SCIENTIFIC ARTICLE

Treatment of Recurrent Dupuytren Contracture in Joints Previously Effectively Treated With Collagenase *Clostridium histolyticum*

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Purpose Collagenase *Clostridium histolyticum* (CCH) is approved for the treatment of adults with Dupuytren contracture with a palpable cord. This open-label, phase 4 study evaluated the safety and efficacy of CCH for the retreatment of recurrent contractures in joints that were previously effectively treated with CCH.

Methods Patients participating in a long-term follow-up study who had contracture recurrence (increased $\geq 20^\circ$ with a palpable cord) after successful treatment in the previous study were eligible. Recurrent joint contractures were treated with up to 3 CCH injections ($\sim$ 1 month apart). Patients were followed for 1 year to evaluate safety. Assessments included change in joint contracture, range of motion, and the percentage of joints that achieved contracture of 5° or less at day 30 after the last injection.

Results The efficacy analysis included 51 patients with 1 treated joint per patient (31 metacarpophalangeal, 20 proximal interphalangeal). A total of 35 joints (69%) received 1 injection, 12 (24%) received 2 injections, and 4 (8%) received 3 injections. Fifty-seven percent of joints achieved contracture of 5° or less (29 of 51). Overall, 86% (43 of 50) patients had a 20° or greater increase in range of motion. The adverse event profile was consistent with previous studies. One ligament injury was reported.

Conclusions At a short-term follow-up of 1 year, recurrent contracture in joints previously successfully treated with CCH may be effectively retreated with up to 3 injections of CCH. *(J Hand Surg Am. 2017;42(5):391.e1-e8. Copyright © 2017 by the American Society for Surgery of the Hand. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).)*

Type of study/level of evidence Therapeutic IV.

Key words Dupuytren contracture, collagenase *Clostridium histolyticum*, recurrence.

Online Exclusive

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Received for publication April 11, 2016; accepted in revised form February 10, 2017.

The study was funded by Auxilium Pharmaceuticals, Inc., Malvern, PA.

B.J.B. reports receiving research grants from Auxilium Pharmaceuticals, Inc. C.A.P. reports receiving research grants from and serving as a consultant for Auxilium Pharmaceuticals, Inc. F.T.D.K. reports receiving research grants from and serving as a consultant for Auxilium Pharmaceuticals, Inc. G.J.K. and J.P.T. report being former employees of Auxilium Pharmaceuticals, Inc. T.S. reports being a former employee of Auxilium Pharmaceuticals, Inc., and Endo Pharmaceuticals Inc.

Data from this paper were presented at the American Association for Hand Surgery Annual Meeting, January 8—11, 2014, Kauai, HI, and the American Society for Surgery of the Hand Annual Meeting, September 18—20, 2014, Boston, MA (Peimer CA, et al. *J Hand Surg Am.* 2014;39[9 Suppl]:e33).

All authors contributed equally and each was involved in study design, data acquisition, or data analysis/interpretation and in drafting or critically revising the manuscript. All authors reviewed the final manuscript and gave approval for submission.

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0363-5023/17/4205-0018
http://dx.doi.org/10.1016/j.jhsa.2017.02.010

Dupuytren disease is a fibroproliferative disorder of the palmar fascia characterized by the formation of nodules, collagen cords, or both, in the palm leading to flexion contractures of the fingers.[1,2] Severe contractures can result in functional impairment that interferes with activities of daily living.[2,3]

Surgical options for treatment include extensive interventions such as fasciectomy and dermofasciectomy, as well as less-invasive techniques such as fasciotomy/aponeurotomy and needle aponeurotomy/percutaneous needle fasciotomy.[4,5] Generally, more-extensive procedures result in greater correction of the contracture relative to less-invasive procedures.[6]

Collagenase *Clostridium histolyticum* (CCH) is a minimally invasive treatment that is an alternative to some surgical interventions.[5–7] Collagenase *Clostridium histolyticum* is approved in the United States for the treatment of adults with Dupuytren contracture with a palpable cord. Concurrent treatment of up to 2 affected joints (total of 3 injections) may be performed in the same hand.[7] The beneficial outcomes of its use were observed in 2 phase 3 studies.[8,9] In these 2 placebo-controlled studies (CORD I[8] and CORD II[9]), rates of clinical success (ie, correction of contracture to 0°–5°) were significantly higher with CCH than with placebo.[8,9]

Recurrence of Dupuytren contracture presents a challenge regardless of the intervention used, although recurrence is generally more common either after less-extensive surgical procedures[4] or when a lesser degree of initial correction is achieved.[4,6] Available data on recurrence rates after specific interventions vary widely. In a systematic review of treatments for Dupuytren contracture (open partial fasciectomy, needle aponeurotomy, and collagenase injection), reported recurrence rates were similar after open partial fasciectomy and collagenase injection (12%–39%), but higher rates of recurrence were reported after needle aponeurotomy (50%–58%).[10] However, comparing recurrence rates among published studies is difficult because individual studies have surveyed different follow-up times and used a variety of definitions of recurrence.[10–12]

Treatment options for recurrent contractures after initial correction may include collagenase and surgery.[13] Published data on outcomes of surgical treatments specifically for recurrent contractures are somewhat limited.[14,15] Complications, such as digital nerve or digital artery injuries, may be more common with surgical interventions for recurrent contractures relative to initial treatment.[16]

Collagenase *Clostridium histolyticum* may be considered an appropriate treatment option for recurrent contractures in adults, provided there is a palpable cord to inject. Bainbridge and colleagues[17] analyzed data from phase 3 studies and found that the efficacy and safety of CCH treatment were similar regardless of whether patients previously had surgery to correct Dupuytren contracture on the hand with the CCH-treated joint. However, to date, no data have been published on the use of CCH for recurrence in joints previously treated with CCH. This study was conducted to assess the safety and efficacy of CCH in the retreatment of recurrent contractures in joints that were previously effectively treated with CCH.

MATERIALS AND METHODS

Study design and ethics

This open-label phase 4 study was conducted from March 2012 to October 2013 at 12 sites in the United States, Australia, and Europe (NCT01498640). The study protocol was approved by the local ethics committees, and research was carried out in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines. All participants provided written informed consent before the initiation of any study-specific procedures and were free to discontinue at any time.

Patients

Eligible patients were adult men and women with Dupuytren contracture who were participating in a long-term follow-up study (Collagenase Option for Reduction of Dupuytren Long-Term Evaluation of Safety Study [CORDLESS]), the eligibility criteria of which have been published previously.[18] To be eligible for the current study, patients from the CORDLESS study had to have at least 1 joint with the following: (1) effectively treated with CCH (contracture $\leq 5°$ at day 30 after the last CCH injection) in a previous phase 3 study (CORD I,[8] CORD II,[9] JOINT I,[19] or JOINT II[19]), (2) an increase in contracture of 20° or greater compared with the contracture at day 30 after the last CCH injection in that previous phase 3 study, and (3) a palpable cord. Patients were excluded if they were pregnant, lactating, or planned to become pregnant during the study, were hypersensitive to CCH, or were receiving, planned to receive, or had received anticoagulant medication within 7 days before CCH injection (except for $\leq$ 150 mg aspirin daily and nonprescription nonsteroidal anti-inflammatory drugs).

Treatments and study visits

A single recurrent joint was identified for retreatment at the enrollment visit. Joints were classified at baseline

as "low severity" (ie, metacarpophalangeal [MCP] contracture $\leq 50°$ or proximal interphalangeal [PIP] contracture $\leq 40°$) or "high severity" (ie, MCP contracture $> 50°$ or PIP contracture $> 40°$). The cord affecting the recurrent joint was treated with up to 3 injections of CCH (0.58 mg per injection). Injections were separated by approximately 1 month. At 24 hours ($\pm$ 4 hours) after CCH injection, a finger extension procedure was performed to disrupt the cord. The use of local anesthesia before the finger extension procedure was permitted at the investigator's discretion. Details of the injection and finger extension procedures have been previously published.[8] After the finger extension procedure, the patient was fitted with a hand orthosis and instructed to wear the orthosis nightly for up to 4 months. Patients were also instructed to perform a series of finger flexion and extension exercises at home. Follow-up visits were conducted approximately 30 days after each injection and at about day 365 after the last injection. Additional visits could be scheduled, if needed, at the discretion of the investigator. At approximately 30 days after injection, a determination was made as to whether the joint would receive additional treatment. Reasons for not administering additional CCH injections included (1) no palpable cord to inject, (2) the patient reported satisfaction with the improvement in contracture, (3) the patient was not satisfied but did not want additional treatment, (4) adverse event (AE) or other injection-related reaction, or (5) other reasons (eg, lack of health insurance coverage, family issues, aversion to needles or injections, concerns about pain).

Assessments and outcomes

Efficacy: Treatment result assessments were performed by the investigator or a qualified designee. Finger goniometry was used to measure contracture of the affected joint before injection, after each finger extension procedure, and at 30 days ($\pm$ 5 days) and 365 days ($\pm$ 30 days) after each injection. Outcomes included (1) change from baseline and percentage change from baseline in fixed flexion contracture (FFC), (2) changes from baseline in range of motion (ROM), and (3) achievement of an FFC of 5° or less at 30 days after the last injection. An analysis of the percentage of patients who had an increased ROM of 20° or achieved FFC of 5° or less was also performed, although this analysis was not prespecified.

Safety: Safety assessments included a physical examination at the enrollment visit, vital signs at each visit, and laboratory assessments (hematology, blood chemistry, and urinalysis) at enrollment and at day 365 ($\pm$ 30 days). Serum samples to test for anti-AUX-I and anti-AUX-II antibodies, neutralizing antibodies to AUX-I and AUX-II, and matrix metalloproteinases (MMP) cross-reactivity were obtained at day 30 after the last injection and at day 365 ($\pm$ 30 days). Adverse events were recorded throughout the study period and treatment-emergent AEs (AEs with an onset or worsening from the time of administration of the first CCH injection to completion or discharge from the study) were reported in the current analysis. Serious AEs (SAEs) are AEs that result in death, are life-threatening, require inpatient hospitalization, or result in persistent or significant disability/incapacity, congenital anomaly/birth defect, or other medically important events that could have jeopardized the patient or required intervention to prevent 1 of the other outcomes. Intensity of AEs was characterized as mild (transient and easily tolerated by the patient), moderate (caused discomfort and interrupted usual activities), or severe (caused considerable interference with usual activities and may have been incapacitating or life-threatening). The relationship of AEs to treatment was assessed as probable, possible, or not related, at the discretion of the investigator.

Statistical analysis

The sample included all patients who received 1 or more doses of CCH. Efficacy analyses were performed in all patients who received 1 or more injections, had 1 or more efficacy measures after injection, and had a recurrent joint contracture retreatment. Because of the open-label nature of the study, all efficacy and safety data were summarized descriptively. Categorical variables were summarized using counts and percentages. Means, medians, SDs, and minimum and maximum values were calculated for continuous variables.

RESULTS

Patient population

Of the 52 patients enrolled (Table 1), 1 patient had treatment of a nonrecurrent joint and was excluded from efficacy analyses (Table 2). Among the treated joints, 69% (35 of 51) received 1 injection, 24% (12 of 51) received 2 injections, and 8% (4 of 51) received 3 injections. In addition, 1 patient with a contracted PIP joint did not have a baseline ROM assessment and was excluded from the ROM analyses (n = 50).

Efficacy

Fifty-seven percent of joints achieved FFC of 5° or less (Fig. 1A). Most (67%) MCP joints required 3 injections to achieve FFC of 5° or less, whereas 35% and

TABLE 1. Demographic and Baseline Clinical Characteristics

Characteristic	Sample Population (n = 52)
Age, y, mean (SD)	66.5 (9.5)
Male, n (%)	50 (96.2)
Age at onset, y, mean (SD)*	50.8 (12.7)
Prior treatment, n (%)†	
CCH during trials included in CORDLESS‡	52 (100.0)
No treatment other than CCH in CORDLESS trials‡	38 (73.1)
Fasciectomy	9 (17.3)
CCH other than that provided as part of CORDLESS trials‡	6 (12.0)
Needle aponeurotomy	4 (7.7)
Fasciotomy	1 (1.9)
Other	1 (1.9)
Number of previous CCH injections, mean (SD) [range]§	3.4 (1.9) [1–8]
Time since last CCH injection (months), median (SD) [range]	50.2 [3.6–58.8]
Required lidocaine for finger extension procedure, n (%)	29 (55.8)

*Data available for 41 patients.

†Prior treatment could occur on any joint and was not limited to the joints treated in the current study. Patients could have reported ≥ 1 prior treatment and > 1 report of the same treatment in an individual patient was counted only once. A total of 6 patients had prior treatment(s) for the joints treated in this study, including 2 who had fasciectomies, 3 who had needle aponeurotomies, and 3 who had CCH injections (2 patients had more than 1 type of prior treatment to the same joint).

‡All patients were recruited from CORDLESS, a long-term follow-up study that included patients who received CCH injection during multiple double-blind (CORD I and CORD II) and open-label trials (JOINT I and JOINT II).[13] To be included in the current analysis, patients from the CORDLESS study had to have at least 1 joint meeting the following conditions: (1) effectively treated with CCH (contracture ≤ 5° at day 30 after the last CCH injection) during CORDLESS, (2) an increase in contracture ≥ 20° compared with the contracture at day 30 after the last CCH injection, and (3) a palpable cord.

§In a prior phase 3 study or with commercially available CCH.

TABLE 2. Characteristics of Treated Joints

Characteristic	MCP (n = 31)	PIP (n = 20)	Total (n = 51)
Finger, %			
Little	26	65	41
Ring	61	25	47
Middle	10	5	8
Index	3	5	4
Baseline FFC in current study, degrees (SD)	40 (15)	46 (21)	42 (18)
Time from success in previous phase 3 study to recurrence, d, mean (SD) [range]	902 (377) [128–1,468]	755 (223) [532–1,504]	844 (331) [128–1,504]
Time from recurrence to first CCH injection in current study, d, mean (SD) [range]*	691 (365) [84–1,406]	788 (198) [231–993]	729 (312) [84–1,406]

*Calculated as the date of the first injection of the current study minus the date of recurrence of the treated joint reported in previous studies.

40% of PIP joints achieved FFC of 5° or less after 1 and 2 injections, respectively. Among patients who did not achieve FFC of 5° or less and did not receive the maximal 3 CCH injections, 16% of patients refused additional CCH injections because they were satisfied with their improvement after initial treatment. Other reasons for not receiving the maximal number of CCH injections included lack of an injectable palpable cord (14%), dissatisfaction with treatment (2%), AEs (2%), and other reasons (6%; FFC of 15° and joint considered functional [n = 1], joint considered unsuitable for further injection [n = 1], and difficulty with drug administration [n = 1]). Most patients (74%) had an increase in ROM of at least 20°. Overall, 86% of

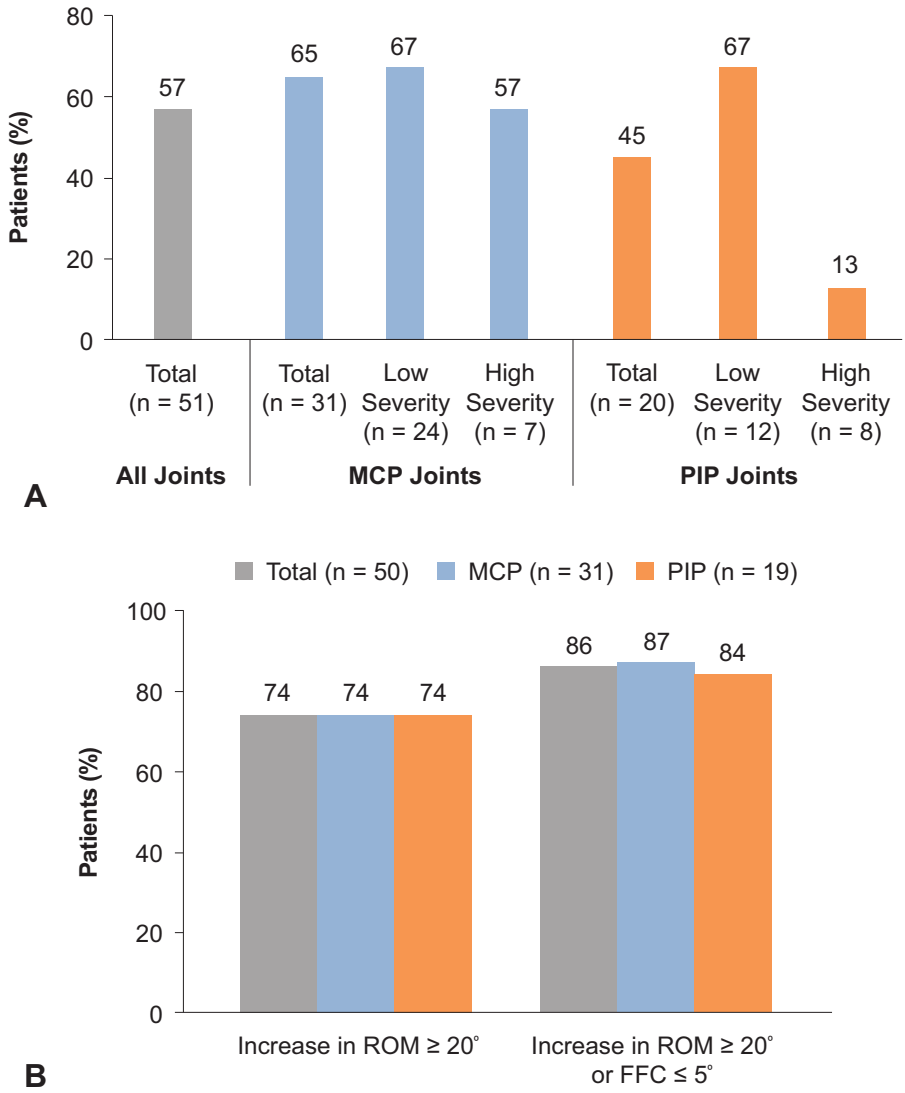

FIGURE 1: **A** Joints achieving FFC $\leq 5°$ and **B** those patients who had at least a 20° increase in ROM or FFC $\leq 5°$.

patients had an increase in ROM of at least 20° or FFC of 5° or less (Fig. 1B).

Mean improvement in FFC and ROM from baseline was comparable for MCP and PIP joints (Table 3). Percentage change in FFC from baseline was greater in MCP joints (83%) than in PIP joints (69%), although the overall mean change in degrees was similar between the groups (MCP joints, 40° at baseline to 7° 30 days after last injection, change of 33°; PIP joints, 46° at baseline to 15° 30 days after last injection, change of 31°). A similar percentage of patients with MCP and PIP joints achieved an ROM of at least 20° or FFC of 5° or less (Fig. 1B).

Safety

At least 1 AE was reported by 46 of 52 patients (89%; Table 4). Four patients reported 6 SAEs (Table 5). No systemic hypersensitivity reactions or tendon injuries were reported. One patient complained of persistent pain over the A2 pulley area. No bowstringing of flexor tendon was noted on examination and the pain resolved by 6 months.

Most patients had antibodies to AUX-I (96%) and AUX-II (96%) at the baseline visit. Thirty days after retreatment with CCH, mean log antidrug antibody titers increased from 3.8 to 5.8 for anti-AUX-I, and from 3.4 to 5.8 for anti-AUX-II. Anti-AUX-I and anti-AUX-II titers remained increased (mean log titers, ≥ 5) through the day 365 visit. Fifty-six percent (24 of 43) of patients with anti-AUX-I antibody log titers of 5 or greater and 73% (33 of 45) of patients with anti-AUX-II antibody log titers of 5 or greater also had neutralizing antibodies to AUX-I and AUX-II, respectively. By the day 365

TABLE 3. Efficacy Outcomes

Fixed Flexion Contracture	MCP (n = 31)	PIP (n = 20)
Baseline, °, mean (SD)	40 (15)	46 (21)
Day 30 (after last injection), °, mean (SD)	7 (12)	15 (16)
Change from baseline, °, mean (SD)	33 (16)	31 (19)
Percentage change from baseline, mean, %	83	69
Low baseline severity*	84	74
High baseline severity†	79	62
Range of motion		
Baseline, °, mean (SD)‡	54 (15)	60 (21)
Day 30 (after last injection), °, mean (SD)	85 (16)	86 (16)
Change from baseline, °, mean (SD)‡	31 (18)	27 (17)

*Data available for 24 MCP and 12 PIP.
†Data available for 7 MCP and 8 PIP.
‡Data missing for 1 PIP.

TABLE 4. Most Frequently Reported AEs (≥ 5% of Patients)*

AE	Patients, n (%) (n = 52)
Edema peripheral (swelling of the treated extremity)	32 (62)
Contusion	23 (44)
Pain in extremity	16 (31)
Injection-site pain	10 (19)
Pruritus	10 (19)
Injection-site hematoma	8 (15)
Lymphadenopathy	8 (15)
Skin laceration	7 (13)
Injection-site pruritus	5 (10)
Injection-site swelling	5 (10)
Hypertension	3 (6)

*All AEs, occurring in ≥ 5% of patients and noted in table, were mild or moderate.

TABLE 5. Serious Adverse Events

SAE	Patients, n (%) (n = 52)
Cerebellar infarction	1 (2)
Acute myocardial infarction*	1 (2)
Acute coronary syndrome*	1 (2)
Chest pain*	1 (2)
Dupuytren contracture recurrence†	1 (2)
Urosepsis	1 (2)

*Serious adverse events were experienced by the same patient.
†This patient had a reduction in contracture of the left little PIP joint from an FFC of 80° at baseline to an FFC of 65° approximately 30 d after a single CCH injection. At least 254 d after the last CCH injection, the patient was hospitalized for surgical treatment (open fasciectomy and PIP joint release) of a recurrent contracture (FFC of 50° at d 365) at the same joint.

visit, the percentage of patients who tested neutralizing antibody−positive decreased. Rates of achieving FFC of 5° or less and improvement in FFC 30 days after last injection were comparable for patients with or without neutralizing antibodies, and improvement in FFC was maintained through the day 365 visit, even among patients who had persistent neutralizing antibodies. Anti-AUX-I and anti-AUX-II did not show any cross-reactivity with any of the 5 human MMPs (MMP-1, -2, -3, -8, and -13) that were tested. All tested negative.

DISCUSSION

In this study, mean time to recurrence of joint contracture after the final injection of CCH in previous trials was approximately 2 years. Of joints that experienced recurrent contracture and received subsequent CCH injections, 57% achieved FFC of 5° or less. The percentage of patients who achieved FFC of 5° or less was higher in MCP joints (65%) than in PIP joints (45%), as is also found with other treatment methods that address original and recurrent contractures.[1,5,11,16]

The pretreatment contracture severity for recurrent joints treated in the current study (MCP joints, 40°; PIP joints, 46°) was slightly lower than the initial pretreatment severity of joints treated in phase 3 trials

(CORD I [MCP joints, 48°; PIP joints, 55°] and CORD II [MCP joints, 50°; PIP joints, 56°]).[8,9] Efficacy results in the joints that were retreated with CCH in the current study are consistent with results after initial CCH treatment in phase 3 studies. For example, in CORD I and CORD II, the percentage of patients who had reduction of contraction to 5° or less were 77% and 65%, respectively, in MCP joints, and 40% and 28%, respectively, in PIP joints.[8,9]

Differences in the treatment protocols for the current study compared with the phase 3 studies should be noted when considering these data. In the phase 3 studies, patients received additional CCH injections (up to 3 per joint) until the treated joint reached contracture of 5° or less,[8,9] whereas, in the current study, additional injections (again, up to a maximum of 3 per joint) were at the discretion of the investigator and the patient. In addition, the administration of local anesthesia before the finger extension procedure was permitted in the current study, whereas in the phase 3 CORD I and II studies it was not.

Adverse events were mostly mild to moderate, local, and generally consistent with the known safety profile of CCH. The incidence of AEs in the current study was generally similar to the incidence observed during the phase 3 studies after CCH treatment to the same joints, except for lower incidences of injection site pain (19% vs 32% and 38%), and injection site swelling (10% vs 21% and 36%), and a higher incidence of pruritus (19% vs 11%).[8,9] No tendon injuries or other treatment-related SAEs were reported. There were no reports of systemic hypersensitivity reactions, despite antidrug antibody titers being elevated at the start of treatment. Thus, CCH retreatment does not appear to be associated with an increased risk for local AEs, SAEs, or systemic hypersensitivity reactions relative to initial treatment.

Potential limitations of the study include the sample size of 52 treated joints (51 joints evaluated for efficacy). As a result, it is not possible to make broad conclusions from the data, especially as they pertain to the safety profile of CCH for recurrent disease. In addition, the data capture an early response to treatment. Secondary recurrence was not assessed for an extended period of time and the study was not designed to evaluate the presence or influence of risk factors for recurrence. Because the joints in this study had good responses to CCH in the past, this might be considered a type of selection bias.

Overall, the results of this study show that, at a 1-year follow-up, recurrent Dupuytren contracture may be successfully retreated with up to 3 injections of CCH in 57% of patients who were previously successfully treated with CCH.

ACKNOWLEDGMENTS

The authors thank MedVal Scientific Information Services, LLC, and Synchrony Medical Communications, LLC, West Chester, PA, for providing medical writing and editorial assistance, which was funded by Endo Pharmaceuticals Inc., Malvern, PA. Funding to support this study was provided by Auxilium Pharmaceuticals, Inc., Malvern, PA.

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