Clinical Efficacy, Safety and Tolerability of Collagenase Clostridium Histolyticum for the Treatment of Peyronie Disease in 2 Large Double-Blind, Randomized, Placebo Controlled Phase 3 Studies

Martin Gelbard,*,† Irwin Goldstein,‡ Wayne J. G. Hellstrom,§ Chris G. McMahon,‡ Ted Smith,‡ James Tursi,‡ Nigel Jones,‡ Gregory J. Kaufman‡ and Culley C. Carson III‡

From the Urology Associates Medical Group (MG), Burbank, Department of Urology, University of California-Los Angeles (MG), Los Angeles, and San Diego Sexual Medicine (IG) and University of California-San Diego (IG), San Diego, California, Department of Urology, Tulane University Health Sciences Center (WJGH), New Orleans, Louisiana, University of Sydney (CGM), Sydney and Australian Centre for Sexual Health (CGM), St. Leonards, New South Wales, Australia, Auxilium Pharmaceuticals, Inc. (TS, JT, GJK), Malvern, Pennsylvania, Auxilium Pharmaceuticals, Inc. (NJ), Cardiff, United Kingdom, and University of North Carolina (CCC), Chapel Hill, North Carolina

Purpose: IMPRESS (Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies) I and II examined the clinical efficacy and safety of collagenase Clostridium histolyticum intralesional injections in subjects with Peyronie disease. Co-primary outcomes in these identical phase 3 randomized, double-blind, placebo controlled studies included the percent change in the penile curvature abnormality and the change in the Peyronie disease questionnaire symptom bother score from baseline to 52 weeks.

Materials and Methods: IMPRESS I and II examined collagenase C. histolyticum intralesional injections in 417 and 415 subjects, respectively, through a maximum of 4 treatment cycles, each separated by 6 weeks. Men received up to 8 injections of 0.58 mg collagenase C. histolyticum, that is 2 injections per cycle separated by approximately 24 to 72 hours with the second injection of each followed 24 to 72 hours later by penile plaque modeling. Men were stratified by baseline penile curvature (30 to 60 vs 61 to 90 degrees) and randomized to collagenase C. histolyticum or placebo 2:1 in favor of the former.

Results: Post hoc meta-analysis of IMPRESS I and II data revealed that men treated with collagenase C. histolyticum showed a mean 34% improvement in penile curvature, representing a mean ± SD −17.0 ± 14.8 degree change per subject, compared with a mean 18.2% improvement in placebo treated men, representing a mean −9.3 ± 13.6 degree change per subject ($p < 0.0001$). The mean change in Peyronie disease symptom bother score was significantly improved in treated men vs men on placebo (−2.8 ± 3.8 vs −1.8 ± 3.5, $p = 0.0037$). Three serious adverse events (corporeal rupture) were surgically repaired.

Conclusions: IMPRESS I and II support the clinical efficacy and safety of collagenase C. histolyticum for the physical and psychological aspects of Peyronie disease.

Key Words: placebos, penile induration, microbial collagenase, randomized controlled trials as topic, clinical trials as topic

Abbreviations and Acronyms

AE = adverse event

CCh = collagenase Clostridium histolyticum

IIEF = International Index of Erectile Function

ITT = intent to treat

mITT = modified ITT

PD = Peyronie disease

PDQ = PD questionnaire

Accepted for publication January 23, 2013.

Study received investigational research board/independent human research ethics committee approval.

Supported by Auxilium Pharmaceuticals, Malvern, Pennsylvania.

* Correspondence: Urology Associates Medical Group, 2601 West Alameda, Suite 416, Burbank, California 91505 (telephone: 818-843-1702; FAX: 818-843-0380; e-mail: mgelbard@ucla.edu).

† Financial interest and/or other relationship with Auxilium and Biospecifics Technologies.

‡ Financial interest and/or other relationship with Auxilium.

§ Financial interest and/or other relationship with American Medical Systems, Auxilium, Coloplast, Cook, Endo, Johnson & Johnson, Lilly, Medtronic, NIH, Slate, Theralogix, VIVUS.

For another article on a related topic see page 350.

Peyronie disease can be physically and psychologically devastating for subjects and their partners.[1–4] Surgery, which is an option for severe curvature abnormality and/or treatment resistant erectile dysfunction in the stable phase of disease, is often reserved for the most severe cases due to

0022-5347/13/1901-0199/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2013.01.087
Vol. 190, 199-207, July 2013
Printed in U.S.A.

the potential risk of serious complications, including penile shortening, glans numbness, neurovascular injury, infection and erectile dysfunction.[5–7] A key benefit of minimally invasive treatment is the improvement in PD signs, such as penile curvature abnormality and psychosocial symptoms, with less than the treatment related morbidity than occurs with surgery. However, controlled data showing efficacy are limited for most historically available minimally invasive treatments.[8–10]

CCh, a purified mixture of AUX-I and II collagenases, is an investigational, intralesional, minimally invasive intervention with evidence of tolerability and efficacy in subjects with PD based on early clinical studies.[11–15] CCh is approved by the United States Food and Drug Administration, European Medicines Agency and Health Canada for use in adults who have Dupuytren contracture with a palpable cord. CCh is injected into the Dupuytren cord, followed by a finger extension procedure to further disrupt the cord, which has been enzymatically weakened by CCh.[16,17]

A phase 2b study of men with PD showed that up to 6 injections of 0.58 mg CCh into the primary Peyronie plaque significantly reduced the penile curvature abnormality at 36 weeks compared with placebo (29.7% vs 11.0%, $p = 0.001$).[18] The PD specific subject reported symptom bother domain, which assesses subject bother due to painful erection, erect penis appearance and PD impact during intercourse and on intercourse frequency, showed a significant decrease in CCh treated men compared with those on placebo ($p = 0.05$). In subjects randomized to penile plaque modeling, which is the gradual, gentle stretching of the flaccid penis in the opposite direction of curvature, a 32.4% improvement in penile curvature was noted in men treated with CCh vs 2.5% worsening in men on placebo ($p < 0.001$). CCh treatment with penile plaque modeling also significantly decreased the PD specific symptom bother domain compared with placebo (-3.6 vs -0.1, $p = 0.004$).

We present the results of 2 large identical multiinstitutional phase 3, double-blind, randomized, placebo controlled studies of CCh treatment for PD (IMPRESS I and II). These studies were done in parallel to examine CCh treatment through a maximum of 8 injections of 0.58 mg CCh in men with PD. After 52 weeks of treatment, co-primary objectives included the percent improvement from baseline in penile curvature and the change from baseline in the PD symptom bother domain score vs placebo on the PDQ. Tolerability (safety) was also determined.

MATERIALS AND METHODS

Study Population

The CCh phase 3 study program included 2 large, identical, prospective, 1-year, multi-institutional, double-blind, randomized, placebo controlled studies, that is IMPRESS I (NCT01221597) and II (NCT01221623). Men with PD were enrolled from 64 sites across the United States and Australia with 32 sites per study, including 27 in the United States and 5 in Australia. Study accrual for IMPRESS I and II began in September 2010. IMPRESS I was completed by April 2012 and IMPRESS II was completed by March 2012. The supplementary Appendix (http://jurology.com/) lists study population inclusion criteria. All participants provided written informed consent and were free to discontinue treatment at any time. The study protocol was approved by an investigational research board/independent human research ethics committee and performed in accordance with Good Clinical Practice guidelines.

Study Design

The point of maximal penile curvature was recorded as the distance from the corona to the maximum point of curvature after injecting prostaglandin E1 or trimix into a corpus cavernosum to induce erection. The primary direction of curvature was determined as right or left lateral, dorsolateral or dorsal. Ventral curvature was excluded from analysis. Men were stratified by the degree of the penile curvature abnormality (30 to 60 or 61 to 90 degrees) and randomized to the CCh or placebo group 2:1 in favor of CCh. Investigators were blinded to subject randomization to CCh or placebo and treatments were packaged in visually identical drug kits.

Each treatment cycle included 2 injections of CCh (0.58 mg) or placebo, which were directly injected into the primary plaque at the point of maximal penile curvature abnormality by a standardized injection technique with an interval of approximately 24 to 72 hours between each injection. Approximately 24 to 72 hours after the second injection of each treatment cycle subjects underwent investigator penile plaque modeling. Using the plaque as a fulcrum point, the investigator applied firm, steady pressure to elongate and stretch the penis. The penis was held in this position for 30 seconds. The procedure was repeated 3 times. Subjects were instructed to perform standardized home penile modeling 3 times daily using a similar procedure during the 6-week period between each treatment cycle. Subjects were also advised to gently attempt to straighten the penis without pain during spontaneous erection.

The active placebo group received up to 8 placebo injections (10 mM tris and 60 mM sucrose) and plaque modeling. The treatment cycle was repeated after 6 weeks for up to 4 treatment cycles. After the first treatment cycle, subsequent treatment cycles were not administered if the penile curvature abnormality was reduced to less than 15 degrees or the investigator determined further treatment was not clinically indicated.

Measures

The co-primary efficacy end points included the percent improvement from baseline in penile curvature and the change from baseline in the PD symptom bother domain. The percent change in penile curvature from baseline to week 52 vs placebo was assessed using standardized goniometer measurements. The change in the total score of the PD symptom bother domain (4 questions with a total

score range of 0 to 16) from baseline to week 52 vs placebo was assessed using the PDQ, which was developed for use in the phase 3 program, as described by the manufacturer (http://www.auxilium.com/PDQ).

Seven secondary efficacy objectives were examined. The proportion of treatment responders was assessed using the global assessment of PD questionnaire. A treatment responder was defined as a subject with a global score of at least 1 (improved in a small but important way). A decrease in the severity of PD psychological and physical symptoms was assessed by the PDQ. These questions refer to the severity of physical symptoms and concerns of men with PD during vaginal intercourse. The change in the IIEF overall satisfaction domain was examined. The percent of composite responders was compared between the groups. Composite responder was defined as a man with 20.0% or greater improvement in penile curvature plus an improvement in the PDQ PD bother score of 1 or greater, or a change from reporting no sexual activity at screening to reporting sexual activity. The remaining secondary efficacy objectives included the change in penile plaque consistency, penile length and the penile pain domain of the PDQ in subjects with a pain score of 4 or greater at baseline screening.

Safety was evaluated by the investigators at all study visits. They examined the incidence of treatment related AEs and the change from baseline in laboratory values and vital signs. Possible treatment related serious AEs, including corporeal rupture and penile hematoma, were included. Immunogenicity was assessed by measuring anti-AUX-I and II antibody levels.

Data Analysis

Power calculations determined that a sample size of 252 subjects was sufficient to measure the effects of treatment (CCh vs placebo) with power of at least 95% with $\alpha = 0.05$ for each co-primary end point. A sample size of 300 (200 allocated to CCh and 100 allocated to placebo) was determined sufficient to examine tolerability and account for a 15% dropout rate.

The predefined ITT population included all randomized men who received at least 1 CCh injection. Subjects were included regardless of eligibility to complete the PDQ. The ITT population of 832 men was included on safety analysis. The predefined mITT population of 612 men was included on co-primary efficacy analysis, including those with penile curvature abnormality measurement, and a PDQ response at baseline and at least 1 subsequent time point after the first CCh injection. The mITT population appropriately excluded subjects who were not sexually active within 3 months of baseline assessment since they were ineligible to complete the PDQ.

Efficacy analysis was completed for each study individually. Post hoc meta-analysis combining data from the 2 studies was done to improve statistical power for evaluating secondary outcomes. Co-primary and secondary efficacy analyses examined the change from baseline to week 52 using last observation carried forward for subjects who were not evaluated at week 52.

We used ANOVA with factors for drug, baseline penile curvature stratum, study (IMPRESS I or II), and the interaction between drug and baseline penile curvature. The Cochran-Mantel-Haenszel test was used to compare treatment groups for subject global responder and composite responder outcomes, controlling for baseline penile curvature stratum and study (IMPRESS I or II). A combination of the Bonferroni and Hochberg procedures was used to test multiple hypotheses for secondary end points.[19] For the 2 co-primary end points the treatment difference had to be statistically significant for each individual test using a 2-sided test and a type 1 error of 0.05 to claim efficacy and perform secondary analyses. Serial and parallel gatekeeping procedures were used to control the family wise error rate between families of primary and secondary efficacy end points.[20] All statistical analysis was done with SAS®, version 9.1.

RESULTS

Figure 1 shows subject randomization and allocation, and subjects lost to followup. No statistically significant difference was observed between the treatment groups in any demographic or baseline clinical characteristic (table 1). Table 2 shows individual study and combined post hoc meta-analysis outcomes. Post hoc meta-analysis outcomes using the mITT population (except the composite responder analysis that used the ITT population) are also reported.

Co-Primary Efficacy

The mean ± SD penile curvature abnormality at baseline was 50.1 ± 14.4 and 49.3 ± 14 degrees in men on CCh and placebo, respectively. CCh treated subjects showed a mean percent improvement in penile curvature abnormality of 34.0%, equivalent to a mean change per subject of −17.0 ± 14.8 degrees (table 2). A mean 18.2% percent improvement in penile curvature was noted in placebo treated men, equivalent to a mean change per subject of −9.3 ± 13.6 degrees. The change in curvature and the percent improvement in the placebo group were significantly less than in the CCh group (each $p < 0.0001$). The mean change in the PD symptom bother domain score was significantly improved in the CCh group vs the placebo group (−2.8 ± 3.8 vs −1.8 ± 3.5, $p = 0.0037$, table 2).

Secondary Efficacy

The secondary end points of improvement from baseline in the percent of global responders, PDQ psychological and physical symptoms, IIEF overall satisfaction, percent of composite responders and plaque consistency showed consistent trends toward greater improvement in CCh treated men than those on placebo in IMPRESS I and II (table 2). The post hoc meta-analysis that combined the study databases to improve statistical power revealed statistical significance in all secondary end points except penile length and penile pain based on the multiple comparison algorithm.

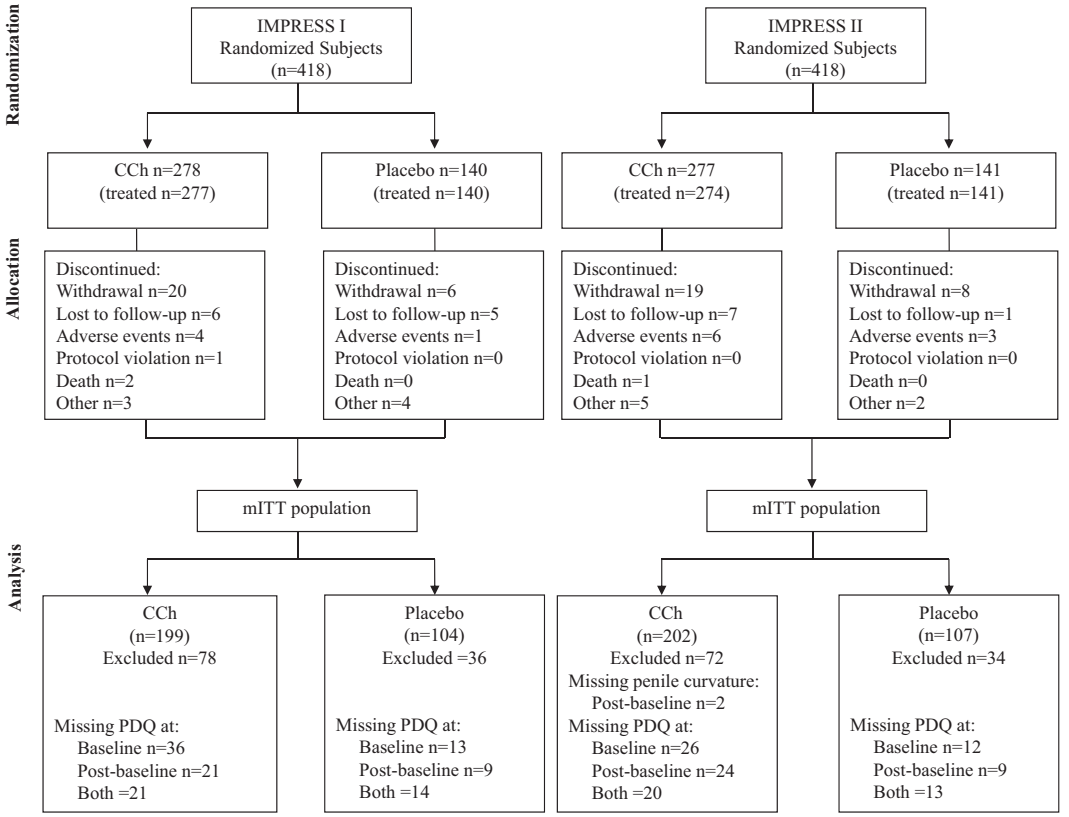

Figure 1. Flow diagram of phase 3 studies. Subjects deemed eligible for study began treatment within 21 days. Subjects were randomized and treatment began on same day.

Safety and Tolerability

The maximum possible treatment cycle of 8 injections was administered in 434 of 551 CCh treated men (approximately 78.8%) and 247 of 281 placebo treated men (87.9%). Treatment related AEs local to the penis and groin after up to 4 treatment cycles were found in 464 men (84.2%) treated with CCh vs 102 (36.3%) who received placebo. As assessed by the investigators, AEs were typically mild or moderate and 3,200 of 4,049 (approximately 79.0%) resolved without intervention within 14 days. Table 3 shows the most common (affecting 1.0% or greater of subjects) treatment related AEs, which occurred at a greater incidence in the treatment group than the placebo group. The most frequently reported AEs (45.0% or greater) in CCh treated men included penile ecchymosis, penile swelling and penile pain. Six men experienced treatment related serious AEs, including corporeal rupture in 3 and penile hematoma in 3 (see Appendix). The 3 corporeal ruptures and 1 hematoma were successfully repaired surgically. One penile hematoma successfully resolved without intervention and the other resolved with aspiration. The percent of subjects with clinically significant laboratory or vital sign parameters was similar in the CCh and placebo groups.

Of 539 CCh treated men 404 (75%) and 288 (53.4%) had positive AUX-I and II anti-drug antibodies, respectively, after treatment cycle 1. By week 52 positive AUX-I and II antibodies developed in 482 of 486 (99.2%) and 479 of 487 CCh treated men (98.4%), respectively. No systemic immunological events were reported.

DISCUSSION

These large, double-blind, placebo controlled studies support the efficacy and safety of CCh treatment for the physical and psychological aspects of PD. In IMPRESS I and II CCh treated men showed a significantly greater percent reduction in the penile curvature abnormality and significantly greater improvement in subject reported PD bother compared with placebo. Post hoc meta-analysis revealed greater improvement from baseline in the percent of global responders, PDQ psychological and physical symptoms, IIEF overall satisfaction, percent of composite responders and plaque consistency in CCh treated men compared with those on placebo. CCh did not shorten penile length. The PD AE profile is similar to that of the Dupuytren clinical program, in that most AEs were local to the treated area, mild or moderate in severity and resolved without intervention before the next scheduled injection.

Table 1. *ITT population demographic and baseline clinical characteristics*

	IMPRESS I		IMPRESS II		IMPRESS I + II Combined Analysis	
	CCh	Placebo	CCh	Placebo	CCh	Placebo
No. subjects	277	140	274	141	551	281
Mean ± SD age/median (range)	57.9 ± 8.2/59 (28–79)	58.2 ± 8.9/59 (30–81)	57.3 ± 8.8/58 (23–84)	57.6 ± 7.5/58 (33–78)	57.6 ± 8.5/59 (23–84)	57.9 ± 8.3/59 (30–81)
No. ethnicity (%):						
Hispanic or Latino	4 (1.4)	3 (2.1)	15 (5.5)	7 (5.0)	19 (3.4)	10 (3.6)
Not Hispanic or Latino	273 (98.6)	137 (97.9)	259 (94.5)	134 (95.0)	532 (96.6)	271 (96.4)
No. race (%):						
Black	10 (3.6)	2 (1.4)	6 (2.2)	3 (2.1)	16 (2.9)	5 (1.8)
White	261 (94.2)	136 (97.1)	267 (97.4)	137 (97.2)	528 (95.8)	273 (97.2)
No. PD family history (%):						
No	194 (97.0)	95 (95.0)	193 (93.7)	97 (95.1)	387 (95.3)	192 (95.0)
Yes	6 (3.0)	5 (5.0)	13 (6.3)	5 (4.9)	19 (4.7)	10 (5.0)
Unknown	77	40	68	39	145	79
Mean ± SD yrs PD history (range)	3.9 ± 4.0/2.7 (1–35.9)	4.8 ± 6.2/2.9 (1–50.8)	4.2 ± 4.2/3.0 (1.1–30.9)	3.4 ± 2.5/2.9 (1.1–17.1)	4.1 ± 4.1/2.9 (1.0–35.9)	4.1 ± 4.8/2.9 (1.0–50.8)
No. penile curvature deformity degrees (%):						
30–60	218 (78.7)	112 (80.0)	207 (75.5)	106 (75.2)	425 (77.1)	218 (77.6)
Greater than 60	59 (21.3)	28 (20.0)	67 (24.5)	35 (24.8)	126 (22.9)	63 (22.4)
No. penile trauma (%)	66 (23.8)	33 (23.6)	63 (23.0)	38 (27.0)	129 (23.4)	71 (25.3)
No. ED medical history (%)	128 (46.2)	75 (53.6)	134 (48.9)	76 (53.9)	262 (47.5)	151 (53.7)

Table 2. *Co-primary and secondary clinical outcomes at week 52 (last observation carried forward) in CCh vs placebo treated subjects*

	IMPRESS I		IMPRESS II		IMPRESS I + II Combined Analysis	
	CCh	Placebo	CCh	Placebo	CCh	Placebo
No. subjects	199	104	202	107	401	211
			Co-primary			
Mean ± SD penile curvature/median (range):						
Baseline (degrees)	48.8 ± 13.9/45.0 (30–85)	49.0 ± 13.9/49.0 (30–89)	51.3 ± 14.8/50.0 (30–90)	49.6 ± 14.1/45.0 (30–85)	50.1 ± 14.4/48.0 (30–90)	49.3 ± 14.0/46.0 (30–89)
Wk 52 (degrees)	31.0 ± 18.1/30.0 (0–90)	39.0 ± 17.7/39.5 (0–79)	35.1 ± 15.1/35.0 (0–82)	41.1 ± 14.6/40.0 (10–80)	33.1 ± 16.8/32.0 (0–82)	40.0 ± 16.2/40.0 (0–80)
% Change	−37.6 ± 30.3/−37.8 (−100–66)	−21.3 ± 29.9/−18.8 (−100–94)	−30.5 ± 27.7/−31.1 (−100–44)	−15.2 ± 28.7/−16.7 (−76–67)	−34.0/−34.8 (−100–63)	−18.2/−18.2 (−100–94)
p Value*	0.0005	—	0.0059	—	<0.0001	—
Mean ± SD PDQ PD bother:						
Baseline	7.5 ± 3.5	7.4 ± 3.6	7.4 ± 3.6	8.2 ± 3.7	7.5 ± 3.5	7.8 ± 3.7
Wk 52	4.2 ± 3.7	5.4 ± 3.8	5.0 ± 3.9	6.5 ± 4.2	4.6 ± 3.8	6.0 ± 4.0
Change	−3.3 ± 3.8	−2.0 ± 3.5	−2.4 ± 3.6	−1.6 ± 3.5	−2.8 ± 3.8	−1.8 ± 3.5
p Value*	0.0451	—	0.0496	—	0.0037	—
			Secondary (family 1)			
% Wk 52 global responders (%)†	66.2	29.1	55.4	29.9	60.8	29.5
p Value*	<0.0001	—	<0.0001	—	<0.0001	—
Mean ± SD PDQ PD symptoms:‡						
Baseline	10.9 ± 5.1	9.9 ± 5.0	10.6 ± 4.8	11.2 ± 5.1	10.8 ± 5.0	10.6 ± 5.1
Wk 52	7.7 ± 5.4	8.4 ± 5.1	8.0 ± 5.3	10.2 ± 5.9	7.9 ± 5.3	9.3 ± 5.6
Change	−3.2 ± 5.2	−1.6 ± 4.5	−2.6 ± 4.8	−1.0 ± 4.8	−2.9 ± 5.0	−1.3 ± 4.6
p Value	0.0268§	—	0.0340§	—	0.0021*	—
Mean ± SD IIEF overall satisfaction:						
Baseline	5.5 ± 2.4	5.6 ± 2.5	5.7 ± 2.4	5.6 ± 2.5	5.6 ± 2.4	5.6 ± 2.5
Wk 52	6.6 ± 2.6	6.1 ± 2.5	6.6 ± 2.4	5.9 ± 2.6	6.6 ± 2.5	6.0 ± 2.6
Change	1.0 ± 2.6	0.5 ± 2.4	1.0 ± 2.3	0.3 ± 2.4	1.0 ± 2.4	0.4 ± 2.4
p Value	0.0800§	—	0.1168§	—	0.0189*	—
			Secondary (family 2)			
% Wk 52 composite responder‖	50.6	25.4	42.3	30.6	46.6	28.0
p Value	<0.0001*	—	<0.0249§	—	<0.0001*	—
Mean ± SD penile plaque consistency change from baseline¶	−0.7 ± 1.0	−0.6 ± 0.8	−0.8 ± 1.0	−0.4 ± 0.9	−0.8 ± 1.0	−0.5 ± 0.9
p Value	0.3085§	—	0.0144§	—	0.0133*	—

Table 2. *(continued)*

	IMPRESS I		IMPRESS II		IMPRESS I + II Combined Analysis	
	CCh	Placebo	CCh	Placebo	CCh	Placebo
Mean ± SD penile length (cm):						
Baseline	10.4 ± 1.8	10.8 ± 1.7	10.5 ± 2.3	10.7 ± 2.5	10.5 ± 2.0	10.7 ± 2.1
Wk 52	10.8 ± 1.8	11.0 ± 1.9	11.0 ± 2.2	10.9 ± 2.4	10.9 ± 2.0	10.9 ± 2.2
Change	0.4 ± 1.3	0.1 ± 1.1	0.5 ± 1.3	0.2 ± 1.5	0.4 ± 1.3	0.2 ± 1.3
p Value§	0.6321	—	0.0248	—	0.0408	—
Mean ± SD PDQ penile pain:**						
Baseline	9.4 ± 4.7	7.3 ± 4.3	8.3 ± 4.4	10.1 ± 5.1	8.8 ± 4.6	8.9 ± 4.9
Wk 52	4.3 ± 4.6	3.3 ± 4.9	4.5 ± 5.2	5.7 ± 5.9	4.4 ± 4.9	4.6 ± 5.6
Change	−5.1 ± 5.2	−4.0 ± 4.1	−3.8 ± 5.9	−4.5 ± 5.4	−4.4 ± 5.6	−4.3 ± 4.8
p Value§	0.7965	—	0.6949	—	0.9672	—

* Significant vs placebo based on multiple comparison algorithm.
† Subjects reporting PD improved in small but important way, or moderately or much improved after treatment.
‡ PDQ Physical and Psychological Symptoms domain includes 6 questions and total possible score of 0 to 30.
§ Not significant vs placebo based on multiple comparison algorithm.
‖ ITT population with 20% or greater penile curvature reduction from baseline and 1 or greater PDQ PD bother score reduction or change from reporting no sexual activity at screening to sexual activity, including 277 on CCh and 140 on placebo in IMPRESS I, 274 on CCh and 141 on placebo in IMPRESS II for total of 551 on CCh and 281 on placebo in IMPRESS I and II.
¶ Flaccid penis primary plaque consistency classified as 5—hard, 4—firm throughout, 3—moderate firmness, 2—soft or 1— nonpalpable.
** mITT population with pain score 4 or greater at screening, including 77 on CCh and 40 on placebo in IMPRESS I, 87 on CCh and 51 on placebo in in IMPRESS II for a total of 164 on CCh and 91 on placebo in IMPRESS I and II, and PDQ Penile Pain domain includes 3 questions and total possible score of 0 to 30.

The demonstration of CCh efficacy and safety in these large, placebo controlled studies is clinically important. Historically, minimally invasive study designs often exclude a placebo control group, which is especially important for PD, given the variable disease course and frequent study limitations of small subject samples and short followup.[8] Clinical significance was noted when study subjects were asked to assess the overall change (much improved to much worse) in the symptoms and effects of PD on their life. Of CCh treated men 60.8% were global responders compared with 29.5% who received placebo. Figure 2 visually shows this result.

Key strengths of the current study include the large, multi-national subject group, the randomized, double-blind, placebo controlled design, and the co-primary physical penile curvature abnormality and psychological PD symptom bother efficacy outcomes. Limitations include the minimal characteristic diversity of the subject population, which consisted primarily of white men with mature Peyronie plaques and moderate penile curvature. Men with calcified plaques that would prevent proper CCh injection, as evident by radiographic evaluation, penile x-ray or penile ultrasound, and those with ventral curvature were excluded from study. All subjects received injections and penile plaque modeling, making this a comparison between treatment and active placebo groups. Eligibility for completing the PDQ required sexual activity within the previous 3 months. However, the composite responder analysis comparing men with improved penile curvature and PD bother or a change in sexual activity included all subjects.

Table 3. *Treatment related AEs in 1% or more of CCh treated subjects and at greater incidence than placebo after up to 4 treatment cycles*

Preferred Term	No. CCh (%)	No. Placebo (%)
Overall	551	281
All AEs	464 (84.2)	102 (36.3)
Penile ecchymosis*	441 (80.0)	73 (26.0)
Penile swelling†	303 (55.0)	9 (3.2)
Penile pain‡	250 (45.4)	26 (9.3)
Blood blister	25 (4.5)	0
Penile blister	18 (3.3)	0
Penile erythema	17 (3.1)	3 (1.1)
Pruritus genital	17 (3.1)	0
Painful erection	16 (2.9)	0
Erectile dysfunction	10 (1.8)	1 (0.4)
Skin discoloration	10 (1.8)	0
Procedural pain	9 (1.6)	2 (0.7)
Injection site vesicles	7 (1.3)	0
Localized edema	7 (1.3)	0
Dyspareunia	6 (1.1)	0
Injection site pruritus	6 (1.1)	0
Nodule	6 (1.1)	0
Suprapubic pain	6 (1.1)	0

* Including injection site hematoma (mostly reported as injection site bruising), penile hematoma (mostly reported as penile bruising), contusion, ecchymosis, penile hemorrhage (mostly reported as penile ecchymosis) and injection site hemorrhage (mostly reported as injection site ecchymosis).
† Including injection site swelling, penile edema, penile swelling, local swelling, scrotal swelling and injection site edema.
‡ Including injection site pain, penile pain and injection site discomfort.

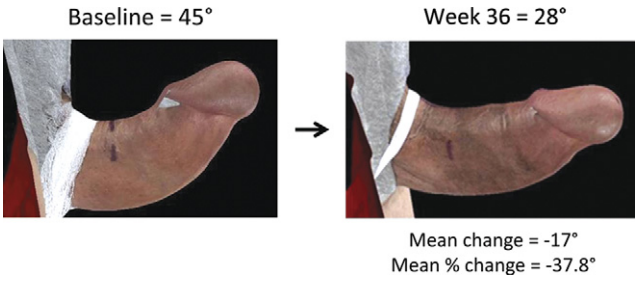

Figure 2. Three-dimensional photography of penile curvature shows that CCh intralesional injection resulted in penile curvature decrease from 45 degrees at baseline to 28 degrees at 36 weeks.

CONCLUSIONS

CCh is an investigational, novel, minimally invasive treatment for PD. Findings from IMPRESS I and II, 2 independent, double-blind, placebo controlled studies, reveal the efficacy and tolerability of CCh for improving the co-primary outcomes of physical penile curvature and the psychological subject reported PD symptom bother domain of the PDQ in adults with PD. Together the studies show the reproducibility of the treatment effects.

ACKNOWLEDGMENTS

Dr. Lynanne McGuire, MedVal Scientific Information Services, L.L.C. provided medical writing and editorial assistance. This manuscript was prepared according to the International Society for Medical Publication Professionals' "Good Publication Practice for Communicating Company-Sponsored Medical Research: the GPP2 Guidelines."

APPENDIX

Treatment related serious AEs in CCh treated subjects

Serious AEs	Resolution
Corporeal rupture (3 cases):	Surgical repair
During intercourse within 14-day requested no intercourse period after CCh injection	
During intercourse with mis-thrust	
During vigorous intercourse 14 days after treatment cycle 3	
Penile hematoma (3 cases):	
Penile hematoma	Spontaneously healed
Superficial hematoma with no evidence of tunical or corporeal disruption	Treated with aspiration
Cystic hematoma with no tunical defect noted at Nesbit plication surgery	Surgical exploration

REFERENCES

1. Taylor FL and Levine LA: Peyronie's disease. Urol Clin North Am 2007; **34:** 517.
2. Rosen R, Catania J, Lue T et al: Impact of Peyronie's disease on sexual and psychosocial functioning: qualitative findings in patients and controls. J Sex Med 2008; **5:** 1977.
3. Smith JF, Walsh TJ, Conti SL et al: Risk factors for emotional and relationship problems in Peyronie's disease. J Sex Med 2008; **5:** 2179.
4. Nelson CJ, Diblasio C, Kendirci M et al: The chronology of depression and distress in men with Peyronie's disease. J Sex Med 2008; **5:** 1985.
5. Taylor FL and Levine LA: Surgical correction of Peyronie's disease via tunica albuginea plication or partial plaque excision with pericardial graft: long-term follow up. J Sex Med 2008; **5:** 2221.
6. Chung E, Clendinning E, Lessard L et al: Five-year follow-up of Peyronie's graft surgery: outcomes and patient satisfaction. J Sex Med 2010; **8:** 594.
7. Benson JS, Abern MR and Levine LA: Penile shortening after radical prostatectomy and Peyronie's surgery. Curr Urol Rep 2009; **10:** 468.
8. Muller A and Mulhall JP: Peyronie's disease intervention trials: methodological challenges and issues. J Sex Med 2009; **6:** 848.
9. Ralph D, Gonzalez-Cadavid N, Mirone V et al: The management of Peyronie's disease: evidence-based 2010 guidelines. J Sex Med 2010; **7:** 2359.
10. Russell S, Steers W and McVary KT: Systematic evidence-based analysis of plaque injection therapy for Peyronie's disease. Eur Urol 2007; **51:** 640.
11. Gelbard MK, James K, Riach P et al: Collagenase versus placebo in the treatment of Peyronie's disease: a double-blind study. J Urol 1993; **149:** 56.
12. Gelbard MK, Walsh R and Kaufman JJ: Collagenase for Peyronie's disease experimental studies. Urol Res 1982; **10:** 135.
13. Jordan GH: The use of intralesional clostridial collagenase injection therapy for Peyronie's disease: a prospective, single-center, non-placebo-controlled study. J Sex Med 2008; **5:** 180.
14. Gelbard MK, Lindner A and Kaufman JJ: The use of collagenase in the treatment of Peyronie's disease. J Urol 1985; **134:** 280.
15. French MF, Mookhtiar KA and Van Wart HE: Limited proteolysis of type I collagen at hyperreactive sites by class I and II Clostridium histolyticum collagenases: complementary digestion patterns. Biochemistry 1987; **26:** 681.
16. Hurst LC, Badalamente MA, Hentz VR et al: Injectable collagenase clostridium histolyticum for Dupuytren's contracture. N Engl J Med 2009; **361:** 968.
17. Gilpin D, Coleman S, Hall S et al: Injectable collagenase clostridium histolyticum: a new non-surgical treatment for Dupuytren's disease. J Hand Surg Am 2010; **35:** 2027.
18. Gelbard M, Lipshultz LI, Tursi J et al: Phase 2b study of clinical efficacy and safety of collagenase clostridium histolyticum in patients with Peyronie's disease. J Urol 2012; **187:** 2268.
19. Hochberg Y: A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988; **75:** 800.
20. Dmitrienko A, Molenberghs G, Chuang-Stein C et al: Multiple comparisons and multiple endpoints. In: Analysis of Clinical Trials Using SAS®: A Practical Guide. Cary, North Carolina: SAS Institute 2005; pp 67–127.