Endo Pharmaceuticals Inc.
1400 Atwater Drive
Malvern, PA 19355 USA

COLLAGENASE CLOSTRIDIUM HISTOLYTICUM (CCH)

EN3835-103

A PHASE 1, OPEN-LABEL STUDY TO ASSESS THE SAFETY AND PHARMACOKINETICS OF A SINGLE DOSE OF CCH (3.36 MG) IN SUBJECTS WITH EDEMATOUS FIBROSCLEROTIC PANNICULOPATHY

IND 110,077

Date:

Original Protocol: 14 February 2017

Amendment 1: 07 September 2018

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

Confidentiality Statement

2. SUMMARY OF CHANGES

Protocol amendments and amended informed consent forms (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 07 September 2018. The primary reason for this amendment is to update the protocol with the latest safety information. 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 Section 8.1.1	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 8.1.1 was updated to explain this change.
Section 3 Clinical Trial Monitor	Name and Contact Information	TEXT DELETED
Section 3 Medical Monitor	[redacted]	[redacted]
Section 8.1.1 Collagenase Clostridium Histolyticum	Updated	Section updated to include results from completed Phase 2a study EN3835-201 and ongoing studies.
Section 8.2.1 Pharmacokinetics	Section updated to reflect new data.	*The following text was added to the discussion of the results for study AUX-CC-805 (paragraph 2):* The maximal plasma concentrations of AUX-I and AUX-II were < 29 ng/mL and < 71 ng/mL, respectively, and were observed within approximately 10 minutes after injection. *The following new text was added to the end of the section:* In study EN3835-104, subjects received subcutaneous administration of CCH 0.84 mg (12 injections) in two quadrants (left and right buttocks) for the treatment of EFP. No quantifiable plasma concentrations of AUX-I or AUX-II at any time point (t = 5, 10, 20, and 30 minutes and 1, 2, 4, 8, 12, 24, 48, 168, and 504 hours) after dosing were observed among the 17 evaluable subjects.

Section	Original Text	Revised Text/Reason for Change
Section 8.3 (formerly Section 8.4) Summary of Known Risks and Benefits	The following events have been commonly observed: bruising and edema at the site of injection. Subjects should be observed for 30 minutes post dose to monitor for possible hypersensitivity reactions. Preliminary studies have indicated that CCH may improve symptoms associated with EFP. Additional data from this study may help to support the clinical effect in female subjects with EFP.	The following events have been commonly observed: local injection site reactions (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 in ≥2% of 189 CCH-treated women were reported: 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. Although a thorough benefit of CCH has not been fully evaluated in the treatment of EFP, the efficacy results from the Phase 2b study and previous EFP studies warranted further development.
Section 10.2 Selection of Dose	Updated	Section updated to include supporting data from additional and ongoing studies.
Section 10.4 Study Drug Reconstitution	New stability data indicates [redacted]	After reconstitution with the sterile diluent, the study drug solution can be kept at room temperature (20°C to 25°C/68°F to 77°F) [redacted]
Section 11.2 Subject Exclusion Criteria	Exclusion Criterion 14	List of previous CCH studies in which participation would exclude subjects was expanded to include EN3835-205, EN3835-302, EN3835-303, EN3835-304, and EN3835-209.
Section 11.3Subject Discontinuation Criteria	New subsections (Section 11.3.1 and Section 11.3.2) added to distinguish between subjects discontinued/withdrawn from treatment and subjects discontinued/withdrawn from the study.	Subjects who discontinue or are withdrawn from treatment will be encouraged to complete all other study procedures. Subjects who discontinue or are withdrawn from the study will be encouraged to complete end of study procedures. No additional procedures will be done for subjects who withdraw consent except collection of AE information.

Section	Original Text	Revised Text/Reason for Change
Section 14.5.2 Reporting Adverse Events and Serious Adverse Events Section 14.6 Special Reporting Situations	The title of the Endo SAE reporting form has been updated (formerly 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.
Section 14.7.1 Pregnancy Testing	Changed to allow site flexibility in pregnancy testing.	Section title changed to **14.7.1 Pregnancy Testing** and serum pregnancy testing added.
Section 17.1 Study Drug Identity	Updated	Updated to reflect current manufacturer and composition details.
Section 20.3 Subject Information and Consent	Removed assent and legally authorized representative consent.	All subjects must be fully consented and able to read and sign the consent form.
Section 23.6 Subject Confidentiality	All subject records submitted to Endo or its designee will be identified only by ~~initials and~~ subject number.	Endo will not use initials as subject identifiers. *New text:* All subject records submitted to Endo or its designee will be identified only by subject number.
Appendix A Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS)	Text Removed: ~~While viewing the subjects, the Investigator will be instructed to answer the following question: Today, how would you rate the severity of this patient's cellulite in the area selected for treatment using the CR-PCSS? If the buttock is the treated region, the Investigator will use the CR-PCSS for the buttock to make their evaluation; if the thigh is the treated region, the Investigator will use the CR-PCSS for the thigh to make their evaluation. In each case, the Investigator will make his/her assessment independently.~~	To make instruction consistent with other EN3835 protocols

3. SPONSOR CONTACT INFORMATION

Table 1: Sponsor Contact Information

Role in Study	Name	Telephone and Email Address
Medical Monitor	[redacted]	[redacted]
SAE Reporting Pathway	Not applicable – report through Endo SAE Pathway	[redacted]

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

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 1, Open-Label Study to Assess the Safety and Pharmacokinetics of a Single Dose of EN3835 (3.36 mg) in Subjects with Edematous Fibrosclerotic Panniculopathy	
Lead Principal Investigator: [redacted]	
Study period: Estimated date first subject enrolled: 3rd Quarter 2018 Estimated date last subject completed: 4th Quarter 2018	**Phase of development:** Phase 1
Objectives: **Primary:** The primary objectives of this study are to assess safety, and determine if there is systemic exposure, following a subcutaneous single dose of EN3835 (3.36 mg) as 12 injections per quadrant in 4 quadrants concurrently (0.84 mg per quadrant) in adult women with edematous fibrosclerotic panniculopathy (EFP), commonly known as cellulite.	
Study Design: This is a Phase 1, open-label, single-dose administration study of the safety, pharmacokinetics (PK), and immunogenicity of CCH.	
Number of subjects (planned): Approximately 12 subjects will be enrolled to receive the full dose of study drug on Day 1. A minimum of 10 subjects should complete the study with PK profiles for evaluation.	
Study center(s): 1 site in the United States	
Diagnosis and inclusion/exclusion criteria: To be enrolled in this study subjects must be nonpregnant, nonlactating females ≥ 18 years of age with evidence of cellulite in 4 quadrants (right or left buttock or the right or left posterolateral thigh) as assessed by as mild, moderate or severe using the Investigator using the Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS) at the Screening Visit. Subjects must have a body mass index (BMI) between 20.0 and 35.0 kg/m^2, be judged to be in good health, and be willing to apply sunscreen to the dosing quadrants before each exposure to the sun while participating in the study. Subjects with coagulation disorders, evidence or history of malignancy, or history of keloidal scarring or abnormal wound healing will be excluded. Subjects with a history of lower extremity thrombosis or post-thrombosis syndrome, vascular disorders, inflammation or active infection, or active cutaneous alteration (including rash, eczema, psoriasis, or skin cancer) within the area to be treated and subjects who a tattoo located within 2 cm of the site of injection will also be excluded. Subjects may not have had liposuction, injections, radiofrequency device treatments, laser treatment, or surgery within the treatment quadrants during the 12-month period before injection of study drug; Endermologie® or similar treatments within the treatment quadrants during the 6-month period before injection of study drug; massage therapy within the treatment quadrants during the 3-month period before injection of study drug; or creams to prevent or mitigate EFP within the treatment quadrants during the 2-week period before injection of study drug. Subjects must not have participated in a previous cellulite clinical trial of CCH.	

Name of Sponsor/Company: Endo Pharmaceuticals Inc.
Name of Investigational Product: CCH
Name of Active Ingredient: Collagenase clostridium histolyticum
Investigational product, dosage, and mode of administration: Investigational product is CCH. A single dose of 3.36 mg of CCH will be administered as 12 subcutaneous injections (CCH 0.84 mg) per quadrant concurrently in 4 quadrants for a total of 48 injections. A quadrant is defined as one of the following: left buttock, right buttock, left posterolateral thigh, or right posterolateral thigh. The study drug (CCH) will be injected subcutaneously while subject is in a prone position using a syringe with a 30-gauge ½-inch needle. Each injection site will receive a single skin injection of study drug administered as three 0.1-mL aliquots (for a total injection volume of 0.3 mL per injection; an injection volume of 3.6 mL per quadrant and a total injection volume of 14.4 mL).
Duration of study: 43 days (includes screening phase) **Screening Phase:** Up to 21 days **Dosing Phase:** Subjects will be admitted to the research unit on the afternoon of Day −1. Dosing will occur on Study Day 1. Subjects will remain in the research unit for collection of the PK samples out to 24 hours post dose. They will then be discharged after the last sample is collected on Study Day 2. **Follow up:** Subjects will return to the study unit on Day 3, 8, and 22 for outpatient follow-up PK, immunogenicity, and safety assessments. The last scheduled outpatient visit to the clinic for assessments is on Study Day 22.
Criteria for evaluation: **Safety:** The safety of CCH will be evaluated through the collection of adverse events (AEs), including a targeted assessment of local/systemic reactions to the dose. Vital sign measurements and clinical laboratory testing will also be performed. **Pharmacokinetics**: Subjects will have blood samples collected for the determination of plasma AUX-I and AUX-II concentrations before dosing and 5, 10, 20, and 30 minutes, then at 1, 2, 4, 8, 12, and 24 hours after dosing while confined to the research unit. Subjects will return for PK blood draws at 48 (Day 3), 168 (Day 8), and 504 (Day 22) hours post dose on an outpatient basis. All blood samples are to be collected within 10% of the nominal time. The following PK parameters will be determined for each subject who has quantifiable plasma concentrations at any time during the 504-hour period following the last injection: maximum drug concentration (C_{max}), time to maximum drug concentration (T_{max}), area under the plasma concentration time curve from time of dosing (0) to the time of last quantifiable concentration (AUC_{0-t}), and area under the plasma concentration time curve from time of dosing (0) to infinity (AUC_{0-inf}). **Immunogenicity:** Blood samples will be collected pre-dose on Day 1 and on Day 22 after dosing for possible determination of anti-AUX-I and anti-AUX-II antibodies in serum; assay of these samples will be conducted only if clinical signs and/or PK results warrant determinations. Descriptive statistics (percent positive measurements and average antibody level) will be calculated for anti-drug antibody titers at each visit if antibody determinations are conducted. **Cellulite Severity Evaluation:** Cellulite will be assessed by the Investigator's rating of cellulite severity using the CR-PCSS at the Screening visit and on Day 22.

Name of Sponsor/Company: Endo Pharmaceuticals Inc.

Name of Investigational Product: CCH

Name of Active Ingredient: Collagenase clostridium histolyticum

Statistical methods:

Sample Size Consideration: No formal sample size calculations were performed. Completion of 10 subjects will provide sufficient data to meet the PK study objectives.

Cellulite Severity Analysis: Evaluations will be done on the quadrants using the CR-PCSS at Screening and Day 22. Change from baseline in cellulite severity will be computed. The Screening and Day 22 ratings will be summarized with counts and percentages at each level of severity and with mean and standard deviation (SD). The change from baseline value will be summarized with counts and percentages at each possible change value and with mean and SD. The cellulite severity population will be used to summarize the cellulite severity data.

Pharmacokinetic Analysis: PK data will be summarized through data tabulations, descriptive statistics, and graphic presentations, as appropriate. Actual blood sampling times will be used in all PK analyses. $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} will be summarized with descriptive statistics (number, mean, SD, median, minimum, and maximum) as well as the geometric mean and coefficient of variation (CV). Geometric means and CV will be calculated for the log transformed parameters, using the following SAS formula:

$$CV\ (\%) = SQRT[\exp(SD^2)-1] * 100$$

T_{max} will be summarized with descriptive statistics (number, mean, SD, median, minimum, and maximum) only.

If all subjects have all PK concentrations below the limit of quantification (BLQ), then all PK parameters will be summarized as not calculable.

[redacted]

5. SCHEDULE OF EVENTS

	Inpatient at the Research Unit				Follow-up Outpatient Visits (OPV)		
Event	**Screening**	**Admit to Clinic**	**Dose**	**Discharge from Clinic**	**OPV**	**OPV**	**OPV**
Study Day	**Day −22 to Day −2**	**Day −1**	**Day 1**	**Day 2** (24 hours post dose)	**Day 3** (48 hours post dose)	**Day 8** (168 hours post dose)	**Day 22/ End of Study** (504 hours post dose)
Informed Consent[a]	X						
Inclusion/Exclusion[b]	X	X					
Medical History/EFP History Including Previous Treatments	X						
Prior Concomitant Medications/Procedures	X	X	X	X	X	X	X
Physical Examination:	X						
Body Weight	X						X
Height	X						
Fitzpatrick Skin Type	X						
Vital Signs[c]	X	X	X	X	X	X	X
12-Lead ECG	X						
Clinical Laboratory Tests[d]	X						X
Pregnancy Test	X	X					
Urine Drug Screen[e]	X	X					
Alcohol Breath Test	X	X					
Investigator's Cellulite Assessment: Thigh/Buttocks							
Investigator-Reported Photonumeric Cellulite Severity Scale (CR-PCSS)[f]	X						X
Select/Mark Dimples Within the Quadrants – Predose			X				

	Inpatient at the Research Unit				Follow-up Outpatient Visits (OPV)		
Event	**Screening**	**Admit to Clinic**	**Dose**	**Discharge from Clinic**	**OPV**	**OPV**	**OPV**
Study Day	**Day −22 to Day −2**	**Day −1**	**Day 1**	**Day 2** (24 hours post dose)	**Day 3** (48 hours post dose)	**Day 8** (168 hours post dose)	**Day 22/ End of Study** (504 hours post dose)
Single Dose (48 injections)[g]			X				
Pharmacokinetic Blood Sampling[h]			X	X	X	X	X
Blood collection for possible Anti-AUX-I/ Anti-AUX-II Antibody Levels/Neutralizing Antibodies to AUX-I and AUX-II[i]			X				X
Assess Any Injection Site Reactions in the Areas That Were Dosed			X	X	X	X	X
Adverse Events[j]	X	X	X	X	X	X	X

[a] Performed and signed prior to any study-required assessments.
[b] Should be reassessed and verified prior to dosing.
[c] Blood pressure (systolic/diastolic), respiratory rate, and radial pulse taken up to 4 hours pre-dose and 15 and 30 minutes post dose. Oral body temperature will be included at Screening, Admission Day -1, on Day 1 pre-dose and at 30 minutes post dose, and on Day 2. All vital signs include oral temperature to be taken before blood sampling on the Day 3, 8, and 22 OPVs. Vital signs should be taken after the subject rests for at least 5 minutes.
[d] The list of clinical laboratory tests for safety is given in Table 4.
[e] Screen for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, opiates, and/or propoxyphene at the Screening visit and on Day −1. Test must be negative.
[f] The Investigator's CR-PCSS assessment score must be a 2, 3, or 4 for study entry.
[g] The 48 subcutaneous injections (12 injections per quadrant in 4 quadrants concurrently) comprise the single dose.
[h] Blood collection (10 mL each) for PK measurement of plasma AUX-I and AUX-II concentrations are to be taken before dosing and at 5, 10, 20, and 30 minutes and 1, 2, 4, 8, 12 , 24, 48, 168, and 504 hours after dosing. All blood samples are to be collected within 10% of the nominal time. The exact time of collection will be noted in the source document and eCRF.
[i] Collect blood for immunogenicity testing before injection on Day 1 prior to dosing and again on Study Day 22 at approximately 504 hours after dosing. (Collect 3 × 5 mL of blood for immunogenicity testing at both time points.). NOTE: Assay of these samples will be conducted only if clinical signs and/or PK results warrant determinations.
[j] AEs/SAEs will be captured from time of informed consent signature until Study Day 22. There is no time limit on collection of SAEs felt to be related to study drug.

6. TABLE OF CONTENTS AND LIST OF TABLES

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

7. LIST OF ABBREVIATIONS

Table 2: List of Abbreviations

Abbreviation	Explanation
AE	Adverse event
AUC	Area under the concentration time curve
AUC_{0-inf}	Area under the plasma concentration versus time curve from time of dosing (0) to infinity
AUC_{0-t}	Area under the plasma concentration versus time curve from time of dosing (0) to the time of last quantifiable concentration
AUX-I	Clostridial class I collagenase
AUX-II	Clostridial class II collagenase
BLQ	Below limit of quantification
BMI	Body mass index
CFR	Code of Federal Regulations
C_{max}	Observed maximum plasma concentration
CR-PCSS	Clinician-Reported Photonumeric Cellulite Severity Scale
CV	Coefficient of variation
DHHS	Department of Health and Human Services
ECG	Electrocardiogram
eCRF	Electronic case report form
EFP	Edematous fibrosclerotic panniculopathy
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IB	Investigator Brochure
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug application
IRB	Institutional Review Board
OPV	Outpatient visit
OTC	Over-the-counter
PCI	Potentially clinically important
PK	Pharmacokinetics

Table 2: List of Abbreviations (Continued)

Abbreviation	Explanation
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum concentration

8. INTRODUCTION

8.1. Background of 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 (Kahn 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; Kahn 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 (Kahn 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 (Kahn 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 (Kahn 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 (Kahn 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.

8.1.1. Collagenase Clostridium Histolyticum (CCH)

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 for EFP. 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 CCH

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.

8.2.1. Pharmacokinetics

Data from a definitive Phase 1 single-dose study (AUX-CC-855) and a Phase 3b multiple-dose study (AUX-CC-861) confirmed that there is no quantifiable systemic exposure following a single or 2 concurrent injection(s) of EN3835 (0.58 mg) into the cord(s) of the affected finger(s) in subjects with Dupuytren's contracture or following the subsequent procedure to disrupt the cord. The results of both clinical studies indicate that no detectable absorption of any EN3835-derived components occurs in subjects under conditions of clinical use. These findings are consistent with local inactivation of EN3835, most likely as the result of complex formation with alpha-2-macroglobulin (α2M), a serum protein that serves as a substrate/inhibitor for proteases of a variety of types (Endo, 2017).

Following each of 2 intralesional administrations, separated by 24 hours, of EN3835 (0.58 mg) into the penile plaque of 19 subjects with Peyronie's disease (AUX-CC-805), plasma levels of AUX-I and AUX-II in subjects with quantifiable levels (79% and 40% for AUX-I and AUX-II, respectively) were minimal and short-lived. The maximal plasma concentrations of AUX-I and AUX-II were < 29 ng/mL and < 71 ng/mL, respectively, and were observed approximately within 10 minutes after injection. All plasma levels were below the limits of quantification within 30 minutes following dosing. There was no evidence of accumulation following 2 sequential injections of EN3835 administered 24 hours apart. No subject had quantifiable plasma levels 15 minutes after modeling of plaque on Day 3 (ie, 24 hours after injection 2 on Day 2).

In study AUX-CC-830, where subjects received 10 subcutaneous injections for the treatment of EFP at increasing doses ranging from 0.0029 mg to 0.464 mg, no quantifiable plasma concentrations of AUX-I and AUX-II at any time point through 24 hours post injection were observed among the 93 subjects who were evaluable for pharmacokinetics (PK).

In study EN3835-102, subjects received subcutaneous administration of CCH 0.84 mg (12 injections) in 1 quadrant (left buttock, right buttock, left posterolateral thigh, or right posterolateral thigh) for the treatment of EFP. No quantifiable plasma concentrations of AUX-I or AUX-II at any time point (t = 5, 10, 20, and 30 minutes and 1, 2, 4, 8, 12, 24, 48, 168, and 504 hours) after dosing were observed among the 11 evaluable subjects.

In study EN3835-104, subjects received subcutaneous administration of CCH 0.84 mg (12 injections) in two quadrants (left and right buttocks) for the treatment of EFP. No quantifiable plasma concentrations of AUX-I or AUX-II at any time point (t = 5, 10, 20, and 30 minutes and 1, 2, 4, 8, 12, 24, 48, 168, and 504 hours) after dosing were observed among the 17 evaluable subjects.

8.3. Summary of Known Risks and Benefits

A summary of safety risks is provided in the IB (Endo, 2017). The following events have been commonly observed: local injection site reactions (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 in ≥2% of 189 CCH-treated women: 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.

Although a thorough benefit of CCH has not been fully evaluated in the treatment of EFP, the efficacy results from the Phase 2b study and previous EFP studies warranted further development.

8.4. Rationale

This study will evaluate the safety, PK, and immunogenicity of a single 3.36-mg dose of CCH administered as 48 subcutaneous injections, ie, CCH 0.84 mg as 12 injections per quadrant in 4

quadrants concurrently, in subjects with EFP. A quadrant is defined as a left buttock, right buttock, left posterolateral thigh, or right posterolateral thigh.

This study will provide insight to the PK profile and safety of concurrent subcutaneous injections of CCH 0.84 mg/quadrant into 4 quadrants in anticipation of use in the real world by clinicians skilled in the art of aesthetic medicine of dosing more than 1 quadrant, or maximizing the potential situation in which clinicians shorten the time between injection sessions (21 days in clinical trials).

9. OBJECTIVES

9.1. Primary Objective

The primary objectives of this study are to assess safety and determine if there is systemic exposure, following a subcutaneous single dose of CCH (3.36 mg) as 12 injections per quadrant in 4 quadrants concurrently (0.84 mg per quadrant) in adult women with EFP.

10. INVESTIGATIONAL PLAN

10.1. Study Design

This is a Phase 1, open-label PK study. This study will be performed at a single center located in the United States.

Following an up to 21-day screening period, subjects will be admitted to the clinical research unit (Day −1) the day before the dosing of CCH (Day 1) and will remain in the study unit until after the 24-hour post-dose PK sample is collected on Day 2. Twelve (12) subjects will be admitted on Day −1 to receive the full dose of the study drug on Day 1. Subjects will return to the study unit on Day 3, 8, and 22 for outpatient follow-up safety and PK assessments. A minimum of 10 subjects should complete the study with PK profiles for evaluation.

The complete schedule of events is provided in Section 5.

10.2. Selection of Dose

Data from the Phase 2a EFP dose-ranging study (AUX-CC-831) suggested that CCH (0.84 mg) was effective in the treatment of EFP based on improvement in the severity of cellulite as determined by both the Investigator and the subject. There were no safety concerns following administration of up to 3 treatment sessions at 21-day intervals (ie, Day 1, 22, and 43) of CCH 0.84 mg (Endo, 2017). The safety profile of CCH 0.84 mg was similar to that observed in previous clinical studies with CCH (collagenase clostridium histolyticum) for injection for intralesional use in the treatment of Dupuytren's contracture and Peyronie's disease in that that the majority of AEs bruising, discoloration, pain, and swelling) occurred at the site of injection and resolved before the next scheduled treatment.

The immunogenicity profile of CCH in the Phase 2a EFP dose-ranging study showed ≥ 93% of subjects in the CCH 0.48-mg and CCH 0.84-mg groups were positive for antibodies to AUX-I and AUX-II; the profile is similar to that observed in the Dupuytren's contracture and Peyronie's disease programs.

The results from the Phase 2b EFP study (EN3835-201) further suggested that CCH 0.84 mg 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 CCH 0.84 mg in the treatment of EFP. Safety findings from the Phase 2b EFP study were similar to that observed in the Phase 2a study, in that 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 was also similar to the Phase 2a study.

No new safety signals have been seen to date in ongoing Phase 2 and Phase 3 studies where 2 quadrants are being treated with 0.84 mg per quadrant.

Based on the efficacy and safety findings from previous studies using 0.84 mg per quadrant and the objective of determining the PK profile following concurrent treatment of 4 quadrants, a dose of 3.36 mg was selected for this study.

10.3. Selecting and Marking Dimples and Injection Sites

Selection of dimples to be treated in the 4 quadrants is at the discretion of the Investigator. Dimples must be well defined and evident when the subject is standing in a consistent relaxed pose (without the use of any manipulation such as skin pinching or muscle contraction).

Before injection on Day 1, the Investigator or qualified designee will begin the session by selecting dimples within the quadrants that are well defined, evident when the subject is standing, and suitable for dosing; the dosing consists of 48 injections (12 injections per quadrant) on Study Day 1.

Because the goal of even a single dose administration is to potentially improve the aesthetic appearance of the entire quadrant, the Investigator will be instructed to select dimples that in his or her opinion would most improve the aesthetic appearance of the entire quadrant.

For each dimple selected, the Investigator or qualified designee will choose 12 injection sites per quadrant (injection sites within a dimple should be spaced approximately 2 cm apart, if a dimple requires more than 1 injection) and 4 quadrants for a total of 48 injection sites. Each injection site will be marked with a "dot" using a surgical marker. For round dimples, the "dot" will be placed in the center of the dimple.

10.4. Study Drug Reconstitution

Before reconstitution, remove the vials containing the lyophilized study drug powder and the vials containing the sterile diluent from the refrigerator and allow the vials to stand at room temperature for 15 minutes. Designated study personnel will visually inspect the study drug vial to determine the integrity and acceptability of the lyophilized drug product for reconstitution. The cake should be white and intact, with no signs of erosion.

Each vial of study drug powder will be reconstituted according to the Reconstitution Instructions. Study personnel will maintain a record of the date and time of reconstitution.

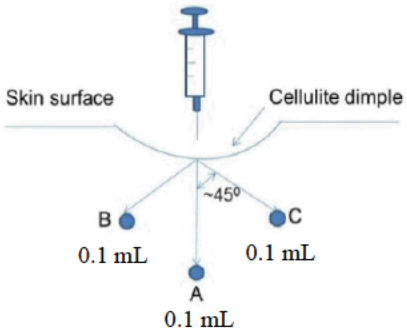
After reconstitution with the sterile diluent, the study drug solution can be kept at room temperature (20°C to 25°C/68°F to 77°F) [redacted] hours prior to administration.

10.5. Study Drug Administration at Each Injection Site

Study drug will be injected subcutaneously while the subject is in a prone position using a syringe with a 30-gauge ½-inch needle. Forty-eight (48) injection sites (12 sites per quadrant) will be selected (see Section 10.3). Each injection site will receive 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 (0.5 inches) from the tip of the needle to the hub or base of the needle without downward pressure.

Sixteen (16) syringes (4 syringes per quadrant) will be prepared for dosing on Day 1. Each syringe will contain 0.9 mL of study drug (ie, 3 injections in each syringe). Forty-eight (48) skin injections of 0.3 mL will be administered within the 4 quadrants (12 injections per quadrant) during the dosing session (injection volume of 3.6 mL per quadrant and a total injection volume of 14.4 mL).

Figure 1: Study Drug Administration



Needle Tip Position A: Position the needle at 90° angle perpendicular to the skin surface at the injection site and inject one 0.1-mL aliquot of study drug by gently pushing on the syringe plunger.

Needle Tip Position B: Withdraw the needle slightly (but not so much as to remove from the injection site) and reposition approximately 45° (but not more than 45°) off vertical and above the long axis of the dimple and inject one 0.1-mL aliquot of study drug) by gently pushing on the syringe plunger.

Needle Tip Position C: Withdraw the needle slightly (but not so much as to remove from the injection site) and reposition approximately 45° (but not more than 45°) off vertical and below the long axis of the dimple and inject one 0.1-mL aliquot of study drug by gently pushing on the syringe plunger.

Withdraw needle from the skin completely and move to the next identified injection site. Complete a total of three 0.3-mL injections (each administered as three 0.1-mL aliquots) and discard the first syringe appropriately. Use the second, third and fourth syringes to complete dosing in the quadrant (three 0.3-mL injections per syringe, each injection administered as three 0.1-mL aliquots). Twelve skin injections of 0.3 mL will be administered within each quadrant during the dosing and 4 quadrants will be concurrently treated; a total of 48 injections will be given on Day 1.

After dosing the subject will remain prone for at least 5 minutes. The blood draws for PK sampling will begin at 5 minutes after the completion of the last dose injection.

The total number of dimples treated and the total number injections administered during dosing on Day 1 will be recorded.

NOTE: CCH is a foreign protein and the Investigator should be prepared to address and manage an allergic reaction should it occur. At the time of each injection, a 1:1000 solution of epinephrine for injection, 50-mg diphenhydramine injection or a suitable equivalent, and oxygen must be available. The Investigator and site staff must be familiar with the use of the rescue medication.

10.6. Care Procedures After Injection

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 injection 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 site with hypoallergenic tape. The dressing will be removed by the clinic staff in the evening.

10.7. Identity of Investigational Product

The investigational product vials will be labeled as CCH. CCH is a sterile lyophilized powder containing 0.46 mg of collagenase clostridium histolyticum [redacted]

CCH sterile diluent for reconstitution is 0.6% sodium chloride and 0.03% calcium chloride dehydrate filled into 2-mL vials.

10.8. Discussion of Study Design

This is a Phase 1, open-label study of CCH to assess the safety and determine the PK of CCH in female subjects with EFP following a single subcutaneous dose administration of CCH 3.36 mg as 12 injections per quadrant in 4 quadrants concurrently (0.84 mg per quadrant).

11. SELECTION AND WITHDRAWAL OF SUBJECTS

11.1. Subject Inclusion Criteria

No subject will be dosed until all eligibility criteria have been satisfied. In order to be eligible to participate in the study, subjects must meet the following criteria:

1. Be a female ≥18 years of age
2. Have evidence of cellulite within 4 quadrants (a quadrant is defined as a left buttock, right buttock, left posterolateral thigh or right posterolateral thigh) as assessed by the Investigator using the Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS) at the Screening visit; has a score of 2 (mild), 3 (moderate) or 4 (severe) as reported by the Investigator (CR-PCSS) in 4 quadrants at the Screening visit
3. Have a body mass index (BMI) between 20.0 and 35.0 kg/m^2, and intends to maintain stable body weight throughout the duration of the study (a variation of ≤10% from baseline body weight is permitted)
4. Be willing to apply sunscreen to the dosing quadrants 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 pregnancy test at the Screening visit and on Day -1 at admission (before injection of study drug); and be using an effective contraception method (eg, abstinence, intrauterine device [IUD], hormonal [estrogen/progestin] contraceptives, or double barrier control) for at least 1 menstrual cycle prior to study enrollment and for the duration of the study; or be menopausal defined as 12 months of amenorrhea in the absence of other biological or physiological causes, as determined by the Investigator; or post-menopausal for at least 1 year; or be surgically sterile (ie, hysterectomy, bilateral oophorectomy, tubal ligation).
7. Be willing and able to cooperate with the requirements of the study
8. Voluntarily sign and date an informed consent form approved by the Institutional Review Board/Independent Ethics Committee/Human Research Ethics Committee (IRB/IEC/HREC)

11.2. Subject Exclusion Criteria

A subject will be excluded from study participation if she:

1. 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.

2. 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) in areas to be treated
   c. Inflammation or active infection
   d. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer
   e. Has a tattoo located within 2 cm of the site of injection
3. Requires the following concomitant medications before or during participation in the trial:
   a. Anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication (except for ≤150 mg aspirin daily) within 7 days before injection of study drug
4. Has a positive test on a urine drug screen for drugs of abuse
5. Has a history of drug or alcohol abuse
6. Has used any of the following for the treatment of EFP on the legs or buttock 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 quadrants 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 quadrants during the 12-month period before injection of study drug
   c. Endermologie or similar treatments within the treatment quadrants during the 6-month period before injection of study drug
   d. Massage therapy within the treatment quadrants during the 3-month period before injection of study drug
   e. Creams (eg, Celluvera™, TriLastin®) to prevent or mitigate EFP within the treatment quadrants during the 2-week period before injection of study drug
7. Is presently nursing a baby or providing breast milk for a baby
8. Intends to become pregnant during the study
9. Intends to initiate an intensive sport or exercise program during the study
10. Intends to initiate a weight reduction program during the study

11. Has received an investigational drug or treatment within 30 days before injection of study drug
12. Has a known systemic allergy to collagenase or any other excipient of study drug
13. Has received any collagenase treatments at any time prior to treatment
14. Has been 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, EN3835-303, EN3835-304, and/or EN3835-209.

11.3. Subject Discontinuation Criteria

Subjects who have signed the informed consent may be discontinued or withdrawn from study treatment or the entire study at any time at their own request, or any time at the discretion of the investigator for the following reasons:

- An AE
- A protocol violation (reason must be specified, for example: lack of compliance with the protocol requires visits and assessments, use of a prohibited concomitant medication, failure to meet inclusion/exclusion criteria after study entry, 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)

11.3.1. Subject Discontinuation/Withdrawal from Treatment

Subjects who discontinue, or are withdrawn from study treatment for any reason, will be encouraged to complete all other study procedures as detailed in the schedule of events and provide any additional follow-up information as required by the study. If the subject specifically indicates that they will not participate in any further evaluations, they will be withdrawn from the study.

The date the subject discontinues or is withdrawn from treatment and the reason for treatment discontinuation/withdrawal will be recorded.

11.3.2. Subject Discontinuation/Withdrawal from Study

Subjects who discontinue, or are withdrawn from the study for any reason, will be encouraged to complete all end-of-study procedures as detailed in the schedule of events.

If, however, a subject withdraws consent, no end-of-study procedures are required except the collection of AE information. This information should be recorded in the source documentation and the eCRF.

The date the subject discontinues or is withdrawn from the study and the reason for study discontinuation/withdrawal will be recorded.

11.3.3. Replacement Procedures

Subjects who discontinue or are withdrawn from study treatment will not be replaced.

Subjects who discontinue or are withdrawn from the study will not be replaced.

12. TREATMENT OF SUBJECTS

12.1. Study Overview

The schedule of events to be performed at each visit is shown in Section 5. Further details on activities that occur on each study day are provided below. After obtaining informed consent, the full assessment of eligibility will be conducted prior to study entry.

Following a screening period of up to 21 days, subjects will be admitted to the research unit on Day −1. Subjects will be dosed on Study Day 1, and will receive 48 subcutaneous injections of CCH in 4 quadrants (12 injections per quadrant, concurrently in 4 quadrants). The post-injection PK sampling will begin within 5 minutes following the completion of the last injection.

Subjects will be discharged on Study Day 2 after the 24-hour post-injection blood collection and return for outpatient visits and complete the required blood draws and assessments, as described in the schedule of events in Section 5. The end of study visit is scheduled for Study Day 22. AEs will be monitored and recorded throughout the study.

The study activities should occur as described on each study day.

12.2. Informed Consent

Signed and dated informed consent will be obtained from each subject before any study procedures are undertaken, or before any changes to the subject's medication regimen are made. Details about how the informed consent will be obtained and documented are provided in Section 20.3.

12.3. Study Entry

A subject who gives written informed consent and who satisfies all eligibility criteria may be entered into the study. The following demographic information will be required for study entry:

- Subject initials
- Date of birth
- Gender

The subject will be assigned a unique subject identification number in sequential order.

12.4. Assessments: Listed by Each Study Day

12.4.1. Day −22 to Day −2: Screening Period

The Investigator 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). The Investigator will provide information about the study to subjects who appear to meet the criteria for participation in the study.

During the screening period, the Investigator or qualified designee will obtain a medical 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 and family history), and history of tobacco and alcohol use (never, current, former).

Subjects meeting the relevant eligibility criteria listed in Section 11 may be enrolled in the study after the nature and purpose of the protocol have been explained and written informed consent to participate has been voluntarily provided by the subject or their legally authorized representative. The following procedures will be performed in sequential order and documented during the screening period:

1. Obtain written informed consent
2. Evaluate eligibility based on inclusion/exclusion criteria
3. Conduct live assessments of subject's cellulite severity in all 4 quadrants (left and right buttock, left and right posterolateral thigh) using the CR-PCSS
4. Medical history including EFP history
5. Record prior and concomitant medications/procedures
6. Physical examination including measurement of body weight, height, and evaluation of the Fitzpatrick skin type
7. Vital sign measurements
8. 12-lead ECG
9. Collection of samples for:
    a. Clinical laboratory testing
    b. Pregnancy testing
    c. Alcohol breath test
    d. Urine drug screen
10. Monitor AEs

12.4.2. Day −1: Admission to the Clinical Research Unit

Subjects will be admitted to the clinic for the inpatient period on the afternoon of Day −1. The following procedures will be performed and documented:

1. Re-evaluate eligibility based on inclusion/exclusion criteria
2. Record prior and concomitant medications/procedures
3. Vital sign measurements
4. Pregnancy test
5. Alcohol breath test
6. Urine drug screen
7. Monitor AEs

12.4.3. Day 1: Pre-dose and Dosing Activities

On Day 1, a 10-mL blood sample will be collected prior to dosing to document any baseline plasma levels of AUX-I and AUX-II.

In addition, 3 × 5-mL blood samples will be collected as a baseline sample for baseline anti-AUX-I/anti-AUX-II antibody levels/neutralizing antibodies to AUX-I and AUX-II in serum; if it is later determined that antibody assays are warranted based on clinical findings and/or PK results.

Dimples to be treated will be selected and marked and subjects will then be dosed in the 4 quadrants as detailed in Section 10.5.

Adverse events and concomitant medications will be recorded throughout the study.

12.4.4. Day 1: Care Procedures After CCH Injections

Immediately after injection, the Investigator or qualified designee will apply pressure to the injection sites for 3 minutes. Additionally, 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 acute allergic reactions for the first 30 minutes after receiving an injection of study drug (see Section 10.5). A loose bulky gauze dressing may then be applied to the injection areas. Study personnel will remove the dressing in the evening to inspect the injection areas for edema and bruising.

During the first 30 minutes following injection, the subject will be monitored for:

- Signs of an immunological or other clinically significant systemic or local AEs
- Stable vital signs (see Table 5)

Subjects will also be informed as follows:

- Your injection areas may appear bruised and/or swollen
- You may have moderate pain

12.4.5. Day 1: Pharmacokinetic Sampling Post Dose

Collection of blood samples for PK assessment will begin at 5 minutes following the last injection of study drug. Samples (10 mL each) will be collected at the following time points after the last injection on Day 1: at 5, 10, 20, and 30 minutes and 1, 2, 4, 8 and 12 hours after dosing. Blood samples are to be collected within 10% of the nominal time. The exact time of collection will be noted in the source document and eCRF.

12.4.6. Day 2: Discharge from the Research Unit

On the morning of Day 2, the 24-hour PK blood sample will be collected. Subjects will be given breakfast, have their vital signs measured, and be assessed for any AEs (such as site reactions in the dosing areas or any other AE). Beginning on Day 2 and continuing through the outpatient period, subjects will also be instructed as follows:

- Take over-the-counter (OTC) pain medications (eg, acetaminophen) if needed for pain

- If you have severe pain or severe swelling, or any other symptoms, tell your study doctor

Subjects will then be discharged from the clinical research unit.

12.4.7. Day 3: Follow-up Outpatient Visit

On the morning of Day 3, subjects will return to the clinical research unit as an outpatient for the collection of the 48-hour post-dose PK blood sample. Subjects will have their vital signs measured, be assessed for any AEs, have the dosing areas checked, and questioned about taking any concomitant medications. Subjects will then be discharged from the clinical research unit and will be instructed when to return. The site will schedule the Day 8 visit.

12.4.8. Day 8: Follow-up Outpatient Visit

On the morning of Day 8, subjects will return to the clinical research unit as an outpatient for the collection of the 168-hour post-dose PK blood sample. Subjects will have their vital signs measured, be assessed for any AEs, have the dosing areas checked, and questioned about taking any concomitant medications. Subjects will then be discharged from the clinical research unit and will be instructed when to return. The site will schedule the Day 22 visit.

12.4.9. Day 22: End of Study Outpatient Visit

On the morning of Day 22, subjects will return to the clinical research unit as an outpatient for the end of study visit. At this visit, the 504-hour post-dose PK blood sample will be collected. In addition, the 3 × 5-mL blood samples for potential determination of anti-AUX-I/anti-AUX-II antibody levels/neutralizing antibodies to AUX-I and AUX-II in serum will be collected; antibody assays will be conducted only if clinical findings and/or PK results warrant the assays.

The cellulite severity assessments of each of the 4 treated quadrants using the CR-PCSS (live assessment) will be completed by the Investigator (or designee) at this end of study visit.

Subjects will have their vital signs measured, be assessed for any AEs, and questioned about taking any concomitant medications. The body weight will also be taken. Before they are discharged from the study, they will have a blood draw for clinical laboratory tests.

Following completion of all study related assessments and procedures; subjects will then be discharged from the clinical research unit.

12.5. Prior and Concomitant Medications and Procedures

All medications (including OTC medication) administered to or taken by the subject within 3 months prior to the Screening visit will be recorded.

Subjects cannot be taking antiplatelet agents or anticoagulants (except for ≤150 mg aspirin daily) within 7 days before and after the dosing administration. Thereafter, any changes in concomitant medications or new medications added will be recorded.

Any diagnostic, therapeutic, or surgical procedure performed before the study period, including those for the treatment of EFP, should be recorded including the date, indication for, and description of the procedure.

12.5.1. Prohibited Medications or Procedures

The following medications are prohibited 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 the study.

Table 3: Concomitant Medication Restrictions

Drug Class	Restrictions
Anticoagulants	Subjects cannot be taking antiplatelet agents or anticoagulants (except for ≤150 mg aspirin daily) within 7 days before and after the dosing administration.

12.5.2. Prohibited Procedures

The treatments and procedures listed in exclusion criteria 6 are prohibited during the study.

12.6. Treatment Compliance

All subjects will receive study drug administered by a clinician in the clinical research unit.

Accidental or intentional overdoses should be reported to the Sponsor/designee promptly (see Section 14.6.2.1).

12.7. Blinding and Randomization

This study will be conducted as an open-label investigation; no blinding of assigned treatment will occur.

13. ASSESSMENT OF CELLULITE SEVERITY

13.1. Cellulite Severity Analysis

Cellulite severity will be assessed by the Investigator's rating of cellulite severity using the CR-PCSS. Evaluations will be done on each of the 4 quadrants at Screening and Study Day 22.

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 preexisting condition associated temporally with the use of the study medication whether or not considered related to the study medication. AEs 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 preexisting disease
- All clinically relevant laboratory abnormalities or physical findings that occur during the study

A 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 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. 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 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 visit, subjects will be queried regarding any AEs that have occurred since the last visit. Subjects will be asked to volunteer information concerning AEs with a non-leading question such as, "How do you feel?" Study site 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.

When the intensity category of an AE changes, the greatest intensity during that continuous episode should be recorded.

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 14 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 to [redacted] 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 drug. 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 an 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 non-serious should be reported on the eCRF.

14.6. Special Reporting Situations

14.6.1. Adverse Events of Special Interest

[redacted] will be reported as an AE in the eCRF. All AEs will be evaluated for seriousness and severity. If any of these events meet the criteria for an SAE, they will also be reported as such using the procedure outlined in Section 14.5.2.

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 (see Section 12.6) should be reviewed to detect potential instances of overdose (intentional or accidental).

Any study drug overdose during the study should be noted on the study medication eCRF.

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 in Section 14.5.2, 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 Serious Adverse Event (SAE)/

Reportable Event Form and in an expedited manner, but should be noted as non-serious on the form and the Adverse Event eCRF.

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 dosing or within 22 days of the last dose of study medication 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 Pregnancy Form, and any pregnancy-associated SAE using the SAE report form, according to the usual timelines and directions for SAE reporting provided in Section 14.5.2. Monitoring of the pregnancy should continue until conclusion of the pregnancy; 1 or more Pregnancy 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 SAE report form. Spontaneous miscarriages should also be reported and handled as SAEs.

Subjects should be instructed to immediately notify the Investigator of any pregnancies.

Attempts to obtain the pregnancy follow-up and pregnancy outcome information detailed above are necessary even if a subject discontinues from the study 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 non-subjects from such exposure will be reported to the Endo Pharmacovigilance and Risk Management (PVRM) Department (when the non-subject agrees) on the Serious Adverse Event (SAE)/Reportable Event Form for serious adverse experiences 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. Additionally, the drug accountability source documentation at the site should reflect this occurrence.

14.7. Clinical Safety Laboratory Determinations

Clinical laboratory tests will be conducted according to the schedule of events (Section 5). Clinical laboratory tests will be performed by a local laboratory. The results of the tests will be returned to the investigational site.

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 local laboratory.

The Investigator will review all abnormal lab results for clinical significance. Any abnormal clinical laboratory test result meeting the Investigator's criteria for clinical significance will be recorded as an AE or SAE as appropriate (see Section 14.1.1 and Section 14.1.2).

Clinical laboratory parameters that will be measured in this study are listed in Table 4.

Table 4: Clinical Safety 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.

14.7.1. Pregnancy Testing

For women of childbearing potential, a urine pregnancy (dipstick) test or serum pregnancy test will be performed at the Screening visit and at admission (Day −1). Female subjects of childbearing potential must have a negative pregnancy test to enter the study. If necessary, additional urine pregnancy tests or serum pregnancy tests can be performed at any time during the study at the discretion of the Investigator.

14.7.2. Urine Drug Screen

The Investigator will collect urine samples for the screening of the following drugs of abuse: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, opiates, and/or propoxyphene at the Screening visit and on Day −1. Test must be negative before dose administration.

14.7.3. Alcohol Breath Test

The Investigator will administer a breathalyzer test for the screening of alcohol at the Screening visit and on Day −1. Test must be negative before dose administration.

14.8. Immunogenicity Samples for Collection

Immunogenicity variables include anti-AUX-I/anti-AUX-II binding (ie, anti-drug) and neutralizing antibody results. Anti-drug antibody levels will be determined from samples (3 × 5-mL tubes of blood) collected pre-dose on Day 1 and on Day 22; neutralizing antibody levels will be determined for samples collected on Day 1 and Day 22 for the subset of anti-drug antibody positive subjects on Day 22. If testing is warranted, the 3 tubes will be assayed as follows: The first tube will be assayed for the measurement of anti-AUX-I antibodies and for anti-AUX-II antibodies; the second tube will contain the same and be the back-up tube; the third tube will be assayed for neutralizing antibodies. The serum samples obtained will be processed, stored, and then shipped on dry ice to the designated laboratories for the determination of anti-AUX-I and anti-AUX-II antibodies, and neutralizing antibodies according to the instructions in the Laboratory Manual.

Immunogenicity samples will be assayed for antibody levels only if warranted by clinical findings and/or PK results.

14.9. Vital Signs

Vital sign measurements will be documented as described in the schedule of events and as detailed in Table 5. These parameters include radial pulse rate, respiratory rate, systolic and diastolic blood pressure, and oral body temperature. Subjects with systolic blood pressure greater than 180 mm Hg or less than 90 mm Hg or diastolic blood pressure greater than 105 mm Hg or less than 50 mm Hg at Screening or at admission on Day −1 should be excluded from study participation.

Blood pressure (systolic/diastolic), respiratory rate, pulse rate, and oral body temperature will be assessed after the subject has rested for at least 5 minutes.

Table 5: Vital Signs Measurement Throughout the Study

	Systolic/Diastolic Blood Pressure, Respiratory Rate, and Radial Pulse Rate	Oral Body Temperature
Screening	Taken	Taken
Admission	Taken	Taken
Day 1 - Dosing	Taken up to 4 hours pre-dose and at 15 and 30 minutes post dose	Taken up to 4 hours pre-dose and at 30 minutes post dose (not required at the 15-minute post dose draw)
Day 2 - Discharge	Taken before 24-hour PK blood sample	Taken before 24-hour PK blood sample
Day 3 OPV	Taken before 48-hour PK blood sample	Taken before 48-hour PK blood sample
Day 8 OPV	Taken before 168-hour PK blood sample	Taken before 168-hour PK blood sample
Day 22 OPV	Taken before 504-hour PK blood sample	Taken before 504-hour PK blood sample

The Investigator will review all vital sign values for clinical significance. Any vital sign value meeting the Investigator's or Sponsor's criteria for clinical significance will be recorded as an AE or SAE as appropriate (see Section 14.1.1and Section 14.1.2).

14.10. Electrocardiogram

During the screening period, subjects will have a resting 12-lead ECG performed. A qualified physician will interpret, sign, and date the ECGs. ECG assessments must be "within normal limits" or interpreted as "abnormal, not clinically significant" for the subject to be included in the study. 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.

14.11. Physical Examination

During the Screening visit, the Investigator or qualified designee will perform a complete physical examination (by body system) on each subject. Height and body weight will be measured and recorded (body weight will also be recorded at Day 22). Laxity of the skin on the buttocks and/or thighs should be considered to ensure there are no underlying pathologies that would prevent an assessment of EFP severity.

At screening, the Investigator will also assess the subject's skin type using the Fitzpatrick scale.

Only the specific Fitzpatrick Scale shown below (Table 6) may be used during the study.

Table 6: 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

15. ASSESSMENT OF PHARMACOKINETICS

15.1. Study Drug Concentration Measurements

15.1.1. Blood Sample Collections

15.1.1.1. Pharmacokinetic Sample Collection and Processing

Blood collection (10 mL) for PK measurement of plasma AUX-I and AUX-II concentrations are to be taken before dosing and at 5, 10, 20, and 30 minutes and 1, 2, 4, 8, 12, 24, 48, 168, and 504 hours after dosing. Blood samples are to be collected within 10% of the nominal time. The exact time of collection will be noted in the source document and eCRF.

Blood samples will be collected from all subjects participating in the study. Each subject will have 10-mL samples of venous blood drawn and placed into lithium heparin tubes.

Clock times for specimen drawing/collecting, handling (eg, centrifuging, freezing), storage, and shipment to the analytical lab will be logged by study site personnel on the appropriate tracking forms for sample collection, storage, and shipment.

All sample collection and freezing tubes will be clearly labeled in a fashion, which identifies the subject, date, and the collection time. The containers must be securely labeled in a manner that will keep the label attached to the container under the conditions of low temperature freezing.

Serial blood samples for the intensive PK sampling period (initial 12 hours post dose) may be obtained from an indwelling intracatheter or percutaneous venipuncture. If utilized, the intracatheter will be inserted into the subject's vein before the predose sample collection and will be used to collect all scheduled blood samples throughout the day. Immediately prior to each collection time point, 2 to 3 mL of the blood/saline mixture will be withdrawn and discarded (to prevent sample dilution) and the sample withdrawn at the appropriate time point listed in Section 5. Intracatheters will be maintained and kept open with the use of saline flush as needed. Once the blood samples have been obtained, the intra-catheter will be removed.

The plasma samples will be collected, processed, stored, and shipped as described in the Laboratory Manual.

Any deviation from the scheduled sample time should be recorded on the eCRF.

15.1.2. Sample Shipment Guidelines

Samples will be shipped by overnight, priority courier. The samples will be divided into 2 shipments, each containing 1 aliquot of plasma for each time point. After receipt of verification that the first shipment was received by the analytical facility, the second shipment will be processed.

Samples will be shipped only on Monday, Tuesday, or Wednesday to the analytical facility. The shipping address and contact information will be provided in a separate document.

15.2. Total Blood Volume Collected for the Study

The total blood volume expected to be drawn for the study is approximately 233 mL, as follows:

PK Samples: 14 samples × 10 mL/draw = 140 mL.

(Assuming the site uses an indwelling catheter to collect the first 11 samples out to 24 hours, an additional 3 mL of blood will be used for the required flush at each of these time points).

Flush volume (if indwelling catheter is used) = 11 samples × 3 mL flush = 33 mL.

Immunogenicity: (3 × 5-mL tubes of blood) × 2 time points = 30 mL.

Clinical Safety Labs (hematology/clinical chemistry): 15 mL blood × 2 time points = 30 mL.

16. STATISTICAL CONSIDERATIONS AND METHODS

16.1. Determination of Sample Size

Since this is primarily a PK and safety study, no formal sample size calculation was required. Twelve (12) subjects will be enrolled to receive the dose in the study. A minimum of 10 subjects should complete the study. The selection of between 12 and 16 subjects is typical for such trials.

16.2. Subject Populations

Three (3) populations are considered in the statistical analysis of the study.

16.2.1. Safety Population

The safety population is all enrolled subjects who receive at least one CCH injection.

16.2.2. Pharmacokinetic Population

The pharmacokinetic (PK) population is all enrolled subjects who receive the full CCH dose and have sufficient data from the 24-hour PK profile.

16.2.3. Cellulite Severity Population

The cellulite severity population consists of all enrolled subjects who receive at least one CCH injection and have the Screening and Day 22 CR-PCSS evaluation completed.

16.3. Subject Disposition

The number of subjects included in each study population will be summarized. Subjects excluded from the safety, PK, or cellulite severity populations will be listed.

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

16.4. Demographics and Other Baseline Characteristics

Demographic characteristics, including sex, age, age group, race, height, and weight, will be summarized for the safety population, using descriptive statistics. The descriptive summaries will include frequency tables for all categorical response variables and number, mean, standard deviation (SD), median, minimum, and maximum for all continuous variables.

16.5. Cellulite Severity Analyses

Cellulite severity will be assessed by the Investigator's rating of cellulite severity using the CR-PCSS. Evaluations will be done on each of the 4 quadrants at the Screening visit and Day 22. Change from baseline in cellulite severity will be computed. The Screening and Day 22 ratings will be summarized with counts and percentages at each level of severity and with mean and SD. The change from baseline value will be summarized with counts and percentages at each

possible change value and with mean and SD. The cellulite severity population will be used for summarizing the cellulite severity data.

16.6. Safety Analyses

Safety variables include AEs, laboratory parameters, and vital signs and will be analyzed using the safety population.

16.6.1. Prior, Concomitant, and Follow-up Medication

The WHO Drug Dictionary will be used to classify prior and concomitant medications by therapeutic class. The version used in this study will be stated in the Data Management Plan. Prior medication will be defined as any medication with a start date prior to the Day 1 date and are collected at the Screening visit and upon admission to the clinic on Day −1. Concomitant medication is defined as any medication with a start date on or after the Day 1 date or reported as ongoing.

Prior and concomitant medication use will be summarized descriptively by the number and percentage of subjects receiving each medication within each therapeutic class. Multiple use of the same medication by a subject will be counted only once.

16.6.2. Study Drug Exposure

The number of injections of study drug given on Day 1 will be summarized by counts and percentages. Any subject receiving less than 48 injections (12 injections per quadrant) will be listed. The number of dimples treated will be summarized with counts and percentages.

16.6.3. Measurement of Treatment Compliance

All doses are administered while subjects are confined as an inpatient in the clinical research unit. Any dose that was not administered per protocol will be recorded as a protocol deviation by the Investigator.

16.6.4. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code AEs. The version used in this study will be stated in the Data Management Plan.

An AE (classified by preferred term) that started during the treatment period 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 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, and subjects who die (if any).

16.6.5. Vital Signs

Descriptive statistics for vital signs (eg, systolic and diastolic blood pressure, pulse rate, and body temperature) and their changes from baseline at each visit and at the end of study will be presented by dose. Baseline will be the Day 1 pre-dose values.

Vital sign values are potentially clinically important (PCI) if they meet both the observed value criteria and the change from baseline criteria. The criteria for PCI vital sign values will be detailed in the Statistical Analysis Plan (SAP). A listing of subjects with post-baseline PCI values will be provided.

16.6.6. Clinical Safety Laboratory Parameters

Descriptive statistics for clinical laboratory values in International System of Units (SI units) and changes from baseline will be presented for each clinical laboratory parameter.

The number and percentage of subjects with PCI post-baseline clinical laboratory values will be tabulated. The criteria for PCI laboratory values will be detailed in the SAP. A listing of subjects with post-baseline PCI values will be provided.

16.6.7. Immunogenicity

Immunogenicity variables include anti-AUX-I/anti-AUX-II binding and neutralizing antibody results. Antibody assays will be conducted only if clinical signs and/or PK results warrant a need for antibody determinations. If warranted, binding antibody levels will be determined from samples (3 × 5-mL tubes of blood) collected on Day 1 and 22; neutralizing antibody levels will be determined for samples collected on Day 1 and Day 22 for all subjects seropositive for anti-AUX-I or anti-AUX-II at Day 22.

If antibody assays conducted, descriptive statistics (percent of positive measurements and average antibody level) will be presented for anti-AUX-I and anti-AUX-II antibody levels at each time point. Average antibody levels will be summarized on logarithmically transposed titer values. Neutralizing antibodies will be summarized as present or absent at each time point.

16.7. Pharmacokinetic Analyses

16.7.1. Plasma Concentrations

All plasma draws collected outside the protocol specified time window will be listed. This listing will include the nominal time from the injection, the actual time from the injection, and the difference between the 2 times, and the plasma concentrations of AUX-I and AUX-II. Blood samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60-minute sample) relative to the last dose will not be captured as protocol deviations. The exact time of sample collection must be noted on the source document and the eCRF.

A measured drug concentration for plasma AUX-I and AUX-II versus time curve will be produced in graphic form for each subject with at least 1 drug concentration value above quantification limit. Plasma concentrations of plasma AUX-I and AUX-II will be summarized with descriptive statistics (number, mean, SD, median, minimum, and maximum) at each nominal sample time point. If the concentration levels are below the limit of quantification (BLQ) for all subjects at a time point, then not calculable will be reported in the summary table.

16.7.2. Calculation of Pharmacokinetic Variables

Pharmacokinetic data will be summarized through data tabulations, descriptive statistics, and graphic presentations, as appropriate. Actual blood sampling times will be used in all PK analyses.

Pharmacokinetic variables of AUX-I and AUX-II will be estimated from the plasma concentration data using a non-compartmental approach on standard PK software (eg, WinNonlin). Actual sample times (hours, relative to the corresponding administration time) rounded to 2 decimal digits and negative pre-dose times set to zero, will be used in the computation of the PK variables, rather than scheduled times.

The definition and method of determination for each PK parameter are summarized in Table 7.

Table 7: Pharmacokinetic Parameters

Variable	Definition
AUC_{0-t}	Area under the plasma concentration versus time curve from time 0 to the time of last quantifiable concentration (C_t), calculated by linear trapezoidal rule
AUC_{0-inf}	Area under the plasma *c*oncentration versus time curve from time 0 to infinity calculated as $AUC_{0-t} + C_t/\lambda_n$
C_{max}	Observed maximum plasma concentration; the highest concentration observed during a dosage/application interval
T_{max}	The time at which C_{max} was observed
λ_n	Terminal rate constant, calculated as the negative slope of the ln-linear portion of the terminal plasma concentration-time curve

16.7.3. Analysis of Pharmacokinetic Results

AUC_{0-t}, AUC_{0-inf}, and C_{max} will be summarized with descriptive statistics (number, mean, SD, median, minimum, and maximum) as well as the geometric mean and coefficient of variation (CV). Geometric means and CV will be calculated for the log transformed parameters using the following SAS formula:

$$CV\ (\%) = SQRT[\exp(SD^2)-1] * 100$$

T_{max} will be summarized with descriptive statistics (number, mean, SD, median, minimum, and maximum) only.

If all subjects have all PK concentrations BLQ, then all PK parameters will be summarized as not calculable.

16.8. Interim Analysis

No interim analysis is planned for this study.

16.9. Statistical Software

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

17. STUDY DRUG MATERIALS AND MANAGEMENT

17.1. 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, [redacted]

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

17.2. 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.

17.3. 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 refrigerator (2°C-8°C) with locked access until used or returned to Endo. The reconstituted study drug solution should be administered as soon as possible after reconstitution (Section 10.4).

17.4. Study Drug Preparation

Refer to the Reconstitution Instructions for detailed preparation instructions.

For each dose, reconstitute 4 vials of CCH using 4 vials of sterile diluent and prepare 16 syringes (4 syringes for each quadrant) each containing 0.9 mL/syringe.

Used drug and diluent vials should be stored in a secure location until reconciled and returned by the Clinical Research Associate (CRA). Used needles and syringes should be disposed of per local regulations.

Study drug is stable at room temperature for [redacted] Remove drug/prepared syringes from the refrigerator and allow to stand at room temperature for 15 minutes prior to injection of study drug.

17.5. Study Drug Accountability

A drug inventory form must be kept current by the site 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 containers of unused study drug and diluent to Endo or their designee.

17.5.1. 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 unused study drug will be returned, and unit counts will be performed whenever medication is returned. The site must account for all study drug received. At the end of the study, all unused drug supplies will be returned to Endo.

18. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

18.1. 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. At a minimum, all data required to be collected by the protocol should have supporting source documentation for entries in the eCRF, unless the protocol specifies that data can be recorded directly on/in the eCRF or other device.

18.2. 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 the Investigative site for study progress and to verify that standards of Good Clinical Practice (GCP) were followed. Monitors may be present on site for each dosing day. The Investigator is expected to prepare for the monitoring visit, ensuring that all source documents, completed eCRFs, signed consent forms and other study related documents are readily available for review.

18.3. 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 Food and Drug Administration (FDA) or other regulatory agency inspection.

18.4. Institutional Review Board (IRB)

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

18.5. 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.

19. 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 site termination and regulatory authority notification.

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

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.

20. ETHICS

20.1. 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 Summary of Product Characteristics (SmPC) 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 Pharmaceuticals Inc. 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.

20.2. 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, 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.

20.3. Subject Information and Consent

Subjects [if competent], 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, acknowledge 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 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 will be given to the subject and originals will be placed in the Investigator study files.

A unique subject identification (ID) number will be assigned at the time that the subject signs the informed consent form.

[redacted]

21. DATA HANDLING AND RECORDKEEPING

21.1. Data Collection

Endo will provide an electronic data capture (EDC) system for this study. Data collection will involve the use of an 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 electronic case report form (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 sites and closed electronically by the monitor, data management staff or authorized staff at the study site. 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).

Data entries will be corrected by changing the entry in the EDC system. Any changes or corrections to eCRF data will be electronically tracked and will include the reason for correction, who made the correction and the date/time stamp when the correction was made within the audit trail of the EDC system.

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.

21.2. Study Documentation

Upon study completion, the Investigator will be provided with complete electronic copies of the CRF data for his/her files.

22. 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.

23. INVESTIGATOR OBLIGATIONS

23.1. 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.
- 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, as described in Section 20.1
- 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 site 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.

23.2. 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.

23.3. 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 (Section 14.5). The Investigator will inform study subjects of new information regarding the study drug as it becomes available.

23.4. 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 site. 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. All study supplies shall be returned to Endo.

23.5. 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 Pharmaceuticals Inc. will notify Investigators once one of the above 2 timeframes 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.

23.6. Subject Confidentiality

All subject records submitted to Endo or its designee will be identified only by subject number. Subject 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.

24. 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.

25. 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 Name of Investigator

26. REFERENCES

Avram MM. Cellulite: a review of its physiology and treatment. *J Cosmet Laser Ther*. 2004;6(4):181-5.

Boyce S, Pabby A, Chuchaltkaren P, Brazzini B, Goldman MP. Clinical evaluation of a device for the treatment of cellulite: Triactive. *Am J Cosmet Surg*. 2005;22:233-7.

Collis N, Elliot LA, Sharpe C, Sharpe DT. Cellulite treatment: a myth or reality: a prospective randomized, controlled trial of two therapies, Endermologie and aminophylline cream. *Plast Reconstr Surg*. 1999;104(4):1110-4.

DiBernardo BE. Treatment of cellulite using a 1440-nm pulsed laser with one-year follow-up. *Aesthet Surg J*. 2011;31(3):328-41.

Endo Pharmaceuticals Inc. Collagenase clostridium histolyticum for Injection (AA4500/EN3835), Version 8.0. Investigational Brochure; July 2017.

Hexsel D, de Oliveira Dal'Forno T, Mazzuco R. Definition, clinical aspects, classifications, and diagnostic techniques. In: Goldman MP, Hexsel D, eds. *Cellulite: Pathophysiology and Treatment*. 2nd ed. New York, NY: Informa Healthcare; 2010:13-21.

Hexsel DM, Mazzuco R. Subcision: A treatment for cellulite. *Int J Dermatol*. 2000;39(7):539-44.

Khan MH, Victor F, Rao B, Sadick NS. Treatment of cellulite: Part I. Pathophysiology. *J Am Acad Dermatol*. 2010a;62(3):361-70.

Khan MH, Victor F, Rao B, Sadick NS. Treatment of cellulite: Part II. Advances and controversies. *J Am Acad Dermatol*. 2010b;62(3):373-84.

Rawlings AV. Cellulite and its treatment. *Int J Cosmetic Sci*. 2006;28(3):175-90.

Terranova F, Berardesca E, Maibach H. Cellulite: nature and aetiopathogenesis. *Int J Cosmetic Sci*. 2006;28(3):157-67.

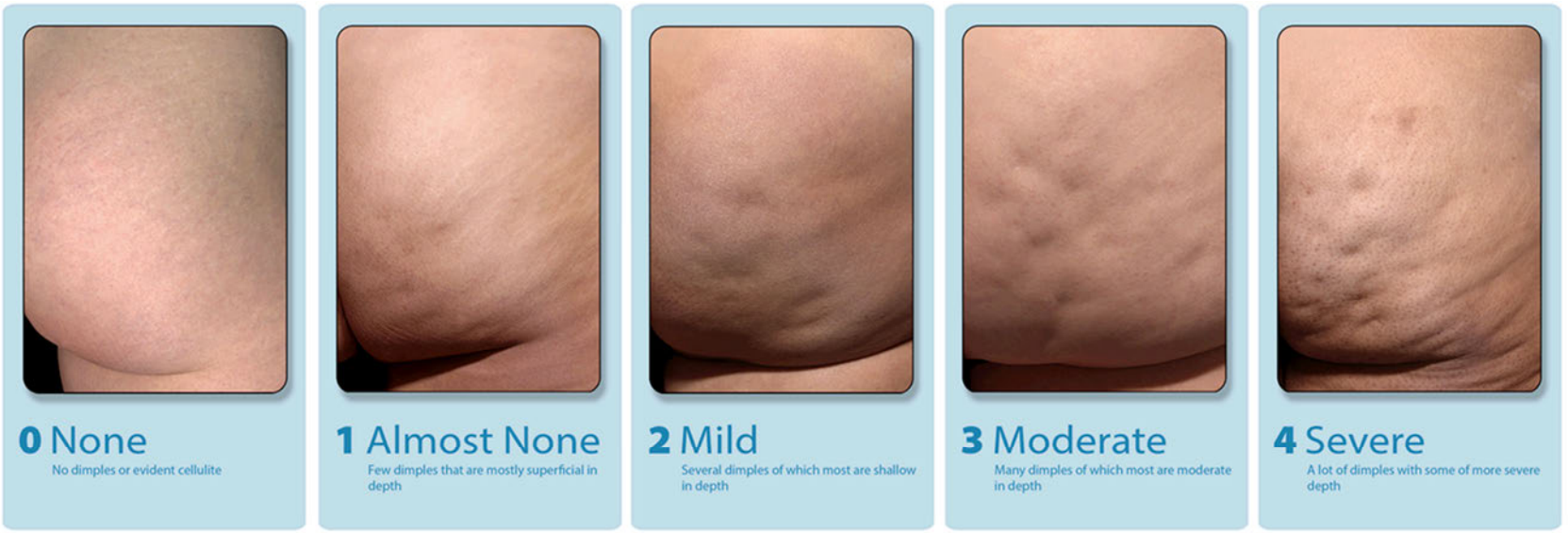
[redacted]

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

Investigator Rating

Prior to enrollment of the first subject, the Investigator will be trained on the use of the CR-PCSS. During the Screening visit, the Investigator will determine severity of cellulite of all 4 quadrants by live assessment, using the CR-PCSS for buttock and thigh (see below). On Day 22, the Investigator will evaluate the 4 quadrants that were dosed, by live assessment.

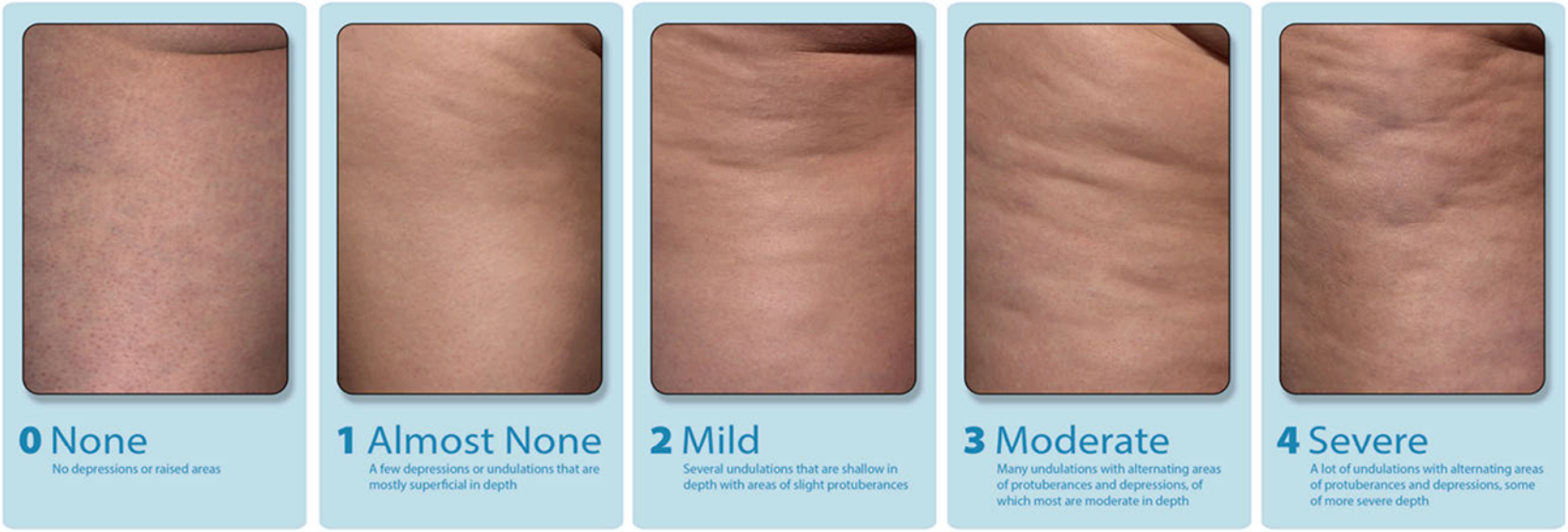
Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) – Buttock



Produced by **CANFIELD Scientific, Inc.**

Version 10.0

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



Produced by **CANFIELD Scientific, Inc.**

Version 10.0

Endo Pharmaceuticals Inc.
1400 Atwater Drive
Malvern, PA 19355 USA

COLLAGENASE CLOSTRIDIUM HISTOLYTICUM (EN3835)

EN3835-103

A PHASE 1, OPEN-LABEL STUDY TO ASSESS THE SAFETY AND PHARMACOKINETICS OF A SINGLE DOSE OF EN3835 (3.36 MG) IN SUBJECTS WITH EDEMATOUS FIBROSCLEROTIC PANNICULOPATHY

IND 110,077

Date:

February 14, 2017

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

Confidentiality Statement

2. SUMMARY OF CHANGES

Not applicable

[redacted]

3. SPONSOR CONTACT INFORMATION

Table 1: Sponsor Contact Information

Role in Study	Name	Telephone and Email Address
Clinical Trial Monitor	[redacted]	[redacted]
Medical Monitor	[redacted]	[redacted]
SAE Reporting Pathway	Not applicable – report through Endo SAE Pathway	[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: EN3835 (collagenase clostridium histolyticum)

Name of Active Ingredient: Collagenase clostridium histolyticum

Title of Study: A Phase 1, Open-Label Study to Assess the Safety and Pharmacokinetics of a Single Dose of EN3835 (3.36 mg) in Subjects with Edematous Fibrosclerotic Panniculopathy

Lead Principal Investigator: To be determined

Study period:	**Phase of development:** Phase 1
Estimated date first subject enrolled: 1Q 2017 Estimated date last subject completed: 2Q 2017	

Objectives:

Primary: The primary objectives of this study are to assess safety, and determine if there is systemic exposure, following a subcutaneous single dose of EN3835 (3.36 mg) as 12 injections per quadrant in 4 quadrants concurrently (0.84 mg per quadrant) in adult women with edematous fibrosclerotic panniculopathy (EFP), commonly known as cellulite.

Study Design: This is a Phase 1, open-label, single-dose administration study of the safety, pharmacokinetics (PK), and immunogenicity of EN3835.

Number of subjects (planned): Approximately 12 subjects will be enrolled to receive the full dose of study drug on Day 1. A minimum of 10 subjects should complete the study with PK profiles for evaluation.

Study center(s): 1 site in the United States

Diagnosis and inclusion/exclusion criteria:

Inclusion criteria:

1. Be a female ≥18 years of age
2. Have evidence of cellulite in 4 quadrants (a quadrant is defined as a right or left buttock or the right or left posterolateral thigh) as assessed by the Investigator using the Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS) at the Screening visit; has a score of 2 (mild), 3 (moderate) or 4 (severe) as reported by the Investigator (CR-PCSS) in 4 quadrants at the Screening visit
3. Have a body mass index (BMI) between 20.0 and 35.0 kg/m^2, and intends to maintain stable body weight throughout the duration of the study (a variation of ≤10% from baseline body weight is permitted)
4. Be willing to apply sunscreen to the dosing quadrants 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 urine pregnancy test at the Screening visit and on Day −1 at admission (before injection of study drug); and be using an effective contraception method (eg, abstinence, intrauterine device [IUD], hormonal [estrogen/progestin] contraceptives, or double barrier control) for at least 1 menstrual cycle prior to study enrollment and for the duration of the study;

or be menopausal defined as 12 months of amenorrhea in the absence of other biological or physiological causes, as determined by the Investigator; or post-menopausal for at least 1 year; or be surgically sterile (ie, hysterectomy, bilateral oophorectomy, tubal ligation).

7. Be willing and able to cooperate with the requirements of the study
8. Voluntarily sign and date an informed consent agreement approved by the Institutional Review Board/Independent Ethics Committee/Human Research Ethics Committee (IRB/IEC/HREC)

Exclusion criteria:

A subject will be excluded from study participation if she:

1. 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.
2. 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) in areas to be treated
   c. Inflammation or active infection
   d. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer
   e. Has a tattoo located within 2 cm of the site of injection
3. Requires the following concomitant medications before or during participation in the trial:
   a. Anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication (except for ≤150 mg aspirin daily) within 7 days before injection of study drug
4. Has a positive test on a urine drug screen for drugs of abuse
5. Has a history of drug or alcohol abuse
6. Has used any of the following for the treatment of EFP on the legs or buttock 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 quadrants 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 quadrants during the 12-month period before injection of study drug
   c. Endermologie® or similar treatments within the treatment quadrants during the 6-month period before injection of study drug
   d. Massage therapy within the treatment quadrants during the 3-month period before injection of study drug
   e. Creams (eg, Celluvera™, TriLastin®) to prevent or mitigate EFP within the treatment quadrants during the 2-week period before injection of study drug
7. Is presently nursing a baby or providing breast milk for a baby

8. Intends to become pregnant during the study
9. Intends to initiate an intensive sport or exercise program during the study
10. Intends to initiate a weight reduction program during the study
11. Has received an investigational drug or treatment within 30 days before injection of study drug
12. Has a known systemic allergy to collagenase or any other excipient of study drug
13. Has received any collagenase treatments at any time prior to treatment
14. Was a subject in a previous cellulite clinical trial of EN3835: AUX-CC-830, AUX-CC-831, EN3835-102, EN3835-201, and/or EN3835-202

Investigational product, dosage, and mode of administration: Investigational product is EN3835. A single dose of 3.36 mg of EN3835 will be administered as 12 subcutaneous injections (EN3835 0.84 mg) per quadrant concurrently in 4 quadrants for a total of 48 injections. A quadrant is defined as one of the following: left buttock, right buttock, left posterolateral thigh, or right posterolateral thigh.

Study Drug Total Dose	Injection Volume per Each of Injection	Injection Regimen	Total Injection Volume Administered at the Dosing Session
EN3835 (3.36 mg)	0.3 mL injection volume (administered as three 0.1 mL aliquots)	48 subcutaneous injections comprise a single dose	14.4 mL (48 injections × 0.3 mL)

The study drug (EN3835) will be injected subcutaneously while subject is in a prone position using a syringe with a 30-gauge ½-inch needle. Each injection site will receive a single skin injection of study drug administered as three 0.1-mL aliquots (for a total injection volume of 0.3 mL per injection; an injection volume of 3.6 mL per quadrant and a total injection volume of 14.4 mL).

Duration of study: 43 days (includes screening phase)

Screening Phase: Up to 21 days

Dosing Phase: Subjects will be admitted to the research unit on the afternoon of Day −1. Dosing will occur on Study Day 1. Subjects will remain in the research unit for collection of the PK samples out to 24 hours post dose. They will then be discharged after the last sample is collected on Study Day 2.

Follow up: Subjects will return to the study unit on Day 3, 8, and 22 for outpatient follow-up PK, immunogenicity, and safety assessments. The last scheduled outpatient visit to the clinic for assessments is on Study Day 22.

Criteria for evaluation:

Safety: The safety of EN3835 will be evaluated through the collection of adverse events (AEs), including a targeted assessment of local/systemic reactions to the dose. Vital sign measurements and clinical laboratory testing will also be performed.

Pharmacokinetics: Subjects will have blood samples collected for the determination of plasma AUX-I and AUX-II concentrations before dosing and 5, 10, 20, and 30 minutes, then at 1, 2, 4, 8, 12, and 24 hours after dosing while confined to the research unit. Subjects will return for PK blood draws at 48 (Day 3), 168 (Day 8), and 504 (Day 22) hours post dose on an outpatient basis. All blood samples are to be collected within 10% of the nominal time.

The following PK parameters will be determined for each subject who has quantifiable plasma concentrations at any time during the 504-hour period following the last injection: maximum drug concentration (C_{max}), time to maximum drug concentration (T_{max}), and area under the curve (AUC_{0-t} and AUC_{0-inf}).

Immunogenicity: Blood samples will be collected pre-dose on Day 1 and on Day 22 after dosing for possible determination of anti-AUX-I and anti-AUX-II antibodies in serum; assay of these samples will

be conducted only if clinical signs and/or PK results warrant determinations. Descriptive statistics (percent positive measurements and average antibody level) will be calculated for anti-drug antibody titers at each visit if antibody determinations are conducted.

Cellulite Severity Evaluation: Cellulite will be assessed by the Investigator's rating of cellulite severity using the CR-PCSS at the Screening visit and on Day 22.

Statistical methods:

Sample Size Consideration: No formal sample size calculations were performed. Completion of 10 subjects will provide sufficient data to meet the PK study objectives.

Cellulite Severity Analysis: Evaluations will be done on the quadrants using the CR-PCSS at Screening and Day 22. Change from baseline in cellulite severity will be computed. The Screening and Day 22 ratings will be summarized with counts and percentages at each level of severity and with mean and standard deviation (SD). The change from baseline value will be summarized with counts and percentages at each possible change value and with mean and SD. The cellulite severity population will be used to summarize the cellulite severity data.

Pharmacokinetic Analysis: PK data will be summarized through data tabulations, descriptive statistics, and graphic presentations, as appropriate. Actual blood sampling times will be used in all PK analyses. $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} will be summarized with descriptive statistics (number, mean, SD, median, minimum, and maximum) as well as the geometric mean and coefficient of variation (CV). Geometric means and CV will be calculated for the log transformed parameters, using the following SAS formula:

$$CV\ (\%) = SQRT[\exp(SD^2)-1] * 100$$

T_{max} will be summarized with descriptive statistics (number, mean, SD, median, minimum, and maximum) only.

If all subjects have all PK concentrations below the limit of quantification (BLQ), then all PK parameters will be summarized as not calculable (NC).

[redacted]

5. SCHEDULE OF EVENTS

	Inpatient at the Research Unit				Follow-up Outpatient Visits (OPV)		
Event	**Screening**	**Admit to Clinic**	**Dose**	**Discharge from Clinic**	**OPV**	**OPV**	**OPV**
Study Day	**Day −22 to Day −2**	**Day −1**	**Day 1**	**Day 2** (24 hours post dose)	**Day 3** (48 hours post dose)	**Day 8** (168 hours post dose)	**Day 22/ End of Study** (504 hours post dose)
Informed Consent[a]	X						
Inclusion/Exclusion[b]	X	X					
Medical History/EFP History Including Previous Treatments	X						
Prior Concomitant Medications/Procedures	X	X	X	X	X	X	X
Physical Examination:	X						
Body Weight	X						X
Height	X						
Fitzpatrick Skin Type	X						
Vital Signs[c]	X	X	X	X	X	X	X
12-Lead ECG	X						
Clinical Safety Laboratory Tests[d]	X						X
Urine Pregnancy Test	X	X					
Urine Drug Screen[e]	X	X					
Alcohol Breath Test	X	X					
Investigator's Cellulite Assessment: Thigh/Buttocks							
Investigator-Reported Photonumeric Cellulite Severity Scale (CR-PCSS)[f]	X						X
Select/Mark Dimples Within the Quadrants – Pre-dose			X				

	Inpatient at the Research Unit				Follow-up Outpatient Visits (OPV)		
Event	**Screening**	**Admit to Clinic**	**Dose**	**Discharge from Clinic**	**OPV**	**OPV**	**OPV**
Study Day	**Day −22 to Day −2**	**Day −1**	**Day 1**	**Day 2** (24 hours post dose)	**Day 3** (48 hours post dose)	**Day 8** (168 hours post dose)	**Day 22/ End of Study** (504 hours post dose)
Single Dose (48 injections)[g]			X				
Pharmacokinetic Blood Sampling[h]			X	X	X	X	X
Blood collection for possible Anti-AUX-I/ Anti-AUX-II Antibody Levels/Neutralizing Antibodies to AUX-I and AUX-II[i]			X				X
Assess Any Injection Site Reactions in the Areas That Were Dosed			X	X	X	X	X
Adverse Events[j]	X	X	X	X	X	X	X

[a] Performed and signed prior to any study-required assessments.
[b] Should be reassessed and verified prior to dosing.
[c] Blood pressure (systolic/diastolic), respiratory rate, and radial pulse taken up to 4 hours pre-dose and 15 and 30 minutes post dose. Oral temperature will be included at Screening, Admission Day -1, on Day 1 pre-dose and at 30 minutes post dose, and on Day 2. All vital signs include oral temperature to be taken before blood sampling on the Day 3, 8, and 22 OPVs. Vital signs should be taken after the subject rests for at least 5 minutes.
[d] The list of clinical laboratory tests for safety is given in Table 4.
[e] Screen for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, opiates, and/or propoxyphene at the Screening visit and on Day −1. Test must be negative.
[f] The Investigator's CR-PCSS assessment score must be a 2, 3, or 4 for study entry.
[g] The 48 subcutaneous injections (12 injections per quadrant in 4 quadrants concurrently) comprise the single dose.
[h] Blood collection (10 mL each) for PK measurement of plasma AUX-I and AUX-II concentrations are to be taken before dosing and at 5, 10, 20, and 30 minutes and 1, 2, 4, 8, 12 , 24, 48, 168, and 504 hours after dosing. All blood samples are to be collected within 10% of the nominal time. The exact time of collection will be noted in the source document and CRF.
[i] Collect blood for immunogenicity testing before injection on Day 1 prior to dosing and again on Study Day 22 at approximately 504 hours after dosing. (Collect 3 × 5 mL of blood for immunogenicity testing at both time points.). NOTE: Assay of these samples will be conducted only if clinical signs and/or PK results warrant determinations.
[j] AEs/SAEs will be captured from time of informed consent signature until Study Day 22. There is no time limit on collection of SAEs felt to be related to study drug.

AE=Adverse event; CRF=Case report form; CR-PCSS=Clinician-Reported Photonumeric Cellulite Severity Scale; ECG=Electrocardiogram; EFP=Edematous fibrosclerotic panniculopathy; OPV=Outpatient visit; PK=Pharmacokinetics; SAE=Serious adverse event

6. TABLE OF CONTENTS AND LIST OF TABLES

TABLE OF CONTENTS

[redacted]

[redacted]

LIST OF TABLES

7. LIST OF ABBREVIATIONS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
AUC	Area under the concentration time curve
$AUC_{0\text{-}inf}$	Area under the plasma concentration versus time curve from time of dosing (0) to infinity
$AUC_{0\text{-}t}$	Area under the plasma concentration versus time curve from time of dosing (0) to the time of last quantifiable concentration
AUX-I	Clostridial class I collagenase
AUX-II	Clostridial class II collagenase
BLQ	Below limit of quantification
BMI	Body mass index
CFR	Code of Federal Regulations
C_{max}	Maximum concentration
CRF	Case report form
CR-PCSS	Clinician-Reported Photonumeric Cellulite Severity Scale
CV	Coefficient of variation
DHHS	Department of Health and Human Services
ECG	Electrocardiogram
EFP	Edematous fibrosclerotic panniculopathy
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug application
IRB	Institutional Review Board
NC	Not calculable
OTC	Other the counter
PCI	Potentially clinically important

Table 2: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
PK	Pharmacokinetics
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum concentration

8. INTRODUCTION

8.1. Background of 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 an alteration of skin topography.(1) The condition manifests as dimpled skin, described as an orange-peel, cottage cheese, or mattress texture, particularly in the gluteal-femoral region.(2,3) EFP is caused by herniation of subcutaneous fat lobules through the dermohypodermal junction. This creates an uneven surface with dimpling.(1) 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.(1,3)

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.(4)

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.(1) 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.(1)

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.(2) There are a higher percentage of thinner, perpendicular hypodermal septa in women with EFP than in men.(1) 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 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.

8.1.1. EN3835 (Collagenase Clostridium Histolyticum)

Endo Pharmaceuticals Inc. (Endo) is developing EN3835 for the treatment of EFP. Because EN3835 is a proteinase 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. EN3835 targets the collagenase structural matrix (eg, dermal septa) at the site of injection and does not require systemic exposure to be effective.

EN3835 is a parenteral lyophilized product comprised of 2 collagenases in an approximate 1:1 mass ratio, Collagenase I (AUX-I, clostridial class I collagenase) and Collagenase II (AUX-II; clostridial class II collagenase). These collagenases are isolated and purified from the fermentation of *Clostridium histolyticum*. Collagenase AUX-I is a single polypeptide chain containing approximately 1000 amino acids of known sequence and with a molecular weight of 114 kDa. Collagenase AUX-II is also approximately 1000 amino acids long and has a molecular weight of 113 kDa. These collagenases are not immunologically cross-reactive and have different specificities, such that together they become synergistic, providing a very broad hydrolyzing reactivity toward collagen. Clostridial collagenases are proteinases that can hydrolyze the triple-helical region of collagen under physiological conditions.

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

8.2. Summary of Nonclinical Studies

Information in support of the safety and efficacy of EN3835 has been derived from nonclinical studies reported in the published literature and/or conducted by Biospecifics Technologies Corporation (BTC) or Auxilium Pharmaceuticals, LLC (Auxilium).(5) Collective results from these studies indicate that when EN3835 is injected into tissues composed primarily of dense fibrous connective tissue arranged in larger fibrils (tunica albuginea, Peyronie's plaque, tendon, pericardium, or Dupuytren's cord), either in vitro or in vivo, lysis was focal, well circumscribed and primarily confined to tissue directly adjacent to the injection site. In contrast, lysis following injection into loosely arrayed fibrous connective tissue composed of smaller fibrils (corpus cavernosum or subcutaneous tissue) was more diffuse. These findings collectively support the potential efficacy of EN3835 in the treatment of localized fibrotic conditions such as edematous fibrosclerotic panniculopathy in the clinic.

8.2.1. Pharmacokinetics

Data from a definitive Phase 1 single-dose study (AUX-CC-855) and a Phase 3b multiple-dose study (AUX-CC-861) confirmed that there is no quantifiable systemic exposure following a single or 2 concurrent injection(s) of EN3835 (0.58 mg) into the cord(s) of the affected finger(s) in subjects with Dupuytren's contracture or following the subsequent procedure to disrupt the cord. The results of both clinical studies indicate that no detectable absorption of any EN3835-derived components occurs in subjects under conditions of clinical use. These findings are consistent with local inactivation of EN3835, most likely as the result of complex formation with alpha-2-macroglobulin (α2M), a serum protein that serves as a substrate/inhibitor for proteases of a variety of types.(5)

Following each of 2 intralesional administrations, separated by 24 hours, of EN3835 (0.58 mg) into the penile plaque of 19 subjects with Peyronie's disease (AUX-CC-805), plasma levels of AUX-I and AUX-II in subjects with quantifiable levels (79% and 40% for AUX-I and AUX-II, respectively) were minimal and short-lived. All plasma levels were below the limits of quantification within 30 minutes following dosing. There was no evidence of accumulation following 2 sequential injections of EN3835 administered 24 hours apart. No subject had

quantifiable plasma levels 15 minutes after modeling of plaque on Day 3 (ie, 24 hours after injection 2 on Day 2).

In study AUX-CC-830, where subjects received 10 subcutaneous injections for the treatment of EFP at increasing doses ranging from 0.0029 mg to 0.464 mg, no quantifiable plasma concentrations of AUX-I and AUX-II at any time point through 24 hours post injection were observed among the 93 subjects who were evaluable for pharmacokinetics (PK).

In study EN3835-102, subjects received subcutaneous administration of EN3835 0.84 mg (12 injections) in 1 quadrant (left buttock, right buttock, left posterolateral thigh, or right posterolateral thigh) for the treatment of EFP. No quantifiable plasma concentrations of AUX-I or AUX-II at any time point (t = 5, 10, 20, and 30 minutes and 1, 2, 4, 8, 12, 24, 48, 168, and 504 hours) after dosing were observed among the 11 evaluable subjects.

8.3. Early Development Studies with EN3835 for the Treatment of Edematous Fibrosclerotic Panniculopathy

The early development studies are described in the Investigator's Brochure (IB).(5)

8.4. Summary of Known Risks and Benefits

A summary of safety risks is provided in the IB.(5) The following events have been commonly observed: bruising and edema at the site of injection. Subjects should be observed for 30 minutes post dose to monitor for possible hypersensitivity reactions.

Preliminary studies have indicated that EN3835 may improve symptoms associated with EFP. Additional data from this study may help to support the clinical effect in female subjects with EFP.

The efficacy and safety of EN3835 in subjects receiving anticoagulant medications (other than low-dose aspirin, eg, up to 150 mg per day) within 7 days prior to EN3835 administration is not known. Therefore, EN3835 should be used with caution in subjects with coagulation disorders including subjects receiving concomitant anticoagulants (except for low-dose aspirin).

8.5. Rationale

This study will evaluate the safety, PK, and immunogenicity of a single 3.36-mg dose of EN3835 administered as 48 subcutaneous injections, ie, EN3835 0.84 mg as 12 injections per quadrant in 4 quadrants concurrently, in subjects with EFP. A quadrant is defined as a left buttock, right buttock, left posterolateral thigh, or right posterolateral thigh.

This study will provide insight to the PK profile and safety of concurrent subcutaneous injections of EN3835 0.84 mg/quadrant into 4 quadrants in anticipation of use in the real world by clinicians skilled in the art of aesthetic medicine of dosing more than 1 quadrant, or maximizing the potential situation in which clinicians shorten the time between injection sessions (21 days in clinical trials).

9. OBJECTIVES

9.1. Primary Objective

The primary objectives of this study are to assess safety, and determine if there is systemic exposure, following a subcutaneous single dose of EN3835 (3.36 mg) as 12 injections per quadrant in 4 quadrants concurrently (0.84 mg per quadrant) in adult women with EFP.

10. INVESTIGATIONAL PLAN

10.1. Study Design

This is a Phase 1, open-label PK study. This study will be performed at a single center located in the United States.

Following an up to 21-day screening period, subjects will be admitted to the clinical research unit (Day -1) the day before the dosing of EN3835 (Day 1) and will remain in the study unit until after the 24-hour post-dose PK sample is collected on Day 2. Twelve (12) subjects will be admitted on Day −1 to receive the full dose of the study drug on Day 1. Subjects will return to the study unit on Day 3, 8, and 22 for outpatient follow-up safety and PK assessments. A minimum of 10 subjects should complete the study with PK profiles for evaluation.

The complete schedule of events is provided in section 5.

10.2. Selection of Dose

The data from the Phase 2a EFP dose-ranging study (AUX-CC-831) suggest that EN3835 (0.84 mg) is most effective in the treatment of EFP based on improvement in the severity of cellulite as determined by both the Investigator and the subject, although the EN3835 (0.48 mg) group did show improvement in some of the efficacy parameters.(5)

There were no safety concerns following administration of up to 3 treatment sessions at 21-day intervals (ie, Day 1, 22, and 43), of EN3835 0.84 mg in the treatment of EFP.(5) The safety profile of EN3835 0.84 mg in the treatment of EFP was similar to that observed in the EN3835 0.06-mg group and the EN3835 0.48-mg group. No notable differences were observed across the 3 treatment groups.

Safety findings from the Phase 2a EFP dose-ranging study are similar to those observed in previous clinical studies with EN3835 (collagenase clostridium histolyticum) for injection, for intralesional use in the treatment of Dupuytren's contracture and Peyronie's disease in that that the majority of adverse events (AEs; bruising, discoloration, pain, and swelling) occurred at the site of injection and resolved before the next scheduled treatment.

The immunogenicity profile of EN3835 in the Phase 2a EFP dose-ranging study showed ≥93% of subjects in the EN3835 0.48-mg and EN3835 0.84-mg groups were positive for antibodies to AUX-I and AUX-II; the profile is similar to that observed in the Dupuytren's contracture and Peyronie's disease programs.

Based on the efficacy and safety findings from the Phase 2a EFP dose-ranging study of EN3835 0.84 mg per quadrant and the objective of determining the PK profile following concurrent treatment of 4 quadrants, a dose of 3.36 mg was selected for this study.

10.3. Selecting and Marking Dimples and Injection Sites

Selection of dimples to be treated in the 4 quadrants is at the discretion of the Investigator. Dimples must be well defined and evident when the subject is standing in a consistent relaxed pose (without the use of any manipulation such as skin pinching or muscle contraction).

Before injection on Day 1, the Investigator or qualified designee will begin the session by selecting dimples within the quadrants that are well defined, evident when the subject is standing, and suitable for dosing; the dosing consists of 48 injections (12 injections per quadrant) on Study Day 1.

Because the goal of even a single dose administration is to potentially improve the aesthetic appearance of the entire quadrant, the Investigator will be instructed to select dimples that in his or her opinion would most improve the aesthetic appearance of the entire quadrant.

For each dimple selected, the Investigator or qualified designee will choose 12 injection sites per quadrant (injection sites within a dimple should be spaced approximately 2 cm apart, if a dimple requires more than 1 injection) and 4 quadrants for a total of 48 injection sites. Each injection site will be marked with a "dot" using a surgical marker. For round dimples, the "dot" will be placed in the center of the dimple.

10.4. Study Drug Reconstitution

Before reconstitution, remove the vials containing the lyophilized study drug powder and the vials containing the sterile diluent from the refrigerator and allow the vials to stand at room temperature for 15 minutes. Designated study personnel will visually inspect the study drug vial to determine the integrity and acceptability of the lyophilized drug product for reconstitution. The cake should be white and intact, with no signs of erosion.

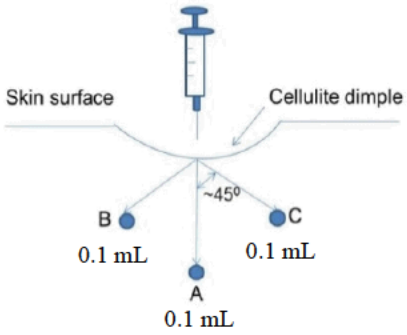
Each vial of study drug powder for reconstitution will be diluted according to the Reconstitution Instructions. Study personnel will maintain a record of the date and time of reconstitution.

After reconstitution with the sterile diluent, the study drug solution can be kept at room temperature (20°C to 25°C/68°F to 77°F) [redacted]

10.5. Study Drug Administration at Each Injection Site

Study drug will be injected subcutaneously while the subject is in a prone position using a syringe with a 30-gauge ½-inch needle. Forty-eight (48) injection sites (12 sites per quadrant) will be selected (see section 10.3). Each injection site will receive 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 the following figure. The depth of injection corresponds to the length of the treatment needle (0.5 inches) from the tip of the needle to the hub or base of the needle without downward pressure.

Sixteen (16) syringes (4 syringes per quadrant) will be prepared for dosing on Day 1. Each syringe will contain 0.9 mL of study drug (ie, 3 injections in each syringe). Forty-eight (48) skin injections of 0.3 mL will be administered within the 4 quadrants (12 injections per quadrant) during the dosing session.



Needle Tip Position A: Position the needle at 90° angle perpendicular to the skin surface at the injection site and inject one 0.1-mL aliquot of study drug by gently pushing on the syringe plunger.

Needle Tip Position B: Withdraw the needle slightly (but not so much as to remove from the injection site) and reposition approximately 45° (but not more than 45°) off vertical and above the long axis of the dimple and inject one 0.1-mL aliquot of study drug) by gently pushing on the syringe plunger.

Needle Tip Position C: Withdraw the needle slightly (but not so much as to remove from the injection site) and reposition approximately 45° (but not more than 45°) off vertical and below the long axis of the dimple and inject one 0.1-mL aliquot of study drug by gently pushing on the syringe plunger.

Withdraw needle from the skin completely and move to the next identified injection site. Complete a total of three 0.3-mL injections (each administered as three 0.1-mL aliquots) and discard the first syringe appropriately. Use the second, third and fourth syringes to complete dosing in the quadrant (three 0.3-mL injections per syringe, each injection administered as three 0.1-mL aliquots). Twelve skin injections of 0.3 mL will be administered within each quadrant during the dosing and 4 quadrants will be concurrently treated; a total of 48 injections will be given on Day 1.

After dosing the subject will remain prone for at least 5 minutes. The blood draws for PK sampling will begin at 5 minutes after the completion of the last dose injection.

The total number of dimples treated and the total number injections administered during dosing on Day 1 will be recorded.

NOTE: EN3835 is a foreign protein and the Investigator should be prepared to address and manage an allergic reaction should it occur. At the time of each injection, a 1:1000 solution of epinephrine for injection, 50-mg diphenhydramine injection or a suitable equivalent, and oxygen must be available. The Investigator and site staff must be familiar with the use of the rescue medication.

10.6. Care Procedures After Injection

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 injection 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 site with hypoallergenic tape. The dressing will be removed by the clinic staff in the evening.

10.7. Identity of Investigational Product

The investigational product vials will be labeled as EN3835. EN3835 is a sterile lyophilized powder containing 0.46 mg of collagenase clostridium histolyticum, [redacted]

EN3835 sterile diluent for reconstitution is 0.6% sodium chloride and 0.03% calcium chloride dehydrate filled into 2-mL vials.

10.8. Discussion of Study Design

This is a Phase 1, open-label study of EN3835 to follow the safety and determine the PK of EN3835 in female subjects with EFP following a single subcutaneous dose administration of EN3835 3.36 mg as 12 injections per quadrant in 4 quadrants concurrently (0.84 mg per quadrant).

11. SELECTION AND WITHDRAWAL OF SUBJECTS

11.1. Subject Inclusion Criteria

No subject will be dosed until all eligibility criteria have been satisfied. In order to be eligible to participate in the study, subjects must meet the following criteria:

1. Be a female ≥18 years of age
2. Have evidence of cellulite within 4 quadrants (a quadrant is defined as right or left buttock or the right or left posterolateral thigh) as assessed by the Investigator using the Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS) at the Screening visit; has a score of 2 (mild), 3 (moderate) or 4 (severe) as reported by the Investigator (CR-PCSS) in 4 quadrants at the Screening visit
3. Have a body mass index (BMI) between 20.0 and 35.0 kg/m^2, and intends to maintain stable body weight throughout the duration of the study (a variation of ≤10% from baseline body weight is permitted)
4. Be willing to apply sunscreen to the dosing quadrants 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 urine pregnancy test at the Screening visit and on Day -1 at admission (before injection of study drug); and be using an effective contraception method (eg, abstinence, intrauterine device [IUD], hormonal [estrogen/progestin] contraceptives, or double barrier control) for at least 1 menstrual cycle prior to study enrollment and for the duration of the study; or be menopausal defined as 12 months of amenorrhea in the absence of other biological or physiological causes, as determined by the Investigator; or post-menopausal for at least 1 year; or be surgically sterile (ie, hysterectomy, bilateral oophorectomy, tubal ligation).
7. Be willing and able to cooperate with the requirements of the study
8. Voluntarily sign and date an informed consent agreement approved by the Institutional Review Board/Independent Ethics Committee/Human Research Ethics Committee (IRB/IEC/HREC)

11.2. Subject Exclusion Criteria

A subject will be excluded from study participation if she:

1. 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.

2. 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) in areas to be treated
   c. Inflammation or active infection
   d. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer
   e. Has a tattoo located within 2 cm of the site of injection
3. Requires the following concomitant medications before or during participation in the trial:
   a. Anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication (except for ≤150 mg aspirin daily) within 7 days before injection of study drug
4. Has a positive test on a urine drug screen for drugs of abuse
5. Has a history of drug or alcohol abuse
6. Has used any of the following for the treatment of EFP on the legs or buttock 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 quadrants 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 quadrants during the 12-month period before injection of study drug
   c. Endermologie or similar treatments within the treatment quadrants during the 6-month period before injection of study drug
   d. Massage therapy within the treatment quadrants during the 3-month period before injection of study drug
   e. Creams (eg, Celluvera™, TriLastin®) to prevent or mitigate EFP within the treatment quadrants during the 2-week period before injection of study drug
7. Is presently nursing a baby or providing breast milk for a baby
8. Intends to become pregnant during the study
9. Intends to initiate an intensive sport or exercise program during the study
10. Intends to initiate a weight reduction program during the study

11. Has received an investigational drug or treatment within 30 days before injection of study drug
12. Has a known systemic allergy to collagenase or any other excipient of study drug
13. Has received any collagenase treatments at any time prior to treatment
14. Was a subject in a previous cellulite clinical trial of EN3835: AUX-CC-830, AUX-CC-831, EN3835-102, EN3835-201, and/or EN3835-202

11.3. Subject Discontinuation Criteria

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

- An AE
- A protocol violation (reason must be specified, for example: lack of compliance, use of a prohibited concomitant medication, failure to meet inclusion/exclusion criteria after study entry, 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)

If a subject discontinues from the study, all end-of-study procedures should be conducted as detailed in the schedule of events. The date a subject discontinues and the reason for discontinuation will be recorded in the source documentation and case report form (CRF). If, however, a subject withdraws consent, no end-of-study procedures are required except the collection of AE information. This information should be recorded in the source documentation and the CRF.

11.3.1. Replacement Procedures

Subjects who discontinue from the study will not be replaced.

12. TREATMENT OF SUBJECTS

12.1. Study Overview

The schedule of events to be performed at each visit is shown in section 5. Further details on activities that occur on each study day are provided below. After obtaining informed consent, the full assessment of eligibility will be conducted prior to study entry.

Following a screening period of up to 21 days, subjects will be admitted to the research unit on Day −1. Subjects will be dosed on Study Day 1, and will receive 48 subcutaneous injections of EN3835 in 4 quadrants (12 injections per quadrant, concurrently in 4 quadrants). The post-injection PK sampling will begin following the completion of the last injection.

Subjects will be discharged on Study Day 2 after the 24-hour post-injection blood collection and return for outpatient visits and complete the required blood draws and assessments, as described in the schedule of events in section 5. The end of study visit is scheduled for Study Day 22. AEs will be monitored and recorded throughout the study.

The study activities should occur as described on each study day.

12.2. Informed Consent

Signed and dated informed consent will be obtained from each subject before any study procedures are undertaken, or before any changes to the subject's medication regimen are made. Details about how the informed consent will be obtained and documented are provided in section 20.3, Subject Information and Consent.

12.3. Study Entry

A subject who gives written informed consent and who satisfies all eligibility criteria may be entered into the study. The following demographic information will be required for study entry:

- Subject initials
- Date of birth
- Gender

The subject will be assigned a unique subject identification number in sequential order.

The subject identification number will consist of 8 digits. The first 4 digits represent the study site number followed by a 4-digit subject number.

12.4. Assessments: Listed by Each Study Day

12.4.1. Day −22 to Day −2: Screening Period

The Investigator 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).

The Investigator will provide information about the study to subjects who appear to meet the criteria for participation in the study.

During the screening period, the Investigator or qualified designee will obtain a medical 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 and family history), and history of tobacco and alcohol use (never, current, former).

Subjects meeting the relevant eligibility criteria listed in section 11 may be enrolled in the study after the nature and purpose of the protocol have been explained and written informed consent to participate has been voluntarily provided by the subject or their legally authorized representative. The following procedures will be performed in sequential order and documented during the screening period:

1. Obtain written informed consent
2. Evaluate eligibility based on inclusion/exclusion criteria
3. Conduct live assessments of subject's cellulite severity in all 4 quadrants (left and right buttock, left and right posterior thigh) using the CR-PCSS
4. Medical history including EFP history
5. Record prior and concomitant medications/procedures
6. Physical examination including measurement of body weight, height, and evaluation of the Fitzpatrick skin type
7. Vital sign measurements
8. 12-lead ECG
9. Collection of samples for:
    a. Clinical laboratory testing
    b. Urine pregnancy testing
    c. Alcohol breath test
    d. Urine drug screen
10. Monitor AEs

12.4.2. Day −1: Admission to the Clinical Research Unit

Subjects will be admitted to the clinic for the inpatient period on the afternoon of Day −1. The following procedures will be performed and documented:

1. Re-evaluate eligibility based on inclusion/exclusion criteria
2. Record prior and concomitant medications/procedures
3. Vital sign measurements
4. Urine pregnancy test
5. Alcohol breath test

6. Urine drug screen
7. Monitor AEs

12.4.3. Day 1: Pre-dose and Dosing Activities

On Day 1, a 10-mL blood sample will be collected prior to dosing to document any baseline plasma levels of AUX-I and AUX-II.

In addition, 3 × 5-mL blood samples will be collected as a baseline sample for baseline anti-AUX-I/anti-AUX-II antibody levels/neutralizing antibodies to AUX-I and AUX-II in serum; if it is later determined that antibody assays are warranted based on clinical findings and/or PK results.

Subjects will then be dosed in the 4 quadrants as detailed in section 10.5.

12.4.4. Day 1: Care Procedures After EN3835 Injections

Immediately after injection, the Investigator or qualified designee will apply pressure to the injection sites for 3 minutes and instruct the subject to continue applying pressure for another 5 minutes. Additionally, 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 acute allergic reactions for the first 30 minutes after receiving an injection of study drug (see section 10.5). A loose bulky gauze dressing may then be applied to the injection areas. Study personnel will remove the dressing in the evening to inspect the injection areas for edema and bruising.

During the first 30 minutes following injection, the subject will be monitored for:

- Signs of an immunological or other clinically significant systemic or local AEs
- Stable vital signs (see Table 5)

Subjects will also be instructed as follows:

- Your injection areas may appear bruised and/or swollen
- You may have moderate pain

12.4.5. Day 1: Pharmacokinetic Sampling Post Dose

Collection of blood samples for PK assessment will begin at 5 minutes following the last injection of study drug. Samples (10 mL each) will be collected at the following time points after the last injection on Day 1: at 5, 10, 20, and 30 minutes and 1, 2, 4, 8 and 12 hours after dosing. Blood samples are to be collected within 10% of the nominal time. The exact time of collection will be noted in the source document and CRF.

12.4.6. Day 2: Discharge from the Research Unit

On the morning of Day 2, the 24-hour PK blood sample will be collected. Subjects will be given breakfast, have their vital signs measured, and be assessed for any AEs (such as site reactions in the dosing areas or any other AE). Beginning on Day 2 and continuing through the outpatient period, subjects will also be instructed as follows:

- Take over-the-counter (OTC) pain medications (eg, acetaminophen) if needed for pain
- If you have severe pain or severe swelling, or any other symptoms, tell your study doctor

Subjects will then be discharged from the clinical research unit.

12.4.7. Day 3: Follow-up Outpatient Visit

On the morning of Day 3, subjects will return to the clinical research unit as an outpatient for the collection of the 48-hour post-dose PK blood sample. Subjects will have their vital signs measured, be assessed for any AEs, have the dosing areas checked, and questioned about taking any concomitant medications. Subjects will then be discharged from the clinical research unit and will be instructed to return and schedule the visit on Day 8.

12.4.8. Day 8: Follow-up Outpatient Visit

On the morning of Day 8, subjects will return to the clinical research unit as an outpatient for the collection of the 168-hour post-dose PK blood sample. Subjects will have their vital signs measured, be assessed for any AEs, have the dosing areas checked, and questioned about taking any concomitant medications. Subjects will then be discharged from the clinical research unit and will be instructed to return and schedule the visit on Day 22.

12.4.9. Day 22: End of Study Outpatient Visit

On the morning of Day 22, subjects will return to the clinical research unit as an outpatient for the end of study visit. At this visit, the 504-hour post-dose PK blood sample will be collected. In addition, the 3 × 5-mL blood samples for potential determination of anti-AUX-I/anti-AUX-II antibody levels/neutralizing antibodies to AUX-I and AUX-II in serum will be collected; antibody assays will be conducted only if clinical findings and/or PK results warrant the assays.

The cellulite severity assessments of each of the 4 treated quadrants using the CR-PCSS (live assessment) will be completed by the Investigator at this end of study visit.

Subjects will have their vital signs measured, be assessed for any AEs, and questioned about taking any concomitant medications. The body weight will also be taken. Before they are discharged from the study, they will have a blood draw for clinical safety labs.

Following completion of all study related assessments and procedures, subjects will then be discharged from the clinical research unit.

12.5. Prior and Concomitant Medications and Procedures

All medications (including OTC medication) administered to or taken by the subject within 3 months prior to the Screening visit will be recorded.

Subjects cannot be taking antiplatelet agents or anticoagulants (except for ≤150 mg aspirin daily) within 7 days before and after the dosing administration. Thereafter, any changes in concomitant medications or new medications added will be recorded.

Any diagnostic, therapeutic, or surgical procedure performed before the study period, including those for the treatment of EFP, should be recorded including the date, indication for, and description of the procedure.

12.5.1. Prohibited Medications or Procedures

The following medications are prohibited 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 the study.

Table 3: Concomitant Medication Restrictions

Drug Class	Restrictions
Anticoagulants	Subjects cannot be taking antiplatelet agents or anticoagulants (except for ≤150 mg aspirin daily) within 7 days before and after the dosing administration.

12.5.2. Prohibited Procedures

The treatments and procedures listed in exclusion criteria 6 are prohibited during the study.

12.6. Treatment Compliance

All subjects will receive study drug administered by a clinician in the clinical research unit.

Accidental or intentional overdoses should be reported to the Sponsor/designee promptly (see section 14.6.2.1, Overdose).

12.7. Blinding and Randomization

This study will be conducted as an open-label investigation; no blinding of assigned treatment will occur.

13. ASSESSMENT OF CELLULITE SEVERITY

13.1. Cellulite Severity Analysis

Cellulite severity will be assessed by the Investigator's rating of cellulite severity using the CR-PCSS. Evaluations will be done on each of the 4 quadrants at Screening and Study Day 22.

14. ASSESSMENT OF SAFETY

14.1. Definitions

14.1.1. Adverse Events

An adverse event (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 preexisting condition associated temporally with the use of the study medication whether or not considered related to the study medication. AEs 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 preexisting disease
- All clinically relevant laboratory abnormalities or physical findings that occur during the study

A treatment-emergent adverse event (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 observed or volunteered problems, complaints, signs or symptoms must be recorded on the AE page of the CRF, 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. 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 visit, subjects will be queried regarding any AEs that have occurred since the last visit. Subjects will be asked to volunteer information concerning AEs with a non-leading question such as, "How do you feel?" Study site personnel will then record all pertinent information in the source documents and the CRF. 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 CRF 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.

When the intensity category of an AE changes, the greatest intensity during that continuous episode should be recorded.

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 CRF 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 Study Day 22; 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 14 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 to [redacted] by the Investigator using the Endo Clinical Trial Report Form for SAEs 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 Study Day 22. SAEs that occur within 22 days, following cessation of the study treatment, or within 22 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 an 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 non-serious should be reported on the CRF.

14.6. Special Reporting Situations

14.6.1. Adverse Events of Special Interest

There are no AEs of special interest anticipated in this study.

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 (see section 12.6) should be reviewed to detect potential instances of overdose (intentional or accidental).

Any study drug overdose during the study should be noted on the study medication CRF.

An overdose is not an AE per se, however all AEs associated with an overdose should both be entered on the Adverse Event CRF and reported using the procedures detailed in section 14.5.2, Reporting of Serious Adverse Events, 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 Clinical Trial Report Form for SAEs and in an expedited manner, but should be noted as non-serious on the form and the Adverse Event CRF.

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 dosing or within 22 days of the last dose of study medication 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 SAE report form, according to the usual timelines and directions for SAE reporting provided in section 14.5.2. Monitoring of the pregnancy should continue until conclusion of the pregnancy; 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 SAE report form. Spontaneous miscarriages should also be reported and handled as SAEs.

Subjects should be instructed to immediately notify the Investigator of any pregnancies.

Attempts to obtain the pregnancy follow-up and pregnancy outcome information detailed above are necessary even if a subject discontinues from the study because of pregnancy.

14.6.4. AEs/SAEs Experienced by Non-subjects Exposed to Study Medication

Non-subjects 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 non-subjects from such exposure will be reported to the Endo Pharmacovigilance and Risk Management (PVRM) Department (when the non-subject agrees) on the departmental form for serious adverse experiences regardless of whether the event is serious or not. Instructions for completing the form for events experienced by non-subjects will be provided. SAEs occurring in non-subjects 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 site should reflect this occurrence.

14.7. Clinical Safety Laboratory Determinations

Clinical laboratory tests will be conducted according to the schedule of events (section 5). Clinical laboratory tests will be performed by a local laboratory. The results of the tests will be returned to the investigational site.

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 local laboratory.

The Investigator will review all abnormal lab results for clinical significance. Any abnormal clinical laboratory test result meeting the Investigator's criteria for clinical significance will be recorded as an AE or SAE as appropriate (see section 14.1.1, Adverse Events, and section 14.1.2, Serious Adverse Events).

Clinical laboratory parameters that will be measured in this study are listed in Table 4.

Table 4: Clinical Safety 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.

14.7.1. Urine Pregnancy Testing

For women of childbearing potential, a urine pregnancy (dipstick) test will be performed at the Screening visit and at admission (Day −1). Female subjects of childbearing potential must have a negative pregnancy test to enter the study. If necessary, additional urine pregnancy tests can be performed at any time during the study at the discretion of the Investigator.

14.7.2. Urine Drug Screen

The Investigator will collect urine samples for the screening of the following drugs of abuse: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, opiates, and/or propoxyphene at the Screening visit and on Day −1. Test must be negative before dose administration.

14.7.3. Alcohol Breath Test

The Investigator will administer a breathalyzer test for the screening of alcohol at the Screening visit and on Day −1. Test must be negative before dose administration.

14.8. Immunogenicity Samples for Collection

Immunogenicity variables include anti-AUX-I/anti-AUX-II binding (ie, anti-drug) and neutralizing antibody results. Anti-drug antibody levels will be determined from samples (3 × 5-mL tubes of blood) collected pre-dose on Day 1, and on Day 22; neutralizing antibody levels will be determined for samples collected on Day 1 and Day 22 for the subset of anti-drug antibody positive subjects on Day 22. If testing is warranted, the 3 tubes will be assayed as follows: The first tube will be assayed for the measurement of anti-AUX-I antibodies and for anti-AUX-II antibodies; the second tube will contain the same and be the back-up tube; the third tube will be assayed for neutralizing antibodies. The serum samples obtained will be processed, stored, and then shipped on dry ice to the designated laboratories for the determination of anti-AUX-I and anti-AUX-II antibodies, and neutralizing antibodies according to the instructions in the Laboratory Manual.

Immunogenicity samples will be assayed for antibody levels only if warranted by clinical findings and/or PK results.

14.9. Vital Signs

Vital sign measurements will be documented as described in the schedule of events and as detailed in Table 5. These parameters include radial pulse rate, respiratory rate, systolic and diastolic blood pressure, and oral body temperature. Subjects with systolic blood pressure greater than 180 mm Hg or less than 90 mm Hg or diastolic blood pressure greater than 105 mm Hg or less than 50 mm Hg at Screening or at admission on Day −1 should be excluded from study participation.

Blood pressure (systolic/diastolic), respiratory rate, pulse rate, and body temperature will be assessed after the subject has rested for at least 5 minutes.

Table 5: Vital Signs Measurement Throughout the Study

	Systolic/Diastolic Blood Pressure, Respiratory Rate, and Radial Pulse Rate	Oral Body Temperature
Screening	Taken	Taken
Admission	Taken	Taken
Day 1 - Dosing	Taken up to 4 hours pre-dose and at 15 and 30 minutes post dose	Taken up to 4 hours pre-dose and at 30 minutes post dose (not required at the 15-minute post dose draw)
Day 2 - Discharge	Taken before 24-hour PK blood sample	Taken before 24-hour PK blood sample
Day 3 OPV	Taken before 48-hour PK blood sample	Taken before 48-hour PK blood sample
Day 8 OPV	Taken before 168-hour PK blood sample	Taken before 168-hour PK blood sample
Day 22 OPV	Taken before 504-hour PK blood sample	Taken before 504-hour PK blood sample

OPV=Outpatient visit; PK=Pharmacokinetics

The Investigator will review all vital sign values for clinical significance. Any vital sign value meeting the Investigator's or Sponsor's criteria for clinical significance will be recorded as an AE or SAE as appropriate (see section 14.1.1, Adverse Events, and section 14.1.2, Serious Adverse Events).

14.10. Electrocardiogram

During the screening period, subjects will have a resting 12-lead ECG performed. A qualified physician will interpret, sign, and date the ECGs. ECG assessments must be "within normal limits" or interpreted as "abnormal, not clinically significant" for the subject to be included in the study. 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.

14.11. Physical Examination

During the Screening visit, the Investigator or qualified designee will perform a complete physical examination (by body system) on each subject. Height and body weight will be measured and recorded. Laxity of the skin on the buttocks and/or thighs should be considered to ensure there are no underlying pathologies that would prevent an assessment of EFP severity.

At screening, the Investigator will also assess the subject's skin type using the Fitzpatrick scale.

Only the specific Fitzpatrick Scale shown below (Table 6) may be used during the study.

Table 6: 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

15. ASSESSMENT OF PHARMACOKINETICS

15.1. Study Drug Concentration Measurements

15.1.1. Blood Sample Collections

15.1.1.1. Pharmacokinetic Sample Collection and Processing

Blood collection (10 mL) for PK measurement of plasma AUX-I and AUX-II concentrations are to be taken before dosing and at 5, 10, 20, and 30 minutes and 1, 2, 4, 8, 12, 24, 48, 168, and 504 hours after dosing. Blood samples are to be collected within 10% of the nominal time. The exact time of collection will be noted in the source document and CRF.

Blood samples will be collected from all subjects participating in the study. Each subject will have 10-mL samples of venous blood drawn and placed into lithium heparin tubes.

Clock times for specimen drawing/collecting, handling (eg, centrifuging, freezing), storage, and shipment to the analytical lab will be logged by study site personnel on the appropriate tracking forms for sample collection, storage, and shipment.

All sample collection and freezing tubes will be clearly labeled in a fashion, which identifies the subject, date, and the collection time. The containers must be securely labeled in a manner that will keep the label attached to the container under the conditions of low temperature freezing.

15.1.1.2. Plasma Samples

Serial blood samples for the intensive PK sampling period (initial 12 hours post dose) may be obtained from an indwelling intra-catheter or percutaneous venipuncture. If utilized, the intra-catheter will be inserted into the subject's vein before the pre-dose sample collection and will be used to collect all scheduled blood samples throughout the day. Intra-catheters will be maintained and kept open with the use of saline flush as needed. Once the blood samples have been obtained, the intra-catheter will be removed.

Immediately prior to each collection time point, 2 to 3 mL of the blood/saline mixture will be withdrawn and discarded (to prevent sample dilution) and the sample withdrawn at the appropriate time point listed in section 5.

The plasma samples will be collected, processed, stored, and shipped as described in the Laboratory Manual.

Any deviation from the scheduled sample time should be recorded on the CRF.

15.1.1.3. Immunogenicity Testing: Anti-AUX-I and Anti-AUX-II Antibodies and Neutralizing Antibodies to AUX-I and AUX-II

Blood samples for the determination of serum anti-AUX-I and anti-AUX-II antibody levels and neutralizing antibodies to anti-AUX-I and anti-AUX-II will be collected pre-dose on Day 1 and at the Day 22 outpatient visit. These samples will be assayed for antibody levels only if clinical findings and/or PK results warrant immunogenicity profiling.

The serum samples obtained will be split into 3 vials, before forwarding to Endo's appointed laboratories for the determination of anti-AUX I and anti-AUX II antibodies and neutralizing antibodies to EN3835.

The immunogenicity samples will be collected, processed, stored, and shipped as described in the Laboratory Manual.

15.1.2. Sample Shipment Guidelines

Samples will be shipped by overnight, priority courier. The samples will be divided into 2 shipments, each containing 1 aliquot of plasma for each time point. After receipt of verification that the first shipment was received by the analytical facility, the second shipment will be processed.

Samples will be shipped only on Monday, Tuesday, or Wednesday to the analytical facility. The shipping address and contact information will be provided in a separate document.

15.2. Total Blood Volume Collected for the Study

The total blood volume expected to be drawn for the study is approximately 233 mL, as follows:

PK Samples: 14 samples × 10 mL/draw = 140 mL.

(Assuming the site uses an indwelling catheter to collect the first 11 samples out to 24 hours, an additional 3 mL of blood will be used for the required flush at each of these time points).

Flush volume (if indwelling catheter is used) = 11 samples × 3 mL flush = 33 mL.

Immunogenicity: (3 × 5-mL tubes of blood) × 2 time points = 30 mL.

Clinical Safety Labs (hematology/clinical chemistry): 15 mL blood × 2 time points = 30 mL.

16. STATISTICAL CONSIDERATIONS AND METHODS

16.1. Determination of Sample Size

Since this is primarily a PK and safety study, no formal sample size calculation was required. Twelve (12) subjects will be enrolled to receive the dose in the study. A minimum of 10 subjects should complete the study. The selection of between 12 and 16 subjects is typical for such trials.

16.2. Subject Populations

Three (3) populations are considered in the statistical analysis of the study.

16.2.1. Safety Population

The safety population is all enrolled subjects who receive at least one EN3835 injection.

16.2.2. Pharmacokinetic Population

The pharmacokinetic (PK) population is all enrolled subjects who receive the full EN3835 dose and have sufficient data from the 24-hour PK profile.

16.2.3. Cellulite Severity Population

The cellulite severity population consists of all enrolled subjects who receive at least one EN3835 injection and have the Screening and Day 22 CR-PCSS evaluation completed.

16.3. Subject Disposition

The number of subjects included in each study population will be summarized. Subjects excluded from the safety, PK, or cellulite severity populations will be listed.

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

16.4. Demographics and Other Baseline Characteristics

Demographic characteristics, including sex, age, age group, race, height, and weight, will be summarized for the safety population, using descriptive statistics. The descriptive summaries will include frequency tables for all categorical response variables and number, mean, standard deviation (SD), median, minimum, and maximum for all continuous variables.

16.5. Cellulite Severity Analyses

Cellulite severity will be assessed by the Investigator's rating of cellulite severity using the CR-PCSS. Evaluations will be done on each of the 4 quadrants at the Screening visit and Day 22. Change from baseline in cellulite severity will be computed. The Screening and Day 22 ratings will be summarized with counts and percentages at each level of severity and with mean and SD. The change from baseline value will be summarized with counts and percentages at each

possible change value and with mean and SD. The cellulite severity population will be used for summarizing the cellulite severity data.

16.6. Safety Analyses

Safety variables include AEs, laboratory parameters, and vital signs and will be analyzed using the safety population.

16.6.1. Prior, Concomitant, and Follow-up Medication

The WHO Drug Dictionary will be used to classify prior and concomitant medications by therapeutic class. The version used in this study will be stated in the Data Management Plan. Prior medication will be defined as any medication with a start date prior to the Day 1 date and are collected at the Screening visit and upon admission to the clinic on Day −1. Concomitant medication is defined as any medication with a start date on or after the Day 1 date or reported as ongoing.

Prior and concomitant medication use will be summarized descriptively by the number and percentage of subjects receiving each medication within each therapeutic class. Multiple use of the same medication by a subject will be counted only once.

16.6.2. Study Drug Exposure

The number of injections of study drug given on Day 1 will be summarized by counts and percentages. Any subject receiving less than 48 injections (12 injections per quadrant) will be listed. The number of dimples treated will be summarized with counts and percentages.

16.6.3. Measurement of Treatment Compliance

All doses are administered while subjects are confined as an inpatient in the clinical research unit. Any dose that was not administered per protocol will be recorded as a protocol deviation by the Investigator.

16.6.4. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code AEs. The version used in this study will be stated in the Data Management Plan.

An AE (classified by preferred term) that started during the treatment period 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 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, and subjects who die (if any).

16.6.5. Vital Signs

Descriptive statistics for vital signs (eg, systolic and diastolic blood pressure, pulse rate, and body temperature) and their changes from baseline at each visit and at the end of study will be presented by dose. Baseline will be the Day 1 pre-dose values.

Vital sign values are potentially clinically important (PCI) if they meet both the observed value criteria and the change from baseline criteria. The criteria for PCI vital sign values will be detailed in the Statistical Analysis Plan (SAP). A listing of subjects with post-baseline PCI values will be provided.

16.6.6. Clinical Safety Laboratory Parameters

Descriptive statistics for clinical laboratory values in International System of Units (SI units) and changes from baseline will be presented for each clinical laboratory parameter.

The number and percentage of subjects with PCI post-baseline clinical laboratory values will be tabulated. The criteria for PCI laboratory values will be detailed in the SAP. A listing of subjects with post-baseline PCI values will be provided.

16.6.7. Immunogenicity

Immunogenicity variables include anti-AUX-I/anti-AUX-II binding and neutralizing antibody results. Antibody assays will be conducted only if clinical signs and/or PK results warrant a need for antibody determinations. If warranted, binding antibody levels will be determined from samples (3 × 5-mL tubes of blood) collected on Day 1 and 22; neutralizing antibody levels will be determined for samples collected on Day 1 and Day 22 for all subjects seropositive for anti-AUX-I or anti-AUX-II at Day 22.

If antibody assays conducted, descriptive statistics (percent of positive measurements and average antibody level) will be presented for anti-AUX-I and anti-AUX-II antibody levels at each time point. Average antibody levels will be summarized on logarithmically transposed titer values. Neutralizing antibodies will be summarized as present or absent at each time point.

16.7. Pharmacokinetic Analyses

16.7.1. Plasma Concentrations

All plasma draws collected outside the protocol specified time window will be listed. This listing will include the nominal time from the injection, the actual time from the injection, and the difference between the 2 times, and the plasma concentrations of AUX-I and AUX-II. Blood samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60-minute sample) relative to the last dose will not be captured as protocol deviations. The exact time of sample collection must be noted on the source document and the CRF.

A measured drug concentration for plasma AUX-I and AUX-II versus time curve will be produced in graphic form for each subject with at least 1 drug concentration value above quantification limit. Plasma concentrations of plasma AUX-I and AUX-II will be summarized with descriptive statistics (number, mean, SD, median, minimum, and maximum) at each nominal sample time point. If the concentration levels are below the limit of quantification (BLQ) for all subjects at a time point, then not calculable (NC) will be reported in the summary table.

16.7.2. Calculation of Pharmacokinetic Variables

Pharmacokinetic data will be summarized through data tabulations, descriptive statistics, and graphic presentations, as appropriate. Actual blood sampling times will be used in all PK analyses.

Pharmacokinetic variables of AUX-I and AUX-II will be estimated from the plasma concentration data using a non-compartmental approach on standard PK software (eg, WinNonlin). Actual sample times (hours, relative to the corresponding administration time) rounded to 2 decimal digits and negative pre-dose times set to zero, will be used in the computation of the PK variables, rather than scheduled times.

The definition and method of determination for each PK parameter are summarized in Table 7.

Table 7: Pharmacokinetic Parameters

Variable	Definition
AUC_{0-t}	Area under the plasma concentration versus time curve from time 0 to the time of last quantifiable concentration (C_t), calculated by linear trapezoidal rule
AUC_{0-inf}	Area under the plasma *c*oncentration versus time curve from time 0 to infinity calculated as $AUC_{0-t} + C_t/\lambda_n$
C_{max}	Observed maximum plasma concentration; the highest concentration observed during a dosage/application interval
T_{max}	The time at which C_{max} was observed
λ_n	Terminal rate constant, calculated as the negative slope of the ln-linear portion of the terminal plasma concentration-time curve

16.7.3. Analysis of Pharmacokinetic Results

AUC_{0-t}, AUC_{0-inf}, and C_{max} will be summarized with descriptive statistics (number, mean, SD, median, minimum, and maximum) as well as the geometric mean and coefficient of variation (CV). Geometric means and CV will be calculated for the log transformed parameters using the following SAS formula:

$$CV\ (\%) = SQRT[\exp(SD^2)-1] * 100$$

T_{max} will be summarized with descriptive statistics (number, mean, SD, median, minimum, and maximum) only.

If all subjects have all PK concentrations BLQ, then all PK parameters will be summarized as NC.

16.8. Interim Analysis

No interim analysis is planned for this study.

16.9. Statistical Software

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

17. STUDY DRUG MATERIALS AND MANAGEMENT

17.1. Study Drug Identity

EN3835 is manufactured by [redacted] Endo.

EN3835 is a sterile lyophilized powder containing 0.46 mg of collagenase clostridium histolyticum, [redacted].

EN3835 sterile diluent for reconstitution is manufactured by [redacted] The diluent is 0.6% sodium chloride and 0.03% calcium chloride dehydrate filled into 2-mL vials. Sterile vials of lyophilized EN3835 and sterile diluent will be provided in bulk by Endo.

17.2. Study Drug Packaging and Labeling

Each vial of study drug and diluent will minimally be labeled with protocol, contents, Sponsor identification, storage, administration/use, and appropriate cautions statements.

17.3. 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 refrigerator (2°C-8°C) with locked access until used or returned to Endo. The reconstituted study drug solution should be administered as soon as possible after reconstitution and further dilution (section 10.4).

17.4. Study Drug Preparation

Refer to the Reconstitution Instructions for detailed preparation instructions.

For each dose, reconstitute 8 vials of EN3835 using approximately 10 vials of sterile diluent and prepare 16 syringes (4 syringes for each quadrant) each containing 0.9 mL/syringe.

Used drug vials should be stored in a secure location until reconciled and returned by the Clinical Research Associate (CRA). Dispose of used diluent vials, needles, syringes and sterile mixing vial per local regulations.

Study drug is stable at room temperature for [redacted]
Remove drug/prepared syringes from the refrigerator and allow it to stand at room temperature for 15 minutes prior to injection of study drug.

17.5. Study Drug Accountability

A drug inventory form must be kept current by the site 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 containers of unused study drug to Endo or their designee.

17.5.1. 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 unused study drug will be returned, and unit counts will be performed whenever medication is returned. The site must account for all study drug received. At the end of the study, all unused drug supplies will be returned to Endo.

18. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

18.1. 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. At a minimum, all data required to be collected by the protocol should have supporting source documentation for entries in the CRF, unless the protocol specifies that data can be recorded directly on/in the CRF or other device.

18.2. 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 CRF.

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

18.3. 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 Food and Drug Administration (FDA) or other regulatory agency inspection.

18.4. Institutional Review Board (IRB)

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

18.5. 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.

19. 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 site termination and regulatory authority notification.

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

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 Conference on 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.

20. ETHICS

20.1. 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 Summary of Product Characteristics (SmPC) 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 Pharmaceuticals Inc. 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.

20.2. 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, 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.

20.3. Subject Information and Consent

Subjects [if competent], 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.

Subjects unable to give written informed consent must have orally assented to the procedures; written informed consent must be obtained from their parent, legal guardian, or legally authorized representative (LAR) in accordance with the appropriate state laws, where applicable. The consent/assent 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 (her parent, legal guardian, or LAR) 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 she may withdraw from the study at any time.

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

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

A unique subject identification (ID) number will be assigned according to section 12.3 at the time that the subject signs the informed consent form.

21. DATA HANDLING AND RECORDKEEPING

21.1. Data Collection

Endo will provide an electronic data capture (EDC) system for this study. Data collection will involve the use of an 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 electronic case report form (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 sites and closed electronically by the monitor, data management staff or authorized staff at the study site. 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).

Data entries will be corrected by changing the entry in the EDC system. Any changes or corrections to eCRF data will be electronically tracked and will include the reason for correction, who made the correction and the date/time stamp when the correction was made within the audit trail of the EDC system.

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.

21.2. Study Documentation

Upon study completion, the Investigator will be provided with complete electronic copies of the CRF data for his/her files.

22. 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.

23. INVESTIGATOR OBLIGATIONS

23.1. 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.
- 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, as described in section 20.1
- 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 site 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.

23.2. 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.

23.3. 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 (section 14.5). The Investigator will inform study subjects of new information regarding the study drug as it becomes available.

23.4. 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 site. 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. All study supplies shall be returned to Endo.

23.5. 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 Pharmaceuticals Inc. will notify Investigators once one of the above 2 timeframes 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 Drew 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.

23.6. Subject Confidentiality

All subject records submitted to Endo or its designee will be identified only by initials and subject number. Subject 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.

24. 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.

25. 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 Name of Investigator

26. REFERENCES

1. Khan MH, Victor F, Rao B, Sadick NS. Treatment of cellulite: Part I. Pathophysiology. *J Am Acad Dermatol*. 2010;62(3):361-70.
2. Hexsel D, de Oliveira Dal'Forno T, Mazzuco R. Definition, clinical aspects, classifications, and diagnostic techniques. In: Goldman MP, Hexsel D, eds. *Cellulite: Pathophysiology and Treatment*. 2nd ed. New York, NY: Informa Healthcare; 2010:13-21.
3. Rawlings AV. Cellulite and its treatment. *Int J Cosmet Sci*. 2006;28(3):175-90.
4. Terranova F, Berardesca E, Maibach H. Cellulite: nature and aetiopathogenesis. *Int J Cosmet Sci*. 2006;28(3):157-67.
5. Investigational Brochure: Collagenase Clostridium Histolyticum for Injection (AA4500/EN3835), Version 7.0. Endo Pharmaceuticals Inc.; May 2016.

[redacted]

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

Investigator Rating

Prior to enrollment of the first subject, the Investigator will be trained on the use of the CR-PCSS. During the Screening visit, the Investigator will determine severity of cellulite of all 4 quadrants by live assessment, using the CR-PCSS for buttock (Figure 1) and thigh (Figure 2). On Day 22, the Investigator will evaluate the 4 quadrants that were dosed, by live assessment.

While viewing the subjects, the Investigator will be instructed to answer the following question: Today, how would you rate the severity of this patient's cellulite in the area selected for treatment using the CR-PCSS? If the buttock is the treated region, the Investigator will use the CR-PCSS for the buttock to make their evaluation; if the thigh is the treated region, the Investigator will use the CR-PCSS for the thigh to make their evaluation. In each case, the Investigator will make his/her assessment independently.

Figure 1: Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS) for the Buttock

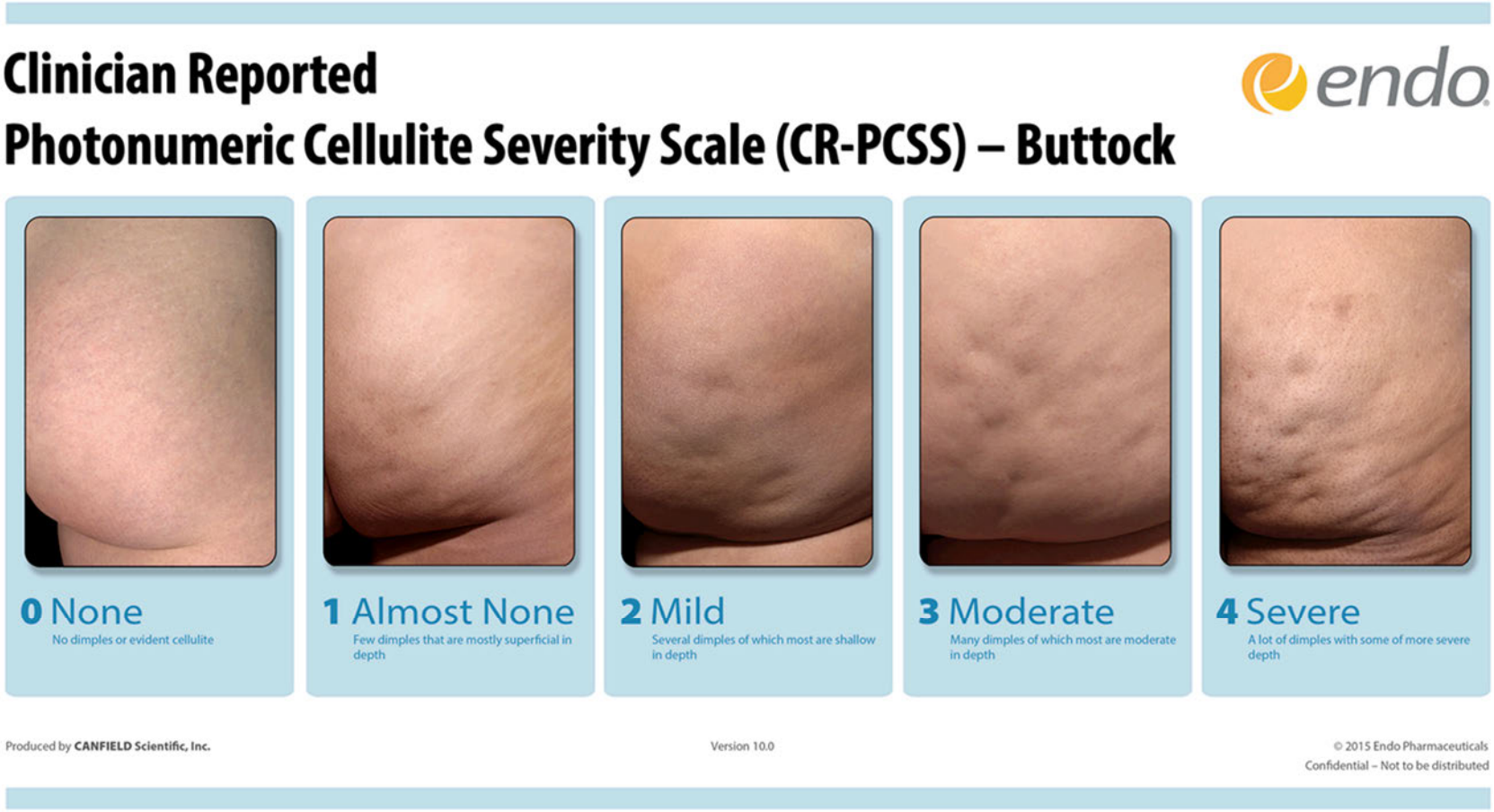


Figure 2: Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS) for the Thigh