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

EN3835-224

A PHASE 2 MULTICENTER, OPEN-LABEL, RANDOMIZED, PARALLEL-GROUP, MULTIPLE-DOSE STUDY TO ASSESS THE EFFECTIVENESS, SAFETY AND SATISFACTION WITH COLLAGENASE CLOSTRIDIUM HISTOLYTICUM GRID TECHNIQUE INJECTIONS OF BUTTOCK OR THIGH CELLULITE WITH LAXITY IN ADULT FEMALES

Sponsor Name: Endo Pharmaceuticals Inc.

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

Regulatory Agency Identifier Number(s): IND 110077

Original Protocol: July 27, 2020

Protocol Amendment 1: December 03, 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]

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[redacted]

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Summary of Changes in Amendment 1

The EN3835-224 Protocol was revised with the following changes:

- Text in Sections 1.1 (Synopsis: Overall Design) and 4.1 (Study Design: Overall Design was revised from:

  …up to 21 days…

  to:

  …up to ~~21~~ **28** days…
- Text in Section 1.1 (Synopsis: Overall Design) was revised from:

  The duration of the study from first subject first visit to last subject last visit will be dependent on the ability of the sites to identify and enroll eligible subjects. The entire study is expected to require approximately 12 months to complete.

  to:

  The duration of the study from first subject first visit to last subject last visit will be dependent on the ability of the sites to identify and enroll eligible subjects. The entire study is expected to require approximately 12 months to complete**, however, the duration of the study may be changed due to possible COVID-19 impacts**.
- Figure 1 in Section 1.2 was revised to remove text describing assessments to be performed and intervals for treatment.
- Table 1 in Section 1.3 (Schedule of Activities) was revised by changing header for screening from (Day -21 to Day -1) to (Day -28 to Day -1).

[redacted]

- Table 1 in Section 1.3 (Schedule of Activities) footnote g was added to the Hexsel CSS Subsection D Activities column. Subsequent footnotes in the table were renumbered.
- Table 1 in Section 1.3 (Schedule of Activities) original footnote i (now j) was revised from:

  [redacted]

  to

  [redacted]
- Table 1 in Section 1.3 (Schedule of Activities) original footnote k (now l) was revised from:

  At the Day 28 and Day 84 visits, the investigator has the option to skip treatment or proceed with a treatment session for a new sub-area.

  to:

At the **Treatment Phase visits after** Day 1 ~~28 and Day 84 visits~~, the investigator has the option to skip treatment or proceed with a treatment session for a new sub-area..

- Text in Section 4.1 (Study Design: Overall Design) was revised from:

  The study is expected to enroll subjects over a 3-month period. The entire study is expected to require approximately 12 months to complete.

  to:

  The study is expected to enroll subjects over a **period of approximately** 3 month**s** ~~period~~. The entire study is expected to require approximately 12 months to complete**, however, the duration of the study may be changed due to possible COVID-19 impacts**.

- Text in Section 5.2 (Subject Exclusion Criteria), Criteria 1 was revised from:

  Has concurrent diseases that might interfere with the conduct of the study, confound the interpretation of the study results, or endanger the participant's well-being, (eg, evidence or history of malignancy unless there has been no recurrence in at least 5 years since treatment, or any significant hematological, endocrine, cardiovascular, respiratory, renal, hepatic, neurologic, psychiatric or gastrointestinal disease).

  to:

  Has concurrent diseases that might interfere with the conduct of the study, confound the interpretation of the study results, or endanger the participant's well-being, (eg, evidence or history of malignancy**, other than excised basal cell carcinoma and adequately treated squamous cell carcinoma of skin,** unless there has been no recurrence in at least 5 years since treatment), or any significant hematological, endocrine, cardiovascular, respiratory, renal, hepatic, neurologic, psychiatric or gastrointestinal disease.

- Text in Section 5.2 (Subject Exclusion Criteria), Criteria 10 was revised from:

  The sponsor's medical monitor will be required to review the results for confirmation of eligibility in the case of any of the following: abnormalities in ECGs indicating corrected QT interval (QTc) prolongation of 470 ms or greater, ST-T wave abnormalities, or evidence of previous infarct, abnormalities in clinical laboratory values involving elevations above the normal range for alanine aminotransferase, total bilirubin, and aspartate aminotransferase.

  to:

  The sponsor's medical monitor will be required to review the results for confirmation of eligibility in the case of any of the following: abnormalities in ECGs indicating corrected QT interval (QTc) prolongation of 470 ms or greater, ~~ST-T wave abnormalities, or evidence of previous infarct,~~ abnormalities in clinical laboratory values involving elevations above the normal range for alanine aminotransferase, total bilirubin, and aspartate aminotransferase.

- Text in the last sentence of the second paragraph of Section 5.4 (Screen Failures) was revised from:

  The period from the start of screening related procedures at the Screening Visit to the Day 1 Visit must not exceed 21◦days, inclusive of any repeat screening procedures.

to:

The period from the start of screening related procedures at the Screening Visit to the Day 1 Visit ~~must not exceed 21~~ **can last up to 28** days, inclusive of any repeat screening procedures.

- Text in the first paragraph of Section 6.3 (Selection of Treatment Regions and Treatment Intervals) was revised from:

  During the 6 scheduled visits in the Treatment Phase, the investigator will determine the total number of treatments the subject will receive. [redacted] The investigator must encourage subjects to complete all 6 scheduled visits and all visit activities in the Treatment Phase.

  to:

  During the 6 scheduled visits in the Treatment Phase, the investigator will determine the total number of treatments the subject will receive. [redacted] The investigator must encourage subjects to complete all 6 scheduled **Treatment Phase** visits and all visit activities in the Treatment Phase **as per the Schedule of Activities**.

- Text in Section 6.3 (Selection of Treatment Regions and Treatment Intervals) item 1 on the list was revised from:

  1. The area selected for injection into the thigh will be in the posterolateral portion and will avoid the area of the inferior margin of the intragluteal fold to the upper popliteal crease (inferior to the gluteal sulcus/horizontal crease and the posterior upper thigh).

  …

  4. [redacted]

  6. Execute the option to proceed, or not to proceed, with a treatment on Day 28. A decision not to proceed with treatment will be based on one, or both, of the following criteria being met:

     a. No new sub-area identified to be treated.

     b. Presence of moderate or severe ongoing injection site reactions in the overall treatment area.

to:

1. The area selected for injection into the thigh will be in the posterolateral portion and will avoid the area of the inferior margin of the intragluteal fold ~~to the upper popliteal crease~~ (inferior to the gluteal sulcus/horizontal crease and the posterior upper thigh) **and the upper popliteal crease.**

…

4. [redacted] The actual number of injections administered at each treatment visit should be clearly captured.
5. [redacted]
6. Execute the option to proceed, or not to proceed, with a treatment on **Treatment Phase visits after** Day **1** ~~28~~. A decision not to proceed with treatment will be based on one, or both, of the following criteria being met:
   a. No new sub-area identified to be treated.
   b. Presence of moderate or severe ongoing injection site reactions in the overall treatment area.

- The text in the first paragraph of Section 8.1 was revised from:

  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.

  to:

  ~~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.~~ **As part of eligibility confirmation investigators will submit photographs of either the thighs, or the buttocks, to the sponsor for consideration as an overall treatment area. The sponsor-designated central reviewer will only review for the submitted treatment area. If the subject is determined to be ineligible by the central reviewers for the selected treatment area, the investigator may submit photographs of the other treatment area from the same subject for reconsideration of eligibility. The sponsor can provide additional clarification for reconsideration of eligibility of a subject.**

- The text in the last paragraph of Section 8.1 was revised from:

  Inclusion/exclusion criteria will be re-reviewed at Visit 1 prior to dosing on Day 1. Only subjects deemed eligible by the sponsor designated reviewer will be allowed to proceed with screening activities and receive study treatment. 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.

to:

Inclusion/exclusion criteria will be re-reviewed at Visit 1 prior to dosing on Day 1. Only subjects deemed eligible by the sponsor-designated reviewer will be allowed to proceed with screening activities and receive study treatment. **Subjects deemed ineligible in the overall submitted treatment area(s) by the sponsor-designated reviewer will be considered screen failures (note that at least 1 submitted treatment area must be determined as eligible for a subject to be enrolled).** ~~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.

- Text in Section 8.2.1.6 (Hexsel Cellulite Severity Scale) was revised from:

  This assessment will be conducted at the Screening Visit and all study visits.

- [redacted]

  to:

  [redacted]

  to:

  [redacted]

- Text in Section 8.3.6 (Electrocardiogram) was revised from:

  If the ECG report shows a QTc prolongation of 470 ms or greater, ST-T wave abnormalities, or evidence of previous infarct, the investigator should repeat the ECG within 1 hour.

  to:

  If the ECG report shows a QTc prolongation of 470 ms or greater~~, ST-T wave abnormalities, or evidence of previous infarct,~~ the investigator should repeat the ECG within 1 hour.

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 Phase 2 Multicenter, Open-label, Randomized, Parallel-group, Multiple-dose study to Assess the Effectiveness, Safety and Satisfaction with Collagenase Clostridium Histolyticum Grid Technique Injections of Buttock or Thigh Cellulite with Laxity in Adult Females	
Study period: Estimated date first subject enrolled: 01 October 2020 Estimated date last subject completed: 01 June 2021	**Phase of development:** Phase 2

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To assess the efficacy of CCH for the treatment of cellulite in the presence of dermal laxity using the Investigator Global Aesthetic Improvement Scale (I-GAIS)	• Proportion of 1-level responders (+1 or better score) on the I-GAIS for either buttock or either thigh at Day 180
Secondary	
• To assess the efficacy of CCH for the treatment of cellulite in the presence of dermal laxity using the I-GAIS	• Proportion of 1-level responders (+1 or better score) on the I-GAIS for either buttock or either thigh at Study Days 28, 56, 84, 112, and 140 • I-GAIS ratings at Study Days 28, 56, 84, 112, 140, and 180
• To assess the efficacy of CCH for the treatment of cellulite in the presence of dermal laxity using subject assessments	• Proportion of 1-level responders (+1 or better score) on the Subject Global Aesthetic Improvement Scale (S-GAIS) for either buttock or either thigh at Study Days 28, 56, 84, 112, 140, and 180 • The change from baseline to Day 180 in the Body-Q Appraisal of the individual item cellulite scores and total score.
• To assess the effectiveness of CCH for the treatment of cellulite in the presence of dermal laxity using Subsection D of the Hexsel Cellulite Severity Scale (CSS)	• The change from baseline to each Study Visit (Day 28 through the Day 180 Visit) in Hexsel CSS Subsection D severity score.

• To assess the safety and tolerability of CCH for the treatment of cellulite in the presence of dermal laxity	• Proportion (incidence) of subjects reporting each adverse event (AE), treatment-emergent adverse event (TEAE), treatment-related AE, and adverse event of special interest (AESI). Change from baseline reported at each visit for vital signs, potentially clinically important vital signs, clinical laboratory tests, and potentially clinically important laboratory tests.
• To assess the immunogenicity of CCH in the treatment of cellulite in the presence of dermal laxity	• Anti- Clostridial class I collagenase (AUX-I) and Anti- Clostridial class II collagenase (AUX-II) antibody levels • Neutralizing antibodies to AUX-I and AUX-II
[redacted]	
• [redacted]	• [redacted]
• [redacted]	• [redacted]
• [redacted]	• [redacted]

Overall Design:

This is a Phase 2, open-label, randomized, parallel-group, multiple-dose, safety and effectiveness study designed to evaluate 2 different CCH dose concentrations and aliquot volumes delivered via uniform grid injection techniques in female subjects presenting with both mild to moderate cellulite and moderate to severe dermal laxity of the buttocks, or thighs, and with a body mass index 18 to < 29.9kg/m^2 (normal or overweight).

Following determination of eligibility based on photography and Inclusion/Exclusion assessment, the investigator will propose each eligible subject for treatment of either both buttocks, or both thighs. A sponsor-designated reviewer will confirm subject eligibility for thighs or buttocks treatment based on review of screening images of areas to be treated. Prior to randomization, the sponsor will categorize the thighs or buttocks of each eligible subject for the following characteristics: mild cellulite with moderate dermal laxity, mild cellulite with severe dermal laxity, moderate cellulite with moderate dermal laxity and moderate cellulite with severe dermal laxity. This pre-randomization cohort management process is intended to try to ensure enrollment of the desired scope of study participants. Subjects will then be randomized to receive treatment in either Cohort A (Uniform 0.1-mL 1-Aliquot GRID injection technique) or Cohort B (Uniform 0.3-mL 2-Aliquot GRID injection technique) in a 1:1 ratio.

During the 6 scheduled Treatment Phase visits the investigator will determine the total number of treatments the subject will receive, and can incrementally treat new sub-areas at consecutive Treatment Phase visits. Specific injection sites (sub-areas) within the overall treatment area will not be dosed more

frequently than every 56 days. [redacted] Subjects will return to the study site for all 6 scheduled Treatment Phase visits to complete assessments, even if not receiving treatment during the visit.

Subjects will participate in the study for approximately 29 weeks, including a screening period of up to 28 days. The duration of the study from first subject first visit to last subject last visit will be dependent on the ability of the sites to identify and enroll eligible subjects. The entire study is expected to require approximately 12 months to complete however, the duration of the study may be changed due to possible COVID-19 impacts.

Disclosure Statement: This is an open-label safety and efficacy study with 2 treatment cohorts.

Number of Subjects (planned):

Approximately 32 subjects will be enrolled into the study such that approximately 24 evaluable subjects complete the study.

Treatment Groups and Duration:

Subjects will be randomized to treatment (for both of their treatment areas) to either Cohort A or Cohort B in a 1:1 ratio.

[redacted]

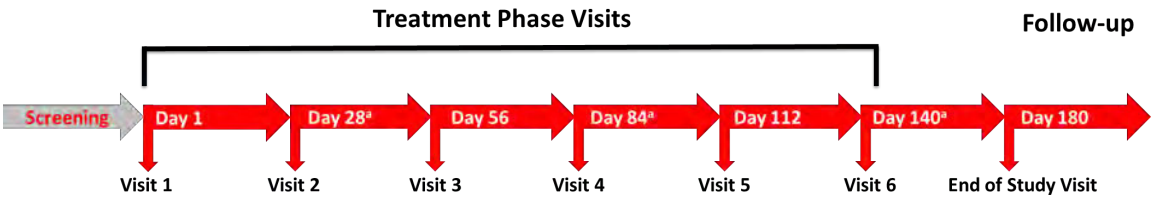
The total amount of CCH to be administered per subject over the course of the study will not exceed 10.08 mg.

Data Monitoring Committee: No data monitoring committee will be used for this study.

1.2. Study Schema

Figure 1: Study Design Overview

Subject will receive at least 3 and up to 6 treatment sessions (both buttocks or both thighs)
Sub-areas that are treated within each overall treatment area will not be dosed more frequently than every 56 days



[a]The investigator has the option to skip the treatment session

1.3. Schedule of Activities

Table 1: Schedule of Activities

Activities	Screening	Treatment Phase[a]						Follow-up
	(Day -28 to Day -1)	Day 1 Visit 1	Day 28 (±3 day) Visit 2	Day 56 (±3 day) Visit 3	Day 84 (±3 days) Visit 4	Day 112 (±3 days) Visit 5	Day 140 (±3 days) Visit 6	Day 180 End of Study/ Early Termination Visit (±10 days)
Informed consent[b]	X							
Inclusion/exclusion criteria review	X	X[c]						
[redacted]		X	X	X	X	X	X	X
Imaging for eligibility confirmation[d]	X							
Medical and cellulite history (including previous treatment)	X							
Physical examination	X							X
Height	X							
Weight	X	X						X
Fitzpatrick skin type	X							
Vital signs[e]	X	X	X	X	X	X	X	X
12-lead ECG	X							X
Clinical safety laboratories	X							X
Anti-AUX-I/Anti-AUX-II antibody level sample		X						X
Serum pregnancy test	X							X
Urine pregnancy test		X	X	X	X	X	X	
CR-PCSS	X							
I-GAIS[f]			X	X	X	X	X	X
S-GAIS[f]			X	X	X	X	X	X

Table 1: Schedule of Activities (Continued)

Activities	Screening	Treatment Phase[a]						Follow-up
	(Day -21 to Day -1)	Day 1 Visit 1	Day 28 (±3 day) Visit 2	Day 56 (±3 day) Visit 3	Day 84 (±3 days) Visit 4	Day 112 (±3 days) Visit 5	Day 140 (±3 days) Visit 6	Day 180 End of Study/ Early Termination Visit (±10 days)
Body-Q		X						X
Hexsel CSS Subsection D[g]	X[h]	X	X	X	X	X	X	X
[redacted]		[redacted]						
[redacted]		[redacted]						[redacted]
Assignment of treatment area (buttocks or thighs)	X							
Confirm eligibility		X						
Randomize treatment arm		X						
Digital photography[k]		X	X	X	X	X	X	X
Study intervention administration		X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	
Prior/Concomitant medications/procedures	Collect throughout the study							
AEs	Collect throughout the study							

[a] During unscheduled visits the investigator or designee may perform any study procedure deemed clinically necessary (eg, vital signs, clinical laboratory assessments, pregnancy test, etc).
[b] Performed prior to any study-required assessments.
[c] Should be reassessed and verified prior to dosing.
[d] All subjects will have 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 Study Operations Manual.
[e] On treatment phase visit days (Days 1, 28, 56, 84, 112, and 140) 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).

[f] These assessments, which will be based on digital photographs, are performed separately for each of 2 treatment areas and must be completed before study intervention administration on those visits. If at a treatment visit, use photographs taken before marking treatment area.

[g] [redacted]

[h] Subjects with Hexsel CSS Subsection D score greater than 3 at screening are excluded. A score greater than 3 is defined as an appearance significantly worse than exhibited in the Hexsel CSS Subsection D severe (score = 3) image.

[i] Collected after treatment on Study Day 1 and is assessed for the overall subject and not per treatment areas.

[j] [redacted]

[k] Photographs will be taken before and after marking the treatment areas. [redacted] For subjects not receiving treatment during a treatment phase visit a photograph will be taken but no marking will be done and no postmarking photograph will be taken. Please see the Photography Manual for details.

[l] Subjects will receive at least 3, and up to 6 treatment sessions. The investigator will determine the total number of treatments the subject will receive and can incrementally treat new sub-areas at consecutive treatment phase visits. Specific injection sites (sub-areas) within the overall treatment area will not be dosed more frequently than every 56 days. At the Treatment Phase visits after Day 1, the investigator has the option to skip treatment or proceed with a treatment session for a new sub-area. [redacted] After treatment subjects will be provided with compression garments that they will be required to wear.

AE=Adverse event; CR-PCSS=Clinician-reported Photonumeric Cellulite Severity Scale; CSS= Cellulite Severity Scale; ECG=Electrocardiogram; I-GAIS=Investigator Global Aesthetic Improvement Scale; S-GAIS=Subject Global Aesthetic Improvement Scale

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.

This study is designed to assess the safety and efficacy of CCH for the treatment of edematous fibrosclerotic panniculopathy (commonly known as cellulite) in the presence of dermal laxity.

2.1. Study Rationale

The results from the Phase 3 studies (EN3835-302 and EN3835-303) suggest that CCH 0.84 mg per treatment area (buttock) is an effective treatment of cellulite based on improvement in the severity of cellulite as determined by the investigator and the subject. There were no significant safety concerns following 3 doses of 0.84 mg per treatment area in the treatment of cellulite in the Phase 3 pivotal trials as well as other studies incorporating repeated dosing sessions. In Phase 2 studies EN3835-201 and EN3835-202, 73 individual subjects received a total of 6 treatment sessions 21 to 56 days apart; and treatment-related adverse events (AEs) remained similar to those that received 3 treatment sessions approximately 21 days apart. No new safety signals were seen in these subjects who received a second treatment course consisting of 3 treatment sessions. The immunogenicity profile of CCH in the Phase 3 cellulite studies is similar to previous EN3835 studies and programs and has not been shown to impair efficacy.

Dermal laxity and cellulite are interdependent pathologies, in that they are linked, and each aggravates the other (Hexsel et al, 2006). Women without cellulite are reported to have less dermal laxity. Both cellulite and dermal laxity are associated with findings of weaker connective tissue architecture. In the presence of dermal laxity, cellulite becomes more apparent (Dobke et al, 2002). It has been observed that dermal laxity frequently occurs in body areas characterized by thinner skin with potentially less retentive capacity over fat, such as the buttocks and thighs (Hexsel et al, 2001).

To date, studies of the use of CCH in the treatment of cellulite have excluded subjects with significant dermal laxity. This exclusion was based on the presumed understanding of the mechanism of action of CCH. Our understanding of the mechanism of action of CCH (remodeling of subdermal architecture) has evolved and suggests that CCH treatment could be of benefit to subjects with both cellulite and moderate to severe dermal laxity.

Endo Pharmaceuticals Inc. (Endo), with support from aesthetic medicine specialists, is proposing the current study to investigate CCH in the treatment of cellulite in subjects with moderate to severe dermal laxity in buttocks and thighs, and to compare 2 different CCH injection techniques. These injection techniques are intended to further elucidate improved methods to treat the deep dimpling that often occurs with cellulite in the presence of dermal laxity.

2.2. Background

Collagenases are proteinases that hydrolyze collagen in its native triple helical conformation under physiological conditions. To investigate the use of collagenases in the treatment of cellulite, Endo has developed a novel formulation of AUX-I and AUX-II referred to as CCH.

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 cellulite 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 for use in the treatment of cellulite is provided in the Qwo™ package insert (Qwo Prescribing Information).

2.3. Risk/Benefit Assessment

The results of all Phase 2 and 3 studies conducted demonstrated a consistent effect of CCH in reducing the severity of cellulite. The results of 2 Phase 3 pivotal efficacy studies (Studies EN3835-302 and EN3835-303) established the efficacy of CCH administration in the treatment of moderate to severe cellulite in the buttocks of adult women when injected subcutaneously at a dose of 0.84 mg per treatment area every 21 days for 3 treatment visits. A treatment area was defined as a single buttock receiving up to 12 injections, 0.3 mL each (up to a total of 3.6 mL), of CCH. Two treatment areas (2 buttocks) were treated at each visit; a reduction in the severity of cellulite was observed as assessed by validated assessment scales as early as 21 days after administration of the first treatment session of CCH and was sustained throughout the 71-day double-blind study period. Furthermore, overall patient-reported satisfaction, emotional impact,

and visual appearance measures showed a greater and statistically significant improvement in the CCH group over the placebo group. The treatment-emergent adverse events (TEAEs) observed were predominantly localized injection site reactions that were nonserious, primarily mild to moderate in severity, transient, and decreased in frequency with each subsequent treatment session.

More detailed information about the known and expected risks and reasonably expected AEs can be found in the Qwo™ package insert (Qwo Prescribing Information).

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3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the efficacy of CCH for the treatment of cellulite in the presence of dermal laxity using the Investigator Global Aesthetic Improvement Scale (I-GAIS)	• Proportion of 1-level responders (+1 or better score) on the I-GAIS for either buttock or either thigh at Day 180
Secondary	
• To assess the efficacy of CCH for the treatment of cellulite in the presence of dermal laxity using the I-GAIS	• Proportion of 1-level responders (+1 or better score) on the I-GAIS for either buttock or either thigh at Study Days 28, 56, 84, 112, and 140 • I-GAIS ratings at Study Days 28, 56, 84, 112, 140, and 180
• To assess the efficacy of CCH for the treatment of cellulite in the presence of dermal laxity using subject assessments	• Proportion of 1-level responders (+1 or better score) on the Subject Global Aesthetic Improvement Scale (S-GAIS) for either buttock or either thigh at Study Days 28, 56, 84, 112, 140 and 180 • The change from baseline to Day 180 in the Body-Q Appraisal of the individual item cellulite scores and total score
• To assess the effectiveness of CCH for the treatment of cellulite in the presence of dermal laxity using Subsection D of the Hexsel Cellulite Severity Scale (CSS)	• The change from baseline to each Study Visit (Day 28 through the Day 180 Visit) in Hexsel CSS Subsection D severity score
• To assess the safety and tolerability of CCH for the treatment of cellulite in the presence of dermal laxity	• Proportion (incidence) of subjects reporting each AE, TEAE, treatment-related AE, and adverse event of special interest (AESI). Change from baseline reported at each visit for vital signs, PCI vital signs, clinical laboratory tests, and PCI laboratory tests
• To assess the immunogenicity of CCH in the treatment of cellulite in the presence of dermal laxity	• Anti-AUX-I and Anti-AUX-II antibody levels • Neutralizing antibodies to AUX-I and AUX-II
[redacted]	
• [redacted]	• [redacted]

Objectives	Endpoints
• [redacted]	• [redacted]
• [redacted]	• [redacted]

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, open-label, randomized, parallel-group, multiple-dose, safety and effectiveness study designed to evaluate 2 different CCH dose concentrations and aliquot volumes delivered via uniform grid injection techniques in female subjects presenting with both mild to moderate cellulite and moderate to severe dermal laxity of the buttocks, or thighs, and with a body mass index (BMI) of 18 to < 29.9kg/m^2 (normal or overweight).

The primary objective of the study is to assess the effectiveness of CCH for the treatment of cellulite in the presence of dermal laxity using investigator assessment of improvement as measured by I-GAIS (Investigator Global Aesthetic Improvement Scale). At screening, cellulite severity will be assessed by the investigator using the Clinician-reported Photonumeric Cellulite Severity Scale (CR-PCSS), and severity of dermal laxity will be measured by the Hexsel CSS scale (Subsection D). Only subjects with a CR-PCSS score of only 2 or 3 will be included in the study. Subjects with a dermal laxity severity score of greater than 3 will be excluded. (Note: A dermal laxity severity score greater than 3 is defined as an appearance significantly worse than exhibited in the Hexsel CSS Subsection D severe image [score = 3].)

Following determination of eligibility based on photography and Inclusion/Exclusion assessments, the investigator will propose each eligible subject for treatment of either both buttocks, or both thighs. The sponsor will confirm subject eligibility for treatment of the thighs or buttocks based on review of screening images of areas to be treated. Prior to randomization each eligible subject's buttocks and thighs will be categorized into the following characteristic groups: mild cellulite with moderate dermal laxity, mild cellulite with severe dermal laxity, moderate cellulite with moderate dermal laxity and moderate cellulite with severe dermal laxity.

This pre-randomization process will be used in an attempt to fill the desired categories as depicted in Table 2.

Table 2: Intended Distribution of Subject Treatment Area Characteristics and Locations

Criteria	CR-PCSS 2 (mild cellulite)	CR-PCSS 3 (moderate cellulite)
Hexsel CSS Subsection D 2 (moderate laxity)	8 Buttocks	8 Buttocks
	8 Thighs	8 Thighs
Hexsel CSS Subsection D 3 (severe laxity)	8 Buttocks	8 Buttocks
	8 Thighs	8 Thighs
Total	32 treatment areas	32 treatment areas

Note: A total of 32 subjects are expected to contribute a total of 64 treatment areas. Each subject's 2 treatment areas may be allocated to different categories according to the severity of cellulite and severity of dermal laxity.

Subjects will then be randomized to treatment with either Cohort A (Uniform 0.1-mL 1-Aliquot GRID injection technique) or Cohort B (Uniform 0.3-mL 2-Aliquot GRID injection technique) in a 1:1 ratio.

[redacted]

The treatment cohorts will differ in concentrations/aliquot volumes/number of aliquots per injection but neither cohort will exceed the maximum total dose per treatment area (up to 0.84 mg per each buttock or thigh) per treatment session. Details of the injection techniques can be found in the Study Operations Manual.

[redacted]. Subjects will return to the study site for all 6 scheduled visits and all visit activities in the Treatment Phase.

This study is planned to be conducted at approximately 2 study sites. Subjects may participate in the study for a total of up to approximately 29 weeks, including a screening period of up to 28 days, an active treatment period of 20 weeks and a Follow-up Visit 40 (± 10) days after the last dose of study drug. A minimum of 24 evaluable subjects are required for the primary analysis. The duration of the study from first subject first visit to last subject last visit will be dependent on the ability of the sites to identify and enroll eligible subjects. The study is expected to enroll subjects over a period of approximately 3-months. The entire study is expected to require approximately 12 months to complete, however, the duration of the study may be changed due to possible COVID-19 impacts.

4.2. Scientific Rationale for the Study Design

The results from the Phase 3 cellulite studies (EN3835-302 and EN3835-303) suggest that CCH 0.84 mg per treatment area (buttock) is an effective treatment of cellulite based on improvement in the severity of cellulite as determined by the investigator and the subject.

In Phase 3 pivotal trials of the treatment of cellulite with CCH there were no significant safety concerns following 3 doses of 0.84 mg per treatment area. No significant safety concerns were raised in other studies of CCH incorporating repeated dosing sessions. In Phase 2 studies EN3835-201 and EN3835-202, 73 individual subjects received a total of 6 treatment sessions 21 to 56 days apart; and treatment-related AEs remained similar to those that received 3 treatment sessions approximately 21 days apart. No new safety signals were seen in these subjects who received a second treatment course consisting of 3 treatment sessions. The immunogenicity profile of CCH in the Phase 3 cellulite studies is similar to previous studies and programs and has not been shown to impair efficacy.

Dermal laxity and cellulite are interdependent pathologies, in that they are linked and aggravate each other (Hexsel et al, 2006). Women without cellulite are reported to have less dermal laxity. Both cellulite and dermal laxity are associated with findings of weaker connective tissue architecture. And in the presence of dermal laxity, cellulite becomes more apparent (Dobke et al, 2002). It has been observed that dermal laxity frequently occurs in body areas characterized by thinner skin with potentially less retentive capacity over fat, such as the buttocks and thighs (Hexsel et al, 2001).

Therefore Endo, with support from aesthetic medicine specialists, proposes to investigate CCH in the treatment of cellulite with moderate to severe dermal laxity in buttocks and thighs, and to compare 2 different methods of CCH administration which are intended to further evaluate improved methods to treat the deep dimpling that often occurs with cellulite in the presence of dermal laxity.

4.3. Justification for Dose

The dosage of CCH chosen for this study is based on the data and experience from several earlier studies as well as the completed Phase 3 clinical studies. The dose of 1.68 mg (0.84 mg per region) has been shown to be safe and well-tolerated. The multiple doses of up to 6 treatment sessions are supported by the safety profile generated in previous Phase 2 and 3 studies as described above.

4.4. End of Study Definition

A subject is considered to have completed the study if the subject has completed the Day 180 End of Study 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 ≥ 18 and ≤ 55 years of age at the time of consent.
2. Have a BMI of 18 to < 29.9 kg/m^2.
3. At the Screening Visit, have either both buttocks or both posterolateral thighs with:
   a. A score of 2 or 3 (mild or moderate cellulite) as reported by the investigator using the CR-PCSS, and
   b. a Hexsel CSS Subsection D “Grade of Laxity, Flaccidity, or Sagging Skin” score of 2 or 3 (moderate or severe) as determined by the investigator.
4. 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 and for 28 days after any active treatment period. Acceptable forms of contraception include hormonal measures (oral contraceptive pills, contraceptive patch, contraceptive ring, and injections), intrauterine devices, double barrier method (condom plus diaphragm, condom or diaphragm plus spermicidal gel or foam), surgical sterilization of the male partner, and abstinence.

5. Be willing and able to comply with all protocol required visits and assessments, including eligibility photographs of the mid-back to mid- posterolateral-thigh taken during screening that will be submitted to a sponsor-designated reviewer to confirm eligibility (Section 8.1).
6. 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).
7. 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 and on Study Day 1, the subject:

1. Has a history of hypersensitivity or allergy to collagenase or any other excipient of CCH. Has concurrent diseases that might interfere with the conduct of the study, confound the interpretation of the study results, or endanger the participant's well-being, (eg, evidence or history of malignancy, other than excised basal cell carcinoma and adequately treated squamous cell carcinoma of skin, unless there has been no recurrence in at least 5 years since treatment), or any significant hematological, endocrine, cardiovascular, respiratory, renal, hepatic, neurologic, psychiatric or gastrointestinal disease. If there is a history of such disease but the condition has been stable for more than 5 years and is judged by the investigator not to interfere with the participant's participation in the study, the participant may be included, with the documented approval of the Medical Monitor.
2. At the Screening Visit has a CR-PCSS score of less than 2 or greater than 3 for the area to be treated (buttocks or thighs) and/or has a Hexsel CSS Subsection D "Grade of Laxity, Flaccidity, or Sagging Skin" score of less than 2 or greater than 3 (severe) for the area to be treated (buttocks or thighs).
3. Has a coagulation disorder which requires anticoagulant or antiplatelet medication during the study (except for ≤ 150 mg aspirin daily), or has taken anticoagulant or antiplatelet medication within 14 days before injection of study treatment (except for ≤ 150 mg aspirin daily).
4. Is a prisoner, an individual with impaired decision making capacity, 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), or in the judgment of the investigator the subject is disadvantaged and vulnerable to coercion due to lack of education, or due to poor economic circumstances.
5. Has participated in a previous investigational study of CCH, received any collagenase treatments at any time prior to treatment in this study and/or has received previous treatment with CCH for cellulite, or received treatment with an investigational product within 30 days (or 5 half-lives, whichever is longer) of the Screening Visit.

6. Is pregnant and/or is breast-feeding or plans to become pregnant and/or to breast-feed during the course of the study, or for 28 days after the last dose of study intervention.
7. Has a history of scarring due to keloids or abnormal wound healing.
8. 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, vasculitis, varicose veins, telangiectasia).
    c. Inflammation or active infection (including lesions that indicate an active infection).
    d. Active cutaneous alteration including but not limited to rash, eczema or psoriasis.
    e. A tattoo or other artificially inflicted body marker within 2 cm of any injection site.
    f. Has a mole located within 2 cm of any injection site.
9. Has history of drug or alcohol abuse within the 5 years prior to the Screening Visit.
10. Has evidence of clinically significant abnormalities, as judged by the investigator, in any of the following: physical examination findings, electrocardiogram (ECG), clinical laboratory values, or vital signs. The sponsor's medical monitor will be required to review the results for confirmation of eligibility in the case of any of the following: abnormalities in ECGs indicating corrected QT interval (QTc) prolongation of 470 ms or greater, abnormalities in clinical laboratory values involving elevations above the normal range for alanine aminotransferase, total bilirubin, and aspartate aminotransferase.
11. Has used any of the following for the treatment of cellulite on either thigh or either buttock within the specified timelines, 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); 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 cellulite 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 cellulite during the 2-week period before injection of study treatment.
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 participant to be unsuitable for the study.

15. For the subset of subjects participating in the collection of ultrasound data, the following exclusions will apply: subjects will be excluded who have: a history of a spinal laminectomy, a previous history or presence of vascular abnormalities (eg, deep vein thrombosis, thrombophlebitis), a healing fracture, an impaired sensation within, or near, the planned treatment area, or any implants within, or near, the planned treatment area.

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 can last up to 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(ia) 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 can last up to 28 days. Subjects may be rescreened only once; however subjects whose rescreening process was interrupted by COVID-19 related delays may be rescreened for a second time.

6. STUDY TREATMENT

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

6.1. Selecting the Treatment Region

The treatment region, either 2 buttocks or 2 thighs (but not both) will be selected by the investigator. All subjects must have the following:

- a cellulite score of 2 (mild) or 3 (moderate) on the CR-PCSS assessment

  and

- a dermal laxity score of 2 (moderate) or 3 (severe) on the Hexsel CSS Subsection D assessment.

Once a subject's treatment areas are classified to the defined categories in Table 2, pre-randomization will be performed with the interactive response technology (IRT) cohort management module. Pre-randomization will be used to manage recruitment such that approximately equivalent numbers of subjects are enrolled for treatment of buttocks vs thighs, mild vs moderate cellulite, and moderate vs severe dermal laxity.

The IRT service provider will generate the randomization code and manage the implementation of randomization using the IRT system. The subjects will be randomized to either Cohort A (Uniform 0.1-mL 1-Aliquot GRID injection technique) or Cohort B (Uniform 0.3-mL 2-Aliquot GRID injection technique) in a 1:1 ratio. Endo, the investigators, and the subjects are not blinded to treatment assignment.

6.2. 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 1.68 mg of CCH inclusive of both treatment areas (2 buttocks or 2 thighs) per treatment visit (total maximum dose of 1.68 mg per treatment session during 6 treatment sessions [Days 1, 28 (±3), 56 (±3), 84 (±3), 112 (±3), and 140 (±3)] for a maximum total dose of 10.08 mg). [redacted] (see Table 3).

Table 3: Study Treatment Administration

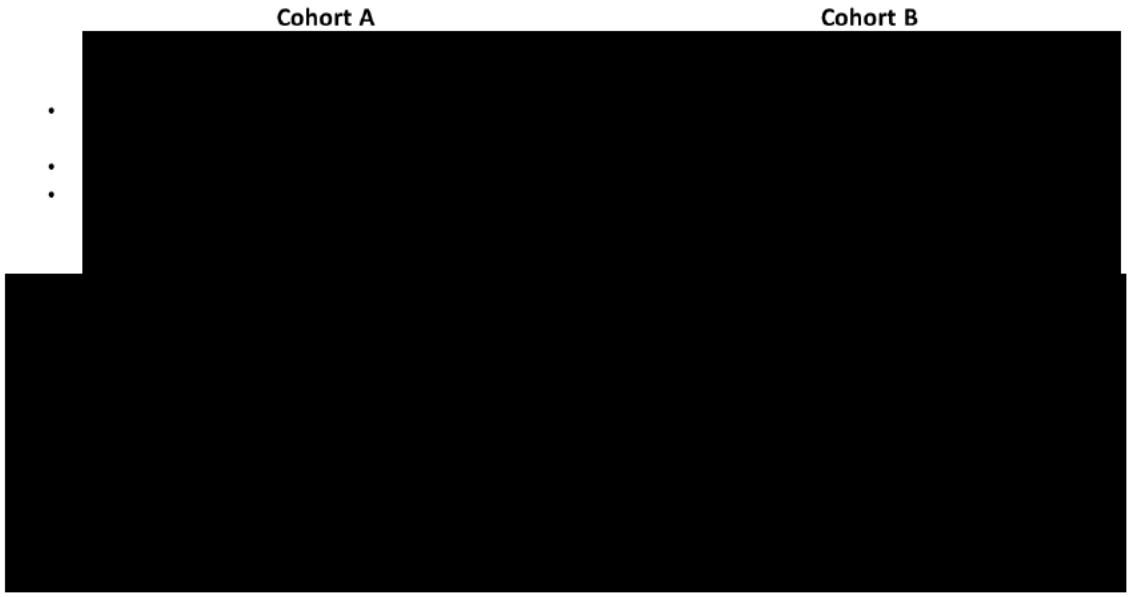
Cohort Name	**A**	**B**
Injection Technique	Uniform 0.1-mL 1-Aliquot GRID	Uniform 0.3-mL 2-Aliquot GRID
Product Name	CCH	CCH
Number of Subjects	N = 16 (8 buttocks and 8 thighs)[a]	N = 16 (8 buttocks and 8 thighs)[a]
Injection Volume (mL) × Aliquot(s) = Total Injection Volume	0.1 mL × 1 = 0.1 mL	0.3 mL × 2 = 0.6 mL
Concentration (mg/mL)	[redacted]	[redacted]
Maximum CCH Dose/ Treatment Area	1.68 mg (0.84 mg per buttock or thigh)	1.68 mg (0.84 mg per buttock or thigh)
Maximum Injection Volume/Visit	[redacted]	[redacted]
Maximum Number of Injection Sites/Subject/Visit	[redacted]	[redacted]
Cumulative CCH Dose 3 Treatment Visits 6 Treatment Visits	 5.04 mg 10.08 mg	 5.04 mg 10.08 mg

[a] Number of subjects shown for buttocks and thighs treatment represents the ideal distribution.

[redacted]

The injection techniques for Cohorts A and B are illustrated in Figure 2.

Figure 2: [redacted]



For more detailed instructions consult the Study Injection Guide.

6.3. Selection of Treatment Regions and Treatment Intervals

During the 6 scheduled visits in the Treatment Phase, the investigator will determine the total number of treatments the subject will receive. [redacted] he investigator must encourage subjects to complete all 6 scheduled Treatment Phase visits and all visit activities in the Treatment Phase as per the Schedule of Activities. During a subject's treatment session the investigator will:

1. Identify and mark sub-areas to be treated in each treatment area. The area selected for injection into the thigh will be in the posterolateral portion and will avoid the area of the inferior margin of the intragluteal fold (inferior to the gluteal sulcus/horizontal crease and the posterior upper thigh) and the upper popliteal crease. Additional information on the treatment area selection and marking are described in the Study Operations Manual.
2. [redacted]
3. Administer up to 0.84 mg CCH in each treatment area, at each treatment phase visit; with actual dose administered at each treatment visit clearly captured.
4. [redacted]

[redacted] The actual number of injections administered at each treatment visit should be clearly captured.

5. [redacted]
6. Execute the option to proceed, or not to proceed, with a treatment on Treatment Phase visits after Day 1. A decision not to proceed with treatment will be based on one, or both, of the following criteria being met:
   a. No new sub-area identified to be treated.
   b. Presence of moderate or severe ongoing injection site reactions in the overall treatment area.
7. At any treatment phase visit after Day 1, if, in the investigator's clinical judgment, the clinical presentation of a subject's cellulite dimples with dermal laxity is found satisfactory or resolved, the investigator may choose to stop further treatment.

All subjects must complete all 6 scheduled Treatment Phase visits at Days 1, 28 (±3), 56 (±3), 84 (±3), 112 (±3), 140 (±3), and 180 (±10) regardless of the number of treatment sessions. After the completion of a 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. Following treatment, the subjects will be provided with compression garments that must be worn. Refer to the Study Operations Manual for additional guidelines on the use of compression garments.

6.4. Study Treatment Preparation/Handling/Storage/Accountability

Vials of 1.84 mg CCH and its diluent (8 mL) will be uniquely numbered for dispensing via the IRT system to the appropriate subject. 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.

Additional information on preparation, handling, storage, and accountability of the study treatment is described in the Pharmacy Binder.

6.5. Measures to Minimize Bias

This is an open label study; however, the specific treatment taken by each subject will be randomly assigned using IRT.

6.5.1. Interactive Response Technology

The investigator or designee will utilize the 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. The IRT service provider will generate the randomization code and manage the implementation of randomization using the IRT system. Endo, the investigators and the subjects are not blinded to treatment assignment.

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 30 days prior to the Screening Visit) and concomitant (taken from the Screening Visit through the End of Study Visit) medications and nondrug therapies (eg, blood transfusions, oxygen supplementation, physical therapy, etc) received will be recorded.

In addition, all prior treatments for the disease/condition under study will be recorded with start and stop date, dose, unit, frequency and route of administration.

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 cellulite (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 cellulite.

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.

6.7.2. Rescue Medication

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.

6.8. Study Treatment Modification

At any visit after Day 1, the investigator can choose not to continue treatment if there are moderate or severe ongoing injection site reactions in the overall treatment area or if there are no new areas to treat, or if the cellulite and laxity have sufficiently resolved.

7. DISCONTINUATION FROM STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

Subjects who discontinue from study treatment 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 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 140).

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 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.

If implications from COVID-19 cause subjects to miss study visits during the Treatment Phase additional subjects may be enrolled, at the discretion of the sponsor, in order to obtain a minimum of 24 subjects with sufficient efficacy assessments for overall objective and endpoint analysis purposes.

7.2. Subject Discontinuation/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.

If implications from COVID-19 cause subjects to miss study visits during the Treatment Phase additional subjects may be enrolled, at the discretion of the sponsor, in order to obtain a minimum of 24 subjects with sufficient efficacy assessments for overall objective and endpoint analysis purposes.

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 (Table 1). 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 Study 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.

8.1. Eligibility Confirmation

As part of eligibility confirmation investigators will submit photographs of either the thighs, or the buttocks, to the sponsor for consideration as an overall treatment area. The sponsor-designated central reviewer will only review for the submitted treatment area. If the subject is determined to be ineligible by the central reviewers for the selected treatment area, the investigator may submit photographs of the other treatment area from the same subject for reconsideration of eligibility. The sponsor can provide additional clarification for reconsideration of eligibility of a subject.

For these eligibility confirmation photographs, the subject will be 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 Study Operations Manual.

Inclusion/exclusion criteria will be re-reviewed at Visit 1 prior to dosing on Day 1. Only subjects deemed eligible by the sponsor-designated reviewer will be allowed to proceed with screening activities and receive study treatment. Subjects deemed ineligible in the overall submitted treatment area(s) by the sponsor-designated reviewer will be considered screen failures (note that at least 1 submitted treatment area must be determined as eligible for a subject to be enrolled). 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. During any COVID-19 interruption remote efficacy assessments (I-GAIS, S-GAIS, Hexsel CSS Subsection D, Body-Q Appraisal of Cellulite, CR-PCSS-Buttock, CR-PCSS-Thigh, and [redacted] are not allowed due to potential bias.

8.2.1. 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.

8.2.1.1. Subject Global Aesthetic Improvement Scale

The S-GAIS is a 7-level scale ranging from 3 (very much improved) to −3 (very much worse). Subjects will use the S-GAIS to determine the degree of improvement of each buttock or thigh

by comparing the cellulite from the Day 1 pretreatment (baseline) image of each buttock or each thigh to the images taken at the subsequent visits specified in the Schedule of Activities.

8.2.1.2. 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). The Body-Q Appraisal of Cellulite will be conducted at Days 1 and 180.

8.2.1.3. 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) at Screening to determine study eligibility. 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.

8.2.1.4. 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) at Screening to determine study eligibility. 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.

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

8.2.1.5. Investigator Global Aesthetic Improvement Scale

The I-GAIS is a 7-level scale ranging from 3 (very much improved) to −3 (very much worse). 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) image of each buttock or each thigh to the images taken at the subsequent visits specified in the Schedule of Activities.

The I-GAIS assessments will be based on digital photographs, are performed separately for each of 2 treatment areas and must be completed before study intervention administration on those visits. At treatment visits, the photographs taken before marking the treatment areas will be used.

8.2.1.6. Hexsel Cellulite Severity Scale

The Hexsel CSS is a photonumeric scale that looks at 5 key morphologic features of cellulite using a 4-point scale from a low of 0 to a high of 3 (Hexsel et al, 2009; Nürnberger and Müller, 1978).

The investigator or qualified designee will use the Hexsel CSS Subsection D to assess the severity of dermal laxity in each buttock or each thigh independently. This assessment should be made while the subject is in the standing position with relaxed gluteus muscles. This assessment will be conducted at the Screening Visit and all study visits, and should be performed prior to the 3D digital photography assessments, if possible.

8.2.1.7. [redacted]

[redacted]

8.2.1.8. [redacted]

[redacted]

8.2.1.9. [redacted]

[redacted]

8.3. Safety Assessments

All safety assessments will be performed at times outlined in the Schedule of Activities. Additional (unscheduled) safety assessments may be performed as needed.

8.3.1. Medical and Cellulite History

Medical and cellulite 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, alcohol, or illegal drug 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.

8.3.2. Physical Examination

The complete physical examination will 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, extremities, and other systems or organs of note.

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 examination findings for clinical significance. Any physical examination 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 Type

The Fitzpatrick Skin Scale is a 6-level scale (levels I-VI) for assessment of skin color and propensity for tanning to categorize skin types. 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. 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, 28, 56, 84, 112, and 140), 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. It will not be necessary to measure the 15 and 30 minute vital signs time points from subjects who do not receive treatment during a treatment visit.

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).

8.3.6. 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 a QTc prolongation of 470 ms or greater, the investigator should repeat the ECG within 1 hour. If the initial findings are confirmed, the investigator should exclude/withdraw the subject from study participation. The finding will be recorded as an AE and the subject will be withdrawn due to the AE.

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

8.3.7. Clinical Safety Laboratory Determinations

Clinical safety laboratory tests will be conducted according to the Schedule of Activities. Required clinical laboratory tests are outlined in Section 10.2. Clinical safety laboratory tests will be performed by a designated central laboratory. Each site will be provided with instructions on 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.

8.3.8. 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 any further 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 (excluding the disease under study). A condition present at baseline that worsens after initiation of study treatment will be captured as an AE; the onset date will be the date the event worsened. The AE should be recorded in standard medical terminology when possible.

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/End of Study 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.

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 and nonserious AESIs 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 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 Investigators 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 and follow-up information detailing the progress and outcome should be submitted on one or more Pregnancy Form(s). A Two Month Follow-Up Pregnancy Report form detailing the status of the infant should also 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

Anti-AUX-I and anti-AUX-II antibodies and anti-AUX-I and anti-AUX-II neutralizing antibodies will be evaluated in samples (4-mL tubes of blood) collected from all subjects at times outlined in the Schedule of Activities. These samples will be tested by the sponsor or sponsor's designee. The titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies and/or further characterize the immunogenicity of study treatment.

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 2 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.

9. STATISTICAL CONSIDERATIONS AND METHODS

9.1. Sample Size Determination

The sample size for this exploratory Phase 2 study was based on the minimum number of treatment area assessments (N=64 treatment areas, among 32 subjects) that could contribute to an initial clinical evaluation of tolerability and response to CCH treatment in a population of subjects with both mild to moderate cellulite and moderate to severe dermal laxity. This population will also allow a comparison across the 2 randomized treatment arms that utilize a grid pattern for dosing. This study is not statistically powered to detect a difference in response across the 2 treatment cohorts.

9.2. Populations for Analysis

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

- The Safety Population is defined as all enrolled participants who received at least 1 injection of CCH. All safety analyses will be based on this population.
- The Intent-to-Treat (ITT) Population is defined as all enrolled participants who received at least 1 injection of CCH.
- The Modified Intent-to-Treat (mITT) Population is defined as all ITT participants who have at least 1 valid I-GAIS assessment after an injection of CCH. All efficacy/effectiveness analysis will be based on this 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 database lock.

9.3.1. Efficacy Analysis

Refer to the Statistical Analysis Plan for details of the efficacy analyses.

9.3.1.1. Analyses of the Primary Efficacy Endpoint

The proportion of subjects with improved (+1 or better) score on the I-GAIS for either buttock or either thigh at Day 180 will be summarized and its 95% CI will be provided.

9.3.1.2. Analyses of Secondary Efficacy Endpoints

For responder endpoints, the proportion of responders at each scheduled visit and its 95% CI at Day 180 will be provided. For change from baseline parameters, descriptive statistics (n, mean, SD, median, minimum and maximum) at each scheduled visit and 95% CI of the mean at Day 180 will be provided.

9.3.1.3. Analyses of Tertiary Efficacy Endpoints

All exploratory efficacy/effectiveness endpoints will be summarized using appropriate descriptive statistics by time point and treatment area.

9.3.2. Safety Analyses

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

Refer to the Statistical Analysis Plan for details of 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 TEAE events that are new in onset or aggravated in severity following treatment) will be included in all summaries. SAEs (including death) will be summarized. AESI incidence will be summarized.

9.3.3. Other Analyses

The incidence of subjects meeting specific potentially clinically important (PCIs) criteria for both vital signs and clinical safety laboratory results will be summarized.

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

No interim analysis is planned for this study.

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 Code of Federal Regulations (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 practice (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 Pharmaceuticals Inc. 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 Assurance Number will satisfy this requirement for IRBs in the United States).

The study protocol, the informed consent form (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 Pharmaceuticals Inc.

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.

If appropriate, the ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate in this optional research will not provide this separate signature.

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 monitoring committees will be used for this study.

10.1.6. Dissemination of Clinical Study Data

Aggregate results data may 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 Pharmaceuticals Inc. 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 Pharmaceuticals Inc.

10.2. Appendix 2: Clinical Laboratory Tests

Hematology	**Biochemistry**	**Urinalysis**
Hemoglobin	Glucose	Glucose
Hematocrit	Sodium	Protein
Red blood cells	Potassium	Specific gravity
White blood cells	Calcium	pH
Platelets	Chloride	Ketones
White blood cell differential	CO_2	Bilirubin
Prothrombin time	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 (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.

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).

An 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: any form of cancer, 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.

See Section 10.6 for laboratory tests that indicate severe liver injury (possible Hy's Law) must be reported as an SAE.

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 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 day 180/End of Study Visit or until 28 days after the last dose of study treatment for those who terminate early. SAEs that occur within 28 days, following cessation of the study treatment, or within 28 days, following premature discontinuation from the study for any reason, must also be reported within the same timeframe. Any SAE that is felt by the investigator to be related to the study medication must be reported regardless of the amount of time since the last dose received. Follow-up information collected for any initial report of an SAE must also be reported to the sponsor within 24 hours of receipt by the investigator.

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

All SAEs should be sent 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 8.3.8.

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
BMI	Body mass index
CFR	Code of Federal Regulations
CR-PCSS	Clinician-reported Photonumeric Cellulite Severity Scale
CSS	Cellulite Severity Scale
ECG	Electrocardiogram
eCRF	Electronic case report form
FDA	Food and Drug Administration
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
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-treat
mITT	Modified intent-to-treat
QTc	Corrected QT interval
SAE	Serious adverse event
S-GAIS	Subject Global Aesthetic Improvement Scale
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal

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

[redacted]

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