 6.10	0.50, 19.60	0.60, 11.10
Duration group (years)				
≤1	8 (14.8)	5 (25.0)	15 (26.3)	7 (43.8)
1.1-2	17 (31.5)	5 (25.0)	20 (35.1)	5 (31.3)
2.1-3	13 (24.1)	6 (30.0)	5 (8.8)	1 (6.3)
>3	16 (29.6)	4 (20.0)	17 (29.8)	3 (18.8)

Most subjects had no calcifications (54%) or non-contiguous stippling of the penis (44.9%). There were no clinically significant abnormalities on Doppler ultrasound.

Non procedural medication commonly taken during the study included acetylsalicylic acid 22.4%, ibuprofen 11.6%, tamsulosin 10.2%, benzodiazepine 9.5%, and SSRI 8.8%. Drugs used to treat erectile dysfunction were taken by 17.7%.

Table 19: Study AUX-CC-801 Baseline characteristics Peyronie's disease questionnaire

Parameter	With Modeling (N=68)		Without Modeling (N=66)	
	AA4500 (N=50)	Placebo (N=18)	AA4500 (N=50)	Placebo (N=16)
Intercourse Discomfort (Max=15)				
Mean (SD)	5.6 (3.81)	6.3 (3.82)	5.8 (3.65)	6.1 (3.86)
Median	5.0	4.0	5.0	5.5
Min, Max	0, 13	2, 15	0, 12	0, 12
Intercourse Constraint (Max=12)				
Mean (SD)	7.7 (3.23)	9.1 (2.18)	8.1 (2.36)	7.9 (3.19)
Median	8.0	9.0	8.0	9.0
Min, Max	0, 12	5, 12	2, 12	0, 12
Penile Pain (Max=40)				
Mean (SD)	6.2 (7.05)	3.7 (5.44)	5.5 (6.08)	5.4 (4.91)
Median	4.0	1.0	3.0	5.0
Min, Max	0, 29	0, 17	0, 21	0, 20
Peyronie's Disease Symptom Bother (Max=20)				
Mean (SD)	8.6 (4.43)	7.6 (4.62)	7.5 (3.86)	8.7 (3.77)
Median	8.0	8.5	7.0	9.5
Min, Max	2, 17	2, 16	1, 14	1, 14

7.1.4.10. Results for the primary efficacy outcome

Penile curvature

Overall, there was a 29.7% improvement in penile curvature in the AA4500 group compared to an 11.0% improvement in the placebo group (p=0.001). However when the results were analysed based on those who received modelling or not, the improvements were only significant in those who received modelling. In the group that received modelling, penile curvature improved by 32.4% in those who received AA4500 compared to a deterioration of 2.5% in those that received the placebo. In the group that did not receive modelling, there was an improvement of around 27% in both AA4500 and placebo groups. There was no direct comparison in the response to AA4500 in those who received modelling versus those who did not. However the interaction term for drug and modelling was significant, indicating that both the study drug and modelling procedure were important determinants of the outcome, see Table 20 and Figure 7.

Table 20: Study AUX-CC-801 Mean change and mean % change from baseline in penile curvature at Week 36 with and without modelling (mITT)

	With Modeling (N=74)			Without Modeling (N=71)		
	AA4500 (N=54)	Placebo (N=20)	p-value[a]	AA4500 (N=55)	Placebo (N=16)	p-value[a]
Screening (baseline) value						
Mean (SD)	54.7 (15.18)	51.9 (15.88)		54.1 (15.08)	48.9 (14.31)	
Min, Max	33, 89	30, 90		30, 90	30, 80	
Week 36 value (LOCF)						
Mean (SD)	37.2 (18.49)	52.5 (17.78)		39.1 (15.70)	35.9 (16.52)	
Min, Max	5, 85	20, 85		10, 80	5, 60	
Change from baseline						
Mean (SD)	-17.5 (15.28)	0.6 (13.16)	<0.001	-15.0 (14.04)	-13.0 (10.66)	0.618
Min, Max	-60, 40	-20, 40		-50, 7	-30, 0	
Modeling (drug) p-value[b]	0.349					
Overall p-values[c]						
Drug	<0.001					
MDL	0.044					
Drug*MDL	0.004					
% Change from baseline						
Mean (SD)	-32.4 (30.71)	2.5 (27.56)	<0.001	-27.1 (23.14)	-27.9 (26.70)	0.913
Min, Max	-92, 100	-33, 89		-75, 19	-86, 0	
Modeling (drug) p-value[b]	0.306					
Overall p-values[c]						
Drug	0.001					
MDL	0.018					
Drug*MDL	<0.001					

Data source: Table 14.2.2.1

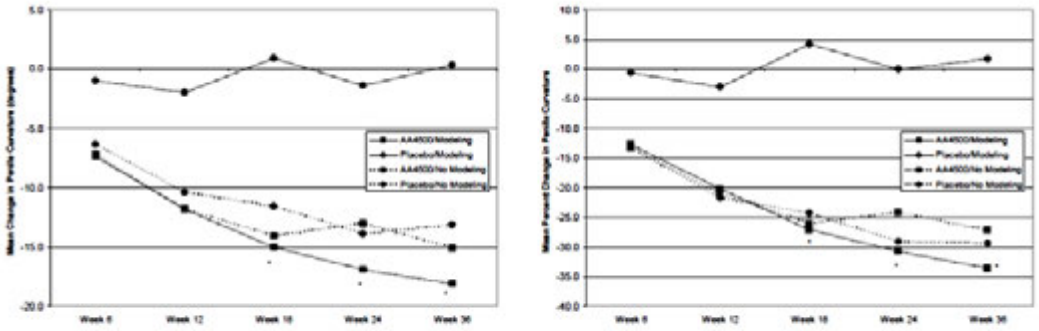
MDL=modeling

[a] Drug effect p-value with/without modeling, calculated from factorial ANOVA analysis.

[b] Modeling effect p-value with drug, which was calculated from factorial ANOVA analysis.

[c] Drug p-value - overall drug effect with/without modeling, MDL p-value - overall modeling effect with/without drug, and Drug*MDL p-value - drug-by-modeling interaction from using ANOVA with factors for drug, modeling and drug-by-modeling interaction.

Figure 7: Mean change and mean percent change from baseline in penile curvature over time, with and without modelling (mITT)



Data source: Table 14.2.2.1

*Statistically significant difference vs. placebo/modeling (p<0.001 for mean change and mean percent change).

Comment: The deterioration in the placebo group who received modelling is different from the results of other studies (AUX-CC-803 and AUX-CC-804). The investigator attributed the lack of effect with no modelling to be due to an improvement of 40% in penile curvature in 5 subjects in the placebo arm. This highlights the known variability of progression of Peyronie's disease and difficulty assessing the efficacy of treatment.

PDQ

The version of the PDQ in this study contained 4 items - intercourse discomfort, intercourse constraint, penile pain and Peyronie's symptom bother score. There was a statistically significant difference between AA4500 and placebo groups only in the Peyronie's symptom bother score, see Table 21.

Table 21: Study AUX-CC-801 Mean change from baseline in PDQ total score for each scale at Week 36

	Study Drug	
	AA4500 (N=100)	Placebo (N=34)
Intercourse Discomfort		
Mean (SD) screening (baseline) value	5.7 (3.71)	6.2 (3.78)
Min, Max	0, 13	0, 15
Mean (SD)Week 36 value (LOCF)	4.9 (3.39)	5.8 (4.15)
Min, Max	0, 13	0, 15
Mean (SD) change from baseline	-0.8 (3.46)	-0.4 (4.27)
Min, Max	-11, 6	-8, 15
Intercourse Constraint		
Mean (SD) screening (baseline) value	7.9 (2.82)	8.5 (2.72)
Min, Max	0, 12	0, 12
Mean (SD)Week 36 value (LOCF)	6.4 (3.29)	7.8 (3.33)
Min, Max	0, 12	0, 12
Mean (SD) change from baseline	-1.5 (3.31)	-0.7 (3.65)
Min, Max	-10, 9	-8, 12
Penile Pain		
Mean (SD) screening (baseline) value	5.8 (6.56)	4.5 (5.19)
Min, Max	0, 29	0, 20
Mean (SD)Week 36 value (LOCF)	3.5 (4.51)	4.0 (6.32)
Min, Max	0, 21	0, 27
Mean (SD) change from baseline	-2.4 (6.32)	-0.5 (5.30)
Min, Max	-27, 14	-12, 16
Peyronie's Disease Symptom Bother		
Mean (SD) screening (baseline) value	8.1 (4.16)	8.1 (4.21)
Min, Max	1, 17	1, 16
Mean (SD)Week 36 value (LOCF)	5.5 (4.15)	7.3 (5.12)
Min, Max	0, 19	1, 20
Mean (SD) change from baseline	-2.6 (4.63)*	-0.8 (3.63)
Min, Max	-14, 7	-10, 6

Data source: Tables 14.2.3.1.1, 14.2.3.2.1, 14.2.3.3.1, and 14.2.3.4.1

* Statistically significant difference vs. placebo (p=0.046) (overall drug effect; Table 14.2.3.4).

Among subjects who received modelling, the reduction in Peyronie's symptom bother score was statistically significantly greater in AA4500 treated subjects than in the placebo group. There was no significant difference in the groups without modelling or the other PDQ items.

IIEF questionnaire

There were no clinically meaningful differences between AA4500 and placebo groups with/without modelling in the IIEF questionnaire domains of erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction.

Peyronie's disease global assessment

A responder was defined in a subject who had recorded that his Peyronie's disease had improved in a small but important way (score=1), moderately improved (score=2), or much improved (score=3).

More subjects who received AA4500 responded (56.3%) than received placebo (29.4%), see Table 22.

Table 22: Study AUX-CC-801: Summary of Peyronie's disease global assessment responders (mITT)

Parameter Responder[a]	Study Drug AA4500 (N=109) n (%)	 Placebo (N=36) n (%)
Discomfort during intercourse (GAQ1)		
No	50 (49.5)	21 (63.6)
Yes	51 (50.5)	12 (36.4)
Not done	2	1
Restrictions of positions during intercourse (GAQ2)		
No	61 (60.4)	27 (84.4)
Yes	40 (39.6)	5 (15.6)
Not done	2	2
Pain during erection and ejaculation (GAQ3)		
No	58 (56.9)	26 (76.5)
Yes	44 (43.1)	8 (23.5)
Not done	1	0
Bothersome effects of Peyronie's Disease (GAQ4)		
No	50 (48.5)	24 (70.6)
Yes	53 (51.5)	10 (29.4)
Not done	0	0
Overall symptom and effects of Peyronie's Disease (GAQ5)		
No	45 (43.7)	24 (70.6)
Yes	58 (56.3)	10 (29.4)
Not done	0	0

Data source: Table 14.2.6.1

Note: Percentages are based on the numbers of subjects with non-missing response in global assessment.

[a] A responder was defined as a subject who recorded that his Peyronie's disease had either improved in a small but important way (score=1), moderately improved (score=2), or much improved (score=3) in each corresponding global assessment question.

There was a small mean increase in penile length (0.7cm SD 1.25 versus 0.5cm SD 1.24), and decrease in penile plaque area (92.3 (SD 179) versus 102.5 (SD 197.05)) in the AA4500 and placebo groups. The statistical significance of this is not given. The clinical significance of this is uncertain. The large SDs are noted, indicating the large amount of variability.

Sixteen spontaneous penile events occurred, all in the AA4500 group. Eleven of these subjects received modelling.

7.1.4.11. Correlation between PDQ and other outcome variables

There was very poor correlation between penile curvature and individual items on the PDQ, see Table 23.

Table 23: Study AUX-CC-801 Correlation between penile curvature and items of PDQ

	Baseline		Week 36	
	Correlation coefficient*	p	Correlation coefficient*	p
Intercourse discomfort	-0.82	0.287	0.201	0.021
Intercourse constraint	0.168	0.051	0.418	<0.001
Penile pain	-0.120	0.183	0.082	0.713
Peyronie's symptom bother score	0.034	0.691	0.224	0.010

*Pearson correlation coefficient

Cognitive debriefing study to assess the content validity of the PDQ and global assessment of peyronie's disease

Auxilium developed the PDQ to assess treatment efficacy. Revisions were made based on feedback from the study endpoints and label development and subsequent qualitative studies. The study used to validate the questionnaire was a cross sectional, qualitative study involving 1:1 semi structured interview with 34 subjects. The modifications made to the questionnaire as a result of this study and subsequent discussions with the FDA are displayed below (Table 24).

Table 24: Modifications made to the PDQ as a result of Study AUX-CC-801 and subsequent discussions

Domain	Question	Analyses Findings
Intercourse Discomfort/Fear	Q1: Afraid of damaging penis	Relevant (64.7%)
	Q2: Afraid penis might bend/collapse	Relevant (73.5%)
	Q3: Afraid of pain/discomfort	**Dropped:** Redundant with Q10
	Q5: Afraid semen will be stopped up	**Dropped:** Based on results of Phase 2b psychometric validation (low variability) and Round 2 cognitive debriefing interview (confusion item, low item relevance); floor effect (≥ 50% disagreed strongly)
	Q9: Some positions uncomfortable	Relevant (91.2%)
Intercourse Constraint	Q4: Afraid of trouble inserting penis	Relevant (91.4%)
	Q6: Feel penis is not large enough	**Dropped:** Based on results of Phase 2b psychometric validation (low variability) and Round 2 cognitive debriefing interview (low item relevance)
	Q7: Give up certain positions	Relevant (91.2%)
	Q8: Some positions awkward	Relevant (94.1%)
Peyronie's disease Symptom Bother	Q14: Bothered by pain in erect penis	Relevant (64.7%)
	Q15: Bothered by ejaculation problems	**Dropped:** Based on results of Phase 2b psychometric validation (low variability); Round 2 cognitive debriefing interview (low item relevance); floor effect (≥ 50% not at all bothered)
	Q16: Bothered by appearance of penis	Relevant (91.2%)
	Q18: Bothered by physical problem	Changed back to an earlier version of the PDQ that was specific to Peyronie's disease
	Q20: Bothered by less frequent intercourse	Relevant (95.5%)
Penile Pain	Q10: Pain/discomfort in non-erect penis	Relevant (65%) in subset of subjects
	Q11: Pain/discomfort in erect penis	Relevant (73%)
	Q12: Pain/discomfort during vaginal intercourse	Relevant (68%)
	Q13: Pain/discomfort during ejaculation	**Dropped:** (low item relevance)

7.1.5. Supporting studies

7.1.5.1. AUX-CC-802

This was a Phase III, open label study of the safety and efficacy of AA4500 administered twice per treatment cycle for up to four treatment cycles in men with Peyronie's disease.

The study included 19 sites in the USA and New Zealand and 22 sites in Europe. In the dossier, study outcomes are given for the total and European groups separately. As the results were very similar, the evaluator has reported the overall results.

The first subject enrolled in November 2010, the last subject completed in August 2012.

The subjects included all subjects who had received a placebo in a previous Auxilium sponsored study (including AUX-CC-801), or who had received a treatment cycle in the pharmacokinetic study (AUX–CC-805) or were treatment naïve.

Eligibility criteria

- Age > 18 years
- Diagnosis of Peyronie's disease for at least 12 months
- In a stable relationship with a female partner/spouse for at least 3 months prior to screening and willing to have sexual intercourse
- Curvature deformity of at least 30 degrees in the later, dorsal or lateral/dorsal plane

The exclusion criteria were the same as that described for studies AUX-CC-803 and AUX-CC-804.

Treatment

The treatment received was AA4500 0.58 mg reconstituted with 0.03% calcium chloride in 0.9% sodium chloride to a volume of 0.25 mL. Subjects received up to 4 treatment cycles. Each treatment cycle was 2 injections separated by 24-72 h. The cycle was repeated if needed after 42 ± 5 days. Treatment was discontinued if the penile curvature was <15 degrees, the investigator determined no further treatment was necessary, or due to adverse effects. All subjects received modelling.

Comment: It is unclear if the subjects from Study AUX-CC-805 received a total of 4 treatment cycles or an additional four treatment cycles to the cycle received as part of the pharmacokinetic study.

Efficacy endpoints

The co-primary endpoints were the change from baseline curvature to Week 36 and the change from baseline total score in the Peyronie's disease bother score of the PDQ to Week 36.

The secondary endpoints included responder analysis based on global assessment of Peyronie's disease; change from baseline in severity of Peyronie's symptoms of the PDQ, change from baseline in IIEF overall satisfaction score; change from baseline in penile plaque consistency score; change from baseline in penile length, change from baseline in penile pain.

Table 25: Study AUX-CC-802 assessments

	Treatment				Follow-up (Nominal week)	
	Cycle 1	Cycle 2	Cycle 3	Cycle 4	FU 1 (week 24)	FU 2 (week 36)
Procedures	Day 1 (Injection 1)	Day 42 (± 5 days) (Injection 1)	Day 84 (± 5 days) (Injection 1)	Day 126 (± 5 days) (Injection 1)	Day 168 (± 7 days)	Day 252 (± 7 days)
Concomitant medications/procedures	X	X	X	X	X	X
PDQ					X	X
Dispense VDMA			X		X	
IIEF					X	X
Global assessment of PD					X	X
Penile PE (flaccid penis)		X[c]	X[c]	X[c]	X	X
• Identification of all plaques						X
• Injection site reactions/local tolerability	X	X	X	X	X	X
• Penile length measurement		X[c]	X[c]	X[c]	X	X
• Penile pain on palpation		X[c]	X[c]	X[c]	X	X
• Primary plaque consistency	X[c]	X[c]	X[c]	X[c]	X	X
Vital signs	X[c]	X[c]	X[c]	X[c]	X	X
Clinical laboratories		X[c]	X[c]	X[c]		X
Anti-AUX-I/anti-AUX-II antibody levels and neutralizing antibodies to AUX-I and AUX-II		X[c,d]	X[c,d]	X[c,d]	X	X
Pharmacological stimulant to induce erection		X[e]	X[e]	X[e]	X	X
• Penile curvature measurements		X[e]	X[e]	X[e]	X	X
• Mark point of maximum concavity on the 1° plaque		X[e]	X[e]	X[e]		
• Direction of curvature		X[e]	X[e]	X[e]	X	X
Study drug administration	X[g]	X[g,i]	X[g,i]	X[g,i]		
Investigator penile plaque modeling[h]	X	X	X	X		
Subject home modeling	X[j]	X[j]	X[j]	X[j]	X	
Adverse events	X	X	X	X	X	X
Discharge from the study						X

PD=Peyronie's disease; PDQ=Peyronie's disease questionnaire; US=ultrasound; PE=physical examination; FU=follow-up; VDMA=vaginal intercourse memory aid (NOTE: The VDMA will not be collected or returned to the study doctor. It will serve only as a personal reminder to assist subjects in answering some of the PDQ questions that may be asked during the study).

a Before the first injection of the treatment cycle.

b Up to 4 hours before injection, and 15, 30, and 45 minutes after injection, and before discharge. Vital signs must be stable for a period of at least 60 minutes before the subject can be discharged from the unit.

c All subjects, including those who are not receiving treatment at Treatment Cycle 2, Treatment Cycle 3, and/or Treatment Cycle 4 will have immunogenicity testing.

d Blood sample for anti-AUX-I and anti-AUX-II antibody levels and the neutralizing potential of antibodies to AUX-I and AUX-II.

e Study drug may be administered on the same day after the completion of these assessments provided the subject's erection has detumesced and the penis is flaccid. If this is not possible, complete these assessments at least 1 day but not more than 4 days before the administration of study drug. Ensure that study drug administration is within the treatment window indicated above.

f Two injections separated by approximately 24 hours to 72 hours. Each injection administered into the primary plaque of the flaccid penis.

g If the subject's penile curvature has been reduced to < 15° after the first, second, or third cycle of injections or if the investigator determines that further treatment is not clinically indicated (eg, adverse events; allergic reactions), subsequent treatment cycles will not be administered.

h The investigator/qualified designee will model the plaque approximately 24 hours to 72 hours after the last injection of the treatment cycle after penile anesthesia has been administered.

i Subject home modeling for the 6-week period following the investigator modeling visit in the treatment cycle.

Statistics and sample size

The sample size was determined by the number of subjects required to have received AA4500 in order to have a 90% probability of detecting at least 2 or more adverse events where the actual underlying event rate was 0.5%. There were already 500 treated subjects in AUX-CC-803 and AUX-CC-804. This study added an addition 300 subjects to reach the target number.

Results

A total of 348 subjects were enrolled in the study, 88.2% completed the study. The main reason for premature discontinuation was withdrawal of consent, see Table 26.

Table 26: Study AUX-CC-802 subject disposition

	All Subjects
Screened subjects	406
Enrolled subjects	348
ITT population[a]	347 (100.0)
PM population[b]	339 (97.7)
PDQ population[c]	240 (69.2)
mITT population[d]	238 (68.6)
PP population[e]	199 (57.3)
Completed[f]	306 (88.2)
Discontinued, n (%):	41 (11.8)
Withdrawal by subject	18 (5.2)
Lost to follow-up	10 (2.9)
Adverse event	5 (1.4)
Protocol violation	0
Death	0
Other	8 (2.3)
Days in study[g]	n=347
Mean (SD)	237.4 (53.38)
Median	253.0
Min, Max	1, 330

The subjects were primarily White (96%). The median age was 57 years (range 23-77), 51.9% had never smoked. The median duration of Peyronie's disease was 2 years, range 0.6 to 29.4 years. Erectile dysfunction was a feature in 34.6%. Peyronie's disease symptomatology is

described in Table 27. Most subjects had < 2.5 cm of penile shortening, moderate- severe plaque, no pain in the erect penis, moderate to severe distress as a result of the Peyronie's disease.

Of the 347 subjects in this study, 13 subjects were taking testosterone or derivatives, 20 were taking benzodiazepines, 72 were taking drugs for erectile dysfunction (alprostadil, sildenafil, tadalafil, trimix, vardenafil), and 29 were taking antidepressants.

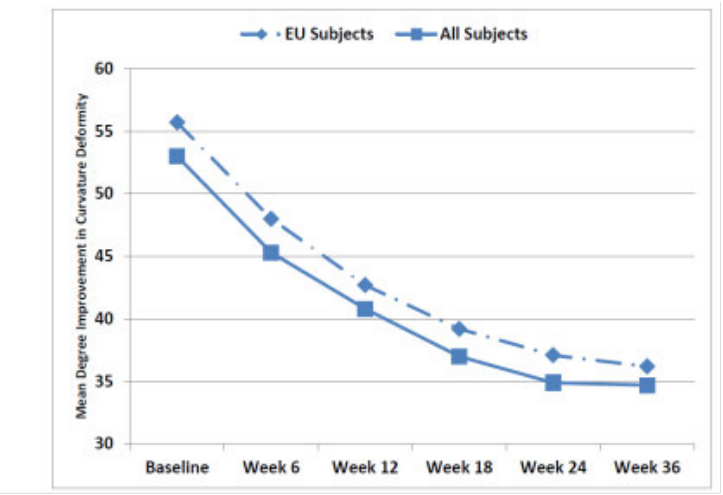
Table 27: Study AUX-CC-802 Peyronie's symptomatology at baseline

Parameter	All Subjects N=347
Subject-reported penile shortening, n (%)	
None	65 (18.7)
>0 to ½ inch	86 (24.8)
>½ inch to 1 inch	119 (34.3)
>1 inch to 2 inches	69 (19.9)
>2 inches	8 (2.3)
Subject-reported presence of penile plaque/lesion, n (%)	
None	39 (11.2)
Mild	93 (26.8)
Moderate	177 (51.0)
Severe	38 (11.0)
Subject-reported curvature deformity, n (%)	
Mild	26 (7.5)
Moderate	189 (54.5)
Severe	132 (38.0)
Subject-reported pain in erect penis, n (%)	
None	225 (64.8)
Mild	83 (23.9)
Moderate	35 (10.1)
Severe	4 (1.2)
Subject-reported change in penile shape, n (%)	
None	197 (56.8)
Mild	85 (24.5)
Moderate	48 (13.8)
Severe	17 (4.9)
Subject-reported decrease in rigidity/stability with erection, n (%)	
None	172 (49.6)
Mild	77 (22.2)
Moderate	77 (22.2)
Severe	21 (6.1)
Subject-reported distress over Peyronie's disease, n (%)	
None	26 (7.5)
Mild	53 (15.3)
Moderate	165 (47.6)
Severe	103 (29.7)

Treatment with AA4500 resulted in:

- An improvement in curvature deformity from a baseline mean of 53˚ to a value at Week 36 of around 34.7˚ ($p<0.05$). The mean % change in penile curvature was around 33% regardless of baseline curvature.

Figure 8: AUX-CC-802: Mean degree of curvature deformity over time



- A reduction in subject reported Peyronie's bother on the PDQ, mean change from baseline: 3.3 (max score 16), 95% CI -2.8 to -3.7.
- An improvement in overall global assessment of Peyronie's disease by at least 1 point in 72.3%.
- An improvement in Peyronie's disease physical and psychological symptoms of 4.2 (of total score of 24) points, 95% CI 3.6 to 4.9.
- An improvement in IIEF satisfaction of 1.1 points (max score 10), 95% CI: 0.8 to 1.4.
- Softening of penile plaques in most penile plaques that were graded as hard, or firm at baseline.
- Increase in flaccid penile length of 0.4 cm (95% CI: 0.2 to 0.5).
- An improvement in Peyronie's disease pain score.
- A mean improvement in erectile function, orgasmic function, sexual desire, intercourse satisfaction, sexual activity.

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

The original data from the pooled Studies AUX-CC-803 and AUX-CC-804 was not provided in the dossier however the EMA evaluation report contained a summary of this. The sponsor states that the meta-analysis was performed to increase the precision of the end points and better understand and characterise the secondary efficacy endpoints.

The following outcomes were found:

- A statistically significant greater improvement in the AA4500 group (60.8%) compared to the placebo group (29.5%) for the overall global response to Peyronie's disease.
- A statistically significant greater improvement in the Peyronie's disease physical and psychological symptom score (range 0-24) of -2.9 in the AA4500 group and -1.3 in the placebo group.
- A statistically significant greater improvement in the IIEF (range 0-10) score of -1.0 in the AA4500 group and -0.4 in the placebo group.
- Analysis of co-primary endpoints for intrinsic and extrinsic factors

- There was a trend to greater improvement in curvature deformity as the duration of Peyronie's disease increased
- Younger men (<45 years) had a greater improvement in curvature deformity and bother scale than older men

7.2.1. Evaluator's conclusions on the clinical efficacy of Xiaflex for Peyronie's disease

The sponsor has provided two randomised controlled trials (RCT) and two supporting trials for the use of Xiaflex in Peyronie's disease. The total number of patients exposed in the RCT was over 800, giving the trials adequate power to assess a difference in primary efficacy outcomes.

The studies showed an improvement in the primary efficacy outcomes of penile curvature and penile bother in both the placebo and treatment groups. These improvements were greater in the group that received Xiaflex. However there was a considerable variability in outcomes within the subjects studied. There was no significant difference between placebo and AA4500 in many of the secondary outcomes in the individual RCTs, however when the data were pooled there were significant improvements in psychological elements (PDQ and IIEF) in the AA4500 group.

The placebo effect was significant, and may have had a physiological basis. In a rat model of Peyronie's disease, injections with normal saline resulted in histological changes with decreased staining for collagen and an increased erectile function assessed by injections of saline and cavernous nerve stimulation. However it needs to be noted that in the clinical trials, the subjects had Peyronie's of relatively short duration and no calcifications on ultrasound, which in prospective studies have been the group most likely to regress. A RCT by design should eliminate the effect of variability in outcome factors by defining a large enough sample size. The evaluator notes that the SD for % improvement chosen for curvature deformity chosen for the power calculations was 20% but the real variability in the clinical trial was in the order of 30%. %. In reviewing the design for both studies, AUXCC-803 and AUX-CC-804, the sample size calculation was based on an expectation of SD equal to 30%. As an example of what was observed, the results in AUX-CC-803 for penile curvature, were a SD of 30.3% for AA4500 and 29.9% for placebo, very close to what was anticipated when the sample size was calculated.

The lack of correlation between changes in penile curvature and measures of penile distress and sexual function is noteworthy. This demonstrates the complexity of Peyronie's disease. The patients' experience (suffering) goes beyond the shape of the penis into the psychological domain. The measurement of erectile function as an outcome factor for Peyronie's disease is clouded by this psychological factor as well as the other diseases present in this group of patients which impact erectile function (smoking, diabetes, hypertension, hyperlipidaemia, anxiety, depression).

The use of the PDQ strengthened the studies in that it provided a measure of psychological effect from treatment. However the validity of this is questionable given the low Pearson correlation co-efficient and discrepancy between the PDQ outcomes and patient reported erectile dysfunction as an adverse effect (see Section 8.4.4).

The clinical trials have included a select group of patients with Peyronie's disease, which may not be representative of the population that presents to the GP or urologist with a bend or plaque on the penis or erectile dysfunction. The sponsor's proposed indications and contraindications in the PI do not accurately reflect the patients chosen in the clinical trials.

Peyronie's disease is relatively common. Although not life threatening, it contributes to considerable distress for patients and results in sexual dysfunction, depression and anxiety. The high retention rates in the study demonstrate how motivated these patients were to receive treatment.

The natural history of Peyronie's disease is for regression in a minority, stability in some, deterioration in most. Pain tends to improve over time. There is limited evidence about the safety and efficacy of other non-operative treatments for Peyronie's disease. Clinical trials have demonstrated some efficacy of intralesional verapamil or interferon; topical verapamil; oral potassium para-aminobenzoate and colchicine. Surgical treatment is indicated in patients with stable disease (for at least 3 months) with the aim of correcting curvature and allowing satisfactory intercourse. The risks of surgery include penile shortening, erectile dysfunction, penile numbness, recurrent curvature, palpation of knots and stitches under the skin, the need for circumcision. Literature reports would suggest a relatively good outcome from surgery, but these reports are retrospective and not RCTs.

8. Clinical safety

8.1. Studies providing evaluable safety data

In Studies AUX-CC 803, AUX-CC-804, AUX-CC-801, AUX-CC-802 the following safety data were collected:

- General adverse events (AEs) were assessed by history and examination. They were described using MEDRA terms.
- AEs of particular interest, including:
  - Erectile function
  - Development of anti AUX I and AUX II antibodies
- Laboratory tests, including biochemistry and haematology, were performed at baseline and before each cycle of therapy.
- ECG was performed at baseline only
- Doppler ultrasound was performed at baseline in all studies and at week 52 in Study AUX-CC-801

8.2. Other studies evaluable for safety

8.2.1. AUX-CC-805

Safety was assessed as part of this pharmacokinetic study. Safety parameters were described as counts and percentages. Comparisons between groups were made using Fishers exact test.

8.3. Subject exposure

A summary of subject exposure to AA4500 and placebo in clinical trials is listed below in Table 28.

Table 28: Exposure to AA4500 and comparators in clinical studies

	Total subjects	Number of treatment cycles	Duration of trial	AA4500	Placebo
AUX-CC-801	147	3	36 weeks	111	36
AUX-CC-802	347	4	Up to 36 weeks	347	-
AUX-CC-803	417	4	52 weeks	227	140
AUX-CC-804	415	4	52 weeks	274	141
AUX-CC-805	20	1	29 days	20	-

In Study AUX-CC-803, the majority of AA4500 (77.3%) and placebo (86.4%) subjects received all 8 injections, and modelling (70.6 and 76.4%). Sixteen subjects did not receive injections due to an AE (all in the AA4500 group), 28 did not receive an injection as their curve was < 15% (mostly in the active group). Four subjects in the active group were unable to perform modelling due to pain or blistering.

In Study AUX-CC-804, the majority of AA4500 subjects (80.3%) and placebo subjects (89.4%) received all injections. Twelve subjects did not receive all injections due to an adverse event, 19 subjects did not receive an injection as their penile curvature was < 15˚. Most of these were in the AA4500 group. Modelling occurred in 73% of the AA4500 group and 83% of the placebo group. Subjects in the placebo group more commonly refused modelling because of bruising or other adverse events.

In AUX –CC-801, 93.2% of the subjects received 6 doses of AA4500 (Table 29).

Table 29: Study AUX-CC-801 Summary of exposure

	With Modeling (N=74)		Without Modeling (N=73)	
	AA4500 (N=54) n (%)	Placebo (N=20) n (%)	AA4500 (N=57) n (%)	Placebo (N=16) n (%)
Study drug injection				
Treatment Cycle 1, Injection 1	54 (100.0)	20 (100.0)	57 (100.0)	16 (100.0)
Treatment Cycle 1, Injection 2	54 (100.0)	20 (100.0)	55 (96.5)	16 (100.0)
Treatment Cycle 2, Injection 1	53 (98.1)	20 (100.0)	54 (94.7)	16 (100.0)
Treatment Cycle 2, Injection 2	52 (96.3)	20 (100.0)	54 (94.7)	16 (100.0)
Treatment Cycle 3, Injection 1	52 (96.3)	19 (95.0)	52 (91.2)	16 (100.0)
Treatment Cycle 3, Injection 2	52 (96.3)	19 (95.0)	51 (89.5)	16 (100.0)
Total number of injections				
1	0 (0.0)	0 (0.0)	2 (3.5)	0 (0.0)
2	1 (1.9)	0 (0.0)	1 (1.8)	0 (0.0)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	1 (1.9)	1 (5.0)	2 (3.5)	0 (0.0)
5	1 (1.9)	0 (0.0)	1 (1.8)	0 (0.0)
6	51 (94.4)	19 (95.0)	51 (89.5)	16 (100.0)

Data source: Table 14.2.1

Note: Ten (10) subjects did not receive all six injections: two (1054-1651, 9146-1769) received one injection only; two (1064-1059, 1185-1018) received two injections; four (1101-1411, 9141-1705, 9146-1766, 1185-1008) received four injections; and two (9146-1755, 9146-1761) received five injections. Eight of these subjects discontinued the study early and two subjects completed the study; Subject 1185-1008 achieved a penile curvature of <15° after the fourth injection, and Subject 9146-1755 did not have the second injection in Treatment Cycle 2 due to a missed visit.

In AUX-CC-802, 81.3% of subjects received 4 cycles of treatment (Table 30).

Table 30: Study AUX-CC-802 Summary of exposure

Parameter	All Subjects N=347 n (%)
Study drug injection	
Treatment Cycle 1, Injection 1	347 (100.0)
Treatment Cycle 1, Injection 2	342 (98.6)
Treatment Cycle 2, Injection 1	337 (97.1)
Treatment Cycle 2, Injection 2	327 (94.2)
Treatment Cycle 3, Injection 1	315 (90.8)
Treatment Cycle 3, Injection 2	310 (89.3)
Treatment Cycle 4, Injection 1	285 (82.1)
Treatment Cycle 4, Injection 2	282 (81.3)
Total number of injections	
1	2 (0.6)
2	8 (2.3)
3	4 (1.2)
4	14 (4.0)
5	5 (1.4)
6	34 (9.8)
7	10 (2.9)
8	270 (77.8)

8.4. Adverse events

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

8.4.1.1. AUX-CC-803

Treatment emergent adverse events (TEAE) were more common in the AA4500 group (92.4%) than the placebo group (60%) and were generally related as 'mild' by the investigator. Common events included penile haematoma (61.7% versus 13.6%), penile pain (43% versus 7.9%), penile swelling (41.2% versus 0.7%), injection site pain (25.3% versus 3.6%), penile haemorrhage (21.7% versus 10%), injection site haematoma (16.2% versus 10%), penile oedema (16.2% versus 0.7%), injection site swelling (10.8% versus 0%), contusion (10.1%

versus 0%), ecchymosis (9.4% versus 0%), injection site haemorrhage (5.4% versus 7.1%), see Table 31.

Table 31: Study AUX-CC-803 Treatment emergent adverse events (ITT)

	AA4500 (N=277) n (%)	Placebo (N=140) n (%)
Subjects with ≥1 TEAE*	256 (92.4)	84 (60.0)
Gastrointestinal disorders	27 (9.7)	11 (7.9)
Diarrhoea	4 (1.4)	4 (2.9)
General disorders and administration site conditions	127 (45.8)	28 (20.0)
Injection site discomfort	8 (2.9)	2 (1.4)
Injection site haematoma	45 (16.2)	14 (10.0)
Injection site haemorrhage	15 (5.4)	10 (7.1)
Injection site oedema	8 (2.9)	1 (0.7)
Injection site pain*	70 (25.3)	5 (3.6)
Injection site swelling*	30 (10.8)	0 (0.0)
Local swelling*	9 (3.2)	0 (0.0)
Localised oedema	6 (2.2)	0 (0.0)
Nodule	7 (2.5)	0 (0.0)
Infections and infestations	55 (19.9)	29 (20.7)
Bronchitis	3 (1.1)	3 (2.1)
Lower respiratory tract infection*	0 (0.0)	3 (2.1)
Nasopharyngitis	12 (4.3)	3 (2.1)
Sinusitis	11 (4.0)	3 (2.1)
Upper respiratory tract infection	9 (3.2)	7 (5.0)
Injury, poisoning and procedural complications	56 (20.2)	14 (10.0)
Contusion*	28 (10.1)	0 (0.0)
Procedural pain	9 (3.2)	5 (3.6)
Investigations	20 (7.2)	12 (8.6)
Blood glucose increased	4 (1.4)	4 (2.9)
Blood triglycerides increased	5 (1.8)	3 (2.1)
Musculoskeletal and connective tissue disorders	40 (14.4)	14 (10.0)
Musculoskeletal pain	7 (2.5)	2 (1.4)
Nervous system disorders	28 (10.1)	11 (7.9)
Headache	10 (3.6)	5 (3.6)
Renal and urinary disorders	8 (2.9)	5 (3.6)
Nephrolithiasis	1 (0.4)	3 (2.1)
Reproductive system and breast disorders	232 (83.8)	41 (29.3)
Erectile dysfunction*	10 (3.6)	0 (0.0)
Erection increased*	0 (0.0)	3 (2.1)
Painful erection*	10 (3.6)	0 (0.0)
Penile blister*	10 (3.6)	0 (0.0)
Penile haematoma*	171 (61.7)	19 (13.6)
Penile haemorrhage*	60 (21.7)	14 (10.0)
Penile oedema*	45 (16.2)	1 (0.7)
Penile pain*	119 (43.0)	11 (7.9)
Penile swelling*	114 (41.2)	1 (0.7)
Prostatitis*	0 (0.0)	3 (2.1)
Pruritus genital*	13 (4.7)	1 (0.7)
Scrotal swelling	7 (2.5)	2 (1.4)
Skin and subcutaneous tissue disorders	60 (21.7)	6 (4.3)
Blood blister*	9 (3.2)	0 (0.0)
Ecchymosis*	26 (9.4)	0 (0.0)
Skin hyperpigmentation	6 (2.2)	0 (0.0)
Vascular disorders	15 (5.4)	5 (3.6)
Hypertension	8 (2.9)	2 (1.4)

Data source: Table 14.3.1.2.1 and Table 14.3.2.6

* Statistically significant difference between AA4500 and placebo based on Fisher exact test (p<0.0412).

8.4.1.2. AUX-CC-804

One or more TEAEs occurred in 92% of the AA4500 group and 62.4% of the placebo group. The most common events were penile haematoma (60.2% versus 15.6%), penile pain (35% versus 5.7%), penile swelling (34.7% versus 1.4%), injection site haematoma (22.3% versus 11.3%), penile haemorrhage (15.7% versus 0.7%), injection site pain (15% versus 2.8%), penile oedema (14.6% versus 0%), injection site swelling (12.8% versus 1.4%), contusion (9.9% versus 0.7%), blood blister (6.2% versus 0%). The investigator rated these as mild to moderate. These events generally resolved without treatment, Table 32.

Table 32: Study AUX-CC-804 Treatment emergent adverse events in >2% of either treatment group (ITT)

	AA4500 (N=274) n (%)	Placebo (N=141) n (%)
Subjects with ≥1 TEAE	252 (92.0)	88 (62.4)
Gastrointestinal disorders	17 (6.2)	8 (5.7)
Diarrhoea	6 (2.2)	1 (0.7)
General disorders and administration site conditions	112 (40.9)	24 (17.0)
Injection site haematoma	61 (22.3)	16 (11.3)
Injection site haemorrhage	10 (3.6)	3 (2.1)
Injection site pain	41 (15.0)	4 (2.8)
Injection site swelling	35 (12.8)	2 (1.4)
Local swelling	7 (2.6)	0 (0.0)
Infections and infestations	38 (13.9)	17 (12.1)
Nasopharyngitis	7 (2.6)	3 (2.1)
Upper respiratory tract infection	7 (2.6)	3 (2.1)
Injury, poisoning and procedural complications	42 (15.3)	9 (6.4)
Contusion	27 (9.9)	1 (0.7)
Muscle rupture	0 (0.0)	3 (2.1)
Musculoskeletal and connective tissue disorders	24 (8.8)	16 (11.3)
Arthralgia	2 (0.7)	4 (2.8)
Back pain	9 (3.3)	7 (5.0)
Nervous system disorders	20 (7.3)	9 (6.4)
Dizziness	4 (1.5)	3 (2.1)
Reproductive system and breast disorders	211 (77.0)	35 (24.8)
Erectile dysfunction	7 (2.6)	2 (1.4)
Painful erection	6 (2.2)	0 (0.0)
Penile blister	8 (2.9)	0 (0.0)
Penile erythema	13 (4.7)	3 (2.1)
Penile haematoma	165 (60.2)	22 (15.6)
Penile haemorrhage	43 (15.7)	1 (0.7)
Penile oedema	40 (14.6)	0 (0.0)
Penile pain	96 (35.0)	8 (5.7)
Penile swelling	95 (34.7)	2 (1.4)
Scrotal swelling	7 (2.6)	0 (0.0)
Skin and subcutaneous tissue disorders	44 (16.1)	4 (2.8)
Blood blister	17 (6.2)	0 (0.0)
Ecchymosis	12 (4.4)	0 (0.0)
Skin discolouration	6 (2.2)	0 (0.0)
Vascular disorders	8 (2.9)	10 (7.1)
Hypertension	3 (1.1)	9 (2.2)

Data source: Table 14.3.1.2.1 and Table 14.3.2.6

8.4.1.3. AUX-CC-801

Treatment emergent adverse events were common in both groups, but more so in those who received AA4500. The following adverse events were more common in the AA4500 group than the placebo group: injection site bruising (90.1% versus 50%), injection site oedema (49.5 versus 0%), injection site pain (55% versus 13.9%), contusion (22.5% versus 5.6%), and penile pain (12.6% versus 0%). Other common adverse events in the AA4500 group included painful erection (6.3%), and injection site pruritis (5.4%). There was no statistically significant difference in adverse events in the AA4500 group between those who received modelling and those who did not. The investigator assessed most of the TEAE as mild or moderate.

8.4.1.4. AUX-CC-805

Treatment related adverse events occurred in all subjects. Injection site pain was noted in 15 subjects, procedural pain was observed in 6. Penile haemorrhage was reported in 19, pain in 4, swelling in 6, a blister in one. The investigator rated these events as generally mild. Procedural pain was considered to be severe in one subject.

Local treatment related adverse events resolved with time, the duration of resolution was around 22 days for penile haemorrhage, 2-28 days for injection site pain, 1-15 days for procedural pain, 2-8 days for penile swelling, and 1-2 days for painful erection.

8.4.1.5. AUX-CC-802

Treatment emergent adverse events were reported in 91.6%, and were considered related to the study drug in 85.3%. Common TEAE included penile haematoma (51.9%), penile pain (34.6%), injection site pain (26.8%), penile swelling (26.2%), injection site haematoma (24.2%),

penile haemorrhage (22.8%), penile oedema (14.1%), injection site swelling (11.5%), and painful erection (5.5%); Table 33.

Table 33: Study AUX-CC-802 Treatment emergent adverse events (ITT)

Body System Preferred Term	All Subjects N=347 n (%)
Subjects with ≥1 TEAE	318 (91.6)
Gastrointestinal disorders	19 (5.5)
Diarrhoea	8 (2.3)
General disorders and administration site conditions	169 (48.7)
Fatigue	5 (1.4)
Injection site haematoma	84 (24.2)
Injection site haemorrhage	17 (4.9)
Injection site pain	93 (26.8)
Injection site pruritus	7 (2.0)
Injection site swelling	40 (11.5)
Local swelling	7 (2.0)
Pyrexia	7 (2.0)
Infections and infestations	41 (11.8)
Influenza	5 (1.4)
Nasopharyngitis	12 (3.5)
Injury, poisoning and procedural complications	54 (15.6)
Contusion	13 (3.7)
Procedural pain	16 (4.6)
Musculoskeletal/connective tissue disorders	31 (8.9)
Back pain	6 (1.7)
Nervous system disorders	21 (6.1)
Headache	13 (3.7)
Renal and urinary disorders	12 (3.5)
Haematuria	5 (1.4)
Reproductive system and breast disorders	276 (79.5)
Erectile dysfunction	12 (3.5)
Painful erection	19 (5.5)
Penile erythema	12 (3.5)
Penile haematoma	180 (51.9)
Penile haemorrhage	79 (22.8)
Penile oedema	49 (14.1)
Penile pain	120 (34.6)
Penile plaque	6 (1.7)
Penile swelling	91 (26.2)
Skin and subcutaneous tissue disorders	57 (16.4)
Blood blister	12 (3.5)
Ecchymosis	17 (4.9)
Pigmentation disorder	8 (2.3)
Vascular disorders	20 (5.8)
Haematoma	7 (2.0)
Hypertension	8 (2.3)

Comment: The data demonstrates that local reactions are common after injections. However, the way in which the data is coded and presented is misleading as bruising could be defined in a number of ways for example, bruise, haematoma, ecchymosis or contusion, either on the penis or at the injection site. Listing these individually may not accurately reflect the true prevalence. However, adding them up may overestimate it if the one event was described using a number of terms.

8.4.2. Deaths and other serious adverse events

8.4.2.1. AUX-CC-803

There were two deaths during the study, both unrelated to the treatment. One death was due to motor vehicle accident, the other due to a pulmonary embolus in the context of bronchogenic cancer.

One 43 year old man experienced a penile fracture/corporal rupture during intercourse 12 days after the second injection of the third treatment cycle. A 50 year old man developed a penile haematoma 13 days after the second injection of treatment Cycle 3 that healed spontaneously. A

67 year old man developed a penile haematoma 2 days after the second injection of treatment Cycle 2. This subject required surgical exploration and subsequently had a Nesbit correction for his Peyronie's disease.

8.4.2.2. AUX-CC-804

One subject died during the study due to hypertrophic cardiomyopathy. This was considered not related to the study drug by the investigator.

Fifteen subjects had serious non-fatal treatment TEAE. In three subjects these were considered related to the study drug. A 61 year old man developed a severe penile haematoma on the day of the first injection of the fourth cycle. The haematoma was aspirated (0.5 mL blood) and no further treatments were given. A 27 year old developed a fracture of the penis during intercourse 29 days after the second injection of the fourth cycle. The fracture was treated surgically. A 64 year old man developed a fracture 15 days after the second injection of the third cycle that was treated surgically.

Other SAEs are listed in Table 34.

Table 34: Study AUX-CC-804 SAE in the ITT population

		AA4500 (N=274)		Placebo (N=141)	
Preferred Term [a]	Body System [a]	Subjects n (%)	Occurrence [b] n	Subjects n (%)	Occurrence [b] n
Any Serious AE		12 (4.4)	12	4 (2.8)	5
Atrial fibrillation	Cardiac disorders	2 (0.7)	2	0 (0.0)	0
Fracture of penis	Injury, poisoning and procedural complications	2 (0.7)	2	0 (0.0)	0
Bacteraemia	Infections and infestations	1 (0.4)	1	0 (0.0)	0
Hypertrophic cardiomyopathy	Cardiac disorders	1 (0.4)	1	0 (0.0)	0
Joint injury	Injury, poisoning and procedural complications	1 (0.4)	1	0 (0.0)	0
Penile haematoma	Reproductive system and breast disorders	1 (0.4)	1	0 (0.0)	0
Prostate cancer	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.4)	1	0 (0.0)	0
Rectal cancer metastatic	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.4)	1	0 (0.0)	0
Syncope	Nervous system disorders	1 (0.4)	1	0 (0.0)	0
Tibia fracture	Injury, poisoning and procedural complications	1 (0.4)	1	0 (0.0)	0
Appendicitis	Infections and infestations	0 (0.0)	0	1 (0.7)	1
Arthralgia	Musculoskeletal and connective tissue disorders	0 (0.0)	0	1 (0.7)	1
Arthritis	Musculoskeletal and connective tissue disorders	0 (0.0)	0	1 (0.7)	2
Intestinal obstruction	Gastrointestinal disorders	0 (0.0)	0	1 (0.7)	1

8.4.2.3. AUX-CC-801

No subjects died during the study.

There were 5 subjects with serious adverse events requiring hospitalisation. None of these were considered by the investigator to be related to the study drug. These events included a 57 year old man with an exacerbation of osteoarthritis in the placebo group, and a 60 year old man with worsening of arthritis in the AA4500 group. A 66 year old man developed chest pain 104 days after the second injection of the third cycle, a 59 year old man became unwell with sepsis 107 days after the second injection of the third cycle and had neck pain 33 days after this, and a 51 year old man was involved in a motor vehicle accident.

8.4.2.4. AUX-CC-805

There were no deaths or other serious adverse events.

8.4.2.5. AUX-CC-80-2

There were no deaths.

There were three serious adverse events related to the study drug. A 32 year old man was hospitalised for a penile haematoma which occurred 1 day after the second injection of the first cycle. This resolved and the subject continued all 4 treatment cycles. A 69 year old man developed a penile haematoma 22 days after the second injection of the first cycle after intercourse. This resolved and the subject completed the remaining 3 treatment cycles. A 42 year old man developed corporal rupture during vigorous intercourse the day after the study drug was administered.

There were a further 10 events considered unrelated to the study drug. These included 2 cases of prostate cancer, 1 myocardial infarction, 1 deep vein thrombosis (DVT), 1 device occlusion, 1 inguinal hernia, 1 joint injury, 1 episode of mania, 1 case of nephrolithiasis, 1 pulmonary embolism, and 1 tendon rupture.

Comment: Spontaneous penile events including penile popping were included as an efficacy end point. However, penile popping may be due to penile rupture. On evaluation of the individual events for penile popping in the dossier, very few of these were associated with bruising. Thus, although popping can be associated with penile rupture (where you would expect bleeding and pain) it may also be a benign event.

8.4.3. Discontinuation due to adverse events

8.4.3.1. AUX-CC-803

There were 5 subjects in the AA4500 arm and 1 subject in the placebo arm who discontinued due to AE. There was 1 discontinuation due to penile haematoma in the active arm and one patient in the placebo arm discontinued after he was diagnosed with penile carcinoma. All other AE were not related to the study drug.

8.4.3.2. AUX-CC-804

Seven subjects in the AA4500 arm and 3 subjects in the placebo arm experienced a TEAE that led to study discontinuation. Most of these events were considered to be related to the study drug.

8.4.3.3. AUX-CC-801

Two subjects discontinued due to adverse events probably related to AA4500. This included a subject in the AA4500/modelling group who developed penile pain and oedema on Day 10 that lasted 32 days, and a subject in the AA4500/no modelling group who developed bruising, oedema and a rash on Day 2 that lasted 7 days.

8.4.3.4. AUX-CC-805

No patients discontinues due to adverse events.

8.4.3.5. AUX-CC-802

Five subjects discontinued due to adverse events, three were considered related to the study drug (corporal rupture, penile haematoma, blood blister). The other two events included joint dislocation and painful erection.

8.4.4. Erectile dysfunction and related events

8.4.4.1. AUX-CC-803

Ten subjects, all in the AA4500 group, had adverse events coded as erectile dysfunction. All but one subject had minimal change or an improvement in IIEF erectile function from screening to Week 52. All but one subject had minimal change or an improvement in penile curvature. Only one patient had a pre-existing history of erectile function.

8.4.4.2. AUX-CC-804

Nine subjects were coded as having experienced TEAE due to erectile dysfunction during the study. Seven subjects in the AA4500 group and 2 in the placebo group. All but 2 subjects had either minimal change or an improvement in the erectile function scores from screening to Week 52. All but 2 subjects had an improvement in curvature deformity from baseline to Week 52.

8.4.4.3. AUX-CC-801

Five subjects were coded as having TEAE as erectile dysfunction. The details are described in Table 35.

Table 35: Study AUX-CC-801. Subjects with TEAE coded as erectile dysfunction

Subject Number	Age	Verbatim Term	Onset Day/ Stop Day Trt Cycle, Inj	Severity/ Relationship to study drug/study procedure/ procedural medications	Action Taken	IIEF Scores Baseline/ LOCF	Comments
AA4500/modeling							
1106-1304	71	Cavernosal venous arterial deficiency	248/253 3,2	Mild Possible/ Possible/Not related	Dose not changed	24/29	Screening Doppler: Abnormal NCS (asymmetric peak systolic flow velocity) Week 36: Abnormal CS (minimal but significant changes – decreased resistive index, delayed systolic rise time in right cavernosal artery, peak systolic velocity 5-22 cm/s, consistent with arterial insufficiency)
1106-1306	62	Decrease in rigidness of erection	11/191 1,2	Mild Possible/Not related/Not related	Dose not changed	29/28	Screening Doppler: WNL Week 36: Abnormal NCS (asymmetry in peak systolic flow >10 cm/s). No evidence of venous leak
1185-1012	38	Increased difficulty with erections	8/ongoing 1,2	Mild Possible/Possible/Possible	Dose not changed	11/6	Screening and Week 36 Doppler: WNL
AA4500/without modeling							
1106-1307	70	(COVD) Corporal veno-occlusive dysfunction	246/ongoing 3,2	Mild Possible/Not related/Not related	Dose not changed	30/29	Screening Doppler: WNL Wk 36: Abnormal NCS (hemodynamics consistent with venous leak) – decrease resistive index and moderately increased diastolic blood flow
1189-1805	63	Vasculogenic ED veno-occlusive by penile duplex Doppler ultrasound	250/ongoing 3,2	Moderate Possible/Not related/Possible	Dose not changed	22/17	Screening Doppler: Abnormal NCS (peak systolic flow = 22 cm/s) Week 36 : Abnormal CS (veno-occlusive vasculogenic ED = dec resistive index = 0.55) Of note: ED at screening

Data source: Appendix 16.2, Listings 16.2.4, 16.2.7 and data on file

CS=clinically significant, ED=erectile dysfunction; Inj=Injection, NCS=not clinically significant, Trt=Treatment, WNL=within normal limits

All 5 cases of erectile dysfunction received AA4500. There was an apparent change in Doppler ultrasound in 4 subjects, only 2 were thought of be of clinical significance by the investigator.

Eight subjects experienced a worsening of their Peyronie's disease symptomatology. Six of these men received AA4500. The symptoms described included calcification of the penis and buckling of the glans during penetration; a lump under the penile skin, buckling of the penis with erection, decreased erection beyond the plaque (3 subjects), and increased penile indentation (2 subjects). The investigator attributed some of these as due to the study drug.

Two men had decreased sensation of the glans detected by biothesiometry.

Comment: There seems to be a discrepancy between patient's experience of erectile function and the clinical outcomes measured. This questions the validity of the IIEF. Four out of 5 subjects in Study AUX-CC-801 had a change in the Doppler ultrasound result. There were no Doppler ultrasounds reported for patients with erectile dysfunction in other studies. The significance of these changes is uncertain. Changes in vascular function in patients with Peyronie's disease at baseline and a progression of vascular dysfunction over time have been reported. However, the effect of the study drug cannot be excluded.

8.4.5. Laboratory tests

Laboratory function was assessed as part of studies AUX-CC-801, AUX-CC-802, AUX-CC-803 and AUX-CC-805. There were no significant abnormalities of laboratory function detected; in particular no deterioration of LFT or haemoglobin. CK was not measured.

8.4.6. Vital signs

There were no clinically significant changes in vital signs in any of the studies.

8.4.7. Anti-AUX I and anti AUX II antibodies and neutralising antibodies

8.4.7.1. AUX-CC-803

Most subjects (99.2%) of subjects developed AUX I and AUX II antibodies at Week 24. Neutralising antibodies developed in up to 37.7% to AUX I and 47.1% to AUX II. The risk of developing neutralising antibodies was not related to AUX antibody titre.

8.4.7.2. AUX-CC-804

All subjects developed antibodies to AUX I and AUX II by Week 24. Three subjects had antibodies to AUX I and 6 subjects had antibodies to AUX II at baseline. Up to 57.1% of the subjects who developed AUX I antibodies developed neutralising antibodies. The titre of AUX I did not correlate to the risk of developing neutralising antibodies. Up to 25% of subjects with AUX II developed neutralising antibodies. The titre of AUX II did not correlate with the likelihood of developing antibodies. The clinical significance of this is uncertain.

8.4.7.3. AUX-CC-805

No subject had positive antibodies at screening. 50% of subjects had positive antibodies to AUX-1 and 30% had antibodies to AUX II on Day 29. Two of 10 subjects positive for anti-AUX I on Day 29 were positive for neutralising antibodies. No subjects with anti-AUX II had neutralising antibodies.

8.4.7.4. AUX-CC-801

Three subjects had antibodies to AUX-1 and 2 subjects had antibodies to AUX II at screening. All subjects treated with AA4500 developed antibodies to AUX-1 and AUX II by week 36. The antibody titre had no correlation with adverse events.

8.5. Post-marketing experience

The evaluator reviewed the most recent PSUR from August 2014.

This covered the reporting period 28 August 2013 to 27 February 2014. At that time, Xiaflex had marketing authority in the USA from 2 February 2010 for Dupuytren's contracture and from 4 November 2013 for Peyronie's disease. Xiaflex was granted marketing authority on 2 February 2011 in Europe for Dupuytren's contracture and from 7 August 2013 in Australia for Dupuytren's contracture. During the reporting period, there had been no action taken in relation to the experimental use or marketing of Xiaflex.

8.5.1. Exposure

There had been 3656 subjects participate in clinical trials. Of these 3470 were exposed to Xiaflex and 71 received blinded treatments.

Data from marketing estimated an exposure of approximately 59,645 subjects worldwide. Of these, 13,117 had been exposed during the reporting period. Forty eight patients were from Australia.

Table 36: Signal and risk evaluation (from Table 6-11 of the PSUR)

Risk	Data from clinical trials, post marketing reports, and literature reviews	Evaluator comment
Local reactions	No SAE in clinical trials Post marketing: 76 events in 49 cases. One SAE (pain in extremity) 34 recovered, 12 not recovered, 4 recovering, 26 unknown	The number of cases not recovered is a concern, however this is post marketing data and the reporting may have been incomplete
Immune mediated reactions including anaphylaxis	No SAE in clinical trials Post marketing: 35 events in 24 cases. Ten cases were coded as hypersensitivity. One SAE (a patient with known allergies to dust, dogs, nuts, cats and grass developed pruritis, rash, flushing, anxiety, dyspnoea and nausea within 30 minutes of injection). The patient was treated with antihistamine, steroids and adrenalin and recovered in 2 h. 19 recovered, 5 not recovered, 2 recovering and 9 unknown.	
Skin lesions	No SAE in clinical trials. Post marketing data: 26 events in 23 cases, all non-serious. 9 recovered, 5 not recovered, 1 recovering, 11 unknown.	The number of cases not recovered is a concern.
Tendon/Ligament rupture or injury	No clinical trial cases. Post marketing: 7 events in 6 cases. 6 events were considered SAE.	
Medication errors	No clinical trials data Post marketing: 13 events in 11 cases. All were considered non serious. All events were due to health care provider errors. Events included the needle popping off the syringe, injection of the wrong dose, injection of multiple joints at the same time, recommended time between injections was not observed.	These events occurred despite a risk management plan.
Injection site bleeding in patients with coagulation disorders	There were no cases from clinical trials. There was insufficient information about the use of anti-coagulant medication or pre-existing coagulation disorders from post marketing data or literature reviews	

Risk	Data from clinical trials, post marketing reports, and literature reviews	Evaluator comment
Reactions related to cross reactivity with endogenous MMPs	No clinical trials data. Five cases were reported from post marketing data; one case each of arthralgia, musculoskeletal pain, musculoskeletal stiffness, myalgia, Raynaud's phenomenon. All were considered non serious. No cases were reported in the literature.	
Use in the elderly (> 65 years)	Overall there were 58 cases representing 40% of the total dataset. In the clinical trials data, there were 11 SAE relating to 9 cases, all considered unrelated to the study drug. In the post marketing dataset, there were 103 events including 39 administrative site conditions and injury, 28 procedural complications. There was a report from a literature review of an elderly female who experienced an extensive haematoma and impaired vascular flow on Doppler ultrasound.	The data is incomplete, but the relative number of cases is of concern. It is plausible that elderly people may have more adverse reactions as skin and connective tissue loose elasticity and become more fibrotic. Thus, anatomical structures can be more mobile and drugs extravasate more commonly.

8.6. Safety issues with the potential for major regulatory impact

These include TEAE and have been discussed in previous sections.

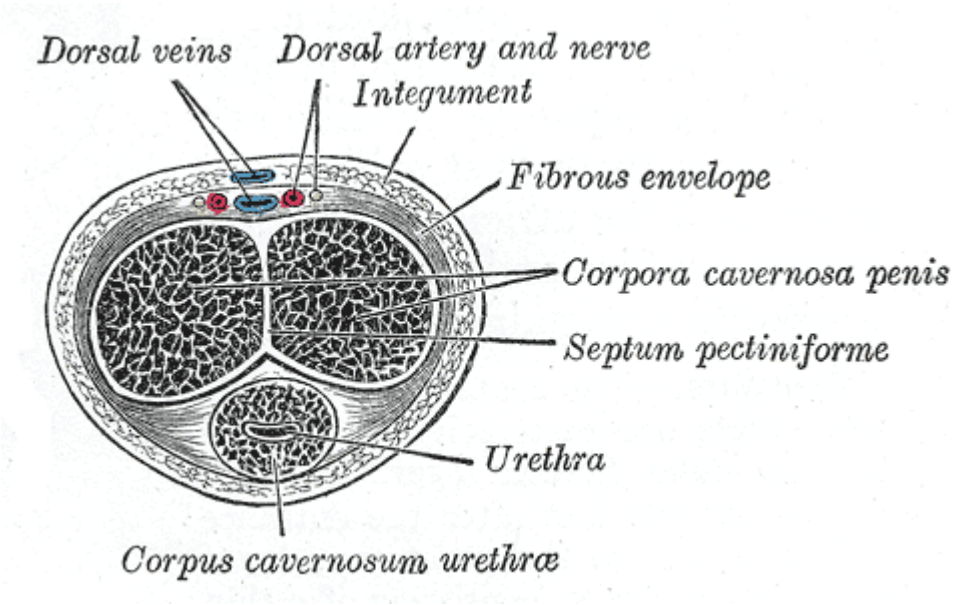
8.7. Evaluator's overall conclusions on clinical safety

Data for over 800 subjects with Peyronie's disease exposed to AA4500 was available from clinical trials. Most patients had received 3 of 4 treatment cycles of AA4500. In Study AUX-CC-803, 77% of active subjects and 86% of placebo subjects received all 4 complete cycles, that is, 8 injections. In Study AUX-CC-804, 80% of active subjects and 89% of placebo subjects received all 4 complete cycles, that is, 8 injections.

There was a high incidence of local reactions to the injection. The most common reactions were bruising, swelling and pain at the injection site or penis. The investigator rated these as mild or moderate. A small number of patients discontinued due to adverse effects or refused modelling. Local reactions generally resolved within 2-4 weeks.

A small number of patients experienced serious adverse events. There were 5 cases (0.5%) of corporal rupture described, all during intercourse. Four of these were coded as SAE. Three cases required surgical management, two were managed conservatively. Nine subjects (0.9%) reported a combination of penile ecchymosis or haematoma, sudden penile detumescence, and/or penile popping. This was a concern as penile fracture cannot be excluded. All subjects were managed conservatively. No patients experienced urethral injury however such an injury would be more likely to occur with ventral plaques see Figure 9.

Figure 9: Cross sectional image of the penis



It is unknown if the adverse events are due to inadvertent injection of collagenase into other tissue, or extravasation of the collagenase to other tissue, or collagenase exerting a less specific effect for Type I and III collagen in humans than has been demonstrated in vitro and in animal models.

More patients in who received AA4500 (about 3.6%) (across Studies AUX-CC-803 and AUX-CC-804, this is 3.1% [17/551]) than placebo (about 0.01%) (across Studies AUXCC- 803 and AUX-CC-804, this is 0.7% [2/281]) coded as having erectile dysfunction as a TEAE during the study. It is unclear how many of these had erectile dysfunction at baseline, however overall the prevalence of erectile dysfunction was similar in the treatment groups at baseline and across all studies. The one study that performed Doppler ultrasound at the study endpoint identified abnormalities in those that developed erectile dysfunction. The impact of AA4500 or other factors on these Doppler ultrasound findings is unknown.

One case of acute hypersensitivity in a patient being treated for Dupuytren's contracture has been reported in post market setting.

The frequency of adverse effects in clinical trials where investigators would have undergone training and became very familiar with the technique is a concern. In addition, there were a number of dosing and administrative errors despite a comprehensive physician training program in the countries Xiaflex has been registered in.

Unknown safety areas include the use in the elderly, use in the context of coagulation therapy, and the impact of Xiaflex on subsequent surgery.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of Xiaflex for the treatment of Peyronie's disease are:

- Improvement in penile curvature of around 16˚ (30-38%), compared to around 10˚ (15-20%) in the placebo group
- Improvement in Peyronie's bother scale by 2.4-3.3 points (scale 0-15) points compared to 1.6-2.0 in the placebo group

- Improvement in erectile function, and sexual function

9.2. First round assessment of risks

The known risks of Xiaflex for the treatment of Peyronie's disease:

- High risk of local reaction- bruising, pain, oedema
- < 1% risk of corporal rupture

Potential risks include:

- Dosing and administration errors
- Injection into tissues adjacent to the Peyronie's plaque for example, urethra, blood vessels, corpus cavernosa
- Hypersensitivity
- Systemic exposure to collagenase
- Increase rate of adverse events in the elderly as they have looser connective tissue
- Increased rate of complications with subsequent surgery
- Off label use

9.3. First round assessment of benefit-risk balance

Overall, the benefit-risk balance of Xiaflex for Peyronie's disease is favourable. This is based on a positive improvement in Peyronie's symptomatology and clinical need for an efficacious non-invasive treatment option. However a number of changes to the submission are required to minimise the potential risks and ensure patients are adequately informed.

The evidence provided indicates Xiaflex has some benefit in improving penile deformity due to Peyronie's disease, and results in improvement in psychological symptoms, erectile and sexual function as a result. However there is large variability in individual responses, and a significant placebo effect. Peyronie's disease is not life threatening but is disabling to sufferers. There are few other efficacious non-invasive treatment options. Surgery is an option for men with stable disease and a significant curvature deformity and retrospective studies support its efficacy. However, it is also associated with risks and not all men are willing to undergo such an invasive procedure.

The risks of local reactions are high, but these are considered mild and resolve with time. Some subjects in the trial have had deterioration in erectile function as a result of treatment. There have been a few cases of corporal rupture. These cases have all been in men who have had vigorous intercourse. There is a potential risk of dosing error, and injury to surrounding tissue due to extravasation or incorrect injection technique.

There have been a small number of applications for unregistered use of this medicine. An analysis of data from SASB applications as of April 2015 showed a total of 20 applications in 2014, and 7 so far in 2015. The requested were from a small number of doctors.

9.4. First round recommendation regarding authorisation

At this stage, the clinical evaluator would recommend approval of Xiaflex for the treatment of men with Peyronie's disease, subject to changes to the indications, dosage and administration, the RMP and a satisfactory response to the clinical questions.

The sponsor proposed the following indication:

Xiaflex is indicated for the treatment of male adults with Peyronie's disease and a palpable plaque and curvature deformity.

These indications open the treatment with Xiaflex with a much broader population to that was studied in the clinical trials.

The evaluator recommends the indication be changed to:

Xiaflex is indicated for the treatment of Peyronie's disease of greater than 12 months duration, penile curvature of greater than 30˚, and palpable plaque.

The rational for this is to exclude those who may regress spontaneously, and where penile deformity is unlikely to be of clinical significance (penile curvatures up to 30˚ are within the normal range). This new indication is also more consistent with what has been approved in the USA and Europe.

The sponsor proposes that Xiaflex should be administered by a physician appropriately trained in the correct administration of the product and experienced in the diagnosis and treatment of male urological disease. Although this is appropriate, it has the potential to limit patient access to treatment. It would be anticipated that the majority of doctors administering Xiaflex would be urologists, who are experts in the management of male urological disease. However as Australia is a large country with a significant population living in outer metropolitan, rural or remote areas where there may be limited access to an urologist; the need for GPs or surgeons to do procedures such as this is sometimes required. In addition, many procedures in Australia (for example, intra-articular injections, renal biopsies, liver biopsies) are now done with imaging guidance by interventionist radiologists.

Other changes suggested to the PI and CMI are in relation to making the information more reader friendly and minimising risks. The changes suggested to the RMP relate to the addition of extra groups at potential risk of adverse effects (that is, elderly, those who have subsequent surgical procedures and those who receive off label treatment with Xiaflex)

10. Clinical questions

10.1. Pharmacodynamics

10.1.1. Question 1

If the Xiaflex is administered locally and does not destroy the collagen beyond the plaque, how does the sponsor explain the bleeding and corporal rupture seen?

10.1.2. Question 2

Please provide more information to justify the doses used in the clinical studies. Would a smaller dose have similar efficacy but better safety?

10.2. Efficacy

10.2.1. Question 3

Regarding the PDQ: Please provide a rationale for the cut off for ± 0.3 as the Pearson correlation co-efficient used for convergent and divergent validity

10.2.2. Question 4

Please provide subgroup analyses for penile curvature and Peyronie's bother score for the following subgroups:

a. Age
b. Duration of Peyronie's disease
c. Baseline curvature
d. Baseline erectile dysfunction
e. Use of antidepressant medication
f. Use of PDE5 inhibitors

10.2.3. Question 5

Study AUX-CC-801: Please provide an analysis of the penile curvature in those treated with AA4500 comparing the groups with and without modelling.

10.3. Safety

10.3.1. Question 6

Could the sponsor please comment on the role of ultrasound or CT guided injections for administration of Xiaflex. Has this been performed in a clinical trial or is the sponsor aware of any centres in the USA doing this? Has the safety of this form of administration been compared to blind injections?

10.3.2. Question 7

Is there any information about how the use of collagenase impacts upon subsequent surgical outcomes?

10.3.3. Question 8

Please comment on the significance of the Doppler ultrasound findings in those who developed erectile dysfunction in Study AUX-CC-801. Could they be due to Xiaflex?

10.3.4. Question 9

Please explain the rationale for the 2 week period to abstain from sexual intercourse. Several cases of corporal rupture occurred at around 2 weeks. Should this be longer?

10.3.5. Question 10

Please provide the rationale for the packaging of 3 mL diluent and 0.90mg of Xiaflex when only a fraction of this is used. There is the potential for dosing errors as 3 mL diluent is delivered in the pack (only 0.39 mL is required to make up the powder to the correct concentration for the Peyronie's disease indication). Of 0.39 mL inserted into the vial for reconstitution, only 0.25 mL is to be delivered to the patient. In addition the correct preparation relies upon the physicians having the appropriately small syringes and needles for the procedure. This issue was also raised in the evaluation for Dupuytren's disease. The sponsor argued that the chance of a dosing error is minimal as the full amount of reconstituted Xiaflex is not able to be extracted from the vial. This was accepted at that time. However, the risk of local reactions is higher when Xiaflex is injected into the penis.

Has the sponsor considered other ways to minimise the risk of dosing errors. For example, is it possible for the package to contain the exact amount of powdered Xiaflex and diluent and/or small syringes to assist in the preparation? Could pharmacists prepare the Xiaflex for injection in syringes prior to dispensing it?

10.3.6. Question 11

Please explain the proposed mechanism to ensure only physicians trained in the use of Xiaflex are able to access it in Australia. Please outline the process of supply of this medicine through the pharmacist and/or distributer after the doctor writes a prescription.

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

11.1. Pharmacodynamics

Question 1: If the Xiaflex is administered locally and does not destroy the collagen beyond the plaque, how does the sponsor explain the bleeding and corporal rupture seen?

11.1.1.1. Sponsor's response

The bleeding may be due to the effect of Xiaflex on the small venules located within or near the collagen plaque, and/or secondary pharmacodynamics effects of the collagen fragments generated by the collagenolytic activity of Xiaflex on collagen. In addition, there may be an effect on small vessels by the needle during the injection process. The results of in vitro studies demonstrate that Xiaflex disrupts predominantly Type I and III collagen in plaques, but at higher doses and longer incubation times may affect Type IV collagen in small veins.

11.1.1.2. Evaluator's comment

The response is acceptable. There is sufficient information in the PI in relation to this issue.

Question 2: Please provide more information to justify the doses used in the clinical studies. Would a smaller dose have similar efficacy but better safety?

11.1.1.3. Sponsor's response:

The sponsor has provided a table describing the dose finding studies. The dose is justified based on greater efficacy with larger doses, with minimal changes in safety. Bleeding and corporal rupture were also observed at smaller doses.

11.1.1.4. Evaluator's comment

The response is acceptable

11.1. Efficacy

Question 3: Regarding the PDQ: Please provide a rationale for the cut off for ± 0.3 as the Pearson correlation co-efficient used for convergent and divergent validity.

11.1.1.1. Sponsor's response

References are provided to support this cut off. They discuss the limitations of a numerical value for a correlation co-efficient, as the significance varies with the parameters being compared. Any value of statistical significance is of potential importance.

In behavioural sciences, there are a number of factors that need to be considered when interpreting effect sizes. Many questionnaires and surveys measure outcomes in arbitrary units. A partial solution to this was the use of 'rho' values. The operational definitions 'small' (r= 0.1), medium (r=0.3), large (r= 0.5) are somewhat arbitrary. It is noted that the conventions were set forth throughout with much diffidence, qualifications and invitations not to employ them if possible as they had low reliability. Although these values seem low, these values may represent

stronger degrees of association than is apparent. Ozer (1985) has suggested that r is better marker of the proportion of variance than r^2. Contrary to this, Oakes (1982) has written that the strength of association indicated by correlation coefficients is systematically and substantially overestimated. Rosenthal and Rubin have emphasised that in many circumstances, particularly when at least variable is binary, the amount of association is greater than r^2. They have also reinforced the importance of considering the contexts of the issues involved when interpreting the size of an effect.

11.1.1.2. Evaluator's comments

The response is acceptable.

Question 4: Please provide subgroup analyses for penile curvature and Peyronie's bother score for the following subgroups:

a. Age

b. Duration of Peyronie's disease

c. Baseline curvature

d. Baseline erectile dysfunction

e. Use of antidepressant medication

f. Use of PDE5 inhibitors

11.1.1.3. Sponsor's response

The sponsor has provided the analysis of subgroups requested based on pooled results of AUX CC 803 and 804.

a. *Age*: There was very little effect of age on curvature response. Younger men tended to have greater improvement on Peyronie's bother score.

b. *Duration of disease*: The mean percentage improvement in curvature deformity was greater for men with longer duration of disease (> 2years). There was no significant impact on Peyronie's disease bother score.

c. *Initial curvature*: The improvement in penile curvature was not affected by the initial degree of penile curvature. There was marginally less improvement in penile bother scores in the groups with higher initial penile curvature [3.1 (30-45 ^{0} curvature) versus 2.7 (45 to 60^{0}curvature) versus 2.5 (61 to 90^{0}curvature)].

d. *Baseline erectile function:* Subjects with none to mild/moderate erectile dysfunction at baseline tended to have a greater mean percent improvement in curvature deformity compared with men who had no sexual activity/no sexual intercourse at baseline and men who had moderate to severe erectile dysfunction at baseline. However, the number of men with no sexual activity/no sexual intercourse (N=16) and those with moderate to severe erectile dysfunction (N=67) at baseline were too few to draw any definitive conclusions.

   Men with moderate to severe erectile dysfunction at baseline tended to have a greater reduction in Peyronie's bother score compared to men who had no sexual activity/no sexual intercourse at baseline or those with none to mild/moderate erectile dysfunction at baseline. However, the number of men with no sexual activity (N=16) and those with moderate to severe erectile dysfunction (N=67) at baseline were too few to draw any definitive conclusions.

e. *Antidepressant use:* Subjects who used an antidepressant medication during the study tended to have a numerically greater mean percent improvement in curvature deformity (38.7% versus 33.2%) and a numerically greater reduction in patient

reported PD bother (3.2 versus 2.8) compared with men who did not use an antidepressant medication.

f. *PDE5 usage:* Subjects who used a PDE5 inhibitor during the study tended to have a numerically greater mean percent improvement in curvature deformity (36.4% versus 32.8%) and a numerically greater reduction in patient-reported PD bother (3.1 versus 2.7)compared with men who did not use a PDE5 inhibitor.

11.1.1.4. Evaluator comment

The response is acceptable. There does not appear to be any significant trends for efficacy in the subgroups.

Question 5: Study AUX-CC-801: Please provide an analysis of the penile curvature in those treated with AA4500 comparing the groups with and without modelling.

11.1.1.5. Sponsor's response

The table below demonstrates a numerical but not statistically significant improvement in penile curvature when patients treated with Xiaflex receive modelling after the procedure.

Table 37: Effect of penile modelling on change in penile curvature in Study AUX-CC-801

	AA4500 with Modelling (N=54)	AA4500 without Modelling (N=55)	P value[a]
Change from Baseline-Degrees (mean±SD)	-17.5°±15.28°	-15.0°±14.04°	0.3686
% Change from Baseline- % (mean±SD)	-32.4%±30.71%	-27.1%±23.14%	0.3064

11.1.1.6. Evaluator comment

The sponsor has stated that the results of this study formed the basis of the use of modelling in ongoing clinical trials and in clinical practice. However, the evaluator does not agree that the results of this analysis support the recommendation to use modelling with Xiaflex.

11.1. Safety

Question 6: Could the sponsor please comment on the role of ultrasound or CT guided injections for administration of Xiaflex. Has this been performed in a clinical trial or is the sponsor aware of any centres in the USA doing this? Has the safety of this form of administration been compared to blind injections?

11.1.1.1. Sponsor response

Ultrasound or CT guided injections were not performed in the clinical trials and the sponsor is not aware of any centres in the USA that routinely perform guided injections for administration of Xiaflex. As the plaque is very superficial and generally located just under the thin penile skin it is easy to palpate and thus direct the needle into it. The sponsor is only aware of one circumstance where an urologist is using ultrasound guidance. That is in the unusual case of a very thin plaque where ultrasound could help prevent going through the far side of the plaque.

11.1.1.2. Evaluator's comment

The response is acceptable.

Question 7: Is there any information about how the use of collagenase impacts upon subsequent surgical outcomes?

11.1.1.3. Sponsor's response

Levine and Larsen reported a retrospective case series of 7 patients who received Xiaflex treatment and underwent surgical procedures. Surgical techniques included partial plane excision and grafting and/or tunica albuginea plication. The results indicated that there were no anatomical difficulties or complications secondary to the effects of prior Xiaflex treatment.

Study AUX-CC-810 is a 5 year follow up study of individuals previously treated with Xiaflex for Peyronie's disease. It was initiated in November 2014. Of the 260 patient's enrolled, 6.9% reported having corrective surgery. There was no information about complications of surgery available.

The global safety database was searched for all events related to surgery in cases of Peyronie's disease treated with Xiaflex. One relevant case was identified. A 36 year old man treated with 2 injections of Xiaflex to correct a 30^0 curvature of the penis. Four days after the procedure he experienced penile swelling and oedema. Because of the possibility of corporal rupture he was taken to surgery, no rupture was identified but a plication procedure to correct the curvature was performed. The surgery was uneventful.

11.1.1.4. Evaluator comment

The response is acceptable. From the limited information available, there is no data to suggest that Xiaflex alters the outcome of subsequent surgical procedures.

Question 8: Please comment on the significance of the Doppler ultrasound findings in those who developed erectile dysfunction in Study AUX-CC-801. Could they be due to Xiaflex?

11.1.1.5. Sponsor's response

In the 5 subjects who had abnormal Doppler ultra sound findings, 3 subjects had no clinical symptoms and in 2 subjects symptoms did not correlate with ultrasound findings. None of the patients experienced corporal rupture, which is the only plausible mechanism by which Xiaflex may have caused abnormal ultrasound findings.

11.1.1.6. Evaluator's comment

The response is acceptable. The evaluator has a better understanding that the ultrasound results represent changes in the arterial or venous flow to the corpus cavernosa which is not anatomically related to the site of the Xiaflex injections.

Question 9: Please explain the rationale for the 2 week period to abstain from sexual intercourse. Several cases of corporal rupture occurred at around 2 weeks. Should this be longer?

11.1.1.7. Sponsor's response

Penile erection and vigorous activity during sexual intercourse could lead to corporal rupture soon after treatment with Xiaflex if there was any unintentional weakening of the tunica albuginea from medication that might have leaked out of the treated plaque.

Therefore, subjects were instructed not to resume sexual activity for a minimum of 2 weeks following injection. A period of 2 weeks was initially chosen based on early reports of some cases of corporal rupture occurring within that timeframe. This timeframe was also chosen to enable resolution of the majority of local adverse events such as penile hematoma.

The instruction to avoid sexual activity for a minimum of 2 weeks is further supported by reports of 2 corporal ruptures in the Phase III trials that occurred during sexual intercourse during that 2 week period.

11.1.1.8. Evaluator's response

In Studies AUX-CC-803 and 804, there were 2 cases of penile fracture that occurred more than 14 days after the Xiaflex procedure, and one case that occurred within 14 days after the procedure. Further analysis of the timing and risk factors for severe local adverse reactions is recommended.

Question 10: Reconstitution of the solution

11.1.1.9. Sponsor's response

The sponsor has reviewed the frequency of local reactions due to treatment emergent adverse events in patients treated with Xiaflex for either Dupuytren's contracture (97.8%) or Peyronie's disease (92.2%). There was no evidence that local reactions were more common after Xiaflex.

There were no reports of dosing errors in clinical trials programs or in post marketing reports. There were, however, 3 cases of reconstitution errors whereby the wrong amount of diluent was added to the vial. In all cases, the drug was not administered to the patient.

The sponsor conducted a study titled 'Evaluation of Volume that can be withdrawn by a healthcare provider from a Xiaflex vial after withdrawal of the appropriate dose volume'. Although the study was performed in relation to its use in Dupuytren's contracture, the report is applicable to Peyronie's disease as the volume of Xiaflex used for Peyronie's disease is identical to that used for MP joints of Dupuytren's contracture. The results show that the theoretical volume remaining in the vial after the removal of a dose for a MP joint is 0.14 mL. However, the volume able to be withdrawn is generally only 0.08 mL (95% CI 0.07 to 0.1ml).

11.1.1.10. Evaluator's comment

The response is acceptable. The sponsor has thoughtfully considered the reconstitution of the vial.

Question 11: Please explain the proposed mechanism to ensure only physicians trained in the use of Xiaflex are able to access it in Australia. Please outline the process of supply of this medicine through the pharmacist and/or distributer after the doctor writes a prescription.

11.1.1.11. *Sponsor's response*

The Peyronie's disease training program will closely follow the model already implemented in Australia for Dupuytren's contracture.

Physicians completing the online education and training program will be asked to complete an online version of the Declaration/Consent form which automatically uploads the information onto the web platform database. Information collected in the database will be used by the Wholesale Distributor to confirm Certification prior to product distribution.

A controlled distribution system will ensure that only Certified Prescribers will be able to receive product from Actelion's authorised Distributor. The pharmacy ordering process will be tailored to ensure that specific personal information on the prescriber is supplied by the ordering pharmacy at the time product is ordered from the Distributor. Every order received by the Distributor will be checked against the Certified Prescriber List database prior to shipping product to pharmacy. Product will only be shipped to prescribers whose name appears on the Certified Prescriber List.

Where the prescriber's name is not on the Certified Prescriber List, the Distributor will withhold shipment of product and notify the pharmacy that the prescriber needs to undertake Actelion's

education and training program to enable Certification and subsequent receipt of product. The sponsor will maintain an updated list of physicians who have been trained and 'certified' on the use of Xiaflex. A report will be provided to the TGA in PSURs (or separately) on the success of the distribution system as a risk minimisation activity, including any occurrence where product was inadvertently used by a non-certified prescriber.

11.1.1.12. Evaluator comment

The response is acceptable. The evaluator notes that no practical component is included. The opinion of the RMP evaluation team regarding the success of the Dupuytren's program and suitability of this program for Peyronie's disease is relevant.

Question 12: Please explain what happens if Xiaflex is inadvertently spilt onto surrounding skin or the administrator's fingers or splashes into eyes? Are any extra precautions needed? Is there specific advice as to how to minimise the effect?

11.1.1.13. Sponsor's response

Nonclinical studies of exposure (that is, acute oral, dermal, inhalation toxicity; acute eye or dermal irritation or skin sensitization) have not been carried out. However, adverse events from accidental exposure to the skin or eyes that is promptly washed is not expected to result in adverse effects. The outer layer of the skin is composed of dead epithelial cells filled with keratin (not a target of collagenase) and the outer layer of the visible eye is covered by the conjunctiva (non-keratinised, stratified squamous epithelium and goblet cells) over the sclera and non-keratinised, stratified, squamous epithelium over the cornea. Collagen is not a component of these surfaces.

11.1.2. Evaluator's comments

There is currently no information in the PI or CMI in relation to the precautions that need to be taken to avoid contact between the reconstituted solution and skin or conjunctival mucosa. There is no information provided as to how to manage inadvertent spills or contact between collagenase and skin or conjunctival mucosa.

11.2. Changes to the PI

The sponsor has revised the indication to:

> *Xiaflex is indicated for the treatment of adult men with Peyronie's disease with a palpable plaque and a curvature deformity of at least 30 degrees at the start of therapy.*

The rationale for this was that this is the approved indication in the EU and USA.

The sponsor did not agree with the evaluator's recommendation to limit the indication to men who had had Peyronie's disease for more than 12 months. The sponsor has described a post hoc analysis of treating subjects with Peyronie's disease less than 12 months was afforded in the Phase IIb Study AUX-CC-801. Study AUX-CC-801 had an inclusion criterion that the subject had to have a diagnosis of Peyronie's disease for at least 6 months before the first dose of study drug. Results from subjects diagnosed with disease for 6-12 months and from those subjects diagnosed with disease ≥12 months were compared (Levine et al J Urol 2015). In subjects with Peyronie's duration of 6 to <12 months (n=22, Xiaflex; n=12, placebo), a 38% mean improvement in penile curvature was observed following Xiaflex treatment versus a 19.8% mean improvement for placebo (p=0.08). For duration of ≥ 12 months (n=78, Xiaflex; n=22, placebo), a 27.6% mean improvement in penile curvature was observed following Xiaflex treatment versus a 7.3% mean improvement for placebo (p=0.004). For the bother domain, similar score improvements were observed for subjects with duration of 6 to <12 months) or ≥ 12 months). Most adverse events (AEs) in the Xiaflex-treated group occurred at the injection

site (penile bruising, pain, oedema, contusion) and were mild/moderate in severity; AE profiles were comparable regardless of the duration of Peyronie's disease.

The sponsor has emphasised the importance of refraining from vigorous sexual intercourse for 2 weeks after Xiaflex.

12. Second round benefit-risk assessment

12.1. Second round assessment of benefits

The benefits of Xiaflex for the proposed indication are unchanged as a result of the second round evaluation.

The benefits of Xiaflex for the treatment of adult men with Peyronie's disease and disease duration of greater than 12 months with a curvature deformity of greater than 30 degrees are:

- Improvement in penile curvature of around 16˚ (30-38%), compared to around 10˚ (15-20%) in the placebo group
- Improvement in Peyronie's bother scale by 2.4-3.3 points (scale 0-15) points compared to 1.6-2.0 in the placebo group
- Improvement in erectile function, and sexual function

Unknown potential benefits:

- It is presumed but unknown if Xiaflex prevents the need for surgery for the treatment of Peyronie's disease.

The evaluator is not convinced of the efficacy of the modelling procedure used with Xiaflex from Study AUX-CC-801. However, as subsequent studies used the modelling procedure and this is standard clinical practice, at this time it is reasonable to include this in the PI.

12.2. Second round assessment of risks

The sponsor has addressed a number of concern's the evaluator had around the safety of Xiaflex. There is limited data about the impact of Xiaflex on subsequent surgical procedures, however from the data available there does not appear to be any signals. The sponsor has carefully considered the packaging and reconstitution of Xiaflex.

The known risks of Xiaflex for the treatment of Peyronie's disease are as follows:

- High risk of local reaction- bruising, pain, oedema
- < 1% risk of corporal rupture

Potential risks include:

- Dosing and administration errors
- Injection into tissues adjacent to the Peyronie's plaque for example, urethra, blood vessels, corpus cavernosa
- Hypersensitivity
- Systemic exposure to collagenase
- Increase rate of adverse events in the elderly as they have looser connective tissue
- Off label use

In addition, there are a number of outstanding questions which have not been sufficiently addressed by the sponsor to date:

1. What is the evidence that abstaining form sexual activity for 2 weeks is effective (or is needed) to mitigate the risk of corporal rupture. Are all forms of sexual activity potentially dangerous, or is it only vigorous sexual intercourse or sexual activities in certain positions that are a potential risk?
2. Is there sufficient evidence to support a positive risk benefit ratio for the use in patients with a duration of Peyronie's disease less than 12 months?

12.3. Second round assessment of benefit-risk balance

The clinical trials submitted have adequately demonstrated the efficacy for Xiaflex for the treatment of penile curvature and symptoms associated with Peyronie's disease. Treatment is associated with acute local adverse effects which are generally mild and resolve with time. There is a small risk of corporal rupture. These risks are well described in the PI, CMI and physician training programme. In addition, the use of Xiaflex will be limited to physicians experienced ion the treatment of male urological disease and have undergone the training program.

Thus, the risk-benefit balance for Xiaflex for the proposed indication used by adequately trained health professionals and given to patients who have been fully informed of the potential adverse effects is favourable.

The efficacy for patients with duration of disease less than 12 months is less well defined. The risk benefit ratio in this group of men is unknown as the disease may regress spontaneously in some of these men.

12.4. Second round recommendation regarding authorisation

The evaluator would recommend approval of Xiaflex for use in adult men with Peyronie's disease with a palpable plaque and a curvature deformity of at least 30 degrees at the start of therapy with the following conditions:

1. That a statement in relation to the need to do training to use Xiaflex and how to access this is included in the PI.
2. That the results of Study AUX-CC-810 be submitted to the TGA when it is complete.
3. Changes be made to the summary of safety concerns including
    a. Use in the elderly- this was recommended by the clinical evaluator in the first evaluation report (see section 11.3). The sponsor has not provided any information as to why this was not included
4. That the RMP team are satisfied that the sponsor has sufficient pharmacovigilance activities for the risks identified in the summary of safety concerns.
5. That changes are made to the PI and CMI around protection against and treatment of inadvertent contact between collagenase and the skin or conjunctiva.

13. References

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