

Clinical Trial Results Summary
Study AUX-CC-802

Name of Sponsor/Company: Auxilium Pharmaceuticals, Inc.	
Name of Finished Product: AA4500	
Name of Active Ingredient: Collagenase clostridium histolyticum	
Title of Study: A Phase 3, Open-Label 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	
Investigators: Multicenter	
Study center(s): 32 investigative sites in the United States, Europe, and New Zealand enrolled subjects in the study.	
Publications (reference): None.	
Studied period: 252 days Date first subject enrolled: 16-Nov-2010 Date last subject completed: 07-May-2012	Phase of development: Phase 3
Objectives: The objectives of this study were to assess the safety and effectiveness of AA4500 in men with Peyronie's disease.	
<p>Methodology: This was a Phase 3, open-label study of the safety and efficacy of AA4500 0.58 mg in subjects with Peyronie's disease. Subjects were screened for study eligibility within 21 days before the initial injection of study drug in the first treatment cycle. Enrollment included all subjects who met the eligibility criteria and who received placebo in a previous Auxilium-sponsored study (including AUX-CC-801), received one treatment cycle of AA4500 in the pharmacokinetic study (AUX-CC-805), or were naïve subjects in the United States, New Zealand, or Europe.</p> <p>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.</p> <p>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).</p>	
Number of subjects (planned and analyzed): 300 subjects were planned; 348 subjects were enrolled (Subject 5609-7405 was enrolled but not treated and excluded from the ITT population). 347 subjects were treated and analyzed (ITT population).	
Diagnosis and main criteria for inclusion: Healthy male subjects ≥18 years of age with a diagnosis of Peyronie's disease for at least 12 months before the first dose of study drug and a curvature deformity of at least 30° in the dorsal, lateral, or dorsal/lateral plane were eligible. Subjects were to have been in a stable relationship with a female partner/spouse for at least 3 months before screening and willing to have vaginal intercourse with that partner/spouse.	
Test product, dose and mode of administration, batch number: AA4500 0.58 mg injected directly into the penile plaque, after reconstitution with sterile diluent (0.03% calcium chloride dihydrate in 0.9% sodium chloride). The volume of injection was 0.25 mL. Lot numbers were: C0370, C0407, and C0527 for AA4500 and C0358 for diluent.	
Duration of treatment: Subjects received up to four treatment cycles (two injections separated by approximately 24 to 72 hours, repeated after 42±5 days).	

Reference therapy, dose and mode of administration, batch number: None

Criteria for evaluation:

Efficacy:

Efficacy was assessed by percent improvement from baseline in curvature deformity, change from baseline in Peyronie's disease bother domain, responder analysis based on subject global assessment, change from baseline in the severity of Peyronie's disease physical and psychological symptoms, change in overall satisfaction domain of the International Index of Erectile Function (IIEF), change in penile plaque consistency, change in penile length, and change in the penile domain of the Peyronie's disease questionnaire (PDQ) in subjects with penile pain score ≥ 4 at baseline.

Safety:

Safety was evaluated through the monitoring of AEs, clinical laboratory evaluation, vital signs, change in the erectile function domain of the IIEF, and immunogenicity data.

Statistical Methods: The intent-to-treat (ITT) population was defined as all randomized subjects who had at least one injection of study drug. All safety, immunogenicity, and subject-reported overall sexual activity within the last 3 months were summarized based on this population. The penile measurement population was defined as all ITT subjects who had a curvature deformity measurement at screening and had at least one curvature deformity measurement post the first injection of the study drug. The PDQ population was defined as all ITT subjects who had a non-missing Peyronie's disease bother score at screening and had a non-missing Peyronie's disease bother score post the first injection of the study drug. The modified intent-to-treat (mITT) population was defined as all ITT subjects who were both in the PDQ and penile measurement populations. As described in the protocol, 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 population for efficacy since they were ineligible to complete the PDQ; all efficacy endpoints were analyzed using this population. The per-protocol population was defined as all mITT subjects who had a curvature deformity measurement at Week 36, had a non-missing Peyronie's disease bother score at Week 36, and had no protocol violations that would have affected efficacy evaluation.

Efficacy:

The co-primary endpoints were:

- change/percent change from baseline curvature deformity from baseline to Week 36
- change from baseline total score in Peyronie's disease bother of the PDQ from baseline to Week 36

For the primary and secondary endpoints, the 95% confidence interval was provided using a large sample size approximation.

Secondary endpoints 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 from baseline in IIEF overall satisfaction score
- composite responder based on change from baseline in curvature deformity and either Peyronie's disease bother score or the reporting of sexual activity
- change from baseline in penile plaque consistency score
- change from baseline in penile length
- change from baseline in penile pain of the PDQ in subset of subjects with a baseline pain score ≥ 4

Tertiary efficacy endpoints included:

- change from baseline in IIEF, erectile function, orgasmic function, sexual desire, and intercourse satisfaction scores
- spontaneous penile events

Safety:

All treatment-emergent AEs (TEAEs) (regardless of causality, related to study drug, related to study drug by Treatment Cycle [1-4] or posttreatment phase, and related to study drug by duration categories [<14 days, 14-21 days, and >21 days]) 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 at Week 6, Week 12, Week 18, and Week 36. 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 pre-discharge). The baseline value was the vital sign measure immediately pre-dose for that injection. The summary was done by for each injection and time point. Vital signs were summarized at Week 6, Week 12, Week 18, Week 24, and Week 36.

The count and percentage of subjects with Sponsor-defined clinically significant laboratory and vital signs values at any time during the study were also presented.

Titer values for antibody response to clostridial type I collagenase (AUX-I) and clostridial type II collagenase (AUX-II) were summarized with descriptive statistics after log-transformation at Week 6, Week 12, Week 18, Week 24, and Week 36. Samples for neutralizing antibody testing were collected and banked in case an analysis was requested during regulatory review.

SUMMARY

EFFICACY RESULTS:

Overall findings from this study showed that subjects treated with AA4500 had:

- A statistically significant mean percent improvement in curvature deformity and a statistically significant mean reduction in patient-reported Peyronie's disease bother from baseline to Week 36 (LOCF).
- The percentage of responders based on the overall global assessment of Peyronie's disease at Week 36 (LOCF) was statistically significant.
- A statistically significant improvement from baseline to Week 36 (LOCF) in Peyronie's disease physical and psychological symptoms.
- A statistically significant improvement from baseline to Week 36 (LOCF) in IIEF overall satisfaction.
- The percentage of responders based on a change in curvature deformity $\geq 20\%$ and either a change in Peyronie's disease bother score ≥ 1 from baseline to Week 36 (LOCF) or a change from reporting no sexual activity at screening to reporting sexual activity was statistically significant.
- A statistically significant change from baseline to Week 36 (LOCF) in penile plaque consistency. Penile plaques classified as 'hard or solid' or 'firm throughout' at baseline tended to become softer after treatment.
- The mean penile length increase from baseline to Week 36 (LOCF) was statistically significant.
- A statistically significant improvement from baseline to Week 36 (LOCF) in Peyronie's disease penile pain score.

SAFETY RESULTS:

Overall safety findings from this study were as follows:

- Common ($\geq 5.0\%$ of subjects) TEAEs were penile haematoma (51.9%; ~60% had the verbatim 'penile bruising'), penile pain (34.6%), injection site pain (26.8%), penile swelling (26.2%), injection site haematoma (24.2%), penile haemorrhage (22.8%; all had the verbatim 'penile ecchymosis'), penile oedema (14.1%), and injection site swelling (11.5%).
- The majority of subjects had TEAEs or treatment-related TEAEs that were at most mild or moderate in severity, as assessed by the investigator.
- Most subjects had TEAEs that were related to study drug, as assessed by the investigator.
- A total of 13 subjects experienced at least one non-fatal treatment-emergent SAE. Three subjects experienced SAEs that were considered by the investigator to be related to study drug (penile haematoma [n=2] and corporal rupture [n=1]).
- A total of five subjects experienced at least one TEAE that led to study discontinuation. Three events (fracture of penis, penile haematoma, and blood blister) were considered by the investigator to be related to study drug.
- Twelve subjects experienced TEAEs that coded to erectile dysfunction during the study. All were mild (n=9) or moderate (n=3) in intensity. The 10 subjects who had both a screening and Week 36 IIEF erectile function score had either a minimal change or an improvement in the IIEF erectile function score from screening to Week 36.
- No clinically concerning trends were observed with regard to hematology and chemistry laboratory parameter results, vital sign results, or immunogenicity results.
- Despite the high percentage of subjects who developed anti-drug antibodies, there was no evidence of AA4500-related systemic antibody mediated hypersensitivity reactions following treatment with AA4500.