# Dupuytren Contracture Recurrence Following Treatment with Collagenase Clostridium Histolyticum (CORDLESS Study): 3-Year Data

Clayton A. Peimer, MD, Philip Blazar, MD, Stephen Coleman, MBBS, F. Thomas D. Kaplan, MD, Ted Smith, PhD, James P. Tursi, MD, Brian Cohen, PhD, Gregory J. Kaufman, MD, Tommy Lindau, MD, PhD

**Purpose** To evaluate long-term efficacy and safety of collagenase clostridium histolyticum (CCH) after the third year of a 5-year nontreatment follow-up study, Collagenase Option for Reduction of Dupuytren Long-Term Evaluation of Safety Study.

**Methods** This study enrolled Dupuytren contracture patients from 5 previous clinical studies. Beginning 2 years after their first CCH injection, we re-evaluated patients annually for joint contracture and safety. Recurrence in a previously successfully treated joint (success = 0° to 5° contracture after CCH administration) was defined as 20° or greater worsening in contracture in the presence of a palpable cord or medical/surgical intervention to correct new or worsening contracture. We assessed partially corrected joints (joints reduced 20° or more from baseline contracture but not to 0° to 5°) for nondurable response, also defined as 20° or greater worsening of contracture or medical/surgical intervention.

**Results** Of 1,080 CCH-treated joints (648 metacarpophalangeal [MCP]; 432 proximal interphalangeal [PIP]; n = 643 patients), 623 (451 MCP, 172 PIP) had achieved 0° to 5° contracture in the original study. Of these joints, 35% (217 of 623) recurred (MCP 27%; PIP 56%). Of these recurrences, an intervention was performed in 7%. Of the 1,080 CCH-treated

*From the College of Human Medicine, Michigan State University, Marquette General Healthcare, Marquette, MI; Brigham and Women's Hospital, Boston, MA; the Hand and Upper Limb Clinic, Brisbane, Australia; the Indiana Hand to Shoulder Center, Indianapolis, IN; Auxilium Pharmaceuticals, Inc., Malvern, PA; and Pulvertaft Hand Centre, Kings Treatment Centre, Royal Derby Hospital, Derby, UK.*

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The CORDLESS investigators were: Edward Akelman, MD (Rhode Island Hospital, Providence, RI); Chris Bainbridge, MBBS (Pulvertaft Hand Centre, Derby, UK); Brian Bear, MD (Rockford Orthopedic Associates, Rockford, IL); Mark R. Belsky, MD (Newton-Wellesley Hospital, Newton, MA); Philip Blazar, MD (Brigham and Women's Hospital, Boston, MA); Michel Boeckstyns, MD (Gentofte Hospital, Copenhagen, Denmark); Dean Boyce, MBBS (Morriston Hospital, Swansea, UK); Stephen Coleman, MBBS (Rivercity Hospital, Auchenflower, Queensland, Australia); Lars Dahlin, MD (University Hospital Malmo, Malmo, Sweden); William DeVries, MD (Alpha Clinical Research, Clarksville, TN); Joel L. Frazier, MD (Health Research Institute, Oklahoma City, OK); David Gilpin, MD (Rivercity Hospital, Auchenflower, Queensland, Australia); Stephen Hall, MBBS (Emeritus Research, Malvern, Victoria, Australia); Markku Harkonen, MD (Koskiklinikka, Tampere, Finland); Vincent Hentz, MD (Stanford Hospital and Clinics, Palo Alto, CA); John Hood, MD (Hand Microsurgery and Reconstructive Orthopaedics, Erie, PA); Robert N. Hotchkiss, MD (Hospital for Special Surgery, New York, NY); Anthony Houston, MBBS (Caboolture Clinical Research Centre, Caboolture, Queensland, Australia); Lawrence C. Hurst, MD (Department of Orthopaedics, SUNY at Stony Brook, Stony Brook, NY); Allan Ibsen, MD (Rigshospitalet, Copenhagen, Denmark); Graeme Jones, MBBS (Menzies Research Institute, Hobart, Tasmania, Australia); F. Thomas D. Kaplan, MD (Indiana Hand Center, Indianapolis, IN); Jeffrey Karrasch, MBBS (Peninsula Clinical Research, Kippa Ring, Queensland, Australia); Bent Lange, MD (Dronninglund Sygehus, Dornninglund, Denmark); Richard Lawson, MD (Royal North Shore Hospital, St. Leonards, New South Wales, Australia); Scott McPherson, MD (TRIA Orthopaedic Center, Minneapolis, MN); Roy Meals, MD (Private Practice, Los Angeles, CA); J. Mark Melhorn, MD (PriVia, Wichita, KS); Rick Milner, MD (Royal Victoria Infirmary, Newcastle, UK); Nash Naam, MD (Southern Illinois Hand Center, Effingham, IL); Clayton A. Peimer, MD (Michigan State University, Marquette, MI); Troy Pierce, MD (St. Alexius Medical Center, Bismark, ND); Douglas Roeshot, MD (University Orthopedics Center, State College, PA); Nebojsa Skrepnik, MD (Tucson Orthopaedic Institute, Tucson, AZ); Teresa Sligh, MD (Providence Clinical Research, Burbank, CA); Philip Waller, MD (Accurate Clinical Research, Houston, TX); Stephan Wilbrand (Akademiska University Hospital, Uppsala, Sweden); Jarkko Vasenius, MD (Dextra, Helsinki, Finland); and Jon Zoltan, MD (Hope Research Institute, Phoenix, AZ).

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**Corresponding author:** Clayton A. Peimer, MD, College of Human Medicine, Michigan State University, Hand Surgery Office, 1414 W. Fair Avenue, Suite 249, Marquette, MI 49855; e-mail: clayton.peimer@mghs.org.

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joints, 301 were partially corrected in the original study. Of these, 50% (150 of 301; MCP: 38% [57 of 152]; PIP: 62% [93 of 149]) had nondurable response. We identified no new long-term or serious adverse events attributed to CCH during follow-up. Anti-clostridial type I collagenase and/or anti-clostridial type II collagenase antibodies were reported for 96% or more of patients who received 2 or more CCH injections and 82% who received 1 injection.

**Conclusions** The recurrence rate, which is comparable to other standard treatments, and the absence of long-term adverse events 3 years after initial treatment indicate that CCH is an effective and safe treatment for Dupuytren contracture. Most successfully treated joints had a contracture well below the threshold for surgical intervention 3 years after treatment. Recurrence rates among successfully treated joints were lower than nondurable response rates among partially corrected joints. *(J Hand Surg 2013;38A:12–22. Copyright © 2013 by the American Society for Surgery of the Hand. All rights reserved.)*

**Type of study/level of evidence** Therapeutic IV.

**Key words** Collagenase clostridium histolyticum, Dupuytren contracture, recurrence, safety.

DUPUYTREN CONTRACTURE, DESCRIBED in the medical literature as early as 1614,[1] is most often a slowly progressive fibroproliferative disorder characterized by development of nodules and collagen cords within the palmar fascia of the hand.[1–3] With progressive cord formation, flexion contractures of metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints impair hand function.[3,4]

There is no cure for Dupuytren contracture, and because the condition is progressive, recurrence after treatment is often considered inevitable over a patient's lifetime.[5] Reported postsurgical recurrence rates vary from 0% to 85%,[6–16] depending on the patient, comorbidity, and disease characteristics at the time of initial surgery; type of intervention; and duration of follow-up.[6,7,17–19] An important source of variation in published recurrence rates is the lack of a consensus definition for recurrence.[6] The most commonly used definition,[6,19] "reappearance of Dupuytren tissue in a previously operated area," is subjective and not relevant to medical treatments. Although not yet commonly used, a precise and objective definition recently reported after percutaneous needle fasciotomy is "worsening of total passive extension deficit $\geq 30°$."[15,16]

Collagenase clostridium histolyticum (CCH; Xiaflex, Auxilium Pharmaceuticals, Malvern, PA; and Xiapex; Pfizer Limited, Kent, UK) is a Food and Drug Administration (FDA)- and European Commission–approved enzymatic treatment for adult patients with Dupuytren contracture with a palpable cord.[20] The CCH formulation consists of 2 distinct collagenases (clostridial type I collagenase [AUX-I] and clostridial type II collagenase [AUX-II]). These 2 enzymes were shown *in vitro* to cleave collagen strands at complementary terminal and internal sites into peptide fragments that are rapidly degraded.[21] Collagenase clostridium histolyticum efficacy in advanced Dupuytren contracture has been demonstrated in well-controlled clinical trials (level I evidence), where it reduced contractures and increased range of active motion[18,22–26]. In the Collagenase Option for Reduction of Dupuytren (CORD) I trial (N = 308), 64% of CCH-injected cords versus 7% of placebo-injected cords ($P < .001$) met the study-defined primary end point of contracture reduction to within 0° to 5° of full extension within 30 days of the last injection.[24] Similar results were found in CORD II (N = 66), where 44% versus 5% of cords injected with CCH versus placebo, respectively, achieved this end point ($P < .001$).[25] Although it has not been definitively determined, it is possible that the procedures used in the studies (eg, injection, cord manipulation, and splinting) contributed to the success in a limited number of placebo-treated patients. Collective results from phase 2 and 3 registry trials (> 1,000 patients, up to 8 injections of 0.58 mg CCH)[20] demonstrated that CCH was safe. Adverse events (AEs) were largely localized to the injection site and resolved within a week without sequelae.

Because recurrence risk is a key consideration when assessing treatment options from the patient, health care system, and insurer perspectives,[17,27] we initiated this prospective, long-term, 5-year follow-up study, CORD Long-Term Evaluation of Safety Study (CORDLESS), to determine the incidence of recurrence after treatment with CCH in previous clinical studies. The interim cumulative 3-year recurrence in CCH-treated joints achieving the primary efficacy end point (ie, fixed flexion contracture [FFC] $\leq 5°$ in the index study) is reported here, as is the durability of response in joints that did not achieve clinical success but had measurable

improvement (ie, a contracture reduction from a baseline of ≥ 20° in the study of origin).

## MATERIALS AND METHODS

### CCH treatments and end points in previous clinical studies

Patients were eligible to participate in CORDLESS if they participated in any of the previous studies: two 9-month, open-label CCH trials (JOINT I and JOINT II); two 12-month, double-blind trials (CORD I and CORD II); and 1 open-label extension (CORD I extension). For inclusion in the previous study, patients had to be 18 years of age or older, with Dupuytren contracture affecting at least 1 MCP joint (contracture ≥ 20° to ≤ 100°) or 1 PIP joint (contracture ≥ 20° to ≤ 80°). Exclusion criteria included treatment of the joint to be injected within 90 days before CCH treatment. Full exclusion criteria have been reported previously.[24–26]

Each cycle of treatment consisted of a single injection of 0.58 mg CCH into the cord followed by a finger extension the next day, with 30 days of follow-up.[24–26] An individual cord could receive a maximum of 3 CCH injection cycles to achieve the primary end point of success (FFC ≤ 5°), but if patients had multiple fingers involved, they could not receive more than 8 total injections. The decision to reinject was at the combined discretion of the patient and physician. Secondary end points included the proportion of joints that achieved measurable improvement (contracture reduction of ≥ 20° from baseline); percent decrease in joint contracture; and increase in the range of motion of the affected joint in degrees. We assessed safety by the occurrence of AEs, serious AEs (SAEs), contracture recurrence, and immunogenic response.

### CORDLESS study design and population

The CORDLESS study is a long-term nontreatment follow-up investigation. Patients who received 1 or more CCH injections in their study of origin (ie, JOINT I, JOINT II, CORD I, CORD I extension, or CORD II) and who had 1 or more posttreatment assessments were offered enrollment into CORDLESS. All study sites had local or central institutional review board or ethics committee approval, and research was carried out in compliance with the Declaration of Helsinki as currently amended. Those who agreed to participate in annual follow-up visits and signed written informed consent were eligible for inclusion. A small travel honorarium, paid by the individual study sites, was available for patients who participated. There were no added exclusion criteria from the initial studies. The CORDLESS study was registered on ClinicalTrials.gov (NCT00954746). A total of 39 of 47 investigative sites that had enrolled patients in the previous CCH studies participated in CORDLESS. Participants were free to discontinue at any time.

Enrolled patients had a complete medical history taken and are being observed once per calendar year for 4 years (year 2 through year 5 after the first injection) with 6 or more months between consecutive visits. The study is ongoing, and this report includes analyses of interim data from year 3. We provided investigators with a summary of the outcome for all joints in each patient (ie, recurrence in the previous study, effectively treated, not effectively treated, not treated, not previously evaluated). The FDA and the European Commission did not approve CCH until 2010 (United States) and 2011 (Europe); it became commercially available only after the year 2 follow-up evaluations. Therefore, no patients were or could be retreated with CCH for the first 2 years.

Of 950 eligible patients from the original studies, 643 (68%) were enrolled in CORDLESS and had at least 1 follow-up evaluation (Fig. 1). Demographics and disease characteristics at baseline for CORDLESS participants were similar to those from the 5 previous CCH studies (Table 1). Of the 643 patients enrolled in CORDLESS, 16 received 1 (n = 10), 2 (n = 3), or 3 (n = 3) additional CCH injections after the year 2 follow-up visit. We treated 22 different joints in these 16 patients (9 joints with a new cord, 9 joints retreated for recurrence, 3 joints treated for nondurability, and 1 joint that was not effectively treated initially).

### CORDLESS objectives and definitions

The objectives of the ongoing CORDLESS study were to assess, at the year 2 through year 5 follow-up visits: (1) recurrence of contracture in joints that had achieved clinical success in the study of origin; (2) nondurability of response in joints that had showed measurable improvement in the study of origin but had not obtained the strict definition of clinical success; and (3) long-term safety after CCH injections. Recurrence, nondurability, and progression were prospectively defined for successfully treated joints, partially corrected joints, and ineffectively treated joints, respectively, as an increase in joint contracture 20° or greater in the presence of a palpable cord, or as the need for the joint to have further medical or surgical intervention (which could include CCH injection) to correct new or worsening contracture. We did not count joints with the presence of one criterion but not the other (ie, contracture 20° or greater but no palpable cord, or a palpable cord but contracture not 20° or greater) as having recurrence or nondurability. We defined worsening of contracture for success-

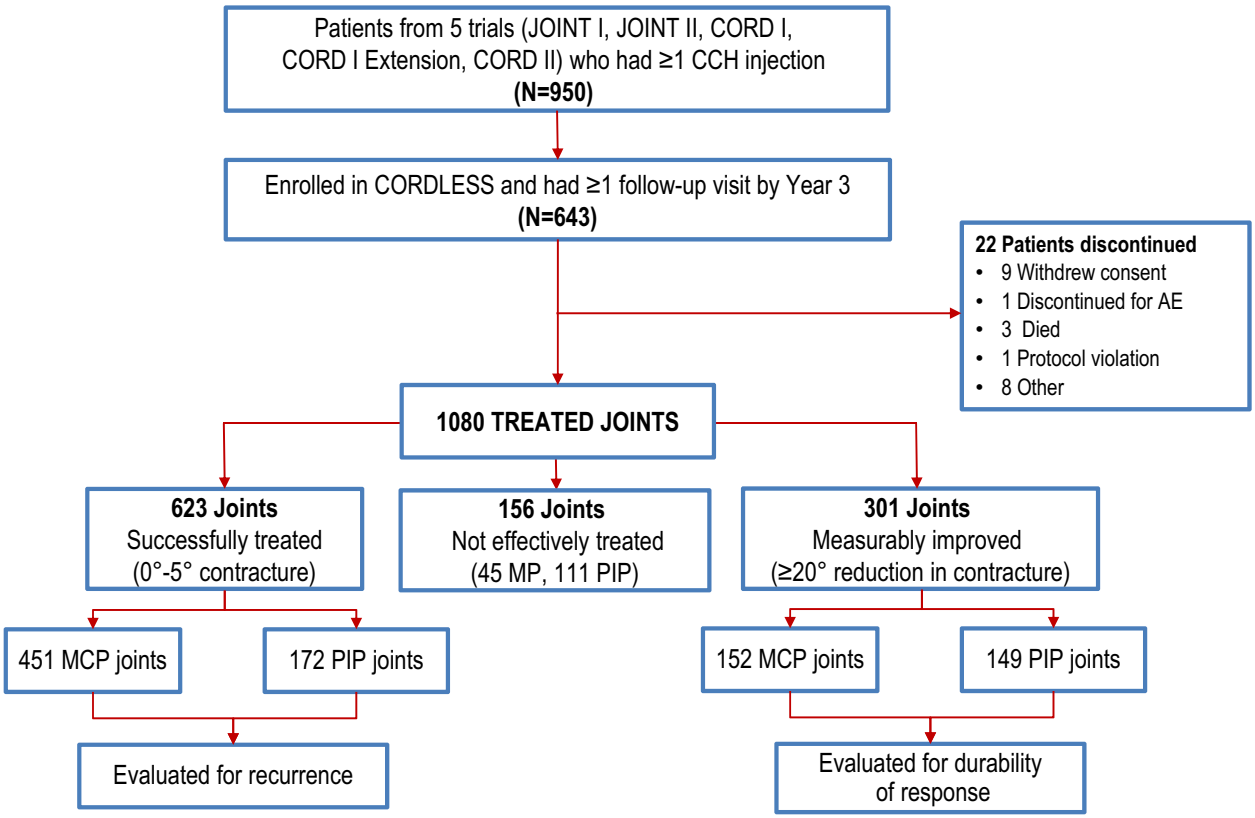


**FIGURE 1:** Distribution of patients and joints treated with CCH in 5 previous trials and evaluated for recurrence and durability of response in CORDLESS. In 2 of the 5 trials (JOINT I and JOINT II, open-label and nonrandomized), patients could receive up to a total of 5 injections of 0.58 mg CCH. In the 2 blinded, randomized trials (CORD I and CORD II), patients were randomized 2:1 (CCH: placebo), followed by open-label extension phases. In these, patients could receive up to 8 injections of 0.58 mg CCH. In all trials, individual cords could receive up to 3 injections of CCH.

fully treated or partially corrected joints as an increase in contracture of 20° or more with or without a palpable cord, or when the joint required further medical or surgical intervention. Pretreatment severity of disease (ie, before CCH injection in the study of origin) was defined as low (FFC $\leq$ 50° for MCP joints and $\leq$ 40° for PIP joints) or high (FFC $>$ 50° for MCP joints and $>$ 40° for PIP joints).

Any AEs or SAEs that occurred were reported, and we collected blood samples at the yearly visits to determine anti-AUX-I and anti-AUX-II antibody levels.

### Statistical analyses

We calculated the nominal incidence of recurrence rates and summarized AEs and SAEs. The investigator determined the causal relationship of the AE or SAE to the phase 3 CCH injection. We evaluated immunogenic responses as anti-AUX-I and anti-AUX-II titers over time. We carried out analyses to compare the subset of patients or joints assessed in CORDLESS with those enrolled in the 5 prior studies, to ascertain that the CORDLESS subset was representative of the overall population. A 1-sample *t*-test was used for continuous parameters comparing the mean of the current study with the mean value recorded in the previous study. We also used a 1-sample chi-square test of hypothesized proportions equal to that observed in the previous study.

## RESULTS

### Treatment outcomes in study of origin

Among the 643 CORDLESS patients, 1,080 joints (648 MCP and 432 PIP) were previously treated. Table 2 summarizes initial treatment outcomes for CORDLESS and the prior CCH studies.

### Outcomes in successfully treated joints

Recurrence occurred in 35% (217 of 623) of the successfully treated joints over the 3-year follow-up (year 1, 19; year 2, 103; year 3, 95). Thus, 406 successfully treated joints (65%) showed a sustained response to

**TABLE 1. Baseline Characteristics of Study Populations**

| | Previous CCH Studies (N = 950)[a] | CORDLESS Population (N = 643)[a] | *P* Value |
|---|---|---|---|
| Mean age[b] (y [±SD]) | 63 (9.6) | 66 (9.4) | |
| Male sex (n [%]) | 793 (84) | 542 (84) | .59 |
| White race (n [%]) | 949 (100) | 643 (100) | 1.00 |
| Family history of Dupuytren disease | | | 1.00 |
| Yes (n [%]) | 411 (43) | 278 (43) | |
| No (n [%]) | 538 (57) | 364 (57) | |
| Unknown (n) | 1 | 1 | |
| Mean age at diagnosis (y [±SD]) | 53 (12.5) | 54 (12.4) | .34 |
| Mean duration of disease (y [±SD]) | 10 (9.2) | 10 (9.3) | .94 |
| Mean no. of affected joints (± SD) | 2.9 (2.0) | 2.8 (2.0) | .50 |
| Type of affected joints (n [%]) | | | .20 |
| 1 MCP/0 PIP | 143 (15) | 112 (17) | |
| ≥ 2 MCP/0 PIP | 141 (15) | 103 (16) | |
| 0 MCP/1 PIP | 139 (15) | 90 (14) | |
| 0 MCP/≥ 2 PIP | 88 (9) | 47 (7) | |
| ≥ 1 MCP/≥ 1 PIP | 437 (46) | 290 (45) | |
| Hands affected (n [%]) | | | .95 |
| 1 | 596 (63) | 403 (63) | |
| Both | 352 (37) | 239 (37) | |
| Physician rating of severity[c] | | | .22 |
| Mild (n [%]) | 202 (21) | 154 (24) | |
| Moderate (n [%]) | 516 (54) | 341 (53) | |
| Severe (n [%]) | 230 (24) | 146 (23) | |
| Missing (n) | 2 | 2 | |
| Baseline contracture of treated joints (° [± SD]) | 44.5 (18.7) | 43.8 (18.5) | |
| Joints measured (n) | 1,547 | 994 | |

[a]N values refer to number of patients; of the 950 patients in the original studies, 643 elected to enroll in CORDLESS.
[b]We determined age in the previous CCH studies at the time of enrollment in the previous study. We determined age in CORDLESS at the time of enrollment in CORDLESS.
[c]Physician rating of Dupuytren severity was obtained at day of first injection in previous study. Percentages are based on the number of nonmissing assessments.

**TABLE 2. Treatment Outcome**

| | Previous CCH Studies (N = 950)[a] | | | CORDLESS Population (N = 643)[a] | | |
|---|---|---|---|---|---|---|
| Parameter | MCP | PIP | Total | MCP | PIP | Total |
| Total number of joints treated | 920 | 648 | 1,568 | 648 | 432 | 1,080 |
| Joints successfully treated (n [%]) | 618 (67) | 220 (34) | 838 (53) | 451 (70) | 172 (40) | 623 (58) |
| Joints measurably improved (n [%]) | 221 (24) | 223 (34) | 444 (28) | 152 (23) | 149 (34) | 301 (28) |
| Joints not effectively treated (n [%]) | 81 (9) | 205 (32) | 286 (18) | 45 (7) | 111 (26) | 156 (14) |

[a]N values refer to number of patients; of the 950 patients in the original studies, 643 elected to enroll in CORDLESS.

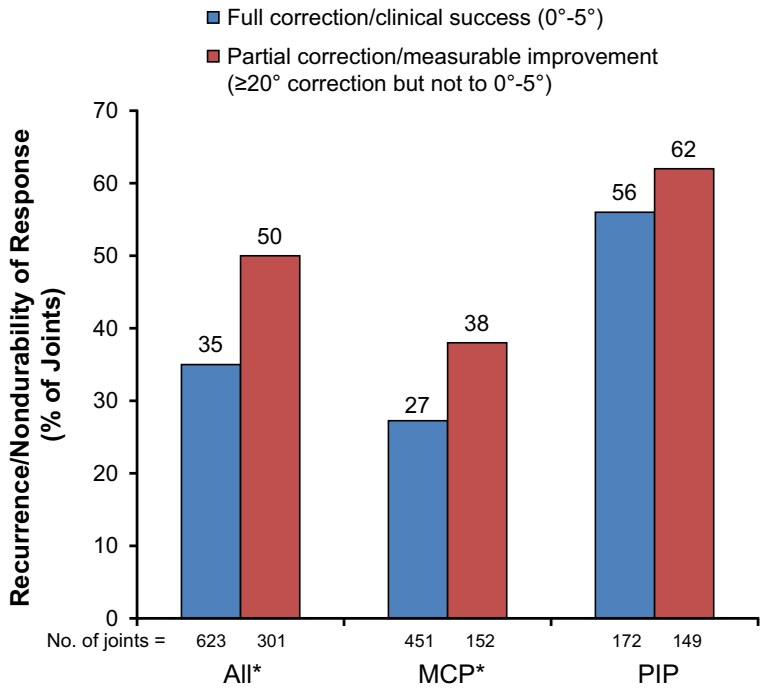


**FIGURE 2:** Recurrence and nondurability of response in successfully treated (n = 623) and measurably improved (n = 301) joints, by year of follow-up. Protocol-defined recurrence (blue bar) in joints that had achieved the primary end point of clinical success in previous CCH studies (ie, full correction) and nondurability of response (red bar) in joints that had measurable improvement in previous CCH studies (ie, partial correction). *$P < .05$ for full correction (clinical success) versus partial correction (measurable improvement).

CCH over 3 years. The recurrence rate was higher for PIP joints (56%) than MCP joints (27%) (Fig. 2).

Of the successfully treated joints, 495 (79%) (374 MCP and 121 PIP) had low and 128 (21%) (77 MCP and 51 PIP) had high pretreatment severity. Figure 3 shows recurrence rates by initial severity.

Table 3 summarizes mean measured FFC in successfully treated joints. The FFC levels in nonrecurrent joints remained similar to (MCP) or slightly higher (PIP) than at the time of treatment success (Fig. 4).

Overall, 43 (30 MCP and 13 PIP) successfully treated joints (7%) had medical or surgical correction during the 3-year follow-up period (these 43 patients are included among the 217 with recurrence).

### Outcomes in measurably improved (partially corrected) joints

By year 3, 150 of 301 joints (50%) with measurable improvement met criteria for lack of durability of response (year 1, 3; year 2, 96; year 3, 51). Proximal interphalangeal joints showed a lower durability of response than MCP joints (Fig. 2). We observed the least durable response in high-severity PIP joints (data not shown). Table 3 summarizes FFC in measurably improved joints. The decrease in FFC was less durable in PIP joints than MCP joints. Overall, 27 joints (14 MCP and 13 PIP) with measurable improvement (9%) needed surgical correction. Compared with joints treated to clinical success, joints with partial correction had a higher recurrence rate (50% vs 35%; $P < .001$, Fisher's exact test).

### Worsening of contracture in successfully treated and measurably improved (partially corrected) joints

Among 924 joints that were either fully corrected or partially corrected, 353 (38%) had a worsening of contracture, defined as an increase in joint contracture 20° or greater (with or without a palpable cord), or as further medical/surgical intervention. Rates of worsening were 28% (168 of 603) for MCP joints and 58% (185 of 321) for PIP joints.

### Outcomes in joints not effectively treated

A total of 156 joints were not effectively treated with CCH by the original criteria. Of these, 59 joints (38%) progressed (15 of 45 MCP and 44 of 111 PIP).

### Safety during follow-up in CORDLESS

During the 3-year follow-up period, 193 of 643 patients experienced 370 AEs, mostly mild or moderate (Table 4); 31 patients (4.8%) had severe AEs, none of which

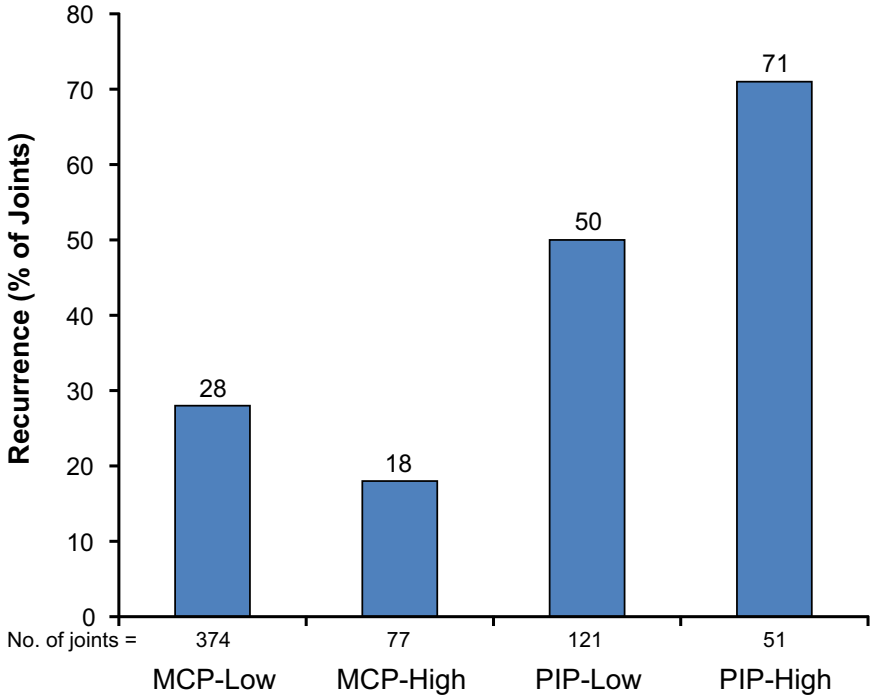


**FIGURE 3:** Year 3 recurrence of MCP and PIP joints by baseline severity, in joints that achieved clinical success in the study of origin. MCP-Low, baseline contracture 50° or less; PIP-Low, baseline contracture 40° or less.

were considered by the investigator to be related to treatment.

Over the 3-year follow-up period, 96% or more of patients who had received 2 or more CCH injections in the original study were positive for anti-AUX-I and/or anti-AUX-II antibodies, as were 82% who received 1 injection. There was no correlation of antibody titer to AEs or SAEs.

## DISCUSSION

In this study, most joints (65%) successfully treated with CCH had a durable correction. Three years after treatment, the overall recurrence rate, based on the objective definition used, was 35%, with a lower rate in MCP joints (27%) than PIP joints (56%). The finding that recurrence was highest in severely affected PIP joints (71%) was expected, because PIP joints are known to be less responsive to other therapeutic interventions[28–30] and to have less durable improvement.[31]

That only 7% of the 623 joints achieving success required surgery or other medical intervention during the 3-year follow-up period is important and encouraging. In addition, recurrent joints still had not regressed to pretreatment mean FFC levels after 3 years. The posttreatment change in contracture for nonrecurrent joints (ie, those that did not meet the threshold of an increase ≥ 20° for recurrence during the 3-y follow-up) progressed slowly, particularly for MCP joints, which maintained FFC levels at year 3 similar to those at the time of treatment success. Because surgery is generally recommended when contracture exceeds 30°,[1,32,33] this population presumably may not require additional treatment for some time.

With some surgical procedures, the more successful the original contracture correction, the better the prognosis is for avoiding recurrence.[31] Our data support that correction of Dupuytren contracture to 0° to 5° with CCH—as opposed to partial correction—also predicts a lower recurrence rate. We believe that these data will help clinicians advise patients about the treatment course and likelihood for repeat interventions. Moreover, because repeat surgical procedures have been associated with higher complication rates than index surgery,[34] the risk for mid- and late-term recurrence is an important consideration when assessing early and later treatment options.[17,27]

### Study limitations

Loss to follow-up is an important issue in long-term trials, and one-third of patients who were treated with CCH in the 5 previous studies did not enroll in CORDLESS. In some cases, patients may have been originally enrolled at sites that declined to participate in the follow-up study. If we were to find

**TABLE 3. Mean (±SD) FFC Progression Over Time**

| | FFC (mean ± SD) | % Decrease From Pretreatment Baseline[a] |
|---|---|---|
| CORDLESS population, all joints | | |
| Baseline[b] (n = 994) | 44° ± 19° | |
| Day 30[c] (n = 994) | 13° ± 18° | 75 |
| Year 1[d] (n = 976) | 15° ± 21° | 68 |
| Year 2 (n = 989) | 22° ± 24° | 50 |
| Year 3 (n = 991) | 23° ± 25° | 46 |
| Joints successfully treated | | |
| All joints | | |
| Baseline (n = 593) | 38° ± 16° | |
| Day 30 (n = 593) | 1° ± 2° | 97 |
| Year 1 (n = 586) | 5° ± 9° | 86 |
| Year 2 (n = 589) | 11° ± 16° | 66 |
| Year 3 (n = 590) | 13° ± 18° | 60 |
| MCP joints | | |
| Baseline (n = 429) | 37° ± 16° | |
| Day 30 (n = 429) | 1° ± 2° | 98 |
| Year 1 (n = 423) | 3° ± 8° | 90 |
| Year 2 (n = 426) | 8° ± 13° | 76 |
| Year 3 (n = 427) | 9° ± 15° | 71 |
| PIP joints | | |
| Baseline (n = 164) | 38° ± 16° | |
| Day 30 (n = 164) | 2° ± 2° | 94% |
| Year 1 (n = 163) | 9° ± 10° | 73% |
| Year 2 (n = 163) | 20° ± 19° | 41% |
| Year 3 (n = 163) | 23° ± 19° | 31% |
| Joints measurably improved | | |
| All joints | | |
| Baseline (n = 271) | 57° ± 16° | |
| Day 30 (n = 271) | 25° ± 15° | 57% |
| Year 1 (n = 265) | 25° ± 22° | 59% |
| Year 2 (n = 270) | 32° ± 25° | 45% |
| Year 3 (n = 271) | 33° ± 26° | 42% |

[a]Percent decrease from pretreatment baseline refers to the percent change from pretreatment baseline in the study of origin to the specific time point in each row, including the initial posttreatment observation at ay 30, as well as years 1 through 3.
[b]Pretreatment baseline from study of origin.
[c]Day 30 of original study.
[d]Final measurement in original study.

substantial differences among these populations, the recurrence rates in CORDLESS would have been overestimated or underestimated. However, comparative analysis found that the patients and joints assessed in this CORDLESS study were representative of those in the previous CCH studies. Thus, it is our opinion that the observed recurrence rates are reliable and therefore generalizable to the initial CCH study population.

Further considerations remain to be addressed. For example, patient satisfaction is an important component in determining treatment success. Patient satisfaction data were collected in this study but will be reported elsewhere. In addition, there are unanswered questions outside the scope of this study regarding potential biological or demographic differences between recurrent and nonrecurrent patient subsets that remain as topics for future evaluation.

## Recurrence after surgery

Definitions used to describe recurrence have been highly variable, vague, or nonexistent.[6] Without executing a head-to-head study, comparing recurrence rates after CCH with other interventions presents a challenge. One meta-analysis indicates that recurrence rates after surgery range from 0% to 71%, noting that definitions of recurrence varied or went undefined.[6] "Reappearance of Dupuytren tissue in the operative field" and "a lesion requiring reoperation" are definitions applied to surgical interventions.[6] Others have used "limitation of daily activities" to define recurrence,[6] which we believe is both subjective and too general to be useful.

In a 5-year follow-up study of needle aponeurotomy, van Rijssen et al[16] defined recurrence as worsening of a total passive extension deficit of 30° or greater for a treated finger. They reported that 85% of patients who had been treated by percutaneous needle fasciotomy had a mean time to recurrence of 2.3 years, whereas 24% of patients who underwent limited fasciectomy experienced recurrence after a mean of 3.7 years.

Considering the wide variation of reported recurrence rates and the stringent definitions used in our study, the durability of the correction after CCH treatment seems acceptable. Hypothetically, if we had used the 30° or greater definition of recurrence for CORDLESS, a parameter that has been used by others[15,16] and that typically is the threshold that suggests that more surgery is indicated,[1,19,32,33] the 3-year recurrence rate would have been 22% (16% MCP and 38% for PIP). However, because the studies by van Rijssen and colleagues[15,16] evaluated recurrence rates in all joints (not only successfully treated joints) for up to 5 years after treatment, any comparisons with the data presented here must be interpreted cautiously.

Iatrogenic and postsurgical complications have been

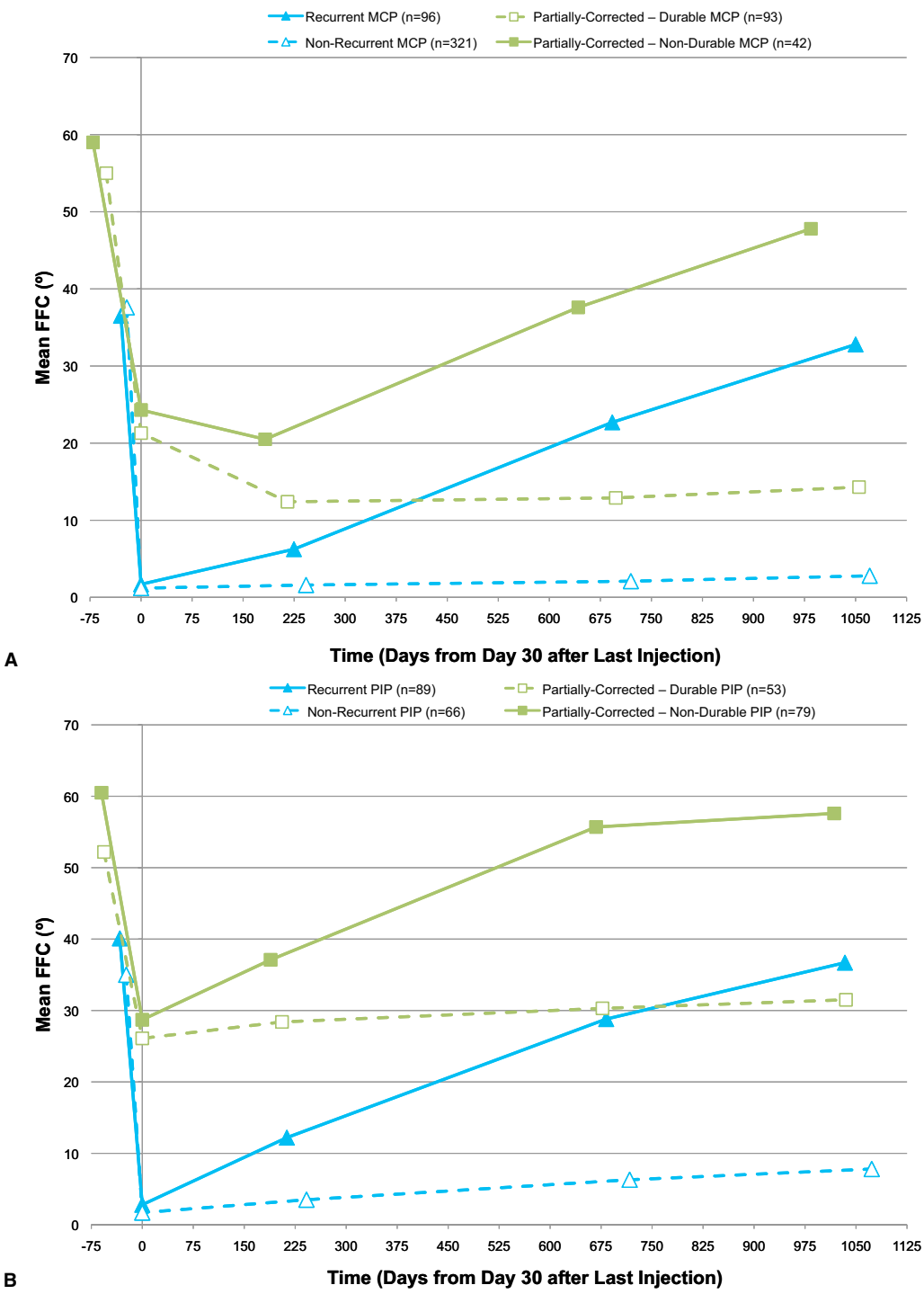


**FIGURE 4:** Fixed flexion contracture before CCH treatment and during 3-year follow-up in successfully treated and partially corrected joints: **A** MCP and **B** PIP. Data do not include joints that received medical or surgical interventions.

reported in 17% to 50% of cases, depending on surgical method and disease severity, and often higher if the surgery is a reoperation.[28,30,35–39] According to a recent systematic review of 41 papers reporting complications of fasciectomy in Dupuytren patients (n = 5 to n = 2,919),[34] major complications occurred in 16% of cases, the most common being complex regional pain syndrome (6%), digital nerve injury (3%), infection (2%), digital artery injury (2%), and hematoma (2%). Digital nerve and artery injuries may be more common with surgery for recurrence.[34] Wound-healing complications, although minor, occurred in 23% of reported cases.

By contrast, as observed in CORDLESS and as

**TABLE 4. Most Common Adverse Events and Serious Adverse Events During the 3-Year Follow-Up Period**

| | n (%) |
|---|---|
| Adverse events | 193 (30) |
| Osteoarthritis, mild | 16 (3) |
| Hypertension | 10 (2) |
| Cataract | 9 (1) |
| Atrial fibrillation | 7 (1) |
| Serious adverse events | 50 (8) |
| Atrial fibrillation | 4 (< 1) |
| Small intestinal obstruction | 4 (< 1) |
| Cerebrovascular accident | 3 (< 1) |
| Nephrolithiasis | 3 (< 1) |
| Osteoarthritis | 3 (< 1) |
| Death | 3 (< 1) |

previously reported,[24,25] serious complications from CCH injections are rare. Across all studies in which 1,082 patients have been treated during clinical studies thus far (with more than 2,600 injections), 3 flexor tendon ruptures (0.3%) and 1 ligament–flexor pulley injury (0.1%) have occurred.[20] In over 11,000 injections given in the first 17 months after FDA approval of CCH, 5 additional flexor tendon ruptures have been reported.[40]

These CORDLESS data reinforce the safety of up to 8 CCH injections, with no long-term complications occurring during the 3-year follow-up. Whereas most patients exhibited positive anti-AUX-I and/or anti-AUX-II antibody responses, there were no systemic allergic reactions, even in patients retreated with collagenase for recurrence. Collagenase clostridium histolyticum injections meet many of the goals for successful treatment for Dupuytren contracture: namely, (1) correction of finger deformity and corresponding improvement in range of motion, (2) infrequent complications, (3) short recovery, and (4) durability of treatment benefits.[41] These data suggest that joints treated to complete clinical success (0° to 5°) have a lower recurrence rate than joints with only a partial correction (measurable improvement), and that treating PIP joints with less severe contractures will lower recurrence for those joints. We believe that the 3-year recurrence data, combined with the initial efficacy and safety already published, make CCH a useful option for the treatment of Dupuytren contracture. The CORDLESS study is ongoing and will provide long-term data about recurrence of Dupuytren contracture for 5 years after participation in the CCH trials.

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