Endo Pharmaceuticals Inc.
1400 Atwater Drive
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EN3835-305

A REAL WORLD, MULTICENTER, OPEN-LABEL, MULTIPLE DOSE STUDY TO ASSESS THE EFFECTIVENESS OF, AND SATISFACTION WITH, CCH TREATMENT OF BUTTOCK OR THIGH CELLULITE IN ADULT FEMALES

Sponsor Name: Endo Pharmaceuticals Inc.

Sponsor Legal Registered Address: 1400 Atwater Drive Malvern, PA 19355

Regulatory Agency Identifier Number: IND 110077

Original Protocol: 19 September 2019

Amendment 1: 06 November 2019

Amendment 2: 06 February 2020

Amendment 3: 01 June 2020

The sponsor of the Investigational New Drug Application (IND) is Endo Global Aesthetics Limited (EGAL); however, Endo Pharmaceuticals Inc. (Endo) is authorized to act and to communicate on behalf of EGAL. The sponsor is responsible for the conduct of the study, analysis of the data, and preparation of the clinical study report.

[redacted]

PROTOCOL AMENDMENT 3 SUMMARY OF CHANGES

Amendment 3 was incorporated into the protocol on 01 June 2020. The major reason for this amendment is to modify the protocol due to the interruption caused by the COVID-19 public health emergency. The COVID-19 public health emergency has disrupted the conduct of clinical research throughout the world. At Endo Pharmaceuticals Inc. (Endo), ensuring the safety of clinical study participants is our primary concern. In addition, the integrity of data obtained from clinical trials must be ensured.

Endo initiated study EN3835-305 at multiple sites in 2019. The first subject was dosed with CCH on 21 November 2019. Screening was halted for the study on 13 April 2020 due to the COVID-19 public health emergency. As of 13 April 2020, a total of 121 subjects had begun dosing and completed Day 1 treatment. Of those, 87 subjects had completed Day 22 and of those, 63 subjects had completed all 3 dosing visits up to Day 43.

As of 01 May 2020, a number of subjects were more than 1 week outside of the window for their next visit. In order to ensure subject safety and protect data integrity, Endo, in accordance with the *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency* (March 2020, updated 14 May 2020), will allow virtual visits for safety assessments. In addition, subjects will be allowed to continue in the study and complete remaining dosing and assessments when the investigational sites re-open as follows:

- Subjects who were in screening (those who had completed or were in the process of screening) for the study at the time of the COVID-19 interruption but who had not been dosed with CCH will repeat all screening assessments to determine eligibility, if willing to do so. All repeat screening assessments must be completed within the screening window. Rescreening of subjects is allowed in the current protocol.
- Subjects who had received any dose of CCH in the study prior to COVID-19 interruption will be allowed to continue in the study and complete all remaining dosing and assessments, if willing to do so in accordance with the scheduling outlined in Section 1.2.
- Subjects who receive their first dose of CCH after the COVID-19 interruption will complete the study as per the protocol.

Major updates to specific sections of the protocol that are impacted are outlined below, other minor changes that do not impact study conduct or participant safety were also made.

Section 1.1-Synopsis

The estimated date of last subject completion has been changed from November 2020 to January 2021.

Section 1.1-Synopsis and Section 3 Objectives and Endpoints

Objectives and Endpoints: The objectives and endpoints have been clarified to reflect the new visit windows. So that objectives and endpoints that were outlined for specific study days (eg, Day 90) have been updated to indicate the study visit (ie, the Day 90 Visit).

Section 1.1-Synopsis and Section 4.1 Overall Design

These sections have been modified to indicate the duration of subject's participation will be approximately 200 days (approximately 7 months) plus the length of any COVID-19 delay. In addition, the duration of the study has been increased from 1 year to 14 months.

Section 1.2 Schedule of Activities

A note has been added to describe the scheduling of visits for subjects who experienced COVID-19 interruptions.

Section 2.1-Study Rationale

The rationale for changes to the study due to the COVID-19 public health emergency (as outlined above) has been added to the end of this section.

Section 5.4 Screen Failures

An exception has been added for any rescreening process interrupted by COVID-19, subjects may be rescreened for a second time.

Section 8.2 Efficacy Assessments

Text has been added to indicate that due to the potential of bias, virtual efficacy assessments (Body-Q Appraisal of Cellulite, Body Dysmorphic Disorder Questionnaire,CR-PCSS-Buttock, I-GAIS, [redacted] are not allowed.

Section 8.3 Safety Assessments

Text was added to this section to allow virtual visits to assess safety during any COVID-19 interruption in accordance with the *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency* (March 2020, updated 14 May 2020).

PROTOCOL AMENDMENT 2 SUMMARY OF CHANGES

Amendment 2 was incorporated into the protocol on 06 February 2020. The major reason for this amendment was to extend the screening period to allow for additional safety assessments. Additional changes were made to clarify procedures.

The major revisions to the protocol are:

- Revised the screening period from "approximately 14 days" or "14 days" to "up to 28 days" or "28 days" (Sections 1.1, 1.2, 4.1, and 5.4).
- [redacted]
- Included the following statement "In the event that any safety laboratory testing results are unavailable prior to the subject's first dosing visit, the investigator will notify the sponsor to discuss on a case-by-case basis, prior to administering any study treatment to the subject" in Sections 1.2 (Footnote b of Table 1) and Section 8.3.8.

- Revised exclusion Criteria 4b, Section 5.2, from "Vascular disorder (eg, varicose veins, telangiectasia)" to "A current vascular disorder (eg, varicose veins, telangiectasia)."
- Revised exclusion Criteria 11 to denote providing breast milk in any manner is not permitted (Section 5.2). The original text "Is pregnant and/or is providing breast milk or plans to become pregnant and/or to provide breast milk during the course of the study" was revised to "Is pregnant and/or is providing breast milk **in any manner**, or plans to become pregnant and/or to provide breast milk during the course of the study."
- Included reference in Section 6.3 to the Pharmacy Manual for information on how subjects receiving treatment to the thigh may receive dosing via an updated injection technique if their I-GAIS score improved by at least +1. Added Footnote k to dosing on Days 22 and 43 in Table 1 stating the same information.
- Noted in Section 6.3 that vital signs must be stable before the subject leaves direct observation. The original text "The subject's vital signs should be stable before the subject can leave direct observation" was revised to "The subject's vital signs ~~should~~ **must** be stable before the subject can leave direct observation."
- Noted in Section 6.4 that the appropriate temperature control conditions should be maintained for all study treatments. The original text "The investigator or designee will confirm that appropriate temperature control conditions have been maintained during transit for all study treatments received and that any discrepancies are reported and resolved prior to study treatment administration" was revised to "The investigator or designee will confirm that appropriate temperature control conditions have been maintained ~~during transit~~ for all study treatments received and that any discrepancies are reported and resolved prior to study treatment administration."
- Revised the definition of adverse events and serious adverse events to remove the exclusion of the disease under study (Section 8.4). The original text "This would include AEs resulting from concurrent illness, reactions to concurrent medication use, or progression of disease states (excluding the disease under study)" was revised to "This would include AEs resulting from concurrent illness, reactions to concurrent medication use, or progression of disease states ~~(excluding the disease under study)~~."
- Revised text in Sections 6.7, 8.3.9, and 8.4.1 to clarify the text regarding the handling of subjects who terminated early.

  Original text in Sections 6.7:

  > The start and stop date, dose, unit, frequency, route of administration, and indication for all prior (taken within the 90 days prior to the Screening Visit) and concomitant (taken from the Screening Visit through the Day 180 Visit) medications and nondrug therapies (eg, blood transfusions, oxygen supplementation, physical therapy, etc) received will be recorded.

  Revised text:

  > The start and stop date, dose, unit, frequency, route of administration, and indication for all prior (taken within the 90 days prior to the Screening Visit) and concomitant (taken from the Screening Visit through the Day 180~~/Early Termination~~ Visit **or for**

28 days after the last study treatment for those who terminate early) medications and nondrug therapies (eg, blood transfusions, oxygen supplementation, physical therapy, etc) received will be recorded.

Original text in Section 8.3.9:

For all female subjects of childbearing potential, the subject's agreement to use contraception throughout their study participation (Screening Visit through the Day 180/Early Termination Visit, or for a minimum of 28 days after the last dose of study treatment for subjects who early terminate) will be documented.

Revised text:

For all female subjects of childbearing potential, the subject's agreement to use contraception throughout their study participation (Screening Visit through the Day 180~~/Early Termination~~ Visit, or for a minimum of 28 days after the last dose of study treatment for subjects who ~~early~~ terminate **early**) will be documented.

Original text in Section 8.4.1:

All SAEs and AEs will be collected by the investigator from the time of signing the informed consent through the Day 180/Early Termination Visit or for 28 days after the last study treatment for those who early terminate. This will include any AEs that are ongoing at the time of completion/termination of the study. All ongoing AEs must be followed until resolution or for 28 days after the subject's last study treatment, whichever comes first.

Revised text:

All SAEs and AEs will be collected by the investigator from the time of signing the informed consent through the Day 180~~/Early Termination~~ Visit or for 28 days after the last study treatment for those who ~~early~~ terminate **early**. ~~This will include any AEs that are ongoing at the time of completion/termination of the study.~~ All ongoing AEs must be followed ~~until~~ **to** resolution or **until the Day 180 Visit or** for 28 days after the subject's last study treatment **visit for subjects who terminate early**, whichever comes first.

PROTOCOL AMENDMENT 1 SUMMARY OF CHANGES

Amendment 1 was incorporated into the protocol on 06 November 2019. The major reasons for this amendment are to clarify the methodology for the Investigator Global Aesthetic Improvement Scale (I-GAIS) and to allow the use of compression garments post-treatment. No other changes were made.

The major revisions to the protocol are:

- Investigators who are physicians will determine the degree of improvement in cellulite by comparing the Day 1 pretreatment image of each buttock or each thigh to the images taken at the subsequent visits specified in the Schedule of Activities, rather than by comparing Day 1 images to live subject assessments (Section 8.2.2.5).
- Compression to the treatment area is allowed at the discretion of the investigator. If compression at the treatment area is used by the subject, the start and stop date and type of compression used will be recorded in the source documents and the electronic caser report form (eCRF) (see Section 6.3).

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1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company: Endo Pharmaceuticals Inc.

Name of Investigational Product: CCH

Name of Active Ingredient: Collagenase clostridium histolyticum

Title of Study: A real world, multicenter, open-label, multiple dose study to assess the effectiveness of, and satisfaction with, CCH treatment of buttock or thigh cellulite in adult females

Lead Principal Investigator: Not applicable

Study Period:	**Phase of Development:** 3b
Estimated date first subject enrolled: November 2019 Estimated date last subject completed: January 2021	

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To assess the efficacy of CCH treatment of buttock or thigh cellulite at the Day 90 Visit in adult females.	• The proportion of subjects with improved (+1 or better) score on the Investigator Global Aesthetic Improvement Scale (I-GAIS) for either buttock or either thigh at the Day 90 Visit.
Secondary	
• To assess the efficacy of CCH in the treatment of buttock or thigh cellulite in adult females.	• The proportion of subjects with improved (+1 or better) score on I-GAIS for either buttock or either thigh at the Day 22, 43, and 180 Visits.
• To assess the effectiveness of CCH in the treatment of buttock cellulite in adult females.	• Mean change from baseline in CR-PCSS for each buttock at the Day 22, 43, 90, and Day 180 Visits.
• To assess subject satisfaction with CCH treatment of buttock or thigh cellulite in adult females.	• Mean change from baseline in Body-Q™ Appraisal of Cellulite for buttock or thigh treated subjects at the Day 90 and Day 180 Visits.
• To assess the safety and tolerability of CCH when administered to adult female subjects with buttock or thigh cellulite.	• Proportion of subjects reporting each treatment-emergent adverse events (TEAEs) and adverse events of special interest (AESIs). • Actual and change from baseline at each visit for vital signs and for each clinical laboratory test parameter. • Percentage of subjects with positive antibody titers for anti-AUX I and anti-AUX II and neutralizing antibodies

[redacted]

Name of Sponsor/Company: Endo Pharmaceuticals Inc.
Name of Investigational Product: CCH
Name of Active Ingredient: Collagenase clostridium histolyticum
Overall Design: This is a multicenter, open-label, multiple dose, 2 cohort, Phase 3b study to assess the safety and efficacy of CCH in adult women with mild or moderate edematous fibrosclerotic panniculopathy (EFP). Approximately 200 subjects will be screened in order to dose approximately 150 subjects in 2 cohorts. Cohort 1 will include approximately 80 subjects with mild or moderate EFP in the posterolateral thighs and Cohort 2 will include approximately 70 subjects with mild or moderate EFP in the buttocks. Following a screening period of up to 28 days, qualified subjects (determined by investigator assessment and Endo's Eligibility Confirmation process) will receive 0.84 mg of CCH per treatment area (each buttock or each thigh) for a total dose of 1.68 mg in both buttocks or both thighs per treatment session × 3 treatment sessions (Day 1, Day 22, and Day 43). Subjects will have follow-up visits at approximately 90 and 180 days after Day 1. [redacted] Subjects will participate in the study for approximately 200 days (approximately 7 months) plus the length of any COVID-19 delay. The duration of the study from first subject first visit to last subject last visit will be dependent upon the ability of sites to identify and enroll subjects. The entire study is expected to require approximately 14 months to complete.
Disclosure Statement: This is an open-label safety and efficacy study with 2 treatment cohorts (buttocks or thighs).
Number of Subjects (planned): Approximately 200 subjects will be screened, so that 150 subjects (80 thigh, 70 buttock) receive study drug and approximately 135 subjects complete the study.
Treatment Groups and Duration: All subjects will receive 3 treatment sessions 21 to 35 days apart and consisting of 0.84 mg of CCH in each treatment area (each buttock or each thigh for a total dose of 1.68 mg). The total amount of CCH to be administered per subject over the course of the study will not exceed 5.04 mg.
Data Monitoring Committee: No data monitoring committee will be used for this study.

1.2. Schedule of Activities

Table 1: Schedule of Activities

Activities	Screening (Day -28 to Day -1)	Day 1 (Treatment Session I)	Day 22 (+7 Days) (Treatment Session II)	Day 43 (+14 Days) (Treatment Session III)	Day 90 (+14 Days)	Day 180 (+14 Days)/ Early Termination
Informed consent[a]	X					
Inclusion/exclusion criteria review[b]	X	X				
Medical and Surgical history	X					
EFP history	X					
Prior medications (including all prior medications for cellulite)[b]	X	X				
Physical examination	X				X	X
Height	X					
Weight	X	X	X	X	X	X
Fitzpatrick Skin Type	X					
Hexsel CSS Subsection D[b]	X					
Vital signs	X	X[c]	X[c]	X[c]	X	X
ECG	X					
Hematology, chemistry, and urinalysis	X				X	X
Serum pregnancy test	X					
Urine pregnancy test		X	X	X	X	X
Immunogenicity sample collection		X			X	X
Body-Q Appraisal of Cellulite[d]	X				X	X
Body Dysmorphic Disorder Questionnaire						X
Imaging for eligibility confirmation	X					

Table 1: Schedule of Activities (Continued)

Activities	Screening (Day -28 to Day -1)	Day 1 (Treatment Session I)	Day 22 (+7 Days) (Treatment Session II)	Day 43 (+14 Days) (Treatment Session III)	Day 90 (+14 Days)	Day 180 (+14 Days)/ Early Termination
Eligibility confirmation[e]	X					
Selection of treatment region (both buttocks or both thighs)	X					
[redacted]						
[redacted]		X	X	X	X	X
CR-PCSS[h]	X	X	X	X	X	X
I-GAIS[i]			X	X	X	X
Select and mark up to 12 target dimples for CCH injection in each treatment area (each buttock or each thigh)		X	X	X		
[redacted]		X	X	X	X	X
Study drug administration		X	X[j]	X[j]		
[redacted]				X		
[redacted]					X	
Concomitant medications	X	X	X	X	X	X
Injection site reactions/local tolerability in areas treated		X	X	X	X	X
All other AEs[k]	Monitored throughout the study					

[a] Performed prior to any study-required assessments, unless exceptions granted for standard of care procedures.

[b] Should be reassessed and verified prior to dosing. In the event that any safety laboratory testing results are unavailable prior to the subject's first dosing visit, the investigator will notify the sponsor to discuss on a case-by-case basis, prior to administering any study treatment to the subject.

[c] Vital signs will be collected up to 4 hours prior to, and at 15 and 30 minutes after, study treatment administration on Days 1, 22, and 43.

[d] Assessment should be completed independently of, and prior to, any investigator cellulite assessments (CR-PCSS, I-GAIS, [redacted]

[e] Provided by an evaluator designated by the sponsor.

[f] Before and after marking target dimples at treatment visits. No manipulation of the treatment area should be done prior to the "before" images.
[redacted].

[h] CR-PCSS-Buttock and CR-PCSS-Thigh will both be done at screening. Thereafter, only buttock treated subjects will be assessed by CR-PCSS-Buttock.

[i] I-GAIS will be completed after CR-PCSS when both are required at the same visit.

[j] Subjects receiving treatment to the thigh may receive dosing via an updated injection technique if their I-GAIS score has improved by at least +1. Refer to the pharmacy manual for all injection techniques.

[k] AEs/SAEs will be captured from the time of informed consent signature until the Day 180/Early Termination Visit or until 28 days after last dose of study drug whichever is later. There is no time limit on collection of SAEs felt to be related to study treatment.

Note: Unless otherwise stated above or outlined below (and with the exception of injection site reactions/local tolerability in the areas treated), all assessments should be completed prior to dosing on treatment days (Days 1, 22, and 43).

Rescheduling visits that were out of window due to the COVID-19 interruption (see COVID-19 Trial Impact Mitigation Instructions for EN3835 - 305 v1.0 - 13May2020 FINAL for details)
Protocol deviations will be recorded for all subjects who had visits outside of the windows outlined in this Schedule of Activities, regardless of reason (including all subjects who experienced the COVID-19 interruption). The reason for out of window visits will be recorded.

Every effort will be made to conduct the Day 180 visit no more than 180 (+14) days after the first dose of CCH for all subjects. Those subjects who received any dose of CCH prior to the COVID-19 interruption (13 April 2020) will be allowed to remain in the study if willing to do so, and if they can abide by the following:

- Subjects who had completed only the Day 1 Visit and received their first dose of CCH prior to the COVID-19 interruption will have the Day 22 Visit scheduled at the earliest possible date upon the reopening of the site but no later than 100 days after their first dose of CCH. For these subjects, the Day 43 visit will be scheduled no less than 21 days after the Day 22 Visit and the Day 90 Visit will be scheduled for no less than 28 days after the Day 43 Visit but should not precede the Day 180 Visit by less than 45 days. The Day 180 Visit will remain scheduled for 180 (+14) days after the first dose of CCH.

- Subjects who had completed only the Day 1 and Day 22 Visits and received their first 2 doses of CCH prior to the COVID-19 interruption will have the Day 43 Visit scheduled at the earliest possible date upon the reopening of the site but no later than 121 days after their first dose of CCH. For these subjects, the Day 90 Visit will be scheduled for no less than 28 days after the Day 43 Visit and the Day 180 Visit will occur no less than 45 days after the Day 90 Visit.

- Subjects who had completed only the Day 1, 22, and 43 Visits and received all 3 doses of CCH prior to the COVID-19 interruption will have the Day 90 Visit scheduled at the earliest possible date upon the reopening of the site. For these subjects the Day 180 Visit will be scheduled for no less than 45 days after the Day 90 Visit and will remain scheduled for 180 (+14) days after the first dose of CCH.

2. INTRODUCTION

CCH is a parenteral lyophilized product comprised of 2 collagenases in an approximate 1:1 mass ratio, Collagenase I (Clostridial class I collagenase [AUX-I]) and Collagenase II (Clostridial class II collagenase [AUX-II]). CCH is a novel formulation of an existing product (XIAFLEX®) that is currently approved for use in adults with Dupuytren's contracture and Peyronie's disease.

2.1. Study Rationale

The results from Phase 2 and Phase 3 studies show CCH 0.84 mg given per treatment area (1 buttock or 1 thigh) is an effective treatment of edematous fibrosclerotic panniculopathy (EFP, commonly known as cellulite) based on improvement in the severity of cellulite as determined by the Investigator and the subject. There were no safety concerns following 3 doses of 0.84 mg of CCH per treatment area. The majority of adverse events (AEs) occurred at the site of injection and resolved before the next scheduled treatment in these studies. The immunogenicity profile of CCH has been consistent across all studies.

The Phase 3 studies conducted to date have only included CCH treatment in the buttocks, therefore further investigation of drug safety and efficacy is needed for treatment in the thighs.

Input provided to the sponsor from aesthetic medicine specialists indicates a desire to investigate CCH in the treatment of cellulite in the buttocks and thighs in a real world setting allowing for additional inclusion criteria and for additional endpoints to measure the effectiveness of CCH in a manner that more closely mimics clinical practice.

The COVID-19 public health emergency has disrupted the conduct of clinical research throughout the world. At Endo Pharmaceuticals Inc. (Endo), ensuring the safety of clinical study participants is our primary concern. In addition, the integrity of data obtained from clinical trials must be ensured.

Endo initiated study EN3835-305 at multiple sites in 2019. The first subject was dosed with CCH on 21 November 2019. Screening was halted for the study on 13 April 2020 due to the COVID-19 public health emergency. As of 13 April 2020, a total of 121 subjects had begun dosing and completed Day 1 treatment. Of those, 87 subjects had completed Day 22 and of those, 63 subjects had completed all 3 dosing visits up to Day 43.

As of 01 May 2020, a number of subjects were more than 1 week outside of the window for their next visit and there was no indication that the sites would be able to re-open within the following 2 weeks. In order to ensure subject safety and protect data integrity, Endo, in accordance with the *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency* (March 2020, updated 14 May 2020), will allow virtual visits for safety assessments. In addition, subjects will be allowed to continue in the study and complete remaining dosing and assessments when the investigational sites re-open as follows (and with subject consent):

- Subjects who were in screening (those who had completed or were in the process of screening) for the study at the time of the COVID-19 interruption but who had not been dosed with CCH will repeat all screening assessments to determine eligibility, if

willing to do so. All repeat screening assessments must be completed within the screening window. Rescreening of subjects is allowed in the current protocol.

- Subjects who had received any dose of CCH in the study prior to COVID-19 interruption will be allowed to continue in the study and complete all remaining dosing and assessments, if willing to do so and in accordance with the scheduling outlined in Section 1.2.
- Subjects who receive their first dose of CCH after the COVID-19 interruption will complete the study as per the protocol.

2.2. Background

EN3835 is a parenteral lyophilized product comprised of 2 collagenases in an approximate 1:1 mass ratio, AUX-I and AUX-II. EN3835, marketed as XIAFLEX®, is currently approved for use in adults with Dupuytren's contracture and Peyronie's disease. These collagenases are proteinases that hydrolyze collagen in its native triple helical conformation under physiological conditions, resulting in lysis of collagen deposits in a Dupuytren's cord and/or Peyronie's plaque.

To investigate EN3835 in the treatment of EFP, commonly known as cellulite, Endo Pharmaceuticals Inc. (Endo) has developed a novel formulation of EN3835, referred to hereafter as CCH, with a different concentration and volume of the approved EN3835 formulation.

Cellulite is an aesthetic condition that can be understood as an imbalance between the structural characteristics and biomechanical properties (ie, the delicate containment and extrusion forces) at the subdermal junction (Rudolph et al, 2019). As such, the goals of cellulite treatment are to strengthen the subdermal interface and/or to release the fibrous septae via various types of subcision (Rudolph et al, 2019). The fibrous septae has been recognized as a contributory underlying cause of cellulite and as a target of treatment for cellulite by anatomical and image analyses studies (Hexsel et al, 2009; Hexsel et al 2016; Mirrashed et al, 2004; Nürnberger and Müller, 1978; Piérard et al, 2000; Querleux et al, 2002).

A number of therapies have been utilized in an attempt to treat cellulite, much of the evidence for their efficacy is anecdotal, subjective, or based only on patient self-assessment and many of the treatments have undesirable side effects (Avram, 2004; Collis et al, 1999; Khan et al, 2010; Hexsel and Mazzuco, 2000). Some of the historical treatments for EFP have included weight loss, pharmacological agents (eg, xanthines, retinoids, lactic acid, and herbals), Endermologie® or lipomassage, mesotherapy, radiofrequency, subcision (including powered subcision, eg, Cellfina®), and laser (including Triactive® and CelluLaze™) (Boyce et al, 2005; DiBernardo, 2011; Hexsel and Mazzuco, 2000; Khan et al, 2010). However, there remains an unmet need for safe and effective nonsurgical therapies to improve the aesthetic outcome in women with cellulite. CCH has the potential to effectively lyse the subdermally located fibrous septae, the underlying cause of the skin dimpling in women with cellulite, at the site of injection.

The results from previous studies have shown improvement in the severity of cellulite, as determined by both the investigator and the subject, in subjects treated with CCH administered at a dose of 0.84 mg per treatment area (1 buttock or 1 thigh) every 21 days for 3 sessions. Across all previous studies, CCH has demonstrated an acceptable safety and immunogenicity profile.

The majority of AEs occurred at the site of injection, were mild to moderate in nature, and often resolved within 2 to 3 weeks without any sequelae.

A detailed description of the chemistry, pharmacology, efficacy, and safety of CCH is provided in the current edition of the Investigator's Brochure.

The purpose of this study is to examine the efficacy and safety of CCH administered as 0.84 mg per treatment area in the buttocks or thighs of adult women with EFP at 3 treatment sessions up to 35 days apart and to assess efficacy using the Investigator Global Aesthetic Improvement Scale (I-GAIS) and other measures.

2.3. Risk/Benefit Assessment

Current treatments for EFP have limited efficacy and undesirable side effects. There remains an unmet need for safe and effective nonsurgical therapies to improve the aesthetic outcome in women with cellulite.

The following AEs have been commonly observed in subjects treated with CCH for EFP: local injection site reactions including injection site bruising, injection site swelling, and injection site pain. 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.

More detailed information about the known and expected benefit, risks, and reasonably expected AEs associated with CCH can be found in the current version of the Investigators Brochure.

Risks associated with ultrasound are rare; however, subjects undergoing ultrasound may experience slight heating of tissues and the creation of cavitations (small pockets of gas) within the body. The long term effects of these events are unknown.

All other procedures and activities in this study are generally accepted as standard of care for patients with EFP and do not present any increased risk to the subjects.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the efficacy of CCH treatment of buttock or thigh cellulite at the Day 90 Visit in adult females.	• The proportion of subjects with improved (+1 or better) score on I-GAIS for either buttock or either thigh at the Day 90 Visit.
Secondary	
• To assess the efficacy of CCH in the treatment of buttock or thigh cellulite in adult females.	• The proportion of subjects with improved (+1 or better) score on I-GAIS for either buttock or either thigh at the Day 22, 43, and 180 Visits.
• To assess the effectiveness of CCH in the treatment of buttock cellulite in adult females.	• Mean change from baseline in CR-PCSS for each buttock at the Day 22, 43, 90, and 180 Visits.
• To assess subject satisfaction with CCH treatment of buttock or thigh cellulite in adult females.	• Mean change from baseline in Body-Q Appraisal of Cellulite for buttock or thigh treated subjects at the Day 90 and Day 180 Visits.

Objectives	Endpoints
• To assess the safety and tolerability of CCH when administered to adult female subjects with buttock or thigh cellulite.	• Proportion of subjects reporting each treatment-emergent adverse event (TEAEs) and adverse events of special interest (AESIs). • Actual and change from baseline at each visit for vital signs and for each clinical laboratory test parameter. • Percentage of subjects with positive antibody titers for anti-AUX-I and anti-AUX-II and neutralizing antibodies.
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is a real world, multicenter, open-label, multiple dose, 2 cohort, Phase 3b study to assess the safety and efficacy of CCH in adult women with mild or moderate EFP. Approximately 200 subjects will be screened in order to dose approximately 150 subjects in 2 cohorts. Cohort 1 will include approximately 80 subjects with mild or moderate EFP in the posterolateral thighs and Cohort 2 will include approximately 70 subjects with mild or moderate EFP in the buttocks.

Following a screening period of up to 28 days, qualified subjects (determined by investigator assessment and Endo's Eligibility Confirmation process) will receive 0.84 mg of CCH per treatment area (each buttock or each thigh) for a total dose of 1.68 mg in both buttocks or both thighs per treatment session × 3 treatment sessions (Day 1, Day 22 [+7 days], and Day 43 [+14 days]). Subjects will have follow-up visits at approximately 90 and 180 days after Day 1.

[redacted]

Subjects will participate in the study for approximately 200 days (approximately 7 months) plus the length of any COVID-19 delay. The duration of the study from first subject first visit to last subject last visit will be dependent upon the ability of sites to identify and enroll subjects. The entire study is expected to require approximately 14 months to complete.

4.2. Scientific Rationale for the Study Design

This is an open-label exploratory study to support ongoing clinical research of CCH in EFP and to better understand its potential use in clinical practice.

4.3. Justification for Dose

The results from a Phase 2b study (EN3835-201) suggested that CCH 0.84 mg per treatment area (1 buttock or 1 thigh) is safe and effective. The Phase 3 studies (EN3835-302 and EN3835-303) using the same dose in each buttock showed a similar safety profile with most AEs being mild to moderate in severity and transient. The immunogenicity profile of CCH has been consistent across all clinical studies to date. Therefore, the dose of 0.84 mg per treatment area (each buttock or each thigh – for a total dose of 1.68 mg of CCH for 2 buttocks or 2 thighs) will be used in this study.

4.4. End of Study Definition

A subject is considered to have completed the study if the subject has completed the Day 180 visit.

The end of the study is defined as the completion of the final assessment for the last subject enrolled in the trial.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1. Subject Inclusion Criteria

In order to be eligible to participate in the study, at the Screening Visit and on Study Day 1, subjects must:

1. Be female and ≥ 18 and ≤ 60 years of age at the time of consent.
2. Have both buttocks or both posterolateral thighs with:
    a. A score of 2 or 3 (mild or moderate) as reported by the investigator using the Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS).
    b. A Hexsel Cellulite Severity Scale (CSS) Subsection D "Grade of Laxity, Flaccidity, or Sagging Skin" score of 0 (absence of laxity, flaccidity, or sagging skin), or 1 (slightly draped appearance) at the Screening Visit only.
3. Have a body mass index (BMI) score between 18.0 kg/m^2 and 30.0 kg/m^2 and intends to maintain stable body weight (≤ 10% change from the Day 1 Visit weight) throughout the duration of the study (from the Screening Visit through the Day 180/Early Termination Visit).
4. Be willing to apply sunscreen to the treatment areas before each exposure to the sun for the duration of the study (from the Screening Visit through the Day 180/Early Termination Visit).

5. Be judged by the investigator to be in good health, based upon the results of a medical history, physical examination, electrocardiogram (ECG), and laboratory profile at screening.
6. Be of nonchildbearing potential (history of hysterectomy, bilateral oophorectomy, bilateral tubal ligation, or postmenopausal with no history of menstrual flow in the 12 months prior to the Screening Visit); or, if of childbearing potential, be nonpregnant, nonlactating, and agree to use effective contraception when with a male partner for the duration of the study. Acceptable forms of contraception include hormonal measures (oral contraceptive pills, contraceptive patch, contraceptive ring, injections, etc), intrauterine devices, double barrier method (condom plus diaphragm, condom or diaphragm plus spermicidal gel or foam), surgical sterilization of the male partner, and abstinence.
7. Have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test prior to dosing at each treatment session.
8. Be willing and able to comply with all protocol required visits and assessments.
9. Be able to read, understand, and independently complete patient reported outcome instruments in English.
10. Be adequately informed and understand the nature and risks of the study and be able to provide consent as outlined in Section 10.1.3.

5.2. Subject Exclusion Criteria

A subject is ineligible for study participation if, at the Screening Visit or on Day 1, the subject:

1. Is from a vulnerable population, as defined by the United States (US) Code of Federal Regulations (CFR) Title 45, Part 46, Section 46.111(b) and other local and national regulations, including but not limited to, employees (temporary, part-time, full-time, etc) or a family member of the research staff conducting the study, or of the sponsor, or of the contract research organization, or of the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).
2. Has a history of sensitivity or allergy to collagenase or any other excipient of CCH.
3. Has any of the following systemic conditions:
    a. Coagulation disorder.
    b. Evidence or history of malignancy (other than excised basal-cell carcinoma) unless there had 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 will be discussed with the Medical Monitor.
    e. Evidence of clinically significant abnormalities on physical examination, vital signs, ECG, or clinical laboratory values.

4. Has any of the following local conditions in the areas to be treated (both buttocks or both thighs):
   a. History of lower extremity thrombosis or post-thrombosis syndrome.
   b. A current vascular disorder (eg, varicose veins, telangiectasia).
   c. Inflammation or active infection.
   d. Active cutaneous alteration including rash, eczema, or psoriasis.
   e. A tattoo or other artificially inflicted body marker.
   f. Has a mole located within 2 cm of any injection site.
5. Has skin laxity or linear undulations on the treatment region (both buttocks or both thighs) that can be effaced by lifting skin.
6. Has a Hexsel CSS Subsection D "Grade of laxity, flaccidity, or sagging skin" of 2 (moderate draped appearance) or 3 (severe draped appearance).
7. Requires anticoagulant or antiplatelet medication during the study or has received anticoagulant or antiplatelet medication (except for ≤ 150 mg aspirin daily) within 7 days before injection of study treatment.
8. Has used any of the following for the treatment of EFP on either thigh or either 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 during the 12-month period before dosing with study treatment.
   b. Injections (eg, mesotherapy, dermal fillers, biostimulatory fillers); radiofrequency device treatments; laser treatment; buttock or thigh implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision) during the 12-month period before injection of study treatment.
   c. Any investigational treatment for EFP on a buttock or thigh during the 12-month period before the injection of study treatment.
   d. Endermologie or similar treatments during the 6-month period before injection of study treatment.
   e. Massage therapy during the 3-month period before injection of study treatment.
   f. Creams (eg, Celluvera™, TriLastin®) and/or home therapies to prevent or mitigate EFP during the 2-week period before injection of study treatment.
9. Has received any collagenase treatments at any time prior to treatment in this study and/or has received previous treatment with EN3835 or CCH for cellulite.
10. Has received treatment with an investigational product within 30 days (or 5 half-lives, whichever is longer) of the Screening Visit.
11. Is pregnant and/or is providing breast milk in any manner, or plans to become pregnant and/or to provide breast milk during the course of the study.
12. Intends to initiate an intensive sport or exercise program during the study.
13. Intends to initiate an intensive weight reduction program during the study.

14. Has any other condition(s) that, in the investigator's opinion, might indicate the subject to be unsuitable for the study.

5.3. Lifestyle Considerations

See Section 5.1 and Section 5.2.

5.4. Screen Failures

Screen failures are defined as subjects who consent to participate in this study but are not subsequently treated. Eligibility confirmation by the sponsor or designee is required for this study (see Section 8.1).

Subjects will be allowed to repeat any single screening assessment/procedure once, if necessary, if it is within the screening window. The subject will not be considered a screen failure unless the repeat assessment/procedure result does not meet eligibility criteria. The period from the start of screening related procedures at the Screening Visit to the Day 1 Visit must not exceed 28 days, inclusive of any repeat screening procedures.

Subjects who do not meet all of the eligibility criteria at the Screening or Day 1 Visits will be deemed a screen failure and the following information must be recorded for all subjects who are screen failures:

- Demography (age, gender, race/ethnicity).
- Reason for screen failure.
- Which eligibility criterion was not met.
- Any AEs (including serious adverse events [SAEs]) experienced by the subject.

A subject who is a screen failure at the Screening Visit may be rescreened with approval from the sponsor. The subject must repeat all screening procedures. The period from the start of rescreening related procedures to the study treatment must not exceed 28 days. Subjects may be rescreened only once; however subjects whose rescreening process was interrupted by COVID-19 may be rescreened for a second time.

6. STUDY TREATMENT

Study treatment is defined as any investigational treatment, marketed product, placebo, or device intended to be administered to a study subject according to the study protocol.

6.1. Selecting the Treatment Region

Selection of the treatment region (both buttocks or both thighs) will be at the discretion of the investigator and in accordance with the distribution required for the study. Cohort 1 will include approximately 80 subjects with mild or moderate EFP in the posterolateral thighs and Cohort 2 will include approximately 70 subjects with mild or moderate EFP in the buttocks.

No subjects will be treated in both the buttocks and the thighs.

6.2. Selecting and Marking Target Dimples for Treatment

For treatment, the investigator or qualified designee will select up to 12 dimples within each treatment area (each buttock or each thigh) that are well-defined, evident when the subject is standing, and suitable for treatment. These dimples will be designated as the target dimples, and will be treated at each treatment session (Days 1, 22, and 43) as long as they remain visible. If less than 12 target dimples are identified and treated at the Day 1, Day 22, or Day 43 Visits, then the target dimples will be treated first, thereafter additional other dimples within the same treatment area may be treated at the discretion of the investigator as long as the maximum dose per treatment area (each buttock or each thigh) does not exceed 0.84 mg.

For each target dimple selected for treatment, the investigator or qualified designee will choose injection sites (injection sites within a dimple should be spaced approximately 2 cm apart, if a dimple requires more than 1 injection; locating at least one injection site at the nadir, if present, of the dimple). 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; for elongated dimples, "dots" will be spaced out approximately 2 cm along the longer axis of the dimple. The investigator or qualified designee will then use a surgical marker to circle each of the target dimples selected for treatment.

6.3. Treatment Administration

CCH is a sterile lyophilized powder that is reconstituted with a sterile diluent made of 0.6% sodium chloride and 0.03% calcium chloride dihydrate in water. Subjects who qualify for the study will be given a maximum dose of 0.84 mg of CCH per treatment area (buttock or thigh) per treatment visit (total maximum dose of 1.68 mg per treatment session × 3 treatment sessions [Days 1, 22, and 43] for a maximum total dose of 5.04 mg), administered as up to 12 subcutaneous injections per buttock or thigh (see Table 2).

In this study, the reconstitution volumes and angles of injection will be different for the buttocks and the posterolateral thighs. However, the total dose in each treatment area (each buttock or each thigh) will be no more than 0.84 mg of CCH per treatment session.

Buttock cellulite dimple injections will consist of administration of 0.3 mL of reconstituted CCH, administered in 3 aliquots of 0.1 mL each. For thighs, cellulite dimple injections will consist of 1.5 mL of reconstituted CCH, administered in 5 aliquots of 0.3 mL each.

Specific instructions for CCH reconstitution and administration, including the injection techniques, will be provided in the Pharmacy Manual. For subjects being treated in the thighs who show an improvement in the I-GAIS scale of at least a +1 level at Day 22 or Day 43, please refer to the Pharmacy Manual for updated injection technique guidance.

Table 2: Study Treatment

Treatment Area	Dose per Each Injection	Injection Volume per Each Injection	Number of Injections at Each Treatment Visit	Dose (mg) at Each Treatment Visit	Injection Volume (mL) per Each Treatment Visit	Cumulative EFP Dose
Buttock	CCH 0.07 mg	0.3 mL (given as three 0.1 mL aliquots)	Up to 12 per buttock × 2 buttocks = up to 24 injections	Up to 0.84 mg per buttock × 2 buttocks = up to 1.68 mg (12 injections per buttock × 0.07 mg/injection × 2 buttocks)	Up to 3.6 mL per buttock × 2 buttocks = up to 7.2 mL (24 injections × 0.3 mL)	Maximum of 5.04 mg (3 treatment visits × 0.84 mg per buttock × 2 buttocks)
Thigh	CCH 0.07 mg	1.5 mL (given as five 0.3 mL aliquots)	Up to 12 per thigh × 2 thighs = up to 24 injections	Up to 0.84 mg per thigh × 2 thighs = up to 1.68 mg (12 injections per thigh × 0.07 mg/injection × 2 thighs)	Up to 18 mL per thigh × 2 thighs = Up to 36 mL (24 injections × 1.5 mL)	Maximum of 5.04 mg (3 treatment visits × 0.84 mg per thigh × 2 thighs)

Study treatment will be injected subcutaneously while the subject is in a prone position. Treatment will consist of up to 12 injections per treatment area (each buttock or each thigh) for a total of up to 24 injections in 2 buttocks or in 2 thighs per treatment visit.

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

After the completion of dosing at each treatment session, the investigator or qualified designee will apply a sterile dressing to the injection areas with hypoallergenic tape. The subject will be instructed to remove the dressing in the evening.

At the discretion of the investigator, compression at the treatment area may be recommended to the subject. If compression at the treatment area is used by the subject, the start and stop date and type of compression used will be recorded in the source documents and the eCRF.

6.4. Study Treatment Preparation/Handling/Storage/Accountability

Vials of 1.84 mg CCH and its diluent (8 mL) will be supplied in kits. Each vial of study treatment and diluent will minimally be labeled with contents, sponsor identification, storage, administration/use, and appropriate caution statements. CCH and the diluent must be stored in an appropriate, secure area. Study treatment must be kept in a temperature-monitored refrigerator (2°C to 8°C) with locked access until used or returned to Endo.

The investigator or designee will confirm that appropriate temperature control conditions have been maintained for all study treatments received and that any discrepancies are reported and resolved prior to study treatment administration.

Only subjects enrolled in the study will receive study treatment and only authorized study staff will dispense study treatment.

In accordance with the International Council for Harmonisation (ICH) requirements, at all times the investigator will be able to account for all study treatment furnished to the study site. An accountability record will be maintained for this purpose. The investigator must maintain accurate records indicating dates and quantity of study treatment received, to whom it was administered (subject-by-subject accounting), and accounts of any study treatment accidentally or deliberately destroyed. All unused study treatment not involved in immediate subject treatment will be maintained under locked, temperature-controlled storage at the study site.

Please refer to the Pharmacy Manual for complete information regarding preparation, handling, storage, and accountability of study treatment.

6.5. Measures to Minimize Bias

This is an open-label, nonrandomized study; measures to minimize bias using treatment blinding or randomization are not applicable to this study.

6.5.1. Interactive Response Technology

The investigator or designee will utilize an interactive response technology (IRT) system to register subjects at screening. Each subject's unique identification (ID) number will be assigned by the IRT system and will be used to identify the subject for the duration of the study within all systems and documentation. If the subject is not eligible to receive study treatment, or should discontinue from the study, the subject ID number will not be reassigned to another subject. Specific instructions for the use of the IRT system will be included in the IRT User Manual.

The investigator must maintain a subject master log linking the subject ID to the subject's name. The investigator must follow all applicable privacy laws in order to protect a subject's privacy and confidentiality. Information that could identify a subject will be masked on material received by the sponsor.

6.6. Study Treatment Compliance

All subjects will receive study treatment administered by the investigator at the study site. All dosing information will be recorded for each subject visit. Drug inventory will be maintained in the IRT system for each site, and all original containers of used and unused study treatment and diluent will be returned to the sponsor (or designee) at the end of the study.

Accidental or intentional overdoses should be reported to the sponsor/designee promptly (see Section 8.5).

6.7. Prior and Concomitant Medications and Procedures

The start and stop date, dose, unit, frequency, route of administration, and indication for all prior (taken within the 90 days prior to the Screening Visit) and concomitant (taken from the Screening Visit through the Day 180 Visit or for 28 days after the last study treatment for those who terminate early) medications and nondrug therapies (eg, blood transfusions, oxygen supplementation, physical therapy, etc) received will be recorded.

In addition, all prior treatments for EFP will be recorded with start and stop date, dose, unit, frequency and route of administration.

The use of compression at the treatment areas is allowed during the study at the discretion of the investigator. Compression is considered a concomitant procedure and will be recorded appropriately, if used.

6.7.1. Prohibited Medications and Procedures

The following medications are prohibited for subjects during the study:

- Anticoagulants (warfarin, heparin, direct thrombin inhibitors, Factor X inhibitors) and antiplatelet agents (aspirin > 150 mg/day and P2Y12 inhibitors, such as clopidogrel), which can cause additional bruising. However the use of aspirin at a dose level of ≤ 150 mg per day will be permitted during study.

The following procedures/treatments are not allowed in the selected treatment region (both buttocks or both thighs) during the course of the study (from the Screening Visit through the Day 180 End of Study/Early Termination Visit):

- Liposuction.
- Any injectable treatment (eg, KYBELLA) or any similar treatment that could destroy fat cells and/or remove fat deposits.
- Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; buttock implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision).
- Any investigational treatment for EFP (other than CCH as prescribed in this study).
- Endermologie or similar treatments.
- Massage therapy.
- Creams (eg, Celluvera, TriLastin) and/or home therapies to prevent or mitigate EFP.

If any prohibited medication or procedure is used during the study, all pertinent information will be recorded. The designated study medical monitor must be informed immediately so the sponsor may determine whether to continue the subject in the study.

7. DISCONTINUATION FROM STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

Subjects who discontinue from study treatment or withdraw from the study for any reason after the Day 1 dosing will be encouraged to complete the remaining study visits and evaluations and provide any additional follow-up information as required by the study, unless the subject specifically indicates that they will not participate in any further evaluations. The date of, and reason for, study treatment discontinuation will be recorded.

Permanent study treatment discontinuation is required for the following:

- The subject becomes pregnant during the active treatment phase of the study (Day 1 through Day 43).

Discontinuation of study treatment for abnormal liver function should be considered by the investigator when a subject meets one of the conditions outlined in Section 10.6.

If a clinically significant cardiac finding is identified (including but not limited to changes from baseline in corrected QT interval [QTc]) after the start of study treatment, the investigator or a qualified designee will determine if the subject can continue in the study and if any change in management is needed.

Subjects who discontinue from study treatment at any time after the first dose of study drug will not be replaced.

7.2. Subject Withdrawal from the Study

Subjects may withdraw from the study at any time at their own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. The date of and reason for withdrawal from the study will be recorded.

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such withdrawal of consent. If a subject withdraws from the study, the subject may request destruction of any samples taken and not yet tested. The investigator must document this in the site study records.

A subject may be withdrawn from the study for the following medical or administrative reasons:

- Withdrawal by subject (reason must be specified).
- An AE.
- Death.
- A protocol violation (reason must be specified, for example: lack of compliance, use of a prohibited concomitant medication, etc).
- 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 Early Termination procedures should be conducted as detailed in the Schedule of Activities. The date a subject discontinues and the reason for discontinuation will be recorded in the source documentation and the electronic case report form (eCRF). If, however, a subject withdraws consent, no additional procedures are required except the collection of AE information. This information should be recorded in the source documentation and the eCRF.

Subjects who have been withdrawn from the study at any time after the first dose of study drug will not be replaced.

7.3. Lost to Follow-up

A subject will be considered lost to follow-up if the subject repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and to ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls, and if necessary, a certified letter to the subject's last known mailing address; or local equivalent methods). These attempts will be documented.
- Should the subject continue to be unreachable, the subject will be considered to have withdrawn from the study.

Subjects who have been lost to follow-up at any time after the first dose of study drug will not be replaced.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Activities (Section 1.2). Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct. Protocol waivers or exemptions are not allowed. The details of activities outlined in the Clinical Operations Manual must be followed or will result in a protocol deviation.

Urgent safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue study treatment and/or be withdrawn from the study.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screen failure, as applicable.

Procedures conducted as part of the subject's routine clinical management and obtained before signing of the informed consent form (ICF) may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities.

8.1. Eligibility Confirmation

All subjects will have eligibility photographs of the mid-back to mid-thigh taken during screening that will be submitted to a sponsor designated reviewer to confirm eligibility. For these eligibility confirmation photographs the subject will be standing in a consistent, standardized relaxed standing pose (ie, standing position with relaxed gluteus muscles) and will be wearing a standardized photographic garment. Specific instructions for taking the eligibility confirmation

photographs as well as for providing them to, and receiving confirmation (or lack thereof) from, the sponsor designated reviewer will be provided in the Clinical Operations Manual.

Only subjects deemed eligible for the study by sponsor designated reviewer will be allowed to receive study treatment. Subjects deemed ineligible by the sponsor designated reviewer will be considered screen failures.

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

8.2. Efficacy Assessments

Efficacy assessments will be evaluated at times specified in the Schedule of Activities. Below is a general description of each of these assessments. Specific instructions and questionnaires/forms (where appropriate) will be provided in the Study Operations Manual. Due to the potential of bias, virtual efficacy assessments (Body-Q Appraisal of Cellulite, Body Dysmorphic Disorder Questionnaire, CR-PCSS-Buttock, I-GAIS, [redacted] and [redacted] are not allowed.

8.2.1. Imaging for Outcome Assessments

Although digital photographs are not direct efficacy measurements, digital photography will be utilized in the assessment of certain efficacy measurements (ie, to assess certain cellulite severity parameters at specific intervals). At screening, the investigator or qualified designee will photograph each of the 2 treatment areas (both buttocks and both thighs) independently using a sponsor-supplied standardized digital camera in a standardized manner. For subsequent visits only the areas receiving treatment (both buttocks or both thighs) will be photographed. The subject will be standing in a consistent, relaxed standing pose (ie, standing position with relaxed gluteus muscles) for each photography session and will be wearing a standardized photographic garment as described in the Photography Manual. These photographs will be taken before and after marking of the treatment area for dosing at treatment visits.

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

8.2.2. Subject and Investigator Cellulite Assessments

Investigator cellulite assessments are independent of the subject assessments. Therefore, all subject cellulite assessments must be completed before the investigator's cellulite assessments are initiated. Subject assessments will occur while the subject is alone with no study site personnel in the room. Investigators will be instructed not to verbalize their ratings while in the presence of the subject and vice versa.

8.2.2.1. Body-Q Appraisal of Cellulite

The Body-Q Appraisal of Cellulite is a subset of questions from the Body-Q questionnaire that was developed to measure patient perceptions of weight loss and/or body contouring (Scott et al, 2012).

8.2.2.2. Clinician-reported Photonumeric Cellulite Severity Scale - Buttock

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

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

8.2.2.3. Clinician-reported Photonumeric Cellulite Severity Scale - Thigh

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

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

8.2.2.4. Hexsel Cellulite Severity Scale

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

Investigators who are physicians will independently use the Hexsel CSS Section D (laxity, flaccidity or sagging of skin) to assess the severity of laxity in each buttock or each thigh at the Screening Visit to determine subject eligibility. This assessment should be made while the subject is in the standing position with relaxed gluteus muscles.

8.2.2.5. Investigator Global Aesthetic Improvement Scale

Investigators who are physicians will use the I-GAIS to determine the degree of improvement of each buttock or thigh by comparing the cellulite from the Day 1 pretreatment (baseline) outcome image of each buttock or each thigh to the images taken at the subsequent visits specified in the Schedule of Activities. In visits where both I-GAIS and CR-PCSS are scheduled, I-GAIS assessment will occur after the CR-PCSS assessment to avoid introducing potential bias to the static CR-PCSS assessment by the investigator.

[redacted]

8.3. Safety Assessments

All safety assessments will be performed at the times outlined in the Schedule of Activities. Virtual visits are allowed to assess safety during any COVID-19 interruption, in accordance with the *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency* (March 2020, updated 14 May 2020). Additional (unscheduled) safety assessments may be performed as needed.

8.3.1. Medical and Surgical History

Medical and surgical history will be obtained at the Screening Visit. Medical history will include a review of the following systems: general, dermatological, respiratory, cardiovascular, gastrointestinal, genitourinary, gynecological, endocrine, musculoskeletal, hematological, neuropsychological, immune (allergies), and head, eyes, ears, nose, and throat. Historical and current medical conditions including date of last menstrual period will be recorded. History of tobacco and alcohol use (never, current, former) will also be collected.

Surgical history will include a review of all surgical procedures completed in the prior 5 years and any surgery completed at any time in the treatment area.

EFP history will include the start date of the condition and any family history of EFP.

8.3.2. Physical Examination

The complete physical examination will follow the sites standard of care and may include evaluation of the head, eyes, ears, nose, throat, neck (including thyroid), cardiovascular system (including assessment of heart, peripheral pulses, presence or absence of edema), lungs, abdomen (including liver and spleen, bowel sounds), lymph nodes, musculoskeletal system (including spine, joints, muscles) neurological system (including cranial nerves, reflexes, sensation, strength), skin (excluding cellulite), extremities, and other conditions of note.

[redacted]

All examinations will be performed by a physician or health professional listed on the Form FDA 1572 and licensed to perform physical examinations. The investigator will review all physical exam findings for clinical significance. Any physical exam finding meeting the investigator's or sponsor's criteria for clinical significance will be recorded as an AE or SAE as appropriate.

8.3.3. Height and Weight

Height will be collected at screening only. Weight will be collected as outlined in the Schedule of Activities. Any change from the Screening Visit in subject weight that is considered by the investigator to be clinically significant will be recorded as an AE (or SAE, if appropriate).

8.3.4. Fitzpatrick Skin Scale

The Fitzpatrick Skin Scale is a 6-level scale (levels I-VI) for assessment of skin color and propensity for tanning. The skin types range from level I: Pale white skin, blue/hazel eyes, blond/red hair, always burns, does not tan to level VI: Dark brown or black skin, never burns, always tans darkly. The investigator (or designee) will determine the Fitzpatrick Skin Type for all subjects at screening.

8.3.5. Body Dysmorphic Disorder Questionnaire

The Body Dysmorphic Disorder Questionnaire (BDDQ) is validated, 4-question self-administered assessment tool used to screen for body dysmorphic disorder (Phillips, 2005). The BDDQ will be administered to all subjects at the Day 180/Early Termination Visit.

8.3.6. Vital Signs

Vital signs will be obtained after the subject has been seated for 5 minutes (minimum) and will include systolic and diastolic blood pressures, pulse rate, respiratory rate, and body temperature. The results, date, and time for all vital sign assessments will be recorded.

On study treatment days (Days 1, 22, and 43), vital signs will be taken up to 4 hours prior to dosing and at 15 minutes and 30 minutes after dosing (body temperature is not required at the 15 minute postdose time point). The subject's vital signs must be stable, or repeated until stable before the subject can leave direct observation.

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, if appropriate).

8.3.7. Electrocardiogram

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

If the ECG report shows QT prolongation with QTc $\geq$ 450 ms, the investigator should repeat the ECG within 1 hour. If the initial findings are confirmed, the investigator should exclude the subject from study participation.

The investigator will review all other ECG results for clinical significance. Any ECG result meeting the investigator's criteria for clinical significance will be recorded as an AE (or SAE, if appropriate).

8.3.8. Clinical Laboratory Determinations (Chemistry, Hematology, and Urinalysis)

Clinical laboratory tests will be conducted according to the Schedule of Activities. Required clinical laboratory tests are outlined in Section 10.2. Clinical laboratory tests will be performed by a designated central laboratory. Each site will be provided with instructions for specimen collection, preparation, packaging and transport. The results of the tests will be returned to the investigational sites.

Samples for laboratory testing may be collected under fasted or nonfasted conditions. Fasting early morning samples are preferred, but a random daytime sample is acceptable. The date and time of the sample collection must be documented on the laboratory report. Investigators must review and sign laboratory reports and document the clinical significance of each laboratory abnormality. New clinically significant laboratory abnormalities or clinically significant changes in laboratory values will be reported as AEs (or SAEs, if appropriate).

Clinical laboratory test data will be reviewed by the investigator, or designee, and additional clinical laboratory tests may be ordered at his/her discretion (eg, if the results of any clinical laboratory test falls outside the reference range or clinical symptoms necessitate additional testing to ensure safety). Any additional testing will be performed by the designated central laboratory (or local laboratory if needed to ensure subject safety). In the event that any safety laboratory testing results are unavailable prior to the subject's first dosing visit, the investigator will notify the sponsor to discuss on a case-by-case basis, prior to administering any study treatment to the subject.

8.3.9. Pregnancy Testing

All female subjects of childbearing potential will have serum and/or urine pregnancy tests at the time points outlined in the Schedule of Activities. Results must be available prior to protocol mandated study treatment. Subjects with positive results at the Screening Visit or on Day 1 will be ineligible for study entry. Any female subject that becomes pregnant during the study will be immediately withdrawn from treatment and will have the pregnancy reported as per Section 8.4.5.

For all female subjects of childbearing potential, the subject's agreement to use contraception throughout their study participation (Screening Visit through the Day 180 Visit, or for a minimum of 28 days after the last dose of study treatment for subjects who terminate early) will be documented.

8.4. Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Section 10.3.

All AEs, including both observed or volunteered problems, complaints, signs or symptoms must be recorded, regardless of whether associated with the use of study treatment. 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.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs and AEs will be collected by the investigator from the time of signing the informed consent through the Day 180 Visit or for 28 days after the last study treatment for those who terminate early. All ongoing AEs must be followed to resolution or until the Day 180 Visit or for 28 days after the subject's last study treatment visit for subjects who terminate early, whichever comes first.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs and SAEs after conclusion of subject study participation. However, if the investigator learns of any SAE, including death, at any time after the subject has been discharged from the study, and the investigator considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and submitting SAE reports are provided in Section 10.3.

8.4.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

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 nonleading question such as, "How do you feel?" Study site personnel will then record all pertinent information. The study drug compliance record should also be reviewed to detect potential intentional or unintentional overdoses.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed to resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up. Further information on follow-up procedures is provided in Section 10.3.

8.4.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities regarding the safety of the study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of the study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements regarding safety reporting to regulatory authorities, IRBs/IECs, and investigators.

Investigator safety reports must be prepared for suspected, unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy, and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (ie, summary or listing of SAEs) from the sponsor will review and then file it with the Investigator's Brochure, and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5. Pregnancy

All subject pregnancies that are identified during or after this study, where the estimated date of conception is determined to have occurred during study drug therapy or within 28 days of the last dose of study treatment 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. 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, or any other serious events) must additionally be reported as such using the Serious Adverse Event (SAE)/Reportable Event Form (see Section 10.3). Spontaneous miscarriages should also be reported and handled as SAEs.

Subjects will be instructed to immediately notify the investigator of any pregnancies.

A subject who becomes pregnant must immediately be discontinued from study treatment but may remain in the study if the investigator judges that the potential benefit to the subject outweighs any potential risk to the subject and/or the fetus, and the subject continues to give informed consent for further participation. The investigator should counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

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

8.4.6. AEs/SAEs Experienced by Nonsubjects Exposed to Study Treatment

Nonsubjects are persons who are not enrolled in the study but have been exposed to study treatment, including instances of diversion of study treatment. All such AEs/SAEs occurring in nonsubjects from such exposure will be reported to Endo (when the nonsubject agrees) on the Serious Adverse Event (SAE)/Reportable Event Form regardless of whether the event is serious

or not. Instructions for completing the form for events experienced by nonsubjects will be provided. SAEs occurring in nonsubjects exposed to study medication will be processed within the same SAE reporting timelines as described in Section 10.3. Additionally, the drug accountability source documentation at the site should reflect this occurrence.

8.4.7. Adverse Events of Special Interest

AESIs for this study include:

- Bruising, ecchymosis, hematomas, and contusions that occur remote to the site of drug administration.
- Any hypersensitivity reactions.
- Local AEs associated with the injection site, including bruising, pain, nodules/mass, ulceration, erythema, pruritus, swelling, and/or induration.

These events will be reported as AEs 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 10.3.

8.5. Treatment Overdose

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

Any treatment 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 10.3, even if the events do not meet seriousness criteria. If the AE associated with an overdose does not meet seriousness criteria, it must still be reported using the Endo Serious Adverse Event (SAE)/Reportable Event Form and in an expedited manner, but should be noted as nonserious on the form and the Adverse Event eCRF.

8.6. Pharmacokinetics

Not applicable.

8.7. Pharmacodynamics

Not applicable.

8.8. Genetics

Not applicable.

8.9. Biomarkers

8.9.1. Immunogenicity Assessments

Serum samples will be collected and will be tested for binding anti-AUX-I and anti-AUX-II antibodies. When immunogenicity samples are required on a Treatment Day, the sample will be collected prior to study treatment administration. The samples also will be tested for neutralizing antibodies at times to be determined by the sponsor.

The serum samples obtained will be processed, stored and then shipped frozen on dry ice to Endo's appointed laboratory for the determination of anti-AUX-I and anti-AUX-II antibodies. Specific instructions for the collection, processing, storage, handling and shipment of the immunogenicity samples will be provided in a separate document.

De-identified immunogenicity samples may be stored for a maximum of 5 years (or according to local regulations) following the last subject's last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to study treatment; develop methods, assays, prognostics and/or companion diagnostics related to specify the intervention target, disease process, pathways associated with disease state, and/or mechanism of action of the study treatment.

8.10. Medical Resource Utilization and Health Economics

Not applicable.

9. STATISTICAL CONSIDERATIONS AND METHODS

9.1. Sample Size Determination

The proposed sample size is 150 subjects (70 buttocks subjects and 80 thigh subjects). The sample size is based on the rate of I-GAIS responders defined as subjects with an I-GAIS rating of "Improved", "Much Improved", or "Very Much Improved" on Day 90.

The sample size calculation was based on the following assumptions: 1) the proportion of 1-level I-GAIS responders is 70% for buttocks and 60% for thighs (based on results from earlier studies of CCH in EFP), 2) the estimated proportion of 1-level I-GAIS responders in this study will be no less than 60% for buttocks and 50% for thighs with a 95% chance, and 3) the dropout rate will be approximately 10%.

9.2. Populations for Analysis

For the purposes of analysis, the following populations are defined:

- The Safety Population will include all subjects who receive at least 1 injection of study treatment. All safety evaluations will be based on the Safety Population.
- The Evaluable Population will include all subjects who receive at least 1 injection of study treatment and have at least 1 I-GAIS evaluation. All efficacy evaluations will be based on the Evaluable Population.

9.3. Statistical Hypotheses and Analyses

This section provides a general summary of the statistical methods to be used in analyzing study data. A more detailed statistical analysis plan will be developed and finalized prior to the interim analysis.

9.3.1. Efficacy Analysis

The primary efficacy endpoint of the proportion of subjects with improved (+1 or better) score on I-GAIS for either buttock or either thigh at Day 90 will be summarized by cohort using appropriate summary statistics and its 95% confidence interval will be provided.

All secondary and exploratory efficacy endpoints will be summarized using appropriate descriptive statistics by time point and cohort.

9.3.2. Safety Analyses

All subjects who receive at least 1 dose of study drug will be included in the safety analyses.

9.3.2.1. Adverse Events

AEs will be coded using MedDRA by preferred term within system organ class. The number of AEs and the number of subjects reporting AEs will be listed and summarized descriptively by body system, preferred term, severity, and causality for each treatment group. Only TEAEs (events that are new in onset or aggravated in severity following treatment) will be included in all summaries. SAEs (including death) will be listed.

9.3.2.2. Vital Signs and Clinical Laboratory Tests

Descriptive statistics will be presented for actual and change from baseline at each visit for vital signs and for each clinical laboratory test parameter.

9.3.3. Other Analyses

Anti-AUX-I and anti-AUX-II antibody levels and neutralizing antibody levels will be summarized using descriptive statistics for the actual value at the visit.

9.4. Interim Analysis

Because of the lower responder rate for thigh (60%) and an anticipated high drop-out rate (10%), an interim data analysis will be done when approximately the first 40 Cohort 1 (thigh) subjects complete their Day 90 assessments. The interim analysis will include the primary endpoint (the proportion of subjects with improved [+1 or better] score on I-GAIS for either thigh at Day 90) and mean change from baseline in Body-Q Appraisal of Cellulite at Day 90 for thigh treated subjects.

Depending on the outcome of the interim analysis for the primary endpoint, the study sample size may be revisited.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

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 Food and Drug Administration (FDA) guidelines for Good Clinical Practices (GCP) and in accordance with the ethical principles that have their origins in the Declaration of Helsinki defined in 21 CFR, 312.120.

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/IEC members that demonstrates appropriate composition or other documentation of assurance of appropriate composition per local and national regulations (eg, a Department of Health and Human Services [DHHS] Assurance Number will satisfy this requirement for IRBs in the US).

The study protocol, the ICF, 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, 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 Investigator's Brochure, Package Insert, or Summary of Product Characteristics, 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/IEC and the signature page, signed by the investigator, has been received by Endo. Where the protocol is amended to eliminate or reduce the risk to the subject, the amendment may be implemented before IRB/IEC review and approval. However, the IRB/IEC 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.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after the completion of the study.

10.1.3. Informed Consent Process

The ICF must be approved by the sponsor and the IRB/IEC before any subject provides consent. The investigator will provide the sponsor with a copy of the IRB/IEC-approved ICF and a copy of the IRB/IEC's written approval before the start of the study.

The ICF must contain all applicable elements of informed consent and the mandatory statements as defined by national and local regulations, including confidentiality.

At the Screening Visit (and at other time as may be required by the study or when changes are made to the consent form), subjects will read the consent form(s) and any privacy authorization as required by local and national regulations (such as the Health Insurance Portability and Accountability Act [HIPAA] authorization form), after being given an explanation of the study. Before signing the consent form(s) and the privacy authorization form (if applicable), subjects will have an opportunity to ask questions about the study and discuss the contents of these forms with study site personnel. The consent/assent process shall be recorded in source documents.

Subjects must assent understanding of and voluntarily sign these forms in compliance with ICH GCP and all applicable national and international regulations, before participating in any study-related procedures. Subjects will be made aware that they may withdraw from the study at any time for any reason.

All versions of each subject's signed ICF must be kept on file by the site for possible inspection by regulatory authorities and the sponsor. Signed copies of the consent form(s) and the privacy authorization form, if applicable, will be given to the subject.

The subjects will be made aware of their right to see and copy their records related to the study for as long as the investigator has possession of this information. If the subject withdraws consent and/or HIPAA authorization, the investigator can no longer disclose health information, unless it is needed to preserve the scientific integrity of the study.

10.1.4. Data Protection

Study subjects will be assigned a unique identifier by the sponsor or designee. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure (in accordance with local and/or national law) must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committee Structure

No independent data and/or safety monitoring board will be used for this study.

10.1.6. Dissemination of Clinical Study Data

Aggregate results data will be provided to the sites that actively enrolled subjects into this study after the clinical study report is finalized.

Study results and de-identified individual subject data will be released as required by local and/or national regulation.

10.1.7. Data Quality Assurance

Steps to assure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the 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 noncompliance 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 in a timely fashion and will be 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, 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.

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 for inspection and copying, in keeping with national and local regulations.

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

10.1.8. Source Documents

All subject information recorded in the eCRF will be attributable to source data from the investigational site unless otherwise outlined in this protocol.

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.

The investigator shall retain and preserve 1 copy of all data collected or databases generated in the course of the study, specifically including but not limited to those defined by GCP as essential. Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational medicinal product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. Prior to destruction of any study essential documents, the investigator must first obtain written approval from the sponsor.

10.1.9. Study and Site Closure

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

10.1.10. Publication Policy

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.

10.2. Appendix 2: Clinical Laboratory Tests

Table 3: Clinical Laboratory Tests

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

[a] Microscopic examination will be performed if blood or leukocytes are detected by dipstick.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

10.3.1. Definitions

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).

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 preplanned 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.

10.3.2. 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.

10.3.3. 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.

10.3.4. Reporting Adverse Events and Serious Adverse Events

10.3.4.1. 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 the Day 180/End of Study Visit or for 28 days after the last study treatment in subjects who terminate early. All ongoing AEs must be followed until resolution or until the Day 180/End of Study Visit or until 28 days after the last dose of study medication for subjects who terminate early, whichever comes first.

10.3.4.2. Reporting Serious Adverse Events

Any SAE, including death resulting from any cause, which occurs to any subject participating in this study, must be reported via email or fax by the investigator using the Endo Serious Adverse Event (SAE)/Reportable Event Form within 24 hours of first becoming aware of the SAE. SAEs will be collected by the investigator from the time of signing the informed consent through the Day180/End of Study Visit or until 28 days after the last dose of study treatment (in subjects who terminate early. SAE that occur within 28 days following study treatment discontinuation or within 28 days following premature study withdrawal 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.

All SAEs should be reported via email [redacted] or fax [redacted]

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/IEC per their IRB/IEC policy.

10.3.4.3. Follow-up Procedures for Serious Adverse Events

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

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

See Section 5 and Section 8.3.9.

10.5. Appendix 5: Genetics

Not applicable.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

All events of alanine aminotransferase (ALT) ≥ 3 × upper limit of normal (ULN) and with total bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or ALT ≥ 3 × ULN and international normalized ratio (INR) > 1.5 (if INR measured) which may indicate severe liver injury (possible Hy's Law) must be reported as an SAE as outlined in Section 10.3.4 (excluding studies of hepatic impairment or cirrhosis).

Subjects with confirmed Hy's Law liver injury will be immediately withdrawn from study treatment and no rechallenge will be allowed.

10.7. Appendix 7: Medical Device Incidents

Not applicable.

10.8. Appendix 8: Country-specific Requirements

Not applicable.

10.9. Appendix 9: Abbreviations

Abbreviation	Explanation
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AUX-I	Clostridial class I collagenase
AUX-II	Clostridial class II collagenase
BDDQ	Body Dysmorphic Disorder Questionnaire
BMI	Body mass index
CFR	Code of Federal Regulations
CR-PCSS	Clinician-reported Photonumeric Cellulite Severity Scale
CSS	Cellulite Severity Scale
DHHS	Department of Health and Human Services
ECG	Electrocardiogram
eCRF	Electronic case report form
EFP	Edematous fibrosclerotic panniculopathy
EGAL	Endo Global Aesthetics Limited
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed consent form
ICH	International Council for Harmonisation
ID	Identification
IEC	Independent Ethics Committee
I-GAIS	Investigator Global Aesthetic Improvement Scale
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
QTc	Corrected QT interval
SAE	Serious adverse event
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States

11. 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

12. REFERENCES

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