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Clinical Evaluation of Treatment of Peyronie's Disease With Collagenase Clostridium Histolyticum: Analysis of Penile Curvature Deformity by Duration of Disease and Plaque Calcification

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ABSTRACT

Introduction and Objective: Three phase 3 studies have been conducted to examine the safety and efficacy of collagenase clostridium histolyticum (CCH) in subjects with Peyronie's disease (PD). The effect of CCH on change in penile curvature deformity from baseline to end of study was analyzed by the subjects' duration of disease or degree of plaque calcification.

Methods: All subjects within the phase 3 studies (2 randomized, double-blind, placebo-controlled; 1 open-label [interim data]) and who were treated with CCH received up to 8 injections of CCH (0.58 mg) with 2 injections per cycle separated by about 24 to 72 hours, with the second injection followed 24 to 72 hours later by plaque modeling. A maximum of up to 4 cycles each was allowed, with each cycle separated by a 6-week interval. Penile x-ray or ultrasound findings were used to determine the degree of plaque calcification (no calcification, non-contiguous stippling, and contiguous calcification that did not interfere with the injection).

Results: CCH-treated subjects (N=775) were stratified by duration of disease: 1-2 years (n=280), >2 to ≤4 years (n=266), and >4 years (n=229). Change in mean curvature deformity by duration of disease is shown in **Figure 1** and by degree of plaque calcification in **Figure 2**. Duration of disease had no relationship to the degree of calcification (no calcification=3.8 years, non-contiguous stippling=4.2 years, and contiguous calcification that did not interfere with the injection=3.3 years).

Conclusions: Treatment with CCH resulted in improvements in curvature deformity regardless of duration of disease or level of plaque calcification; although small differences were noted within the subgroups, they are not expected to be clinically meaningful. The observation that the duration of disease had no relationship with the degree of calcification in this population warrants further exploration.

INTRODUCTION

- Peyronie's disease (PD) is a localized, fibrous connective tissue disorder that results in the pathologic deposition of collagen (predominantly Types I and III) in the tunica albuginea of the corpus cavernosum.[1] The clinical presentation may include a palpable scar or palpable bumps or nodules of the penile shaft and complaints of penile pain, sexual dysfunction, and diminished quality of life[2-4]
- The cause of PD is not completely understood. However, it is currently referred to as a wound healing disorder because after trauma to the penis the release of cytokines can activate fibroblast proliferation that may lead to collagen deposition and formation of PD plaque.[1] The hypothesis that PD originates from trauma to the erect penis is generally accepted[2]
- Limited evidence for treatment benefit has been found with minimally invasive treatment options as most clinical studies are small and not well controlled. Surgical correction is recommended when the penile curvature deformity impedes adequate sexual penetration or there is associated erectile dysfunction that does not respond to medical treatment
- The progression of PD may eventually lead to calcification but the mechanism of this process is also poorly understood.[5] There is evidence that the fibrotic plaque tissue contains progenitor cells that in culture can differentiate into osteogenic cells that may eventually lead to ossification through paracrine modulation.[5] Myofibroblasts are shown to originate from intermediate progenitors in certain organs and play a critical role in the development of tissue fibrosis[5]
- In normal wound healing, myofibroblasts disappear by apoptosis after the injury is repaired but are found in abundance in PD plaque in men, suggesting that they may continue to produce collagen and contribute to the progression of PD plaque[5]
- As an active process, it would be expected that the duration of disease would show a relationship to the degree of calcification. In turn, the degree of calcification may affect the prognosis with treatment. Ultrasound appears to be superior to all other methods for the detection of calcifications[6]
- CCH is approved for treatment of adults with Dupuytren's contracture (DC) with a palpable cord.[7] Two identical, randomized, double- blind, placebo-controlled, pivotal, phase 3 clinical trials (IMPRESS I and II) were conducted to investigate the use of CCH (followed by a modeling procedure) in subjects with PD
  - A recently published analysis of this data showed that CCH-treated subjects had a significantly greater improvement in penile curvature deformity compared with placebo subjects (34% vs 18.2%; *P*<0.0001)[8]
  - Significant improvements in the PD symptom bother domain score for CCH-treated subjects compared with placebo subjects were also observed (-2.8±3.8 vs -1.8±3.5; *P*=0.0037)

OBJECTIVE

- To evaluate the role of duration of disease or degree of plaque calcification on change in penile curvature deformity from baseline to the end of study in subjects treated with CCH

METHODS

Study Design

- Post-hoc analysis of 2 identical, randomized, double-blind, placebo-controlled, pivotal, phase 3 clinical trials of 52 weeks duration (IMPRESS I and II) and one open-label, phase 3 clinical trial of 36 weeks duration. The primary purpose of the open-label trial was to treat additional subjects to obtain additional safety information for a more complete evaluation of safety

Eligible Subjects

- Male subjects in good health, aged ≥18 years, with stable disease, and symptoms of PD for at least 12 months before the first dose
- Stable relationship with a female partner for at least 3 months before screening and willing to have vaginal intercourse
- Penile curvature deformity was >30° and <90° in the dorsal, lateral, or dorsal/lateral plane at screening
- Excluded subjects included: those who had known allergy to CCH or excipients, active sexually transmitted disease or HIV, treatment with alternative therapies for PD administered by intralesional route within the past 3 months

Dosing and Administration

- All subjects in the phase 3 clinical trials were treated with CCH injection (0.58 mg) and received up to 8 injections:
  - 2 injections per cycle with each injection separated by about 24 to 72 hours, with the second injection followed 24 to 72 hours later by penile plaque modeling
  - A maximum of up to 4 cycles each was allowed, with each cycle separated by a 6-week interval

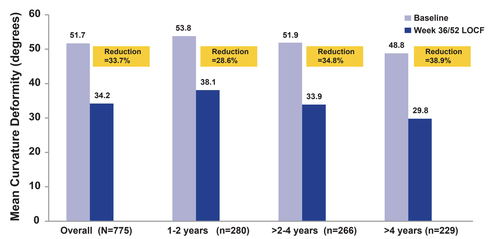
Study Assessments: Co-Primary Endpoints

- During the screening period, each subject had assessment of plaque calcification by penile x-ray or ultrasound to determine if calcification could have prevented proper injection. Non-contiguous stippling of calcium and plaque calcification was acceptable if it did not interfere with the injection of CCH
- A pharmacologic stimulant was used to induce erection, and a goniometry protractor device using a standard method was used for measuring penile curvature deformity
- Change from baseline in penile curvature deformity was evaluated at Weeks 24, 36 (all 3 trials), and 52 (double-blind trials)
- Consistency of the primary plaque was determined in the flaccid penis and rated as hard (solid)=5, firm throughout=4, moderate firmness=3, soft=2, or non-palpable=1

RESULTS

- The mean age of the population was 57.4 years (range 23–84), predominantly white, and mean penile curvature deformity at baseline was ≤45° (43.23% of subjects), 46°-60° (31.23% of subjects), and >60° (25.55% of subjects). Mean duration of disease was 3.8 years (range 0.8–35.9)
- Change in mean penile curvature deformity at Weeks 36/52 in CCH-treated subjects (N=775) who were stratified by duration of disease is shown in **Figure 1**

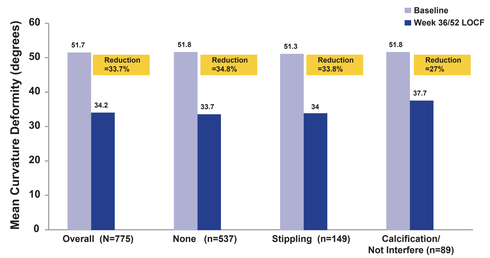
Figure 1. Mean Penile Curvature Deformity at Baseline and Week 36/52 LOCF* by Duration of Disease



*Last observation carried forward (LOCF); Week 36, open-label trial; Week 52, double-blind trials

- Duration of disease had no relationship to the reduction in penile curvature deformity
- Change in mean penile curvature deformity by degree of plaque calcification is shown in **Figure 2**. X-ray or ultrasound findings were used to define categories of no calcification, non-contiguous stippling and calcification (that does not interfere with the CCH injection)

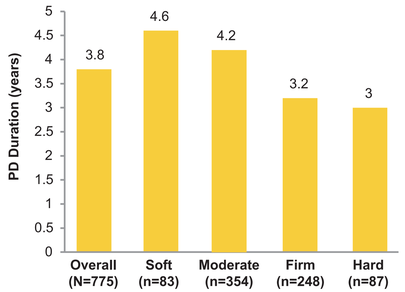
Figure 2. Mean Penile Curvature Deformity at Baseline and Week 36/52 LOCF* by Degree of Plaque Calcification



*Last observation carried forward (LOCF); Week 36, open-label trial; Week 52, double-blind trials

- Degree of plaque calcification had no relationship to the reduction in penile curvature deformity
- Mean duration of disease (years) by plaque consistency at baseline is shown in **Figure 3**

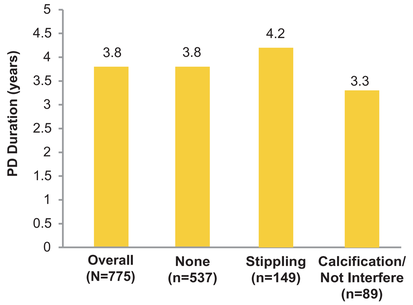
Figure 3. Mean Duration of Peyronie's Disease by Plaque Consistency at Baseline



Duration	Overall	Soft	Moderate	Firm	Hard
1-2 years	36.27%	18.07%	29.38%	48.39%	47.13%
>2-4 years	34.33%	42.17%	36.16%	30.65%	29.89%
> 4 years	29.40%	39.76%	34.46%	20.97%	22.99%

- Soft and moderate plaque consistencies were associated with longer duration of disease, as compared with firm and hard plaque consistencies (ANOVA, *P*<0.01); <30% of plaques were soft or moderate vs approximately 50% were firm or hard at 1 to 2 years (**Figure 3 Table**). Mean duration of disease according to plaque consistency category was: soft=4.6 years, moderate=4.2 years, firm=3.2 years, hard=3 years
- Mean duration of disease (years) by calcification at baseline is shown in **Figure 4**

Figure 4. Mean Duration of Peyronie's Disease by Calcification at Baseline



Duration	Overall	None	Stippling	Not Interfere
1-2 years	36.13%	36.69%	32.89%	38.2%
>2-4 years	34.32%	34.08%	32.89%	38.2%
>4 years	29.55%	29.24%	34.23%	23.6%

- Duration of disease had no relationship to degree of calcification (no calcification=3.8 years, non-contiguous stippling=4.2 years, and contiguous calcification that did not interfere with the injection=3.3 years)

CONCLUSIONS

- Treatment with CCH resulted in improvements in penile curvature deformity, regardless of duration of disease or degree of plaque calcification. Some small differences were noted within the subgroups, but they are not expected to be clinically meaningful
- In this study population, duration of disease had no clinically meaningful relationship to plaque consistency or degree of calcification
- Although there was no association between duration of disease and degree of calcification, further exploration is needed to develop a better understanding of the relationship of duration of disease and degree of plaque calcification. In this study, it was acceptable for subjects to have noncontiguous stippling of calcium and plaque calcification if it did not interfere with the injection of CCH. Subjects who had plaques with calcification that interfered with the injection were excluded. Also, the study was not designed to examine the natural progression of plaque calcification over time

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DISCLOSURES

Speaker, clinical investigator, advisor for Auxilium (IG); investigator for Amgen, Auxilium, Dendreon, Janssen, Astellas, Medivation, Endo, Argos, Spectrum, Orion, Neogenomics, FKD, Glaxo, BNIT, SWOG and RTOG; speaker for Dendreon, Amgen, Glaxo, Medivation and Astellas; consultant for Dendreon, Bayer, Algaeta, Amgen, Janssen, Medivation, Astellas, Spectrum, and AVEO Oncology; consultant and shareholder of Swan Valley Medical (LK); speaker, clinical investigator for Auxilium (JM); Auxilium employees (TS, GK); consultant/advisor, clinical investigator for Auxilium (RS)

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