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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xiapex

International non-proprietary name: COLLAGENASE CLOSTRIDIUM HISTOLYTICUM

Procedure No. EMEA/H/C/002048/II/0044

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Definition
ADAs	antidrug antibodies
AE	adverse event
A2M	alpha-2-macroglobulin
AUX-I	clostridial type I collagenase
AUX-II	clostridial type II collagenase
BTC	Biologics Technologies Corp.
ED	erectile dysfunction
ESWT	extracorporeal shock wave therapy
IIEF	International Index of Erectile Function
ISE	integrated summary of efficacy
ISS	integrated summary of safety
ITT	intent-to-treat
LOCF	last observation carried forward
mITT	modified intent-to-treat
MMPs	matrix metalloproteinases
NS	not significant
PBO	placebo
PD	Peyronie's disease
PDQ	Peyronie's Disease Questionnaire
PRO	Patient Reported Outcome
RCT	randomized controlled trials
SAE	serious adverse event
TEAE	treatment-emergent adverse event
TIMPs	tissue inhibitors of metalloproteinases

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Swedish Orphan Biovitrum AB (publ) submitted to the European Medicines Agency on 12 June 2014 an application for a variation.

This application concerns the following medicinal product:

Centrally authorised Medicinal product: **For presentations: See Annex A**	**Common name:**
Xiapex	COLLAGENASE CLOSTRIDIUM HISTOLYTICUM

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

The Marketing authorisation holder (MAH) applied for a new indication for the treatment of Peyronie's disease in adult men with a palpable plaque and curvature deformity. Consequently, the MAH proposed the update of sections 2, 3, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC.

The Package Leaflet was proposed to be updated in accordance.

Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 9.0.

The variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet

Information on paediatric requirements

Pursuant to Article 13 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/139/2009 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition

related to the proposed indication.

Applicant's request(s) for consideration

Additional data protection / marketing exclusivity

The applicant requested consideration of its application in accordance with Article 14(11) of Regulation (EC) No 726/2004 - one year of market protection for a new indication which provides a significant clinical benefit in comparison with existing therapies.

Scientific advice

The applicant received Scientific Advice from the CHMP on 1 December 2010. The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Martina Weise Co-Rapporteur: Pierre Demolis

Timetable	Dates
Submission date	12 June 2014
Start of procedure:	27 June 2014
CHMP Rapporteur Assessment Report	18 August 2014
CHMP Co-Rapporteur Assessment Report	18 August 2014
PRAC Rapporteur Assessment Report	26 August 2014
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	11 September 2014
Rapporteur Revised Assessment Report	19 September 2014
Request for supplementary information (RSI)	25 September 2014
CHMP Rapporteur Assessment Report	17 November 2014
PRAC Rapporteur Assessment Report	17 November 2014
PRAC Rapporteur Updated Assessment Report	25 November 2014
Rapporteur Revised Assessment Report	12 December 2014
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	4 December 2014
CHMP adoption of report on the novelty of the indication/significant clinical benefit for Xiapex in comparison with existing therapies (Appendix 1)	18 December 2014
CHMP Opinion	18 December 2014

2. Scientific discussion

2.1. Introduction

Xiapex (collagenase clostridium histolyticum also referred to as AA4500) is a parenteral lyophilized product comprised of two collagenases AUX-I and AUX-II. These collagenases bind and selectively digest fibrillar collagen or collagen-derived peptides by hydrolyzing the triple helical region of collagen under physiological conditions. Xiapex was granted marketing authorisation in the European Union for the treatment of Dupuytren's contracture on 28 February 2011. The purpose of this application is to extend the indication of Xiapex for the treatment of Peyronie's disease (PD) in adult men.

Peyronie's disease (PD, also known as Induratio penis plastica, IPP) is an idiopathic, connective tissue disorder of the penis and is characterized by the pathological deposition of collagen (types I and III) in the tunica albuginea of the corpus cavernosum. This collagenous plaque replaces the normal elastic fibers of the tunica albuginea and causes penile curvature, which is most evident during erection. The curvature deformity can cause pain during erection and often leads to significant patient bother, distress, and sexual dysfunction. The etiology of PD is not well understood; however, recent research has identified microvascular trauma, abnormal wound healing, and genetic predispositions as potential contributors to development of the condition.

PD is a progressive disorder with up to 48% of men having disease progression if left untreated. In most cases, PD may be divided into an acute inflammatory phase and a chronic phase. The early, acute phase lasts for approximately 6 - 12 months after disease onset and is typically characterized by painful erections and progression in plaque size and deformity. In the chronic phase (12−18 months after onset), erections are no longer painful and the deformity has stabilized. Most men present during the acute phase, but approximately 33% of men do not seek medical care until the stable phase of the disease.

In most men with PD, symptoms gradually worsen during the first year after disease onset; however, one retrospective review of medical records in 307 men with PD reported that a small percentage of patients experienced complete resolution of PD symptoms after 8 months of follow-up. With regard to long-term prognosis, the medical literature offers few additional insights. However, because the morbidity associated with PD often relates to chronic impairments in sexual functioning and psychological status, further long-term studies are warranted to obtain a better understanding of prognostic factors that may contribute to the deterioration, improvement, or resolution of PD symptoms.

The incidence and prevalence of PD has not been studied extensively. In Europe, the latest prevalence estimates were published in 2001 and 2002. In three cross-sectional, population-based studies, PD prevalence estimates were in 3% of men aged 30−80 years in Germany (Schwarzer et al., 2001, Sommer et al., 2002) and in 7% of men aged 50−69 years in Italy (La Pera et al., 2001). Disease onset commonly occurs in older men (mean age, 53 years; range, 19–83 years) (Hellstrom, 2009) and has been associated with a history of penile trauma (Brant et al., 2007, Casabe et al., 2011, Zargooshi, 2004) and genetic predisposition (Qian et al., 2004, Dolmans et al., 2012). Associated comorbidities include diabetes, vascular disease, erectile dysfunction (ED), depression, and Dupuytren's contracture (Ralph et al., 2010).

As a result of the lack of a clear understanding of the etiopathophysiology, a cure has not been found. Several factors should be considered for the therapeutic management of patients with PD, including the duration of disease, presence or absence of pain with erection, the severity of penile deformity, and the adequacy of erectile function (Hellstrom, 2009). A variety of treatment options have been used.

Conservative treatment options are multiple and diverse and include oral (colchicine, tamoxifen, pentoxyphylline, vitamin E, potassium para-aminobenzoate) and topical (verapamil) agents, intralesional injections (corticosteroids, iloprost, interferon, verapamil), extracorporeal shock wave therapy (ESWT), iontophoresis, and others.

The value of many published reports has been questioned as most were not well controlled, often had a small number of subjects in various phases of stability and with limited reports on objective measures of deformity change. Studies focus on reduction of pain that appears to resolve with time untreated, and reduction of plaque size, which has never been found to correlate with curvature improvement.

Following a consensus statement of leading experts (Ralph et al. 2010, The Management of Peyronie's disease: Evidence-based 2010 Guidelines) reduction of erect penile deformity (i.e. curve, narrowing, shortening) is the most critical outcome measure.

Surgical interventions are indicated when PD has reached the chronic phase and penile morphology, including plaque size and curvature, has been stable for ≥3 months. The goals of surgery are to correct penile deformity and improve erectile and sexual function. Therefore, surgery is typically only appropriate for patients who cannot achieve intercourse owing to the severity of their deformity and/or those with refractory ED that fails to respond to medical treatment. In addition, patients who have extensive plaque calcification are typically best treated with surgery, as nonsurgical approaches have not been shown to be beneficial in this circumstance. Surgery is typically not indicated for patients whose penile deformity does not prevent intercourse, because of the risk of postoperative ED (Ralph et al., 2010).

In the expert statement (Ralph et al. 2010) it is summarised that surgery remains the gold standard for correcting erect penile deformity in the man with stable disease. However, potential postoperative complications include excessive penile shortening, reduced penile sensitivity, palpable nodules, and ED.

Since AA4500 is a proteinase that can hydrolyze the triple-helical region of collagen under physiological conditions, AA4500 may have the potential to be effective in lysing collagen deposits such as those in the plaque that cause the curvature deformity and subsequent bother and distress in patients with Peyronie's disease.

Plaque disruption enables correction of the offending curvature deformity and may preclude the resultant morbidity and extensive recovery time associated with invasive surgical procedures.

The proposed dose of AA4500 is 0.58 mg to be administered as an intralesional injection into the Peyronie's plaque that causes curvature deformity. A treatment cycle consists of two AA4500 injection procedures and a penile modeling procedure. Each injection is administered 1 to 3 days apart. The penile modeling procedure is performed 1 to 3 days after the second injection of each treatment cycle. The treatment cycle may be repeated at approximately 6-week intervals. Up to four treatment cycles (for a total of eight injection procedures and four modeling procedures) may be administered to the plaque that causes the curvature deformity.

One treatment course is defined to consist of a maximum of four treatment cycles. In the two pivotal phase III studies covering a 1-year double-blind treatment duration patients were given the option to receive up to four treatment cycles. The safety of more than one treatment course of Xiapex for PD is not known.

2.2. Non-clinical aspects

2.2.1. Introduction

In below non-clinical assessment emphasis is given to newly submitted data in support of the new indication. Relevant data previously submitted for the indication Dupuytren contracture is mentioned for completeness.

Throughout this section, AA4500 doses are expressed in units of enzyme activity to allow comparison between studies and the peer-reviewed literature. The activity of AA4500 (BTC Process 1 and AA4500 Process 3) = 17,241 U/mg protein, ie, 10,000 units for a clinical dose of 0.58 mg protein. This provides a more accurate basis for the comparison of results across studies, as doses are thus compared on a pharmacologically similar basis.

For ease of comparison across studies and species, standard body weights and body surface area formulae were used to convert the mg of AA4500 administered/animal to the equivalent dose in U/kg and U/m^2). A standard human body weight of 70 kg (with a body surface area of 1.797 m^2) has been

employed to derive the Human Equivalent Dose (HED) on a body weight and surface area basis (143 U/kg and 5565 U/m^2 respectively).

2.2.2. Pharmacology

Primary pharmacodynamic studies

Two additional primary pharmacodynamics studies were conducted to support the use of AA4500 for treatment of Peyronie's disease: an in vitro study of the effect of AA4500 injected into Peyronie's plaque tissue explants (Study RU-001) and an in vivo study of the collagenolytic effect of AA4500 injected subcutaneously in Göttingen minipigs (Study WIL-696007).

An overview of the pharmacodynamics studies is presented in the Table below.

Table: Tissue Explant Culture Studies and in vivo Collagenolytic Study Performed with Commercial Manufactured AA4500 (or early BTC process material, Purified Research-Grade Collagenase)

Study Type	Collagenase and Dose/Concentration Used	Route of Administration	Study Endpoints	Reference
Collagenolysis on type I collagen	AUX-I, AUX-II, and AA4500	In vitro incubation	SDS-PAGE analyses of collagen digestion pattern	H-ADTR-2008-01.00
Peyronie's plaque Dupuytren's cord	AA4500	Intralesional injection	Hydroxyproline release (collagen lysis rate) Light microscopy (histomorphology, collagen lysis) Immunostaining (type I, II, IV collagen)	RU-001
Peyronie's plaque Tunica albuginea Corpus cavernosum Pericardium	Purified research-grade collagenase (Worthington, CLSPA) 10-400 U	Incubation (collagen digestion rate) Injection (histomorphology)	Amino acid release by ninhydrin reaction (collagen digestion rate) and tissue weight Light microscopy (histomorphology)	Gelbard et al, 1982
Dupuytren's cord	AA4500 (early BTC process) 150-3600 U	Injection	Mechanical loading (tensile modulus and breaking force determination) Light microscopy (histomorphology) Picrosirius red staining (collagen subtype characterization)	Starkweather et al, 1996
In vivo Göttingen minipig	AA4500 5-259 U/injection	Subcutaneous injection	Light Microscopy (histopathology, trichrome and picrosirius red stain)	WIL-696007

The results from these studies can be summarized as follows:

- AUX-I and AUX-II directly lysed type I collagen in vitro and, when mixed at an approximate 1:1 ratio as in AA4500, demonstrated a synergistic effect, ie, the lysis of collagen generated by AA4500 was greater (more fragments and at a faster rate) than the summation of the fragmentation pattern generated by the individual AA4500 intermediate components.

- The rate of collagen digestion was greatest at early timepoints (first four hours of incubation of Peyronie's plaques or tunica albuginea), with no differences in digestion rate noted between different tissues. Digestion was essentially complete in 12 to 24 hours following injection or incubation of tissues (evidenced by loss of up to 99% of tissue dry weight and/or loss of trichrome staining).

- Lysis following injection into tissues was focal, well circumscribed and primarily confined to tissue directly adjacent to the injection site (more focal in Dupuytren's cord than Peyronie's plaque).

- Immunostaining of AA4500 treated explant tissues demonstrated that AA4500 selectively lyses type I and III, while sparing type IV collagen.

- No damage to non-collagenous tissue elements (elastic fibers, arteries, arterioles, nerve fibers, and fibroblasts) are detected following exposure to AA4500 (early BTC process) or purified research-grade collagenase, with the exception that disruption of small venules and the perineurium do occur in injected tissues. This is consistent and supports the selectivity demonstrated by immunostaining.

- Collagen digestion resulting from injection of the early BTC process material into fibroproliferative collagen (Dupuytren's cords) increases the elasticity of the remaining tissue (93% decrease in the mean tensile modulus 24 hours following injection with 3600 U) and decreases the amount of force needed to rupture the tissue to physiologically achievable levels (~ 2.7 to 4.1 megapascals, estimated normal extensor forces in the human finger, in cords treated with ≥300 U).

Secondary Pharmacodynamics

Local secondary pharmacodynamic effects have been described, including inflammatory responses and regenerative changes reflecting enhanced wound healing, probably resulting from the release of small, pharmacologically active collagen fragments. The relevance of these effects has been discussed during the original MAA for XIAPEX. No additional studies on secondary pharmacodynamics were conducted to support the use of AA4500 in treatment of Peyronie's disease. This is considered acceptable.

Safety Pharmacology

No studies were conducted to support of the use of AA4500 in treatment of Peyronie's disease. Given that systemic exposure was limited or not quantifiable following local administration by a clinically relevant route of exposure in nonclinical species this is acceptable.

Pharmacodynamic Drug Interactions

Literature on drug interactions indicates that some antibiotics may have limited inhibitory activity of clostridial collagenase in vitro. Given the therapeutic use of these antibiotics, clinical concomitant treatment with AA4500 is unlikely to occur. Studies have not been conducted with AA4500. This is considered acceptable.

2.2.3. Pharmacokinetics

Methods of Analysis

No additional studies were conducted to support of the use of AA4500 in treatment of Peyronie's disease.

Absorption

Systemic exposure was evaluated following single and repeated intrapenile administration in dogs to support the use of AA4500 in the treatment of Peyronie's disease (Study TRL 520, this study had already been submitted as supportive information during the original MAA).

In Study TRL 520, dogs received injections ranging from approximately 140 to 1430 U/animal into the tunica albuginea three times weekly every four weeks for a total of three cycles (nine doses). Plasma level profiles were evaluated on the first day of dosing of the first treatment cycle (Day 1) and following the last dose in the third cycle (Day 61). To evaluate effects on sites of inadvertent administration, additional groups of dogs received single doses of approximately 1430 or 2570 U/animal of AA4500 injected into the tunica albuginea, corpus cavernosum, urethra, or subcutaneous tissue adjacent to the main vein, artery, and nerve of the penis (referred to as the VAN complex).

In the repeat-dose phase of the study almost all plasma samples were below the limit of quantification for both AUX-I (12.5 ng/mL) and AUX-II (37.5 ng/mL) following the first dose on Day 1. No animals had quantifiable plasma levels on Day 61. In the single dose phase of the study, sporadic low levels of AUX-I and AUX-II were only quantifiable five minutes postdose from four animals injected into highly vascular sites (the corpus cavernosum or urethra). Overall, the results of the plasma analysis of AUX-I and AUX-II indicate that there were no consistently quantifiable systemic levels of the AA4500 in plasma. No toxicokinetic analysis could be performed on these data due to lack of sufficient AA4500 levels over time in the plasma in any of the treatment groups.

Distribution

New data were not provided. No distribution studies have been performed with AA4500 for original marketing authorisation.

Metabolism

New data were not provided. No metabolism studies have been performed with AA4500 for original marketing authorisation.

Excretion

New data were not provided. No studies on excretion of AA4500 have been performed with AA4500 for original marketing authorisation.

Pharmacokinetic Drug Interactions

New data were not provided. No pharmacokinetic drug interaction studies have been performed with AA4500 for original marketing authorisation.

Other Pharmacokinetic Studies

Antibody Responses

As an exogenous protein administered by local injection, antibody responses to AA4500 are anticipated to occur in the majority of treated animals or human subjects. Because these antibodies have the potential to alter the pharmacokinetic profiles of AA4500 components (AUX-I and AUX-II), the formation of antibodies were usually evaluated in the repeat dose studies in which toxicokinetic assessment was also performed.

Following repeated intrapenile injection in dogs (TRL 520), both anti-AUX-I and anti-AUX-II antibody titers were apparent and detected in all animals at all dose levels following the last dose and at the end of the recovery period.

2.2.4. Toxicology

To support the use of AA4500 in Peyronie's disease, three new non-GLP toxicology study reports are submitted with this variation application.

Table: Additional Nonclinical Toxicology Studies, submitted with this MA Variation

Study Type and Duration / GLP Status	Route of Administration	Species / Cell Line	Study Number	Lot Number	Collagenase (Process)	Source
Non pivotal						
Single Dose / Acute						
non-GLP	Intrapenile	Dog	TRL 507	7280	AA4500 (Process 3)	Horsham
non-GLP	Intrapenile	Dog	TRL 510	7280	AA4500 (Process 3)	Horsham
non-GLP	SC Injection	Minipig/ Göttingen	WIL-696007	7280	AA4500 (Process 3)	Horsham

In addition to these new toxicological study reports, a supplemental toxicokinetic analysis report (PKPD-005-2012-01) is provided.

As already submitted in the original MAA for Dupuytren's contracture, a study evaluating the toxicity following intrapenile injection into the dog penis is provided.

Table: Nonclinical Study already submitted with the XIAFLEX MAA for Dupuytren's Contracture

Study Type and Duration / GLP Status	Route of Administration	Species / Cell Line	Study Number	Lot Number	Collagenase (Process)	Source
Pivotal Studies						
Repeat-Dose Toxicity						
Single/Repeat Dose GLP	Intrapenile Injection	Dog	TRL 520	NFF-0035	AA4500 (Process 3)	Cobra
GLP = Good Laboratory Practice; Cobra = Cobra Biomanufacturing, Plc;						

These studies (two of which were conducted with the drug product manufactured according to the final commercial process, AA4500-Process 3 Horsham) are designed to characterize the local and systemic toxicity after single and repeated administration as a surrogate for extravasation from the Peyronie's plaque or misapplication into surrounding penile structures adjacent to the clinically intended site of administration.

Single dose toxicity

Single-dose and acute (5 day) intrapenile administration toxicity studies (TRL 507 and TRL 510) in dogs were conducted in support of the use of AA4500 for treatment of Peyronie's disease. Relevant findings are summarized in the table below.

Table: Non-GLP Single / Repeat-Dose studies with intrapenile application in dogs

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses	Gender and No. Per Group	NOAEL (MTD)	Noteworthy Findings	Study Number
Dogs/ Beagle	Intrapenile injection (various sites) (2 mM $CaCl_2$ in 0.9% NaCl, 40,000 U/mL)	Variable (1 to 6 days) Single doses followed by repeated dosing q48h X 3 doses	Single dose: 0, 5000, 10,000 and 15,000 U/animal (1667, 3333, and 5000 U/site X 3 sites/dog) Dose escalation: 140, 430 and 1430 U/dose (q48h)	Males Single dose: 3/group Dose escalation: 1/group	ND[a] (1430 U/dose for single, 140 U/dose for repeated, dosing)	• Euthanasia required at ≥ 9825 U/animal (≥ 3275 U/site X 3 sites/dog) due to clinical signs (tremors, recumbency) & injection site responses (bruising, swelling, bleeding from the bulbus glandis). • Dose-responsive swelling and bruising of injected tissues noted at all dose levels; effects limited ability to access tissues for repeated injection at 1430 U/dose	TRL 507
Dogs/ Beagle	Intrapenile injection (various sites) (2 mM $CaCl_2$ in 0.9% NaCl, 40,000 U/mL)	1 or 6 days (3 doses q48h)	Repeat dose: 140, or 430 U/dose Single dose: 2570 U/dose	Males 3/group	ND[a] (2570 U/dose for single, 140 U/dose for repeated dosing)	• Local reactions (bruising and/or swelling) limited repeated dosing at ≥ 430 U/dose • Correlating histologic findings (hemorrhage, subacute inflammation, neovascular proliferation and/or focal lysis of the tunica albuginea). • Partial to complete reversal of findings with 14 d recovery • Reaction severity varied by injection site (corpus cavernosum/urethra > vein-artery-nerve complex > tunica albuginea)	TRL 510

[a] ND = not determined

In non-GLP study TRL 507 AA4500 was injected into four specific locations of the dog's penis [tunica albuginea (TA), corpus cavernosum (CC), vein-artery-nerve complex (VAN), and urethra (UR)]. The study was conducted in three phases.

Phase 1 of Study TRL 507 consisted of methods development and evaluated the effects of injection of AA4500 in three of the target sites, the tunica albuginea (TA), corpus cavernosum (CC), and vein-artery-nerve complex (VAN). A volume of 0.10 mL/site was determined to be the maximum volume that could be consistently confined within the injection site of interest. Groups of three dogs received total doses of 0 (0.125 mL/site), 1621 (0.040 mL/site), 3276 (0.08 mL/site), and 5000 (0.125 mL/site) U/injection site (corresponding to approximate doses of 0, 4863, 9828 and 15,000 U/animal, approximate doses of 0, 607.9, 1228.5 and 1875 U/kg based on the mean dog weight of ~8 kg, or approximate doses of 0, 12,158, 24,570 and 37,500 U/m2) were selected for initial evaluation.

The subsequent dose escalation study (Phase 2 of Study TRL 507) was conducted in three of the sites [tunica albuginea (TA), corpus cavernosum (CC), and VAN complex (VAN)] in order to determine the optimum dose for a subsequent GLP study (TRL 520). Three dogs were assigned to each of the sites (one dog/site) and received single escalating doses of AA4500. The initial dose chosen was ~138 U/animal (13.8 U/kg, or 276 U/m2) and the dose was elevated after a period of at least 48 hours if the dose was tolerated (ie, the degree of local reaction (swelling and/or bruising) was not severe enough to preclude accurate placement of the next dose).

A separate dose escalation study (phase 3 of Study TRL 507) was performed to determine the optimum dose for the subsequent GLP study for injections into the urethra. The dose escalation study was carried out in the same fashion as for the previous three sites. The dose level of ~431 U/dose was considered the highest dose that would permit accurately placed repeated injections every 48 hours.

A dose-range finding non-GLP study (TRL 510), was conducted in order to determine the maximal tolerated dose for repeated administration at approximately every 48 hours over a period of a week for a subsequent subchronic GLP study (TRL 520). In study TRL 510, AA4500 was administered to 25 male Beagle dogs either as single dose or approximately every 48 hours over a period of a week into or adjacent to one of four anatomic sites [tunica albuginea (TA), corpus cavernosum (CC), vein-artery-nerve complex (VAN), or urethra (UR)] in the penis and to evaluate the local changes resulting from these injections and their reversibility following a 14-day recovery period. For the repeat dose portion, twenty-four dogs were assigned to one of eight groups (3/group/dose level/injection site) and were scheduled to receive AA4500 administered by local injection into their assigned sites at either ~138 or ~431 U/dose q48 h X 3 doses.

Study TRL 520 consisted of a single-dose phase and a repeat-dose phase. The single dose phase was conducted in order to evaluate potential effects of misapplication of AA4500 on penile structures surrounding the target injection site in Peyronie's disease. The repeat-dose phase was intended to evaluate the potential effects following repeat administration into the target injection site in Peyronie's disease. In the single dose phase of Study TRL 520 dogs (3 or 5/group) received single doses of 0, ~1430 or ~2570 U/dose of AA4500 (0, 143 or 257 U/kg; and 0, 3473, or 6235 U/m2; respectively) via injection into the tunica albuginea, corpus cavernosum, urethra, or VAN complex.

Table: GLP Single / Repeat-Dose study TRL 520 with intrapenile application in dogs

Type of Study	Species/Strain	Method of Administration	Duration of Dosing	Doses[a, b]	GLP Compliance	Testing Facility	Study Number	Location in Module 4
Repeat-Dose Toxicity: Nonpivotal Studies (continued)								
	Dog/Beagle (Males)	Intrapenile (Corpus cavernosum, tunica albuginea, urethra, or VAN complex)	Single Dose	0, 1430, 2570 U/animal (0, 143, 257 U/kg) (0, 3432, 6168 U/m^2)	Yes	Toxicology Research Laboratory	520	4.2.2.2
		Intrapenile (tunica albuginea)	62 Days (3x/week, every 4 weeks) With 30-Day Recovery	0, 140, 430, 1430/1050 U/animal (0, 14, 43, 143/105 U/kg) (0, 336, 1032, 3432/2520 U/m^2)				

BTC = Biospecifics Technologies Corporation; GLP = Good Laboratory Practice; VAN = Main vein, artery and nerve of the penis.
[a] For comparison across studies performed with early BTC process, BTC Process 1, and AA4500 – Process 3 Cobra or Horsham, doses are expressed in Units/animal (U/mL for in vitro studies), regardless of how they are expressed in the original reports, as units are the most accurate designation of quantity of active enzyme administered. For conversion of doses to U/kg and U/m^2, animals were assumed to weigh 0.02, 0.25, 0.4, and 10 kg with body surface areas of 0.007, 0.036, 0.05, and 0.412 m^2 for mouse, rats, guinea pig, and dog, respectively (note: in Study 520, doses were administered on a U/kg basis, so the U/animal values are approximations).
[b] Unless specified otherwise, for repeat-dose toxicity studies, the no observed adverse effect level (NOAEL) or no observed effect level (NOEL) are underlined.

Single-dose local toxicity studies by intrapenile injection or (as submitted during the original MAA) subcutaneous injection into the hindlimb of rats or subcutaneous and intratendon injection into the forelimb of dogs, demonstrated that AA4500-induced adverse effects are localized to the site of injection and the draining lymph node and are qualitatively similar across both species and sex.

Repeat dose toxicity

The repeated dose toxicity of AA4500 has been investigated by a clinically relevant route (intrapenile in dog). Dose levels selected for this study were based on the results of single or acute toxicity studies with local administration (see studies TRL 507 and 510).

In the repeat-dose phase of Study TRL 520, dogs received injections of 0, 140, 430, or 1430 U/animal (0, 14, 43, or 143 U/kg; and 0, 336, 1032, or 3432 U/m^2) into the tunica albuginea 3x weekly every four weeks for a total of three cycles (nine doses). The high dose was lowered to approximately 1050 U/animal (105 U/kg; 2520 U/m^2) for the second and third cycles due to excessive local reactions.

Anti-AA4500 antibodies were detected in all repeat-dose dogs following the last dose on Day 61 and persisted or increased in most dogs 28 days after the last dose. However, no adverse systemic effects were reported and the clinical signs related to AA4500 administration occurred with approximately equal frequency and severity during all dosing weeks in the study.

After single- or repeat-dose intrapenile injections into dogs, clinical signs and gross necropsy observations related to AA4500 treatment were confined to the injection site and consisted of discoloration/bruising of the penis and/or adjacent skin and swelling of the penis. Both findings were seen at all dose levels, with the incidence and persistence of the findings in general reflecting the dose level (although dose responses were not robust or consistently noted across the different injection sites). Corresponding histologic findings consisted of hemorrhage and inflammation (affecting both the adventitial tissue of the penis and the surrounding subcutaneous tissue of the prepuce or inguinal skin), and neovascular proliferation in the penile adventitial tissue. With the exception of subcutaneous hemorrhage and inflammation in the inguinal/preputial skin, all findings were present in the 0 U/dose animals but in general were more severe or extensive in animals receiving AA4500, however, with no clear dose response. Non-collagenous structures (in particular, arteries, nerves and large veins) were unaffected by AA4500 administration although lysis (necrosis) was seen in smaller veins comprised mostly of collagen and minimal smooth muscle. Collagen lysis of the tunica albuginea was detected in some animals after single administration but was not detected in any animals following repeated administration of AA4500. Partial to complete reversal was noted following a 30-day recovery period.

Genotoxicity

No additional studies on genotoxicity were conducted to support the use of AA4500 in treatment of Peyronie's disease. This is considered acceptable. AA4500 was neither mutagenic nor clastogenic in the available studies conducted in vivo or in vitro. Furthermore, according to ICH S6, genotoxicity studies for proteins are usually not necessary.

Carcinogenicity

In accordance with relevant regulatory guidance (ICH S1A and ICH S6), carcinogenicity studies with AA4500 were not conducted. This is acetaple, based on the intermittent and limited clinical dosing regimen, the very limited systemic exposure in animal studies, and minimal and brief or nonquantifiable exposure in humans, and the negative results in genetic toxicity tests in vitro and in vivo. In view of these factors there is little potential for carcinogenicity and no special advice on carcinogenic risk is included in the SmPC.

Reproduction toxicity

No additional reproductive and developmental toxicity studies were conducted in support of the use of AA4500 for the treatment of Peyronie's disease this is considered acceptable.

Toxicokinetic data

As Peyronie's disease is extremely rare in patients less than 18 years of age, use of AA4500 in neonates, infants, and children is extremely unlikely. Therefore, studies in juvenile animals are of no clinical relevance and hence have not been conducted with AA4500.

Local tolerance

An additional non-GLP local tolerance study in Göttingen minipigs was performed:

Species/Strain	Method of Administration	Doses (mg/kg)	Gender and No. Per Group	Noteworthy Findings	Study Number
Minipigs/ Göttingen	Subcutaneous injection	844 U/animal, divided into 12 different injections at concentrations ranging from 26 to 2586 U/mL (dose volumes of 0.05, 0.1 or 0.2 mL)	M&F 3/group	• No deaths, unscheduled euthanasia or evidence of systemic toxicity • Swelling noted at injection sites treated with concentrations ≥259 U/mL. • Dark red discoloration of the subcutaneous tissue noted at necropsy at all dose levels • Histology findings: collagen lysis, hemorrhage and/or acute inflammation at all dose levels, skeletal muscle necrosis (panniculus carnosis) at ≥52 U/mL; sporadic perivascular and intramural edema, neovascularization/fibrosis, vascular necrosis, and/or thrombosis at ≥155 U/mL; sporadic arterial intramural hemorrhage at ≥517 U/mL. • Collagen lysis was dose dependent at <259 U/mL, but was generally proportional to the dose volume injected as opposed to the total dose or formulation concentration at ≥259 U/mL.	WIL-696007

Other toxicity studies

Key Toxicologic Responses in Relation to Human Equivalent Dose (HED) / human clinical exposure

The cited animal studies had already been submitted with the original MAA for AA4500, however, as a new aspect, the current calculation of safety margins is based on the clinical dose of AA4500 used for treatment of peyronie´s disease and/or the clinical exposure to AA4500 determined in peyronie´s disease patients.

As systemic exposure was minimal and brief in clinical trials with AA4500, margins are usually expressed in relation to the HED on a body weight and body surface area basis.

<u>Safety margins in case of potential misapplication</u>

Safety margins based on HED

Systemic toxicity is not anticipated under conditions of clinical use, but for the unlikely event that a complete 0.58 mg dose of AA4500 is misapplied during treatment of Peyronie's disease, systemic toxicity has been evaluated and characterized following IV bolus administration in rats.

Following single or repeated IV dosing in rats, at approximately 50x and 25x the HED on a surface area basis (280x or 140x on a body weight basis), death was observed associated with evidence of hemorrhage into the peritoneal cavity and friable livers (in some cases). The liver was the primary target organ following repeated bolus IV administration. The NOEL for systemic toxicity by the IV route was 500 U/animal and provides an adequate margin of safety to account for inadvertent injection of the whole clinical dose into the systemic circulation (2.5x and 14x the HED surface area and body weight basis). The injection site findings noted after IV dosing were consistent with the rat and dog paw studies and demonstrated recovery following the cessation of treatment.

Table: Estimated Safety Margins for Inadvertent IV Exposure in Humans Based on Rat Data and Based on Human Equivalent Dose

Effect	Rat Dose Level/Exposure[a]			X HED/ Predicted Human Exposure based on[b]	
	U/dose	U/kg	U/m^2	U/kg	U/m^2
Min. Lethal dose	10,000	40,000	280,000	280X	50X
Systemic NOEL	500	2000	14,000	14.0X	2.5X
Systemic LOEL[b]	2240	8960	62,222	62.7X	11.2X

HED=human equivalent dose; NOEL=no observed effect level; LOEL= lowest observed effect level

[a] U/kg and U/m^2 estimated based on 0.25 kg body weight.

[b] HED = human equivalent dose, based on a total human dose of 10,000 U correlating to 143 U/kg and 5565 U/m^2 respectively based on a body weight of 70 kg and surface area of 1.797 m^2.

Safety margins based on human clinical exposure

The safety margins based on human exposure after penile plaque injection of 0.58 mg AA4500 compared to rat exposure were large (13X – 564X).

Table: AUX-I – Mean PK Parameters and Safety Margins

AA4500 Dose (mg)	Cmax (ng/mL)	AUCtlast (ng·h/mL)	X Human Cmax[a]	X Human AUCtlast[a]
Human (penile plaque)				
0.58 – Day1	12.6	3.1[b,c]		
0.58 – Day2	12.2	2.4[b,c]		
Rat (IV) – Day 1				
0.029	164	42.3	13X	14X
0.13	1454	373	115X	120X
0.29	8250	2081	654X	671X

[a] Safety margins (X Human Cmax or X Human AUCtlast) were based on Day 1 values.

[b] Subject 1100-8716 was excluded due to insufficient quantities of samples for bioanalysis

[c] Subjects 1100-8704 and 1100-8722 were excluded for bioanalytical reasons (ELISA interference).

Table: AUX-II – Mean PK parameters and Safety Margins

AA4500 Dose (mg)	Cmax (ng/mL)	AUCtlast (ng·h/mL)	X Human Cmax[a]	X Human AUCtlast[a]
Human (penile plaque)				
0.58 – Day1	15.1	2.2[b]		
0.58 – Day2	16.1	2.3[b]		
Rat (IV) – Day 1				
0.029	613	169	40X	77X
0.13	4532	1241	300X	564X
0.29	11665	4166	772X	1894X

[a] Safety margins (X Human Cmax or X Human AUCtlast) were based on Day 1 values.

[b] Subject 1100-8716 was excluded due to insufficient quantities of samples for bioanalysis

[c] Subjects 1100-8704 and 1100-8722 were excluded for bioanalytical reasons (ELISA interference).

Safety margins in case of local application

The key treatment related findings with AA4500 were consistent with the primary and secondary pharmacology and were localized at the site of injection and qualitatively similar across animal species and sexes. Systemic toxicity was not observed following local administration by any route.

2.2.5. Ecotoxicity/environmental risk assessment

In accordance with the CHMP guidance EMEA/CHMP/SWP/4447/00 "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" proteins are exempted from the requirement of an environmental risk assessment (ERA) because they are unlikely to result in significant risk to the environment. As the active ingredient collagenase clostridium histolyticum is composed of two proteins, an environmental risk assessment is not required.

2.2.6. Discussion on non-clinical aspects

The nonclinical pharmacology, pharmacokinetics and toxicology of Xiapex had been characterized during the original MAA. The present discussion focuses on the additionally submitted nonclinical data in support of the current extension application.

Pharmacology: Clostridium collagenases have been well characterized and extensively studied since they were first isolated and purified. Microscopic assessment of tissues exposed to AA4500 confirms that when clostridial collagenase is injected into collagenous tissues the only structures that are affected are those containing fibrillar collagen; elastic fibers, blood vessels with smooth muscle-containing walls, the urethral mucosa and nerve fibers are unaffected. Evaluation of immunostained tissues that have been treated with commercial manufactured AA4500 shows that AA4500 selectively lyses collagen types I and III in pathological collagen tissues and spares non-fibrillar collagen type IV. Additionally, collagen lysis in these structures is limited to a circumscribed area adjacent to the injection site, with little or no evidence of diffusion to distant structures. In contrast, injection in looser fibrous connective tissue structures (subcutis or dermis in multiple species, canine VAN complex, corpus cavernosum or corpus spongiosum,

Peyronie's plaque) results in somewhat greater diffusion of clostridial collagenase and more widespread collagen lysis but the affected area is still localized to the injection site.

Collectively, the available primary pharmacology data support the view that AA4500 administration into localized deposits of pathological (fibrillar) collagen, like that present in Peyronie's disease, will result in therapeutically meaningful lysis and removal of the collagen.

Pharmacokinetics: Absorption: No systemic toxicity and limited to no quantifiable systemic exposure was observed following repeated local administration of AA4500 by clinically relevant routes of exposure into rats and dogs as documented in the original MAA. Further support for the lack of systemic toxicity and limited systemic exposure following local application was provided by the results of the single/repeat dose intrapenile toxicity study in dogs.

Toxicology: *Local adverse effects*: Adverse effects observed in nonclinical studies after administration by the clinically relevant route of injection in the penis or (original MAA) after administration to other structures (e.g. paw/tendons/subcutaneous) were local in nature, and were reversible or showed evidence of ongoing resolution and healing during the recovery period. No evidence of systemic toxicity was reported. This is consistent with the spectrum of adverse effects observed in clinical studies.

Findings in the repeat-dose studies in rats and dogs were consistent with those reported in the single dose studies. In general, the clinical observations were less severe and resolved more rapidly following repeated administration in dogs. Ongoing healing processes were reported at the end of the 28-day recovery period in both species. Similar findings were reported following intrapenile injection into dogs. Treatment related findings following direct injection into superficial digital flexor tendon of the paw or other dense collagenous structures (tunica albuginea) resulted in less severe/extensive findings and more complete recovery than subcutaneous injection into the rat and dog paw or application into the looser fibrous connective tissue structures (corpus cavernosum urethra, and VAN complex) of the dog penis.

Safety margins in case of local application: No systemic toxicity and limited to no quantifiable systemic exposure was observed following repeated local administration of AA4500 by clinically relevant routes of exposure into rats and dogs (original MAA). Further support for the lack of systemic toxicity and limited systemic exposure was provided by the results of the single/repeat dose intrapenile toxicity study.

Safety margins in case of potential misapplication: Clinically, the worst scenario following misapplication of AA4500 into the local vasculature would be injection of the full clinical dose of AA4500 into the local vein or artery or both surrounding the collagen cord. The misapplication would be expected to trigger similar systemic effects as induced by an IV injection. As documented in the orginal MAA, in repeat-dose IV studies in rats, following misapplication of partial or full clinical dose into the local vasculature, no systemic toxicity is to be expected. At ≥11x HED, the systemic toxicity would likely be related to hepatic findings.

2.2.7. Conclusion on the non-clinical aspects

Collectively, the available primary pharmacology data support the view that AA4500 administration into localized deposits of pathological (fibrillar) collagen, like that present in Peyronie's disease, will result in therapeutically meaningful lysis and removal of the collagen.

AA4500 has limited or no quantifiable systemic exposure with no systemic toxicity following local administration, including intrapenile application in dogs. Local findings were restricted to the site of injection and the draining lymph node, with (almost) complete recovery of the gross findings following the cessation of treatment, with ongoing healing processes at the end of the recovery period.

As documented in the original MAA, following IV bolus administration of the commercial drug product, the primary target organ was the liver and a clear systemic NOEL and adequate safety margins were established to account for inadvertent administration of the whole clinical dose into the systemic circulation.

Anti-AA4500 antibodies were generated in almost all animals after local or IV administration; however, no evidence for antibody mediated adverse effects was observed.

Overall, the results of the non-clinical studies with AA4500 support its proposed use in the treatment of Peyronie's disease.

Furthermore, proteins are exempted from the requirement of an environmental risk assessment (ERA) because they are unlikely to result in significant risk to the environment. Xiapex is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the Union were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

The clinical program for AA4500 in the treatment Peyronie's disease (PD) in adults consists of 11 clinical studies: two Phase 1, six Phase 2, and three Phase 3.

Biospecifics Technologies Corp. (BTC) sponsored the first six studies (open-label pilot study, double-blind pilot study, 1001-PEY, 1025-PEY, 1030-PEY, and 1035-PEY) using study drug produced from an earlier comparable manufacturing processes (ie, early BTC process). Each of these early studies was led by a single investigator.

Auxilium has sponsored five studies using the commercial process

AUX-CC-801	phase IIb
AUX-CC-802	open-label safety and efficacy
AUX-CC-803, AUX-CC-804	two identical pivotal placebo-controlled phase III studies
AUX-CC-805	pharmacokinetic study

In the early BTC studies (using the early BTC process) doses were expressed in 'Units of AA4500 activity'. In the latter studies (using Auxilium's optimized commercial process) doses were expressed in 'mg of protein'. AA4500 produced by Auxilium's optimized process has been shown to be comparable to the AA4500 produced by the early BTC process (ie, AA4500 activity ≈ 17,241 U/mg protein).

Thus, the commercial 0.58 mg dose of AA4500 is equivalent to 10,000 U of AA4500.

Table 1: Overview of the AA4500 Clinical Program for the Treatment of Adults With Peyronie's Disease

Study Country	Number Treated	Design	Dosing Regimen	MAA
Phase 1				
Pilot open-label study (USA)	AA4500: 31	Design: Phase 1 open-label pilot study	Dosing: Single intralesional injections on 3 consecutive days as follows: 1st 6 subjects: AA4500 total dose: 270 - 1595 units Remaining 25 subjects: AA4500 total dose: 1739 – 4850 units Topical ß-aminopropionitrile fumarate was applied as an adjuvant in Subjects 7-13 on Days 7-28 Oral ß-aminopropionitrile fumarate 250 mg QID was administered as an adjuvant in the remaining subjects on Days 7-28	No formal database; results based on publication (Gelbard MK et al, 1985).
Pilot double-blind, randomized, placebo-controlled study with an open-label placebo crossover arm Subjects stratified within treatment group by penile deviation angle: Category 1: <30° Category 2: 30 – 60° Category 3: > 60° (USA)	AA4500: 22 Placebo: 27	Phase 1, double-blind, placebo-controlled pilot study	Double-blind: AA4500: 2000 U in 0.5 mL of NaCl containing 2 mM of CaCL Placebo: 0.5 mL of NaCl containing 2 mM of CaCL Total dose categories: Category 1: 3 aliquots AA4500 total dose: 6000 U Placebo: 1.5 mL Category 2: 5 aliquots AA4500 total dose: 10,000 units Placebo: 2.5 mL Category 3: 7 aliquots AA4500 total dose: 14,000 units Placebo: 3.5 mL Open-label: 23 subjects	No formal database; results based on publication (Gelbard MK et al., 1993).
Phase 2				
1001-PEY (USA)	AA4500: 15 Placebo: 15	Phase 2 double-blind, placebo-controlled study – investigator initiated.	AA4500: 10,200 units (divided into 6 syringes; each containing 1700 units in a volume of 0.5 mL 0.9% NaCl containing 2mM CaCl) Placebo: Six 0.5 mL syringes of 0.9% NaCl containing 2mM CaCl Same treatment repeated 3 months later for a total dose of 20,400 units of AA4500.	No formal database; study specific safety summary will be included in ISS

Study Country	Number Treated	Design	Dosing Regimen	MAA
1025-PEY (USA)	AA4500: 5	Phase 2 open-label, investigator-initiated	Up to 5 single injections of AA4500 10,000 units in a volume of 0.5 mL, each separated by 1 week for a total dose of 50,000 units of AA4500.	No formal database; study specific safety summary will be included in
1030-PEY (USA)	AA4500: 25	Phase 2 open-label, investigator-initiated	Single injections of AA4500 10,000 units in a volume of 0.25mL on 3 separate days within a period of 3 to 10 days. The same treatment was repeated 3 months later at the discretion of the investigator for a total dose of 60,000 units of AA4500.	ISS
1035-PEY (USA)	AA4500: 10	Phase 2 open-label, investigator-initiated	Single injections of AA4500 10,000 units in a volume of 0.25mL every other day, or every 3 days if the subject developed ecchymosis). Subjects could receive up to three doses per treatment cycle. The same treatment cycle could be repeated 2 more times (6 weeks and 3 months after the first injection) at the discretion of the investigator for a total dose of 30,000 units of AA4500.	ISS
AUX-CC-801 (USA)	AA4500: 111 Placebo: 36	Phase 2 double-blind, placebo-controlled	Treatment Cycle: 2 single Intralesional injections of AA4500 0.58 mg or placebo separated by 24-72 hours and followed 24-72 hours later by penile plaque modeling (subjects were randomized in a 1:1 ratio at baseline to receive penile plaque modeling or not to receive penile plaque modeling). Up to 4 treatment cycles each separated by 6 weeks with a total dose of up to 3.48 mg (60,000 units) of AA4500.	ISS
AUX-CC-805[a] (USA)	AA4500: 20	Phase 2, open label, single treatment cycle, pharmacokinetic and safety study	Single Treatment Cycle: Two single intralesional injections of AA4500 0.58 mg separated by 24 hours and followed 24 hours later by penile plaque modeling with a total dose of 1.16 mg (20,000 units) of AA4500.	PK and ISS
Phase 3				
AUX-CC-802 (USA, New Zealand, Europe)	AA4500: 348	Phase 3 open-label study	Treatment Cycle: 2 single intralesional injections of AA4500 0.58 mg separated by 24-72 hours and followed 24-72 hours after the second injection of each treatment cycle by penile plaque modeling. Up to 4 treatment cycles each separated by 6 weeks with a total dose of up to 4.64 mg (80,000 units) of AA4500.	ISS

Study Country	Number Treated	Design	Dosing Regimen	MAA
AUX-CC-803 (USA and Australia)	AA4500: 277 Placebo 140	Phase 3 double-blind, placebo-controlled	Treatment Cycle: 2 single intralesional injections of AA4500 0.58 mg or placebo separated by 24-72 hours and followed 24-72 hours after the second injection of each treatment cycle by penile plaque modeling. Up to 4 treatment cycles each separated by 6 weeks with a total dose of up to 4.64 mg (80,000 units) of AA4500.	ISE and ISS
AUX-CC-804 (USA and Australia)	AA4500: 274 Placebo: 141	Phase 3 double-blind, placebo-controlled	Treatment Cycle: 2 single intralesional injections of AA4500 0.58 mg or placebo separated by 24-72 hours and followed 24-72 hours after the second injection of each treatment cycle by penile plaque modeling. Up to 4 treatment cycles each separated by 6 weeks with a total dose of up to 4.64 mg (80,000 units) of AA4500.	ISE and ISS

a Subjects who complete Study AUX-CC-805 rolled into the Phase 3 open-label study AUX-CC-802 to complete Treatment Cycles 2 through 4 and follow-up

2.3.2. Pharmacokinetics

In subjects with Dupuytren's contracture there were no quantifiable levels of AUX-I and AUX-II after single and concurrent injections of AA4500 into Dupuytren's cords within the hand. The Dupuytren's cord is essentially avascular. In contrast, the site of injection in Peyronie's disease is the Peyronie's plaque, which is contiguous with the tunica albuginea and the highly vascular corpora cavernosa. Therefore, a separate pharmacokinetic study, AUX-CC-805, was performed in subjects with Peyronie's disease.

Absorption

The objectives of study **AUX-CC-805** were to determine if there was systemic exposure following two injections (one treatment cycle) of AA4500 0.58 mg (separated by 24 hours) into the primary penile plaque of men with Peyronie's disease, and to evaluate the safety of AA4500 in these subjects.

- **Methodology**

Subjects were screened for study eligibility within 21 days before the initial injection of study drug. Each subject received a single treatment cycle, which included two single injections of AA4500 0.58 mg administered 24 hours apart and followed by a penile plaque modeling procedure 24 hours after the second injection. Subjects were admitted to the study unit the day before the first injection of AA4500 (Day -1) and remained in the study unit until the PK sample was collected after investigator penile plaque modeling on Day 3. Subjects returned to the study unit on Day 4, Day 8, and Day 29 for follow-up PK and safety assessments. Eligible subjects who completed this study could have received up to three additional treatment cycles (for a total of four treatment cycles) in the Phase 3 open-label study, AUX-CC-802 (ie, AUX-CC-805/ AUX-CC-802 rollover subjects). The data collected for subjects during the AUX-CC-805 screening visit were used as the screening data for any additional treatment cycles these subjects received in Study AUX-CC-802.

- **Number of subjects (planned and analyzed)**

20 subjects were planned; 20 subjects were included in the intent-to-treat (ITT) population, and 19 were included in the PK population.

- **Test product, dose and mode of administration, batch number**

AA4500 0.58 mg injected directly into the penile plaque, after reconstitution with sterile diluent (0.3 mg/mL calcium chloride dihydrate in 0.9% sodium chloride). The volume of injection was 0.25 mL. Lot numbers were C0370 for AA4500 and C0358 for diluent.

- **Duration of treatment**

Subjects received one treatment cycle (two injections of study drug with 24 hours between injections).

- **Criteria for evaluation**

Clostridial type I collagenase (AUX-I) and clostridial type II collagenase (AUX-II) enzyme concentrations, maximum concentration from 0 hour to 24 hour evaluation following each injection (Cmax), elapsed hours to reach Cmax within 24 hours following each injection (Tmax), time of last quantifiable concentration from 0 hour to 24 hour evaluation following each injection (tlast), area under the curve of concentration from 0 to the last time point with a quantifiable concentration within 24 hours following each injection (AUC0-tlast), and area under the curve of concentration from 0 to the last time point with a quantifiable concentration and extrapolated to infinity for each injection (AUC0-infinity).

Safety was evaluated through the monitoring of adverse events (AEs), clinical laboratory evaluation, vital signs, and immunogenicity data.

- **Statistical Methods**

The ITT population was defined as all enrolled subjects who had at least one injection of AA4500. All safety, immunogenicity, and subject baseline characteristics were summarized based on this population. The PK population was defined as all ITT subjects who had 0 to 24-hour blood concentration results for AUX-I and/or AUX-II post an injection of AA4500. The PK parameters were summarized using this population. Subjects unable to receive the second injection at the 24-hour time point were not included in the PK analyses for the second injection.

- **Pharmacokinetics**

Pharmacokinetic parameters (Cmax and AUC0-tlast) were determined by non-compartmental analyses using validated software (SAS, version 9.1.3, Cary, NC). AUC0-infinity values were not evaluated, as only three of 20 subjects' profiles had an acceptable extrapolation that was ≤20% of the total area. AUC0-tlast was based on the linear/log-linear trapezoidal rule. Estimation of PK parameter estimates were derived from the following standardized analysis conventions:

1. The concentration at t=0 time point was set to zero if the measured value was <limit of quantification (LOQ)

2. All post treatment values <LOQ were set to "missing data"

3. If concentrations from a subject were all <LOQ then AUC0-tlast and Cmax were imputed to be 0.000 while Tmax was set to "missing data."

Drug accumulation was assessed by ratios of the geometric means and 95% confidence intervals (CIs) for ratios of means of Cmax and AUC0-tlast on Day 2:Day 1 for the 10 subjects with quantifiable profiles after both the first and second injections.

- **Safety**

All treatment-emergent AEs (TEAEs) were summarized by frequency and relationship to study drug. For each of these parameters, TEAEs were presented overall, by preferred term, and severity. Clinical laboratory data (chemistry and hematology) were summarized with descriptive statistics for actual value and change from baseline to Day 29. The count and percentage of subjects with Sponsor-defined clinically significant laboratory values at anytime during the study were also presented.

Vital signs were summarized with descriptive statistics for actual value and change from baseline. Vital signs taken on the injection day were summarized across the different time points 15 minutes after, 30 minutes after, 45 minutes after, and 60 minutes after). The baseline value was the vital sign measure immediately predose for that injection. The summary was done by for each injection and time point. Vital signs were also summarized on Day 3, Day 4, Day 8, and Day 29. The count and percentage of subjects with Sponsor-defined clinically significant vital sign values at any time during the study were also presented.

Titer values for antibody response to AUX-I and AUX-II were summarized with descriptive statistics after log-transformation at baseline (screening) and Day 29. Missing values were not imputed.

Neutralizing antibody responses (negative/positive) to AUX-I and AUX-II were summarized with descriptive statistics at baseline (screening) and Day 29.

- **Analytical methods**

The assay methods are summarized in Table 1.

Table 1: Pharmacokinetic Assay Format for AUX-I and AUX-II in Human Plasma

	AUX-I	**AUX-II**
Assay format	ELISA	
Capture antibody	Rabbit affinity-purified anti-AUX-I polyclonal	Rabbit affinity-purified anti-AUX-II polyclonal
Detection antibody	Biotinylated version of capture antibody	
Test matrix	Human plasma (lithium-heparin)	
Dilution of test matrix	1 in 50	1 in 50

Quantitation range	0.1 – 0.8 ng/ml	0.5 – 10 ng/ml
LOQ in undiluted matrix	5 ng/ml	25 ng/ml
Validation study number	AA41767CH-EB-03	AA41768CH-EB-01
Validation study number for long-term stability	AA41767CH-EB-04	AA41768CH-EB-02

- **Results**

Pharmacokinetics: Subjects were to have plasma samples analyzed for AUX-I and AUX-II at predetermined time points before and after Injection 1 and Injection 2; thus, for each subject, two separate concentration-time profiles, one for each analyte (ie, AUX-I and AUX-II), were obtained. Of the 20 subjects enrolled in this study, one subject was excluded from all concentration-time profiles and PK analyses due to insufficient quantities of plasma for bioanalysis. The 19 remaining subjects had plasma samples analyzed at all planned time points after Injection 1 and Injection 2.

Of the 38 AUX-I profiles, 18% (7/38) had no quantifiable plasma concentrations at any time point through 24 hours post injection. Of the 38 AUX-II profiles, 60% (23/38) had no quantifiable plasma concentrations at any time point through 24 hours post injection.

Two subjects had pre-dose and post-dose plasma values for AUX-I at ≥LOQ at the majority of the collection times through Day 29, which was consistent with possible interference in the AUX-I ELISA. Therefore, the AUX-I concentration-time profiles for these two subjects were considered 'not evaluable' and were not included in the AUX-I PK analyses.

Mean AUX-I and AUX-II PK parameter estimates on Day 1 and Day 2 are shown in Table 2.

Table 2: Mean AUX-I and AUX-II Pharmacokinetic Parameters After Injection 1 and 2

	Day 1: Injection 1		Day 2: Injection 2	
Parameter (units)	**AUX-I**	**AUX-II**	**AUX-I**	**AUX-II**
C_{max} (ng/mL)[a]				
N	17	19	17	19
Mean (SD)	12.6 (8.3)	15.1 (19.2)	12.2 (9.1)	16.1 (23.2)
$AUC_{0\text{-}tlast}$ (ng*h/mL)[a]				
N	17	19	17	19
Mean (SD)	3.1 (2.1)	2.2 (3.9)	2.4 (2.3)	2.3 (4.1)
T_{max} (h)				
N	14	8	13	7
Mean (SD)	0.15 (0.09)	0.16 (0.08)	0.11 (0.07)	0.12 (0.09)

Data source: Tables 14.2.3.1 and 14.2.3.2

[a] Cmax and AUC were imputed as 0.00 if all concentrations were <LOQ for all time points following an injection.

NOTE: Subject 1100-8716 was excluded from all PK analyses due to insufficient quantities of plasma for bioanalysis. Subjects 1100-8704 and 1100-8722 were excluded from AUX-I for bioanalytical reasons (ELISA interference).

For PK evaluable subjects with quantifiable plasma levels of AUX-I and AUX-II, concentrations were low and transient (ie, detected only through the 0.5-hour post-injection time point) on both Day 1 and Day 2. The maximum individual subject concentrations were 28.2 ng/mL for AUX-I and 70.8 ng/mL for AUX-II. In addition, no subject had quantifiable plasma levels 15 minutes after modeling of the plaque on Day 3, which suggests that manual modeling of the penis performed 24 hours after the Day 2 injection does not result in release of AA4500 from the injection site.

The 95% CIs for the ratios of the geometric means for Cmax and AUC0-tlast on Day2:Day 1 each contained 1.00, indicating that the Cmax and AUC0-tlast on Day 2 were not significantly different from that observed on Day 1. These findings confirm that there is no evidence of accumulation of AA4500 in plasma following two sequential injections of AA4500 administered 24 hours apart.

Safety: The most common (≥20.0% of subjects) TEAEs were penile haemorrhage (penile ecchymosis) (95.0%), injection site pain (75.0%), procedural pain (45.0%), penile swelling (30.0%), painful erection (20.0%), and penile pain (20.0%). The majority of subjects had TEAEs or treatment-related

TEAEs that were at most mild or moderate in severity, as assessed by the investigator. All subjects had at least one TEAE that was related to study drug, as assessed by the investigator.

No subject died, experienced a serious AE, prematurely discontinued due to an AE, experienced a spontaneous penile event, corporal rupture, erectile dysfunction, genital disorder male, or sexual dysfunction during the study.

No clinically concerning trends were observed with regard to hematology and chemistry laboratory parameter results or vital sign results.

The immunogenicity profile was as expected, with 50% and 30% of the subjects having positive antibodies to AUX-I and/or AUX-II, respectively, at Day 29. Antibodies titer levels did not appear to be predictive of neutralizing antibody status. No systemic immunologic events were reported. There was no evidence of systemic hypersensitivity or anaphylaxis in any subject immediately after dosing or at any time during the study.

Distribution

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

Elimination

- **Excretion**

Excretion has not been formally examined after treatment with AA4500, and because there is only minimal and transient exposure after local administration directly into Peyronie's plaques and the class nature of AA4500 (a protein), no such studies have been performed with AA4500.

- **Metabolism**

AA4500 is not a substrate for cytochrome P450 or other drug metabolizing enzyme pathways, and thus no active metabolites are expected. Therefore, no metabolism studies have been performed with AA4500.

- **Pharmacokinetics of metabolites**

AA4500 is a protein that is active in its native form, and does not require proteolytic cleavage for activity. Active metabolites are not anticipated for AA4500 by its suggested elimination pathway. Therefore, no work has been done on identification of active metabolites.

Dose proportionality and time dependencies

Because pharmacodynamic activity cannot be evaluated directly or by surrogate biomarkers in subjects and is not a function of systemic exposure, dose and time dependencies have only been evaluated in in vitro model systems.

Special populations

The Phase 3 clinical studies in Peyronie's disease conducted by the MAH have evaluated the safety and efficacy of AA4500 in a subject population that is representative (ie, in age, gender, and race) of the population targeted for commercialization. As systemic exposure to AA4500 was minimal and transient after local administration directly into Peyronie's plaques, no studies are deemed necessary to evaluate

the effects of AA4500 in subjects with impaired hepatic or renal function. In addition, review of the clinical safety database did not show clinically meaningful changes in hepatic or renal function parameters.

Pharmacokinetic interaction studies

Pharmacokinetic drug interactions have not been evaluated. AA4500 is not a substrate for cytochrome P450 or other drug metabolizing enzyme pathways; therefore P450 related metabolic drug interaction is not expected.

Exposure relevant for safety evaluation

Safety pharmacology studies have not been conducted with AA4500. This is in accordance with ICH guidance S7A Safety Pharmacology Studies for Human Pharmaceuticals, 2000) indicating that that the conduct of safety pharmacology studies are not required for components with low or absent systemic exposure or where distribution to other organs or tissues is limited.

2.3.3. Pharmacodynamics

Collagenases are proteinases that hydrolyze collagen under physiological conditions. Xiapex is comprised of a mixture of Class I (AUX-I) and Class II (AUX-II) clostridial collagenases in a defined mass ratio. The two classes of collagenases have similar but complementary substrate specificity. Both collagenases effectively cleave interstitial collagen but at different sites on the molecule; additionally, they prefer different conformations (triple helical versus denatured or cleaved). These differences account for the ability of the two classes of enzymes to digest collagen in a complementary manner. Class I collagenases (α, β, γ, and η) are the products of the *colG* gene, they initiate collagen hydrolysis near the amino and carboxy termini of triple helical domains, and generate large proteolytic fragments. In contrast, the Class II collagenases (δ, ε, and ζ,) are products of *colH* gene, their initial cleavage sites are located within the interior of the collagen molecule, and generate smaller collagen fragments. Both classes of collagenases readily hydrolyze gelatin (denatured collagen) and small collagen peptides, whereas Class II has higher affinity for small collagen fragments. Class I cleaves insoluble triple helical collagen with higher affinity than Class II collagenase. Together, these collagenases work to provide broad hydrolytic activity towards collagen.

Injection of Xiapex into a Peyronie's plaque, which is comprised mostly of collagen, may result in enzymatic disruption of the plaque. Following this disruption of the plaque, penile curvature deformity and patient bother caused by Peyronie's disease are reduced.

Primary and secondary pharmacology

The pharmacologic activity of AA4500 involves selective lysis of collagen at the site of injection (ie, the Peyronie's plaque). Because its therapeutic activity is localized and does not require or result in quantifiable systemic exposure, the primary pharmacodynamic activity of AA4500 cannot be evaluated in subjects and, therefore, such studies have not been undertaken. Instead, evidence for primary pharmacodynamic activity of clinical relevance has been obtained from in vitro studies using excised Dupuytren's cords and Peyronie's plaques and in vivo studies of subcutaneous administration in minipigs. No systemic secondary pharmacodynamic effects have been evaluated or noted in clinical or animal studies. AA4500 is intended for local use, and no quantifiable systemic circulation has been shown

following local administration via the intended route of administration. Therefore, plasma concentration-effect relationships cannot be established.

In vitro inactivation of clostridial collagenase by some antibiotics has been described in the literature. Tetracycline derivatives have been shown to inhibit matrix metalloproteinase-mediated collagen degradation at pharmacologically relevant concentrations and because of a potential confounding influence on efficacy evaluation, subjects who had received doxycycline or another tetracycline derivative during the 14 days before the first dose of study drug were excluded from participation in the clinical studies. Appropriate statement is included in the SmPC.

2.3.4. PK/PD modelling

N/A

2.3.5. Discussion on clinical pharmacology

A pharmacokinetic study has been conducted in the target population. Data from study AUX-CC-805 indicate that there is only low systemic exposure following two injections of AA4500 0.58 mg (separated by 24 hours) into the primary penile plaque of men with Peyronie's disease. Of the 38 AUX-I profiles, 81.6% (31/38) had quantifiable plasma concentrations, of the 38 AUX-II profiles, 39.5% (15/38) had quantifiable plasma concentrations. The maximum individual subject concentrations were 28.2 ng/mL for AUX-I and 70.8 ng/mL for AUX-II. After 30minutes all plasma levels were below the limits of quantification. There was no evidence of accumulation. Further, no patients had quantifiable plasma levels 15 minutes after modelling of the penis performed 24 hours after the Day 2 injection suggesting that manual modeling does not result in release of AA4500 from the injection site.

Because AA4500 is not intended for systemic use and systemic exposure was either non-quantifiable or limited only at the first few hours following the initial dose via clinically relevant routes of administration, there are no systemic primary or secondary pharmacodynamic actions of relevance and no safety pharmacology concerns.

Tetracycline derivatives have been shown to inhibit matrix metalloproteinase-mediated collagen degradation at pharmacologically relevant concentrations. Whilst there is no clinical evidence of an interaction use of Xiapex in patients who have received tetracycline antibiotics (e.g., doxycycline) within 14 days prior to receiving an injection of Xiapex is not recommended. This is appropriately reflected in 4.5 of the SmPC.

2.3.6. Conclusions on clinical pharmacology

Due to the route of administration (local injection) and non-quantifiable systemic bioavailability significant interactions are unlikely. The application is considered approvable from a clinical pharmacology perspective.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

Early Clinical Phase 1 and Phase 2 Studies

Two hundred ninety-nine subjects with Peyronie's disease participated in the early clinical studies of AA4500, which were conducted by BTC (open-label pilot, double-blind pilot, PEY-1001, PEY-1025, PEY-1030 and PEY-1035). Of these, 66 subjects received at least one intralesional injection of AA4500 10,000 U (equivalent to 0.58 mg) into the plaque of the penis. Each of these studies was led by individual clinical investigators seeking to build on the work previously conducted, and each had a different study end point, different methods of evaluation, and different study procedures. The total dose of AA4500 administered in these early studies ranged from 1410 U to 90,000 U.

Efficacy findings from these early studies suggested that the treatment regime utilized in the Phase 2 study PEY-1035 may be effective in the treatment of Peyronie's disease. This treatment regimen consisted of:

- Single injections of AA4500 10,000 U administered into the penile plaque every 2nd or 3rd day of the treatment cycle (for a total of 3 injections) and followed by penile plaque modeling to facilitate disruption of the plaque. This regimen had the option for re-treatment every 6 weeks and 12 weeks, for a total of up to three treatment cycles (total dose: up to 90,000 U).

In study AUX-CC-801 a similar treatment regimen (ie, 2 injections/week for a maximum of three treatment cycles [total dose: up to 3.48 mg or equivalent to 60,000 U]) was tested along with the effect of penile plaque modeling versus no penile plaque modeling on the efficacy and safety of Xiapex in treatment of Peyronie's disease.

AUX-CC-801
A Phase 2b, Double-Blind, Randomized, Placebo-Controlled Study of the Safety and Effectiveness of AA4500 Administered Two Times a Week for Up to Three Treatment Cycles (2 x 3) in Subjects With Peyronie's Disease

Investigators: Multicenter / 12 sites in the United States

Studied period (years): 36 weeks

Date first subject enrolled: 19 August 2008

Data last subject completed: 16 October 2009

Objectives:

The objectives of this study were to:

- assess the treatment sensitivity of the Peyronie's Patient Reported Outcome (PRO) Questionnaire (hereafter referred to as 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.

One hundred forty-seven (n=147) eligible men (111 AA4500 and 36 placebo) were enrolled in the study. Before dosing, subjects were stratified by degree of penile curvature (ie, 30º to 60º or >60º) and then randomized into four treatment groups to receive in a 3:1 ratio either AA4500 0.58 mg or placebo, and in a 1:1 ratio to receive either penile plaque modeling or no penile plaque modeling, as shown in the Table below.

Table 33: Study Drug Assignment in AUX-CC-801

Study Drug	Injection Volume	Treatment Cycle
Penile Plaque Modeling		
AA4500 0.58 mg or placebo	0.25 mL injection volume	• 2 injections separated by 24 to 72 hours, followed by penile plaque modeling 24 to 72 hours after the final injection of each cycle. • Up to 3 treatment cycles each separated by 6 weeks.
No Penile Plaque Modeling		
AA4500 0.58 mg or placebo	0.25 mL injection volume	• 2 injections separated by 24 to 72 hours. • Up to 3 treatment cycles each separated by 6 weeks.

Penile plaque modelling

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 final injection of the treatment cycle, and after penile anesthesia had been administered.

Each injection of AA4500 into the plaque is intended to enzymatically weaken/soften the collagen, which is present in the plaque. After injection of AA4500 in tissue culture explants from Peyronie's plaque, the majority of the biochemically detectable collagen digestion occurred within the first 24 hours in culture. This time point also correlated with significant structural disruption of the collagen fibers observed histologically (Gelbard et al, 1982; RU-001). Therefore, in Study AUX-CC-801, gentle to moderate modeling (stretching or elongating) of the plaque 24 to 72 hours after the second injection of the treatment cycle was included to potentially allow for additional mechanical disruption of the plaque at a time at which the collagen fibers were expected to be weakest.

If the subject's penile curvature had been 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.

Following the maximum three treatment cycles, each subject was followed for additional safety and efficacy assessments at Weeks 18, 24, and 36. Subjects who were randomized to placebo in this study had the opportunity to receive AA4500 in a subsequent protocol.

Diagnosis and main criteria for inclusion

Healthy heterosexual male subjects ≥18 years of age with a diagnosis of Peyronie's disease for at least six months before the first dose of study drug and a penile curvature of at least 30° in the dorsal, lateral, or dorsal/lateral plane were eligible.

Test product, method of administration

AA4500 0.58 mg or placebo injected directly into the penile plaque, after reconstitution with sterile diluent (0.9% NaCl containing 2 mM CaCl2). The volume of injection was 0.25 mL.

Duration of treatment

Subjects received up to three treatment cycles; each cycle was separated by a period of six weeks. During each treatment cycle, subjects received two injections of study drug, with at least 24 hours, but not more than 72 hours, between injections.

Criteria for evaluation

Efficacy
The following parameters were measured in order to establish clinical effectiveness of AA4500 0.58 mg:

- change/percentage change from baseline in penile curvature
- change from baseline total score for each PDQ parameter (Intercourse Discomfort, Intercourse Constraint, Penile Pain, and Peyronie's disease Symptom Bother)
- Change from baseline total score of the International Index of Erectile Function IIEF Questionnaire for each of five domains (erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction)
- change from baseline in penile length, plaque length, plaque width, and plaque area; Peyronie's symptomatology; Peyronie's disease Global Assessment; and the relationship between penile curvature measurements and PDQ response.

Safety

Safety was evaluated through the monitoring of adverse events (AEs), clinical laboratory evaluation, vital signs, immunogenicity, and duplex Doppler ultrasound data.

Efficacy analyses (except for total score of PDQ responses by scale, which were based on the PDQ population) were based on the modified intent-to-treat (mITT) population, defined as all intent-to-treat (ITT) subjects who had at least one penile curvature measurement post-first injection of the study drug.

The ITT population was defined as all randomized subjects who had at least one injection of study drug.

Statistical Methods

Penile curvature, change from baseline, and percent change from baseline in penile curvature were summarized with descriptive statistics at each visit window. Comparison between treatment groups was based on an analysis of variance (ANOVA) with factors for drug (placebo or AA4500 0.58 mg) and modeling (yes/no) and drug-by-modeling interaction. The primary analysis was at Week 36.

Total scores and change from baseline total scores for each of the four scales of the PDQ were analyzed 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 (placebo or AA4500 0.58 mg) and modeling (yes/no) and drug-by-modeling interaction. The primary analysis was at Week 36.

Peyronie's Disease Questionnaire (PDQ)

The PDQ is a disease-specific 15-item, self-administered, paper-and-pencil instrument designed and validated by Auxilium to measure the psychosexual consequences of PD. The PDQ assesses the impact of PD in the following three domains:

- Peyronie's Psychological and Physical Symptoms (6 items)
- Penile Pain (3 items)
- Peyronie's Symptom Bother (6 items).

Subjects completed the items assessing the Peyronie's Psychological and Physical Symptoms based on the last time they had vaginal intercourse (within the last 3 months). A 5-point Likert-type response scale measured the severity of each symptom (none, mild, moderate, severe, very severe). Subjects completed the items assessing Penile Pain based on the last 24 hours or their most recent experience (erection or vaginal intercourse). An 11-point numeric rating scale was used to assess the extent of subjects' pain. Subjects completed the items assessing Peyronie's Symptom Bother based on their most recent/current experience. A 5-point Likert-type response scale (not at all bothered, a little bit bothered, moderately bothered, very bothered, extremely bothered) measured the amount of bother with each item.

Results

Disposition of Subjects

A total of 147 subjects were randomized in the study; 74 subjects were randomized to the modeling group (54 AA4500, 20 placebo) and 73 subjects were randomized to the group without modeling (57 AA4500, 16 placebo). Overall, the most common reason for premature discontinuation from the study was withdrawal of consent (6 subjects).

Demographic and Other Baseline Characteristics

No statistically significant differences were observed among treatment groups (AA4500 with and without modeling, placebo with and without modeling) for any demographic or baseline characteristic. The majority (95.2%) of subjects were white and between 45 and 64 years of age (80.3%). The median age of subjects overall was 58.0 years.

The majority of subjects had not had trauma to the erect penis (77.6%) or penile pain (54.4%). Erectile dysfunction was reported by 44.2% of all subjects. Median duration of Peyronie's disease was shortest in the placebo/without modeling group (1.200 years) and longest in the AA4500/modeling (2.250 years) and placebo/modeling (2.000) groups.

At screening, the majority of subjects had mild or moderate plaque palpability and no pain resp. pain on erection.

No statistically significant differences among treatment groups (AA4500 with and without modeling, placebo with and without modeling) were observed for penile measurements (curvature, penile length, and flaccid measurements of plaque length, width, and area) at screening. Baseline severity of penile curvature was low (i.e. ≤60°) for the majority (70.1%) of subjects.

Table 19: Peyronie's Disease History (ITT Population)

Parameter	With Modeling (N=74)		Without Modeling (N=73)	
	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)

Data source: Table 14.1.3

Overall results

Penile curvature

Subjects who received AA4500 demonstrated a mean reduction (improvement) of 29.7% in penile curvature from baseline to Week 36 (LOCF) (54.4° to 38.2°) compared with an 11.0% mean improvement in curvature seen in placebo subjects (50.6° to 45.1°) (p=0.001) (Table below).

Table 21: Mean Change and Mean Percent Change From Baseline in Penile Curvature at Week 36 (LOCF) (mITT Population)

	Study Drug	
	AA4500 (N=109)	Placebo (N=36)
Screening (baseline) value		
Mean (SD)	54.4 (15.06)	50.6 (15.06)
Min, Max	30, 90	30, 90
Week 36 value (LOCF)		
Mean (SD)	38.2 (17.09)	45.1 (18.93)
Min, Max	5, 85	5, 85
Change from baseline		
Mean (SD)	-16.3 (14.65)[a]	-5.4 (13.77)
Min, Max	-60, 40	-30, 40
% change from baseline		
Mean (SD)	-29.7 (27.16)[b]	-11.0 (30.87)
Min, Max	-92, 100	-86, 89

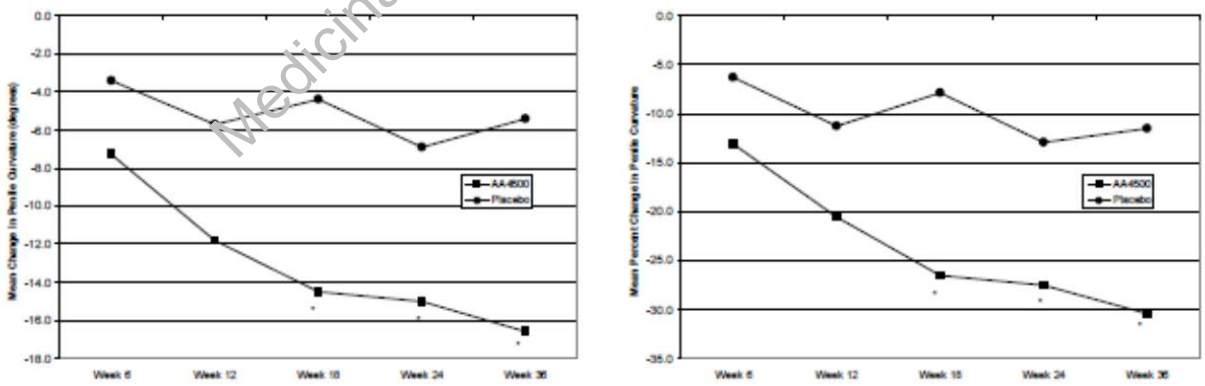
Data source: Table 14.2.2.1.1

[a] Statistically significant difference vs. placebo (p<0.001) (overall drug effect; Table 14.2.2.1).

[b] Statistically significant difference vs. placebo (p=0.001) (overall drug effect; Table 14.2.2.1).

The reduction in penile curvature in AA4500-treated subjects was statistically significantly greater than in placebo subjects at Weeks 18, 24, and 36 (no statistical testing was performed at earlier timepoints) (Figure below). Reduction in AA4500-treated subjects was observed after the first treatment cycle (Week 6), with continued reduction observed through Week 36.

Figure 4: Mean Change and Mean Percent Change From Baseline in Penile Curvature Over Time (mITT Population)



Data source: Table 14.2.2.1.1

*Statistically significant difference vs. placebo for mean change (p≤0.007) and mean percent change (p≤0.016) (Table 14.2.2.1).

Results With/Without Modeling

Among subjects who received modeling, AA4500-treated subjects demonstrated a mean reduction (improvement) of 32.4% in penile curvature from baseline to Week 36 (LOCF) (54.7° to 37.2°) compared with a 2.5% mean worsening in curvature for placebo subjects (51.9° to 52.5°) (p<0.001).

Among subjects who did not receive modeling, AA4500-treated subjects experienced a 27.1% mean improvement in penile curvature from baseline to Week 36 (LOCF) (54.1° to 39.1°), which was not statistically significantly different from the 27.9% mean improvement observed in placebo subjects (48.9° to 35.9°); (p=0.913) (Table below).

Table 22: Mean Change and Mean Percent Change From Baseline in Penile Curvature at Week 36 (LOCF) With and Without Modeling (mITT Population)

	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

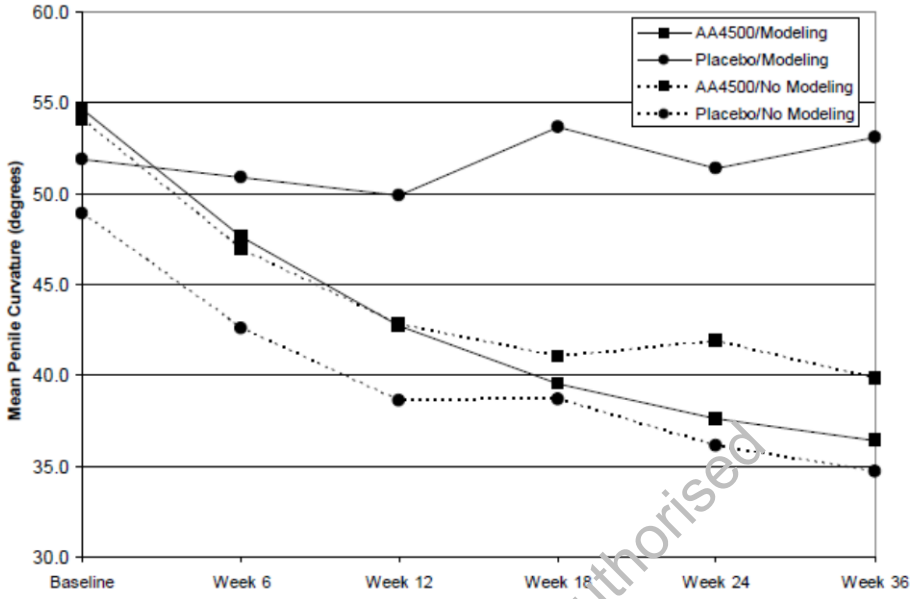
[a] Drug effect p-value with/without modeling, calculated from factorial ANOVA analysis.

[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.

The drug-by-modeling interaction was statistically significant for mean change and mean percent change from baseline to Week 36 (LOCF) in penile curvature (p≤0.004). These significant interactions indicate a statistically significant difference between the treatment effect (AA4500 versus placebo) observed in the modeling group versus the treatment effect observed in the group without modeling.

Figure 7: Mean Penile Curvature Over Time, With/Without Modeling (mITT Population)



Data source: Table 14.2.2.1

The improvement in the placebo subjects is likely due to the fact that five subjects in the placebo/without modeling had an improvement (reduction) in penile curvature of more than 40%. The duration of Peyronie's disease for all five of these subjects was ≤1.3 years at screening.

Table 23: Placebo/Without Modeling Subjects With Reduction in Penile Curvature of >40%

Subject Number	Age	Years Since Diagnosis of Peyronie's Disease	Screening Penile Curvature	Final Penile Curvature/Week	Reduction/ % Reduction in Penile Curvature
1054-1657	56	0.9	45	20/Week 36	25°/56%
1054-1660	57	0.9	60	35/Week 36	25°/42%
1064-1051	61	1.3	33	10/Week 36	23°/70%
1100-1118	61	1.7	80	5/Week 36	30°/86%
1185-1011	59	0.7	41	18/Week 36	23°/56%

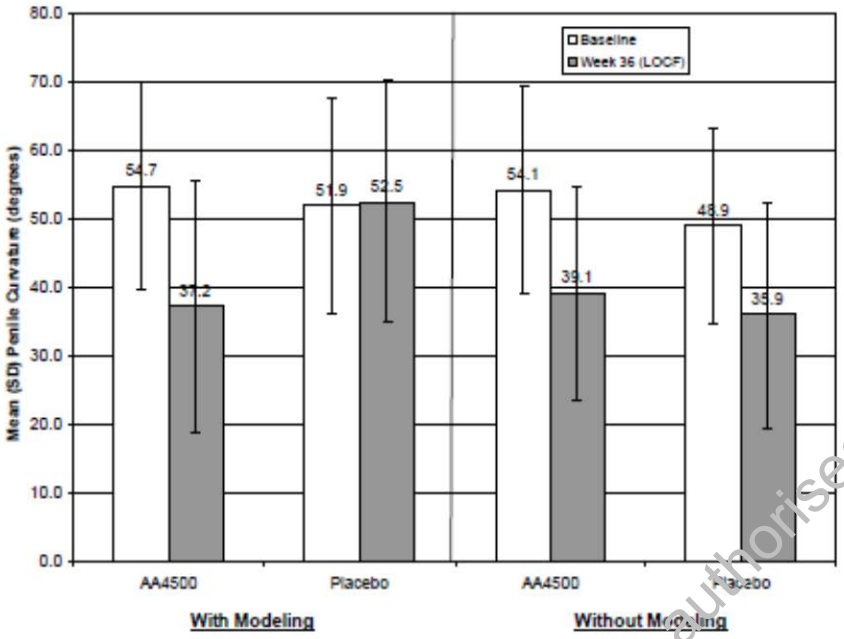
Data source: Appendix 16.2, Listings 16.2.4 and 16.2.6.1

Among the 16 subjects in the placebo no-modeling group, 63% had Peyronie's disease for ≤ 1.5 years compared with only 45% of the 55 subjects in the AA4500 no-modeling group.

The spontaneous remissions in the five placebo subjects support the variable nature of the acute phase of Peyronie's disease, which has been described as typically lasting from 6 to 12 months. Most surgeons will avoid surgical correction of penile curvature during the acute phase due to the variable nature of the disease (Hellstrom and Bivalacqua, 2000) and the possibility of spontaneous remission. This variability likely explains the placebo response demonstrated in this small number of subjects. In addition, due to the small sample sizes in the placebo groups (ie, 20 with modeling; 16 no-modeling) and the 3:1 randomization, this impact was greater than expected.

Mean penile curvature at baseline and Week 36 (LOCF) is shown graphically in the Figure below.

Mean Penile Curvature at Baseline and Week 36 (LOCF), With/Without Modeling (mITT Population)



Peyronie's disease Questionnaire (PDQ) results

Mean improvement (reduction) from baseline to Week 36 (LOCF) in the Peyronie's disease Symptom Bother domain of the PDQ was statistically significantly greater in the AA4500 group than in the placebo group (p=0.046) (Table below). No statistically significant differences between AA4500 and placebo were observed for the scales of Intercourse Discomfort, Intercourse Constraint, or Penile Pain.

Mean Change From Baseline in PDQ Total Score for Each Scale at Week 36 (LOCF) - PDQ Population Overall in AUX-CC-801 (PDQ Version 3)

	AA4500 (N=100)	Placebo (N=34)	p-value[a]
Intercourse Discomfort[b]			
Baseline			
Mean (SD)	5.7 (3.71)	6.2 (3.78)	
Week 36			
Mean (SD) (LOCF)	4.9 (3.39)	5.8 (4.15)	
Mean (SD) change from baseline	-0.8 (3.46)	-0.4 (4.27)	NS
Intercourse Constraint[c]			
Baseline			
Mean (SD)	7.9 (2.82)	8.5 (2.72)	
Week 36			
Mean (SD) (LOCF)	6.4 (3.29)	7.8 (3.33)	
Mean (SD) change from baseline	-1.5 (3.31)	-0.7 (3.65)	NS
Penile Pain[d]			
Baseline			
Mean (SD)	5.8 (6.56)	4.5 (5.19)	
Week 36			
Mean (SD) (LOCF)	3.5 (4.51)	4.0 (5.32)	
Mean (SD) change from baseline	-2.4 (6.32)	-0.5 (5.30)	NS
Peyronie's Disease Bother[e]			
Baseline	100	34	
Mean (SD)	8.1 (4.16)	8.1 (4.21)	
Week 36			
Mean (SD) (LOCF)	5.5 (4.15)	7.3 (5.12)	
Mean (SD) change from baseline	-2.6 (4.65)	-0.8 (3.63)	p=0.046

LOCF=Last observation carried forward; NS=not statistically significant

[a] AA4500 versus placebo

[b] Questions 1, 2, 3, 5, 9; Scale 0 (disagree strongly) to 3 (agree strongly); Maximum score=15

[c] Questions 4, 6, 7, 8; Scale 0 (disagree strongly) to 3 (agree strongly); Maximum score=12

[d] Questions 10, 11, 12, 13; Scale 0 (no pain/discomfort) to 10 (extreme pain/discomfort); Maximum score=40

[e] Questions 14, 15, 16, 18, 20; Scale 0 (not at all bothered) to 4 (extremely bothered); Maximum score=20

Mean Change From Baseline in PDQ Total Score for Each Scale at Week 36 (LOCF) PDQ Population With Modeling in AUX-CC-801 (PDQ Version 3)

	AA4500 (N=50)	Placebo (N=18)	p-value[a]
Intercourse Discomfort[b]			
Baseline			
Mean (SD)	5.6 (3.81)	6.3 (3.82)	
Week 36			
Mean (SD) (LOCF)	4.6 (3.23)	6.1 (4.39)	
Mean (SD) change from baseline	-1.0 (3.84)	-0.2 (3.13)	NS
Intercourse Constraint[c]			
Baseline	7.7 (3.23)	9.1 (2.18)	
Mean (SD)			
Week 36			
Mean (SD) (LOCF)	6.4 (3.49)	8.0 (3.76)	
Mean (SD) change from baseline	-1.3 (3.82)	-1.1 (3.06)	NS
Penile Pain[d]			
Baseline			
Mean (SD)	6.2 (7.05)	3.7 (5.44)	
Week 36			
Mean (SD) (LOCF)	2.1 (2.85)	2.8 (4.61)	
Mean (SD) change from baseline	-4.1 (6.83)	-1.0 (3.75)	NS
Peyronie's Disease Symptom Bother[e]			
Baseline			
Mean (SD)	8.6 (4.43)	7.6 (4.62)	
Week 36			
Mean (SD) (LOCF)	4.9 (4.22)	7.5 (4.92)	
Mean (SD) change from baseline	-3.6 (5.03)	-0.1 (2.38)	p=0.004

LOCF=Last observation carried forward; NS=not statistically significant

[a] AA4500 versus placebo

[b] Questions 1, 2, 3, 5, 9; Scale 0 (disagree strongly) to 3 (agree strongly); Maximum score=15

[c] Questions 4, 6, 7, 8; Scale 0 (disagree strongly) to 3 (agree strongly); Maximum score=12

[d] Questions 10, 11, 12, 13; Scale 0 (no pain/discomfort) to 10 (extreme pain/discomfort); Maximum score=40

[e] Questions 14, 15, 16, 18, 20; Scale 0 (not at all bothered) to 4 (extremely bothered); Maximum score=20

As already shown for penile curvature reduction, there was no statistically significant difference between AA4500 and placebo in the change from baseline in the Peyronie's disease bother domain in the no-modeling group.

Table 35: Mean Change From Baseline in PDQ Peyronie's Disease Bother at Week 36 (LOCF) - PDQ Population, No-Modeling Group in AUX-CC-801

	AA4500 (N=50)	Placebo (N=16)
Peyronie's Disease Symptom Bother[a]		
Screening (baseline) value		
Mean (SD)	7.5 (3.86)	8.7 (3.77)
Week 36 value (LOCF)		
Mean (SD)	6.1 (4.05)	7.2 (5.49)
Mean (SD) change from baseline	-1.5 (3.97)	-1.5 (4.65)
p-value[b]	0.991	

Data source: AUX-CC-801 CSR Table 14.2.3.4

LOCF=last observation carried forward; SD=standard deviation

[a] Questions 14, 15, 16, 18, 20; Scale 0 (not at all bothered) to 4 (extremely bothered); Maximum score=20

[b] AA4500 versus placebo

Rationales for Dosing and Penile Plaque Modelling in the Phase 3 Program

Dosing Cycles

The dosing regimen for the Phase 3 program consisted of two injections of AA4500 0.58 mg with an interval of approximately 24 hours but not more than 72 hours between injections. This regimen was shown to be safe in the Phase 2b study (AUX-CC-801). Treatment cycles in the AUX-CC-801 were six weeks (~42 days) apart for a total of three treatment cycles. Based on the safety results from this study, which showed that most adverse effects of AA4500 were local and resolved before the next injection cycle (see safety section below), the proposed interval between treatment cycles in the Phase 3 program remained at 42 days (± 5 days) and a fourth treatment cycle was added to further support and improve the efficacy results AUX-CC-801 study.

The addition of the fourth treatment cycle is supported by the efficacy and safety findings from the early Phase 2 study, PEY-1035, in which men with Peyronie's disease received up to 9 injections of AA4500 (3 injections/week for up to 3 treatment cycles; total dose up to 90,000 U).

Penile Plaque Modeling

Each injection of AA4500 into the plaque is intended to enzymatically weaken/soften the collagen, which is present in the plaque. After injection of AA4500 in tissue culture explants from Peyronie's plaque, the majority of the biochemically detectable collagen digestion occurred within the first 24 hours in culture. This time point also correlated with significant structural disruption of the collagen fibers observed histologically (Gelbard et al, 1982). Therefore, in the Study AUX-CC-801, gentle to moderate modeling (stretching or elongating) of the plaque 24 to 72 hours after the second injection of the treatment cycle was included to potentially allow for additional mechanical disruption of the plaque at a time at which the collagen fibers were expected to be weakest.

In analyses of the treatment effect specifically examining the effect of AA4500 with or without penile plaque modeling, a statistically significant effect of AA4500 was observed only among subjects who received modeling. Men who received AA4500 and modeling had significant improvement in penile curvature (32.4% improvement versus a 2.5% worsening; $p<0.001$) and a significant improvement in the Peyronie's disease bother domain score (-3.6 versus -0.1; $p=0.004$) of the PDQ. There was no statistically significant difference between AA4500 and placebo in the group with no-modeling. Importantly, there were no clinically meaningful differences in the safety profile of subjects in the modeling versus the no-modeling groups.

Based on the findings from early Phase 2 studies and the AUX-CC-801 study investigators in the Phase 3 program had the option of administering two intralesional injections of AA4500 0.58 mg with an interval of at least 24 hours but no more 72 hours between injections and followed by penile plaque modeling 24 to 72 hours after the final injection of the cycle. Subjects could receive up to four treatment cycles (up to 8 injections; total dose: up to a total dose of 4.64 mg equivalent to 80,000 U).

2.4.2. Main studies

Studies AUX-CC-803 and AUX-CC-804 are identical double-blind, placebo-controlled studies of the efficacy and safety of AA4500 0.58 mg in the treatment of subjects with Peyronie's disease. These studies provide the pivotal efficacy data in support of the use of AA4500 for the treatment of Peyronie's disease. Studies AUX-CC-803 and AUX-CC-804 were conducted in the United States and Australia with AA4500 produced by Auxilium's commercial manufacturing process.

Methods

To demonstrate the efficacy of AA4500 0.58 mg in the treatment of Peyronie's disease, the data from two identical, large, well-controlled, multicenter 12-month Phase 3 studies (AUX-CC-803 and AUX-CC-804) were analyzed. To be eligible for these Phase 3 studies, men had to be at least 18 years of age; be in a stable relationship with a female partner/spouse for at least 3 months before screening and be willing to have vaginal intercourse with that partner/spouse; have symptom(s) of Peyronie's disease for at least 12 months before the first dose of study drug and have evidence of stable disease, as determined by the investigator; have penile curvature of at least 30° in the dorsal, lateral, or dorsal/lateral plane at screening; and be judged to be in good health, based upon the results of a medical history, physical

examination, and laboratory profile. Before treatment in each study, subjects were stratified by degree of penile curvature (ie, 30º to 60º or 61° to 90º) and then randomized in a 2:1 ratio into two treatment groups to receive either AA4500 or placebo.

Study participants

To be eligible for these studies, men had to:

- Be at least 18 years of age
- Be in a stable relationship with a female partner/spouse for at least 3 months before screening and be willing to have vaginal intercourse with that partner/spouse
- Have symptom(s) of Peyronie's disease for at least 12 months before the first dose of study drug and have evidence of stable disease as determined by the investigator
- Have penile curvature of at least 30° in the dorsal, lateral, or dorsal/lateral plane at screening
- Be judged to be in good health, based upon the results of a medical history, physical examination, and laboratory profile.

Before treatment in each study, subjects were stratified by degree of penile curvature (ie, 30º to 60º or 61° to 90º) and then randomized into two treatment groups to receive in a 2:1 ratio either AA4500 0.58 mg or placebo.

Treatments

Treatment Cycles

Qualified subjects could have received up to four treatment cycles; each cycle was separated by a period of 42 days (±5 days). During each treatment cycle, subjects received two injections of study drug with approximately 24 hours to 72 hours between injections. Twenty-four to 72 hours after the second injection of each treatment cycle, the investigator or qualified designee modeled the plaque in an attempt to stretch or elongate the plaque. If the subject's curvature deformity was reduced to <15° after the first, second, or third treatment cycle or if the investigator determined that further treatment was not clinically indicated (eg, adverse events [AEs]; allergic reaction), subsequent treatment cycles were not administered.

Following the maximum of four treatment cycles, each subject was followed for additional safety and efficacy assessments on Days 169 (±7 days), 232 (±7 days), 295 (±7 days), and 365 (±7 days) (nominal weeks 24, 33, 42, and 52). Eligible subjects randomized to placebo in Studies AUX-CC-803 or AUX-C-804 could receive open-label AA4500 treatment at the completion of their double-blind study as part of open-label study AUX-CE-806.

Prostaglandin E1 (PGE1) or trimix (ie, papaverine, phentolamine, and PGE1) was injected into the corpora cavernosa of the penis to induce an erection, which in the opinion of the investigator was sufficient for determining penile curvature during the screening visit; before the 1st injection of the 2nd, 3rd, and 4th treatment cycles; and at the Week 24, Week 42, and Week 52 follow-up visits. As described in the statistical analysis plan, changes from baseline at Week 24, Week 42, and Week 52 were analyzed. At each time point, the angle of curvature deformity was measured with a goniometer protractor device using a standardized method.

Before each injection of AA4500 or placebo and before penile plaque modeling, the investigator could have administered a dorsal and/or a circumferential penile block according to the practice of his/her institution and the subject's willingness to receive penile anesthesia. If preferred, topical anesthesia (eg, EMLA cream) could have been applied before injection and modeling. Anesthesia was supplied by the investigator and administered in accordance with the pharmacy practices at the institution.

After local anaesthesia had been provided (if desired) subjects received either AA4500 or placebo (10 mM tris, 60 mM sucrose; ie, lyophilized formulation buffer) according to the randomization schedule. Study drug was injected directly into the primary penile plaque (at point of maximal concavity) of the flaccid penis using a 1 mL (cc) syringe with a permanently attached 26 or 27 gauge ½ inch (13 mm) needle.

During each treatment cycle, subjects received 2 injections of study drug. Approximately 24 hours to 72 hours after the second injection of each treatment cycle and after penile anaesthesia had been administered (if desired) the investigator modelled the plaque.

Investigator Penile Plaque Modeling

Approximately 24 hours to 72 hours after the final injection of the treatment cycle and after penile anesthesia had been administered (if needed) the investigator or qualified designee modelled the plaque three times according to the instructions of the protocol. If investigator penile plaque modelling was not performed at a protocol-specified time point, the reason for not performing the modelling was to be documented in the eCRF.

Before discharge from the study unit, the investigator or qualified designee instructed subjects in the modeling procedure to be performed at home.

Objectives

The objectives of these studies were to assess the effectiveness of AA4500 as determined by the following analyses at Day 365 (nominal week 52):

• Primary objective: The effectiveness of AA4500 in the treatment of Peyronie's disease based on the co-primary endpoints of change from baseline in the Peyronie's disease bother domain of the PDQ and percent improvement from baseline in penile curvature

• Secondary objectives:

– Reduction in the severity of Peyronie's disease physical and psychological symptoms

– Change in the penile pain domain of the PDQ in subjects with pain at baseline

– A responder analysis based on subject global assessment

– Change in the overall satisfaction domain of the International Index of Erectile Function (IIEF)

– Change in penile plaque consistency

– Change in penile length

Study objective was also to determine the safety of AA4500 in men with Peyronie's disease.

Outcomes / endpoints

The following efficacy endpoints include the co-primary endpoints and the secondary endpoints (ie, first family and second family), which were analyzed in Studies AUX-CC-803 and AUX-CC-804.

A meta-analysis of the pooled data from Studies AUX-CC-803 and AUX-CC-804 is also presented and includes analysis of the same co-primary and secondary endpoints.

Co-Primary Endpoints

The co-primary endpoints were the percent reduction from baseline in curvature deformity and the change from baseline in the patient-reported Peyronie's disease bother domain score at Week 52 (LOCF).

Secondary Efficacy Endpoints

The first family of secondary endpoints (SE#1) included:

- Responder analysis based on the global assessment of the symptoms and effects of PD
- Change from baseline in severity of PD symptoms of the PDQ
- Change in overall satisfaction domain of the International Index of Erectile Function (IIEF)

The second family of secondary endpoints (SE#2) consisted of:

- Penile plaque consistency
- Change in penile length
- Composite responder #1 (ITT population). Composite responder #1 was defined a-priori as a percent reduction from baseline in penile curvature of ≥20% and mean reduction from baseline in patient-reported PD bother score of ≥1 or a change from having no vaginal intercourse at screening to having vaginal intercourse during the study. The threshold values for percent reduction in curvature deformity and mean change in patient-reported bother in this analysis were based on data from the Phase 2b study (AUX-CC-801).

The composite responder #1 analysis represents a sensitivity analysis because it incorporates two groups of subjects who were not counted in the mITT population as follows:

– ITT subjects who were not having vaginal intercourse at baseline but who began having vaginal intercourse during the study were considered 'responders'.

– ITT subjects who were having vaginal intercourse at baseline but had no vaginal intercourse during the study were considered 'non-responders'.

- Change from baseline in penile pain of the PDQ in a subset of subjects with a baseline pain score of at least 4

Tertiary Endpoint

A tertiary endpoint was planned a-priori where the threshold values for percent reduction from baseline in curvature deformity and mean reduction from baseline in patient-reported PD bother score were to be determined post-hoc from the data collected in Phase 3 Studies AUX-CC-803 and AUX-CC-804 (ie, composite responder # 2). The PD bother threshold value of 2 was based on the treatment responsiveness analysis as described in Appendix J.2 of the PRO Dossier.

- Composite responder #2 (ITT population): Composite responder #2 was defined as a percent reduction from baseline in patient-reported PD bother score of ≥2 or a change from having no vaginal intercourse at screening to having vaginal intercourse during the study

Post- hoc analyses based on the mITT population and on the percent reduction in curvature deformity and the change in bother were defined for the Summary of Clinical Efficacy.

- Composite responder #3 (mITT population): Composite responder #3 was defined as a percent reduction from baseline in penile curvature of ≥20% and reduction from baseline in PD bother score of ≥1.
- Composite responder #4 (mITT population): Composite responder #4 was defined as a percent reduction from baseline in penile curvature of ≥20% and reduction from baseline in PD bother score of ≥2.

Side-by-Side Efficacy Analyses

Efficacy results for the co-primary and the seven secondary efficacy parameters are presented side-by-side for each of the double-blind, placebo-controlled clinical studies (AUX-CC-803 and AUX-CC-804) to allow direct comparison of the results from each study.

A multiple comparison algorithm was utilized for the co-primary and the secondary endpoints in each of these studies. Inferential statistics were used to determine significant treatment effects on the efficacy parameters. The analysis of variance (ANOVA) model used the factors of treatment and severity of baseline curvature deformity.

Sample size

An analysis was performed in the AUX-CC-801 study to determine how to define a clinically meaningful change in the bother domain of the PDQ as it relates to improvement in penile curvature.

This analysis was based on the global assessment question (GAQ5) "Since you began your treatment has there been an overall change in the symptoms and effects of Peyronie's disease in your life?". It was determined that a 2.2 point change in the bother domain of the PDQ corresponded to clinical improvement and on the basis of this information, a delta of 2.2 for improvement in the Bother domain was selected for the Phase 3 protocol sample size calculations.

For both pivotal trials: The sample size of 252 subjects with an allocation (2:1) of 168 to active and 84 to placebo would have a power of at least 95% to detect a change in curvature deformity (delta=19%, SD=30%) and bother (delta=2.2, SD=4.5). To have a sufficient safety database, to account for a 15% dropout rate, and to account for subjects who may not have qualified for the mITT population, approximately 400 subjects were planned, with 267 randomized to active and 133 to placebo.

Randomisation

Before dosing, subjects were stratified by degree of penile curvature (ie, 30º to 60º or >60º) and then randomized into two treatment groups to receive in a 2:1 ratio either AA4500 0.58 mg or placebo.

Blinding (masking)

Investigator, study subject, and other study personnel were blinded to study drug treatment. Unblinding was not be permitted unless it was deemed necessary for appropriate treatment of a medical emergency. The study site had the ability to immediately determine treatment identification in the event of an emergency by swiping the label portion of the drug kit with an alcohol pad.

Statistical methods

Efficacy Analysis Populations

The predefined efficacy analysis populations are as follows:

- Intent-to-Treat (ITT) Population: A total of 832 subjects (AA4500, N=551; placebo, N=281) who received at least one dose of study drug in one of the double-blind studies (AUX-CC-803 or AUX-CC-804). Subjects were included regardless of their eligibility to complete the PDQ or the existence of curvature deformity measurements.

- Modified Intent-to-Treat (mITT) Population: The mITT population is the pre-specified efficacy population. A total of 612 intent-to-treat subjects (AA4500, N=401; placebo, N=211) who had both a curvature deformity measurement and a PDQ response at baseline and at least one subsequent time point in their respective double-blind studies were included in the mITT. The mITT population appropriately did not include 220 subjects for the reasons shown in the Table below. Most (n=154) of these subjects were ineligible to complete the PDQ because they reported no vaginal intercourse within 3 months before the screening visit, and consequently were ineligible for the mITT population. All 220 of these subjects were allowed to enroll in the study and were included in the ITT population and followed for safety.

Table 3: mITT Population

Number of ITT subjects ineligible for the mITT population as prescribed by the protocol:	**220**
Reasons:	
No vaginal intercourse within 3 months before screening.	154
Had vaginal intercourse within 3 months before screening but did not complete the PDQ evaluation at any of the post-screening visits.	38
Had vaginal intercourse within 3 months of screening but reported no vaginal intercourse within 3 months of any post-screening PDQ evaluation.	25
Protocol violations: • No post-screening curvature deformity measurements (n=2) • Received verapamil (n=1)	3

Efficacy Analyses

Multiple Comparison Algorithm Summary: Studies AUX-CC-803, AUX-CC-804, and the Meta-Analysis

For both the individual studies and the meta-analysis, individual p-values (i.e., observed p-values) formed a basis for multiple comparisons with type 1 error controlled for the a-priori efficacy endpoints. The overall type 1 error rate was 0.05. Gatekeeping procedures were used to control the family-wise error rate between families of efficacy endpoints (primary and secondary endpoints). The tests of the two co-primary endpoints were the gatekeepers (serial gatekeeping procedure) for the secondary efficacy endpoints (SE). The global test for the family SE#1 of secondary endpoints was the gatekeeper (parallel gatekeeping procedure) for the family SE#2 of secondary endpoints. Within each family of efficacy endpoints, multiple tests to control family-wise error were as shown in the Table below.

Table 4: Multiple Comparisons for Efficacy Endpoints in Studies AUX-CC-803 and AUX-CC-804 and the Meta-Analysis

Type of Endpoints	Efficacy Endpoint	Evaluate Timepoint[a]	Statistical Inference
Primary	▪ % change from baseline in penile curvature deformity ▪ Change from baseline in PD bother score	Week 52 (LOCF)	▪ Two-sided level of significance = 0.05 for comparing treatment difference ▪ Significant difference in both endpoints to claim effectiveness of AA4500 in treatment of PD
Secondary Family #1 (SE#1)	▪ A responder analysis based on subject global assessment ▪ Reduction in the severity of PD symptoms ▪ Change in the overall satisfaction domain of the International Index of Erectile Function (IIEF)	Week 52 (LOCF)	▪ Both two co-primary endpoints must be statistically significant in order to further test secondary endpoints in the family #1 (SE#1) ▪ Two-sided, overall level of significance = 0.05 ▪ Bonferroni's test ▪ If any secondary endpoint in the family is significant, Hochberg (1988) procedure is used for multiple comparisons for the remaining non-significant secondary endpoints plus adjusted overall for secondary endpoints in the family #2 (SE#2)

Type of Endpoints	Efficacy Endpoint	Evaluate Timepoint[a]	Statistical Inference
Secondary Family #2 (SE#2)	▪ Change from baseline in penile plaque consistency score ▪ Change from baseline in penile length ▪ Composite responder based on change in penile curvature and change in PD bother (ITT population [composite responder #1]) ▪ Change from baseline in the penile pain score of the PDQ in subjects with pain at baseline (score ≥ 4)	Week 52 (LOCF)	▪ One or more secondary endpoints in the family #1 (SE#1) and adjusted overall for secondary endpoints in the family #2 (SE#2) must be significant in order to further test secondary endpoints in the family #2 (SE#2) ▪ Two-sided, overall level of significance = $0.05/(4\text{-}s_1)$ where s_1 is number of statistically significant tests for secondary endpoints in the family #1 (SE#1) ▪ Hochberg (1988) procedure is used for multiple comparisons for secondary endpoints in the family #2 (SE#2)

[a] Visits that consist of Weeks 52 (LOCF) for each of primary and secondary endpoints are also summarized.

Results

Participant flow

A total of 832 subjects (AA4500 551 and placebo 281) were enrolled and received up to four treatment cycles (total of up to 8 injections) of AA4500 or placebo to treat the primary penile plaque causing the curvature deformity. The majority (~90%) of subjects in each treatment group completed the study (Table below).

Table 6: Subject Disposition, Intent-to-Treat Subjects - Studies AUX-CC-803 and AUX-CC-804

	AA4500 N=551	Placebo N=281
	N (%)	N (%)
Number of subjects	551 (100.0)	281 (100.0)
AUX-CC-803	277 (50.3)	140 (49.8)
AUX-CC-804	274 (49.7)	141 (50.2)
Number completed study	477 (86.6)	251 (89.3)
Number discontinued study	74 (13.4)	30 (10.7)
Withdrawal by subject	39 (7.1)	14 (5.0)
Lost to follow-up	13 (2.4)	6 (2.1)
Adverse event	10 (1.8)	4 (1.4)
Protocol violation	1 (0.2)	0
Death	3 (0.5)	0
Other	8 (1.5)	6 (2.1)

Data source: ISS Table 14.1.1

Recruitment

Study AUX-CC-804:

First Subject Enrolled 04 October 2010

Last Subject Completed 30 March 2012

Study AUX-CC-804:

First Subject Enrolled 30 September 2010

Last Subject Completed 11 April 2012

Conduct of the study

Three amendments to the original protocols were carried out which are not considered to influence on the conduct of the study.

Baseline data

Demographics

Demographics (Table below) were similar between the AA4500 and placebo groups at baseline. The vast majority (>95%) of subjects were white. Most subjects were between the ages of 45 to 64 years. The distribution of degree of curvature deformity at baseline was also similar between treatment groups.

Table 7: Demographics and Baseline Characteristics, Intent-to-Treat Subjects - Studies AUX-CC-803 and AUX-CC-804

Parameter	AA4500 N=551	Placebo N=281
Age (years)		
N	551	281
Mean (SD)	57.6 (8.50)	57.9 (8.25)
Median	59.0	59.0
Min, Max	23, 84	30, 81
Age category (years), N (%):		
<45	38 (6.9)	15 (5.3)
45 to 54	144 (26.1)	67 (23.8)
55 to 64	269 (48.8)	138 (49.1)
65 to 74	95 (17.2)	58 (20.6)
≥ 75	5 (0.9)	3 (1.1)
Ethnicity, N (%)		
Hispanic or Latino	19 (3.4)	10 (3.6)
Not Hispanic or Latino	532 (96.6)	271 (96.4)
Race, N (%)		
American Indian or Alaska Native	1 (0.2)	0
Asian	4 (0.7)	0
Black or African American	16 (2.9)	5 (1.8)
Native Hawaiian or Other Pacific Islander	0	1 (0.4)
White	528 (95.8)	273 (97.2)
Other	2 (0.4)	2 (0.7)
Country location, N (%)		
United States	457 (82.9)	237 (84.3)
Australia	94 (17.1)	44 (15.7)
Weight, N (%)		
N	551	281
Mean (SD)	89.2 (13.51)	89.8 (14.43)
Median	87.6	89.0
Min, Max	56.8, 147.0	33.0, 147.6
Degree of curvature deformity at baseline, N (%)		
≤45°	255 (46.3)	129 (45.9)
46°-60°	170 (30.9)	89 (31.7)
>60°	126 (22.9)	63 (22.4)

Data source: ISS Table 14.1.2

Peyronie's Disease Risk Factors and History

Risk factors for Peyronie's disease were similar between the AA4500 and placebo groups at baseline (Table below). On average, subjects had a history of Peyronie's disease for 4 years. Approximately 50% of subjects in each group reported a history of erectile dysfunction and approximately 25% experienced trauma to the penis. The most commonly used medical treatment for Peyronie's disease was Vitamin E.

Table 8: Subject History and Risk Factors Associated With Peyronie's Disease, Intent-to-Treat Subjects Studies - AUX-CC-803 and AUX-CC-804

	AA4500 N=551	Placebo N=281
Duration of Peyronie's disease (years)		
N	551	281
Mean (SD)	4.06 (4.14)	4.10 (4.8)
Median	2.9	2.9
Min, Max	1.0, 35.9	1.0, 50.8
Erectile dysfunction, N (%)		
Yes	262 (47.5)	151 (53.7)
Trauma to penis, N (%)		
Yes	129 (23.4)	71 (25.3)
History of the following, N (%)		
Dupuytren's disease	44 (8.0)	18 (6.4)
Ledderhose's disease	1 (0.2)	1 (0.4)
Diabetes	72 (13.1)	31 (11.0)
Family history of following, N (%)		
Peyronie's disease	26 (4.7)	10 (5.0)
Dupuytren's disease	29 (6.2)	20 (8.3)
Ledderhose's disease	0	1 (0.4)
Alcohol Use		
Yes	433 (78.6)	222 (79.0)
Previously	58 (10.5)	31 (11.0)
Tobacco Use		
Yes	59 (10.7)	37 (13.2)
Previously	199 (36.1)	102 (36.3)
Prior treatment for Peyronie's disease, N (%)		
None	241 (43.7)	112 (39.9)
Medical	305 (55.4)	167 (59.4)
Non-Drug (eg, extracorporeal shock wave therapy, mechanical devices)	55 (10.0)	36 (12.8)

Data source: ISS Tables 14.1.2 and 14.1.4

Numbers analysed

In these pivotal studies, a total of 832 subjects with Peyronie's disease were enrolled in the United States and Australia. For details on the predefined efficacy analysis populations see above chapter "Statistical methods".

Outcomes and estimation

Co-primary endpoint results

The co-primary endpoints were achieved in each of the double-blind, placebo-controlled studies; i.e., AA4500 was statistically significantly superior to placebo with respect to the percent improvement from baseline in curvature deformity and the improvement from baseline in patient-reported Peyronie's disease bother based on the multiple comparison algorithm.

Percent Change in Curvature Deformity

Mean curvature deformity at baseline was similar between treatment groups in both studies and consistent across both studies. As shown in the Table below, AA4500 was consistently superior

(p≤0.0059) to placebo with respect to the percent improvement from baseline in curvature deformity in both studies.

Table 10: Mean Percent Change in Curvature Deformity From Baseline to Week 52 - Studies AUX-CC-803 and AUX-CC-804, Modified Intent-to-Treat

	AUX-CC-803		AUX-CC-804	
	AA4500 N=199	Placebo N=104	AA4500 N=202	Placebo N=107
Curvature deformity (degrees): Baseline Mean (SD)	48.8° (13.90)	49.0° (13.89)	51.3° (14.77)	49.6° (14.06)
Week 52[a] Mean (SD)	31.0° (18.05)	39.0° (17.72)	35.1° (15.13)	41.1° (14.6)
% change from baseline	-37.6%	-21.3%	-30.5%	-15.2%
Observed p-value[b]	0.0005	-	0.0059	-
p-value based on multiple comparision[c]	*		*	

Data source: AUX-CC-803 CSR Table 14.2.3.1; AUX-CC-804 CSR Table 14.2.3.1

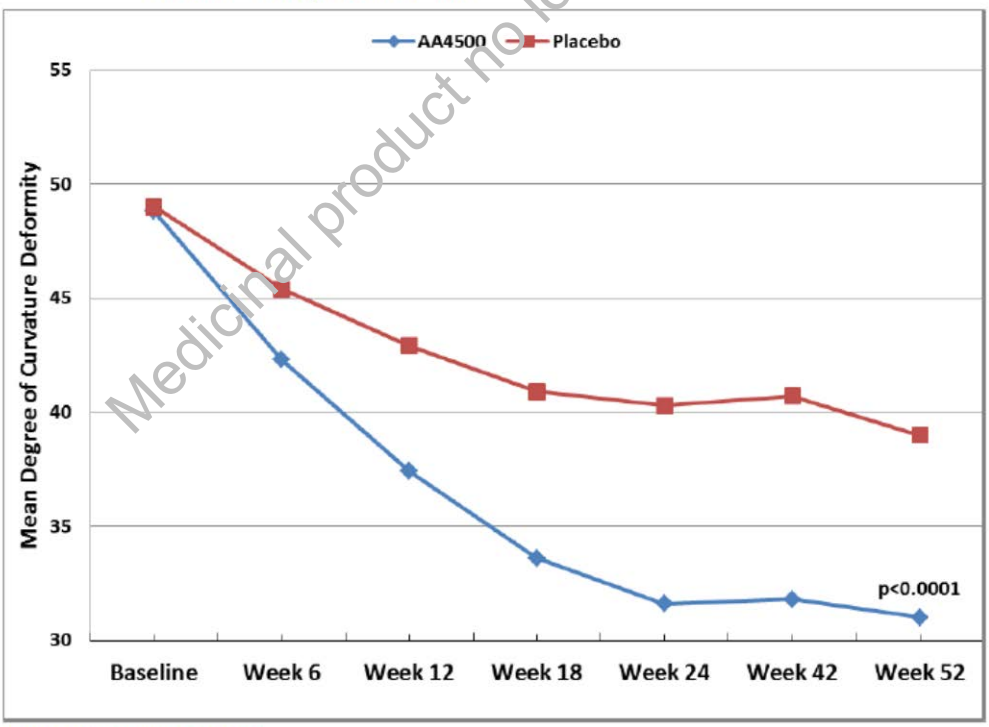
[a] Last observation carried forward (LOCF).

[b] p-values based on an ANOVA with factors for drug, stratum of baseline curvature deformity, and their interaction.

[c] * Represents statistical significance based on the multiple comparison algorithm.

The mean reduction from baseline in curvature deformity over time (Figure below) and the mean percent improvement from baseline in curvature deformity over time (not shown here in detail, please refer to study report) were statistically significantly greater in the AA4500 group compared with the placebo group in both studies starting at Week 24 (approximately 6 weeks after the fourth treatment cycle) and continued through Week 52.

Figure 2: Mean Degree of Curvature Deformity Over the Treatment and Follow-up Periods – Study AUX-CC-803

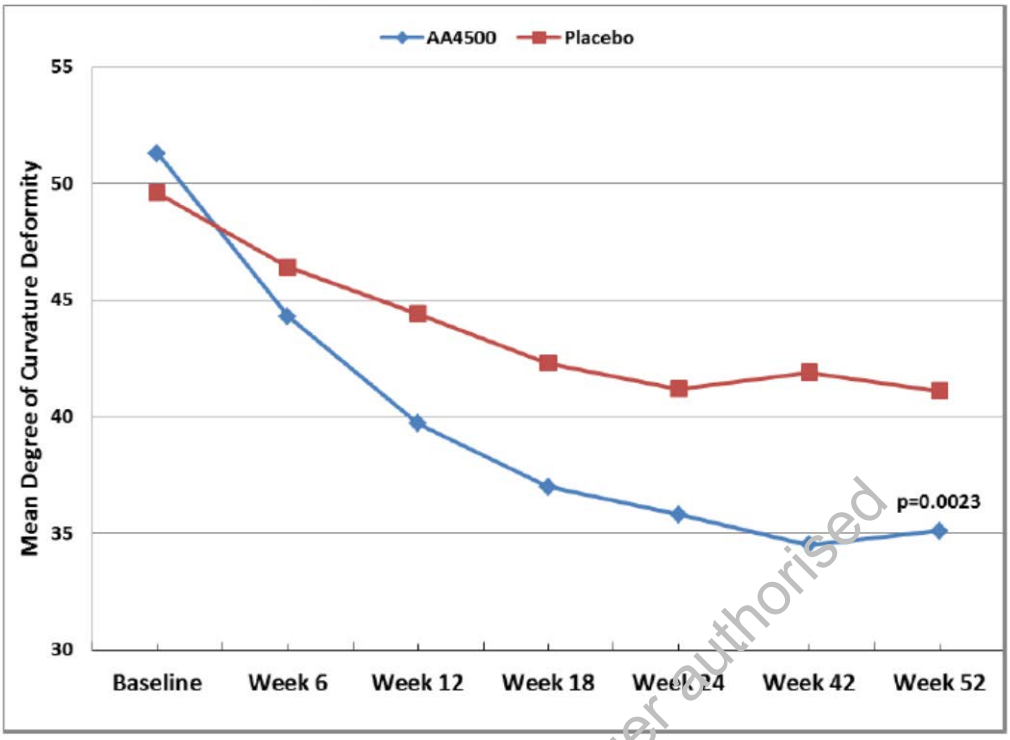


AUX-CC-803 CSR Table 14.2.3.1

Week 52: Last observation carried forward (LOCF).

p-values are based on an ANOVA with factors for drug, stratum of baseline curvature deformity, and their interaction. P-value for the comparison of reduction from baseline to Week 52 (LOCF) of AA4500 versus placebo.

Figure 4: Mean Degree of Curvature Deformity Over the Treatment and Follow-up Periods – Study AUX-CC-804



AUX-CC-804 CSR Table 14.2.3.1
Week 52: Last observation carried forward (LOCF).
p-values are based on an ANOVA with factors for drug, stratum of baseline curvature deformity, and their interaction. P-value for the comparison of reduction from baseline to Week 52 (LOCF) of AA4500 versus placebo.

PDQ Patient-Reported Peyronie's Disease Bother

The PDQ is a disease-specific 15-item, self-administered, paper-and-pencil instrument designed to measure the psychosexual consequences of PD. The PDQ assesses the impact of PD in the following three domains: Peyronie's Psychological and Physical Symptoms (6 items), Penile Pain (3 items), and Peyronie's Symptom Bother (6 items).

Peyronie's disease bother as measured by the PDQ included: bother associated with painful erections; bother associated with appearance of erect penis; bother associated with the impact of Peyronie's disease during intercourse and impact of Peyronie's disease on intercourse frequency. Subjects were asked to rate their bother on a 5-point scale (0 [not bothered at all] to 4 [extremely bothered]) at screening, Week 24, and Week 52.

The mean patient-reported PD bother score at baseline was similar between treatment groups in both studies and was consistent across studies. As shown in the Table and Figures below, AA4500 was consistently superior ($p \leq 0.0496$ to placebo in both studies with respect to the mean reduction from baseline in patient-reported PD bother.

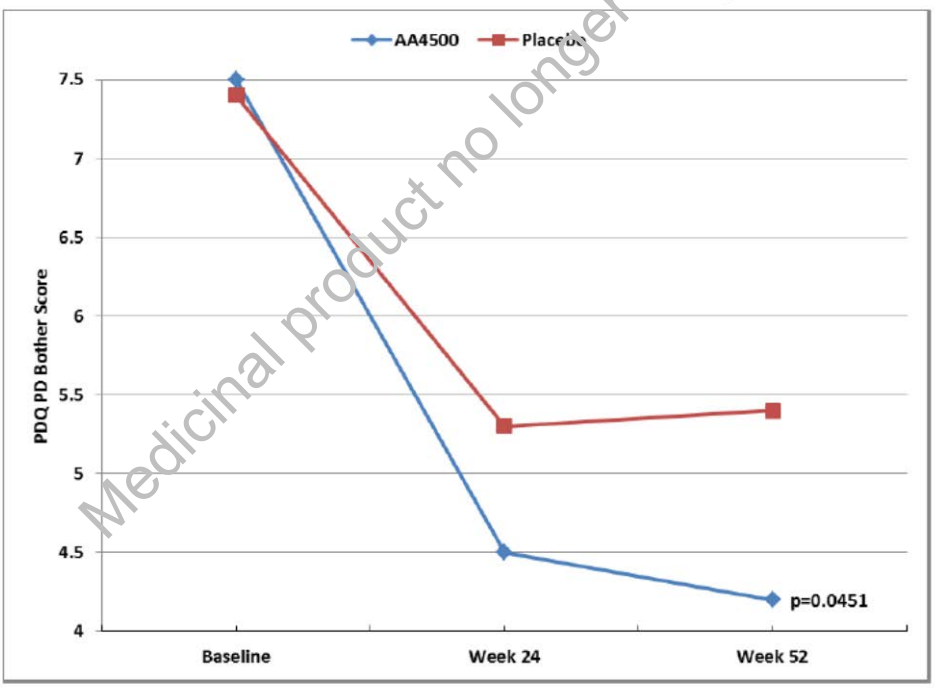
Table 11: Mean Change in Patient-Reported Peyronie's Disease Bother From Baseline to Week 52 - Studies AUX-CC-803 and AUX-CC-804, Modified Intent-to-Treat

	AUX-CC-803		AUX-CC-804	
	AA4500 N=199	Placebo N=104	AA4500 N=202	Placebo N=107
Patient-reported PD bother: Baseline Mean (SD)	7.5 (3.51)	7.4 (3.57)	7.4 (3.56)	8.2 (3.72)
Week 52[a] Mean (SD)	4.2 (3.71)	5.4 (3.78)	5.0 (3.93)	6.5 (4.20)
Change from baseline	-3.3	-2.0	-2.4	-1.6
Observed p-value[b]	0.0451	-	0.0496	-
p-value based on multiple comparison[c]	*		*	

Data source: AUX-CC-803 CSR Table 14.2.4.3.1; AUX-CC-804 CSR Table 14.2.4.3.1
[a] Last observation carried forward (LOCF).
[b] p-values based on an ANOVA with factors for drug, stratum of baseline curvature deformity, and their interaction
[c] * Represents statistical significance based on the multiple comparison algorithm.
PD Bother Score: 0-16. Higher numbers represent greater bother.

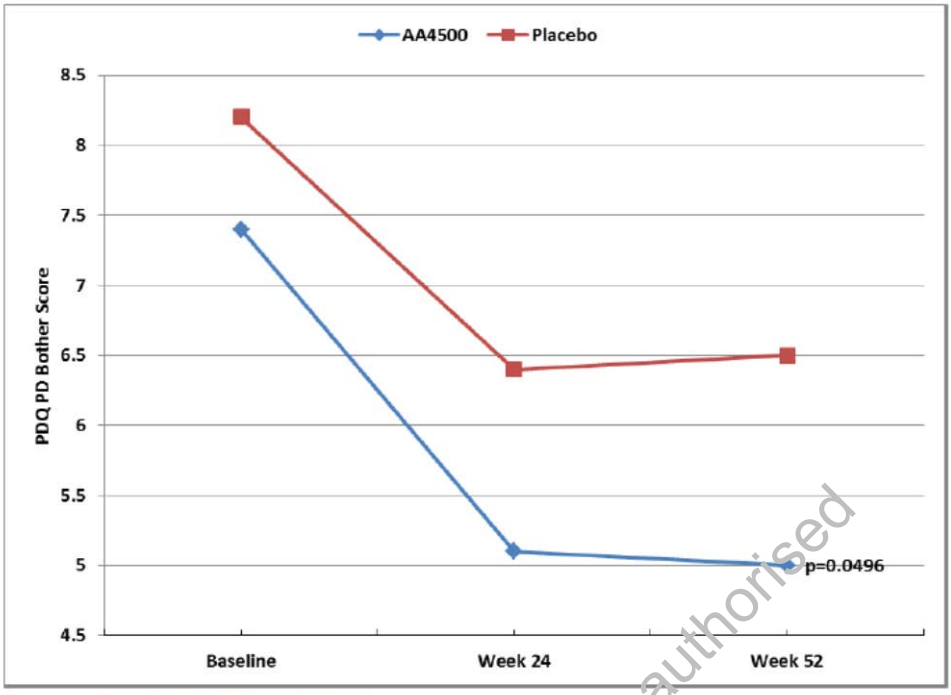
Mean patient-reported Peyronie's disease bother over time is depicted for AUX-CC-803 and AUX-CC-804 in the Figures below.

Figure 7: Mean Patient-Reported Peyronie's Disease Bother Over Time at Baseline, Week 24 and Week 52 – Modified Intent-to-Treat in Study AUX-CC-803



Data source: AUX-CC-803 CSR Table 14.2.4.3.1
Week 52=Last observation carried forward (LOCF).
P-value based on an ANOVA with factors for drug, stratum of baseline curvature deformity, and their interaction.
P-values based on the change from baseline to Week 52 (LOCF) of AA4500 versus placebo.
PD Bother Score: 0-16. Higher numbers represent greater bother.

Figure 8: Mean Patient-Reported Peyronie's Disease Bother Over Time at Baseline, Week 24 and Week 52 – Modified Intent-to-Treat in Study AUX-CC-804



Data source: AUX-CC-804 CSR Table 14.2.4.3.1
Week 52=Last observation carried forward (LOCF).
P-values based on an ANOVA with factors for drug, stratum of baseline curvature deformity, and their interaction. P-values based on the change from baseline to Week 52 (LOCF) of AA4500 versus placebo
PD Bother Score: 0-16. Higher numbers represent greater bother.

Co-Primary Endpoints by Curvature Deformity Stratum

Curvature deformity reduction

A clinically meaningful response to treatment with AA4500 at Week 52 (LOCF) was observed regardless of baseline curvature deformity stratum (Table below, study AUX-CC-803). It should be noted that the number of subjects with a curvature deformity of 61° to 90° at baseline (36 AA4500 subjects and 17 placebo subjects) was lower than that of subjects with a curvature deformity 30° to 60° at baseline (163 AA4500 subjects and 87 placebo subjects).

Table 24: Mean Percent Change From Baseline in Curvature Deformity at Week 52 (LOCF) by Baseline Curvature Deformity Stratum (mITT Population)

	Baseline Curvature Deformity Stratum			
	30° to 60° (N=250)		61° to 90° (N=53)	
	AA4500 (N=163)	Placebo (N=87)	AA4500 (N=36)	Placebo (N=17)
Baseline value				
Mean (SD)	43.7 (9.03)	44.6 (9.74)	72.0 (6.37)	71.9 (8.10)
Min, Max	30, 60	30, 60	62, 85	61, 89
Week 52 value (LOCF)				
Mean (SD)	26.8 (14.84)	34.4 (14.56)	50.2 (19.03)	62.4 (13.66)
Min, Max	0, 79	0, 65	0, 90	32, 79
% change from baseline				
Mean (SD)	-39.1 (31.46)	-22.9 (31.21)	-30.9 (23.51)	-12.8 (20.60)
Min, Max	-100, 66	-100, 94	-100, 6	-51, 30

Data source: Table 14.2.3.2

PDQ Bother scale

In general at baseline, subjects with a curvature deformity 30° to 60º at baseline had as much bother as those with curvature deformity 61º to 90° at baseline (Table below, study AUX-CC-803). A mean decrease in Peyronie's disease bother score was observed regardless of baseline curvature deformity stratum, with the treatment difference favouring AA4500 over placebo.

Table 25: Mean Change From Baseline in Peyronie's Disease Bother Score at Week 52 (LOCF) by Baseline Curvature Deformity Stratum (mITT Population)

	Baseline Curvature Deformity Stratum			
	30° to 60° (N=250)		61° to 90° (N=53)	
	AA4500 (N=163)	Placebo (N=87)	AA4500 (N=36)	Placebo (N=17)
Baseline value				
Mean (SD)	7.6 (3.41)	7.0 (3.61)	7.0 (3.97)	9.2 (2.83)
Min, Max	0, 15	1, 15	0, 15	5, 14
Week 52 value (LOCF)				
Mean (SD)	4.0 (3.44)	4.9 (3.59)	5.1 (4.70)	8.2 (3.63)
Min, Max	0, 15	0, 13	0, 16	2, 13
Change from baseline				
Mean (SD)	-3.6 (3.84)	-2.1 (3.54)	-1.9 (3.52)	-1.0 (3.37)
Min, Max	-13, 5	-11, 5	-11, 4	-8, 4

Data source: Table 14.2.4.3.2

Secondary endpoints

Evaluation of the secondary endpoints (SE) was robust, with a hierarchical testing procedure prospectively defined in both studies. The hypotheses of secondary endpoints in the family SE#1 were tested only when both co-primary endpoints were statistically significant (p-value ≤ 0.05), while secondary endpoints in the family SE#2 were tested only when at least one of the secondary endpoints in the family #1 was statistically significant.

First Family of Secondary Endpoints (SE#1)

The first family of secondary endpoints includes incidence of responders based on overall global assessment of the symptoms and effects of PD; change from baseline in PDQ PD symptom score; and change from baseline in IIEF

Responders Based on Overall Global Assessment of the Symptoms and Effects of Peyronie's Disease

At Week 24 and Week 52, subjects were asked to assess and record the overall change (much improved to much worse) in the symptoms and effects of Peyronie's disease in their lives. A responder was defined as a subject who recorded that his Peyronie's disease was improved in a small but important way; was moderately improved; or was much improved following treatment.

As shown in the Table below, AA4500 was consistently superior (based on the multiple comparison algorithm) to placebo in both studies with respect to the percentage of responders (ie, improvement in the symptoms and effects of Peyronie's disease).

Table 12: Percent Responders at Week 52 Based on Overall Global Assessment of the Symptoms and Effects of Peyronie's Disease - Studies AUX-CC-803 and AUX-CC-804, Modified Intent-to-Treat

	AUX-CC-803		AUX-CC-804	
Week 52[a]	AA4500 N=199	Placebo N=104	AA4500 N=202	Placebo N=107
Much worse (-3)	4 (2.0)	1 (1.0)	3 (1.5)	5 (4.7)
Moderately worse (-2)	5 (2.5)	4 (3.9)	9 (4.5)	2 (1.9)
A little worse (-1)	8 (4.0)	8 (7.8)	15 (7.4)	12 (11.2)
Stayed about the same (0)	50 (25.3)	60 (58.3)	63 (31.2)	56 (52.3)
Improved in a small but important way (+1)	35 (17.7)	9 (8.7)	25 (12.4)	14 (13.1)
Moderately improved (+2)	39 (19.7)	11 (10.7)	49 (24.3)	8 (7.5)
Much improved (+3)	57 (28.8)	10 (9.7)	38 (18.8)	10 (9.3)
Missing	1	1	0	1
Responder, N (%):				
No	67 (33.8)	73 (70.9)	90 (44.6)	75 (70.1)
Yes	131 (66.2)	30 (29.1)	112 (55.4)	32 (29.9)
Missing	1	1	0	0
Observed p-value[b]	<0.0001	-	<0.0001	-
Multiple comparison p-value[c]	*	-	*	-

Data source: AUX-CC-803 CSR Table 14.2.6.1 and Table 14.2.6.2; AUX-CC-804 CSR Table 14.2.6.1 and Table 14.2.6.2

[a] Last observation carried forward (LOCF).

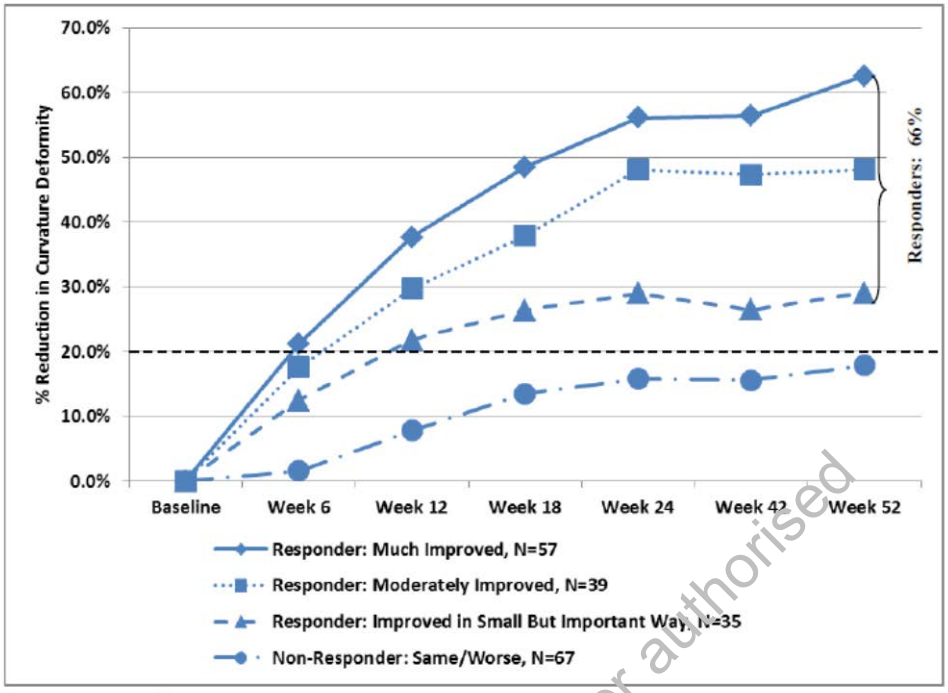
[b] Calculated using the CMH test controlling for stratum of curvature deformity at baseline.

[c] * Represents statistical significance based on the multiple comparison algorithm.

In both studies, there were strong correlations between improvement in each of the co-primary endpoints, and improvement based on the overall global assessment of the symptoms and effects of Peyronie's disease.

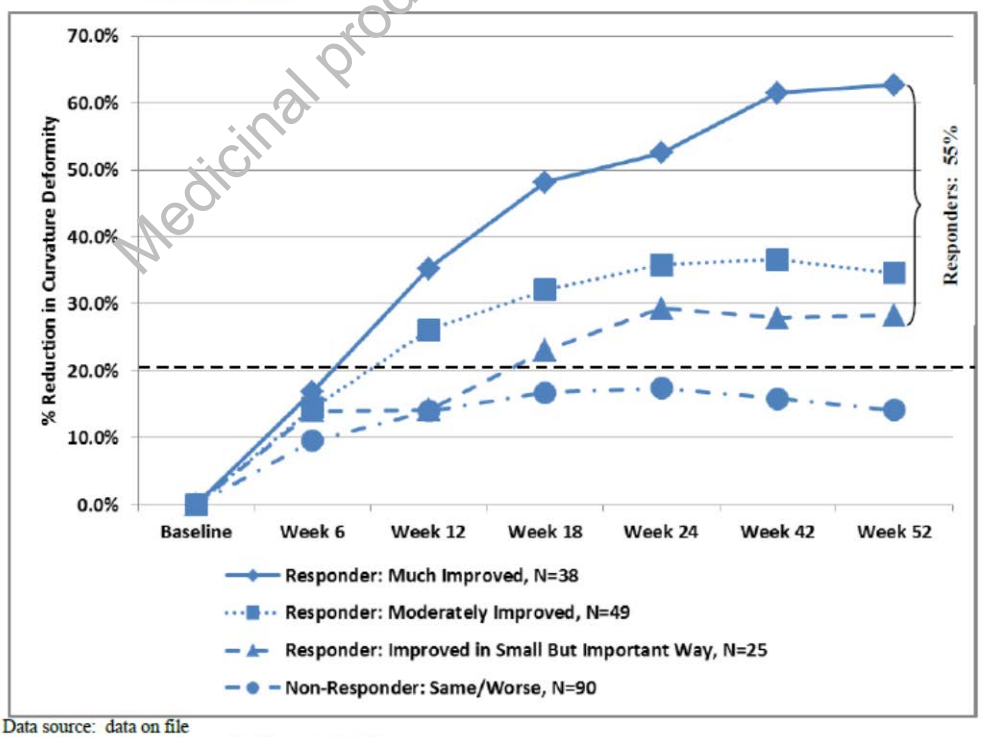
- Subjects who reported 'improved' symptoms and effects of Peyronie's disease in their lives had a mean reduction of at least a 20% from baseline in curvature deformity compared with those subjects who reported 'stable or worsening' symptoms and effects of Peyronie's disease (Figures below).

Figure 9: **Mean Percent Improvement in Curvature Deformity by Subject Global Assessment of Peyronie's Disease – Modified Intent-to-Treat Subjects Who Received AA4500 in Study AUX-CC-803**



Data source: data on file
Week 52: Last observation carried forward (LOCF).
The dotted line represents the separation between responders and nonresponders.

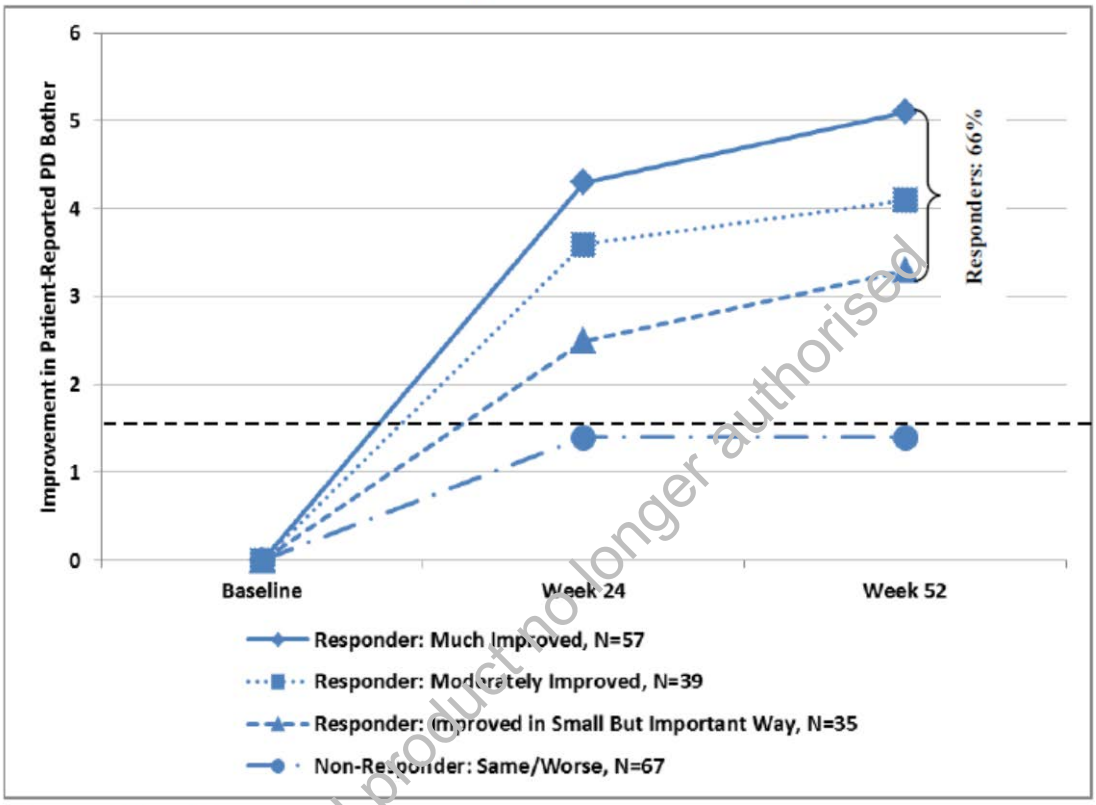
Figure 11: **Mean percent improvement in Curvature Deformity by Subject Global Assessment – Modified Intent-to-Treat Subjects Who Received AA4500 in Study AUX-CC-804**



Data source: data on file
Week 52: Last observation carried forward (LOCF).
The dotted line represents the separation between responders and nonresponders.

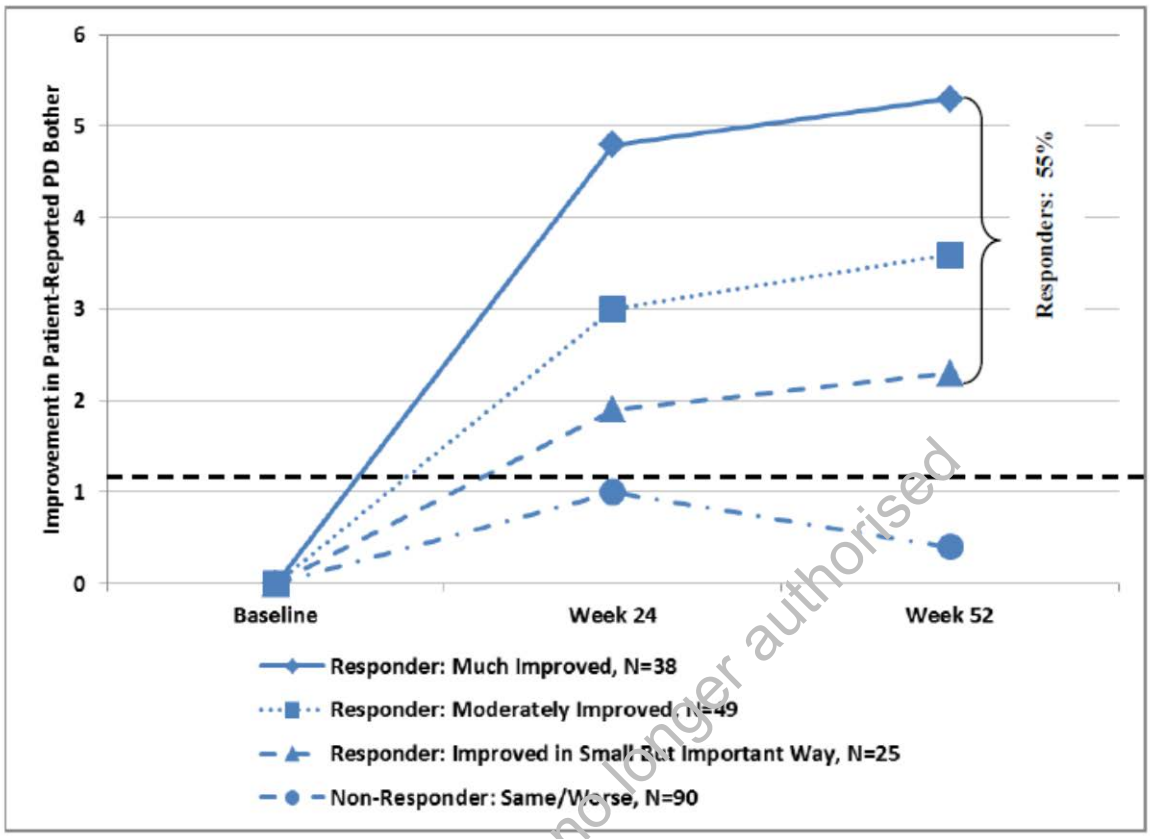
- Subjects who reported 'improved' symptoms and effects of Peyronie's disease in their lives had a mean reduction of at least one point from baseline in their Peyronie's disease bother symptom score compared with those subjects who reported 'stable or worsening' symptoms and effects of Peyronie's disease (Figures below).

Figure 10: Mean reduction in Patient-Reported PD Bother by Subject Global Assessment of Peyronie's Disease – Modified Intent-to-Treat Subjects Who Received AA4500 in Study AUX-CC-803



Data source: data on file
Week 52: Last observation carried forward (LOCF).
The dotted line represents the separation between responders and nonresponders.

Figure 12: Mean Reduction in Patient-Reported PD Bother by Subject Global Assessment – Modified Intent-to-Treat Subjects Who Received AA4500 in Study AUX-CC-804



Data source: data on file
Week 52: Last observation carried forward (LOCF).
The dotted line represents the separation between responders and nonresponders.

PDQ Patient-Reported Peyronie's Disease Physical and Psychological Symptoms

Peyronie's disease physical and psychological problems as measured by the PDQ included: concern about damaging penis; bending or collapsing of penis; trouble inserting erect penis; and difficulty, awkwardness or discomfort with some sexual positions. Subjects were asked to rate the severity of each question on a 5-point scale (0 [none] to 4 [very severe]) at screening, Week 24, and Week 52.

The mean patient-reported PD symptom score at baseline was similar between treatment groups in both studies and consistent across studies. Although there was greater improvement (decrease) from baseline in the severity of PD physical and psychological symptoms in the AA4500 group compared with the placebo group in both studies, the difference between the groups was not statistically significant based on the multiple comparison algorithm (Table below).

Table 13: Mean Change in Patient-Reported Peyronie's Disease Physical and Psychological Symptoms From Baseline to Week 52 - Studies AUX-CC-803 and AUX-CC-804, Modified Intent-to-Treat

	AUX-CC-803		AUX-CC-804	
Week 52[a]	AA4500 N=199	Placebo N=104	AA4500 N=202	Placebo N=107
Patient-reported PD symptoms: Baseline Mean (SD)	10.9 (5.14)	9.9 (4.97)	10.6 (4.82)	11.2 (5.14)
Week 52[a] Mean (SD)	7.7 (5.37)	8.4 (5.10)	8.0 (5.29)	10.2 (5.87)
Change from baseline	-3.2	-1.6	-2.6	-1.0
Observed p-value[b]	0.0268	-	0.0340	-
p-value based on multiple comparison[c]	NS	-	NS	-

Data source: AUX-CC-803 CSR Table 14.2.4.1.1; AUX-CC-804 CSR Table 14.2.4.1.1

[a] Last observation carried forward (LOCF).

[b] Calculated using an ANOVA with factors for drug, baseline curvature deformity stratum, and their interaction.

[c] NS represents not statistically significant based on the multiple comparison algorithm.

PD Symptom Score: 0-24. Higher numbers represent greater symptoms.

International Index of Erectile Function (IIEF) Overall Satisfaction

Subjects completed the IIEF questionnaire during screening, Week 24, and Week 52 to determine their response to each domain of the IIEF. The overall satisfaction domain of the IIEF consisted of two questions: 'How satisfied are you with your overall sex life?' and 'How satisfied have you been with your sexual relationship with your partner?'

The mean IIEF overall satisfaction scores at baseline were similar between the treatment groups in both studies and consistent across studies. Although there was greater improvement (increase) in IIEF overall satisfaction domain score in the AA4500 group compared with the placebo group in both studies, the difference between the groups was not statistically significant based on the multiple comparison algorithm (Table below).

Table 14: Mean Change in IIEF Overall Satisfaction From Baseline to Week 52 - Studies AUX-CC-803 and AUX-CC-804, Modified Intent-to-Treat

	AUX-CC-803		AUX-CC-804	
Week 52[a]	AA4500 N=199	Placebo N=104	AA4500 N=202	Placebo N=107
Patient-reported PD symptoms: Baseline Mean (SD)	5.5 (2.40)	5.6 (2.54)	5.7 (2.39)	5.6 (2.45)
Week 52[a] Mean (SD)	6.6 (2.57)	6.1 (2.50)	6.6 (2.44)	5.9 (2.61)
Change from baseline	1.0	0.5	1.0	0.3
Observed p-value[b]	0.0800	-	0.1168	-
p-value based on multiple comparison[c]	NS	-	NS	-

AUX-CC-803 CSR Table 14.2.5.5.1; AUX-CC-804 CSR Table 14.2.5.5.1

[a] Last observation carried forward (LOCF).

[b] Calculated using an ANOVA with factors for drug, baseline curvature deformity stratum, and their interaction.

[c] NS represents not statistically significant based on the multiple comparison algorithm.

IIEF overall satisfaction score: 0-10. Higher scores indicate improved satisfaction.

Second Family of Secondary Endpoints (SE#2)

The second family of secondary endpoints includes composite responders based on change in curvature deformity and patient-reported PD bother; change from baseline in penile plaque consistency; change from baseline in penile length; and change from baseline in the PD penile pain score.

Composite Responder #1

A composite responder #1 was defined as a subject in the ITT population who satisfied the following two criteria:

- ≥20% reduction from baseline in curvature deformity
- Reduction from baseline in patient-reported PD bother of ≥1 OR a change from having no sexual activity at screening to having sexual activity at the assessment visit

AA4500 was statistically significantly superior to placebo, based on the multiple comparison algorithm, in Study AUX-CC-803 with respect to the percentage of subjects who were composite responders. Although there were more composite responders in the AA4500 group compared with the placebo group in Study AUX-CC-804, the difference between the groups was not statistically significant based on the multiple comparison algorithm (Table below).

Table 15: Composite Responder #1[a] at Week 52 - Studies AUX-CC-803 and AUX-CC-804, Intent-to-Treat

	AUX-CC-803		AUX-CC-804	
Week 52[b]	AA4500 N=277	Placebo N=140	AA4500 N=274	Placebo N=141
Composite responder, N (%):				
Yes	132 (50.6)	33 (25.4)	105 (42.3)	41 (30.6)
No	129 (49.4)	97 (74.6)	143 (57.7)	93 (69.4)
Missing	16	10	26	7
Observed p-value[c]	<0.0001	-	<0.0249	-
Multiple comparison p-value[d]	*	-	NS	-

AUX-CC-803 CSR Table 14.2.7.3; AUX-CC-804 CSR Table 14.2.7.3

[a] ≥20% reduction from baseline in curvature deformity and reduction from baseline in patient-reported PD bother of ≥1 OR a change from having no sexual activity at screening to having sexual activity at the assessment visit

[b] Last observation carried forward (LOCF).

[c] Based on composite responder (yes/no) using CMH test controlling for baseline curvature deformity stratum.

[d] * represents statistical significance based on the multiple comparison algorithm; NS represents not statistically significant based on the multiple comparison algorithm.

Penile Plaque Consistency

The consistency of the primary plaque in the flaccid penis was classified as hard [solid] =5; firm throughout =4; moderate firmness=3; soft=2; non-palpable=1. Primary plaque consistency was assessed at baseline, before each treatment cycle, and at Weeks 24, 33, 42, and 52.

More penile plaques classified as 'hard or solid' or 'firm throughout' at baseline became softer after treatment with AA4500; approximately 10% of palpable plaques at baseline became non-palpable after treatment with AA4500 in both studies; however, the difference between the groups was not statistically significant in Studies AUX-CC-803 and AUX-CC-804 based on the multiple comparison algorithm.

PDQ Patient-Reported Peyronie's Disease Penile Pain

Peyronie's disease pain as measured by the PDQ included: pain/discomfort associated with the penis in the flaccid state; pain/discomfort associated with the penis in the erect state; and pain/discomfort in the penis during vaginal intercourse. Subjects were asked to rate the severity of each question on an 11-point scale (0 [no pain/discomfort] to 10 [extreme pain/discomfort]) at screening, Week 24, and Week 52. Pain is a symptom of Peyronie's disease usually present in the early unstable phase of the disease.

Pain typically resolves with stabilization of the plaque over time. In both AUX-CC-803 and AUX-CC-804, subjects were enrolled with at least 12 months of PD (stable disease). Therefore, only subjects in the modified intent-to-treat population who had a penile pain score of ≥4 at screening were eligible for this analysis. Only about one third of subjects in both studies had pain scores of at least 4 at baseline.

In both studies, the difference between the treatment groups in improvement from baseline in penile pain was not statistically significant in Studies AUX-CC-803 and AUX-CC-804 based on the multiple comparison algorithm, suggesting that pain improved over the 52-week study in all subjects who had pain at baseline. Resolution of penile pain over time in men with Peyronie's disease is characteristic of the disease and may explain these findings.

Meta-Analysis of Secondary Endpoints

As Studies AUX-CC-803 and AUX-CC-804 were identical in design, data from these two studies were pooled in a meta-analysis (post-hoc) to increase the precision for estimation and to further understand and characterize the secondary efficacy endpoints of AA4500 in the treatment of Peyronie's disease. The same multiple comparison algorithm was utilized for the a-priori co-primary and the secondary endpoints in the meta-analysis.

Evaluation of the secondary endpoints (SE) in the meta-analysis was robust, with a hierarchical testing procedure that was prospectively defined in each individual study. As was carried out in each individual study, the hypotheses of secondary endpoints in the family SE#1 were tested only when both co-primary endpoints were statistically significant (p-value ≤ 0.05), while secondary endpoints in the family SE#2 were tested only when at least one of the secondary endpoints in the family #1 was statistically significant.

First Family of Secondary Endpoints (SE#1)

The first family of secondary endpoints includes incidence of responders based on overall global assessment of the symptoms and effects of PD; change from baseline in PDQ PD symptom score; and change from baseline in IIEF overall satisfaction.

Responders Based on Overall Global Assessment of the Symptoms and Effects of Peyronie's Disease

At Week 24 and Week 52, subjects were asked to assess and record the overall change (much improved to much worse) in the symptoms and effects of Peyronie's disease in their lives. A responder was defined as a subject who recorded that his Peyronie's disease was improved in a small but important way; was moderately improved; or was much improved following treatment.

As shown in the Table below, AA4500 was statistically significantly superior to placebo (based on the multiple comparison algorithm) with respect to the percentage of responders at Week 52 (ie, improvement in the symptoms and effects of PD).

Table 22: Meta-Analysis: Percent Responders at Week 52 Based on Overall Global Assessment of the Symptoms and Effects of Peyronie's Disease, Modified Intent-to-Treat - Studies AUX-CC-803 and AUX-CC-804 Pooled

Week 52[a]	AA4500 N=401	Placebo N=211
Much worse (-3)	7 (1.8)	6 (2.9)
Moderately worse (-2)	14 (3.5)	6 (2.9)
A little worse (-1)	23 (5.8)	20 (9.5)
Stayed about the same (0)	113 (28.3)	116 (55.2)
Improved in a small but important way (+1)	60 (15.0)	23 (11.0)
Moderately improved (+2)	88 (22.0)	19 (9.0)
Much improved (+3)	95 (23.8)	20 (9.5)
Missing	1	1
Responder, N (%):		
No	157 (39.3)	148 (70.5)
Yes	243 (60.8)	62 (29.5)
Missing	1	1
Observed p-value[b]	<0.0001	-
Multiple comparison p-value[c]	*	-

Data source: ISE Tables 14.1.7.1 and 14.1.7.2

[a] Last observation carried forward (LOCF).

[b] Calculated using the CMH test controlling for stratum of curvature deformity at baseline and study.

[c] * Represents statistical significance based on the multiple comparison algorithm.

PDQ Patient-Reported Peyronie's Disease Physical and Psychological Symptoms

The mean patient-reported PD symptom score was similar between the AA4500 and placebo groups at baseline. As shown in the Table below, AA4500 was statistically significantly superior to placebo (based on the multiple comparison algorithm) with respect to the improvement (ie, decrease in score) from baseline in patient-reported PD physical and psychological symptoms of Peyronie's disease.

Table 23: Meta-Analysis: Mean Change in Patient-Reported Peyronie's Disease Physical and Psychological Symptoms From Baseline to Week 52, Modified Intent-to-Treat - Studies AUX-CC-803 and AUX-CC-804 Pooled

Week 52[a]	AA4500 N=401	Placebo N=211
Patient-reported PD symptoms: Baseline Mean (SD)	10.8 (4.98)	10.6 (5.09)
Week 52[a]		
Mean (SD)	7.9 (5.33)	9.3 (5.56)
Change from baseline	-2.9	-1.3
Observed p-value[b]	0.0021	-
p-value based on multiple comparison[c]	*	-

Data source: ISE Table 14.1.3

[a] Last observation carried forward (LOCF).

[b] Calculated using an ANOVA with factors for drug, baseline curvature deformity stratum, study, and their interaction.

[c] * represents statistical significant based on the multiple comparison algorithm.

PD Symptom Score: 0-24. Higher numbers represent greater symptoms.

International Index of Erectile Function (IIEF) Overall Satisfaction

The mean IIEF overall satisfaction scores were similar between the AA4500 and placebo groups at baseline. AA4500 was statistically significantly superior to placebo (based on the multiple comparison algorithm) in the mean improvement (increase in score) from baseline in the IIEF overall satisfaction domain (Table below).

Table 24: Meta-Analysis: Mean Change in IIEF Overall Satisfaction From Baseline to Week 52, Modified Intent-to-Treat - Studies AUX-CC-803 and AUX-CC-804 Pooled

Week 52[a]	AA4500 N=401	Placebo N=211
IIEF overall satisfaction: Baseline Mean (SD)	5.6 (2.39)	5.6 (2.49)
Week 52[a]		
Mean (SD)	6.6 (2.50)	6.0 (2.55)
Change from baseline	1.0	0.4
Observed p-value[b]	0.0189	-
p-value based on multiple comparison[c]	*	-

Data source: ISE Table 14.1.6

[a] Last observation carried forward (LOCF).

[b] Calculated using an ANOVA with factors for drug, baseline curvature deformity stratum, study, and their interaction.

[c] * represents statistical significance based on the multiple comparison algorithm.

IIEF overall satisfaction score: 0-10. Higher scores indicate improved satisfaction.

Second Family of Secondary Endpoints (SE#2)

Composite Responder #1

A composite responder #1 was defined as a subject who satisfied the following two criteria:

- ≥20% reduction from baseline in curvature deformity
- Reduction from baseline in patient-reported PD bother of ≥1 OR a change from having no sexual activity at screening to having sexual activity at the assessment visit

The composite responder #1 analysis represents a sensitivity analysis because it incorporates two groups of subjects who were not counted in the mITT population as follows:

– ITT subjects who were not having vaginal intercourse at baseline but who began having vaginal intercourse during the study were considered 'responders'.

– ITT subjects who were having vaginal intercourse at baseline but had no vaginal intercourse during the study were considered 'non-responders'.

As shown in the Table below, AA4500 was statistically significantly superior to placebo (based on the multiple comparison algorithm) with respect to the percentage of subjects who were composite responders #1 at the end of the study.

Table 25: Meta-Analysis: Composite Responder #1[a] at Week 52, Intent-to-Treat - Studies AUX-CC-803 and AUX-CC-804 Pooled

Week 52[b]	AA4500 N=551	Placebo N=281
Composite responder: 20% Improvement in Curvature Deformity and Reduction of ≥1 in PD Bother Score or Change From No Sexual Activity to Sexual Activity		
Composite responder, N (%):		
Yes	237 (46.6)	74 (28.0)
No	272 (53.4)	190 (72.0)
Missing	42	17
Observed p-value[c]	<0.0001	-
Multiple comparison p-value[d]	*	-

Data source: ISE Table 14.1.8

[a] ≥20% improvement in curvature deformity and improvement of ≥1 in PD bother score or change from no sexual activity to sexual activity.

[b] Last observation carried forward (LOCF).

[c] Based on composite responder (yes/no) using CMH test controlling for baseline curvature deformity stratum and study.

[d] * represents statistical significance based on the multiple comparison algorithm.

Comparison of Results in Subpopulations in Studies AUX-CC-803 and AUX-CC-804

Co-Primary Endpoints Subset by Degree of Baseline Curvature Deformity

The mean percent improvement in curvature deformity was similar among subjects with baseline curvature deformity between 30 and 45 degrees (n=194, 34.1%); those with curvature deformity between 46 and 60 degrees (n=124, 33.3%); and those with curvature deformity between 61 and 90 degrees (n=83, 35.1%). These findings are consistent with the mean percent improvement in curvature deformity that was observed in the AA4500 group overall (n=401, 34.0%).

The mean reduction in patient-reported Peyronie's disease bother was similar among subjects with baseline curvature deformity between 30 and 45 degrees (n=194, 3.1); those with curvature deformity between 46 and 60 degrees (n=124, 2.7); and those with curvature deformity between 61 and 90 degrees (n=83, 2.5). These findings are consistent with the mean reduction in patient-reported Peyronie's disease bother that was observed in the AA4500 group overall (n=401, 2.8).

Co-Primary Endpoints Subset by Selected Intrinsic and Extrinsic Factors

The co-primary endpoints, percent change from baseline in curvature deformity and change from baseline in patient-reported Peyronie's disease bother, were analyzed by selected intrinsic factors (duration of disease, age category, race, history of diabetes [yes or no], history of penile trauma [yes or no], history of prior treatment for Peyronie's disease [yes or no])), IIEF Erectile Function at baseline (≤5 [no sexual activity]; 6 to 16 [moderate/severe, severe erectile dysfunction]; 17-30 [mild/moderate, mild, no erectile dysfunction]), and concomitant PDE5 inhibitor usage (yes, no) and by the extrinsic factor of country location for subjects in the mITT population who received AA4500 in Studies AUX-CC-803 and AUX-CC-804.

Duration of Disease

When the percent reduction in curvature deformity was analyzed at Week 52 by duration of Peyronie's disease, there appeared to be a trend toward greater improvement in curvature deformity as the duration of PD increased from ≤2 years (n=134, -28.9%), >2 to < 4 years (n=136, -33.8%) to >4 years (n=131, 39.6%). The reduction of penile curvature in the overall population (n=401) was -34.0%.

Subjects with a duration of disease >4 years also had a greater mean reduction in patient-reported PD bother (-3 vs -2.8 in the overall population).

Age Category

When mean percent improvement in curvature deformity and mean reduction in patient-reported PD bother were analyzed at Week 52 by age categories, younger men (<45 years, n=29, -37.8% in curvature, -4.7 in Bother domain) tended to have a greater mean percent improvement in curvature deformity and a greater improvement in patient-reported PD bother compared with older men (between 45 and 74 years of age, n=370, -31.3% to -36.0% in curvature, -2.6 to -2.8 in Bother domain).

Patients ≥ 75 years had the lowest deformity reduction (-14.5%) on the one hand, but the highest Bother domain reduction (-5.5) of all age groups on the other hand. Since there were so few (N=2) men who were ≥75 years, no definitive conclusions could be drawn about the efficacy of AA4500 in this age category.

Ancillary analyses

Composite Responder #2

The composite responder #2 was planned a-priori where the threshold values for percent reduction from baseline in curvature deformity and mean reduction from baseline in patient-reported PD bother score were to be determined post-hoc from the data collected in Phase 3 Studies AUX-CC-803 and AUX-CC-804 (ie, composite responder # 2). The PD bother threshold value of 2 in the composite responder #2 analysis was based on the treatment responsiveness analysis as described in Appendix J.2 of the PRO Dossier (Module 5.3.5.3 [Peyronie's disease]).

A composite responder #2 was defined as a subject who satisfied the following two criteria:

- ≥20% reduction from baseline in curvature deformity
- Reduction from baseline in patient-reported PD bother of ≥2 OR a change from having no sexual activity at screening to having sexual activity at the assessment visit

As shown in the Table below, AA4500 was statistically significantly (p<0.0001) superior to placebo for the percentage of subjects who were composite responders #2.

Table 29: Composite Responder #2[a] at Week 52, Intent-to-Treat - Studies AUX-CC-803 and AUX-CC-804 Pooled

Week 52[b]	AA4500 N=551	Placebo N=281
Composite responder: 20% Improvement in Curvature Deformity and Improvement of ≥2 in PD Bother Score or Change From No Sexual Activity to Sexual Activity		
Composite responder, N (%):		
Yes	213 (41.8)	64 (24.2)
No	296 (58.2)	200 (75.8)
Missing	42	17
Observed p-value[c]	<0.0001	-

Data source: ISE Table 14.2.1

[a] ≥20% improvement in curvature deformity and improvement of ≥2 in PD bother score or change from no sexual activity to sexual activity.

[b] Last observation carried forward (LOCF).

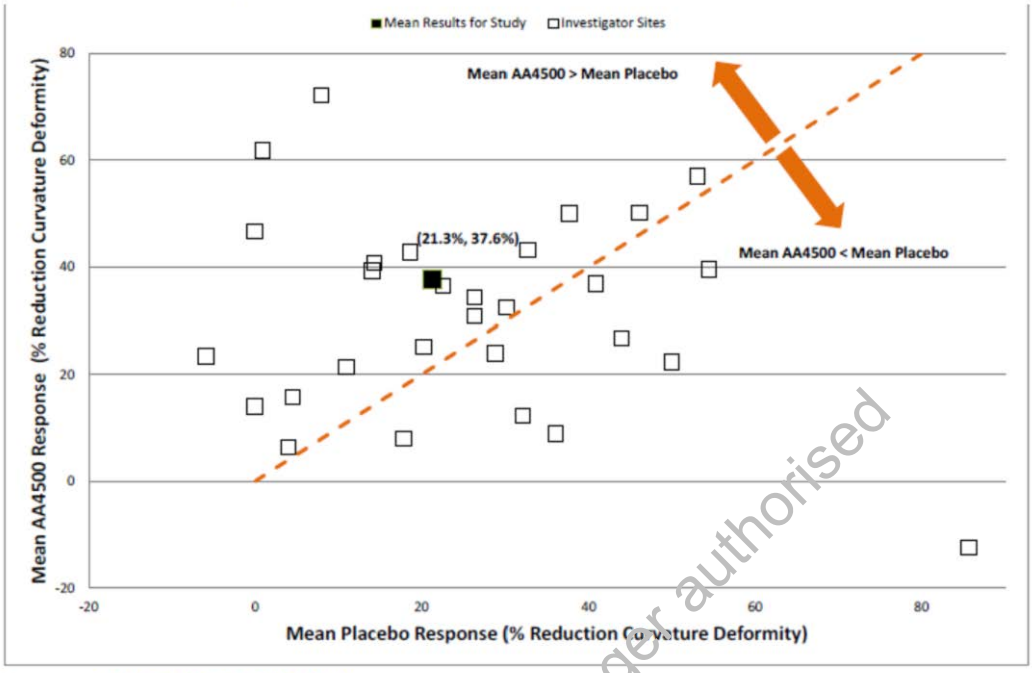
[c] Based on composite responder (yes/no) using CMH test controlling for baseline curvature deformity stratum and study.

Co-Primary Endpoints by Investigative Site in Studies AUX-CC-803 and AUX-CC-804

The distribution of treatment effect for each co-primary endpoint across individual investigator sites support the overall treatment effect observed in each study (ie, AA4500 is statistically superior to placebo

based on the multiple comparison algorithm). The treatment response was greater in the AA4500 group compared with the placebo group in the majority of the investigative sites in both studies.

Figure 19: Mean Percent Change From Baseline in Curvature Deformity by Investigative Site – Study AUX-CC-803



Data source: AUX-CC-803 CSR Table 14.2.3.4
Increase in value on the X and Y axes denote "more reduction in curvature deformity"

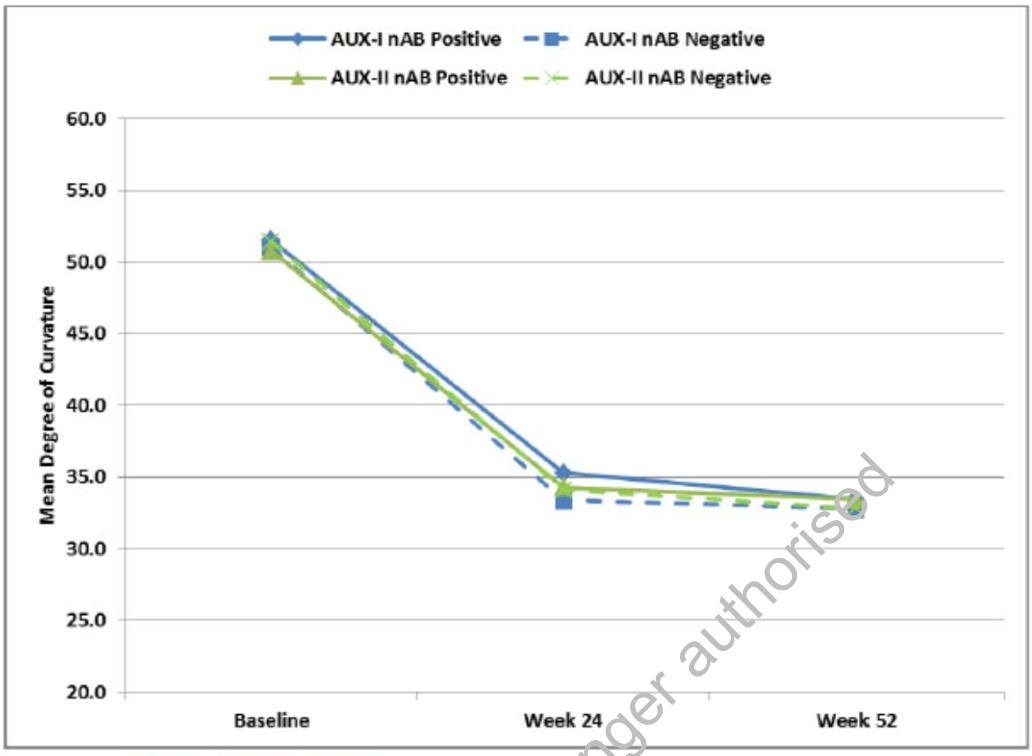
Neutralizing Antibodies (Nab)

Neutralizing Antibodies and Possible Effects on the Efficacy of AA4500

If neutralizing antibodies were to affect the efficacy of AA4500 (ie, curvature deformity) it would be expected that once a subject develops neutralizing antibodies to AUX-I and/or AUX-II there would be little or no further improvement in curvature deformity with subsequent injections and treatment cycles. To determine the potential clinical effect of neutralizing antibodies on the efficacy (ie, improvement in curvature deformity) mean curvature deformity was assessed in subjects who developed neutralizing antibodies at different time points up to week 52 and compared to subjects who were neutralizing antibody negative.

There was no clinically meaningful difference between subjects who were neutralizing antibody positive and those who were neutralizing antibody negative in the degree of curvature deformity. Subjects had similar improvements in curvature deformity regardless of their neutralizing antibody status.

Figure 50: **Mean Degree of Improvement in Curvature Deformity Over Time Subset by Subject Neutralizing Antibody Status at Week 24 - Studies AUX-CC-803 and AUX-CC-804 Pooled**



Data source: ISE Tables 14.5.7 and 14.5.8
AUX-I Nab positive: N=215; AUX-I Nab negative: N=276
AUX-II Nab positive: N=153; AUX-II Nab negative: N=136

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for trial AUX-CC-803

Title: A PHASE 3, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF THE SAFETY AND EFFECTIVENESS OF AA4500 ADMINISTERED TWICE PER TREATMENT CYCLE FOR UP TO FOUR TREATMENT CYCLES (2 x 4) IN MEN WITH PEYRONIE'S DISEASE		
Study identifier	AUX-CC-803	
Design	Phase 3, double-blind, placebo controlled study	
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	12 months not applicable not applicable
Hypothesis	Superiority	

Treatment groups	Active		AA4500 0.58 mg Two injections separated by approximately 24 to 72 hours, repeated after 42 days (±5 days) for up to four treatment cycles N=278
	Placebo		Placebo Two injections separated by approximately 24 to 72 hours, repeated after 42 days (±5 days) for up to four treatment cycles N=140
Endpoints and definitions	Co-primary endpoints		Percent change from baseline in curvature deformity Change from baseline total score in Peyronie's disease bother domain of the PDQ
	The first family of secondary endpoints (SE#1)		included: • responder analysis based on the global assessment of Peyronie's disease • change from baseline in severity of Peyronie's disease symptoms of the PDQ • change in overall satisfaction domain of the IIEF
	The second family of secondary endpoints (SE#2)		• composite responder based on change from baseline in curvature deformity and either Peyronie's disease bother score or the reporting of sexual activity • penile plaque consistency • change in penile length • change from baseline in penile pain of the PDQ in subset of subjects with a baseline pain score of at least 4
Database lock	08 May 2012		

Results and analysis			
Analysis description	**Primary analysis**		
Analysis population and time point description	The modified intent-to-treat (mITT) population: defined as all ITT subjects who were both in the Peyronie's disease questionnaire (PDQ) and penile measurement (PM) populations. Subjects must have had vaginal intercourse within 3 months of any PDQ assessment. If subjects were not sexually active within 3 months of baseline they could not be included in the primary analysis for efficacy since they were ineligible to complete the PDQ. Week 52 (LOCF)		
Descriptive statistics and estimate variability	Treatment group	AA4500	Placebo
	Number of subjects	199	104
	Mean % change from baseline in curvature deformity	-37.6	-21.3
	Standard deviation	30.29	29.89
	Mean change from baseline in PD bother	-3.3	-2.0
	Standard deviation	3.83	3.53
Effect estimate per comparison	Mean % change from baseline in curvature deformity	Comparison groups	AA4500 versus placebo
		P-value	0.0005 Significant based on multiple comparison algorithm
	Mean change from baseline in PD bother	Comparison groups	AA4500 versus placebo
		P-value	0.0451 Significant based on multiple comparison algorithm
Notes	P-values are calculated using ANOVA with factors for drug (TRT), stratum of baseline penile curvature (SEV), and their interaction (TRT*SEV).		

Analysis description	Secondary endpoint analyses		
Descriptive statistics and estimate variability	Treatment group	AA4500	Placebo
	Number of subjects	199	104
	Incidence of responders based on overall global assessment of PD	66.2%	29.1%
Effect estimate per comparison	Incidence of responders based on overall global assessment of PD	Comparison groups	AA4500 versus placebo
		P-value	<0.0001 Significant based on multiple comparison algorithm
Notes	A Responder is defined as a subject who recorded his Peyronie's disease had either improved in a small but important way, moderately improved, or much improved in overall global assessment question. P-value is calculated using CMH test controlling for stratum of baseline penile curvature.		
Descriptive statistics and estimate variability	Treatment group	AA4500	Placebo
	Number of subjects	199	104
	Mean change from baseline in PD physical and psychological symptoms	-3.2	-1.6
	Standard deviation	5.23	4.50
Effect estimate per comparison	Mean change from baseline in PD physical and psychological symptoms	Comparison groups	AA4500 versus placebo
		P-value	0.0268 Not significant based on multiple comparison algorithm
Notes	P-values are calculated using ANOVA with factors for drug (TRT), stratum of baseline penile curvature (SEV), and their interaction (TRT*SEV).		

Descriptive statistics and estimate variability	Treatment group	AA4500	Placebo
	Number of subjects	199	104
	Mean change from baseline in IIEF overall satisfaction	1.0	0.5
	Standard deviation	2.55	2.42
Effect estimate per comparison	Mean change from baseline in IIEF overall satisfaction	Comparison groups	AA4500 versus placebo
		P-value	0.0800 Not significant based on multiple comparison algorithm
Notes	P-values are calculated using ANOVA with factors for drug (TRT), stratum of baseline penile curvature (SEV), and their interaction (TRT*SEV).		

Descriptive statistics and estimate variability	Treatment group	AA4500	Placebo
	Number of subjects	277	140
	Incidence of composite responder based on change from baseline in curvature deformity and either PD bother or the reporting of sexual activity	50.6%	25.4%
Effect estimate per comparison	Incidence of composite responder based on change from baseline in curvature deformity and either PD bother or the reporting of sexual activity	Comparison groups	AA4500 versus placebo
		P-value	<0.0001 Significant based on multiple comparison algorithm
Notes	A Responder is defined as a subject who satisfied the following two criteria at that visit: percent reduction from baseline in penile curvature is 20% or more and reduction from baseline in PDQ PD bother score is 1 or more, or change from reporting no sexual activity at Screening to reporting sexual activity. P-value is calculated based on composite responder (Yes or No) using CMH test controlling for stratum of baseline penile curvature. NOTE: the analysis population is ITT.		
Descriptive statistics and estimate variability	Treatment group	AA4500	Placebo
	Number of subjects	199	104
	Mean change from baseline in penile plaque consistency	-0.7	-0.6
	Standard deviation	0.97	0.84
Effect estimate per comparison	Mean change from baseline in penile plaque consistency	Comparison groups	AA4500 versus placebo
		P-value	0.3085 Not significant based on multiple comparison algorithm
Notes	P-values are calculated based on the difference in penile plaque consistency score from baseline (score @ visit - score @ baseline) using ANOVA with factors for drug (TRT), stratum of baseline penile curvature (SEV), and their interaction (TRT*SEV).		

Descriptive statistics and estimate variability	Treatment group	AA4500	Placebo
	Number of subjects	199	104
	Mean change from baseline in penile length	0.4	0.1
	Standard deviation	1.29	1.11
Effect estimate per comparison	Mean change from baseline in penile length	Comparison groups	AA4500 versus placebo
		P-value	0.6321 Not significant based on multiple comparison algorithm
Notes	P-values are calculated using ANOVA with factors for drug (TRT), stratum of baseline penile curvature (SEV), and their interaction (TRT*SEV).		
Descriptive statistics and estimate variability	Treatment group	AA4500	Placebo
	Number of subjects	77	40
	Mean change from baseline in PD penile pain	-5.1	-4.0
	Standard deviation	5.16	4.09
Effect estimate per comparison	Mean change from baseline in PD penile pain	Comparison groups	AA4500 versus placebo
		P-value	0.7965 Not significant based on multiple comparison algorithm
Notes	P-values are calculated using ANOVA with factors for drug (TRT), stratum of baseline penile curvature (SEV), and their interaction (TRT*SEV). NOTE: mITT patients that had a PD penile pain score of ≥4 at baseline.		

- **Table 2**. Summary of Efficacy for trial AUX-CC-804

• Title: A PHASE 3, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF THE SAFETY AND EFFECTIVENESS OF AA4500 ADMINISTERED TWICE PER TREATMENT CYCLE FOR UP TO FOUR TREATMENT CYCLES (2 x 4) IN MEN WITH PEYRONIE'S DISEASE		
• Study identifier	• AUX-CC-804 •	
• Design	• Phase 3, double-blind, placebo controlled study •	
	• Duration of main phase: • Duration of run-in phase:	• 12 months • not applicable

	• Duration of extension phase:		• not applicable
• Hypothesis	• Superiority		
• Treatment groups	• Active		• AA4500 0.58 mg • Two injections separated by approximately 24 to 72 hours, repeated after 42 days (±5 days) for up to four treatment cycles • N=274
	• Placebo		• Placebo • Two injections separated by approximately 24 to 72 hours, repeated after 42 days (±5 days) for up to four treatment cycles • N=141
• Endpoints and definitions	• Co-primary endpoints	•	• Percent change from baseline in curvature deformity • Change from baseline total score in Peyronie's disease bother domain of the PDQ
	• The first family of secondary endpoints (SE#1)	•	• included: • responder analysis based on the global assessment of Peyronie's disease • change from baseline in severity of Peyronie's disease symptoms of the PDQ • change in overall satisfaction domain of the IIEF
	• The second family of secondary endpoints (SE#2)	•	• composite responder based on change from baseline in curvature deformity and either Peyronie's disease bother score or the reporting of sexual activity • penile plaque consistency • change in penile length • change from baseline in penile pain of the PDQ in subset of subjects with a baseline pain score of at least 4
• Database lock	• 21 May 2012		
• **Results and analysis**			

• **Analysis description**	• **Primary analysis**		
• Analysis population and time point description	• The modified intent-to-treat (mITT) population: defined as all ITT subjects who were both in the Peyronie's disease questionnaire (PDQ) and penile measurement (PM) populations. Subjects must have had vaginal intercourse within 3 months of any PDQ assessment. If subjects were not sexually active within 3 months of baseline they could not be included in the primary analysis for efficacy since they were ineligible to complete the PDQ. • • Week 52 (LOCF)		
• Descriptive statistics and estimate variability	• Treatment group	• AA4500	• Placebo
	• Number of subjects	• 202	• 107
	• Mean % change from baseline in curvature deformity	• -30.5	• -15.2
	• Standard deviation	• 27.70	• 28.66
	• Mean change from baseline in PD bother	• -2.4	• -1.6
	• Standard deviation	• 3.62	• 3.52
• Effect estimate per comparison	• Mean % change from baseline in curvature deformity	• Comparison groups	• AA4500 versus placebo
		• P-value	• 0.0059 • Significant based on multiple comparison algorithm
	• Mean change from baseline in PD bother	• Comparison groups	• AA4500 versus placebo
		• P-value	• 0.0496 • Significant based on multiple comparison algorithm

• Notes	• P-values are calculated using ANOVA with factors for drug (TRT), stratum of baseline penile curvature (SEV), and their interaction (TRT*SEV).		
• **Analysis description**	• **Secondary endpoint analyses**		
• Descriptive statistics and estimate variability	• Treatment group	• AA4500	• Placebo
	• Number of subjects	• 202	• 107
	• Incidence of responders based on overall global assessment of PD	• 55.4%	• 29.9%
• Effect estimate per comparison	• Incidence of responders based on overall global assessment of PD	• Comparison groups	• AA4500 versus placebo
		• P-value	• <0.0001 • Significant based on multiple comparison algorithm
• Notes	• A Responder is defined as a subject who recorded his Peyronie's disease had either improved in a small but important way, moderately improved, or much improved in overall global assessment question. • P-value is calculated using CMH test controlling for stratum of baseline penile curvature.		
• Descriptive statistics and estimate variability	• Treatment group	• AA4500	• Placebo
	• Number of subjects	• 202	• 107
	• Mean change from baseline in PD physical and psychological symptoms	• -2.6	• -1.0

	• Standard deviation	• 4.83	• 4.78
• Effect estimate per comparison	• Mean change from baseline in PD physical and psychological symptoms	• Comparison groups	• AA4500 versus placebo
		• P-value	• 0.0340 • Not significant based on multiple comparison algorithm
• Notes	• P-values are calculated using ANOVA with factors for drug (TRT), stratum of baseline penile curvature (SEV), and their interaction (TRT*SEV).		
• Descriptive statistics and estimate variability	• Treatment group	• AA4500	• Placebo
	• Number of subjects	• 202	• 107
	• Mean change from baseline in IIEF overall satisfactio n	• 1.0	• 0.3
	• Standard deviation	• 2.33	• 2.35
• Effect estimate per comparison	• Mean change from baseline in IIEF overall satisfactio n	• Comparison groups	• AA4500 versus placebo
		• P-value	• 0.1169 • Not significant based on multiple comparison algorithm
• Notes	• P-values are calculated using ANOVA with factors for drug (TRT), stratum of baseline penile curvature (SEV), and their interaction (TRT*SEV).		
• Descriptive statistics and estimate variability	• Treatment group	• AA4500	• Placebo
	• Number of subjects	• 274	• 141

	• Incidence of composite responder based on change from baseline in curvature deformity and either PD bother or the reporting of sexual activity	• 42.3%	• 30.6%
• Effect estimate per comparison	• Incidence of composite responder based on change from baseline in curvature deformity and either PD bother or the reporting of sexual activity	• Comparison groups	• AA4500 versus placebo
		• P-value	• 0.0249 • Not significant based on multiple comparison algorithm
• Notes	• A Responder is defined as a subject who satisfied the following two criteria at that visit: percent reduction from baseline in penile curvature is 20% or more and reduction from baseline in PDQ PD bother score is 1 or more, or change from reporting no sexual activity at Screening to reporting sexual activity. • P-value is calculated based on composite responder (Yes or No) using CMH test controlling for stratum of baseline penile curvature. NOTE: the analysis population is ITT.		
• Descriptive statistics and estimate variability	• Treatment group	• AA4500	• Placebo
	• Number of subjects	• 202	• 107

	• Mean change from baseline in penile plaque consistency	• -0.8	• -0.4
	• Standard deviation	• 0.97	• 0.86
• Effect estimate per comparison	• Mean change from baseline in penile plaque consistency	• Comparison groups	• AA4500 versus placebo
		• P-value	• 0.0144 • Not significant based on multiple comparison algorithm
• Notes	• P-values are calculated based on the difference in penile plaque consistency score from baseline (score @ visit - score @ baseline) using ANOVA with factors for drug (TRT), stratum of baseline penile curvature (SEV), and their interaction (TRT*SEV).		
• Descriptive statistics and estimate variability	• Treatment group	• AA4500	• Placebo
	• Number of subjects	• 202	• 107
	• Mean change from baseline in penile length	• 0.5	• 0.2
	• Standard deviation	• 1.34	• 1.49
• Effect estimate per comparison	• Mean change from baseline in penile length	• Comparison groups	• AA4500 versus placebo
		• P-value	• 0.0248 • Not significant based on multiple comparison algorithm

• Notes	• P-values are calculated using ANOVA with factors for drug (TRT), stratum of baseline penile curvature (SEV), and their interaction (TRT*SEV).		
• Descriptive statistics and estimate variability	• Treatment group	• AA4500	• Placebo
	• Number of subjects	• 87	• 51
	• Mean change from baseline in PD penile pain	• -3.8	• -4.5
	• Standard deviation	• 5.93	• 5.39
• Effect estimate per comparison	• Mean change from baseline in PD penile pain	• Comparison groups	• AA4500 versus placebo
		• P-value	• 0.6949 • Not significant based on multiple comparison algorithm
• Notes	• P-values are calculated using ANOVA with factors for drug (TRT), stratum of baseline penile curvature (SEV), and their interaction (TRT*SEV). NOTE: mITT patients that had a PD penile pain score of ≥4 at baseline.		

Analysis performed across trials (pooled analyses and meta-analysis)

Because Studies AUX-CC-803 and AUX-CC-804 were identical in design and powered to evaluate the co-primary efficacy endpoints, data from these two studies were pooled in a post-hoc meta-analysis to increase the precision for estimation and to further understand and characterize the secondary efficacy endpoints of AA4500 in the treatment of Peyronie's disease. The same multiple comparison algorithm that was utilized for the a-priori co-primary and the secondary endpoints in the individual studies was repeated for the meta analysis. Data is shown in paragraphs above.

Clinical studies in special populations

Dedicated studies in special populations were not performed.

Supportive study

Results from the supportive phase III study AUX-CC-802

The inclusion/exclusion criteria, the efficacy and safety endpoints, and the dosing regimen in this study were identical to the Phase 3 double-blind, placebo-controlled studies (AUX-CC-803 and AUX-CC-804).

The primary purpose of this open-label study was to treat approximately 300 additional subjects, so that when added to the AA4500-treated subjects in the Phase 3 double-blind, placebo-controlled studies, sufficient numbers of AA4500-treated subjects are available to provide an adequate evaluation of safety for the proposed indication.

One further purpose was to include EU subjects to demonstrate transferability of the overall clinical data package to a EU treatment setting. Demographics, baseline medical condition and PD history between all subjects (incl. US, New Zealand, EU) and EU subjects were largely similar.

AUX-CC-802 Study Design

Study AUX-CC-802 was a Phase 3 open-label study in which subjects received up to four treatment cycles of AA4500 0.58 mg in the treatment of Peyronie's disease. Subjects were screened for study eligibility within 21 days before the initial injection of study drug in the first treatment cycle. Enrolment included all subjects who met the eligibility criteria and who received placebo in a previous Auxilium-sponsored study (including the Phase 2b study AUX-CC-801), subjects who received one treatment cycle of AA4500 in the pharmacokinetic study (AUX-CC-805), and naïve subjects in the United States, New Zealand, and Europe. AA4500 was administered and dosed in the same way as in previous phase III trials.

Table 37: Study Drug Assignment

Study Drug	Injection Volume	Treatment Cycle
AA4500 0.58 mg	0.25 mL injection volume	• Two injections separated by approximately 24 to 72 hours • Penile plaque modeling procedure 24 to 72 hours after the second injection of each treatment cycle. Up to four treatment cycles approximately 6 weeks apart.

After the final injection (24 to 72 hours) of each treatment cycle, the investigator or qualified designee (ie, qualified by license, education, and training to perform the study procedure according to local, state, and country requirements) modeled the plaque in an attempt to stretch or elongate the plaque. If the subject's penile curvature was reduced to <15° after the first, second, or third cycle of injections or if the investigator determined further treatment was not clinically indicated (eg, adverse events [AEs], allergic reaction), subsequent treatment cycles were not administered.

Following the maximum of four treatment cycles, each subject was followed for additional safety and efficacy assessments on Days 168 (±7 days) and 252 (±7 days) (nominal weeks 24 and 36).

Enrolment

A total of 348 subjects, including 192 EU subjects, were enrolled in the study. 328 subjects were enrolled directly into this study and 20 subjects were rolled over from AUX-CC-805 (pharmacokinetic study).

Most subjects (88.2% all enrolled subjects, 91.1% EU subjects) completed the study. The most common reason for premature discontinuation from the study was withdrawal of consent among all subjects (5.2%) and lost to follow-up in EU subjects (3.1%).

AUX-CC-802: Demographics

Demographic and baseline characteristics were similar in all subjects and EU subjects. The majority of subjects were white (96.0% all subjects, 97.9% EU subjects) and between 45 and 64 years of age (73.2% all subjects, 77.0% EU subjects). The median age of subjects overall was 57.0 years in all subjects and 55.0 years in EU subjects.

Table 15: Peyronie's Disease History (ITT Population)

Parameter	AA4500 All Subjects N=347	AA4500 EU Subjects N=191
Duration (years) of Peyronie's disease		
Mean (SD)	2.97 (2.815)	2.38 (1.876)
Median	2.00	1.70
Min, Max	0.6, 29.4	0.6, 15.4
Erectile dysfunction, n (%)		
No	227 (65.4)	147 (77.0)
Yes	120 (34.6)	44 (23.0)
Trauma to the penis, n (%)		
No	290 (83.6)	168 (88.0)
Yes	57 (16.4)	23 (12.0)
Family history of Peyronie's disease, n (%)		
No	276 (97.2)	156 (96.9)
Yes	8 (2.8)	5 (3.1)
Unknown	63	30
Prior exposure to AA4500, n (%)		
No	346 (99.7)	191 (100.0)
Yes	1 (0.3)	0

Data source: Table 14.1.3.1 and EU Table 14.1.3.1

At screening, most subjects who received at least one dose of AA4500 had no calcification of the penis (62.2% all subjects, 63.4% EU subjects). The majority of subjects who received at least one dose of AA4500 had:

- Curvature deformity between 30º and 60º (69.5% all subjects, 62.8% EU subjects)
- One penile plaque (84.1% all subjects, 80.1% EU subjects)
- Moderate firmness or firm throughout plaque consistency (77.2% all subjects, 75.9% EU subjects)
- No pain on palpation (84.7% all subjects, 79.1% EU subjects)

The most common (≥10.0% in either population) medical conditions among subjects who received at least one dose of AA4500 included hypertension (29.1% all subjects, 28.3% EU subjects), hypercholesterolaemia (14.7% all subjects, 13.6% EU subjects), and Dupuytren's contracture (10.4% all subjects, 8.4% EU subjects).

The co-primary endpoints were:

- change/percent change from baseline curvature deformity from baseline to Week 36
- change from baseline total score in PD bother of the PDQ from baseline to Week 36

Analysis of Efficacy

The visit distribution of Week 36 (LOCF) by primary endpoint in the final analysis is provided for all subjects and EU subjects, respectively.

Change from baseline in curvature deformity at week 36

Improvement in curvature deformity was similar in all subjects and EU subjects. A statistically significant mean percent improvement of 34.4% and 34.7% in curvature deformity from baseline to Week 36 (LOCF) was observed among all subjects and EU subjects, respectively (Table below).

Table 19: Mean Percent Improvement From Baseline in Curvature Deformity at Week 36 (LOCF) (mITT Population)

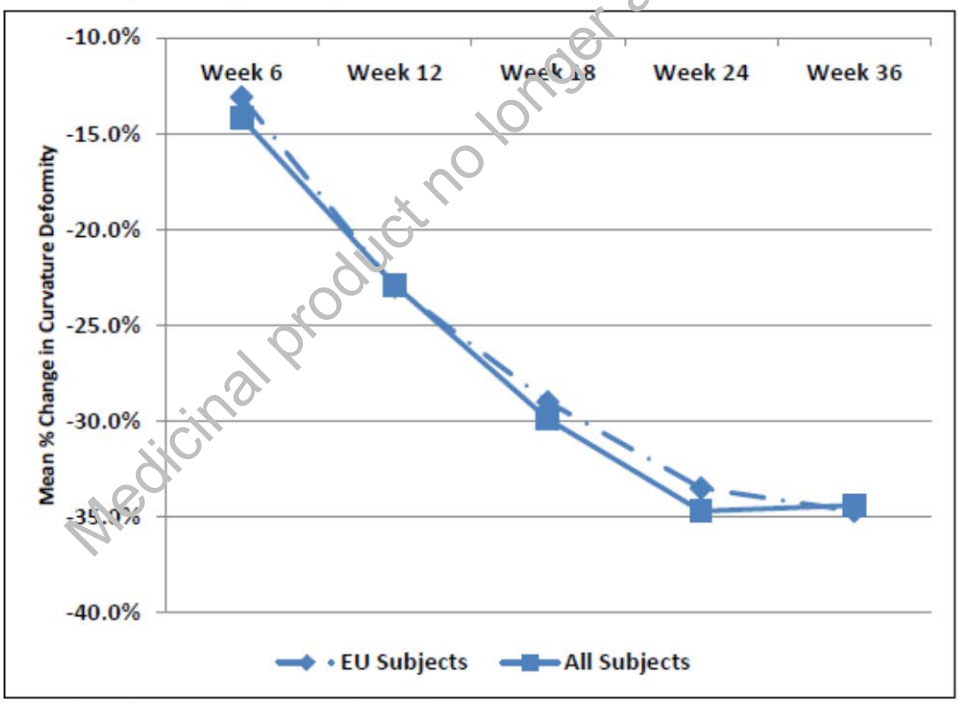
	AA4500	
	All Subjects N=238	EU Subjects N=138
Baseline value Mean (SD) Min, Max	 53.0 (14.82) 30, 90	 55.7 (15.37) 30, 90
Week 36 value (LOCF) Mean (SD) Min, Max	 34.7 (15.26) 0, 75	 36.2 (14.81) 0, 70
Mean % change from baseline 95% CI of mean	-34.4 -37.6, -31.2*	-34.7 -38.6, -30.8*

Data source: Table 14.2.2.1 and EU Table 14.2.2.1

* Based on the 95% CI of the mean not including zero, the percent change from baseline was considered statistically significant.

The mean degree of curvature deformity and mean percent change in curvature deformity were statistically significant at Weeks 24 and 36 (LOCF) for all subjects and EU subjects in the mITT population. The improvement in curvature deformity began after the first treatment cycle (Week 6); continued improvement was seen following each dosing cycle (at least 18 weeks after the first injection), and improvement was maintained through Week 36 (LOCF).

Figure 2: Mean Percent Change From Baseline in Curvature Deformity Over Time (mITT Population)



Data source: Table 14.2.2.1 and EU Table 14.2.2.1
Note: Week 36 value is LOCF.

Change from baseline in subject-reported Peyronie's Disease Bother Score

Improvement in subject-reported Peyronie's disease bother score was similar in all subjects and EU subjects. A statistically significant mean reduction of 3.3 and 2.8 in subject-reported Peyronie's disease bother from baseline to Week 36 (LOCF) was observed among all subjects and EU subjects, respectively (Table below).

Table 20: Mean Change From Baseline in Peyronie's Disease Bother Score at Week 36 (LOCF) (mITT Population)

	AA4500	
	All Subjects N=238	EU Subjects N=138
Baseline value		
Mean (SD)	7.3 (3.52)	6.9 (3.59)
Min, Max	0, 16	0, 14
Week 36 value (LOCF)		
Mean (SD)	4.1 (3.50)	4.1 (3.46)
Min, Max	0, 15	0, 15
Change from baseline		
Mean	-3.3	-2.8
95% CI of mean	-3.7, -2.8*	-3.4, -2.3*

Data source: Table 14.2.3.3.1 and EU Table 14.2.3.3.1

* Based on the 95% CI of the mean not including zero, the change from baseline was considered statistically significant.

Secondary Endpoints

Secondary endpoint efficacy results were similar in all subjects and EU subjects.

Incidence of Responders Based on Overall Global Assessment of Peyronie's Disease

The incidence of responders based on the overall global assessment of Peyronie's disease at Week 36 (LOCF) was statistically significant in both populations (72.3% all subjects, 71.7% EU subjects).

Table 23: Incidence of Responders Based on Overall Global Assessment of Peyronie's Disease at Week 36 (LOCF) (mITT Population)

Global assessment	All Subjects N=238	EU Subjects N=138
Much worse (-3)	1 (0.4)	1 (0.7)
Moderately worse (-2)	7 (2.9)	3 (2.2)
A little worse (-1)	4 (1.7)	2 (1.4)
Stayed about the same (0)	54 (22.7)	33 (23.9)
Improved in a small but important way (1)	41 (17.2)	29 (21.0)
Moderately improved (2)	68 (28.6)	36 (26.1)
Much improved (3)	63 (26.5)	34 (24.6)
Responder[a] status		
Yes	172 (72.3)	99 (71.7)
No	66 (27.7)	39 (28.3)
95% CI of responder rate	66.6, 78.0*	64.2, 79.3*

Data source: Table 14.2.5.1 and Table 14.2.5.2; EU Table 14.2.5.1 and Table 14.2.5.2

[a] A responder was defined as a subject who recorded his Peyronie's disease had either improved in a small but important way, moderately improved, or much improved in overall global assessment question.

* Based on the 95% CI of the responder rate not including zero, the responder rate at Week 36 (LOCF) was considered statistically significant.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

With study AUX-CC-801 it could be shown that in those patients receiving Xiapex plus modelling the largest treatment effect in terms of %-penile curvature reduction (-32.4%) was achieved as compared to the reduction in the overall Xiapex group with or without modelling (-29.7%) and those patients receiving Xiapex but no modelling (-27.1%). Hence, modelling 24 to 72 hours after the second injection of one treatment cycle was taken forward into subsequent phase III studies AUX-CC-803 and AUX-CC-804.

According to the leading expert consensus paper (Ralph et al. 2010) correction of the erect penile deformity (i.e. curve, narrowing, shortening) is the most critical outcome measure. Peyronie's disease has a significant psychological impact on the patient suffering from the disease. In order to introduce a

subjective patient-reported outcome measure, the applicant had designed and developed the first validated instrument to assess the psychosexual consequences of PD. The PDQ is considered a meaningful and acceptable efficacy patient reported outcome measure in PD trials. The choice of co-primary endpoints for the pivotal trials was undertaken on the basis of results received from phase IIb study AUX-CC-801

The efficacy of Xiapex was evaluated in two randomized, double-blind, placebo-controlled, multi-centred trials in 832 (ITT) adult males with Peyronie's disease (Studies 803 and 804). At study entry, patients must have had penile curvature deformity of at least 30 degrees in the stable phase of Peyronie's disease. Patients were excluded if they had a ventral curvature deformity, an isolated hourglass deformity or a calcified plaque that could have interfered with the injection technique. At baseline, the mean duration of PD history of included men (mean age 57-58 years) was 3-5 years. Typically for this stable stage of the disease, pain was not an issue for the vast majority of patients, however, mean penile curvature was pronounced at baseline (48-52° degrees). The curvature deformity often leads to significant bother, distress, and sexual dysfunction among PD patients. Patient Bother was quantified by means of the Peyronie's Disease Bother scale (0-16) and was recorded as 7.4-8.2 across treatment groups at baseline (corresponding to the "moderately bothered" category). The Bother domain score is a composite of the following patient-reported items: concern about erection pain, erection appearance, and the impact of Peyronie's disease on intercourse and on frequency of intercourse. About every second included subject (46.2-53.9% across treatment groups) had a history of erectile dysfunction.

In these trials, patients were given up to 4 treatment cycles of Xiapex or placebo (weeks 0, 6, 12, 18), and were followed in a non-treatment follow-up period (weeks 24 -52). In each treatment cycle, two injections of XIAPEX or two injections of placebo were administered 1 to 3 days apart. A penile modelling procedure was performed on patients at the study site 1 to 3 days after the second injection of the cycle. The treatment cycle was repeated at approximately six-week intervals for up to three additional times, for a maximum of 8 total injection procedures and 4 total modelling procedures. In addition, patients were instructed to perform penile modelling at home for six weeks after each treatment cycle.

Before the first dose of study drug was administered, eligible subjects were stratified by the degree of curvature deformity (30 to 60 degrees, and 61 to 90 degrees) and then randomized into two treatment groups to receive either Xiapex or placebo in a 2:1 ratio. The efficacy population (modified intent-to-treat (mITT) population) comprised a total of 612 intent-to-treat subjects who had both a curvature deformity measurement and a PDQ assessment at baseline and at one or more subsequent time points in Studies 803 and 804, and had engaged in vaginal intercourse within 3 months prior to each PDQ assessment.

The pivotal studies 803 and 804 were conducted in Australia and the US. A further open-label study AUX-CC-802 (including 192/348 EU subjects) was conducted to increase the safety database and to obtain efficacy and safety results in European subjects. Study 802 did not point to any relevant differences between the US/Australian patient population and Europeans in terms of baseline disease conditions and treatment outcome of AA4500.

The studies appear to be well designed and adequate to demonstrate efficacy in Peyronie's disease. The chosen co-primary endpoints and the definition of the study population are acceptable. The set of secondary and other endpoints is considered appropriate. Furthermore the strategy used to control the type I error for multiplicity of comparisons is appropriate. The conduct of the studies is considered to be according to expectations.

Efficacy data and additional analyses

Co-Primary endpoints

As confirmed by prior CHMP Scientific Advice, the co-primary endpoints were defined as:

- the percent change from baseline to Week 52 in penile curvature deformity and;
- the change from baseline to Week 52 in the Bother domain score of the PDQ

AA4500 0.58 mg was statistically superior to placebo with respect to the co-primary endpoints (ie, curvature deformity and patient-reported Peyronie's disease bother) in both clinical studies:

In each study, men treated with AA4500 had a statistically significant ($p \leq 0.0059$) greater percent reduction in curvature deformity compared with men treated with placebo. A relative reduction of penile

curvature deformity (48.8°-51.3° at baseline) of -37.6% (placebo -21.3%, study 803), resp. -30.5% (placebo -15.2%, study 804) was achieved. Hence, at the end of the 1-year observation period a residual curvature of 31.0°-35.1° remained.

Improvement in curvature deformity was apparent after the first treatment cycle (Week 6) with continued improvement noted after each of the three subsequent treatment cycles. The improvement in curvature deformity was maintained through the end of each study (Week 52). No data are available for administration of more than four treatment cycles. Likewise, no data are available on recurrence of penile curvature after more than one year after the first AA4500 injection. The lack of data for more than one course is outlined in the product information and a long term study AUX-CC-810 will be performed to follow up on recurrence rate, immunogenicity (kinetics of titre levels of potentially neutralising collagenase antibodies, long-term effects of MMP cross-allergy), and the potential risks of retreating patients (in relation to immunogenicity) as outlined in the RMP.

Reduction in penile curvature translated in a reduction of patients' bother about PD.

The baseline bother score was 7.4 to 8.2 across treatment arms and studies. Translating the score into bother categories, patients were about moderately bothered at baseline. The PDQ Bother score was assessed at three time points (screening, week 24 and week 52). Hence, increasing reduction of the bother score with increasing number of treatment cycles could not be assessed.

Like already observed for the curvature reduction endpoint, the active and the placebo curves display a similar course with no recurrence of bother between week 24 (assessment of the final injection) and week 52 (end of double-blind treatment period).

At the pre-defined time point at the end of the observation period (week 52), AA4500 was borderline statistically superior to placebo in terms of PDQ Bother score reduction (AUX-CC-803: p=0.0451; AUX-CC-804: p=0.0496).

Secondary endpoints

When being asked the global assessment / overall change in symptoms at week 52, overall 66% (study AUX-CC-803) resp. 55% (AUX-CC-804) rated themselves as having improved in a small but important way, having moderately improved or even having much improved and were thus defined as responders. These responders had a mean reduction in curvature of at least 20% and a reduction of the PDQ Bother score of at least one point as compared to baseline.

The observed reductions in curvature and PDQ Bother score of those rating themselves as having improved (at least in a small but important way) points to the clinical relevance of the therapeutic effect achieved with AA4500 after the four treatment cycles.

Other secondary endpoints (e.g. PDQ Physical and Psychological Symptom Score or International Index of Erectile Dysfunction Overall Satisfaction (IIED) did not demonstrate significant superiority over placebo. when both pivotal studies were separately assessed, however, delivered statistical significance in the pooled analysis of study 803 and 804.

The detection of neutralizing antibodies to either AUX-I or AUX-II did not negatively affect the efficacy of Xiapex in the treatment of PD over the 4-cycle one-year observation period.

2.4.4. Conclusions on the clinical efficacy

Overall, it is concluded that the efficacy of AA4500 in adult men in a stable stage of Peyronie's disease was adequately demonstrated for a course of up to four treatment cycles (corresponding to 8 injections) and an observation period of up to one year.

Limitation of the long term data are outlined in the Product information and additional data on recurrence rate, immunogenicity, and the potential risks of retreating patients will be provided post authorisation from study AUX-CC-810 as outlined in the RMP.

2.5. Clinical safety

The safety of AA4500 was assessed in 7 clinical studies conducted in subjects with Peyronie's disease (Table 3).

Table 3: Studies Included in the Formal Integrated Safety Database

Phase 2 Program					**Phase 3 Program**		
Study Type	**Dose/Regimen Evaluation**	**Dose/Regimen Evaluation**	**Dose/Regimen Evaluation**	**Pharmaco-kinetic**	**Phase 3 Open-Label Program**	**Phase 3 Double Program (Iden Studies)**	
Study Designation	**AUX-CC-1030-PEY**	**AUX-CC-1035-PEY**	**AUX-CC- 801**	**AUX-CC-805**	**AUX-CC-802**	**AUX-CC-803**	
Number of Subjects	N=25 AA4500=25	N=10 AA4500=10	N=147 AA4500=111 Placebo=36[a]	N=20 AA4500=20[b]	N=347 (1[c]) AA4500=347 (23[a]+20[b]+304)	N=417 (1[c]) AA4500=277 Placebo=140	
Injection Regimen	Six injections 0.58 mg (10,000 U) -M[d]	Nine injections 0.58 mg (10,000 U) +M[d]	Six injections 0.58 mg +/-M[d]	Two injections 0.58 mg +M[d]	Eight injections 0.58 mg +M[d]	Eight injections 0.58 mg +M[d]	
Treatment Cycle Regimen	Three injections for two cycles 3 months	Three injections for three cycles 6 weeks	Two injections for three cycles 6 weeks	Two injections for one cycle	Two injections for four cycles 6 weeks	Two injections for four cycles 6 weeks	
Start Date	Nov 1998	Jan 2004	Aug 2008	Sep 2011	Nov 2010	Oct 2010	
Location	United States (One site)	United States (One site)	United States (multi-site)	United States (One site)	United States, New Zealand, Europe (multi-site)	United States, Australia (multi-site)	

[a] 23 of the 36 placebo subjects from AUX-CC-801 rolled over into AUX-CC-802.
[b] 20 subjects who received Treatment Cycle 1 in PK study AUX-CC-805 rolled over into AUX-CC-802 for Treatment Cycles 2, 3, and 4. All safety and efficacy data are included in the AUX-CC-802 Final CSR.
[c] Randomized but not treated were not included (total of five subjects randomized but not treated in the Phase 3 program)
[d] +M=penile modeling included; -M=penile modeling not included

The integrated electronic safety database includes 1044 subjects who received at least one dose of AA4500 0.58 mg. All subgroup analyses were performed on the Phase 3 Studies analysis population, which includes 898 subjects.

Four studies (two Phase 1 studies [Gelbard et al., 1985 and Gelbard et al., 1993] and two Phase 2 studies [AUX-CC-1001-PEY and AUX-CC-1025-PEY]) were not included in the integrated electronic safety database (N=245 who received at least one dose of AA4500), since the Phase 1 studies were pilot studies and AUX-CC-1001-PEY and AUX-CC-1025-PEY were terminated during the early stage of development due to lack of efficacy. Results from these studies are presented separately.

Three main integrated analysis populations were analyzed in order to demonstrate the safety of AA4500 in the treatment of Peyronie's disease:

- The *Phase 3 Double-Blind, Placebo-Controlled Studies analysis population* comprised 551 AA4500 (0.58 mg) subjects and 281 placebo subjects who received at least one injection of double-blind study drug in AUX-CC-803 or AUX-CC-804.
- The *Phase 3 Studies analysis population* comprised 898 subjects who received at least one injection of AA4500 (0.58 mg) in AUX-CC-802, AUX-CC-803, or AUX-CC-804. These three studies

had the same treatment plan, which consisted of four treatment cycles, eight injections per subject, and penile modeling.

- The All Subjects Who Received At Least 1 Dose of AA4500 0.58 mg analysis population (hereafter referred to as the *Global Safety analysis population*) comprised 1044 subjects who received at least one injection of AA4500 (0.58 mg) in any of the seven studies included in the integrated electronic safety database. These studies included a mixture of treatment plans.

Additionally, a safety sub-analysis was performed on those subjects from investigator sites in EU countries that participated in Study AUX-CC-802.

Patient exposure

The extent of exposure for the *Phase 3 Double-Blind, Placebo-Controlled Studies analysis population* is summarized in Table 4. Eight hundred thirty-two (832) subjects (551 AA4500 and 281 placebo) received 6215 (4069 AA4500 and 2146 placebo) injections of study drug. The majority of AA4500 (78.8%) and placebo (87.9%) subjects received all eight injections (ie, four treatment cycles) of study drug.

Table 4: Extent of Exposure – Phase 3 Double-Blind, Placebo-Controlled Studies

Statistic	AA4500 (N=551)	Placebo (N=281)
Injection cycles received, n (%)		
Cycle 1, Injection 1	551 (100.0)	281 (100.0)
Cycle 1, Injection 2	548 (99.5)	280 (99.6)
Cycle 2, Injection 1	531 (96.4)	278 (98.9)
Cycle 2, Injection 2	529 (96.0)	278 (98.9)
Cycle 3, Injection 1	501 (90.9)	263 (93.6)
Cycle 3, Injection 2	497 (90.2)	259 (92.2)
Cycle 4, Injection 1	461 (83.7)	254 (90.4)
Cycle 4, Injection 2	451 (81.9)	253 (90.0)
Total number of injections received, n (%)		
1	2 (0.4)	1 (0.4)
2	10 (1.8)	2 (0.7)
3	1 (0.2)	0 (0.0)
4	31 (5.6)	11 (3.9)
5	3 (0.5)	2 (0.7)
6	57 (10.3)	15 (5.3)
7	13 (2.4)	3 (1.1)
8	434 (78.8)	247 (87.9)
Total, n	4069	2146
Mean (SD)	7.4 (1.37)	7.6 (1.10)

Data source: ISS Table 14.1.3

The extent of exposure for the Phase 3 Studies analysis population is summarized in Table 5. Eight hundred ninety-eight (898) AA4500 subjects received 6614 injections of study drug. The majority of AA4500 subjects (78.4%) received all eight injections (ie, four treatment cycles) of study drug.

Table 5: Extent of Exposure – Phase 3 Studies

Statistic	AA4500 (N=898)
Injection cycles received, n (%)	
Cycle 1, Injection 1	898 (100.0)
Cycle 1, Injection 2	890 (99.1)
Cycle 2, Injection 1	868 (96.7)
Cycle 2, Injection 2	856 (95.3)
Cycle 3, Injection 1	816 (90.9)
Cycle 3, Injection 2	807 (89.9)
Cycle 4, Injection 1	746 (83.1)
Cycle 4, Injection 2	733 (81.6)
Total number of injections received, n (%)	
1	4 (0.4)
2	18 (2.0)
3	5 (0.6)
4	45 (5.0)
5	8 (0.9)
6	91 (10.1)
7	23 (2.6)
8	704 (78.4)
Total, n	6614
Mean (SD)	7.4 (1.41)

Data source: ISS Table 14.3.3

The extent of exposure for the *Global Safety analysis population* is summarized in Table 6. One thousand forty-four (1044) AA4500 subjects received 7466 injections of study drug (mean of 7.0 injections per subject). The majority of AA4500 subjects (67.4%) received eight injections (ie, four treatment cycles) of study drug.

Table 6: Extent of Exposure – Global Safety

Statistic	AA4500 (N=1044)
Injection cycles received, n (%)	
Cycle 1, Injection 1	1044 (100.0)
Cycle 1, Injection 2	1034 (99.0)
Cycle 1, Injection 3	34 (3.3)
Cycle 2, Injection 1	1004 (96.2)
Cycle 2, Injection 2	990 (94.8)
Cycle 2, Injection 3	27 (2.6)
Cycle 3, Injection 1	928 (88.9)
Cycle 3, Injection 2	918 (87.9)
Cycle 3, Injection 3	8 (0.8)
Cycle 4, Injection 1	746 (71.5)
Cycle 4, Injection 2	733 (70.2)
Total number of injections received, n (%)	
1	6 (0.6)
2	20 (1.9)
3	11 (1.1)
4	49 (4.7)
5	12 (1.1)
6	211 (20.2)
7	23 (2.2)
8	704 (67.4)
9	8 (0.8)
Total, n	7466
Mean (SD)	7.2 (1.49)

Data source: ISS Table 14.2.3
Note: Subjects from AUX-CC-805 had one treatment cycle, subjects from AUX-CC-1030-PEY had up to two treatment cycles, subjects from AUX-CC-1035-PEY and AUX-CC-201 had up to three treatment cycles, and subjects from AUX-CC-802, AUX-CC-803, and AUX-CC-804 had up to four treatment cycles. For AUX-CC-801, AUX-CC-802, AUX-CC-803, and AUX-CC-804, subjects received up to two injections for each treatment cycle, while for AUX-CC-1030-PEY and AUX-CC-1035-PEY, subjects received up to three injections for each treatment cycle.

Adverse events

Common Adverse Events: *Phase 3 Double-Blind, Placebo-Controlled Studies*

Treatment-emergent AEs occurring in ≥2.0% of subjects in the Phase 3 Double-Blind, Placebo-Controlled Studies analysis population are presented in Table 7.

Table 7: Percentage of Subjects With Treatment-Emergent (≥2.0% of Subjects in Either Treatment Group) and Treatment-Related Adverse Events – Phase 3 Double-Blind, Placebo-Controlled Studies

Preferred Term[a]	AA4500 (N=551) n (%)		Placebo (N=281) n (%)	
	All Adverse Events	Treatment-Related Adverse Events	All Adverse Events	Treatment-Related Adverse Events
Number (%) of subjects with ≥1 AE	508 (92.2)	464 (84.2)	172 (61.2)	102 (36.3)
Penile haematoma[b]	336 (61.0)	321 (58.3)	41 (14.6)	36 (12.8)
Penile pain	215 (39.0)	202 (36.7)	19 (6.8)	17 (6.0)
Penile swelling	209 (37.9)	196 (35.6)	3 (1.1)	3 (1.1)
Injection site pain	111 (20.1)	102 (18.5)	9 (3.2)	7 (2.5)
Injection site haematoma	106 (19.2)	96 (17.4)	30 (10.7)	22 (7.8)
Penile haemorrhage[c]	103 (18.7)	92 (16.7)	15 (5.3)	14 (5.0)
Penile oedema	85 (15.4)	81 (14.7)	1 (0.4)	1 (0.4)
Injection site swelling	65 (11.8)	64 (11.6)	2 (0.7)	2 (0.7)
Contusion	55 (10.0)	54 (9.8)	1 (0.4)	1 (0.4)
Ecchymosis	38 (6.9)	33 (6.0)	0 (0.0)	0 (0.0)
Blood blister	26 (4.7)	25 (4.5)	0 (0.0)	0 (0.0)
Injection site haemorrhage	25 (4.5)	18 (3.3)	13 (4.6)	7 (2.5)
Nasopharyngitis	19 (3.4)	0 (0.0)	6 (2.1)	0 (0.0)
Penile blister	18 (3.3)	18 (3.3)	0 (0.0)	0 (0.0)
Penile erythema	18 (3.3)	17 (3.1)	4 (1.4)	3 (1.1)
Pruritus genital	18 (3.3)	17 (3.1)	1 (0.4)	0 (0.0)
Erectile dysfunction	17 (3.1)	10 (1.8)	2 (0.7)	1 (0.4)
Local swelling	16 (2.9)	16 (2.9)	0 (0.0)	0 (0.0)
Painful erection	16 (2.9)	16 (2.9)	0 (0.0)	0 (0.0)
Upper respiratory tract infection	16 (2.9)	1 (0.2)	10 (3.6)	0 (0.0)
Headache	15 (2.7)	4 (0.7)	6 (2.1)	1 (0.4)
Back pain	14 (2.5)	3 (0.5)	9 (3.2)	1 (0.4)
Scrotal swelling	14 (2.5)	14 (2.5)	2 (0.7)	2 (0.7)
Sinusitis	14 (2.5)	0 (0.0)	4 (1.4)	0 (0.0)
Injection site oedema	13 (2.4)	13 (2.4)	1 (0.4)	1 (0.4)
Injection site discomfort	12 (2.2)	12 (2.2)	2 (0.7)	2 (0.7)
Musculoskeletal pain	12 (2.2)	0 (0.0)	2 (0.7)	0 (0.0)
Procedural pain	12 (2.2)	9 (1.6)	6 (2.1)	2 (0.7)
Hypertension	11 (2.0)	2 (0.4)	8 (2.8)	0 (0.0)
Arthralgia	5 (0.9)	0 (0.0)	6 (2.1)	0 (0.0)

Data source: ISS Tables 14.1.6 and 14.1.9

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

a Preferred term was coded using MedDRA dictionary (Version 13.1). If multiple AEs were reported for a given preferred term, only one event was counted per subject.

b 92.0% of TEAEs of penile haematoma had the verbatim "penile bruising"; 92.1% of treatment-related AEs of penile haematoma had the verbatim "penile bruising."

c 100% of TEAEs and treatment-related AEs of penile haemorrhage had the verbatim "penile ecchymosis."

The majority of subjects with these TEAEs had events that were considered treatment-related. The majority of subjects with events of upper respiratory tract infection, headache, back pain, musculoskeletal pain, and hypertension had events considered by the investigator to be not related to treatment. None of the events of nasopharyngitis, sinusitis, or arthralgia were considered by the investigator to be related to treatment.

The majority of subjects treated with AA4500 had higher rates of TEAEs and treatment-related AEs compared with subjects treated with placebo. The most frequently reported (≥25.0% of subjects) TEAEs and treatment-related AEs in the AA4500 group were penile haematoma, penile pain, and penile swelling.

Adverse Events in Support of the Product Label

Due to investigator differences in the use of verbatim terms and the subsequent coding of these terms, some preferred terms were grouped to mitigate this disparity in coding. Specifically, penile ecchymosis

included events of injection site haematoma (87% of these events had the verbatim “bruising”), penile haematoma (92.1% of these events had the verbatim “penile bruising”), contusion, ecchymosis, penile haemorrhage (100% of these events had the verbatim “penile ecchymosis”), and injection site haemorrhage (all events except for one had the verbatim “ecchymosis”); penile pain included injection site pain, penile pain, and injection site discomfort; and penile swelling included injection site swelling, penile oedema, penile swelling, local swelling, scrotal swelling, and injection site oedema.

Table 8 displays treatment-related AEs (occurring in ≥1.0% of AA4500-treated subjects and at a greater incidence than placebo) for subjects in the Phase 3 Double-Blind, Placebo-Controlled Studies analysis population in support of the product label, using the grouped AE conventions described above. The majority of these treatment-related AEs were confined to the site of injection. The percentage of subjects with treatment-related AEs confined to the site of injection was higher in AA4500-treated subjects compared to placebo-treated subjects for all treatment-related AEs.

Table 8: Treatment-Related Adverse Events Occurring in ≥1.0% of AA4500 Subjects and at a Greater Incidence Than Placebo After Up to Four Treatment Cycles – Phase 3 Double-Blind, Placebo-Controlled Studies

Preferred Term	AA4500 (N=551) n (%)	Placebo (N=281) n (%)
All adverse reactions	464 (84.2)	102 (36.3)
Penile ecchymosis[a]	441 (80.0)	73 (26.0)
Penile swelling[b]	303 (55.0)	9 (3.2)
Penile pain[c]	250 (45.4)	26 (9.3)
Blood blister	25 (4.5)	0 (0.0)
Penile blister	18 (3.3)	0 (0.0)
Penile erythema	17 (3.1)	3 (1.1)
Pruritus genital	17 (3.1)	0 (0.0)
Painful erection	16 (2.9)	0 (0.0)
Erectile dysfunction	10 (1.8)	1 (0.4)
Skin discolouration	10 (1.8)	0 (0.0)
Procedural pain	9 (1.6)	2 (0.7)
Injection site vesicles	7 (1.3)	0 (0.0)
Localised oedema	7 (1.3)	0 (0.0)
Dyspareunia	6 (1.1)	0 (0.0)
Injection site pruritus	6 (1.1)	0 (0.0)
Nodule	6 (1.1)	0 (0.0)
Suprapubic pain	6 (1.1)	0 (0.0)

Data source: ISS Tables 14.1.9 and 14.1.11.3

a Includes preferred terms of injection site haematoma (87% of these events had the verbatim “bruising”), penile haematoma (92.1% of events had the verbatim “penile bruising”), contusion, ecchymosis, penile haemorrhage (100% of events had the verbatim “penile ecchymosis”), and injection site haemorrhage (all but one of these events had the verbatim “ecchymosis”).

b Includes preferred terms of injection site swelling, penile oedema, penile swelling, local swelling, scrotal swelling, and injection site oedema.

c Includes preferred terms of injection site pain, penile pain, and injection site discomfort.

Adverse Event Summaries by Population Subgroup

Baseline IIEF Erectile Function domain score

No clinically meaningful differences in the incidences and severity of TEAEs by baseline IIEF erectile function domain score (≤ 5 [no sexual activity/no sexual intercourse]; 6 to 16 [moderate/severe, severe]; 17-30 [mild/moderate, mild, none]) were observed.

Concomitant PDE5 usage

No clinically meaningful differences in the incidences of TEAEs by concomitant PDE5 usage (yes/no) were observed.

Age

Although the incidence of contusion, ecchymosis, local swelling, and injection site discomfort appeared to increase with age, no clinically meaningful comparisons of the incidence of these TEAEs by age group (<45, 45-54, 55-64, 65-74, ≥75 years) could be made due to the variability in the sample size for each age group.

Race

Due to the small sample size of non-white subjects (N=37) compared to white subjects (N=861), no clinically meaningful comparisons of the incidence of TEAEs between white and non-white subjects could be made.

Duration of Peyronie's Disease

No clinically meaningful differences in the incidences of TEAEs by duration of Peyronie's disease (≤2 years, >2 to ≤ 4 years, > 4 years) were observed.

Baseline Penile Curvature Deformity Severity

No clinically meaningful differences in the incidences of TEAEs by baseline penile curvature deformity severity (30-45°, 46-60°, 61-90°) were observed.

Penile Trauma History

No clinically meaningful differences in the incidences of TEAEs by penile trauma history (yes/no) were observed.

Diabetes History

No clinically meaningful differences in the incidences of TEAEs by diabetes history (yes/no) were observed.

Prior Peyronie's Disease Treatment

No clinically meaningful differences in the incidences of TEAEs by prior Peyronie's disease treatment (yes/no).

Geographic Location

Some differences in the incidence of specific events (eg, penile haematoma, penile haemorrhage, penile oedema, contusion, ecchymosis) were observed among geographic locations (United States, Australia, Europe); however, these are most likely due to differences in local diagnostic classification of TEAEs.

Serious adverse event / deaths / other significant events

Death

Three of the 1044 AA4500 subjects (two in AUX-CC-803 and one in AUX-CC-804) in the Global Safety analysis population died due to events of:

- Road traffic accident, motorcycle accident (1232-2255).
- Pulmonary embolism (6013-4019): The subject had a history of bronchogenic carcinoma with partial right pneumonectomy and bronchogenic carcinoma metastatic to bone.
- Hypertrophic cardiomyopathy (1209-4963): The subject had a history of atrial fibrillation; atrial flutter; coronary artery disease; ventricular tachycardia; hyperlipidemia; cerebral vascular accident; pulmonary hypertension; hypertension; cardiac ablation (x3); and cardiac conversion.

All deaths were considered unrelated to study drug by the investigators. Narratives for all subject deaths have been provided and allow excluding a relation to treatment.

Serious Adverse Events

A total of 60 (5.7%) AA4500 subjects in the Global Safety analysis population experienced at least one treatment-emergent SAE. Of these, nine subjects experienced SAEs that were considered by the investigator to be related to study drug (Table 9).

Table 9: Subjects With Non-Fatal Serious Adverse Events Considered by the Investigator to be Related to Study Drug – Global Safety

Subject Number	Age	Preferred Term / Verbatim Term	Onset Day / Stop Day Trt Cycle, Inj	Days to Onset Day Relative to Last Injection	Severity / Relationship	Action Taken / SAE Code	Comments
AUX-CC-802							
1101-7806	69	Penile haematoma/ Hematoma of penile shaft and base	24/51 1, 2	22	Moderate/ Related	Drug interrupted/ Inpatient hospitalization	Occurred during intercourse with partner in female dominant position. Was hospitalized and underwent ultrasound. Managed conservatively. Subject resumed regularly scheduled injections and completed all four treatment cycles.
1229-8027	42	Fracture of penis/ Corporal rupture	34/34 1, 2	31	Severe/ Related	Drug withdrawn/ Inpatient hospitalization	Occurred during vigorous sexual intercourse. Surgical repair.
5028-7173	32	Penile haematoma/ Penile bruising	3/4 1, 2	1	Mild/ Probably	Dose not changed/ Inpatient hospitalization	Mild bruising at the site of injection was noted. Admitted to the hospital overnight and ultrasound revealed no convincing evidence of a tunical or corporal disruption. Resolved spontaneously.
AUX-CC-803							
1096-3408	43	Fracture of penis/ Corporal rupture	96/151 3,2	12	Severe/ Related	Drug Withdrawn/ Other medically important event	History of penile trauma. Occurred during intercourse; subject did not wait the requested 2-week hiatus. Surgical repair.
1096-3418	50	Penile haematoma/ Penile hematoma	109/192 3,2	13	Severe/ Related	Drug interrupted/ Persistent or significant disability/ incapacity	Healed spontaneously; subject did not wait the requested 2-week hiatus.

6013-4028	67	Penile haematoma/ Penile hematoma	40/662,2	2	Severe/ Related	Drug withdrawn/ Inpatient hospitalization & other medically important event	Ultrasound on Day 61 suggested a possible corporal rupture; as a result, subject underwent , surgical exploration on Day 66 that was notable for cystic hematoma and the absence of any tunical defect.. Nesbit plication performed to correct Peyronie's disease concurrent to hematoma evacuation.
AUX-CC-804							
1221-5007	61	Penile haematoma/ Penile hematoma	119/1834,1	0	Severe/ Related	Drug withdrawn/ Other medically important event	Occurred the same day as injection. Superficial hematoma with no evidence of tunical or corporal disruption. In-office aspiration yielded 0.5 cc of blood.
1224-5053	27	Fracture of penis/ Corporal rupture	159/1604,2	29	Moderate/ Related	Dose not changed/ Inpatient hospitalization	History of penile trauma. Intercourse with misthrust and subsequent corporal rupture. Surgical repair.
6021-6663	64	Fracture of penis/ Corporal rupture	102/1923,2	15	Mild/ Related	Dose not changed/ Other medically important event	History of penile trauma. Vigorous sexual intercourse 14 days after Treatment Cycle 3. History of possible prior rupture. Managed conservatively.

Data source: ISS Table 14.2.12.2; AUX-CC-802, Appendix 16.2, Listing 16.2.4 and data on file; AUX-CC-803, Appendix 16.2, Listing 16.2.4 and data on file; AUX-CC-804, Appendix 16.2, Listing 16.2.4 and data on file
Trt=Treatment; Inj=Injection.

One additional subject (5805-7432) experienced a corporal rupture that was not a serious AE according to the investigator.

Other significant events

Other Penile Events

Nine (0.9%) AA4500 subjects in the Global Safety analysis population had a combination of penile ecchymoses or hematoma, sudden penile detumescence, and/or a penile "popping" sound or sensation and in these cases, a diagnosis of corporal rupture cannot be excluded (Table 10).

Table 10: Other Penile Events

Study AUX-CC-802	Subject 1100-8710	Popping sensation during spontaneous erection and penile

		ecchymosis
Study AUX-CC-802	Subject 1101-7806	Detumescence and ecchymosis with negative penile examinations and negative Duplex unltrasound findings
Study AUX-CC-803	Subject 1096-3418	Detumescence and bruising in absence of popping
Study AUX-CC-803	Subject 1233-3261	Mild eggplant bruising and detumescence in absence of a popping sound after attemping intercourse 2 days after injection
Study AUX-CC-804	Subject 1104-5106	Popping sound followed by immediate penile bruising
Study AUX-CC-804	Subject 1104-5116	Popping and penile ecchymosis that lasted 1 day
Study AUX-CC-804	Subject 1199-4601	Popping and penile bruising while modeling with an erect penis
Study AUX-CC-804	Subject 1202-5151	Penile bruising and popping
Study AUX-CC-804	Subject 1217-5601	Hematoma and popping

Adverse Events Leading to Study Discontinuation

Nine (0.9%) AA4500 subjects (four in AUX-CC-802 and five in AUX-CC-804) experienced at least one non-serious TEAE that led to study discontinuation in the Global Safety analysis population. All but two events were considered by the investigator to be related to study drug (Table 11).

Table 11: Subjects With Non-Serious Treatment-Emergent Adverse Events Leading to Study Discontinuation – Global Safety

Subject Number	Age	Preferred Term / Verbatim Term	Onset Day / Stop Day Trt Cycle, Inj	Days to Onset Day Relative to Last Injection	Severity / Relationship
AUX-CC-802					
5609-7406	72	Joint dislocation/ Dislocation of left hip	146/not recorded 2, 2	102	Moderate/ Not related
6202-7054	54	Penile haematomaa/ Penile hematoma	83/87 3, 2	3	Moderate/ Related
6204-7103	57	Painful erection/ Immediate penile pain on erection with injection of	44/44 1, 2	42	Moderate/ Not related

		Caverject			
9146-7979	31	Blood blister/ Penile blood blisters	1/1 1, 1	0	Mild/ Related
AUX-CC-804					
1199-4601	70	Penile swelling/ Penile swelling	53/~78 2,2	9	Mild/ Related
1199-4605	54	Erectile dysfunction/ ED	2/Ongoing 1,2	0	Mild/ Related
1222-5918	57	Contusion/ Bruising pelvis	48/76 2,2	3	Moderate/ Related
6019-6552	68	Penile haematoma/ Penile hematoma	124/302 3,2	18	Moderate/ Related
9146-5260	29	Penis disorder/ Worsening of penile indentation	1/82 1,1	0	Moderate/ Related
Data source: ISS Table 14.2.12.3; AUX-CC-802, Appendix 16.2, Listing 16.2.4 and data on file; AUX-CC-804, Appendix 16.2, Listing 16.2.4 and data on file Trt=Treatment; Inj=Injection a Occurred 2 days after penile modeling in the third treatment cycle.					

Penile Haematoma

Penile haematoma was the most frequently reported TEAE (50.0% of subjects) and treatment-related AE (50.2% of subjects) in the in the Global Safety analysis population. A total of four events were considered treatment-related SAEs (Table 9). Additionally, a fifth subject (Subject 5028-7173 from AUX-CC-802) experienced a treatment-related SAE of penile haematoma for which the verbatim term was “penile bruising”.

Corporal Rupture

Injection of AA4500 into collagen-containing structures such as the corpus cavernosum of the penis may result in damage to those structures and may possibly result in an injury such as corporal rupture (penile fracture). Therefore, investigators were instructed to inject AA4500 only into the Peyronie’s plaque and not into the urethra, nerves, blood vessels, corpora cavernosum or other collagen-containing structures of the penis.

Because corporal rupture is a potential risk of intralesional injection of AA4500 into the Peyronie’s plaque and because some subjects were reported to have a penile fracture or tunica tear in the early Phase 1 and Phase 2 Peyronie’s disease studies, Auxilium devised the following strategy to monitor the potential for corporal rupture in the Peyronie’s disease clinical program:

- Corporal rupture was made a targeted adverse event in the Phase 3 clinical studies. As such, a separate eCRF page was created to capture detailed information pertinent to each reported case of corporal rupture among the 898 subjects who received AA44500 in the Phase 3 clinical studies.

- To ensure that investigators were aware of the potential risk for corporal rupture, a training video on the AA4500 injection procedure and penile modeling procedure was provided to all investigators in Phase 3 studies prior to study initiation. The injection procedure and modeling video was also reviewed during the course of each study.
- Training material on corporal rupture was provided to investigators, and patients were also made aware of the risks in the Patient Information Informed Consent Forms . Subjects were also instructed not to resume sexual activity for a minimum of two weeks following injection. A period of two weeks was arbitrarily chosen based on earlier 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.
- The injection procedure and modeling procedures were reviewed again with the investigators during the course of the study as was information regarding the potential risk of corporal rupture.
- Reasons for subject withdrawal of consent were also reviewed by the medical monitor for terms possibly associated with corporal rupture/penile fracture.

Corporal Rupture in the Early Phase 1 and Phase 2 Clinical Studies

Ten of the 280 subjects treated with AA4500 in the early Phase 1 and Phase 2 studies had popping of their penile plaque during a spontaneous or nocturnal erection of the penis or during penile stretching exercises.

Five of these events occurred in Phase 2 Study 1030-PEY. In Study 1030-PEY, subjects were to receive single injections of AA4500 10,000 units in a volume of 0.25mL on 3 separate days within a period of 3 to 10 days. The same treatment was to be repeated 3 months later. During the first treatment series, five subjects had spontaneous popping of their plaques during a spontaneous or nocturnal erection of the penis or during penile stretching exercises. The spontaneous popping of the plaque was classified as a penile fracture in four subjects (Subjects 404, 405, 406, and 421) and as a tear in the tunica albuginea in one subject (Subject 410).

All 5 subjects continued in the study and received 2 or 3 additional AA4500 injections during the 2nd treatment series approximately 3 months later. Four of these five events were mild in intensity, and one was moderate. No subject required surgical intervention and all fractures/tear completely resolved without apparent sequelae. No subject had difficulty with urination or gross hematuria immediately following the event. All five subjects were either “much improved” or “very much improved” in their Peyronie’s disease after receiving AA4500 as determined by the investigator. Most importantly, the events of penile fracture and tear of the tunica albuginea were not considered serious by the investigator and none met the criteria for a serious adverse event.

For the remaining five subjects, one was treated with AA4500 in the first Phase 1 pilot study and experienced a corporal rupture when he attempted intercourse 2 weeks after treatment. He experienced pain and a popping sensation at the injection site, which was followed by ecchymosis. The subject was instructed to bandage the penis and avoid erection for 3 weeks. There was no reported intervention and after healing, the subject’s penis was straighter compared to before treatment. In the second Phase 1 pilot study, another subject treated with AA4500 experienced the verbatim term of “small tear of the tunica” 3 weeks after injection, which was felt as a popping sensation during intercourse and was followed by a small ecchymosis, which he noted after intercourse. The event was treated conservatively without any reported intervention and resolved. The final three events (rupture of the tunica) occurred in the open-label extension of the first pilot study. The investigator’s patient progress notes for this study were reviewed and no additional information is available for these three men.

Corporal Ruptures in the Auxilium-Sponsored Studies (AUX-CC-801, AUX-CC-802, AUX-CC-803, and AUX-CC-804)

Five corporal ruptures/penile fractures were reported in the Auxilium-sponsored Phase 3 clinical studies. Four of these were considered SAEs and are discussed above. One additional subject had a corporal rupture that was not considered a serious adverse event by the investigator.

Spontaneous Penile Events

The term “Spontaneous Penile Event” (SPE) was created at the outset of the Phase 2b program following consultation with clinical investigators and review of available early Phase 1 and Phase 2 study safety data. In these early Phase 1 and Phase 2 studies, investigators reported that popping and cracking of the plaque, as well as “penile fractures” were occurring without evidence of a definitive corporal rupture.

Many of these events resulting in improved outcomes without interrupting the study drug administration in some cases. In order to qualify these events, the term “Spontaneous Penile Event” was created. A spontaneous penile event was a penile event experienced by the subject and considered a positive attribute of study drug treatment by the study subject and/or study investigator.

As shown in Table 12, 199 of the 1009 subjects (19.7%) who received AA4500 in Studies AUX-CC-801, AUX-CC-802, AUX-CC-803, or AUX-CC-804 reported spontaneous penile events.

Table 12: Spontaneous Events in Subjects Who Received at Least One Injection of AA4500 – Intent-to-Treat Population in Studies AUX-CC-801, AUX-CC-802, AUX-CC-803, and AUX-CC-804

Spontaneous Penile Event	AUX-CC-801 N=111	AUX-CC-802 N=347	AUX-CC-803 N=277	AUX-CC-804 N=274	Total N=1009
Yes, N (%)	17 (15.3)	109 (31.4)	36 (12.9)	37 (13.54)	199 (19.7)

Withdrawal by Subject (Informed Consent Withdrawn)

A total of 74 subjects (60 AA4500 and 14 placebo) withdrew consent during the Phase 3 studies. The most common reasons for withdrawal of consent were lack of efficacy (20 subjects; 13 AA4500 and seven placebo) and the ‘subject no longer wanted to be in the study’ (15 subjects; 14 AA4500 and one placebo). Subject 6021-6663 who withdrew consent had a mild corporal rupture that was managed conservatively and considered a serious AE. For all other subjects, there was no reason for withdrawal of consent that was associated with an AE suggestive of corporal rupture or penile fracture.

Immunogenicity

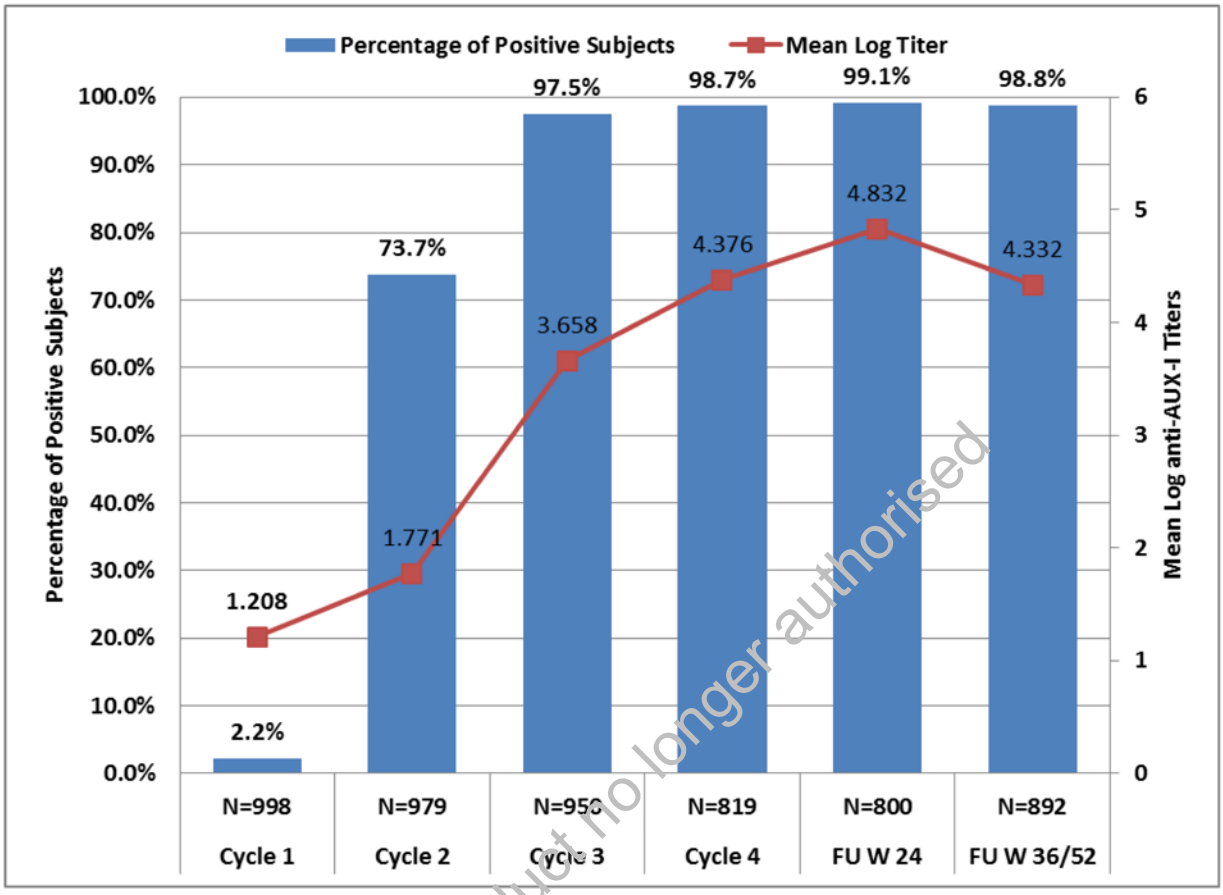
Based on the nature of the drug product, the potential immunogenicity-related clinical risks for AA4500 were evaluated by examining the antibody-mediated effects on safety.

Anti-Drug Antibody Responses

For subjects who received AA4500 in the Peyronie’s clinical studies, the development of anti-drug antibody titers following each treatment cycle (two injections) was similar to that following successive intermittent single injections in subjects who received AA4500 in the Dupuytren’s clinical studies.

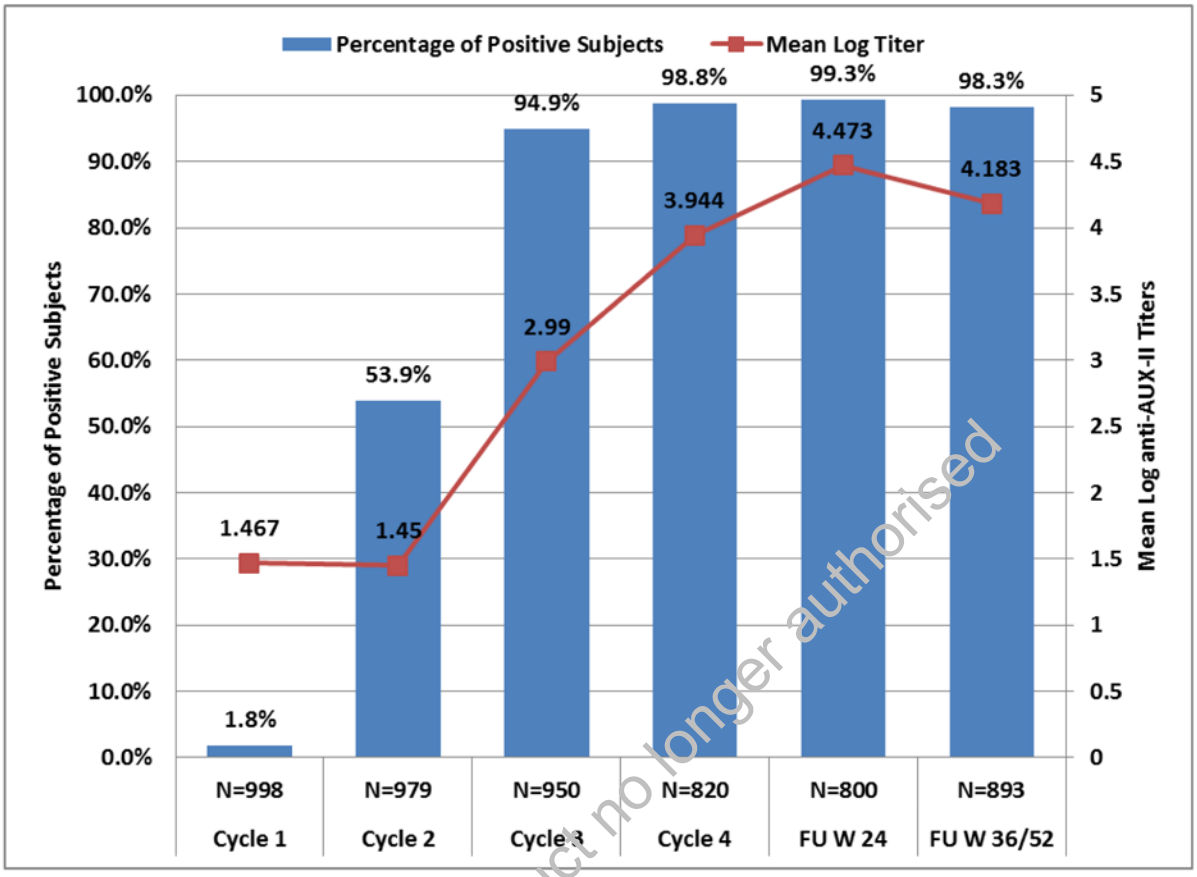
The majority of subjects developed anti-drug antibodies after a single treatment, and the vast majority (≥ 95%) developed anti-drug antibodies after 2 injection cycles (up to 4 injections) in Peyronies disease (Figure 1 and Figure 2).

Figure 1: Anti-AUX-I: Percentage of Peyronie's Subjects With Positive Anti-AUX-I Titers and Log Mean Anti-AUX-I Titer Levels Across Treatment Cycles and Follow-Up – Subjects Who Received At Least 1 Dose of AA4500 0.58 mg and Had an Immunogenicity Evaluation



Data source: ISS Table 14.4.1
EOS=end of study; FU=follow-up; W=week; Cycle=each cycle consists of two injections
Note: EOS was Week 36 for AUX-CC-801 and AUX-CC-802 and Week 52 for AUX-CC-803 and AUX-CC-804

Figure 2: Anti-AUX-II: Percentage of Peyronie's Subjects With Positive Anti-AUX-II Titers and Log Mean Anti-AUX-II Titer Levels Across Treatment Cycles and Follow-Up – Subjects Who Received At Least 1 Dose of AA4500 0.58 mg and Had an Immunogenicity Evaluation



Data source: ISS Table 14.4.1
EOS=end of study; FU=follow-up; W=week; Cycle=each cycle consists of two injections
Note: EOS was Week 36 for AUX-CC-801 and AUX-CC-802 and Week 52 for AUX-CC-803 and AUX-CC-804

Neutralizing Antibody Positive Subjects and Anti-Drug Antibody Titers

The percentage of neutralizing antibody positive subjects peaked at Week 24, which corresponds to the time point in AUX-CC-803 and AUX-CC-804 when anti-drug antibody titers were also at their peak. Among subjects who received up to four treatment cycles of AA4500 for Peyronie's disease, there was no consistent neutralizing antibody profile over the time points tested. In general, subjects tested did not sustain neutralizing antibody positive status over more than one time point.

Antibody-Mediated Effects on Clinical Safety

The incidence of the three most frequently reported adverse events (penile hematoma, penile pain, penile swelling) and the four events possibly consistent with an immunologic event (pruritus genital, injection site pruritus, pruritus, lymphadenopathy) were examined in the safety population of 898 subjects in the Phase 3 clinical program who received up to four treatment cycles of AA4500 (up to eight injections of AA4500 0.58 mg). There was no consistent pattern of an increase in the incidence of adverse events with increasing numbers of treatment cycles (up to 8 injections) of AA4500 (and therefore increasing antibody titers). Also, the median duration of adverse events did not increase with increasing numbers of injections of AA4500 (and therefore increasing antibody titers). There was no correlation between the absence or presence of an adverse event, or the severity of that adverse event and anti-AUX-I or anti-AUX-II antibody titers.

Other Adverse Events Possibly Consistent With Immunologic Events

Review of the Peyronie's disease global AA4500 safety database (N=954) showed four adverse events coded as hypersensitivity or drug hypersensitivity reactions. None of these events were related to AA4500 (ie, allergy exacerbation, possible reaction to lidocaine nerve block [2 subjects], and phenylephrine hypersensitivity). There were no events coded as hypersensitivity that were consistent with a systemic hypersensitivity event.

The global safety database was also reviewed for terms possibly suggestive of/or consistent with localized or systemic hypersensitivity events. There were two reports of urticaria in the AA4500 group.

• One subject in AUX-CC-801 reported hives over his entire body 6 days after the second injection of Treatment Cycle 2. This event was managed with a medrol dose pack and the hives resolved the next day. The subject was retreated with AA4500 approximately six weeks later without premedication and without the re-appearance of hives. This event was considered moderate in intensity and unrelated to study drug.

• One subject in AUX-CC-803 reported urticaria that was local to the extremities; occurred more than 30 days after his final injection; and was considered not related to AA4500.

Three local rashes (local to the injection site, local to an area of the thigh, and local to the penis) were considered related to study drug. Three reports of mild local pruritus were also considered related to study drug.

Laboratory findings

No clinically meaningful effects on laboratory (haematology and chemistry) parameters were observed for any analysis population. No clinically meaningful effects on vital sign parameters (systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, temperature) were observed for any analysis population

Safety related to drug-drug interactions and other interactions

Use of Aspirin

No clinically meaningful differences in the incidence of local treatment-related AEs by use of aspirin (low dose [≤ 165 mg], no aspirin use]) were observed. The sample size for subjects receiving a high dose (>165 mg) of aspirin (N=27) was too small to make any clinically meaningful comparisons (Table 13).

Table 13: Local Treatment-Related Adverse Events by Use of Aspirin – Phase 3 Studies

Preferred Term[a]	AA4500 (N=898)		
	High Dose Aspirin (>165 mg) (N=27) n (%)	Low Dose Aspirin (≤165 mg) (N=192) n (%)	No Aspirin Use (N=699) n (%)
Number (%) of subjects with ≥1 common local related AE	18 (66.7)	165 (85.9)	580 (83.0)
Penile Ecchymosis	16 (59.3)	165 (85.9)	548 (78.4)
Penile haematoma	9 (33.3)	99 (51.6)	397 (56.8)
Penile haemorrhage	7 (25.9)	46 (24.0)	117 (16.7)
Injection site haemorrhage	0	11 (5.7)	20 (2.9)
Injection site haematoma	2 (3.7)	45 (23.4)	134 (19.2)
Contusion	0	22 (11.5)	45 (6.4)
Ecchymosis	4 (14.8)	14 (7.3)	31 (4.4)
Penile Pain	12 (44.4)	91 (47.4)	329 (47.1)
Penile pain	9 (33.3)	69 (35.9)	246 (35.2)
Injection site pain	4 (14.8)	37 (19.3)	153 (21.9)
Injection site discomfort	0	5 (2.6)	13 (1.9)
Penile Swelling	14 (51.9)	106 (55.2)	344 (49.2)
Penile swelling	8 (29.6)	65 (33.9)	218 (31.2)
Penile oedema	4 (14.8)	32 (16.7)	96 (13.7)
Injection site swelling	1 (3.7)	28 (14.1)	74 (10.6)
Local swelling	1 (3.7)	4 (2.1)	18 (2.6)
Scrotal swelling	0	4 (2.1)	10 (1.4)
Injection site oedema	0	6 (3.1)	11 (1.6)

Data source: ISS Table 14.3.13.1

Note: Includes all AEs with a start date on or after the date of the first injection of AA4500 to the Week 24 visit that have a relationship to study drug of possible, probable, or missing. Most common local AEs are AEs grouped into AEs related to Penile Ecchymosis, Penile Pain, and Penile Swelling.

a Preferred terms were coded using MedDRA dictionary (Version 15.1).

Use of Anti-Coagulant Medication

Due to the small sample size of subjects with anti-coagulant medication use (N=21) compared to subjects with no anti-coagulant medication use (N=885), no clinically meaningful comparisons of the incidence of local treatment-related AEs between subjects with anti-coagulant medication use and subjects with no anti-coagulant medication use could be made.

Post marketing experience

Dupuytren's contracture

A search of the Auxilium safety database was performed for all global post-marketing reports received by Auxilium from Dupuytren's contracture product launch until 27 August 2013 (71,388 vials of XIAFLEX®/XIAPEX® sold). The MAH considers the AE profile demonstrated in post-marketing use to be consistent with the profile of the product seen in the Dupuytren's contracture clinical trials and XIAFLEX®/XIAPEX® product insert and medication guide.

Peyronie's disease

N/A

2.5.1. Discussion on clinical safety

With 1044 subjects who received 7466 injections of AA4500 0.58 mg for the treatment of Peyronie's disease worldwide the safety database contains adequate number of subjects. Most adverse events following AA4500 injection were locally to the penis or groin and most commonly include penile hematoma, penile pain, penile swelling, injection site pain and injection site hematoma.

The majority of Peyronie's patients experienced at least one adverse reaction (Global Safety database, 92.5%). Most adverse reactions were locally to the penis or groin and the majority of these events were of mild or moderate severity. Most resolved within 14 days of the injection. The adverse reaction profile was similar after each injection, regardless of the number of injections administered.

The most frequently reported treatment-related AEs in the clinical trials in subjects with Peyronie's disease (Global Safety database) were penile hematoma (50.2%), penile pain (33.5%), penile swelling (28.9%) and injection site pain (24.1%).

Corporal fracture and other serious adverse events related to the penis

Treatment-related SAEs included corporal rupture (fracture of penis) in 4 subjects (0.4%). One additional subject experienced a corporal fracture that was not a serious AE according to the investigator. Nine subjects (0.9%) reported a combination of penile ecchymoses or hematoma, sudden penile detumescence, and/or a penile "popping" sound or sensation. These subjects were managed without surgical intervention. A diagnosis of corporal rupture cannot be excluded. Treatment-related SAEs also included penile hematoma (n=5). Severe penile hematoma was also reported in 39 patients (3.7%). To these SAEs appropriate warning statements are reflected in the Product Information. Corporal rupture or other serious injuries to the penis are made identified risks in the RMP.

Investigator training in the clinical studies included intensive injection technique instructions via manuals and DVDs, workshops and investigator meetings. To ensure the safe application of the drug and considering above SAEs the MAH will ensure that physicians are appropriately trained and provide adequate educational material for the healthcare professionals in the treatment of Peyronie's disease as outlined in Annex II. The training programme will be followed by surveys to follow adequate implementation of the training plans as outlined in the RMP.

Immunogenicity

During clinical studies in Peyronie's disease subjects were tested at multiple time points for antibodies to the protein components of AA4500 (AUX-I and AUX-II). After 6 weeks of cycle 1, 73.7% of patients had antibodies against AUC-I and 53.9% had antibodies against AUX-II. After the 4th cycle nearly all subjects had antibodies to both AUX-I and AUX-II. Neutralizing antibodies were detected in 43.8% and 31.3%, respectively, of subjects tested. There was no apparent correlation of antibody frequency, antibody titers, or neutralizing status to adverse reactions.

There were no observed cases of severe systemic hypersensitivity or anaphylaxis in the clinical development programme for AA4500 in Peyronie's disease. However, an anaphylactic reaction was reported in a post-marketing clinical study in a patient who had previous exposure to AA4500 for the treatment of Dupuytren's contracture.

Appropriate warnings to this potential risk have been included into the product information and the educational material will cover this aspect.

Use of Anti-Coagulant Medication

Except for race and anti-coagulant medication use, which could not be evaluated, no clinically meaningful differences were observed between or among subgroups. No final conclusion can be drawn for subjects receiving a high dose (>165 mg) acetylsalicylic acid since the overall number was too low (27 of 898). The current PI contains the warning (Section 4.4) that use of Xiapex in patients who have received anticoagulants (with the exception of up to 150mg acetylsalicylid acid daily) within 7 days prior receiving an injection is not recommended.

Long-term safety

Follow-up on long term safety is currently ongoing. Study AUC-CC-810 is a long term, non-treatment follow up of patients who received AA450 in the AUX-CC-802, AUX-CC-803 and AUX-CC-804 studies. The final results of study AUC-CC-810 are expected in 4Q 2018. The MAH will submit the long-term results for the use of AA4500 as requested in the RMP.

2.5.2. Conclusions on clinical safety

The safety results indicate that the majority of adverse reactions were non-serious, mild or moderate in intensity, confined to the treated area, and resolved within a short period without sequelae. Among subjects who received at least one dose of Xiapex most subjects experienced adverse reactions in the treated extremity, with the most frequently reported adverse reactions reported being: penile hematoma, penile pain, penile swelling and injection site pain.

All treatment-related SAEs were related to events of the penis, corporal rupture (fracture of penis) in 4 subjects and penile hematoma in 5 subjects. The influence of investigator training on adverse events related to the penis is considered to be crucial for the safe application of the drug. A physician training plan is part of the risk minimisation plan.

Due to the highly immunogenic potential of Xiapex the majority of subjects developed antibodies to the protein components of Xiapex (AUX-I and AUX-II) after the first injection and all subjects had antibodies after the 4th cycle. However, no adverse reactions consistent with systemic hypersensitivity or anaphylactic response were observed in the Peyronie's study programme. However, an anaphylactic reaction was reported in a post-marketing clinical study in a patient who had previous exposure to Xiapex for the treatment of Dupuytren's contracture.

No increase in the number of adverse events with subsequent injections were observed. Antibody titres were not predictive of the rate, severity, or duration of any of the adverse events. This suggests that Antibodies to both AUX-I and AUX-II did not affect the safety profile of Xiapex.

2.5.3. PSUR cycle

Based on the data submitted, the frequency of PSUR submission should be revised to 6 months. Consequently, the PSUR after the next data lock point, 27 February 2015, should cover the period from 28.02.2015 to 27.08.2015 and be submitted within 70 days of the data lock point. Thereafter PSURs should be submitted in accordance with the updated list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 10.0 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Table 14: Summary of the Safety Concerns- Peyronie's disease

Summary of Safety Concerns	
Important identified risks	Corporal rupture or serious injury to the penis
	Local reactions
	Medication errors
Important potential risks	Injection-site bleeding in patients with coagulation disorders, including those on concurrent anti-coagulation therapy
	Severe systemic hypersensitivity/Anaphylaxis

	Reactions related to cross-reactivity with endogenous MMPs (including MSS and development/exacerbation
	Immune mediated reactions
	Skin lesions
	Injury of the urethra
	Off label use in patients with ventral curvature deformity
	Off label use in patients with isolated hourglass deformity
Missing information	Re-treatment with collagenase *clostridium histolyticum* (Xiapex) Long term safety
MMP = matrix metalloproteinase; MSS = MSS = musculoskeletal syndrome.	

Pharmacovigilance plan

Table 15: Ongoing and planned studies in the PhV development plan- Peyronie's disease

Study / Activity Type, Title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status Planned, started,**	**Date for submission of interim or final reports**
Study AUX-CC-806 (open label study for patients who received placebo in the double blind placebo controlled Phase III studies AUX-CC-803 and AUX-CC-804) Category 3	A Phase 3, open-label study of the safety and efficacy of AA4500 0.58 mg in subjects with Peyronie's disease		Ongoing	3Q2014
Study AUX-CC-810 (long-term, nontreatment 2- 5 year follow up of patients who received AA4500 in AUX-CC-802, AUX-CC-803, and AUX CC 804) Category 3	To assess the long-term safety and characterisation of curvature deformity following use of AA4500 in the treatment of adults with Peyronie's disease	Long term safety and immunogenicity	Planned	4Q2018
Survey to evaluate effectiveness of additional risk minimisation measures (educational material) Category 3	Assessment of effectiveness of risk minimisation measures	N/A	Planned	TBD

The RMP was updated including a PASS (category 3 non-interventional PASS) for evaluating the effectiveness of the educational material via survey, as mentioned in Annex II to the opinion. Adjustments to the survey may be necessary during development of the protocol. The protocol will be provided within three months after authorisation.

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Table 16: Summary table of Risk Minimisation Measures- Peyronie's disease

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important Identified Risks		
Corporal rupture (penile fracture) or other serious injury to the penis	SmPC Sections 4.4 and 4.8 Package Leaflet Section 2	Physician training/Educational materials
Local reactions	SmPC Sections 4.8 and 4.9	Physician training/Educational materials
Medication errors	SmPC Section 4.2 and Package leaflet	Physician training/Educational materials
Important Potential Risks		
Injection site bleeding in patients with coagulation disorders, including those on concurrent anti-coagulation therapy	SmPC Sections 4.4 Package Leaflet Section 2	Physician training/Educational materials
Severe systemic hypersensitivity/ Anaphylaxis	SmPC Sections 4.3, 4.4 and 4.8	Physician training/Educational materials
Reactions related to cross-reactivity with endogenous MMPs	SmPC Section 4.4	Physician training/Educational materials
Immune mediated reactions	SmPC Sections 4.3 and 4.4	Physician training/Educational materials
Skin lesions	N/A	N/A
Injury of the urethra	SmPC Section 4.2 and 4.3 Package Leaflet Section 2	Physician training/Educational materials
Off label use in patients with ventral curvature deformity	SmPC Section 4.3 and 4.4 Package Leaflet Section 2	Physician training/Educational materials
Off label use in patients with isolated hourglass deformity	SmPC Section 4.3 and 4.4 Package Leaflet Section 2	Physician training/Educational materials
Missing information		
Re-treatment with collagenase *Clostridium histolyticum*	Not applicable	
Long term safety	Not applicable	

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice without changes.

2.7. Update of the Product information

As a consequence of this new indication, sections 2, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed by QRD and accepted by the CHMP.

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The efficacy of Xiapex was evaluated in two randomized, double-blind, placebo-controlled, multi-centred trials in 832 (ITT) adult males with PD. Xiapex 0.58 mg was statistically superior to placebo with respect to the co-primary endpoints (i.e., curvature deformity and patient-reported Peyronie's disease bother) in both clinical studies:

In each study, men treated with AA4500 had a statistically significant ($p \leq 0.0059$) greater percent reduction in curvature deformity compared with men treated with placebo. A relative reduction of penile curvature deformity (48.8° -51.3° at baseline) of -37.6% (placebo -21.3%, study 803), resp. -30.5% (placebo -15.2%, study 804) was achieved. Improvement in curvature deformity was apparent after the first treatment cycle (Week 6) with continued improvement noted after each of the three subsequent treatment cycles. The improvement in curvature deformity was maintained through the end of each study (Week 52).

Reduction in penile curvature also translated in a reduction of patients' bother about PD. The baseline bother score was 7.4 to 8.2 across treatment arms and studies. Translating the score into bother categories, patients were about moderately bothered at baseline. At the pre-defined time point at the end of the observation period (week 52), Xiapex was statistically superior to placebo in terms of PDQ Bother score reduction (AUX-CC-803: p=0.0451; AUX-CC-804: p=0.0496).

Uncertainty in the knowledge about the beneficial effects

No efficacy data are available for administration of more than four treatment cycles. Likewise, no data are available on recurrence of penile curvature after more than one year after the first Xiapex injection. Limitation on the data is outlined in the product information and the applicant will provide further data post authorisation from the 5 years long term study AUX-CC-810 as specified in the RMP.

Risks

Unfavourable effects

The safety results indicate that the majority of adverse reactions were non-serious, mild or moderate in intensity, confined to the treated area, and resolved within a short period without sequelae. Among subjects who received at least one dose of Xiapex most subjects experienced adverse reactions in the

treated extremity, with the most frequently reported adverse reactions reported being: penile hematoma, penile pain, penile swelling and injection site pain. All treatment-related SAEs were related to events of the penis, corporal rupture (fracture of penis) and penile hematoma. All these events are appropriately reflected in the Product Information.

Due to the highly immunogenic potential of Xiapex the majority of subjects developed antibodies to the protein components of the drug (AUX-I and AUX-II) after the first injection and all subjects had antibodies after the 4th cycle. No adverse reactions consistent with systemic hypersensitivity or anaphylactic response were observed in the Peyronie's study programme. Notwithstanding an anaphylactic reaction was reported in a post-marketing clinical study for the treatment of Dupuytren's contracture in a patient who had previous exposure to Xiapex. It is acknowledged that no increase in the number of adverse events with subsequent injections was observed. Antibody titres were not predictive of the rate, severity, or duration of any of the adverse events. This suggests that Antibodies to both AUX-I and AUX-II did not affect the safety profile of Xiapex.

To mitigate the risks of adverse events related to the penis and potential risks such as anaphylaxis and medication errors during the treatment of Peyronie's disease, a physician training program and subsequent surveys to monitor the implementation of the training plans will be carried out. The training material will cover identified and potential risks as reflected in the RMP and in Annex II. Furthermore these risks are balanced with the appropriate labelling.

Uncertainty in the knowledge about the unfavourable effects

No long term safety data on immunogenicity or on safety of retreating patients are available in the claimed indication. In this respect the MAH is carrying out a long term safety and immunogenicity study to follow subjects who participated in the phase III studies (double-blind and open-label) for up to 5 years as reflected in the RMP.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Clinical studies with Xiapex showed statistically significant and clinically relevant results on curvature deformity and patient-reported Peyronie's disease bother in affected patients.

Improvement in curvature deformity was apparent after the first treatment cycle with continued improvement noted after each of the three subsequent treatment cycles. The improvement in curvature deformity was maintained through the end of each study.

The majority of adverse reactions were confined to the treated area and all treatment-related SAEs were related to events of the penis, corporal rupture and penile hematoma. All these adverse reactions are appropriately reflected in the Product Information and will be covered by the physician training plan as reflected in the RMP and in Annex II.

Whereas antibody titres observed in patients do not seem to affect the safety profile of Xiapex and no adverse reactions consistent with systemic hypersensitivity or anaphylactic response were observed in the Peyronie's study programme an anaphylactic reaction was reported under re-exposure for the treatment of Dupuytren's contracture which justifies to balance these potential risks with appropriate labelling and the physician training plan.

Benefit-risk balance

Xiapex shows in the submitted data package statistically significant superiority over placebo in terms of the two co-primary endpoints, i.e. curvature reduction and reduction in the PDQ Bother Scale. During

Xiapex trials observed AEs were mostly local, mild to moderate in intensity and resolved without sequelae. The benefit-risk-balance for Xiapex in the new proposed indication is considered to be positive.

Discussion on the Benefit-Risk Balance

Xiapex is a novel non-surgical treatment for PD. It is a proteinase that can hydrolyze the triple-helical region of collagen under physiological conditions, and has the potential to be effective in lysing collagen deposits such as those in the plaque, which is composed predominantly of collagen, that cause the curvature deformity and subsequent bother and distress in patients with PD. The injection of Xiapex into the pathologic plaque followed by a penile plaque modelling approximately 24 to 72 hours after injection, allows for the local disruption of the plaque.

The applicant has shown with the submitted study program statistical significant and clinically relevant results. Identified risks such as penile fracture, local reactions and medication errors as well as potential risks like hypersensitivity reactions are considered to be balanced with the current labelling and the educational materials which will ensure the doctors are aware of the important safety information

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, the variation(s) to the terms of the Marketing Authorisation, concerning the following change(s):

Variation(s) accepted		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II

Update of the SmPC with a new indication in the treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy. Consequently, sections 2, 3, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC have been updated. The PL is updated accordingly.

Furthermore, the PI is being brought in line with the latest QRD template version 9.0.

The variation proposed amendments to the SmPC, Annex II and Package Leaflet.

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the

RMP.

An updated RMP shall be submitted annually until renewal and every three years once an indefinite licence is granted.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The MAH shall ensure that all physicians who are expected to prescribe/use Xiapex are appropriately trained in the correct administration of the product and experienced in the diagnosis and management of Dupuytren's contracture and Peyronie's disease.

The MAH, in agreement with the competent authorities in the Member States, shall implement, prior to the launch, an educational programme for physicians aiming to ensure proper injection placement to minimize occurrence of injection-related adverse events and to inform on expected and potential risks associated with the treatment.

The physician educational programme should contain the following key elements:

- Injection technique and dosing interval.
- Proper amount of volumes for both reconstitution and injection differences in the metocarpophalangeal (MP) and proximal interphalangeal (PIP) joints for Dupuytren's contracture and for the Peyronie's disease plaque.
- Recognition and treatment of severe immune-mediated reaction, including anaphylaxis.
- Information on bleeding risk in patients with coagulation disorders including those on concurrent anti-coagulation therapy.
- Information on the potential risk of matrix metalloproteinases (MMP) cross reactivity including the development of musculoskeletal syndrome and exacerbation/initiation of autoimmune disorders.
- Reminder of the need to report adverse events, including medication errors.
- The need to inform the patient about the signs and symptoms associated with the treatment and when to seek attention from the health care provider.
- The summary of product characteristics and the patient information leaflet.

- **Obligation to conduct post-authorisation measures**

- Not applicable

Additional data exclusivity / market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Update of the SmPC with a new indication in the treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy. Consequently, sections 2, 3, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC have been updated. The PL is updated accordingly. Furthermore, the PI was brought in line with the latest QRD template vs. 9.0.

Summary

Please refer to the scientific discussion Xiapex EMEA/H/C/002048/II/44 for further information.

Appendix

1. CHMP AR on the novelty of the indication/significant clinical benefit in comparison with existing therapies

26 May 2015
EMA/CHMP/349968/2015
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report on the significant clinical benefit in comparison with existing therapies in accordance with Article 14(11) of Regulation (EC) No 726/2004

Invented name: Xiapex

International non-proprietary name: COLLAGENASE CLOSTRIDIUM HISTOLYTICUM

Procedure No. EMEA/H/C/2048/II/44

Marketing authorisation holder (MAH): Swedish Orphan Biovitrum AB (publ)

6. Introduction

In accordance with the provisions of Article 14(11) of Regulation (EC) No 726/2004, the Marketing Authorisation Holder (MAH) Swedish Orphan Biovitrum AB has applied for an additional one year marketing protection period in the framework of the Xiapex 0.9 mg powder and solvent for solution for injection Variation procedure EMEA/H/C/2048/II/44.

The request was based on the MAH's position that Xiapex represents a significant clinical benefit in the treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy in comparison with existing therapies.

7. Justification of significant clinical benefit as presented by the MAH

7.1. Demonstration of new therapeutic indication

The MAH is seeking market authorization for Xiapex, collagenase clostridium histolyticum (AA4500) in the new indication of the treatment of Peyronie's disease. Xiapex obtained first authorization in EU for the treatment of Dupuytren's contracture on 28 February 2011. The MAH considers this application supports a new therapeutic indication which will bring a significant clinical benefit in comparison with existing therapies. In accordance with Article 14(11) of Regulation 726/2004, the MAH therefore seeks approval for an additional year of marketing protection for Xiapex.

Peyronie's disease is an idiopathic, connective tissue disorder of the penis and is characterized by the pathological deposition of collagen I and III in the tunica albuginea of the corpus cavernosum (Akkus et al., 1997, Bivalacqua et al., 2000, Somers et al., 1989). The etiology of PD is not well understood; however, recent research has identified microvascular trauma, abnormal wound healing, and genetic predispositions as potential contributors to development of the condition (Moreland and Nehra, 2002, Ralph et al., 2010). The collagenous plaque replaces the normal elastic fibers of the tunica albuginea and causes penile curvature deformity, which is most evident during erection. The curvature deformity leads to significant patient bother, distress, and sexual dysfunction and can cause pain during erection. (Hellstrom, 2009, Ralph et al., 2010).

Collagenase Clostridium Histolyticum (AA4500) is a novel non-surgical treatment for Peyronie's disease. Isolated and purified from the fermentation of the bacterium Clostridium histolyticum, it is a lyophilized compound with a fixed-mass ratio (1:1) mixture of two purified collagenolytic enzymes: clostridial type I collagenase (AUX-I) and clostridial type II collagenase (AUX-II). It is a proteinase that can hydrolyze the triple-helical region of collagen under physiological conditions, and has the potential to be effective in lysing collagen deposits such as those in the plaque, which is composed predominantly of collagen, that cause the curvature deformity and subsequent bother and distress in patients with Peyronie"s disease. The injection of AA4500 into the pathologic plaque followed by a penile plaque modeling approximately 24 to 72 hours after injection, allows for the local disruption of the plaque.

The efficacy of AA4500 0.58 mg in the treatment of Peyronie's disease, was evaluated in two identical, large, well-controlled, multicenter 12-month Phase 3 studies (AUX-CC-803 and AUX-CC-804). In these studies, a total of 832 subjects with Peyronie's disease were enrolled in the United States and Australia. To further contextualize the results from the double-blind, placebo-controlled study population with those from a European population, the safety and efficacy from the subset of European subjects (N =191) were also evaluated in an open-labeled Phase 3 study.

To be eligible for these Phase 3 studies, men had to be at least 18 years of age; be in a stable relationship with a female partner/spouse for at least 3 months before screening and be willing to have vaginal intercourse with that partner/spouse; have symptom(s) of Peyronie's disease for at least 12 months before the first dose of study drug and have evidence of stable disease, as determined by the investigator; have penile curvature of at least 30° in the dorsal, lateral, or dorsal/lateral plane at screening.

7.2. Details of existing therapies

Several factors should be considered for the therapeutic management of patients with PD, including the extent of patient bother/distress, the duration of disease, presence or absence of pain with erection, the severity of penile deformity, and the adequacy of erectile function (Hellstrom, 2009).

Conservative Therapies

Non-surgical approaches are considered first-line therapy for PD, as they are indicated for patients in the early stage of the disease who are experiencing progressive deformity and painful erections. The goal of treatment is to mitigate progression and improve symptoms (Ralph et al., 2010). Conservative treatment options are multiple and diverse and include oral and topical agents, intralesional injections, extracorporeal shock wave therapy (ESWT), iontophoresis, and others (Ralph et al., 2010). Although a relatively large number of randomized controlled trials have been published within the last decade, the overall quality of the studies is quite poor. Thus, the clinical safety and efficacy of these approaches have not been convincingly demonstrated to date.

Surgical Interventions

Surgery is indicated when PD has reached the chronic phase and penile morphology, including plaque size and curvature deformity, has been stable for ≥3 months. The goals of surgery are to correct penile deformity and improve erectile and sexual function. Therefore, surgery is typically appropriate for patients who cannot achieve intercourse owing to the severity of their deformity and/or those patients with refractory ED where placement of an intra-penile prosthesis is required for tumescence. Surgery is typically not indicated for patients whose penile deformity does not prevent intercourse, because of the risk of postoperative ED or other operative complications (Ralph et al., 2010).

Standard surgical interventions for PD can be classified into three categories:

- tunical shortening
- tunical lengthening
- penile prosthesis.

In tunical shortening procedures (Nesbit or modified Nesbit procedures), penile curvature deformity is corrected by plication (ie, suturing across an inward folding of tissue to reduce length) of the tunica albuginea on the convex (longer) side of the penis opposite the point of maximum curvature. Tunical shortening is most appropriate for patients with a less severe penile curvature <70° and adequate penile length to minimize the risk of excessive shortening that may preclude intercourse. Penile shortening is a known complication of this procedure.

Unlike tunical shortening, lengthening procedures involve direct surgical manipulation of the plaque. In plaque excision, an autologous dermal graft is used to repair the tunica albuginea. More recent lengthening techniques involve partial removal of the plaque, whereby only a portion of the plaque is excised and then replaced with a tissue graft. In the plaque incision technique, none of the plaque is removed. Instead, a relaxing incision is made in the plaque and filled with an inlay of graft material. Types of graft used include autologous tissue grafts, allografts or xenografts, and synthetic grafts. These newer

procedures are less likely to impair cavernosal function or cause postoperative ED versus complete excision (Kovac and Brock, 2007). Tunical lengthening procedures are appropriate for patients with good preoperative erectile and penile vascular function, curvature greater than 60–70°, and/or complex deformities.

Finally, the insertion of penile prostheses can allow patients with ED refractory to pharmacologic or vacuum therapy to engage in sexual intercourse. Insertion of non-inflatable or inflatable prostheses is an effective method for maintaining penile length in patients with PD. However, the prosthesis alone is often not sufficient to achieve complete straightening of the penis. Concomitant use of manual modeling (for inflatable prostheses only) or adjuvant reconstructive procedures (ie, tunical shortening or lengthening) is often required for complete correction of the penile deformity.

7.3. Significant clinical benefit based on improved efficacy

Treatment outcomes – Conservative therapies

Oral agents studied in small case series and observational studies include off-label use of vitamin E, carnitine, colchicine, pentoxifylline, and para-aminobenzoate (Potaba®). In general, study results have shown limited therapeutic benefit for correcting penile deformities caused by PD.

Potaba, shown to have anti-inflammatory and antifibrotic effects, is licensed in Germany (Glenwood GmBH, 2011) and the United Kingdom and considered a first-line therapy for PD (Hellstrom, 2009). In a multicenter, randomized, double-blind, placebo-controlled study, 26/35 versus 20/40 of Potaba- and placebo-treated patients, respectively, achieved clinical success, defined as a ≥30% reduction in penile curvature and/or plaque size (Weidner et al., 2005). Among patients with pre-existing penile deviation, there was no significant difference between the Potaba- and placebo-treated patients. However, among those with a straight penis at study start, 5/5 of Potaba and 2/8 of placebo patients remained stable (Weidner et al., 2005). There were no differences in reduction of erectile pain with Potaba versus placebo or for improvement in erection quality (Weidner et al., 2005). The authors suggest that although Potaba does not reduce existing curvature, it may prevent further progression of the deformity.

Topical agents have been all but dismissed as potential therapy for PD; however, two concurrent randomized, double-blind, studies involving the off-label use of topical verapamil (calcium channel blocker) demonstrated significant curvature improvement versus topical magnesium sulfate (weak calcium channel blocker) and topical placebo (Fitch et al., 2007). Erectile pain erection quality was improved in the verapamil treated patients although differences were not statistically significant.

In general, off-label intralesional injections of iloprost, interferon, or verapamil have shown only modest effectiveness for reducing penile curvature or plaque size. However, in an earlier Phase II open-label study of collagenase, a reduction in both curvature and plaque size was seen. Although 28% (7/25) of patients discontinued at some point during the 9-month study, none withdrew owing to injection-related concerns (Jordan, 2008).

Treatment outcomes – Surgical Interventions

There are no published data from randomized controlled trials of surgical interventions for PD. The vast majority of published studies are retrospective reviews of patient charts after follow-up periods of wide-ranging durations. In general, the published studies do not clearly define the treatment groups or the objective and/or subjective endpoints of interest. Almost-certain confounders include the skill of the surgeon(s) performing the procedure, baseline demographic and clinical characteristics of the patients, and the use of multiple procedures with different techniques.

According to the published literature, among patients undergoing tunical shortening surgeries, curvature correction rates varied widely (42−100%). Likewise, 48–94% of patients were able to engage in successful intercourse after surgery. Tunical lengthening procedures are comparably effective; curvature correction rates ranged from 60–100%, and 46–100% of patients had successful intercourse after surgery. However, these techniques can be associated with a greater risk for postoperative ED. In patients with refractory ED secondary to PD, insertion of an inflatable or non-inflatable penile prosthesis – with concomitant adjuvant procedures – is an effective method for achieving complete penile straightening in 61–100% of patients, enabling them to engage in successful sexual intercourse.

Treatment outcomes - Collagenase Clostridium Histolyticum (AA4500)

The co-primary endpoints in the two pivotal trials (AUX-CC-803 and AUX-CC-804) were the percent change from baseline in curvature deformity and the change from baseline in the patient-reported Peyronie's disease bother domain score up to Week 52 (LOCF). After administration of a pharmacological stimulant to induce an erection, the investigator or qualified designee measured the angle of penile deformity three times with a goniometer protractor device using a standard method. All three measurements had to be within 10° of each other; the most severe of the three findings was recorded.

The PDQ Peyronie's disease bother domain included: bother associated with painful erections; bother associated with appearance of erect penis; bother associated with the impact of Peyronie's disease during intercourse; and impact of Peyronie's disease on intercourse frequency. A reduction in the Peyronie's disease bother score (range 0-16) from baseline represented improvement.

AA4500 0.58 mg was statistically superior to placebo with respect to the co-primary endpoints (curvature deformity and patient-reported Peyronie's disease bother) in the clinical studies:

- In each placebo-controlled study, men treated with AA4500 had a statistically significant ($p \leq 0.0059$) greater percent reduction in curvature deformity compared with men treated with placebo.
  Improvement in curvature deformity was apparent after the first treatment cycle (Week 6) with continued improvement noted after each of the three subsequent treatment cycles. The improvement in curvature deformity was maintained through the end of each study (Week 52).
- In each placebo-controlled study, men treated with AA4500 had a statistically significant ($p \leq 0.0496$) greater improvement in patient-reported Peyronie's disease bother compared with men treated with placebo.
- Similar findings were observed among EU subjects who received AA4500 in Study AUX-CC-802.
- Among subjects treated with AA4500, there were no clinically meaningful differences in the mean percent improvement from baseline in curvature deformity or in mean reduction from baseline in patient-reported Peyronie's disease bother when considering any of the following subgroups: race; history of diabetes penile trauma, or prior treatment for PD, severity of baseline erectile dysfunction or concomitant phosphodiesterase type 5 inhibitor use.

7.4. Significant clinical benefit based on improved safety

Safety – Conservative therapies

Overall, conservative therapies are generally well tolerated, although few studies report specific details about the nature and/or frequency of AEs. Oral agents have been associated with gastrointestinal distress (3−6%) (Safarinejad, 2004, Safarinejad, 2009, Safarinejad et al., 2010), and topical applications can produce local skin reactions (5−11%) (Fitch et al., 2007, Riedl et al., 2005) (Error! Reference source not found.). Intralesional therapies are frequently associated with injection-site reactions, including bruising,

swelling, and ecchymosis (22–66%) (Bennett et al., 2007, Jordan, 2008, Moskovic et al., 2012, Pavone et al., 2012). Many patients can also be lost to follow-up after interlesional injections because of pain and trauma from the first injection (Fitch et al., 2007). Patients who receive interferon therapy often experience flu-like symptoms in addition to the local, injection-site reactions (Hellstrom et al., 2006, Inal et al., 2006, Kendirci et al., 2005). Other treatment modalities have been linked to localized bruising, bleeding, and pruritus (Claro et al., 2004, Di Stasi et al., 2004, Gontero et al., 2009, Greenfield et al., 2007).

Safety – Surgical Interventions

Although research has shown that surgical procedures to treat PD are reasonably safe, surgery will not restore penile morphology to its pre-diseased state. Thus, complaints about persistent deformity or unnatural appearance are common, regardless of the technique performed. Postoperative complications include diminished penile sensitivity, penile shortening, and new or worsening ED. Moreover, nearly 20% of patients who undergo surgery for PD may require a secondary procedure owing to residual or recurrent curvature or as a response to more serious complications.

For the Nesbit and modified Nesbit procedures, reported complications include penile shortening, recurrence, and ED. Post-procedural AEs associated with tunical plication include paraphimosis, wound infection, hematoma, and palpable knots. Other suture-related AEs include discomfort, failure, and granuloma. Common complications include penile shortening, reduced penile sensitivity, and painful erection.

Tunical lengthening techniques are associated with a greater risk for postoperative ED. Commonly reported AEs after tunical lengthening surgery include hematoma, palpable knots, and infection. The incidence of reduced penile sensitivity ranges from 2–60%; however, in most studies, rates were ≤15% and normal sensation returned within 6 weeks to 12 months. Recurrence frequently required surgical revision. For penile prostheses, the most frequently reported AE was reduced penile sensitivity and infection. Complications include mechanical failure and urethral injury.

Among the surgical studies included, the reported rates of postoperative residual deformity vary widely and likely depend on a number of factors, including type of procedure, duration of follow-up, definition of residual curvature, and assessment method. For the 15 studies that evaluated residual deformity after penile lengthening procedures, rates ranged from 0% (Rybak et al., 2012) to 40% (Kovac and Brock, 2007) during follow-up periods ranging from 3 months (Horstmann et al., 2011) to 8 years (Simonato et al., 2010). Reported residual deformity rates after penile shortening procedures ranged from 2% (Iacono et al., 2012) to 58% (Nao et al., 2007) during follow-up periods ranging from 3 months (Horstmann et al., 2011) to 7 years (Savoca et al., 2004).

7.5. Significant clinical benefit based on major contribution to patient care

Therapy of Peyronie's disease today includes either so called conservative treatment options or surgical intervention. Common to both alternatives is that they are not optimal for the patient. Apart from a lack of robust studies to evaluate their benefits, each option is associated with limitations in terms of efficacy or safety.

Conservative treatment options are multiple and diverse; however, the clinical safety and efficacy of these conservative treatment approaches have not been convincingly demonstrated to date. Although a relatively large number of studies have been published within the last decade, the overall quality of these studies is quite poor.

Long-standing and well-established surgical approaches for PD generally provide good results by reducing the extent of penile curvature and enabling patients to engage in successful intercourse with

their partner. However, surgery can be associated with serious complications (eg, infection, wound dehiscence) and can result in prolonged recovery times. Surgery is further commonly associated with penile shortening, reduced penile sensitivity, and painful erection. It is not a cure, and revision owing to recurrence is more complex than initial surgery leading to increased rates of intra- and post-operative complications.

AA4500 is a novel non-surgical, less invasive, treatment for Peyronie's disease. The injection of AA4500 into the pathologic plaque, which is composed predominantly of collagen, followed by a penile plaque modeling approximately 1 to 3 days after injection, allows for the local disruption of the plaque. Plaque disruption enables correction of the offending curvature deformity and may preclude the resultant morbidity and extensive recovery time associated with invasive surgical procedures.

The efficacy and safety of therapy has been demonstrated in two independent placebo-controlled Phase 3 studies, and the benefits further substantiated in an open-label Phase 3 study. These studies have shown a clinically and statistically significant, sustained reduction in penile curvature as well as reduced Peyronie's disease bother with AA4500 therapy, thereby enabling patients to engage in successful intercourse with their partner. Therapy was generally safe and well-tolerated, with the majority of adverse events localized to the penis and groin. With appropriate training in injection procedures and provision of relevant product information, the risks associated with treatment can be successfully mitigated. AA4500 provides a novel, clinically proven treatment for Peyronie's disease, and fulfils an unmet need in the EU by providing a nonsurgical treatment for this physically and psychologically debilitating condition.

8. Assessment of the MAH's justification of significant clinical benefit[1]

8.1. Demonstration of new therapeutic indication

AA4500 is a proteinase that can hydrolyze the triple-helical region of collagen under physiological conditions, AA4500 may therefore have the potential to be effective in lysing collagen deposits such as those in the plaque that cause the curvature deformity and subsequent bother and distress in patients with Peyronie's disease.

AA4500 is proposed as a novel non-surgical treatment for Peyronie's disease and targets curvature deformity through the injection of collagenase clostridium histolyticum into the pathologic penile plaque, which is composed predominantly of collagen, and allows for the local disruption of the plaque that causes the curvature deformity.

Plaque disruption enables correction of the offending curvature deformity and may preclude the resultant morbidity and extensive recovery time associated with invasive surgical procedures. Thus, the availability of AA4500 for use in Peyronie's disease would offer the treating urologist an additional nonsurgical treatment option for patients suffering from both the physical and psychological impact of Peyronie's disease and not eligible or not willing to undergo surgical intervention.

[1] In accordance with guidance on elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11-year) marketing protection period
http://ec.europa.eu/health/files/eudralex/vol-2/c/guideline_14-11-2007_en.pdf

8.2. Details of existing therapies

Overall, the MAH's description of currently available options for PD treatment is well founded by literature reports and is endorsed.

There is a lack of a clear understanding of the aetiopathology and, so far, a cure has not been found. Several factors should be considered for the therapeutic management of patients with PD, including the duration of disease, presence or absence of pain with erection, the severity of penile deformity, and the adequacy of erectile function (Hellstrom, 2009). A variety of treatment options have been used.

Conservative treatment options are multiple and diverse and include oral (colchicine, tamoxifen, pentoxyphylline, vitamin E, potassium para-aminobenzoate) and topical (verapamil) agents, intralesional injections (corticosteroids, iloprost, interferon, verapamil), extracorporeal shock wave therapy (ESWT), iontophoresis, and others (Ralph et al., 2010). No pharmacological therapies, except for Potaba in DE and UK, have been formally licensed for the treatment of Peyronie's disease in the EU.

The value of many published reports has been questioned as most were not well controlled, often had a small number of subjects in various phases of stability, had short follow-up phases and with limited reports on objective measures of deformity change. Studies focus on reduction of pain that appears to resolve with time untreated, and reduction of plaque size, which has never been found to correlate with curvature improvement.

Following a consensus statement of leading experts (Ralph et al. 2010, The Management of Peyronie's disease: Evidence-based 2010 Guidelines) reduction of erect penile deformity (i.e. curve, narrowing, shortening) is the most critical outcome measure.

In the most recently published Guideline on Penile Curvature (syn. IPP, Induratio penis plastic) by the European Association of Urology the authors conclude that due to a.m. methodological problems and often contradictory results, it is difficult to provide recommendations in the everyday, real-life setting based on the studies on conservative treatment for PD.

It is reminded that conservative treatment of PD is primarily focused on patients in the early stage of the disease, when symptoms are present and the plaque is not densely fibrotic or calcified. At this stage of the disease 3-13% of patients may show spontaneous remission. Spontaneous remission was also observed as one factor complicating interpretation of the results of phase IIb study AUX-CC-801 where subjects with a minimum disease history of 6 months were included. In order to avoid spontaneous remission as one confounding factor, phase III studies AUX-CC-803 and AUX-CC-804 set the focus on patients at a later stage of the disease (PD symptoms for at least 12 months at study entry).

Surgical interventions are indicated when PD has reached the chronic phase and penile morphology, including plaque size and curvature, has been stable for ≥3 months. The goals of surgery are to correct penile deformity and improve erectile and sexual function. Therefore, surgery is typically only appropriate for patients who cannot achieve intercourse owing to the severity of their deformity and/or those with refractory ED that fails to respond to medical treatment. In addition, patients who have extensive plaque calcification are typically best treated with surgery, as nonsurgical approaches have not been shown to be beneficial in this circumstance. Surgery is typically not indicated for patients whose penile deformity does not prevent intercourse, because of the risk of postoperative ED (Ralph et al., 2010).

In the expert statement (Ralph et al. 2010) it is summarised that surgery remains the gold standard for correcting erect penile deformity in the man with stable disease. However, potential postoperative complications include excessive penile shortening, reduced penile sensitivity, palpable nodules, and ED.

8.3. Significant clinical benefit based on improved efficacy

The efficacy of Xiapex was evaluated in two randomized, double-blind, placebo-controlled, multi-centred trials in 832 (ITT) adult males with Peyronie's disease (Studies 803 and 804). At study entry, patients must have had penile curvature deformity of at least 30 degrees in the stable phase of Peyronie's disease. Patients were excluded if they had a ventral curvature deformity, an isolated hourglass deformity or a calcified plaque that could have interfered with the injection technique. At baseline, the mean duration of PD history of included men (mean age 57-58 years) was 3-5 years. Typically for this stable stage of the disease, pain was not an issue for the vast majority of patients, however, mean penile curvature was pronounced at baseline (48-52° degrees). The curvature deformity often leads to significant bother, distress, and sexual dysfunction among PD patients. Patient Bother was quantified by means of the Peyronie's Disease Bother scale (0-16) and was recorded as 7.4-8.2 across treatment groups at baseline (corresponding to the "moderately bothered" category). The Bother domain score is a composite of the following patient-reported items: concern about erection pain, erection appearance, and the impact of Peyronie's disease on intercourse and on frequency of intercourse. About every second included subject (46.2-53.9% across treatment groups) presented with a history of erectile dysfunction.

In these trials, patients were given up to 4 treatment cycles of XIAFLEX or placebo (weeks 0, 6, 12, 18), and were followed in a non-treatment follow-up period (weeks 24 -52). In each treatment cycle, two injections of XIAFLEX or two injections of placebo were administered 1 to 3 days apart. A penile modelling procedure was performed on patients at the study site 1 to 3 days after the second injection of the cycle. The treatment cycle was repeated at approximately six-week intervals for up to three additional times, for a maximum of 8 total injection procedures and 4 total modelling procedures. In addition, patients were instructed to perform penile modelling at home for six weeks after each treatment cycle.

Before the first dose of study drug was administered, eligible subjects were stratified by the degree of curvature deformity (30 to 60 degrees, and 61 to 90 degrees) and then randomized into two treatment groups to receive either Xiapex or placebo in a 2:1 ratio. The efficacy population (modified intent-to-treat (mITT) population) comprised a total of 613 intent-to-treat subjects who had both a curvature deformity measurement and a PDQ assessment at baseline, and at one or more subsequent time points in Studies 803 and 804, and had engaged in vaginal intercourse within 3 months prior to each PDQ assessment.

Co-Primary endpoints

As confirmed by prior CHMP Scientific Advice, the co-primary endpoints were defined as:

- the percent change from baseline to Week 52 in penile curvature deformity and;
- the change from baseline to Week 52 in the Bother domain score of the PDQ

AA4500 0.58 mg was statistically superior to placebo with respect to the co-primary endpoints (ie, curvature deformity and patient-reported Peyronie's disease bother) in both clinical studies:

In each study, men treated with AA4500 had a statistically significant ($p \leq 0.0059$) greater percent reduction in curvature deformity compared with men treated with placebo. A relative reduction of penile curvature deformity (48.8°-51.3° at baseline) of -37.6% (placebo -21.3%, study 803), resp. -30.5% (placebo -15.2%, study 804) was achieved. Hence, at the end of the 1-year observation period a residual curvature of 31.0°-35.1° remained.

Improvement in curvature deformity was apparent after the first treatment cycle (Week 6) with continued improvement noted after each of the three subsequent treatment cycles. The improvement in curvature deformity was maintained through the end of each study (Week 52). No efficacy data are available for administration of more than four treatment cycles. Likewise, no data are available on recurrence of penile curvature after more than one year after the first AA4500 injection.

Reduction in penile curvature translated in a reduction of patients' bother about PD.

The baseline bother score was 7.4 to 8.2 across treatment arms and studies. Translating the score into bother categories, patients were about moderately bothered at baseline. The PDQ Bother score was assessed at three time points (screening, week 24 and week 52). Hence, increasing reduction of the bother score with increasing number of treatment cycles could not be assessed.

Like already observed for the curvature reduction endpoint, the active and the placebo curves display a similar course with no recurrence of bother between week 24 (assessment of the final injection) and week 52 (end of double-blind treatment period).

At the pre-defined time point at the end of the observation period (week 52), AA4500 was borderline statistically superior to placebo in terms of PDQ Bother score reduction (AUX-CC-803: p=0.0451; AUX-CC-804: p=0.0496).

In the AA4500 treatment arm the PDQ Bother score was 4.2 to 5.0. This translates into the average bother category "a little bit".

Secondary endpoints

When being asked the global assessment / overall change in symptoms at week 52, overall 66% (study AUX-CC-803) resp. 55% (AUX-CC-804) rated themselves as having improved in a small but important way, having moderately improved or even having much improved and were thus defined as responders. These responders had a mean reduction in curvature of at least 20% and a reduction of the PDQ Bother score of at least one point as compared to baseline.

The observed reductions in curvature and PDQ Bother score of those rating themselves as having improved (at least in a small but important way) points to the clinical relevance of the therapeutic effect achieved with AA4500 after the four treatment cycles.

Other secondary endpoints (e.g. PDQ Physical and Psychological Symptom Score or International Index of Erectile Dysfunction Overall Satisfaction (IIED) did not demonstrate significant superiority over placebo when both pivotal studies were separately assessed, however, delivered statistical significance in the pooled analysis of study 803 and 804.

The pivotal studies 803 and 804 were conducted in Australia and the US. A further open-label study AUX-CC-802 (including 192/348 EU subjects) was conducted to increase the safety database and to obtain efficacy and safety results in European subjects. Study 802 did not point to any relevant differences between the US/Australian patient population and Europeans in terms of baseline disease conditions and treatment outcome of AA4500.

Efficacy conclusion

Overall, it is concluded that the efficacy of AA4500 in adult men in a stable stage of Peyronie's disease was adequately demonstrated for a course of up to four treatment cycles (corresponding to 8 injections) and an observation period of up to one year. The Applicant plans to conduct a 5-year study (AUX-CC-810) to provide data on longer-term efficacy of AA4500.

Efficacy of AA4500 has not been formally compared to existing therapies. This is acceptable since only one pharmacological treatment, i.e. Potaba, has been licensed for the treatment of Peyronie's disease in only two EU countries and scientific support for efficacy of other medicinal products used to treat the condition is very weak. Comparison with surgical procedures would have been difficult due to different surgical techniques, the wide range of reported success rates and would not have allowed blinding of the study. In addition, data from well-designed prospective surgery studies are scarce, providing only low

level of evidence. Comparison with placebo is therefore appropriate and demonstrated a clear treatment benefit of AA4500.

8.4. Significant clinical benefit based on improved safety

The safety database contains 1044 subjects who received 7466 injections of AA4500 0.58 mg for the treatment of Peyronie's disease worldwide. Most adverse events following AA4500 injection were locally to the penis or groin and most commonly include penile hematoma, penile pain, penile swelling, injection site pain and injection site hematoma.

The majority of Peyronie's patients experienced at least one adverse reaction (Global Safety database, 92.5%). Most adverse reactions were locally to the penis or groin and the majority of these events were of mild or moderate severity. Most resolved within 14 days of the injection. The adverse reaction profile was similar after each injection, regardless of the number of injections administered.

The most frequently reported treatment-related AEs in the clinical trials in subjects with Peyronie's disease (Global Safety database) were penile hematoma (50.2%), penile pain (33.5%), penile swelling (28.9%) and injection site pain (24.1%).

Corporal fracture and other serious adverse events related to the penis

Treatment-related SAEs included corporal rupture (fracture of penis) in 4 subjects (0.4%). In two of these cases corporal fracture occurred during vigorous sexual intercourse and one subject did not wait the requested 2-week hiatus. One additional subject experienced a corporal fracture that was not a serious AE according to the investigator. Nine subjects (0.9%) reported a combination of penile ecchymoses or hematoma, sudden penile detumescence, and/or a penile "popping" sound or sensation. These subjects were managed without surgical intervention. A diagnosis of corporal rupture cannot be excluded. Treatment-related SAEs also included penile hematoma (n=5). Severe penile hematoma was also reported in 39 patients (3.7%).

The influence of investigator training on adverse events related to the penis seems to be crucial for the safe application of the drug. Investigator training in the clinical studies included intensive injection technique instructions via manuals and DVDs, workshops and investigator meetings and it has to be ensured that the training for the education of physicians in clinical practice is adequate. Thus, AA4500 must be administered by a physician appropriately trained in the correct administration of AA4500 and experienced in the treatment of male urological diseases.

Immunogenicity

During clinical studies in Peyronie's disease subjects were tested at multiple time points for antibodies to the protein components of AA4500 (AUX-I and AUX-II). After 6 weeks of cycle 1, 73.7% of patients had antibodies against AUC-I and 53.9% had antibodies against AUX-II. After the 4th cycle nearly all subjects had antibodies to both AUX-I and AUX-II. Neutralizing antibodies were detected in 43.8% and 31.3%, respectively, of subjects tested. There was no apparent correlation of antibody frequency, antibody titers, or neutralizing status to adverse reactions.

There were no observed cases of severe systemic hypersensitivity or anaphylaxis in the clinical development programme for AA4500 in Peyronie's disease. However, an anaphylactic reaction was reported in a post-marketing clinical study in a patient who had previous exposure to AA4500 for the treatment of Dupuytren's contracture. Thus, physicians must be prepared to address any severe local or systemic allergic reaction. Further data has to be collected post-marketing.

Long-term safety

A follow-up programme for the new proposed indication is ongoing. Study AUC-CC-810 is a long term, non-treatment 2-5 year follow up of patients who received AA450 in the AUX-CC-802, AUX-CC-803 and AUX-CC-804 studies. The final results of study AUC-CC-810 are expected in 4Q 2018. The study protocol is presented within the RMP. The Applicant is requested to submit the long-term results for the use of AA4500 as appropriate.

Safety Conclusion

The safety results indicate that the majority of adverse reactions were non-serious, mild or moderate in intensity, confined to the treated area, and resolved within a short period without sequelae. Among subjects who received at least one dose of AA4500 most subjects experienced adverse reactions in the treated extremity, with the most frequently reported adverse reactions reported being: penile hematoma, penile pain, penile swelling and injection site pain.

8.5. Significant clinical benefit based on major contribution to patient care

Non-surgical approaches are considered first-line therapy for PD, as they are indicated for patients in the early stage of the disease who are experiencing progressive deformity and painful erections. The goal of treatment is to mitigate progression and improve symptoms (Ralph et al., 2010)

Surgery is indicated when curvature impedes adequate sexual penetration or there is an associated ED that fails to respond to medical treatment and should be offered only once the disease has stabilized (Ralph et al. 2010). In the same expert statement it is summarised that surgery is the gold standard for correcting erect penile deformity in the man with stable disease. However, potential postoperative complications include excessive penile shortening, reduced penile sensitivity, palpable nodules, and ED.

Clinical relevant treatment effects and a benign side effect profile could be shown for AA4500 in well-designed randomised controlled trials in patients with stable Peyronie's disease. Considering risks and limitations of surgery, local collagenase injection therapy can be regarded as a desirable treatment alternative in patients with non-calcified plaques providing a major contribution to patient care particularly in patients with preserved erectile function.

A significant clinical benefit based on major contribution to patient care can therefore be concluded.

9. Conclusion

According to the Guideline on Penile Curvature of the European Association of Urology, the surgical correction of curvature should be considered in PD patients at a stable disease state (6 months with no pain and stable deformity, Ralph et al. 2010) and erectile dysfunction not responding to medical treatment. Risks connected to penile surgery like persistent or recurrent curvature, loss of erect length, diminished rigidity, and decreased sexual sensation are described in the literature.

The submitted data package for AA4500 shows clinical relevant treatment effects and a benign side effect profile particularly in patients with preserved erectile function.

Considering risks and limitations of surgery, local collagenase injection therapy can be regarded as a treatment providing a significant clinical benefit based on major contribution to patient care.

10. Recommendation

The CHMP reviewed the data submitted by the Swedish Orphan Biovitrum AB (publ), taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004 and the “Guidance on elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11-year) marketing protection period”, and consider by consensus that the new therapeutic indication brings a significant clinical benefit in comparison with existing therapies.