Two Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trials of Collagenase Clostridium Histolyticum (CCH) for the Treatment of Cellulite

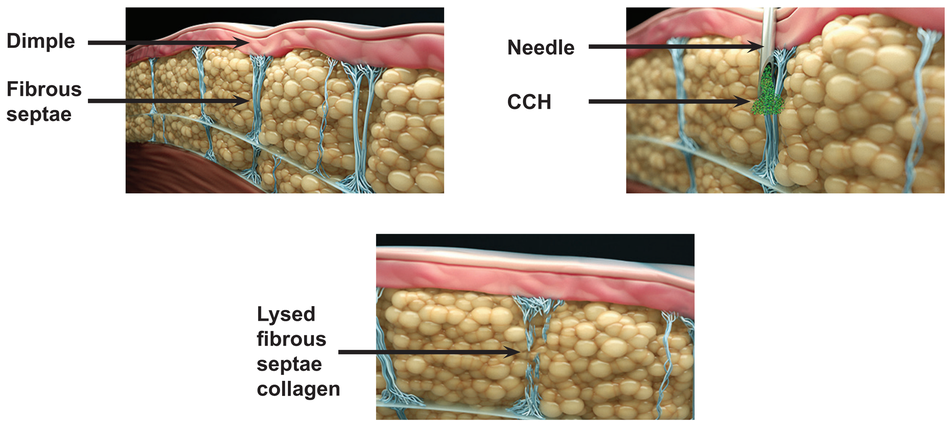
Sabrina Guillen Fabi, MD, FAAD, FAACS[1], Joely Kaufman, MD[2]; John H. Joseph, MD[3]; Michael S. Kaminer, MD[4]; David Hurley, MD[5]; Genzhou Liu, PhD[5]; Michael P. McLane, PhD[5]; Saji Vijayan, MBBS, D. Diab[5]; Lawrence S. Bass, MD, FACS[6]

[1]Cosmetic Laser Dermatology, San Diego, CA, and University of California-San Diego, San Diego, CA, [2]Skin Associates of South Florida, Coral Gables, FL; [3]John H. Joseph Facial Plastic and Reconstructive Surgery, Beverly Hills, CA, [4]SkinCare Physicians, Chestnut Hill, MA, [5]Endo Pharmaceuticals Inc., Malvern, PA, [6]Bass Plastic Surgery PLLC, New York, NY

INTRODUCTION

- Collagen-rich 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. MOA of CCH for the Treatment of Cellulite



CCH = collagenase clostridium histolyticum; MOA = mechanism of action.

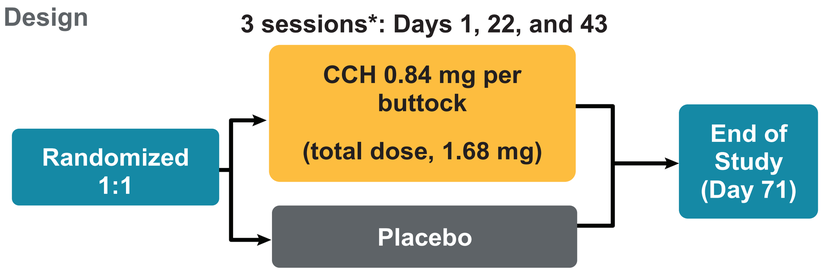
OBJECTIVE

- To evaluate the efficacy and safety of CCH for the treatment of cellulite in 2 identically designed, phase 3, randomized, double-blind, placebo-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

- Adult women with moderate or severe cellulite on the buttocks received up to 3 CCH treatment sessions (**Figure 2**)
  - The same treatment was administered to both buttocks of each patient (CCH or placebo)

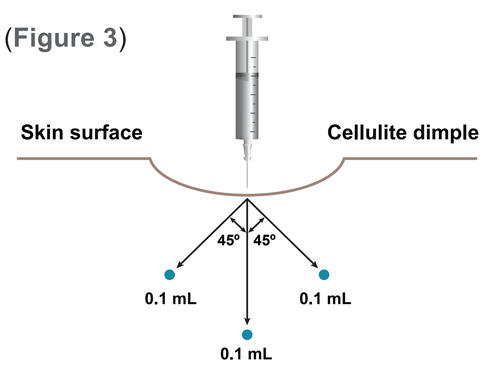
Figure 2. Study Design



*12 injections (0.3 mL/injection) per buttock.
CCH = collagenase clostridium histolyticum.

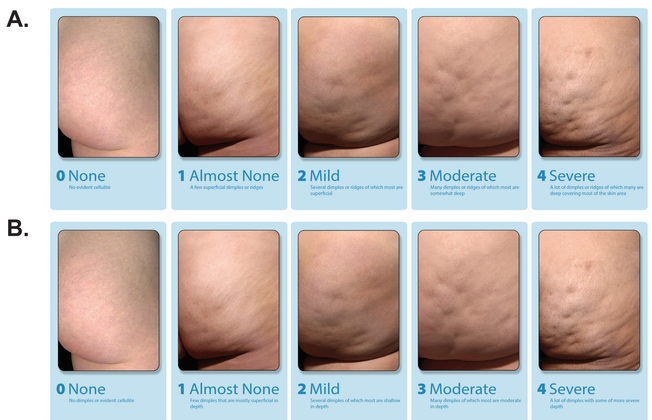
- Each injection was administered as three 0.1-mL aliquots (**Figure 3**)

Figure 3. Injection Technique



- Moderate or severe cellulite was defined as a score of 3 or 4 on the Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) and the Clinician Reported PCSS (CR-PCSS; **Figure 4**)

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



- The primary efficacy endpoint was the percentage of composite responders at Day 71, defined as ≥2-level improvement from baseline in both PR-PCSS and CR-PCSS
- Other endpoints: the percentage of ≥1-level composite responders (key secondary endpoint), mean CR-PCSS score over time, improvement in the Subject Global Aesthetic Improvement Scale (S-GAIS), subject satisfaction, and safety

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**)

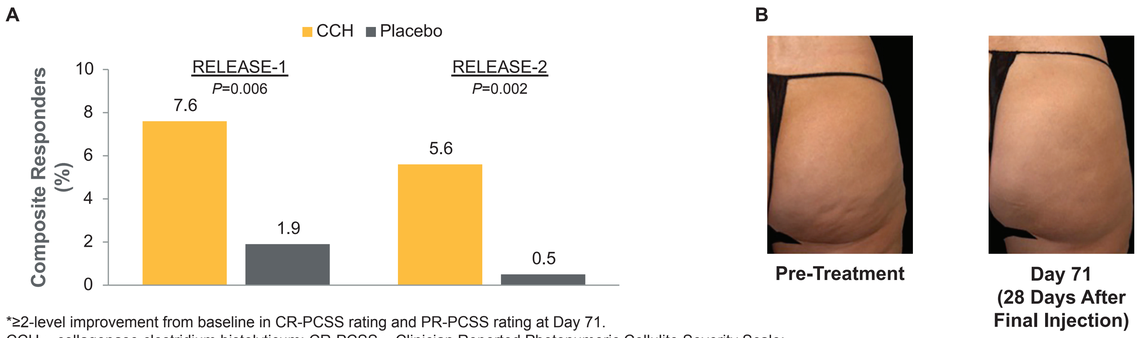
Table 1. Demographics

Parameter	RELEASE-1 CCH (n=210)	RELEASE-1 Placebo (n=213)	RELEASE-2 CCH (n=214)	RELEASE-2 Placebo (n=206)
Mean age, y (range)	47.9 (21-70)	45.8 (22-70)	47.7 (20-78)	45.7 (18-72)
Race, %				
White	74.8	75.6	83.6	79.6
Black	22.4	20.2	13.6	15.5
Other	2.8	4.2	2.8	4.9
BMI category, %*				
Underweight/normal (<25 kg/m^2)	20.5	19.3	17.8	20.9
Overweight (25 to <30 kg/m^2)	32.9	29.2	34.6	29.6
Obese (≥30 kg/m^2)	46.7	51.4	47.7	49.5
Fitzpatrick scale category, %				
I/II (pale white/fair)	26.2	24.4	37.4	30.1
III (darker white)	32.9	35.2	23.4	31.1
IV (light brown)	19.0	16.4	24.8	22.8
V (brown)	15.7	12.7	7.0	8.7
VI (dark brown)	6.2	11.3	7.5	7.3

*Data missing for 1 woman in RELEASE-1 placebo group. BMI = body mass index; CCH = collagenase clostridium histolyticum.

- In both studies, significantly more women treated with CCH than placebo were ≥2-level composite responders at Day 71 (**Figure 5**)

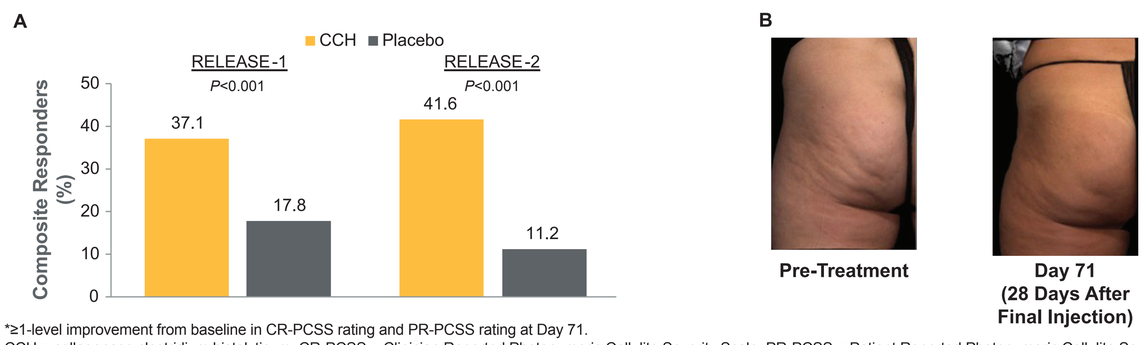
Figure 5. Primary Endpoint: ≥2-Level Composite Response* at Day 71 (A); Example of a 2-Level Composite Response (B)



*≥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 both studies, significantly more women treated with CCH than placebo were ≥1-level composite responders (**Figure 6**)

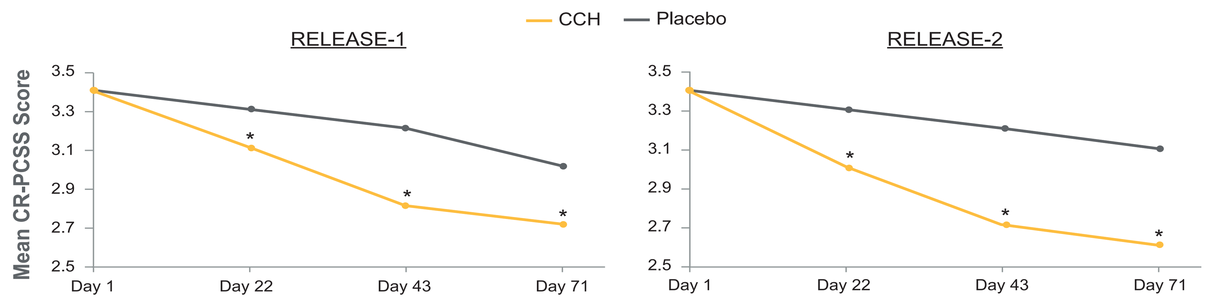
Figure 6. Key Secondary Endpoint: ≥1-Level Composite Response* at Day 71 (A); Example of a 1-Level Composite Response (B)



*≥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.

- In both studies, mean CR-PCSS scores were significantly better with CCH vs placebo at Days 22, 43, and 71 (**Figure 7**)

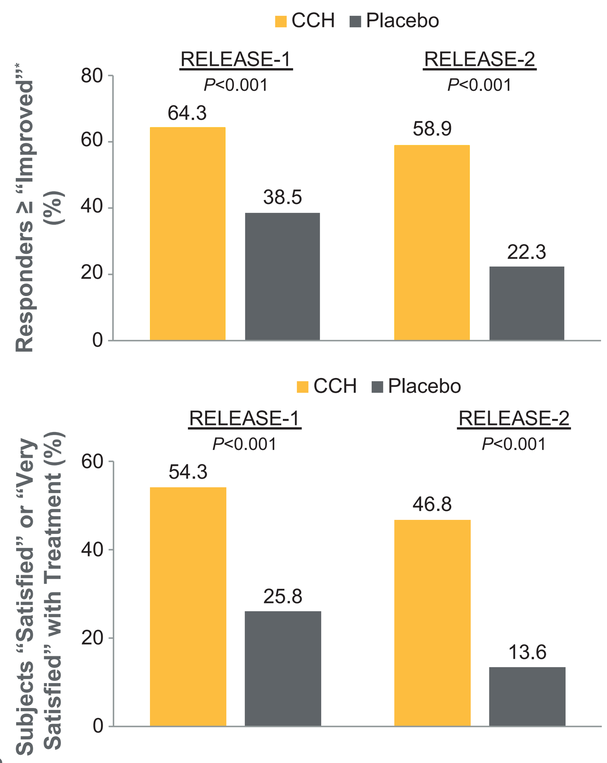
Figure 7. Mean CR-PCSS Scores Over Time



*P<0.001 vs placebo.
CCH = collagenase clostridium histolyticum; CR-PCSS = Clinician Reported Photonumeric Cellulite Severity Scale.

- In both studies, significantly more women treated with CCH vs placebo were S-GAIS responders at Day 71 (**Figure 8**)

Figure 8. S-GAIS Response 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.

- In both studies, significantly more women treated with CCH than placebo were "satisfied" or "very satisfied" with treatment (**Figure 9**)

Figure 9. Subject Satisfaction* at Day 71

*Subject satisfaction with cellulite treatment assessment: 5-level scale ranging from 2 (very satisfied) to −2 (very dissatisfied).
CCH = collagenase clostridium histolyticum.

- The adverse event profile is presented in **Table 2**

Table 2. Adverse Event Profile

Women With an AE, %	RELEASE-1 CCH (n=210)	RELEASE-1 Placebo (n=213)	RELEASE-2 CCH (n=214)	RELEASE-2 Placebo (n=206)
≥1 AE	81.0	38.0	95.3	42.7
AE leading to discontinuation	4.3	0.5	3.7	1.0
Most common AEs (≥7.0% of women in any CCH group)*				
Injection-site bruising	65.2	19.7	90.2	20.4
Injection-site pain	36.2	5.2	59.3	12.6
Injection-site nodule	18.1	0	32.7	1.0
Injection-site pruritus	13.8	0.5	15.9	1.5
Injection-site erythema	3.8	1.9	13.1	8.3
Injection-site discoloration	5.7	0	9.8	1.0
Injection-site mass	8.6	0.5	7.0	0
Injection-site hemorrhage†	11.9	2.3	2.8	0.5
Injection-site swelling	7.1	0	4.2	0.5

*Ordered in table by most common AE in pooled CCH group for the 2 studies. †Preferred for the verbatim term "injection-site ecchymosis."
AE = adverse event; CCH = collagenase clostridium histolyticum.

CONCLUSIONS

- CCH significantly improved cellulite severity and appearance in women with moderate to severe cellulite on the buttocks, using both clinician- and patient-reported outcome measures
- Administration of CCH for cellulite was generally well tolerated
- 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)

ACKNOWLEDGMENTS

The studies were sponsored by Endo Pharmaceuticals Inc., Malvern, PA. Medical writing support was provided by Heather S. Oliff, PhD, Science Consulting Group, LLC, North Tustin, CA under the direction of the authors. Funding for this support was provided by Endo Pharmaceuticals Inc.

REFERENCES

[1]Hexsel D, et al., eds. Update in Cosmetic Dermatology. Berlin: Springer-Verlag; 2013:21-32.
[2]Sadick NS, et al. *Dermatol Surg.* 2019. doi: 10.1097/DSS.0000000000001803 [Epub ahead of print].

DISCLOSURES

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 has 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.

If you do not have a QR code reader on your phone, please download the Quick Scan (iPhone) or QR Droid (Androids) free app from your mobile app store