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COLLAGENASE CLOSTRIDIUM HISTOLYTICUM

CCH

EN3835-209

A PHASE 2A, OPEN-LABEL STUDY EVALUATING THE SAFETY AND DIFFERENT INJECTION TECHNIQUES OF CCH FOR THE TREATMENT OF EDEMATOUS FIBROSCLEROTIC PANNICULOPATHY

IND 110077

NCT03632993

Date:

Original Protocol: 27 June 2018

Amendment 1: 29 August 2018

Auxilium Pharmaceuticals, LLC (Auxilium) (formerly Auxilium Pharmaceuticals, Inc.) was acquired by Endo International plc. in January 2015. The Sponsor of the application remains Auxilium; however, Endo Pharmaceuticals Inc. is authorized to act and to communicate on behalf of Auxilium.

[redacted]

2. SUMMARY OF CHANGES

Protocol amendment(s) and amended informed consent form(s) (as necessary) have been reviewed and approved by the governing IRBs before implementation of the amendment at each study center.

Amendment 1 was incorporated into the protocol on 29 August 2018. The primary reason for this amendment is to remove MRIs and to correct errors in, and update, the original protocol. The major changes to the protocol are outlined below. Revisions in style, minor corrections (such as spelling errors, etc), and other minor changes that do not impact content may also have been made.

Section	Original Text	Revised Text/Reason for Change
Globally and 8.1.2 Collagenase Clostridium Histolyticum	Study drug was originally referred to as EN3835. This has been corrected to CCH throughout the protocol.	EN3835 refers to the approved formulation of the study drug. The formulation used for EFP studies has been modified and is referred to as CCH. Section 8.1.2 was updated to explain this change.
Title Page	NA	The NCT number has been added
3 Sponsor Contact Information	TBD	[redacted] and contact information added
4 Synopsis	Estimated date first subject enrolled: August 2018	Estimated date first subject enrolled: September 2018
4 Synopsis 5 Schedule of Events 7 List of Abbreviations 9.3 Objectives 10.4 Discussion of Study Design 11.2 Exclusion Criteria 12.5 Selecting and Marking Dimples 13.1 3-D Photography 13.2 MRI 17.5 Efficacy Analysis	All subjects enrolled in the study were to have MRIs at Screening, Day 4, Day 8, Day 15, Day 22, Day 43, and Day 71.	MRIs will no longer be performed in this study and all mention of MRIs has been deleted. Exclusion Criteria #3 "Is unable to undergo MRI" and Section 13.2 "MRI" have been deleted in their entirety. Evaluation of septae morphology and the usefulness of MRI in evaluating outcomes of treatment for EFP have been removed from the objectives and endpoints.
10.3.4 Treatment IV Deep and Shallow Injections, 5 Aliquots	Needle positions C and E were incorrect in Figure 4 .	Figure 4 was corrected so the Position C is between positions A and B and Position E is between positions A and D to match the accompanying text.

Section	Original Text	Revised Text/Reason for Change
12.5 Selecting and Marking Dimples	None	The following text was added to clarify the selection of treatment area: If all 4 quadrants (both buttocks and both thighs) meet entry criteria for a single subject, the thighs will be treated. No subject will have treatment in all 4 quadrants (both buttocks and both thighs) during this study.
13.1 3-D Photography	For 3-D photographic images taken on Days 4, 8, 15, 22, 43, and 71, a central assessor blinded to the treatment arm and study visit day will complete a 5-point Likert scale to gauge the level of aesthetic improvement achieved (from baseline) in each treatment area. ~~The assessor will also evaluate change from baseline in the volume of the selected dimples in each treatment area.~~	A central assessor will not evaluate dimple volume.
14.5 Reporting Adverse Events and Serious Adverse Events 14.6 Special Reporting Situations	The title of the Endo SAE reporting form has been updated (formally Clinical Trial Report Form for SAEs) for use in multiple event reporting situations.	The updated name of the Endo event reporting form is: Serious Adverse Event (SAE)/Reportable Event Form.
17.5 Efficacy Assessments	• Change from baseline in the blinded assessor's Likert Scale score of aesthetic appearance in each treatment area (buttocks or thighs) at Days ~~4, 8, 15,~~ 22, 43, and 71 by each treatment arm. • Change from baseline in ~~the blinded assessor's evaluation of~~ dimple depth and volume in each treatment area (buttocks or thighs) Days ~~4, 8, 15,~~ 22, 43, and 71 by treatment arm.	Efficacy endpoints will not be evaluated on Days 4, 8, and 15, and the blinded assessor will not evaluate dimple depth and volume.
17.5 Efficacy Assessments	The central assessor Likert Scale score of aesthetic appearance improvement from baseline in the 3-D photographic image and change from baseline in dimple volume and depth ~~(by MRI and Hexsel CSS)~~…	Dimple depth and volume will not be measured by MRI and Hexsel CSS.
24.6 Subject Confidentiality	All subject records submitted to Endo or its designee will be identified only by ~~initials and~~ code number.	Endo will not use initials as subject identifiers.

3. SPONSOR CONTACT INFORMATION

Role in Study	Name	Telephone and Email Address
Medical Monitor	[redacted]	[redacted]
SAE Reporting Pathway	Not Applicable	[redacted]

A list of other key study personnel and vendors will be provided separately for your reference.

4. SYNOPSIS

Name of Sponsor/Company: Endo Pharmaceuticals Inc.	
Name of Investigational Product: CCH	
Name of Active Ingredient: Collagenase clostridium histolyticum	
Title of Study: A Phase 2a, Open-Label Study Evaluating the Safety and Different Injection Techniques of CCH for the Treatment of Edematous Fibrosclerotic Panniculopathy	
Lead Principal Investigator: [redacted]	
Study period: Estimated date first subject enrolled: September 2018 Estimated date last subject completed: January 2019	**Phase of development:** 2a

Objectives:

Primary:

The primary objective of this study is to assess the treatment effects of CCH when administered by different injection techniques in subjects with edematous fibrosclerotic panniculopathy (EFP).

Secondary:

The secondary objective of this study is to assess the safety of CCH when administered using different injection techniques in subjects with EFP.

Exploratory:

The exploratory objectives of this study include:

- To assess the immunogenicity of CCH in the treatment of EFP.
- To assess the usefulness of 3-D photography in evaluating outcomes of treatment for EFP.

Study Design:

This is a Phase 2a, open-label, multicenter, exploratory study to evaluate the safety and effectiveness of different injection techniques of CCH for the treatment of adult women with mild, moderate or severe EFP (as assessed by the investigator using the Clinician Reported Photonumeric Cellulite Severity Scale [CR-PCSS]).

Approximately 60 subjects will be enrolled, 30 with 2 eligible buttocks (to be dosed in the buttocks) and 30 with 2 eligible thighs (to be dosed in the thighs). No subjects will be treated for EFP in both the buttocks and the thighs. The 30 subjects in each treatment region (buttocks or thighs) will be assigned to 1 of 5 injection technique treatment arms.

Subjects will participate in the study for approximately 92 days. Following a screening period of up to 21 days, subjects will participate in up to 3 treatment visits separated by 21 days (Days 1, 22, and 43). Following the first dose of study drug, subjects will return for assessments on Days 4, 8, 15, 22, 43 and 71.

Number of subjects (planned): Approximately 60

Study centers: Approximately 5 sites in the United States

Name of Sponsor/Company: Endo Pharmaceuticals Inc.

Name of Investigational Product: CCH

Name of Active Ingredient: Collagenase clostridium histolyticum

Diagnosis and inclusion/exclusion criteria:

Healthy, nonpregnant, nonlactating female subjects at least 18 years of age with evidence of cellulite in 2 bilateral treatment areas (defined as right and left buttocks OR right and left posterolateral thighs) will be enrolled in this study.

Subjects will be excluded from the study if they have a coagulation disorder, require anticoagulant or antiplatelet medication, have evidence or history of malignancy (other than excised basal-cell carcinoma) in the previous 5 years, have a history of keloidal scarring or abnormal wound healing, or have a tattoo located within 2 cm of the site of injection. Subjects will also be excluded they have a history of lower extremity thrombosis or post-thrombosis syndrome, a vascular disorder (eg, varicose veins, telangiectasia), inflammation or active infection, severe skin laxity, flaccidity, and/or sagging, or any active cutaneous alteration including rash, eczema, psoriasis, or skin cancer in the areas to be treated.

Subjects who have had any of the following in the area to be treated: liposuction, injections (eg, mesotherapy), radiofrequency device treatments, laser treatment, surgery (including subcision and/or powered subcision), or any investigational treatment for EFP/cellulite in the previous 12 months; Endermologie® or similar treatments in the previous 6 months; massage therapy in the previous 3 months; or creams (eg, Celluvera™, TriLastin®) to prevent or mitigate EFP within the 2 weeks prior to the start of study drug administration will also be excluded from the study.

Investigational product, dosage and mode of administration:

There are 5 treatment arms per region (buttocks or thigh) in this study with each arm representing a different injection technique as follows:

- Treatment I: Shallow Injection, 3 aliquots.
- Treatment II: Shallow injection, 1 aliquot.
- Treatment III: Deep injection, 1 aliquot.
- Treatment IV: Deep and shallow injections, 5 aliquots.
- Treatment V: Shallow injection, 4 aliquots.

Injection techniques differ from each other in, at least but not limited to, concentration of the CCH injectate, angle of injection, depth of injection, volume of injection, and study drug administration at injection site.

Across all treatment arms, study drug will be administered subcutaneously while the subject is in a prone position. Each subject will receive 24 injections for a total dose of 1.68 mg (0.84 mg per treatment region) at each treatment visit. The cumulative CCH dose will be 5.04 mg for each subject that completes the 3 treatment visits.

Duration of study:

Subjects who complete the study will participate for up to 92 days including a 21 day screening period, a 43 day active treatment period, and a 28 day follow-up period.

Reference therapy, dosage and mode of administration: Not applicable

Name of Sponsor/Company: Endo Pharmaceuticals Inc.
Name of Investigational Product: CCH
Name of Active Ingredient: Collagenase clostridium histolyticum
Criteria for evaluation: **Efficacy**: Likert Scale score of aesthetic appearance, Hexsel CSS (B) depression depth scale, and dimple depth and volume. **Safety**: Adverse events, vital signs, and clinical laboratory tests.
Statistical methods: **Sample size consideration:** No sample size estimation was done for this study. **Analysis populations:** Safety Population: The Safety Population will include all subjects who receive at least 1 injection of study drug. All safety analyses will be based on this population. Evaluable Populations: The Evaluable Population will include all subjects in the Safety Population who have completed screening procedures and at least 1 post baseline assessment of the Likert Scale score of aesthetic appearance improvement. All efficacy analysis will be based on this population. **Analyses:** The central assessor Likert Scale score of aesthetic appearance improvement from baseline in the 3-D photographic image, change from baseline in the Hexsel CSS (B) depression depth scale, and change from baseline in dimple volume and depth will be summarized by treatment arm and study visit using appropriate descriptive statistics. In addition, a linear mixed model will be utilized to fit change from baseline of each endpoint with treatment arm, cellulite dimples, and study visit as fixed effects, subject as random effect, and assessments across study visits as repeated measure. The fixed effect estimates and the corresponding 95% confidence intervals will be presented for each endpoint. AEs will be summarized by proportion of subjects experiencing each event and by treatment arm. Descriptive statistics will be presented for actual and change from baseline at each study visit for vital signs and clinical laboratory test results by treatment arm.

5. SCHEDULE OF EVENTS

Procedures	Screening (Day-21 to Day -1)	Day 1	Day 4 (± 1 day)	Day 8 (± 1 day)	Day 15 (± 2 days)	Day 22 (± 2 days)	Day 43 (± 2 days)	End of Study/ Early Termination Day 71 (± 3 days)	Unscheduled Clinic Visit[a]
Informed consent[b]	X								
Inclusion/exclusion criteria review	X	X[c]							
Demographic data	X								
3-D Photography	X	X[d,e]	X	X	X	X[d,e]	X[d,e]	X	
Medical/surgical/EFP history (including previous treatment)	X								
Prior/concomitant medications/procedures	X	X[e]	X	X	X	X	X	X	X
Physical Examination	X							X	X
Height	X								
Weight	X	X[e]						X	X
Fitzpatrick skin type	X								
Vital signs	X	X[f]				X[f]	X[f]	X	X
12-lead ECG	X								
Clincal Laboratory Tests	X							X	X
Anti-AUX-I/anti-AUX-II antibody level sample		X[e]						X	
Serum pregnancy test	X								
Urine pregnancy test		X[e]				X[e]	X[e]	X	X
Assignment of treatment area (buttocks or thighs)	X								

Procedures	Screening (Day-21 to Day -1)	Day 1	Day 4 (± 1 day)	Day 8 (± 1 day)	Day 15 (± 2 days)	Day 22 (± 2 days)	Day 43 (± 2 days)	End of Study/ Early Termination Day 71 (± 3 days)	Unscheduled Clinic Visit[a]
Selection of 2 dimples within each treatment area for volumetric assessment	X	X[e]							
CR-PCSS	X								
Hexsel Depression Depth Scale	X					X	X	X	
Assign Treatment Arm (dosing injection technique)		X[e]							
Mark the dimple injection sites		X[e]				X[e]	X[e]		
Study drug administration		X				X	X		
Injection site reactions/local tolerability in the treated areas		X	X	X	X	X	X	X	X
All other adverse events	X								

[a]During unscheduled visits the investigator or designee may perform any study procedure that they deem clinically necessary (eg, vital signs, clinical laboratory tests, pregnancy test, etc).
[b]Performed prior to any study-required assessments.
[c]Should be reassessed and verified prior to study drug administration.
[d]Complete before and after marking injection sites.
[e]Complete prior to study drug administration.
[f]Vital signs will be collected up to 4 hours prior to, and at 15 and 30 minutes after study drug administration on Days 1, 22, and 43.

6. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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7. LIST OF ABBREVIATIONS

The following abbreviations are used in this study protocol.

Abbreviation or Special Term	Explanation
3-D	3-dimensional
AE	Adverse event
CFR	Code of Federal Regulations
CR-PCSS	Clinician Reported Photonumeric Cellulite Severity Scale
CTA	Clinical Trial Authorization
DHHS	Department of Health and Human Services
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EFP	Edematous fibrosclerotic panniculopathy
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GAIS-I	Investigator Global Aesthetic Improvement Scale
GAIS-S	Subject Global Aesthetic Improvement Scale
IB	Investigator Brochure
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
MAA	Marketing Authorization Application
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
PR-PCSS	Patient Reported Photonumeric Cellulite Severity Scale
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event
WHO	World Health Organization

8. INTRODUCTION

8.1. Background

8.1.1. Edematous Fibrosclerotic Panniculopathy

Edematous fibrosclerotic panniculopathy (EFP), commonly known as cellulite has been defined as a local metabolic disorder of subcutaneous tissues that results in a contour abnormality of the skin (Khan et al, 2010a). The condition manifests as dimpled skin, particularly in the gluteal-femoral region (Hexsel et al, 2010; Rawlings, 2006). EFP is caused by herniation of subcutaneous fat lobules through the dermohypodermal junction and/or shortening of the collagen septa that cross the hypodermal layer and connect the dermis to the underlying fascia. This creates an uneven surface with dimpling (Hexsel et al, 2010; Khan et al, 2010a). EFP is a medical condition resulting in a potentially cosmetically unacceptable alteration of the skin, and affects an estimated 85% to 98% of postpubertal women (Khan et al, 2010a; Rawlings, 2006).

The pathophysiology of EFP is not completely understood, but there are 3 main theories: edema resulting from excessive hydrophilia of the intercellular matrix, alteration of the regional microcirculation, and different anatomical conformation of collagenous subcutaneous tissues in women versus men (Terranova et al, 2006).

It is known that EFP is different from generalized obesity. In generalized obesity, adipocytes undergo hypertrophy and hyperplasia that are not limited to the pelvis, thighs, and abdomen (Khan et al, 2010a). In areas of EFP, adipocytes have physiologic and biochemical properties that differ from adipose tissue located elsewhere. Large, metabolically-stable adipocytes characterize EFP-prone areas; thus, the responsiveness to catecholamine-induced lipolysis is less in EFP tissues compared to visceral fat, which has the greatest responsiveness (Khan et al, 2010a).

Subcutaneous fat lobes are separated from one another by thin, usually rigid strands of collagenous connective tissues, which cross the fatty layers and connect the dermis to the underlying fascia. These septa stabilize the subcutis and divide the fat. In EFP, shortening of the collagen septa due to fibrosis provokes retraction at the insertion points of the trabeculae, causing the depressions that characterize EFP (Hexsel et al, 2010). There are a higher percentage of thinner, perpendicular hypodermal septa in women with EFP than in men (Khan et al, 2010a). Weight gain makes EFP more noticeable, but it may be present even in thin subjects. Genetics may also play a role since EFP tends to run in families.

There are therapies that have been utilized in an attempt to treat cellulite; however, there are no approved pharmacologic treatments. Despite multiple therapeutic modalities, there is little scientific evidence that any of these treatments are beneficial. In fact, much of the evidence is anecdotal, subjective, or based only on patient self-assessment (Avram, 2004). Some of the historical treatments for EFP have included weight loss (Khan et al, 2010b), topical agents (Avram, 2004), massage (Collis et al, 1999), liposuction (Avram, 2004; Khan et al, 2010b), mesotherapy (Khan et al, 2010b), radiofrequency (Khan et al, 2010b), subcision and powered subcision (Hexsel and Mazzuco, 2000), and laser therapies (Boyce et al, 2005; DiBernardo, 2011); some of these treatments may pose an increased risk for adverse effects (Avram, 2004).

There remains an unmet medical need for safe and effective therapies to improve the aesthetic outcome in women with cellulite. To effectively treat cellulite, a therapeutic approach may require disruption of the dermal septa, which are composed of collagen and cause the skin dimpling that is bothersome to many women.

8.1.2. Collagenase Clostridium Histolyticum

EN3835 is currently approved (brand name XIAFLEX®) for: 1) the treatment of adults with Dupuytren's contracture with a palpable cord and, 2) for the treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30° at the start of therapy.

EN3835 is a parenteral lyophilized product comprised of 2 collagenases, isolated and purified from the fermentation of *Clostridium histolyticum,* in an approximate 1:1 mass ratio, Collagenase I (AUX-I, Clostridial class I collagenase) and Collagenase II (AUX-II; Clostridial class II collagenase). Collagenase AUX-I is a single polypeptide chain containing approximately 1,000 amino acids of known sequence and with a molecular weight of 114 kDa. Collagenase AUX-II is also approximately 1,000 amino acids long and has a molecular weight of 113 kDa.

These 2 collagenases are not immunologically cross-reactive and have different specificities, such that together they become synergistic, providing a very broad hydrolyzing reactivity toward collagen. Because these collagenases are proteinases that can hydrolyze the triple-helical region of collagen under physiological conditions, EN3835 has the potential to be effective in lysing subdermal collagen, such as those observed in the dermal septa, which are the underlying cause of the skin dimpling in women with EFP.

Endo Pharmaceuticals Inc. (Endo) learned that a much different concentration of the approved EN3835 formulation was needed to effectively target the collagenase structural matrix (eg, dermal septa) at the site of injection. In addition to this, the obvious physiological and pathological differences in the treatment areas for EFP (compared to approved indications), mandated the need to develop a new formulation of EN3835 to treat this condition. The diluent too had to be optimized so that the new formulation can be diluted more, yet offer greater stability with potentially less injection site adverse events (AE). Thus, Endo developed a new formulation of EN3835 for the treatment of EFP, and this new formulation is hereafter referred to as CCH.

A recent Phase 2b, randomized, double blind, placebo-controlled study (EN3835-201) of 375 women randomized to treatment of one treatment area (quadrant) (quadrant was defined in study EN3835-201 as a left buttock, a right buttock, a left posterolateral thigh or a right posterolateral thigh) of cellulite with CCH 0.84 mg or placebo in a 1:1 ratio assessed the effectiveness and safety of CCH. Efficacy in this study was evaluated based on cellulite assessments using Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS), Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS), Investigator Global Aesthetic Improvement Scale (GAIS-I), Subject Global Aesthetic Improvement Scale (GAIS-S), and Subject Satisfaction with Cellulite Treatment.

Results from the EN3835-201 study demonstrated that treatment (3 visits approximately 21 days apart) improved the cellulite severity of the treatment area as assessed by the primary endpoint of 2-level composite responder analyses, the proportion of responders based on an improvement of

≥ 2 levels in the appearance of cellulite in both the patient PR-PCSS and the clinician CR-PCSS of buttocks and thighs was statistically significantly greater in subjects who received EN3835 0.84 mg (10.6%; $p < 0.001$) compared to subjects who received placebo (1.6%); 1-level (or greater) responders in the PR-PCSS of CCH-treated subjects (72.3%) was significantly greater than 1-level responders in the placebo group (51.6%) ($p < 0.001$); statistically significant ($p \leq 0.001$) improvement in the appearance of cellulite based on the subject S-GAIS were observed in CCH 0.84-mg group (73.1%) compared to the placebo group (44.0%); and 62.9% of subjects in the CCH 0.84 mg group were satisfied or very satisfied with the results of their cellulite treatment compared with only 35.9% of subjects in the placebo group ($p < 0.001$).

The study also demonstrated CCH to be well tolerated with no serious adverse events (SAEs) related to CCH. Safety results from a total of 4 studies (1 pilot, 2 Phase 1, and 2 Phase 2 studies) in which 435 adult females received subcutaneous injections of CCH indicate that the majority of treatment-emergent adverse events (TEAEs) are transient, nonserious, mild or moderate in intensity, and related to the local administration of CCH. The immunogenicity profile after 3 treatments of CCH indicate that greater than 90% of CCH-treated subjects were seropositive for AUX-I and/or AUX-II antibodies; this profile of CCH is similar to that observed in the Dupuytren's contracture and Peyronie's disease programs.

No new safety signals have been seen in ongoing Phase 3 studies of CCH that have treated more than 400 subjects with EFP of the buttocks with 1.68 mg of CCH (0.84 mg per buttock).

A Phase 1, open label safety and pharmacokinetic study of a single dose of CCH 0.84 mg in 11 female subjects with EFP showed that there were no quantifiable levels of AUX-I or AUX-II at any time point after subcutaneous injection of 0.84 mg of study drug into one quadrant. A second Phase 1, open-label safety and pharmacokinetic study of a single dose of CCH 0.84 mg per treatment area in two treatment areas (buttock-buttock, thigh-thigh, or buttock-thigh) concurrently (total dose of 1.68 mg) showed that there were no quantifiable levels of AUX-I or AUX-II at any time point post-dose attributable to the injection of CCH 1.68 mg.

The results from these studies suggest that subcutaneous injections of CCH in the area of cellulite may be a well-tolerated and effective medical treatment for adults with EFP.

8.2. Summary of Nonclinical Studies

Nonclinical studies necessary to support clinical studies have been performed and are summarized in the Investigator Brochure (IB) (Endo, 2017). Nonclinical studies in the following areas were performed: toxicology, reprotoxicity, genotoxicity, and hypersensitivity.

8.3. Summary of Known Risks and Benefits

A summary of safety risks is provided in the IB (Endo, 2017). The following AEs have been commonly observed: local injection site reactions (including injection site bruising, injection site swelling, and injection site pain) for the various approved indications as well as those being investigated.

In the Phase 2b study of CCH in women with EFP, the following treatment related AEs were reported ≥ 2% of 189 CCH-treated female subjects: injection site bruising (75.1%), injection site pain (59.3%), injection site nodule (14.3%), injection site pruritus (11.1%), injection site swelling (7.4%), injection site induration (5.8%), injection site mass (5.3%), injection site

discoloration (3.2%), and injection site erythema (2.1%). These events are similar to events reported in the clinical trials of EN3835 for the approved indications.

Postmarketing safety data are consistent with safety data reported in clinical trials. AEs reported to date in ongoing Phase 3 trials of CCH for the treatment of EFP of the buttocks have not indicated any new safety signals.

8.4. Rationale

The results from the Phase 2b EFP study (EN3835-201) further suggested that CCH 0.84 mg per treatment area (quadrant) is an effective treatment of EFP based on improvement in the severity of cellulite as determined by the Investigator and the subject. There were no safety concerns following 0.84 mg per treatment area in the treatment of EFP. Safety findings from the Phase 2b EFP and ongoing Phase 3 studies are similar to that observed in previous clinical studies with CCH in the treatment of EFP and XIAFLEX in the treatment of Dupuytren's contracture and Peyronie's disease, in that the majority of AEs occurred at the site of injection and resolved before the next scheduled treatment. The immunogenicity profile of CCH in the Phase 2b EFP study is similar in previous studies and programs.

Input from published literature, as well as input from aesthetic medicine specialists, indicated a desire to investigate multiple injection/dosing techniques of CCH for EFP treatment and to examine the role 3-dimensional (3-D) imaging paradigms can play in visualizing the treatment effect of CCH on EFP.

This clinical study protocol will explore these different treatment and outcome assessment paradigm possibilities. Learnings from this study could assist both the sponsor and the aesthetic medicine community in designing future clinical studies.

9. OBJECTIVES

9.1. Primary Objective

The primary objective of this study is to assess the treatment effects of CCH when administered by different injection techniques in subjects with EFP.

9.2. Secondary Objective

The secondary objective of this study is to assess the safety of CCH when administered using different injection techniques in subjects with EFP.

9.3. Exploratory Objectives

The exploratory objectives of this study include:

- To assess the immunogenicity of CCH in the treatment of EFP.
- To assess the usefulness of 3-D photography in evaluating outcomes of treatment for EFP.

10. INVESTIGATIONAL PLAN

10.1. Study Design

This is a Phase 2a, open-label, multicenter, exploratory study to evaluate the safety and effectiveness of different injection techniques of CCH for the treatment of adult women with mild, moderate or severe EFP (as assessed by the investigator using the CR-PCSS).

Approximately 60 subjects will be enrolled, 30 with 2 eligible buttocks (to be dosed in the buttocks) and 30 with 2 eligible thighs (to be dosed in the thighs) at approximately 5 sites in the United States. No subjects will be treated for EFP in both the buttocks and the thighs. The 30 subjects in each treatment region (buttocks or thighs) will be assigned to 1 of 5 injection technique treatment arms on Day 1.

Subjects will participate in the study for approximately 92 days. Following a screening period of up to 21 days, subjects will participate in up to 3 treatment visits separated by 21 days (Days 1, 22, and 43). Following the first dose of study drug, subjects will return for assessments on Days 4, 8, 15, 22, 43 and 71.

The complete schedule of events is provided in Section 5.

10.2. Selection of Doses

The dosage of CCH chosen for this study is based on the experience from several earlier studies as well as ongoing Phase 3 clinical studies. The dose of 1.68 mg (0.84 mg per region) has been shown to be safe and well-tolerated.

10.3. Study Drug Administration

There are 5 treatment arms per region (buttocks or thigh) in this study with each arm representing a different injection technique as follows:

- Treatment I: Shallow Injection, 3 aliquots.
- Treatment II: Shallow injection, 1 aliquot.
- Treatment III: Deep injection, 1 aliquot.
- Treatment IV: Deep and shallow injections, 5 aliquots.
- Treatment V: Shallow injection, 4 aliquots.

Injection techniques differ from each other in, at least but not limited to, concentration of the CCH injectate, angle of injection, depth of injection, volume of injection and study drug administration at injection site.

Across all treatment arms, study drug will be administered subcutaneously while the subject is in a prone position. Each subject will receive 24 injections for a total dose of 1.68 mg (0.84 mg per treatment region) at each treatment visit. The cumulative CCH dose will be 5.04 mg for each subject that completes the 3 treatment visits.

The injection volume and concentration for each treatment arm are outlined in Table 1.

Table 1: Volume and Concentration of CCH Injections by Treatment Arm

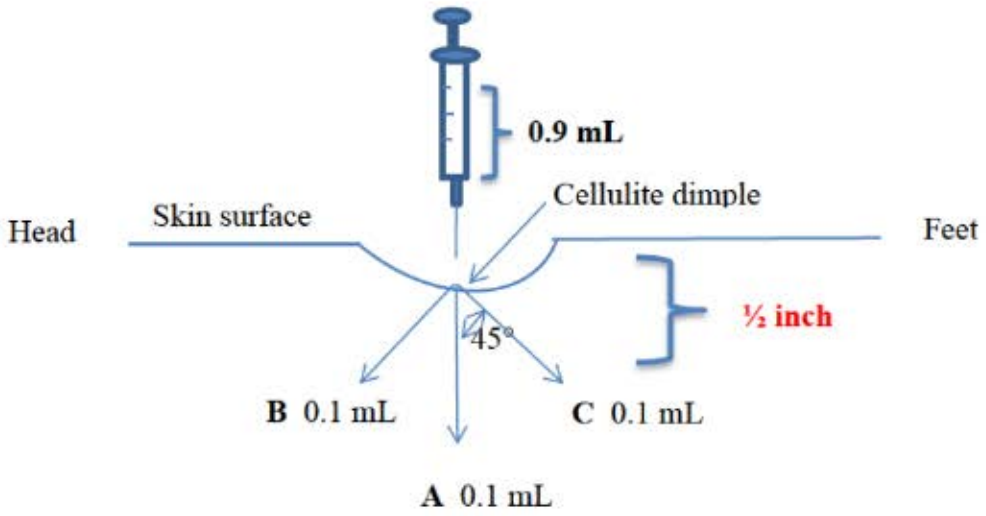
Treatment	Number of subjects/area	Dose/ injection	Volume/injection	Drug concentration/injection	Total volume/treatment visit
Treatment I: Shallow Injection, 3 aliquots	6 (buttocks) 6 (thighs)	0.07 mg	0.3 mL (given as 3- 0.1 mL aliquots)	0.23 mg/mL	7.2 mL (12 injections/ treatment area x 2 treatment areas x 0.3 mL)
Treatment II: Shallow injection, 1 aliquot	6 (buttocks) 6 (thighs)	0.07 mg	0.3 mL (given as 1- 0.3 mL aliquot)	0.23 mg/mL	7.2 mL (12 injections/ treatment area x 2 treatment areas x 0.3 mL)
Treatment III: Deep injection, 1 aliquot	6 (buttocks) 6 (thighs)	0.07 mg	0.3 mL (given as 1- 0.3 mL aliquot)	0.23 mg/mL	7.2 mL (12 injections/ treatment area x 2 treatment areas x 0.3 mL)
Treatment IV: Deep and shallow injections, 5 aliquots	6 (buttocks) 6 (thighs)	0.07 mg	1.5 mL (given as 5- 0.3 mL aliquots)	0.047 mg/mL	36 mL (12 injections/ treatment area x 2 treatment areas x 1.5 mL)
Treatment V: Shallow injection, 4 aliquots	6 (buttocks) 6 (thighs)	0.07 mg	1.2 mL (given as 4- 0.3 mL aliquots)	0.060 mg/mL	28.8 mL (12 injections/ treatment area x 2 treatment areas x 1.2 mL)

10.3.1. Treatment I: Shallow Injection, 3 Aliquots

In Treatment I, study drug will be injected subcutaneously using a 1 mL syringe with 0.1 mL gradients and a 30-gauge ½-inch needle, while the subject lies in a prone position. Each injection will consist of a single skin injection of study drug administered as three 0.1 mL aliquots to Positions A, B, and C (for a total injection volume of 0.3 mL) as shown in Figure 1. The depth of injection corresponds to the length of the treatment needle (1/2 inch) from the tip of needle to the hub or base of needle without downward pressure.

During each treatment visit, 8 syringes (4 syringes per treatment area) will be prepared for dosing. Each syringe will contain 0.9 mL of study drug (3 injections in each syringe).

Figure 1: Treatment I: Shallow Injection, 3 Aliquots



- With the needle positioned perpendicular to skin surface and perpendicular to the long axis of a dimple if the dimple is an elongated trough-like dimple (Position A), push the needle all the way in (1/2 inch) and inject 0.1 mL of study drug by gently pushing the syringe plunger. In most cases, the plane containing injection points A, B, and C will be parallel to the long axis of the subject's body.
- Withdraw the needle slightly and reposition it at an angle of approximately 45° to the skin surface and towards the subject's head (Position B), push the needle all way in and inject 0.1 mL of study drug by gently pushing the syringe plunger. Position B should always be towards the head of the subject.
- Withdraw the needle slightly and reposition it at an angle of approximately 45° to the skin surface and towards the subject's feet (Position C), push the needle all the way in and inject 0.1 mL of study drug by gently pushing the syringe plunger. Position C should always be towards the feet of the subject.
- Withdraw the needle completely from the injection site and proceed to next injection site.
- A syringe with 0.9 mL study drug will be sufficient for 3 injection sites.

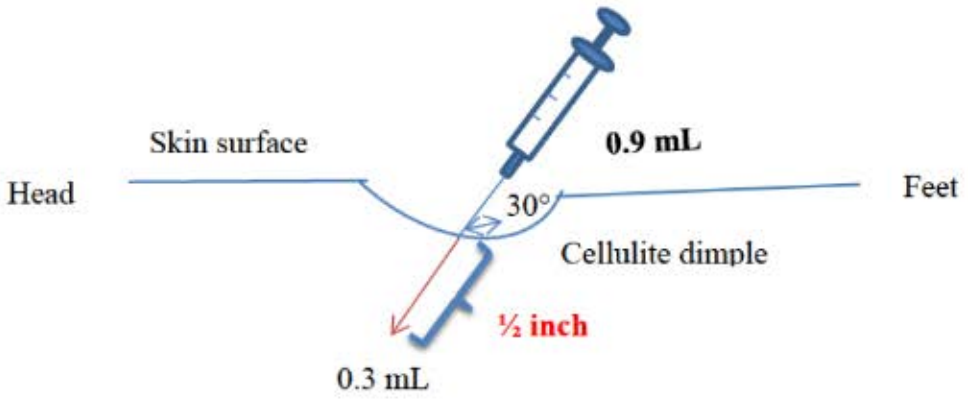
- Use four (4) 0.9 mL syringes in each treatment area (each buttock or each thigh) to administer a total of 12 injections of 0.3 mL (3 aliquots of 0.1 mL each) at 12 injection sites.
- Discard the used needles and syringes.
- A total of 24 injections will be administered across the 2 treatment areas (2 buttocks or 2 thighs) at each treatment visit.

10.3.2. Treatment II: Shallow Injection, 1 Aliquot

In Treatment II, study drug will be injected subcutaneously using a 1 mL syringe with 0.1 mL gradients and a 30-gauge ½-inch needle while the subject is in a prone position. Each injection will consist of a single skin injection of study drug administered as a single shallow injection of a 0.3 mL aliquot as shown in Figure 2. The depth of injection corresponds to the length of the treatment needle (1/2 inch) from the tip of needle to the hub or base of needle without downward pressure.

During each treatment visit, 8 syringes (4 syringes per treatment area) will be prepared for dosing. Each syringe will contain 0.9 mL of study drug (3 injections in each syringe).

Figure 2: Treatment II, Shallow Injection, 1 Aliquot



- With the needle positioned at approximately 30° to the skin surface at the injection site and directed towards subject's head, push the needle all the way in (1/2 inch) and inject 0.3 mL of study drug by gently pushing the syringe plunger.
- Withdraw the needle completely from the injection site and proceed to the next injection site.
- A syringe with 0.9 mL study drug will be sufficient for 3 injection sites.
- Use four (4) 0.9 mL syringes for each treatment area (each buttock or each thigh) to administer a total of 12 injections of 0.3 mL (3 aliquots of 0.1 mL each) at 12 injection sites.

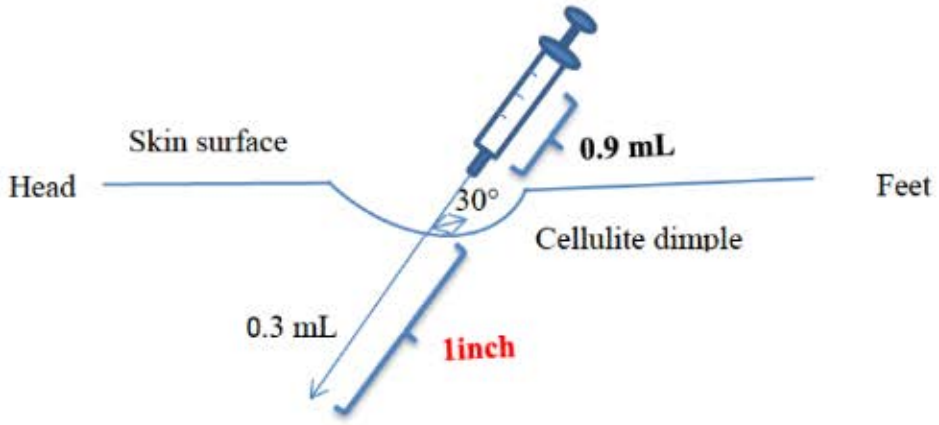
- Discard the used needles and syringes.
- A total of 24 injections will be administered across the 2 treatment areas (2 buttocks or 2 thighs) at each treatment visit.

10.3.3. Treatment III: Deep Injection, 1 Aliquot

In Treatment III, study drug will be injected subcutaneously using a 1 mL syringe with 0.1 mL gradients and a 30-gauge 1-inch needle, while the subject is in a prone position. Each injection will consist of a single skin injection of study drug administered as a single deep injection of a 0.3 mL study drug aliquot as shown in Figure 3. The depth of injection corresponds to the length of the treatment needle (1 inch) from the tip of needle to the hub or base of needle without downward pressure.

During each treatment visit, 8 syringes (4 syringes per treatment area) will be prepared for dosing. Each syringe will contain 0.9 mL of study drug (3 injections in each syringe).

Figure 3: Treatment III: Deep Injection, 1 Aliquot



- With the needle positioned at an angle of approximately 30° to the skin surface at the injection site and directed towards subject's head, push the needle all the way in (1 inch) and inject a single aliquot 0.3 mL of study drug by gently pushing the syringe plunger.
- Withdraw the needle completely from the injection site and proceed to the next injection site.
- A syringe with 0.9 mL study drug will be sufficient for 3 injection sites.
- Use four (4) 0.9 mL syringes in each treatment area (each buttock or each thigh) to administer a total of 12 injections of 0.3 mL (single 0.3 mL aliquots) at 12 injection sites.
- Discard the used needles and syringes.

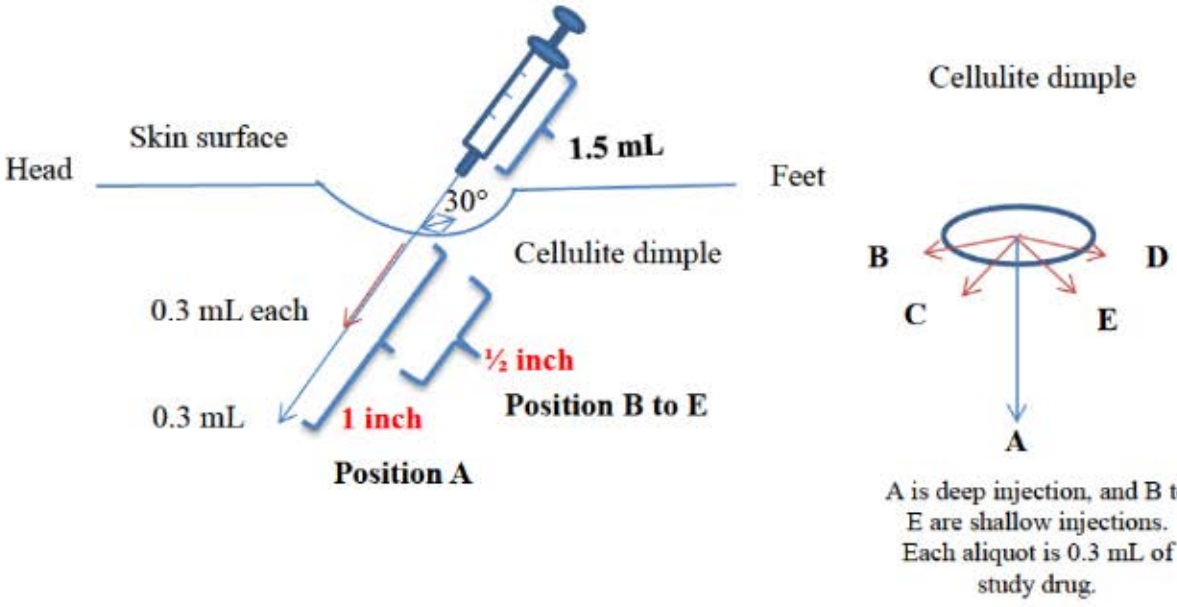
- A total of 24 injections will be administered across 2 treatment areas (2 buttocks or 2 thighs) at each treatment visit.

10.3.4. Treatment IV: Deep and Shallow Injections, 5 Aliquots

In Treatment IV, study drug will be injected subcutaneously using a 3 mL syringe with 0.1 mL gradients and a 30-gauge 1-inch needle, while the subject lies in a prone position. Each injection will consist of a single skin injection of study drug administered as five 0.3 mL aliquots to Position A, B, C, D and E (for a total injection volume of 1.5 mL) as shown in Figure 4. The depth of injection for Position A corresponds to the length of the treatment needle (1 inch) from the tip of needle to the hub or base of needle without downward pressure, and for the rest of the Positions (B to E), the length of the treatment needle corresponds from the tip of the needle to approximately one half (1/2 inch) of the needle length.

During each treatment visit, 24 syringes (12 syringes per treatment area) will be prepared for dosing. Each syringe will contain 1.5 mL of study drug (5 aliquots of 0.3 mL, for each injection, in each syringe).

Figure 4: Treatment IV: Deep and Shallow Injections, 5 Aliquots



- With the needle positioned at an angle of approximately 30° to the skin surface at the injection site and directed towards subject's head, push the needle all the way in (1 inch) and inject 0.3 mL of study drug by gently pushing the syringe plunger.
- Gently withdraw half the length of the needle (1/2 inch), maintaining the 30° angle of the needle to skin surface, and reposition it towards one side of the subject (Position B). Inject 0.3 mL study drug by gently pushing the syringe plunger.
- Maintain the 30° angle of the needle to the skin surface, reposition the needle to midway between Position A and B (Position C, towards subject's shoulder) and inject 0.3 mL of study drug by gently pushing the syringe plunger.

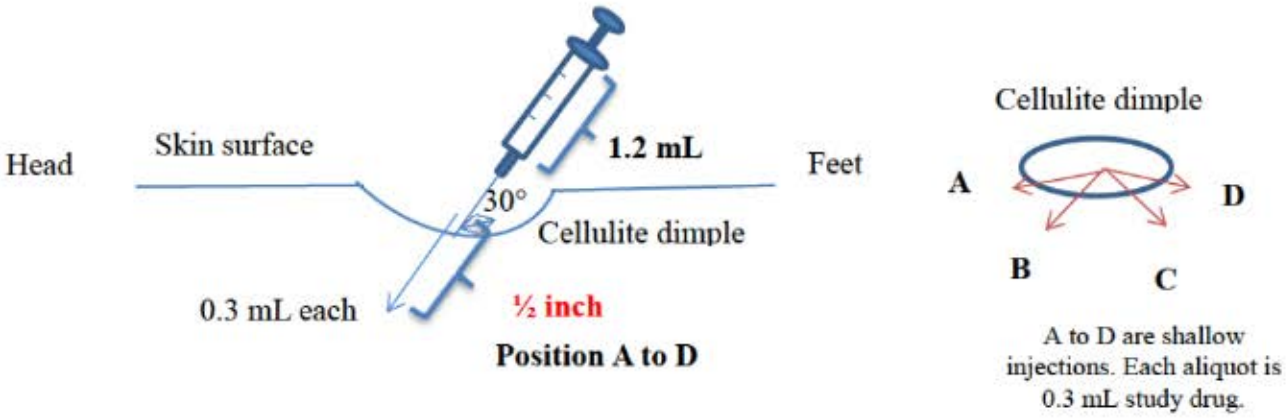
- Maintain the 30° angle of the needle to the skin surface, reposition the needle exactly opposite to Position B (Position D), and inject 0.3 mL of study drug by gently pushing the syringe plunger.
- Maintain the 30° angle of the needle to the skin surface, reposition the needle to midway between Position A and D (Position E, towards subject's other shoulder) and inject 0.3 mL of study drug by gently pushing the syringe plunger.
- A 3 mL syringe with 1.5 mL of study drug will be sufficient for one injection site.
- Use twelve (12) 3 mL syringes in each treatment area (each buttock or each thigh) to administer a total of 12 injections of 1.5 mL (total of 18.0 mL, 5 aliquots 0.3 mL each) at 12 injection sites.
- Discard the used needles and syringes.
- A total of 24 injections will be administered across the 2 treatment areas (2 buttocks or 2 thighs) at each treatment visit.

10.3.5. Treatment V: Shallow Injections, 4 Aliquots

Study drug will be injected subcutaneously using a 3 mL syringe with 0.1 mL gradients and a 30-gauge ½ -inch needle, while the subject lies in a prone position. Each injection will receive a single skin injection of study drug administered as four 0.3 mL aliquots to Position A, B, C and D (for a total injection volume of 1.2 mL) as shown in Figure 5. The depth of injection corresponds to the length of the treatment needle (1/2 inch) from the tip of the needle to the hub or base of the needle without downward pressure.

During each treatment visit, 24 syringes (12 syringes per treatment area) will be prepared for dosing. Each syringe will contain 1.2 mL of study drug (4 aliquots of 0.3 mL each).

Figure 5: Treatment V: Shallow Injections, 4 Aliquots



- With the needle positioned at an angle of approximately 30° to skin surface at the injection site and directed towards one side of the subject, push the needle all the way in (1/2 inch), and inject 0.3 mL of study drug by gently pushing the syringe plunger.

- Maintain the 30° angle of the needle to the skin surface, reposition the needle to approximately 60° from Position A and towards the subject's shoulder (Position B), and inject 0.3 mL of study drug by gently pushing the syringe plunger.
- Maintain the 30° angle of the needle to the skin surface, reposition the needle to approximately 60° from Position B and towards subjects other shoulder (Position C) and inject 0.3 mL of study drug by gently pushing the syringe plunger.
- Maintain the 30° angle of the needle to the skin surface, reposition the needle opposite to position A and towards other side of the subject (Position D) and inject 0.3 mL of study drug by gently pushing the syringe plunger.
- A 3 mL syringe with 1.2 mL of study drug will be sufficient for one injection site.
- Use twelve (12) 3 mL syringes (with 1.2 mL study drug in each) in each treatment area (each buttock or each thigh) to administer a total of 12 injections of 1.2 mL each (total of 14.4 mL, 4 aliquots of 0.3 mL each) at 12 injection sites.
- Discard the used needle sand syringes.
- A total of 24 injections will be administered across 2 treatment areas.

10.3.6. Care Procedures After Injection

NOTE: CCH is a foreign protein and Investigators should be prepared to address and manage an allergic reaction should it occur. At the time of each injection, a 1:1,000 solution of epinephrine for injection, 50-mg diphenhydramine injection or a suitable equivalent, and oxygen must be available with the Investigator and site staff must be familiar with their use. To evaluate the subject for possible immediate immunological AEs, the subject will remain in direct observation of medical personnel who are skilled in the management of an allergic reaction for 30 minutes after receiving the injections of study drug and until the subject exhibits no sign of an immunological or other clinically significant systemic or local AE. The subject's vital signs should be stable before the subject can leave direct observation.

The Investigator or qualified designee will then apply a sterile dressing to the injection areas with hypoallergenic tape. The subject will be instructed to remove the dressing in the evening.

10.4. Discussion of Study Design, Including the Choice of Control Groups

This is an exploratory study to assess the safety and treatment effect of different injection techniques of CCH for the treatment of EFP. The study will also explore the use of 3-D photography in assessing outcomes in EFP. No control groups will be employed.

11. SELECTION AND WITHDRAWAL OF SUBJECTS

11.1. Subject Inclusion Criteria

No subject will be assigned to treatment until all eligibility criteria have been satisfied. To qualify for the study a subject must:

1. Be able to provide voluntary written informed consent prior to the initiation of any study-specific procedures per the policy of the governing Institutional Review Board (IRB)/Independent Ethics Committee (IEC).
2. Be female and at least 18 years of age at the time of consent.
3. Have evidence of cellulite in 2 bilateral treatment areas (defined as right and left buttocks OR right and left posterolateral thighs) as assessed by the Investigator at the Screening visit, and fulfills the following requirements:
   a. has a score of 2 (mild), 3 (moderate) or 4 (severe) as reported by the Investigator (CR-PCSS) in 2 treatment areas (two thighs or two buttocks) at the Screening Visit.
   b. has at least 2 dimples from each treatment area that:
      - are isolated and separated by at least 5 cm from any other dimples.
      - score 2 or 3 on the Hexsel depression scale.
      - have dimple width: length ratio ≥ 0.5.
4. Be willing to apply sunscreen to the dosing areas before each exposure to the sun while participating in the study (ie, screening through end of study).
5. Be judged to be in good health, based upon the results of a medical history, physical examination, and laboratory profile at screening.
6. Have a negative serum pregnancy test at the Screening Visit and negative urine pregnancy at Day 1 (before injection of study drug), be using an effective contraception method (eg, abstinence, intrauterine device, hormonal [estrogen/progestin] contraceptives, or double barrier control) for at least 1 menstrual cycle prior to study enrollment and through Day 71 ; or be menopausal defined as at least 12 months of amenorrhea in the absence of other biological or physiological causes (as determined by the Investigator), or be postmenopausal for at least 1 year, or be surgically sterile (hysterectomy, bilateral oophorectomy, bilateral tubal ligation).
7. Be willing and able to comply with all protocol required study visits and assessments.

11.2. Subject Exclusion Criteria

A subject who meets any of the following criteria will be excluded from the study:

1. Is pregnant or is intending to become pregnant during the study.
2. Is presently nursing/breastfeeding or providing breast milk.
3. Has any of the following systemic conditions:
   a. Coagulation disorder.

b. Evidence or history of malignancy (other than excised basal-cell carcinoma) unless there has been no recurrence in at least 5 years.

c. History of keloidal scarring or abnormal wound healing.

d. Concurrent diseases or conditions that might interfere with the conduct of the study, confound the interpretation of the study results, or endanger the subject's well-being. Any questions about concurrent diseases should be discussed with the Medical Monitor.

e. Evidence of clinically significant abnormalities on physical examination, vital signs, electrocardiogram (ECG), or clinical laboratory values.

4. Has any of the following local conditions in the areas to be treated:

   a. History of lower extremity thrombosis or post-thrombosis syndrome.

   b. Vascular disorder (eg, varicose veins, telangiectasia).

   c. Inflammation or active infection.

   d. Severe skin laxity, flaccidity, and/or sagging.

   e. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer.

5. Has a tattoo located within 2 cm of the site of injection.

6. Requires anticoagulant or antiplatelet medication during the study or has received anticoagulant or antiplatelet medication (except for ≤ 150 mg aspirin daily) within 7 days before injection of study drug.

7. Has used any of the following for the treatment of EFP on the area to be treated within the timelines identified below or intends to use any of the following at any time during the course of the study:

   a. Liposuction within the treatment areas during the 12-month period before injection of study drug.

   b. Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; or surgery (including subcision and/or powered subcision) within the treatment areas during the 12-month period before injection of study drug.

   c. Any investigational treatment for EFP/cellulite on treatment areas during the 12-month period before the injection of study drug.

   d. Endermologie® or similar treatments within the treatment areas during the 6-month period before injection of study drug.

   e. Massage therapy within the treatment areas during the 3-month period before injection of study drug.

   f. Creams (eg, Celluvera™, TriLastin®) to prevent or mitigate EFP within the treatment areas during the 2-week period before injection of study drug.

8. Has received an investigational drug or treatment within 30 days before injection of study drug.

9. Has a known systemic allergy to collagenase or any other excipient of study drug.

10. Has a history of drug or alcohol abuse.
11. Intends to initiate an intensive sport or exercise program during the study.
12. Intends to initiate a weight reduction program during the study.
13. Intends to use tanning spray or tanning booths during the study.
14. Has previously received any collagenase treatments (eg, Santyl® ointment and/or XIAFLEX/XIAPEX®).
15. Was a subject in a previous cellulite clinical trial of CCH: AUX-CC-830, AUX-CC-831, EN3835-102, EN3835-104, EN3835-201, EN3835-202, EN3835-205, EN3835-302, or EN3835-303.
16. Has any other condition(s) that, in the Investigator's opinion, might indicate the subject is unsuitable for the study.

11.3. Subject Discontinuation Criteria

A premature discontinuation will occur when a subject who signed informed consent ceases treatment and/or participation in the study, regardless of circumstances, prior to the completion of the protocol. Subjects can be prematurely discontinued from the study for any of the following reasons:

- An adverse event.
- A protocol violation (reason must be specified, for example: lack of compliance with protocol required study visits/assessments, use of a prohibited concomitant medication, etc).
- Withdrawal by subject (reason must be specified).
- The subject was "lost to follow-up".
- Other reasons (reason must be specified, for example: the subject moved, pregnancy, investigator decision, Sponsor decision to terminate trial, etc).

Subjects who discontinue, or are withdrawn from study treatment for any reason, will be encouraged to complete the remaining study visits and assessments and provide any additional follow-up information as required by the study, unless the subject specifically indicates that they will not participate in any further evaluations. The date a subject discontinues from the treatment and/or study and the reason for discontinuation will be recorded in the source documentation and Electronic Case Report Form (eCRF).

11.3.1. Replacement Procedures

Subjects who discontinue from treatment and/or who discontinue from the study will not be replaced.

12. TREATMENT OF SUBJECTS

12.1. Study Visits

The Schedule of Events to be performed at each study visit is shown in Section 5. Provided below are further details where additional instruction about the assessments that will be performed is deemed to be needed.

12.1.1. Subject Screening

Investigators will be expected to maintain a Screening Log of all potential study subjects. This log will include limited information about the potential subject and the date and outcome of the screening process (eg, enrolled into the study, reason for ineligibility, or refused to participate). Investigators will provide information about the study to subjects who appear to meet the criteria for participation in the study.

12.1.2. Screening Assessments

After obtaining informed consent, the full assessment of eligibility will be conducted and prior to study entry, screening assessments will be performed according to the schedule of events in Section 5.

12.1.3. Demographic Data

The following demographic information will be required for study entry:

- Date of birth.
- Gender.
- Race and ethnicity.

12.1.4. Medical/Surgical/EFP History

During the screening period, the Investigator or qualified designee will obtain a medical and surgical history from each subject that includes relevant diagnoses and/or procedures/therapies with onset/resolutions dates. Medical histories should also include history of EFP (start date, family history, and prior treatment), and history of tobacco and alcohol use (never, current, former).

12.2. Prior and Concomitant Medications and Procedures

All prior medications taken within 90 days before Day 1 will be recorded. All medications (including over-the-counter medications) taken by the subject on Day 1 through the end of the study must be recorded. In addition, all prior treatments (medications or procedures) for EFP must be recorded.

Additionally, any diagnostic, therapeutic or surgical procedures performed during the study period should be recorded including the date, indication for, and description of the procedure.

12.2.1. Prohibited Medications and Procedures

The following medications and procedures are prohibited for subjects during the study:

- Anticoagulants (warfarin, heparin, direct thrombin inhibitors, Factor X inhibitors) and antiplatelet agents (aspirin > 150 mg/day and P2Y12 inhibitors, such as clopidogrel), which can cause additional bruising. However, the use of aspirin at a dose level of ≤ 150 mg per day will be permitted during study.
- Liposuction within the treatment areas.
- Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; or surgery (including subcision and/or powered subcision) in the treatment areas.
- Any investigational treatment for EFP/cellulite on treatment areas or any other investigational drug or treatment.
- Endermologie or similar treatments within the treatment areas.
- Massage therapy within the treatment areas during the 3-month period before injection of study drug.
- Creams (eg, Celluvera, TriLastin) within the treatment areas.

12.3. Treatment Compliance

Subjects will receive study drug administered by the Investigator at the Investigator's site. Accidental or intentional overdoses should be reported to the Sponsor/designee promptly.

12.4. Blinding and Randomization

This study will be conducted as an open-label investigation; no blinding of assigned treatment will occur. Subjects will be sequentially assigned to Treatment Arms A to E at Day 1.

12.5. Selecting and Marking Dimples

If all 4 quadrants (both buttocks and both thighs) meet entry criteria for a single subject, the thighs will be treated. No subject will have treatment in all 4 quadrants (both buttocks and both thighs) during this study.

Selection of dimples to be treated in the treatment areas (both buttocks or both thighs) is at the discretion of the investigator. Dimples must be well defined, evident when the subject is standing in a consistent, standardized relaxed pose (without the use of any manipulation such as skin pinching or muscle contraction), and suitable for treatment. Each subject will receive 3 treatment visits of study drug unless the treatment area is dimple-free at Day 22 and/or Day 43. A dimple-free buttock or thigh at Day1 is precluded by the eligibility criteria. A dimple-free buttock or thigh at Day 22 and/or Day 43 does not preclude treatment of the contralateral buttock or thigh unless it is also dimple-free.

Detailed instructions for the marking and imaging of dimples will be provided in the 3-D Photography Manual.

12.6. CR-PCSS

The CR-PCSS - Buttock (Appendix A) and the CR-PCSS - Thigh (Appendix B) will be used to assess the severity of cellulite of both treatment areas at Screening (each buttock or each thigh independently). The scale is a 5-level photonumeric scale developed specifically for clinicians and used by the Investigator to assess the severity of the subject's cellulite in each buttock or thigh by live assessments. The ratings range from 0 (None) to 4 (Severe) with labels and descriptors to aid the Investigator in the assessments. This assessment should be made while the subject is in the standing position with relaxed gluteus muscles.

Investigators will be trained and qualified on the use of the CR-PCSS prior to assessing any subjects.

13. ASSESSMENT OF EFFICACY

13.1. 3-D Photography

Although 3-D photographs are not direct efficacy measurements, 3-D photography will be utilized in the assessment of treatment effect. The Investigator or qualified designee will photograph each treatment area (each buttock or each thigh) using a Sponsor-supplied standardized 3-D camera in a standardized manner. The subject will be standing for each photography session and will be wearing a standardized photographic garment as described in the 3-D Photography Manual. The Investigator or qualified designee will photograph each of the 2 treatment areas (2 buttocks or 2 thighs) while the subject is standing in a consistent, standardized relaxed pose.

On each treatment day (Day 1, Day 22, and Day 43), 3-D photographs will be taken before and after marking dimples and injection sites. At screening and all other study visit days, a single set of photographs will be taken. 3-D photographs will be taken prior to prior to study drug dosing.

For 3-D photographic images taken on Days 4, 8, 15, 22, 43, and 71, a central assessor blinded to the treatment arm and study visit day will complete a 5-point Likert scale to gauge the level of aesthetic improvement achieved (from baseline) in each treatment area.

All de-identified photographs from this study are the property of Endo and may be utilized for clinical development, scientific communication, marketing, regulatory purposes, and/or legal applications as required/desired by Endo.

13.2. Hexsel Depression Depth Scale

The Hexsel Cellulite Severity Scale (Hexsel CSS) is a photonumeric scale that looks at 5 key morphologic features of cellulite: (A) number of evident depressions, (B) depth of depressions, (C) morphological appearance of skin surface alterations, (D) laxity, flaccidity or sagging of skin, and (E) current classification scale based on medical literature (Hexsel et al, 2009; Nürnberger and Müller, 1978). Each of these features is evaluated on a 4-point scale from a low of 0 to a high of 3. For this study, only (B) depth of depressions will be assessed.

The Investigator or qualified designee will independently use the Hexsel CSS (B) depth of depressions in assess the severity of EFP in each buttock or each thigh (see Appendix C). This

assessment should be made while the subject is in the standing position with relaxed gluteus muscles.

14. ASSESSMENT OF SAFETY

14.1. Definitions

14.1.1. Adverse Events

An AE is any unfavorable or unintended change in body structure (signs), body function (symptoms), laboratory result (eg, chemistry, ECG, X-ray, etc), or worsening of a pre-existing condition associated temporally with the use of the study medication whether or not considered related to the study medication. Adverse events will be captured once a subject has signed the informed consent. AEs include:

- Changes in the general condition of the subject
- Subjective symptoms offered by or elicited from the subject
- Objective signs observed by the Investigator or other study personnel
- All concurrent diseases that occur after the start of the study, including any change in severity or frequency of pre-existing disease
- All clinically relevant laboratory abnormalities or physical findings that occur during the study

A treatment-emergent AE (TEAE) is any condition that was not present prior to treatment with study medication but appeared following treatment, was present at treatment initiation but worsened during treatment, or was present at treatment initiation but resolved and then reappeared while the individual was on treatment (regardless of the intensity of the AE when the treatment was initiated).

All AEs, including both observed or volunteered problems, complaints, signs or symptoms must be recorded on the AE page of the eCRF, regardless of whether associated with the use of study medication. This would include AEs resulting from concurrent illness, reactions to concurrent medication use, or progression of disease states (excluding the disease under study). A condition present at baseline that worsens after initiation of study treatment will be captured as an AE; the onset date will be the date the event worsened. The AE should be recorded in standard medical terminology when possible.

14.1.2. Serious Adverse Events

A serious adverse event (SAE) is defined as an AE that:

- Results in death
- Is immediately life-threatening (there is an immediate risk of death from the AE as it occurred; this does not include an AE that had it occurred in a more serious form may have caused death)

- Results in or prolongs an inpatient hospitalization (Note: a hospitalization for elective or pre-planned surgery, procedure, or drug therapy does not constitute an SAE)
- Results in permanent or substantial disability (permanent or substantial disruption of one's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect (in offspring of a subject using the study medication regardless of time to diagnosis)
- Is considered an important medical event

Important medical events are defined as events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the other serious outcomes. Examples of important medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

14.2. Monitoring Adverse Events

At each study visit, subjects will be queried regarding any AEs that have occurred since the last study visit. Subjects will be asked to volunteer information concerning AEs with a non-leading question such as, "How do you feel?" Study center personnel will then record all pertinent information in the source documents and the eCRF. The study drug compliance record should also be reviewed to detect potential overdoses (intentional/unintentional).

14.3. Relationship to Study Drug

The degree of "relatedness" of the AE to the study medication must be described using the following scale:

- **Not related** indicates that the AE is definitely not related to the study medication.
- **Unlikely related** indicates that there are other, more likely causes and study medication is not suspected as a cause.
- **Possibly related** indicates that a direct cause and effect relationship between study medication and the AE has not been demonstrated, but there is evidence to suggest there is a reasonable possibility that the event was caused by the study medication.
- **Probably related** indicates that there is evidence suggesting a direct cause and effect relationship between the AE and the study medication.

It is the Sponsor's policy to consider "Probably related" and "Possibly related" causality assessments as positive causality. "Not related" and "Unlikely related" causality assessments are considered as negative causality.

Assessments will be recorded on the eCRF and must indicate clearly the relationship being assessed. For example, an AE that appears during a placebo run-in phase would be assessed with respect to the placebo treatment received and/or study procedures conducted during this phase. If the AE continued into an active treatment phase, the relationship would be assessed for the active treatment phase only if the AE worsened.

14.4. Intensity Assessment

The intensity (or severity) of AEs is characterized as mild, moderate, or severe:

- **Mild** AEs are usually transient, requiring no special treatment, and do not interfere with the subject's daily activities.
- **Moderate** AEs introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.
- **Severe** AEs interrupt a subject's usual daily activity and typically require systemic drug therapy or other treatment.

14.5. Reporting Adverse Events and Serious Adverse Events

14.5.1. Reporting Adverse Events

Throughout the study, AEs will be documented on the source document and on the appropriate page of the eCRF whether or not considered treatment-related. This includes any new signs, symptoms, injury or illness, including increased severity of previously existing signs, symptoms, injury, or illness. Conditions existing prior to screening will be recorded as part of the subject's medical history. The Investigator is responsible for assessing the relationship of AEs to the study medication; relationship will be classified as not related, unlikely related, possibly related, or probably related.

All AEs will be collected by the Investigator from the time of signing the informed consent through 28 days after the last dose of study medication; this includes any AEs that are ongoing at the time of completion/termination of the study. All ongoing AEs must be followed until resolution or for 28 days after the subject's last study visit, whichever comes first.

14.5.2. Reporting Serious Adverse Events

Any SAE, including death resulting from any cause, which occurs to any subject participating in this study, must be reported via email or fax by the Investigator using the Endo Serious Adverse Event (SAE)/Reportable Event Form within 24 hours of first becoming aware of the SAE. SAEs will be collected by the Investigator from the time of signing the informed consent through 28 days after the last dose of study medication. SAEs that occur within 28 days, following cessation of the study treatment, or within 28 days, following premature discontinuation from the study for any reason, must also be reported within the same timeframe. Any SAE that is felt by the Investigator to be related to the study medication must be reported regardless of the amount of time since the last dose received. Follow-up information collected for any initial report of an SAE must also be reported to the Sponsor within 24 hours of receipt by the Investigator.

All SAEs will be followed until resolution, stabilization of condition, or until follow-up is no longer possible.

In the event discussion is necessary regarding treatment of a subject, call the Medical Monitor (see contact information in Section 3).

All SAEs should be sent via the email address, or faxed to the fax number, provided in Section 3.

The Sponsor will determine whether the SAE must be reported within 7 or 15 days to regulatory authorities in compliance with local and regional law. If so, the Sponsor (or the Sponsor's representative) will report the event to the appropriate regulatory authorities. The Investigator will report SAEs to the IRB per their IRB policy.

14.5.2.1. Follow-Up Procedures for Serious Adverse Events

To fully understand the nature of any SAE, obtaining follow-up information is important. Whenever possible, relevant medical records such as discharge summaries, medical consultations, and the like should be obtained. In the event of death, regardless of cause, all attempts should be made to obtain the death certificate and any autopsy report. These records should be reviewed in detail, and the Investigator should comment on any event, lab abnormality, or any other finding, noting whether it should be considered a serious or non-serious AE, or whether it should be considered as part of the subject's history. In addition, all events or other findings determined to be SAEs should be identified on the follow-up SAE form and the Investigator should consider whether the event is related or not related to study drug. All events determined to be nonserious should be reported on the eCRF.

14.6. Special Reporting Situations

14.6.1. Adverse Events of Special Interest

Adverse events such as bruising, ecchymosis, hematomas, and contusions that occur remote to the site of drug administration, or any hypersensitivity reactions, including anaphylaxis, will be recorded and evaluated for seriousness and severity.

In addition, local AEs associated with the injection site, including bruising, pain, nodules/mass, ulceration, erythema, pruritus, swelling, and/or induration, will be recorded and evaluated for seriousness and severity.

14.6.2. Overdose/Misuse/Abuse

14.6.2.1. Overdose

Study drug overdose is any accidental or intentional use of study drug in an amount higher than the dose indicated by the protocol for that subject. Study drug compliance should be reviewed to detect potential instances of overdose (intentional or accidental).

Any study drug overdose during the study will be recorded.

An overdose is not an AE per se, however all AEs associated with an overdose should both be entered on the Adverse Event eCRF and reported using the procedures detailed previously, even if the events do not meet seriousness criteria. If the AE associated with an overdose does not meet seriousness criteria, it must still be reported using the Endo Serious Adverse Event (SAE)/ Reportable Event Form and in an expedited manner, but should be noted as nonserious on the form and the Adverse Event eCRF.

14.6.2.2. Misuse/Abuse

Not applicable.

14.6.3. Pregnancy

Any uncomplicated pregnancy that occurs in a subject during this clinical study will be **reported for tracking purposes only**. All subject pregnancies that are identified during or after this study, where the estimated date of conception is determined to have occurred during study drug therapy or within 28 days of the last dose of study drug need to be reported, followed to conclusion, and the outcome reported, even if the subject is discontinued from the study. The investigator should report all pregnancies within 24 hours using the Initial Pregnancy Report Form, and any pregnancy-associated SAE using the Serious Adverse Event (SAE)/Reportable Event Form, according to the usual timelines and directions for SAE reporting. Monitoring of the pregnancy should continue until conclusion of the pregnancy and 1 or more Follow-up Pregnancy Report Form(s) detailing progress, and a Two Month Follow-up Pregnancy Report Form detailing the outcome, should be submitted.

Pregnancy itself is not regarded as an AE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not considered AEs. Any SAEs associated with pregnancy (eg, congenital abnormalities/birth defects/spontaneous miscarriages or any other serious events) must additionally be reported as such using the Serious Adverse Event (SAE)/Reportable Event Form. Spontaneous miscarriages should also be reported and handled as SAEs.

Subjects should be instructed to immediately notify the investigator of any pregnancies. A subject who becomes pregnant must be immediately withdrawn from the study. Attempts to obtain the pregnancy follow-up and pregnancy outcome information detailed above are necessary, even if a subject discontinues treatment because of pregnancy

14.6.4. AEs/SAEs Experienced by Nonsubjects Exposed to Study Medication

Nonsubjects are persons who are not enrolled in the study but have been exposed to study medication, including instances of diversion of study medication. All such AEs/SAEs occurring in nonsubjects from such exposure will be reported to the Endo PVRM Department (when the nonsubject agrees) on the Serious Adverse Event (SAE)/Reportable Event Form regardless of whether the event is serious or not. Instructions for completing the form for events experienced by nonsubjects will be provided. SAEs occurring in nonsubjects exposed to study medication will be processed within the same SAE reporting timelines as described in Section 14.5.2, Reporting Serious Adverse Events. Additionally, the drug accountability source documentation at the center should reflect this occurrence.

14.7. Clinical Laboratory Tests

Clinical laboratory tests will be conducted according to the Schedule of Events (Section 5). Clinical laboratory tests will be performed by a designated central laboratory. Each site will be provided with instructions on specimen collection, preparation, packaging and transport. Refer to the central laboratory manual for further information regarding sample collection, handling, and labeling. The results of the tests will be returned to the investigational sites.

Clinical laboratory test data will be reviewed by the investigator, or designee, and additional clinical laboratory tests may be ordered at his/her discretion (eg, if the results of any clinical laboratory test falls outside the reference range or clinical symptoms necessitate additional testing to ensure safety). Any additional testing will be performed by the designated central laboratory, unless use of a local laboratory is necessary to protect the safety of the subject.

The clinical laboratory parameters that will be measured in this study are listed in Table 2.

Table 2: Clinical Laboratory Tests

Hematology	Biochemistry	Urinalysis
Hemoglobin	Glucose	Glucose
Hematocrit	Sodium	Protein
Red blood cell	Potassium	Specific gravity
White blood cell (WBC)	Calcium	pH
Platelets	Chloride	Ketones
WBC Differential	CO_2	Bilirubin
	Inorganic phosphate	Urobilinogen
	Blood urea nitrogen	Nitrite
	Creatinine	Blood*
	Creatinine clearance	Leukocytes*
	Aspartate transaminase (AST)	
	Alanine transaminase (ALT)	
	Gamma-glutamyl transferase (GGT)	
	Total bilirubin (TBL) (direct bilirubin reflex if elevated)	
	Albumin	
	Alkaline phosphatase (ALP)	
	Uric acid	

* Microscopic examination will be performed if blood or leukocytes are detected by dipstick.

For women of childbearing potential, a serum pregnancy test will be performed at the Screening Visit and urine pregnancy tests will be performed as outlined in the Schedule of Events. Female subjects of childbearing potential must have a negative pregnancy test at the Screening and Day 1 Visits to be enrolled in the study, and prior to any other dosing with study medication. If necessary, additional urine pregnancy tests can be performed at any time during the study at the discretion of the Investigator. Urine pregnancy test kits will be supplied by the Sponsor.

14.8. Anti-AUX-I and Anti-AUX-II Antibodies

Serum samples will be collected before injection on Day1 and at the Day 71 visit and will be tested for binding anti-AUX-I and anti-AUX-II antibody and anti-AUX-I and anti-AUX-II neutralizing antibodies.

The serum samples obtained will be processed, stored and then shipped on dry ice to the designated central clinical laboratory according to the instructions in the laboratory manual.

14.9. Vital Signs

Vital sign measurements will be documented as described in the Schedule of Events. These parameters include pulse rate, respiratory rate, systolic and diastolic blood pressure, and body temperature. Pulse and blood pressure readings will be taken after the subject has been sitting for 5 minutes.

The investigator will review all vital sign values for clinical significance. Any vital sign value meeting the investigator's criteria for clinical significance will be recorded as an AE or SAE as appropriate.

14.10. Electrocardiogram

A 12-lead ECG recording will be conducted at the Screening Visit. The subject should be in a supine position for at least 5 minutes before the recording is conducted. Lead position will be that of a standard 12-lead ECG; no additional or special lead placements will be necessary.

A qualified physician will interpret, sign, and date the ECGs. ECG findings will be documented as normal; abnormal, clinically significant; or abnormal, not clinically significant. The Investigator or qualified designee must sign and date the ECG, thereby acknowledging review of ECG results. ECG assessments must be "within normal limits" or interpreted as "abnormal, not clinically significant" for the subject to be included in the study.

Any ECG result meeting the Investigator's or Sponsor's criteria for clinical significance will be recorded as an AE or SAE as appropriate.

14.11. Physical Examination

All physical examinations will be performed by a physician or health professional listed on the Form FDA 1572 and licensed to perform physical examinations. Height and body weight will be measured and recorded at the times outlined in the Schedule of Events.

The Investigator will review all physical exam findings for clinical significance. Any physical exam finding meeting the Investigator's or Sponsor's criteria for clinical significance will be recorded as an AE or SAE as appropriate.

14.12. Fitzpatrick Scale

At screening, the Investigator will also assess the subject's skin type using the Fitzpatrick scale (Table 3). Only the Fitzpatrick Scale shown below may be used during the study.

Table 3: Fitzpatrick Scale

I	Pale white skin, blue/hazel eyes, blond/red hair	Always burns, does not tan
II	Fair skin, blue eyes	Burns easily, tans poorly
III	Darker white skin	Tans after initial burn
IV	Light brown skin	Burns minimally, tans easily
V	Brown skin	Rarely burns, tans darkly easily
VI	Dark brown or black skin	Never burns, always tans darkly

14.13. Other Safety Assessments

Not applicable.

15. ASSESSMENT OF PHARMACOKINETICS

Not applicable.

16. ASSESSMENT OF PHARMACODYNAMICS

Not applicable.

17. STATISTICAL CONSIDERATIONS AND METHODS

17.1. Determination of Sample Size

No sample size estimation was done for this study.

17.2. Analysis Populations

Two populations are considered in the statistical analysis of the study.

17.2.1. Safety Population

The Safety Population will include all subjects who receive at least 1injection of study drug. All safety analyses will be based on this population.

17.2.2. Evaluable Population

The Evaluable Population will include all subjects in the Safety Population who have completed screening procedures and at least 1 post baseline assessment of the Likert Scale score of aesthetic appearance improvement. All efficacy analysis will be based on this population.

17.3. Subject Disposition

The number of subjects included in each study population will be summarized by treatment arm. Subjects excluded from the Safety and Evaluable Populations will be listed by treatment arm.

The number and percentage of subjects completed and prematurely discontinued during the study will be presented for each treatment arm. Reasons for premature discontinuation from the treatment period as recorded on the termination page of the eCRF will be summarized (number and percentage) by treatment arm for all subjects.

The percentage of premature discontinuations due to AEs will be tabulated and compared between treatment arms.

17.4. Demographics and Other Baseline Characteristics

Demographic and other baseline characteristics (including gender, age, race, height, weight, medical and EFP history) will be summarized by treatment arm, using descriptive statistics. The descriptive summaries will include frequency tables for all categorical response variables and number, mean, standard deviation, minimum, and maximum for all continuous variables.

17.5. Efficacy Analyses

The efficacy endpoints for this study will include:

- Change from baseline in the blinded assessor's Likert Scale score of aesthetic appearance in each treatment area (buttocks or thighs) at Days 22, 43, and 71 by each treatment arm.
- Change from baseline in dimple depth and volume in each treatment area (buttocks or thighs) Days 22, 43, and 71 by treatment arm.
- Change from baseline in the Hexsel CSS (B) depression depth scale at Days 22, 43, and 71 by treatment arm.

The central assessor Likert Scale score of aesthetic appearance improvement from baseline in the 3-D photographic image, change from baseline in the Hexsel CSS (B) depression depth scale, and change from baseline in dimple volume and depth will be summarized by treatment arm and study visit using appropriate descriptive statistics. In addition, a linear mixed model will be utilized to fit change from baseline of each endpoint with treatment arm, cellulite dimples, and study visit as fixed effects, subject as random effect, and assessments across study visits as repeated measure. The fixed effect estimates and the corresponding 95% confidence intervals will be presented for each endpoint.

17.6. Safety Analyses

The safety parameters for this study will include:

- AEs.
- Vital signs.
- Clinical laboratory parameters.

AEs will be summarized by proportion of subjects experiencing each event and by treatment arm. Descriptive statistics will be presented for actual and change from baseline at each study visit for vital signs and clinical laboratory test results by treatment arm.

The parameters for immunogenicity of CCH in this study include:

- Anti-AUX-I/anti-AUX-II antibody levels.
- Neutralizing antibodies to AUX-I and AUX-II.

17.6.1. Prior, Concomitant, and Follow-up Medication

The World Health Organization (WHO) Drug Dictionary will be used to classify prior and concomitant medications by therapeutic class. Prior medication will be defined as any medication taken prior to the first dose of study drug. Concomitant medication is defined as any medication taken between the date of first dose of study drug and the date of last dose of study drug. Any medications started after the last dose of study drug will be considered as follow-up medications.

Prior, concomitant and follow-up medication use will be summarized descriptively by the number and percentage of subjects in for each preferred term (generic name from WHO dictionary) by treatment arm. Multiple use of the same medication by a subject will be counted only once.

17.6.2. Study Drug Exposure

The following information regarding treatment will be summarized per each treatment area (each buttock or each thigh) by treatment arm:

- Total number of treatment visits.
- Number of subjects who had treatment session done or treatment session not done at each treatment visit.
- For subjects who had the treatment session done, the number of subjects who got all required injections per protocol at the treatment visit or who received less than the required injections per protocol.
- Number of injections given at each treatment visit.
- Number of dimples treated at each treatment visit.
- Average number of injections per dimple at each treatment visit.

Subjects who did not receive all 3 treatment visits and who did not receive the required injections per protocol at a treatment visit will be listed.

17.6.3. Measurement of Treatment Compliance

Not applicable as study drug is administered at the center by the investigator.

17.6.4. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code AEs.

An AE (classified by preferred term) that started on or after the date of the first dose of the study drug will be considered a TEAE if it was not present prior to the first dose of study drug, or was present prior to the first dose of study drug but increased in intensity during the treatment period. If more than 1 AE is reported prior to the first dose of study drug and coded to the same

preferred term, then the AE with the greatest intensity will be used as the benchmark for comparison to the AEs occurring during the treatment period which were also coded to that preferred term. Any AE present prior to the first dose of study drug that increases in intensity during the treatment period will be re-entered with a new start date of the date of increased intensity.

Descriptive statistics (the number and percentage) for subjects reporting TEAEs in each treatment arm will be tabulated by system organ class and preferred term; by system organ class, preferred term, and severity; and by system organ class, preferred term, and relationship to study drug. If more than 1 AE is coded to the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to the study drug.

Listings will be presented for subjects with SAEs, subjects with AEs leading to discontinuation of study or study drug, and subjects who die (if any).

17.6.5. Vital Signs

Descriptive statistics for vital signs and their changes from baseline at each study visit and at the end of study will be presented by treatment arm.

17.6.6. Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values in International System of Units and changes from baseline at each assessment time point will be presented by treatment arm for each clinical laboratory parameter.

17.6.7. Physical Examination

Body weight and change from baseline will be presented by treatment arm.

17.6.8. Anti-AUX-I and Anti-AUX-II Antibodies

Anti-AUX-I and anti-AUX-II antibody levels and a subset of subject Anti-AUX-I and anti-AUX-II neutralizing antibodies will be summarized using appropriate descriptive statistics.

17.6.9. Other Safety Measurements

Not applicable.

17.7. Pharmacokinetic Analyses

Not applicable.

17.8. Pharmacodynamic Analyses

Not applicable.

17.9. Other Data (eg, Health Economics/QOL, Pharmacogenetic, etc)

Not applicable.

17.10. Interim Analysis

No interim analysis is planned for this study.

17.11. Statistical Software

Statistical analyses will be performed using Version 9.3 (or higher) of SAS® (SAS Institute, Cary, NC).

18. STUDY DRUG MATERIALS AND MANAGEMENT

18.1. Study Drug Identity

CCH is manufactured and supplied by Endo.

CCH is a sterile lyophilized powder consisting of 0.92 mg of collagenase clostridium histolyticum, 18.9 mg sucrose, 1.1 mg Tris, 37.7 mg mannitol, and hydrochloric acid qs to pH 8.5.

CCH sterile diluent for reconstitution is 0.6% sodium chloride and 0.03% calcium chloride dehydrate in water for injection.

18.2. Study Drug Packaging and Labeling

Each vial of study drug and diluent will minimally be labeled with contents, Sponsor identification, storage, administration/use, and appropriate cautions statements. Study drug vials and diluent vials will be packaged 10 vials per carton.

18.3. Study Drug Storage

All study drug will be provided by Endo. Study drug must be stored in an appropriate, secure area. Study drug must be kept in a temperature-monitored refrigerator (2°C-8°C) with locked access until used or returned to Endo.

18.4. Study Drug Preparation

Refer to the Reconstitution Instructions for detailed preparation instructions to be used for each arm.

For each dose session the Interactive Response Technology (IRT) will assign the appropriate number of drug and diluent vials required based on the arm being dosed.

Used drug/diluent vials should be stored in a secure location until reconciled and returned by the monitor. Dispose of used needles and syringes per local regulations.

The reconstituted study drug solution should be administered as soon as possible after reconstitution. The study drug solution can be kept at room temperature for up to 4 hours following the start of the reconstitution process. If more time is needed prior to injection, refrigerate the reconstituted drug vial/syringe for up to 24 hours. Remove drug/prepared syringes from the refrigerator and allow it to stand at room temperature for 15 minutes prior to injection of study drug.

18.5. Study Drug Accountability

A drug inventory form must be kept current by the center staff designated to be responsible for reconstitution and must be made available to the clinical monitor, Endo employees, IRB/IEC, and regulatory agencies for routine inspection and accountability during monitoring visits. When instructed by Endo, the Investigator agrees to return all original used or unused study drug vials to Endo's return vendor.

18.5.1. Study Drug Handling and Disposal

The Investigator agrees not to supply study drug to any person except to those subjects enrolled in the study. The Investigator is responsible for recording the receipt and use of all drugs supplied and for ensuring the supervision of the storage and allocation of these supplies. All used and unused study drug will be returned, and unit counts will be performed whenever medication is returned. The center must account for all study drug received and its use. At the end of the study, all used and unused drug will be returned to Endo's return vendor.

19. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

19.1. Source Documents

Source documents include but are not limited to original documents, data and records such as hospital/ medical records (including electronic health records), clinic charts, lab results, subject diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, etc. This study allows for direct data entry of CR-PCSS only.

19.2. Study Monitoring

A representative of Endo will meet with the Investigator and his/her staff prior to the entrance of the first subject to review study procedures and methods of recording findings in the eCRF.

After enrollment of the first subject, an Endo representative will be assigned to periodically monitor each Investigator center for study progress and to verify that standards of Good Clinical Practice (GCP) were followed. The Investigator is expected to prepare for the monitor visit, ensuring that all source documents, completed eCRFs, signed consent forms and other study related documents are readily available for review.

19.3. Audits and Inspections

The Investigator shall permit audits and inspections by the Sponsor, its representatives and members of regulatory agencies. The investigator should immediately notify the Sponsor of an upcoming FDA or other regulatory agency inspection.

19.4. Institutional Review Board (IRB)

The Investigator shall permit members of the IRB/IEC to have direct access to source documents.

19.5. Data Recording and Documentation

All data recordings and source documentation (including electronic health records) must be made available to the Sponsor (or designee), FDA and any other regulatory agencies that request access to study records, including source documents, for inspection and copying, in keeping with federal and local regulations.

20. QUALITY CONTROL AND QUALITY ASSURANCE

Steps to assure the accuracy and reliability of data include the selection of qualified principal investigators and appropriate study centers, review of protocol procedures with the principal investigators and associated personnel prior to start of the study, and periodic monitoring visits conducted by the Sponsor or Sponsor representative. Significant and/or repeated non-compliance will be investigated and remedial action instituted when appropriate. Failure to comply with remedial actions may result in investigator center termination and regulatory authority notification.

The Sponsor or its designee will utilize qualified monitors to review and evaluate activities conducted at Investigator Centers.

The data will be entered into the clinical study database and verified for accuracy, following procedures defined by the Sponsor (or designee). Data will be processed and analyzed following procedures defined by the Sponsor (or designee).

The study will be monitored and/or audited at intervals to ensure that the clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the Study Protocol; International Council for Harmonisation (ICH), E6 consolidated guidelines; and other applicable regulations. The extent, nature, and frequency of monitoring and/or audits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity, and enrollment rate. At the conclusion of a program, a compliance statement will be generated by the Sponsor (or designee) listing all audit activities performed during the clinical study.

21. ETHICS

21.1. Ethics Review

Approval by the IRB/IEC prior to the start of the study will be the responsibility of the Investigator. A copy of approval documentation will be supplied to Endo along with a roster of IRB members that demonstrates appropriate composition (a Department of Health and Human Services [DHHS] Assurance Number will satisfy this requirement).

The study protocol, the informed consent form, advertisements, materials being provided to subjects and amendments (if any) will be approved to IRB/IECs at each study center in conformance with ICH E6, the Code of Federal Regulations (CFR), Title 21, Part 56 and any other applicable local laws. The Investigator is responsible for supplying the IRB/IEC with a copy of the current IB, Package Insert, or SPC as well as any updates issued during the study. During the course of the study, the Investigator will provide timely and accurate reports to the

IRB/IEC on the progress of the study, at intervals not exceeding 1 year (or as appropriate), and will notify the IRB/IEC of SAEs or other significant safety findings, per the policy of the IRB/IEC. At the conclusion of the study, the Investigator will submit a final report or close out report to the IRB/IEC and provide a copy to Endo

Any amendment to this protocol will be provided to the Investigator in writing by Endo. No protocol amendment may be implemented (with the exceptions noted below) before it has been approved by the IRB and the signature page, signed by the Investigator, has been received by Endo Where the protocol is amended to eliminate or reduce the risk to the subject, the amendment may be implemented before IRB review and approval. However, the IRB must be informed in writing of such an amendment and approval obtained within reasonable time limits. Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the subject, and must be immediately reported to Endo.

The Investigator will be responsible for supplying updated safety and/or study information to study subjects as it becomes available.

21.2. Ethical Conduct of the Study

This clinical study is designed to comply with the ICH Guidance on General Considerations for Clinical Trials (62 FR 6611, December 17, 1997), Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (62 FR 62922, November 25, 1997), Good Clinical Practice: Consolidated Guidance (62 FR 25692, May 9, 1997) and 21 CFR parts 50, 54, 56 and 312.

The study will be conducted in full compliance with ICH E6(R2), the FDA guidelines for GCP and in accordance with the ethical principles that have their origins in the Declaration of Helsinki defined in 21 CFR, 312.120.

21.3. Subject Information and Consent

Subjects, after having the study explained to them and an opportunity to have their questions answered sufficiently, will give voluntary and written informed consent (in compliance with ICH E6, 4.8 and 21 CFR Parts 50 and 312) before participating in any study-related procedures. The consent shall be written in a language understandable to the subject. Subjects unable to read (illiterate) shall have the consent process performed in the presence of an independent witness who shall also sign the consent. Each subject will read, assent understanding, and sign an instrument of informed consent after having had an opportunity to discuss the study and consent documents with the Investigator before signing, and will be made aware that he/she may withdraw from the study at any time.

In addition to obtaining informed consent, the Investigator is responsible for obtaining any additional documentation to demonstrate compliance with local privacy laws applicable to activities performed.

The consent process shall be recorded in source documents. Signed copies of the informed consent and/or assent will be given to the Subject and originals will be placed in the Investigator study files.

A unique Subject identification number will be assigned at the time that the Subject signs the informed consent form.

22. DATA HANDLING AND RECORDKEEPING

22.1. Data Collection

Data collection will involve the use of an electronic data capture (EDC) system to which only authorized personnel will have access. The system will be secured to prevent unauthorized access to the data or the system. This will include the requirement for a user ID and password to enter or change data. The level of access to the EDC system will be dependent on the person's role in the study.

Study data will be collected from source documents and entered into an eCRF within the EDC system. The Investigator will be responsible for ensuring the eCRFs are completed in a timely manner relative to the subject's visit. In addition to periodic monitoring occurring within the system by a Sponsor monitor, programmatic edit checks will be used to review EDC data for completeness, logic, and adherence to the study protocol. As a result of this monitoring and these checks, queries may be issued electronically to the clinical study centers and closed electronically by the monitor, data management staff or authorized staff at the study center. Additionally, the Investigator will review eCRFs, ensure all missing or corrected data is provided and will sign the eCRF pages with an electronic signature.

An electronic audit trail will be maintained in the EDC system to track all changes made to data entered in the eCRF. Data will be retrievable in such a fashion that all information regarding each individual subject is attributable to that subject. Unless otherwise indicated, all data captured in the eCRF must first be captured in source documents. Data that can be directly recorded in the eCRF will be clearly identified in the section(s) of the protocol that describes the assessment(s).

In addition, any contact with the subject via telephone or other means that provide significant clinical information must be documented in source documents as described above.

22.2. Study Documentation

Upon study completion, the complete eCRF, in portable document format (PDF), will be created from the EDC system. Study centers will be provided with the PDF of the eCRF for their subjects.

23. REPORTING AND PUBLICATION

All data generated in this study are the property of Endo An integrated clinical and statistical report will be prepared at the completion of the study.

Publication of the results by the Investigator will be subject to mutual agreement between the Investigator and Endo

24. INVESTIGATOR OBLIGATIONS

24.1. Regulatory Documents

The Investigator is responsible for creating and/or maintaining all study documentation required by 21CFR 50, 54, 56 and 312, ICH, E6 Section 8, as well as any other documentation defined in the protocol or the Investigator Agreement. The Investigator must maintain the documentation relating to this study and permit Endo or a member of a regulatory agency access to such records.

The Investigator must provide the following key documents to Endo prior to the start of the study:

- A completed and signed Form FDA1572. If during the course of the study any information reported on the Form FDA 1572 changes, a revised Form FDA1572 must be completed and returned to Endo for submission to the FDA. For studies executed outside the United States, documentation required by the governing regulatory authority may be substituted for the Form FDA 1572.
- A fully executed contract.
- The Investigator's Statement page in this protocol signed and dated by the Investigator and any subsequent amendment signature pages.
- The IB acknowledgment of receipt page.
- Curricula vitae for the Principal Investigator and all Sub-Investigators listed on Form FDA 1572, including a copy of each physician's license (if applicable).
- A copy of the original IRB/IEC approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals or shorter intervals defined by the IRB/IEC. All subsequent modifications must be submitted and approved by the IRB.
- A copy of the IRB/IEC-approved informed consent form.
- A list of IRB/IEC members or DHHS Assurance Number.
- Laboratory certifications and normal ranges (if local labs are required by the protocol).
- A financial disclosure agreement completed and signed by the Investigator and all Sub-Investigators listed on Form FDA 1572. Investigator center staff that submitted an initial financial disclosure are also responsible for informing Endo of any changes to their initial financial disclosure form 1 year after the completion of the study.

A complete list of required regulatory documents will be supplied by Endo or its representative.

24.2. Delegation of Responsibilities and Adequate Resources

The Investigator should have adequate time to conduct the study properly and should have an adequate number of qualified staff to assist with the conduct of the study. The Investigator shall delegate tasks only to individuals qualified by education, training and experience to perform the delegated tasks. The Investigator shall have direct oversight of all delegated activities and shall

document delegation of responsibilities. The Investigator is responsible for ensuring all delegated staff have been properly trained on the protocol and their assigned study responsibilities.

24.3. Medical Care of Study Subjects

The Investigator and/or a qualified sub-investigator shall be responsible for the subjects' medical care. Any unrelated medical condition discovered during the course of the study should be communicated to the subject so that they may seek appropriate medical care. The Investigator will report all AEs as required by the protocol. The Investigator will inform study subjects of new information regarding the study drug as it becomes available.

24.4. Use of Investigational Materials

The Investigator will acknowledge that the study drug supplies are investigational and as such must be used strictly in accordance with the protocol and only under the supervision of the Principal Investigator or Sub-Investigators listed on Form FDA1572 (or other regulatory document, depending on region). Study drug must be stored in a safe and secure location. At study initiation, a representative from Endo will inventory the study drug at the center. The Investigator must maintain adequate records documenting the receipt and disposition of all study supplies. Endo or its representative will supply forms to document total inventory as well as subject specific accountability. The Investigator is responsible for monitoring subject's use of the study drug to ensure compliance with the protocol. All study supplies shall be returned to Endo or its designee (this will include empty vials).

24.5. Retention of Records

Federal and local regulations require that the Investigator retain a copy of all regulatory documents and records that support the data for this study (eg, informed consents, laboratory reports, source documents, study drug dispensing records) for whichever of the following is the longest period of time:

- A period of 2 years following the final date of approval by the FDA or other regulatory agency of the study drug for the purposes that were the subject of the investigation; or
- A period of 5 years following the date on which the results of the investigation were submitted to the FDA or other regulatory agency in support of, or as part of, an application for a research or marketing permit for the study drug for the purposes that were the subject of the investigation

Endo will notify Investigators once one of the above 2 time frames has been satisfied.

If the investigation does not result in the submission of the data in support of, or as part of, an application for a research or marketing permit, records must be retained for a period of 2 years following notification by Endo that the entire clinical investigation (not merely the Investigator's portion) is completed, terminated, or discontinued or 2 years following withdrawal of the Investigational New Drug Application (IND)/Clinical Trial Authorization (CTA) or request for marketing approval (New Drug Application [NDA]/Marketing Authorization Application [MAA]).

If the Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. Endo must be notified in writing of the name and address of the new custodian. Study records should not be destroyed without consultation with Endo.

24.6. Subject Confidentiality

All subject records submitted to Endo or its designee will be identified only by code number. Subjects' names are not to be transmitted to Endo. The Investigator will keep a Master Subject List on which the identification number and the full name, address, and telephone number of each subject are listed. It is the Investigators' responsibility to inform study subjects that representatives of the Sponsor, FDA, or other regulatory agencies may review all records that support their participation in the study. The Investigator will adhere to all privacy laws to which he/she is subject.

25. TERMINATION OF STUDY

The Sponsor has the right to suspend or terminate the study at any time. The study may be suspended or terminated for any reason.

26. INVESTIGATOR'S STATEMENT

I agree to conduct the study in accordance with the protocol, and with all applicable government regulations and Good Clinical Practice guidance.

_____ _____/_____/_____

Investigator's Signature Date

_____

Typed/Printed Name of Investigator

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APPENDIX A. CLINICIAN REPORTED PHOTONUMERIC SEVERITY SCALE FOR CELLULITE (CR-PCSS) FOR THE BUTTOCK

APPENDIX B. CLINICIAN REPORTED PHOTONUMERIC SEVERITY SCALE FOR CELLULITE (CR-PCSS) FOR THE THIGH

APPENDIX C. HEXSEL CELLULITE SEVERITY SCALE (CSS) (B) DEPTH OF DEPRESSIONS

Depth of depressions	0 = no depressions 1 = superficial depressions 2 = medium depth depressions 3 = deep depressions