ORIGINAL RESEARCH—PEYRONIE'S DISEASE

Clinical Safety and Effectiveness of Collagenase Clostridium Histolyticum Injection in Patients with Peyronie's Disease: A Phase 3 Open-Label Study

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ABSTRACT

Introduction. Collagenase clostridium histolyticum (CCH; Xiaflex, Auxilium Pharmaceuticals, Inc., Chesterbrook, PA, USA) is a Food and Drug Administration-approved, intralesional treatment for Peyronie's disease (PD).
Aim. The aim of this study was to assess the safety and effectiveness of CCH in the treatment of PD.
Methods. This phase 3, open-label study enrolled subjects who were CCH-naïve, were enrolled in a previous pharmacokinetic study, or had received placebo in an earlier phase 2 CCH study. Each treatment cycle included two intralesional injections of CCH 0.58 mg, approximately 24–72 hours apart, and plaque modeling 24–72 hours after the second injection of each cycle. The treatment cycle was repeated after 6 weeks for ≤4 treatment cycles.
Main Outcome Measures. The co-primary end points were the mean percent change in penile curvature deformity and the mean improvement in PD bother score (range 0–16) from baseline to week 36.
Results. Of the 347 subjects treated with ≥1 injection, 238 had both a penile curvature measurement and a Peyronie's Disease Questionnaire response at baseline and ≥1 subsequent time point. Mean baseline penile curvature deformity was 53.0° and mean PD symptom bother was 7.3. Statistically significant mean improvements from baseline to week 36 were observed in both penile curvature deformity (34.4% [95% confidence interval {CI}, 31.2%, 37.6%]) and PD symptom bother score (3.3 [95% CI, 2.8, 3.7]). Most adverse events (AEs) were mild or moderate in severity and local to the penis. There were three serious treatment-related AEs, two penile hematomas and one corporal rupture; all resolved with treatment.
Conclusions. Potentially clinically meaningful and statistically significant improvements in penile curvature deformity and PD symptom bother scores were observed with intralesional injection of CCH compared with baseline in men with PD. CCH was generally well tolerated, with AEs primarily transient and local to injection site. In conjunction with previous studies, the results of this open-label study support the use of CCH in the treatment of PD. **Levine LA, Cuzin B, Mark S, Gelbard MK, Jones NA, Liu G, Kaufman GJ, Tursi JP, and Ralph DJ. Clinical safety and effectiveness of collagenase clostridium histolyticum injection in patients with Peyronie's disease: A phase 3 open-label study. J Sex Med 2015;12:248–258.**

Key Words. Collagenase Clostridium Histolyticum; Efficacy; Penile Curvature Deformity; Peyronie's Disease; Peyronie's Disease Symptom Bother; Open-Label

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Trial registration: A Study of AA4500 in Men with Peyronie's Disease; ClinicalTrials.gov identifier: NCT01243411.
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Introduction

Peyronie's disease (PD) is a localized connective tissue disorder characterized by formation of a fibrous collagen scar of the tunica albuginea, resulting in penile curvature deformity (e.g., bending, narrowing, hinging, or shortening) during erection [1,2]. Estimates of the prevalence of PD have ranged from 0.4% to 13%, and may be underestimated because of patient reluctance to approach physicians for diagnosis and treatment [2–6]. Although the possibility of resolution is often cited [7–9], documented rates of spontaneous improvement are low (3–13%) [5,10–13].

Patients with PD typically present with a plaque or palpable indurations of the penile shaft, penile curvature deformity during erection, and penile pain [2,14]. These plaques can result in coital difficulties in some patients [15]. Because PD may lead to significant relationship, psychosocial, and emotional problems [16–18], the Peyronie's Disease Questionnaire (PDQ; http://www.auxilium.com/pdq/) was developed and validated in clinical trials to provide a better understanding of the psychosexual impact of PD [19,20]. The International Index of Erectile Function (IIEF) may also be used, although it has not been validated in patients with PD [21,22].

Potential treatments for PD include surgery, minimally invasive treatment options, and medications [5,14,15,23]. Surgical treatment is only indicated for patients with stable disease, and is generally reserved for patients with characteristics such as lack of pain, extensive plaque calcification, penile curvature deformity preventing sexual intercourse, erectile dysfunction refractory to medical therapy, or previous lack of response to nonsurgical therapy [1,5,14,15,23,24]. Although minimally invasive therapies may provide disease stabilization, reduction of deformity, and improved sexual function [14,25], there are limited controlled studies to support their efficacy and safety [25].

Collagenase clostridium histolyticum (CCH) is a novel, nonsurgical, minimally invasive treatment for PD. Intralesional injection therapy with CCH has been approved by the Food and Drug Administration (FDA) for the treatment of adult men with PD with a palpable plaque and curvature deformity of at least 30° at the start of therapy [26]. CCH is a purified mixture of AUX-I and AUX-II collagenases that selectively lyse collagen, the primary component of PD plaques. Purified CCH is also approved in the United States, Europe, Canada, and Australia for the treatment of adults with Dupuytren's contracture (DC) with a palpable cord [27]. Results from two randomized, double-blind, placebo-controlled studies demonstrated that intralesional injection of CCH significantly reduced penile curvature deformity and improved PD symptom bother domain score of the PDQ in adults with PD compared with placebo [28].

Aims

The objective of this open-label study was to further evaluate the safety and effectiveness of CCH in subjects with PD, thereby increasing the available scientific knowledge on this novel treatment for PD. A secondary objective was to examine and provide information on the pharmacokinetics (PK) of CCH.

Methods

Study Design

This phase 3, open-label, multicenter study of CCH in subjects with PD was conducted between November 16, 2010 and August 20, 2012 (study 802; ClinicalTrials.gov identifier: NCT01243411). The study was approved by local institutional review boards/independent ethics committees and was conducted in accordance with the ethical principles of good clinical practice, according to the International Conference on Harmonisation's Harmonized Tripartite Guideline. Each subject voluntarily signed and dated a consent form before study participation.

Subjects

Subjects meeting eligibility criteria (Appendix 1) and who received placebo in the published phase 2b study [29], who received one treatment cycle of CCH in the PK study (805/NCT01430169; n = 20), or who were CCH-naïve were enrolled. Subjects were required to have symptom(s) of PD for at least 12 months before the first dose of study drug and have evidence of stable disease, as determined by the investigator. A total of 40 global sites in the United States, Europe, and New Zealand participated in the study.

Treatment

Each treatment cycle included two intralesional injections of CCH 0.58 mg into the Peyronie's plaque that was causing the curvature deformity, separated by an interval of 24–72 hours between each injection. Treatment cycles were repeated every 6