

# Collagenase Clostridium Histolyticum for the Treatment of Edematous Fibrosclerotic Panniculopathy (Cellulite): A Randomized Trial

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**BACKGROUND** Edematous fibrosclerotic panniculopathy (EFP; cellulite) is associated with thickening and contraction of collagen-rich subdermal septae. Collagenase clostridium histolyticum (CCH) may disrupt collagen-rich septae.

**OBJECTIVE** To evaluate the safety and efficacy of CCH for treatment of EFP.

**MATERIALS AND METHODS** In a randomized, double-blind study, women with moderate or severe EFP of the buttocks or posterolateral thighs (i.e., Clinician Reported Photonumeric Cellulite Severity Scale [CR-PCSS] and Patient Reported Photonumeric Cellulite Severity Scale [PR-PCSS] ratings of 3 to 4, and Hexsel Cellulite Severity Scale score  $\leq 13$ ) received up to 3 treatment sessions (Days 1, 22, and 43) of subcutaneous CCH 0.84 mg or placebo injections. End points included the percentage of 2-level and 1-level composite responders (i.e., had  $\geq 2$ -level or  $\geq 1$ -level improvement in CR-PCSS and PR-PCSS) at Day 71.

**RESULTS** Three hundred seventy-five women (mean age, 46.5 years; 86.4% white) were randomly assigned to CCH ( $n = 189$ ) or placebo ( $n = 186$ ). At Day 71, the percentages of 2-level and 1-level composite responders were greater with CCH (10.6% and 44.6%, respectively) versus placebo (1.6% and 17.9%;  $p < .001$  for both). The most common adverse events were injection-site related.

**CONCLUSION** CCH significantly improved EFP appearance versus placebo; further evaluation of CCH for EFP (cellulite) is warranted.

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**E**dematous fibrosclerotic panniculopathy (EFP), also known as cellulite, occurs in 80% to 98% of postpubertal women but in few men<sup>1-3</sup>; therefore, it may be considered a secondary sexual characteristic. Its preponderance in women is attributable to the effects of estrogen (which promotes fibroblast

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proliferation, collagen formation, lipogenesis, and adipocyte hypertrophy)<sup>4</sup> and sex-specific differences in skin dermal and subcutaneous fat architecture.<sup>5</sup> Cellulite is primarily located on the buttocks and outer thighs<sup>3,4</sup>; its underlying causes have not been fully elucidated, but fat accumulation, hormones (e.g., estrogen, estrogen/testosterone ratio), edema, and sex-dependent fibrogenesis are thought to contribute to and exaggerate cellulite formation.<sup>4</sup> Estrogen, oxidative stress, and inflammation promote proliferation of fibroblasts and formation of collagen and influence fluid retention by altering local vasculature and lymphatic drainage.<sup>4</sup> These, in turn, augment adipose layer thickness and edema, resulting in increased mechanotransduction load on subdermal fibroblasts/myofibroblasts, which may stimulate increased collagen deposition and promote thickening of subcutaneous collagen-rich septae that tether the dermis to the underlying fascia.<sup>4,6-9</sup> In men, the septae are oriented obliquely to the skin surface,<sup>5</sup> thereby preventing extrusion of the underlying tissue. In women, the septae are oriented perpendicular to the skin surface,<sup>5</sup> allowing for displacement of subdermal adipose tissue. The combination of subcutaneous edema, subcutaneous adipose extrusion, and thickening and shortening of the perpendicular fibrous septae (which retracts the dermis) produces the dimpled appearance associated with cellulite.<sup>3,8-11</sup> It is hypothesized that disruption of the collagen septae would correct the contour alteration of cellulite and disrupt the pathogenic positive feedback loop of mechanostimulus on the collagen-producing fibroblasts.<sup>7</sup>

Current cellulite treatments target dermal and/or subcutaneous features, but efficacy has not been evaluated in high-quality, large-scale, placebo-controlled trials.<sup>1</sup> Surgical and laser procedures may remove or disrupt adipose tissue, thicken the dermal layer, sever fibrous tissue bands/septae, and/or smooth the dermal-hypodermis interface to reduce dimpling<sup>3,12,13</sup>; however, they may augment cellulite appearance because of increased local inflammation and activation of fibroblast remodeling. Powered subcision, when used to treat cellulite,<sup>1,14,15</sup> requires surgical incisions that necessitate local anesthesia and may increase infection risk.<sup>12,14</sup> Subcision has also

been associated with substantial bruising and hemosiderin pigmentation, which may require several months to resolve.<sup>14</sup> Noninvasive treatments (e.g., topical creams, massage, and shockwave therapy) may promote lymphatic drainage, providing temporary improvement,<sup>1,3,16-18</sup> but they do not address other pathophysiologic mechanisms; deep massage and laser therapy have also been associated with increased risk of dermal and cutaneous damage (e.g., burns, increased skin laxity).<sup>3,16</sup>

Another concern with cellulite management is the lack of a universally accepted, standardized measure for assessing improvements in cellulite severity.<sup>1</sup> Several cellulite severity rating scales have been developed, but each has limitations.<sup>1</sup> The Hexsel Cellulite Severity Scale (CSS) was validated in women aged 18 to 45 years with Grade I to III cellulite and a mean body mass index of 25 but may be cumbersome because it incorporates multiple pathologic ratings and does not assess cellulite severity from the patient perspective.<sup>19</sup> The modified Investigator Global Aesthetic Improvement Scale (I-GAIS) and Subject Global Aesthetic Improvement Scale (S-GAIS) ask clinicians and patients, respectively, to rate changes in cellulite appearance, based on before and after digital images, which are dynamic assessments by design. To overcome the limitations of these assessments, the buttock- and thigh-specific Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) and Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) were developed to assess cellulite severity from both clinician and patient viewpoints using a photonumeric reference, cellulite severity labels (e.g., “mild” or “moderate”), and corresponding descriptors.<sup>20</sup> Ratings of cellulite severity using the CR-PCSS and PR-PCSS correlate with traditional measures of cellulite severity (e.g., CR-PCSS with Hexsel CSS and PR-PCSS with S-GAIS).<sup>20</sup>

Collagenase clostridium histolyticum (CCH) is composed of 2 purified collagenases (AUX-I and AUX-II) that hydrolyze collagen under physiologic conditions, resulting in disruption of collagen structures (e.g., fibrous septae).<sup>21</sup> CCH is approved by the US Food and Drug Administration for the treatment of collagen-associated disorders (e.g., Dupuytren

contracture with palpable cord or Peyronie disease with palpable plaque and penile curvature deformity of  $\geq 30^\circ$  at initiation of therapy in adults). Regarding EFP, results from a Phase 1 study and a Phase 2 dose-ranging study showed improvement in cellulite appearance with CCH versus placebo.<sup>22,23</sup> The objective of the current study was to assess the efficacy and safety of CCH for the treatment of cellulite.

## Methods

### Study Design

This Phase 2b, randomized, double-blind, placebo-controlled trial was conducted from February through September 2016 (ClinicalTrials.gov identifier: NCT02724644) at 16 US study centers. The study was conducted in accordance with International Conference on Harmonisation Guidelines for Good Clinical Practice and ethical principles of the Declaration of Helsinki. The study protocol was approved by a central institutional review board (Quorum, Seattle, WA), and all patients involved provided written informed consent.

### Patient Population

Women aged 18 years and older were screened for moderate or severe cellulite on the buttocks, posterolateral thighs, or both at the initial study visit. To assess cellulite severity, digital images were taken of 4 cellulite quadrants (i.e., possible treatment areas), one each on the left and right buttocks and the left and right posterolateral thighs. Each patient viewed her digital images privately on a computer monitor and rated the severity of her cellulite in each image using the PR-PCSS (Figure 1A,B). Clinicians rated cellulite severity using the CR-PCSS and the Hexsel CSS; they evaluated cellulite appearance in the same 4 possible treatment areas in real time, while viewing each patient in a relaxed, standing position (Figure 1A,B).<sup>19</sup> Patients who had  $\geq 1$  treatment area with PR-PCSS and CR-PCSS scores of 3 or 4 (i.e., moderate or severe cellulite) and a Hexsel CSS score of  $\leq 13$  were included. One buttock or thigh with moderate or severe cellulite per patient received treatment randomly assigned using an interactive web-response

system. Patients who had received liposuction on the side of the body chosen for treatment and those who had mesotherapy, radiofrequency device treatments, laser treatment, or surgery (e.g., subcision) within the assigned treatment area within the previous year were excluded from further participation. Patients were not permitted to initiate intense sports, exercise activities, or weight-loss programs during the study.

### Treatment

On Day 1, before treatment administration, eligibility of the assigned buttock or thigh was confirmed, and patients were randomly assigned (1:1 ratio within each site; assigned treatment using an interactive web-response system and a block size of 4) to receive either CCH (EN3835) 0.84 mg or placebo. Within the assigned area, clinicians identified dimples for treatment that were visible and well defined when patients were in a relaxed, standing position.

Each patient received 3 treatment sessions separated by approximately 21 days (i.e., Days 1, 22, and 43) unless no treatable dimples were apparent in the assigned treatment area; in that case, cellulite severity was rated as 0 (“none”) on the CR-PCSS. During each treatment session, patients received 12 subcutaneous injections of 0.3 mL CCH 0.84 mg or placebo within the assigned area. The dose of CCH was chosen based on Phase 2a data that demonstrated 0.84 mg CCH provided the greatest improvement in cellulite and had a safety profile comparable with lower CCH doses (0.06 and 0.48 mg).<sup>22</sup>

While patients were in a prone position, each injection was administered as three 0.1-mL aliquots. Injection sites within the dimple were targeted to be approximately 2 cm apart, and CCH was delivered to the area as one aliquot perpendicular to the skin and 2 aliquots at a  $45^\circ$  angle to the left or right of the perpendicular axis. After treatment, patients remained in a prone position ( $\geq 5$  minutes) and were observed for 30 minutes. A sterile dressing was applied to the injection site if necessary. Patients were directed to remove the dressing that evening.

**(A) Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) – Buttock**



**Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) – Buttock**



**(B) Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) – Thigh**



**Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) – Thigh**



**Figure 1.** Assessment of cellulite severity using the PR-PCSS and CR-PCSS for the buttocks (A) and thighs (B). CR-PCSS, Clinician Reported Photonumeric Cellulite Severity Scale; PR-PCSS, Patient Reported Photonumeric Cellulite Severity Scale. © 2017 Auxilium Pharmaceuticals, LLC. All rights reserved.



## Assessments and Study End Points

Cellulite severity was rated using the CR-PCSS, PR-PCSS, and Hexsel CSS at screening, before treatment on Days 1, 22, and 43, and on Day 71 (28 days after treatment). The I-GAIS, S-GAIS, and patient satisfaction ratings were completed at Day 71. For patient satisfaction, patients rated overall satisfaction with treatment results on a 5-point scale from +2 (very satisfied) to -2 (very dissatisfied). The primary end point was percentage of composite 2-level responders (patients with  $\geq 2$ -level improvement from baseline [Day 1] in CR-PCSS rating and PR-PCSS rating) at Day 71. Percentage of patients who achieved a composite  $\geq 1$ -level improvement from baseline in CR-PCSS rating and PR-PCSS rating at Day 71 was a secondary end point. Percentage of patients who met the  $\geq 2$ -level improvement from baseline in CR-PCSS or PR-PCSS ratings (primary composite end point) and  $\geq 1$ -level improvement from baseline in CR-PCSS or PR-PCSS ratings (secondary composite end point) was also evaluated. Additional secondary end points included change from baseline to Day 71 in Hexsel CSS total score, percentage of investigators who rated patients' cellulite as at least "improved" on the I-GAIS (I-GAIS responders), or patients giving a similar rating on the S-GAIS (S-GAIS responders) at Day 71, and ratings of patient satisfaction with treatment. Adverse events (AEs) and anti-AUX antibodies were monitored throughout the study, starting on Day 1.

## Statistics

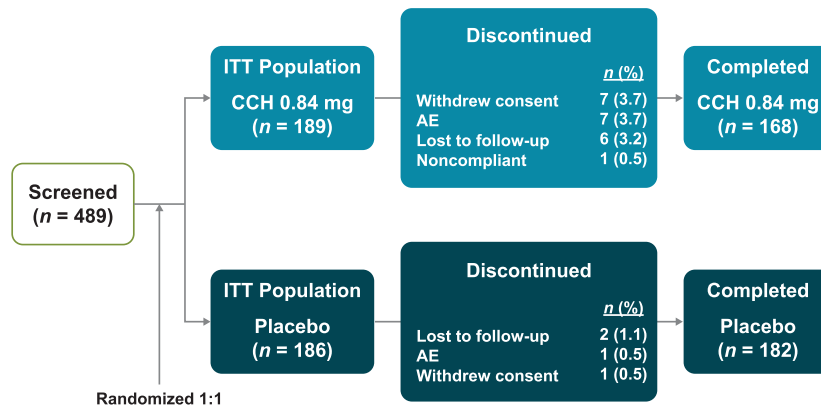
Sample size calculations used the expected percentages of composite response at Day 71 based on Phase 2a study data.<sup>22</sup> The primary efficacy analysis was evaluated in the intent-to-treat (ITT) population (all patients randomly assigned to treatment who received  $\geq 1$  injection of study medication). Secondary efficacy analyses were performed in the modified ITT (mITT) population (i.e., patients in the ITT population who completed  $\geq 1$  post-treatment CR-PCSS and PR-PCSS assessment). Safety parameters were evaluated in all patients who received  $\geq 1$  injection of study medication (safety population). Percentage of composite responders (primary efficacy end point) and

responders for secondary analyses (i.e.,  $\geq 1$ -level and  $\geq 2$ -level improvements from baseline in CR-PCSS and PR-PCSS ratings, and I-GAIS and S-GAIS scores of at least 1 ["improved"]) were compared using the Cochran–Mantel–Haenszel test with adjustment for study center. Change from baseline in Hexsel CSS score was analyzed using analysis of variance, and patient satisfaction was analyzed using the Mann–Whitney test.

## Results

Of 489 patients screened, 375 patients (CCH 0.84 mg,  $n = 189$ ; placebo,  $n = 186$ ) were randomly assigned to treatment and included in the ITT and safety populations (Figure 2), and 361 patients (CCH 0.84 mg,  $n = 177$ ; placebo,  $n = 184$ ) were included in the mITT population. Demographics and baseline characteristics were generally similar between groups (Table 1).

A significantly greater percentage of patients treated with CCH (10.6%) had a  $\geq 2$ -level improvement in both CR-PCSS and PR-PCSS ratings at Day 71 (composite response) versus those receiving placebo (1.6%;  $p < .001$ ; ITT population; Figure 3). Also, at Day 71, 44.6% of patients in the CCH group had a  $\geq 1$ -level improvement in both CR-PCSS and PR-PCSS ratings, versus only 17.9% of patients in the placebo group ( $p < .001$ ; mITT population; Figure 3). Photographic examples of composite response show topologic differences after treatment with CCH (e.g., shallower dimples) versus no improvement (placebo; Figure 4A–C). In addition, a significantly greater percentage of patients treated with CCH 0.84 mg had improvement of  $\geq 2$  levels in CR-PCSS or PR-PCSS ratings versus placebo at Day 43 ( $p \leq .05$ ) and at Day 71 ( $p < .001$ ; Table 2). Significant between-group differences were also observed in percentage of patients who had  $\geq 1$ -level improvement from baseline ( $p < .001$ ). These significant differences were noted at Day 22, Day 43, and Day 71 for CR-PCSS ratings ( $p < .001$  for all) and Day 43 and Day 71 for PR-PCSS ratings ( $p < .001$  for both timepoints). Hexsel CSS scores steadily improved from baseline to Day 71 with CCH, with significant differences beginning at Day 22 (Table 2). Consistent with



**Figure 2.** Patient disposition. AE, adverse event; CCH, collagenase clostridium histolyticum; ITT, intent-to-treat.

results for the CR-PCSS and PR-PCSS ratings, a significantly greater percentage of patients in the CCH group had I-GAIS and S-GAIS scores of  $\geq 1$  at Day 71, indicating cellulite severity was “improved,” “much improved,” or “very much improved” from baseline ( $p < .001$  vs placebo; Table 2). The majority of patients (62.9%) in the CCH treatment group were “satisfied” or “very satisfied” with treatment, versus only 35.9% in the placebo group (Figure 5).

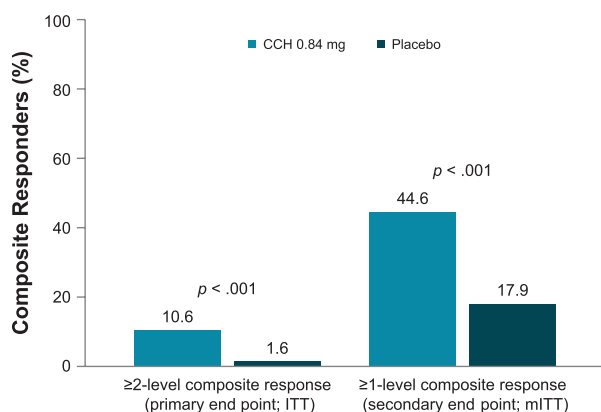
CCH was generally well tolerated. Few patients (3.7%) in the CCH group discontinued because of AEs (Table 3). No treatment-related serious AEs were reported in either treatment group. One serious AE (spontaneous abortion) occurred on Day 72 in a patient who received CCH but was not considered by the investigator to be treatment related. Most AEs were mild or moderate in intensity (92.3% and 96.2% of AEs in CCH and placebo groups,

**TABLE 1. Demographic and Baseline Characteristics (ITT Population)**

Parameter	CCH 0.84 mg (n = 189)	Placebo (n = 186)
Mean age, y (range)	47.2 (18–69)	45.8 (19–70)
Race, n (%)		
White	167 (88.4)	157 (84.4)
Black	15 (7.9)	26 (14.0)
Other	7 (3.7)	3 (1.6)
BMI category, n (%)		
Overweight (25 to <30 kg/m <sup>2</sup> )	68 (36.0)	72 (38.7)
Obese ( $\geq 30$ kg/m <sup>2</sup> )	68 (36.0)	63 (33.9)
Normal (18.5 to <25 kg/m <sup>2</sup> )	51 (27.0)	50 (26.9)
Underweight (<18.5 kg/m <sup>2</sup> )	2 (1.1)	1 (0.5)
Area treated, n (%)		
Left buttock	48 (25.4)	46 (24.7)
Left posterolateral thigh	47 (24.9)	44 (23.7)
Right buttock	46 (24.3)	47 (25.3)
Right posterolateral thigh	48 (25.4)	49 (26.3)
No. of treatment sessions per patient, n (%)		
1	25 (13.2)	3 (1.6)
2	10 (5.3)	8 (4.3)
3	154 (81.5)	175 (94.1)
Mean no. of injections per dimple, n (range)	1.6 (1.0–3.3)	1.5 (1.0–4.0)

\*ITT population.

BMI, body mass index; CCH, collagenase clostridium histolyticum; ITT, intent-to-treat.



**Figure 3.** Composite responders. Composite response was defined as a  $\geq 2$ -level improvement or a  $\geq 1$ -level improvement from baseline (Day 1) in both the CR-PCSS and PR-PCSS ratings at Day 71. ITT population: CCH,  $n = 189$ ; placebo,  $n = 186$ . mITT population: CCH,  $n = 177$ ; placebo,  $n = 184$ . CCH, collagenase clostridium histolyticum; CR-PCSS, Clinician Reported Photonumeric Cellulite Severity Scale; ITT, intent-to-treat; mITT, modified intent-to-treat; PR-PCSS, Patient Reported Photonumeric Cellulite Severity Scale.

respectively). The most common treatment-emergent AEs in both groups were injection-site bruising and injection-site pain (Table 3). At Day 71, all patients who received CCH and underwent immunogenicity testing ( $n = 165$  for AUX-I and  $n = 164$  for AUX-II) had antibodies against AUX-I and AUX-II; however, the percentage of patients who were positive for neutralizing antibodies was 22.5% for neutralizing anti-AUX-I (9 of 40 patients tested) and 7.5% for neutralizing anti-AUX-II (3 of 40 patients tested). No hypersensitivity reactions were observed in the CCH treatment group.

## Discussion

Injections of CCH 0.84 mg administered every 3 weeks over a 43-day period significantly improved moderate to severe cellulite appearance versus placebo. This improvement was reported by both clinicians (CR-PCSS) and patients (PR-PCSS). Although the CR-PCSS and PR-PCSS were developed recently to assess cellulite severity, improvements revealed through use of these scales mirrored results seen with established severity measures (i.e., clinician-reported Hexsel CSS and I-GAIS, and patient-reported S-GAIS).

### (A) 2-Level Composite Response (CCH 0.84 mg)



Day 1  
Pre-treatment

Day 71  
28 Days Post-treatment

### (B) 1-Level Composite Response (CCH 0.84 mg)



Day 1  
Pre-treatment

Day 71  
28 Days Post-treatment

### (C) No Change in CR-PCSS or PR-PCSS (Placebo)



Day 1  
Pre-treatment

Day 71  
28 Days Post-treatment

**Figure 4.** Photographs of composite response with CCH 0.84 mg versus no improvement (i.e., response with placebo). Baseline and Day 71 photographs show a 2-level composite response (A), 1-level composite response (B), and no improvement in the CR-PCSS or PR-PCSS (C). Note the visual improvement of dimpling after CCH treatment. CCH, collagenase clostridium histolyticum; CR-PCSS, Clinician Reported Photonumeric Cellulite Severity Scale; PR-PCSS, Patient Reported Photonumeric Cellulite Severity Scale.

**TABLE 2. Separate Improvement in Additional Measures of Cellulite Severity (mITT Population\*)**

Individual Parameter	CCH 0.84 mg (n = 177)	Placebo (n = 184)
CR-PCSS, n (%)		
≥2-level improvement		
Day 22	5 (3.0)	3 (1.7)
Day 43	14 (8.5)†	6 (3.4)
Day 71†	32 (18.1)§	9 (4.9)
≥1-level improvement		
Day 22	65 (38.7)§	24 (13.3)
Day 43	99 (60.4)§	49 (27.4)
Day 71†	96 (54.2)§	53 (28.8)
PR-PCSS, n (%)		
≥2-level improvement		
Day 22	5 (3.0)	3 (1.7)
Day 43	29 (17.8)†	19 (10.6)
Day 71†	51 (28.8)§	24 (13.0)
≥1-level improvement		
Day 22	58 (34.7)	48 (26.5)
Day 43	107 (65.6)§	78 (43.6)
Day 71†	128 (72.3)§	95 (51.6)
Hexsel CSS, mean (SD)		
Baseline	10.8 (1.35)	10.5 (1.39)
Change from baseline		
Day 22	-0.9 (1.9)¶	-0.2 (1.5)
Day 43	-1.5 (1.9)¶	-0.7 (2.0)
Day 71†	-1.7 (2.2)¶	-0.9 (2.0)
Score of ≥1 at Day 71, # n (%)		
I-GAIS**	110 (62.9)§	60 (32.8)
S-GAIS††	128 (73.1)§	80 (44.0)

\*Patients in the ITT population who completed ≥1 post-treatment CR-PCSS or PR-PCSS assessment.

†Last observation carried forward analysis.

‡ $p \leq .05$  versus placebo.

§ $p < .001$  versus placebo.

||Negative values indicate improvement in cellulite severity.

¶ $p < .001$  versus baseline.

#A score of ≥1 indicates a response of "improved," "much improved," or "very much improved" from baseline.

\*\*CCH, n = 175; placebo, n = 183.

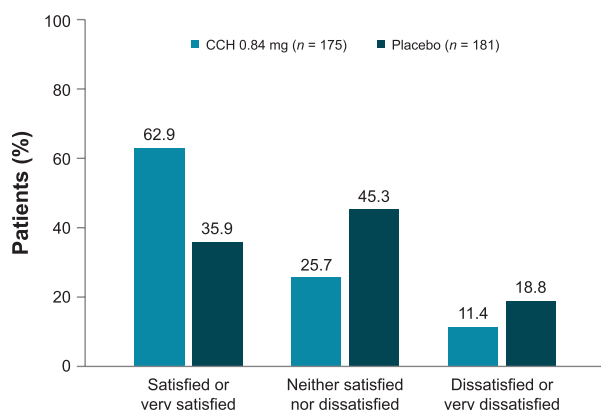
††CCH, n = 175; placebo, n = 182.

CCH, collagenase clostridium histolyticum; CR-PCSS, Clinician Reported Photonumeric Cellulite Severity Scale; CSS, cellulite severity scale; I-GAIS, Investigator Global Aesthetic Improvement Scale; ITT, intent-to-treat; mITT, modified intent-to-treat (population); PR-PCSS, Patient Reported Photonumeric Cellulite Severity Scale; S-GAIS, Subject Global Aesthetic Improvement Scale.

Most of the patients who received CCH were very satisfied/satisfied with their results. CCH treatment did not require post-treatment alterations in physical activity or use of compressive garments necessary with other cellulite therapies that target fibrous septae (i.e., powered subcision).<sup>24</sup> CCH was generally well tolerated, with most AEs localized to the injection site. Adverse events did not cause discontinuation from the study for >95% of patients receiving CCH (n = 7 patients discontinued; 3.7%). Although all patients in the CCH group who were tested developed AUX antibodies, no hypersensitivity reactions were observed in the CCH treatment group. In addition, no pain management or compression garments were required per protocol to mitigate swelling.

There is currently no standardized measure of cellulite severity that has been universally accepted, but several severity rating scales (e.g., modified Hexsel CSS, I-GAIS, and S-GAIS) have been used in clinical trials. The CR-PCSS and PR-PCSS were developed in accordance with US Food and Drug Administration guidance on patient-reported outcome measures and address the limitations of the aforementioned severity scales by providing means for both clinician and patient assessment using a photonumeric scale. In a separate correlation analysis combining data from the CCH and placebo groups (N = 1,500 ratings) of the current trial, ratings of cellulite severity using the CR-PCSS and PR-PCSS were compared with those from established measures of cellulite severity (i.e., Hexsel CSS, I-GAIS, and S-GAIS).<sup>20</sup> Statistically significant correlations between CR-PCSS and Hexsel CSS ratings ( $p < .001$ ) and between PR-PCSS ratings and those of aesthetic changes on the S-GAIS ( $p < .001$ ) at Day 71 were observed,<sup>20</sup> suggesting that the ability of the CR-PCSS and PR-PCSS to measure cellulite severity is similar to that of currently used scales. In addition, ratings obtained using the CR-PCSS and PR-PCSS were correlated with each other for assessment of improvement in both the buttock and thigh regions ( $p < .001$ ),<sup>20</sup> further supporting the validity of these 2 measures. The statistically significant improvements in cellulite severity observed with CCH treatment for all cellulite severity scales examined (CR-PCSS, PR-PCSS,





**Figure 5.** Patient satisfaction with treatment (mITT population). Two patients in the CCH group and 3 patients in the placebo group did not complete the satisfaction survey. CCH, collagenase clostridium histolyticum; mITT, modified intent-to-treat.

Hexsel CSS, I-GAIS, and S-GAIS) reinforce the fact that the CR-PCSS and PR-PCSS adequately evaluate cellulite severity.

Study results collectively suggest that a change of  $\geq 1$  level in both the CR-PCSS and PR-PCSS (composite end point) is clinically meaningful. The percentage of patients who achieved this composite end point, as well as each individual component, was significantly greater with CCH versus placebo ( $p < .001$ ). In addition, significant between-group differences in the percentage of patients who achieved the individual end points (i.e.,  $\geq 1$ -level improvement in CR-PCSS or PR-PCSS) mirrored those observed using other clinician (i.e., Hexsel CSS, and I-GAIS) and patient (S-GAIS)

ratings at the end of the study ( $p < .001$  vs baseline [Hexsel CSS] or placebo [I-GAIS and S-GAIS]). Although additional research is needed to determine a minimal clinically important difference for cellulite, data support  $\geq 1$ -level improvement in both the CR-PCSS and PR-PCSS as potentially clinically meaningful.

The strengths of this study include its randomized, placebo-controlled, double-blind design, the inclusion of a large number of patients ( $n = 375$ ), and the assessment of cellulite severity improvement using multiple validated patient- and clinician-reported scales. However, the study is limited by its homogeneous patient population (e.g., race), evaluation of only patients with moderate to severe cellulite, and lack of nonsubjective end points. Furthermore, some aspects of the study (e.g., dimple marking, injection technique, post-treatment care) have not been thoroughly optimized. In future studies, additional assessments such as the use of biophysical measurements to quantitatively assess changes in skin quality (e.g., cutometer measurements) or topography analyses would be informative, particularly given that ratings of cellulite severity by patients and clinicians may have been influenced by subjective assessment of skin irregularities not attributable to cellulite (e.g., folds or wrinkles secondary to skin laxity). In conclusion, this Phase 2 study demonstrated significant improvement in clinician and patient ratings of EFP (cellulite) appearance with CCH treatment versus placebo.

**TABLE 3. Adverse Events (Safety Population)**

Patients, n (%)	CCH 0.84 mg (n = 189)	Placebo (n = 186)
Any AE	155 (82.0)	50 (26.9)
Discontinuation due to AE	7 (3.7)	1 (0.5)
Any treatment-related AE	153 (81.0)	33 (17.7)
Treatment-emergent AEs*		
Injection-site bruising	142 (75.1)	25 (13.4)
Injection-site pain	112 (59.3)	10 (5.4)
Injection-site nodule	27 (14.3)	0 (0)
Injection-site pruritus	21 (11.1)	1 (0.5)
Injection-site swelling	14 (7.4)	1 (0.5)
Injection-site induration	11 (5.8)	0 (0)
Injection-site mass	10 (5.3)	1 (0.5)

\* $\geq 5\%$  of patients in any treatment group.

AE, adverse event; CCH, collagenase clostridium histolyticum.

Overall, CCH treatment was well tolerated, with a low rate of patient discontinuation due to AEs. Additional clinical evaluation of CCH for the treatment of cellulite is warranted.

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