Collagenase Clostridium Histolyticum (CCH) for the Treatment of Cellulite: Pooled Analyses From Two Phase 3, Randomized, Double-Blind, Placebo-Controlled Trials (RELEASE-1 and RELEASE-2)

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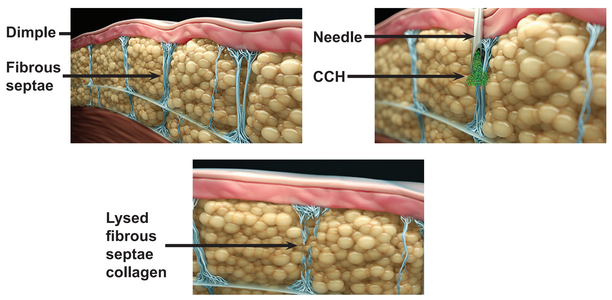
INTRODUCTION

- Collagen-rich fibrous subdermal septae play a role in contour alterations associated with cellulite[1]
- A novel presentation of collagenase clostridium histolyticum (CCH) is being investigated to correct cellulite-related contour alterations via enzymatic disruption of the septae, creating a skin-smoothing effect[2] (**Figure 1**)

Figure 1. Mechanism of Action of CCH for the Treatment of Cellulite



- CCH has been submitted to the FDA for the treatment of moderate to severe cellulite of the buttocks of adult women

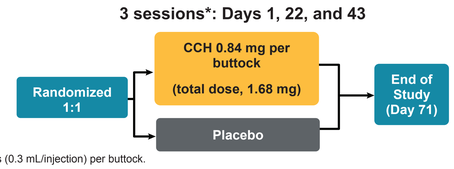
OBJECTIVE

- To assess the efficacy, safety, and tolerability of CCH in the treatment of cellulite of the buttocks in women using pooled data from identically designed phase 3, double-blind, randomized controlled trials (Randomized Evaluation of Cellulite Reduction by Collagenase Clostridium Histolyticum [RELEASE]-1 and RELEASE-2; Clinicaltrials.gov identifiers: NCT03446781 and NCT03428750)

PATIENTS AND STUDY DESIGN

- 843 women with moderate/severe cellulite (score, 3-4 on Patient Reported Photonumeric Cellulite Severity Scale [PR-PCSS] and Clinician Reported PCSS [CR-PCSS]) of the buttocks were treated (Days 1, 22, 43) with subcutaneous CCH 0.84 mg (n=424) or placebo (n=419) per treatment area
- On Day 1, one buttock was randomly assigned as the target buttock. Study subjects, investigators, and sponsor personnel were blinded to study treatment and assignment of the target buttock.
  - The same treatment was administered to the bilateral buttocks of each patient (CCH or placebo)

Figure 2. Study Design



*12 injections (0.3 mL/injection) per buttock.

- Each injection was administered as three 0.1-mL aliquots (**Figure 3**)

Figure 3. Injection Technique

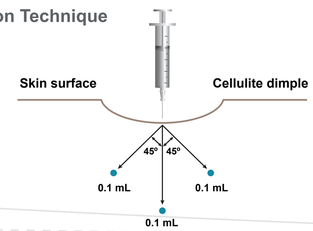
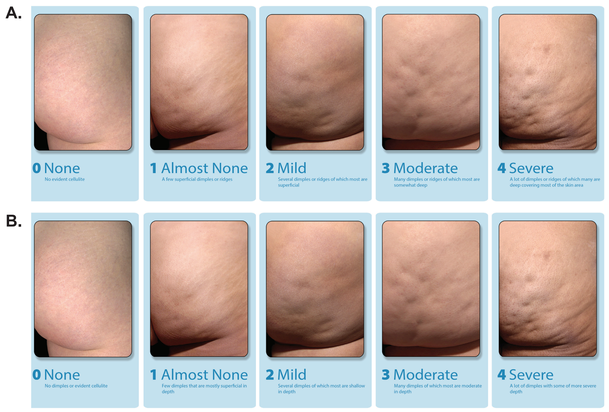


Figure 4. Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) – Buttock (A) and Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) – Buttock (B)



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ENDPOINTS

- The primary efficacy endpoint was the percentage of composite responders at Day 71, defined as ≥2-level improvement from baseline in both the PR-PCSS and CR-PCSS
- Other endpoints: the percentage of ≥1-level composite responders (key secondary endpoint), improvement in the S-GAIS, subject satisfaction, and safety
  - The anchor-based analysis included the use of a 1-way ANOVA model with the Subject Satisfaction with the Cellulite Treatment Assessment (SSCTA) scale group as the independent variable and the PR-PCSS change score as the dependent variable.
  - The SSCTA groups at Day 71 were as follows:
    - +2 Very satisfied with treatment
    - +1 Satisfied with treatment
    - 0 Nether satisfied nor dissatisfied with treatment
    - –1 Dissatisfied with treatment
    - –2 Very dissatisfied with treatment

RESULTS

- 843 women received ≥1 injection (up to 12 injections per buttock per session)
- Patients were well represented in terms of age, BMI, and Fitzpatrick category (**Table 1**)

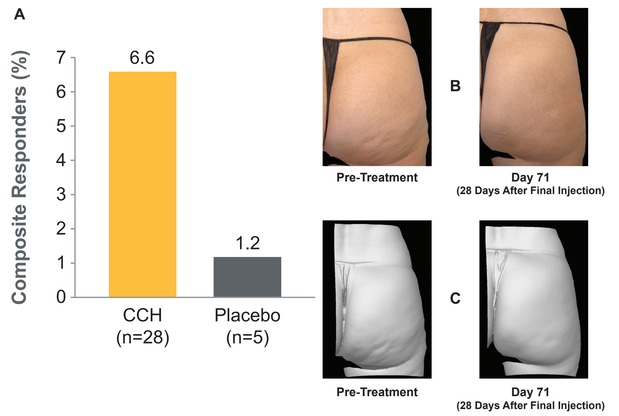
Table 1. Demographics

Category	Study Drug: CCH 0.84 mg/buttock[a] (N = 424)	Study Drug: Placebo[a] (N = 419)	Total[a] (N = 843)
Mean age, y (SD)	**47.8 (10.46)**	**45.8 (10.50)**	**46.8 (10.52)**
Race, n (%)			
White	336 (79.2)	325 (77.6)	661 (78.4)
Black or African American	76 (17.9)	75 (17.9)	151 (17.9)
American Indian or Alaskan Native	4 (0.9)	7 (1.7)	11 (1.3)
Asian	0 (0.0)	3 (0.7)	3 (0.4)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (0.2)	1 (0.1)
Multiple	5 (1.2)	6 (1.4)	11 (1.3)
Other	3 (0.7)	2 (0.5)	5 (0.6)
Body Mass Index category, (kg/m²), n (%)			
Underweight (< 18.5)	1 (0.2)	0 (0.0)	1 (0.1)
Normal Weight (18.5 – < 25)	80 (18.9)	84 (20.1)	164 (19.5)
Overweight (25 – < 30)	143 (33.7)	123 (29.4)	266 (31.6)
Obese (≥ 30)	200 (47.2)	211 (50.5)	411 (48.8)
Missing	0	1	1
Fitzpatrick scale, skin category, n (%)			
I (Pale White)	11 (2.6)	12 (2.9)	23 (2.7)
II (Fair)	124 (29.2)	102 (24.3)	226 (26.8)
III (Darker White)	119 (28.1)	139 (33.2)	258 (30.6)
IV (Light Brown)	93 (21.9)	82 (19.6)	175 (20.8)
V (Brown)	48 (11.3)	45 (10.7)	93 (11.0)
VI (Dark Brown)	29 (6.8)	39 (9.3)	68 (8.1)

[a]Percentages are based on the number of evaluable subjects for each category in each column.

- In the pooled analysis, CCH-treated women were 5.88 times as likely as placebo-treated women to be a ≥2-level composite responder at Day 71 (odds ratio [95% CI], 5.88 [2.25-15.38]; *P*<0.001) (**Figure 5**)

Figure 5. Primary Endpoint: ≥2-Level Composite Responders* of the Target Buttock at Day 71 (A) Examples of a 2-level Composite Response in Color (B) and Grey Scale (C)

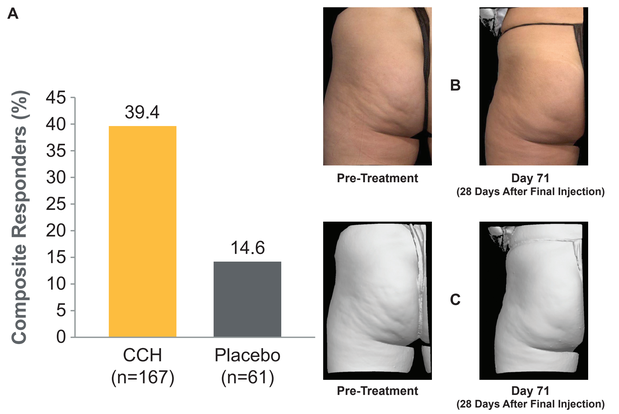


*≥2-level improvement from baseline in CR-PCSS rating and PR-PCSS rating at Day 71.

CCH = collagenase clostridium histolyticum; CR-PCSS = Clinician Reported Photonumeric Cellulite Severity Scale; PR-PCSS = Patient Reported Photonumeric Cellulite Severity Scale.

- In the pooled analysis, CCH-treated women were 3.84 times as likely as placebo-treated women to be a ≥1-level composite responder at Day 71 (3.84 [2.73-5.40]; *P*<0.001 **(Figure 6)**

Figure 6. Key Secondary Endpoint: ≥1-Level Composite Responders* of the Target Buttock at Day 71 (A) Examples of a 1-level Composite Response in Color (B) and Grey Scale (C)



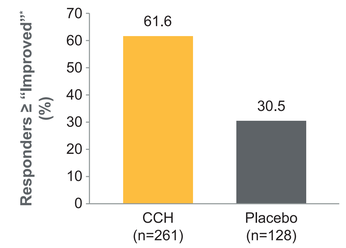
*≥1-level improvement from baseline in CR-PCSS rating and PR-PCSS rating at Day 71.

CCH = collagenase clostridium histolyticum; CR-PCSS = Clinician Reported Photonumeric Cellulite Severity Scale; PR-PCSS = Patient Reported Photonumeric Cellulite Severity Scale.

- Significantly more women treated with CCH had improvement vs. women treated with placebo (56.1% vs 32.9%; *P*<0.001)
- Anchor-based analyses indicated PR-PCSS score change ≥1 was clinically meaningful
- Based on a 1-level satisfaction level in the SSCTA ("satisfied"), the PR-PCSS meaningful change threshold is 1.17 points (approximately 1-level rating change)
- The effect size was statistically large at -2.35

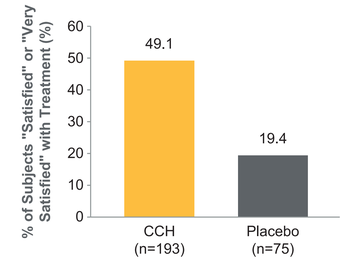
- In the pooled analysis, more women treated with CCH vs placebo had ≥1-level S-GAIS improvement (61.6% vs 30.5%; *P*<0.001) **(Figure 7)** and were "satisfied"/"very satisfied" (49.1% vs 19.4%) **(Figure 8)**

Figure 7. S-GAIS Responders at Day 71



*S-GAIS responders included patients who were "Improved", "Much Improved", or "Very Much Improved" following treatment.
CCH = collagenase clostridium histolyticum; S-GAIS = Subject Global Aesthetic Improvement Scale.

Figure 8. Subject Satisfaction* on the SSCTA Scale at Day 71



*SSCTA: 5-level scale ranging from 2 (very satisfied) to −2 (very dissatisfied).
CCH = collagenase clostridium histolyticum, SSCTA = Subject Satisfaction with Cellulite Treatment Assessment Scale.

- Most adverse events in the CCH group were transient, mild/moderate and injection-site–related (bruising, pain, induration, pruritus, erythema) **(Table 2)**. Only 1 patient in each of the pooled CCH and placebo groups experienced a serious treatment emergent adverse event; none were deemed treatment-related by the investigator.

Table 2: Adverse Reactions through Day 71 that Occurred in ≥2% of CCH-treated Subjects After up to 3 Injections

Adverse Reaction	CCH N=424	Placebo N=419
Injection Site Bruising[a]	**358 (84.4%)**	**88 (21.0%)**
Injection Site Pain[b]	**204 (48.1%)**	**37 (8.8%)**
Injection Site Induration[c]	**148 (34.9%)**	**8 (1.9%)**
Injection Site Pruritus	**62 (14.6%)**	**4 (1.0%)**
Injection Site Erythema	**36 (8.5%)**	**21 (5.0%)**
Injection Site Discoloration[d]	**33 (7.8%)**	**2 (0.5%)**
Injection Site Swelling[e]	**29 (6.8%)**	**1 (0.2%)**
Injection Site Warmth	**14 (3.3%)**	**0 (0.0%)**

[a]Includes preferred terms of injection site bruising, injection site haematoma, and injection site haemorrhage.
[b]Includes preferred terms of injection site pain, and injection site discomfort.
[c]Includes preferred terms of injection site mass, injection site nodule, and injection site induration.
[d]Includes preferred terms of injection site discolouration and injection site hyperpigmentation.
[e]Includes preferred terms of injection site swelling, local swelling, and injection site edema.

CONCLUSIONS

- In this pooled analysis, CCH treatment provided statistically significant improvements in cellulite severity, and patient satisfaction scores
- CCH was well tolerated. Injection site reactions were transient, self-limiting, and generally resolved before the next treatment session.
- A phase 3, open-label, 5-year study is currently ongoing to assess the durability of response of CCH for the treatment of cellulite in women (Clinicaltrials.gov identifier: NCT03526549)
- Data suggests that a PR-PCSS rating change of 1 from Baseline to Day 71 is indicative of meaningful change for patients, as this level of change was associated with ratings of improvement and satisfaction on the SSCTA

DISCLOSURES

M Gold reports being a consultant and clinical investigator for Endo Pharmaceuticals Inc.
J Kaufman reports serving as a clinical investigator and consultant for Endo Pharmaceuticals Inc.
JH Joseph reports being a shareholder and serving as a clinical investigator for Endo Pharmaceuticals Inc.
MS Kaminer reports serving as a clinical investigator and consultant for Endo Pharmaceuticals Inc. and serving as a consultant for Arctic Fox LLC, ExploraMed, and Soliton, Inc.
SG Fabi reports having received research grants from Allergan, Revance Therapeutics, Inc., Endo Pharmaceuticals Inc., Galderma Laboratories, L.P., Bausch Health Companies Inc., and Merz North America, Inc.; reports being a speaker and consultant for Allergan, Galderma Laboratories, L.P., Bausch Health Companies Inc., and Merz North America, Inc.
D Hurley, G Liu, MP McLane, and S Vijayan are employees of Endo Pharmaceuticals Inc.
L Bass reports being an advisory board participant for Endo Pharmaceuticals Inc.; serving as a consultant for Cynosure, A Hologic Company; and being a clinical investigator for Cynosure, A Hologic Company, Endo Pharmaceuticals Inc., and Merz North America, Inc.

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