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

EN3835-212

A PHASE 2a, OPEN-LABEL STUDY TO ASSESS THE IMPACT OF CCH TREATMENT OF BUTTOCK AND THIGH CELLULITE IN ADULT FEMALES USING PHOTONUMERIC SCALES, MAGNETIC RESONANCE IMAGING, AND HISTOPATHOLOGY

Sponsor Name: Endo Pharmaceuticals Inc.

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

Regulatory Agency Identifier Number(s): IND 110077

Original Protocol: 22 October 2019

Amendment 1: 16 January 2020

Amendment 2: 04 March 2020

Amendment 3: 08 May 2020

[redacted]

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.

08 May 2020

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Protocol Amendment 3: 08 May 2020

Amendment 3 was incorporated into the protocol on 08 May 2020. The major reason for this amendment is to modify the protocol due to the interruption caused by the COVID-19 public health emergency. The COVID-19 public health emergency has disrupted the conduct of clinical research throughout the world. At Endo Pharmaceuticals Inc. (Endo) ensuring the safety of clinical study participants is our primary concern. In addition, the integrity of data obtained from clinical trials must be ensured.

Endo initiated Study EN3835-212 at a single investigational site in November 2019. The first subject was dosed with CCH on 26 December 2019. On 18 March 2020, the investigational site suspended Study EN3835-212 due to the COVID-19 public health emergency. At that time, 7 subjects had received at least 1 dose of CCH in the study. Of those 7 subjects, 2 had completed the 3 doses required for the study and 1 subject had completed 2 doses. No subjects had completed all assessments required for the Day 71 Visit or beyond.

On 15 April 2020, all 7 subjects were more than 1 week outside of the visit window for their next dose or for the Day 71 visit and there was no indication that the site would be able to re-open within the following 2 weeks. In order to ensure subject safety and protect data integrity, Endo, in accordance with the *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency* (March 2020, updated 16 April 2020), decided to add additional subjects and modify the assessments required for current subjects when the investigational site re-opens as follows (and with subject consent):

- Subjects who were in screening for the study at the time of interruption (18 March 2020) but who had not been dosed with CCH will repeat all screening assessments to determine eligibility, if willing to do so. All screening assessments must be repeated within the screening window.
- Subjects who had received less than 3 doses of CCH prior to 18 March 2020 will be allowed to continue in the study and may receive any remaining doses with Sponsor approval. These subjects will complete all remaining visits and assessments EXCEPT biopsies and biopsy follow-up visits, if willing to do so. These subjects will be included in the safety assessments for the study, but will not be included in the efficacy assessments. Subjects who received less than 3 doses prior to 18 March 2020 may elect to remain in the study without receiving additional doses.
- Subjects who received all 3 doses of CCH prior to 18 March 2020, will be allowed to continue in the study and complete all remaining visits and assessments (including biopsies and biopsy follow-up visits), if willing to do so. These subjects will be included in the safety assessments for the study, but will not be included in the efficacy assessments. Subjects who received all 3 doses of CCH prior to 18 March 2020 may elect to remain in the study without completing the biopsies and biopsy follow-up visits.

- An additional 12 subjects will be dosed in the study. These subjects will be included in the safety assessments, and all efficacy assessments will be based on the data for these 12 subjects.

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

Section 1.1 Synopsis

Study Period: The estimated date of last subject completion has been changed from November 2020 to October 2021.

Overall Design: The number of subjects to be dosed in the study has been increased from 12 to 19. The subject participation has been updated as outlined above. The approximate duration of the study has been increased from 12 months to 24 months. The per subject duration of participation has been modified to indicate approximately 305 days (10 months) plus any delays due to the COVID-19 public health emergency.

Number of Subjects (planned): Wording has been modified to indicate that approximately 19 subjects will receive study drug so that approximately 12 subjects who did not experience interruptions due to the COVID-19 public health emergency will complete the study.

Section 1.2 Schedule of Activities

Footnote "j" has been amended and added to indicate that subjects who had less than 3 doses of CCH prior to 18 March 2020 will not have the Day 71 or Day 251 biopsies. And footnote "k" was added to indicate subjects who had less than 3 doses of CCH prior to 18 March 2020 will not be required to have the Day 85 and Day 265 biopsy follow-up visits.

Section 2.1 Study Rationale

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

Section 4.1 Overall Design

The section has been updated with the modifications in design for subjects who were screened or dosed prior to 18 March 2020 as outlined above.

Section 4.4 End of Study Definition

This section has been modified as follows: A subject will be considered to have completed the study if the subject received their first dose of study drug after 18 March 2020 and completed the Day 265 visit. Subjects who received their first dose of study drug prior to 18 March 2020 and complete the Day 265 Visit (or the Day 251 Visit if they elect not to have biopsies) also will be considered to have completed the study.

Section 5.4 Screen Failures

The following text was added: Subjects who were screened prior to 18 March 2020 for the study but had not been dosed with CCH may be rescreened. All screening assessments must be repeated within the screening window (35 days).

Section 6.1 Selecting the Treatment Region

The following text was added: For the 12 new subjects who receive their first dose of study drug after 18 March 2020, every attempt will be made to enroll an equal number of subjects across the 2 severity levels in both buttocks and thighs (eg, 3 subjects with moderate buttock cellulite, 3 subjects with severe buttock cellulite, 3 subjects with moderate thigh cellulite, and 3 subjects with severe thigh cellulite).

Section 7.1 Discontinuation of Study Treatment, Section 7.2 Subject Discontinuation/ Withdrawal from Study, and Section 7.3 Lost to Follow-up

These sections have been modified to indicate that all subjects dosed prior to 18 March 2020 will be replaced. In addition, subjects who receive their first dose of study drug after 18 March 2020 and subsequently discontinue from study treatment and/or withdraw from the study and/or are lost to follow-up will not be replaced.

Section 8.2.9 Biopsy Follow-up Examination

This section was updated to indicate that the Day 85 and Day 265 Biopsy Follow-up Visits are not required for subjects who had less than 3 doses of study drug prior to 18 March 2020.

Section 8.6.2 Double Punch Biopsy

This section was updated to indicate that subjects who had less than 3 doses of study drug prior to 18 March 2020 will not have the Day 71 and Day 251 biopsies performed. In addition, subjects who completed 3 doses of CCH prior to 18 March 2020 will have Day 71 or Day 251 biopsies, if willing to do so.

Section 9.2 Populations for Analysis

The Evaluable Population has been redefined to include all subjects in the Safety Population who received their first dose of CCH in this study after 18 March 2020 and who had a baseline and at least 1 postinjection PR-PCSS evaluation.

Section 9.3.1 Efficacy Analysis

This section has been updated to indicate that all secondary and tertiary PR-PCSS, CR-PCSS, and Hexsel efficacy endpoints will be summarized by treatment area (left or right) and region (buttock or thigh) using appropriate descriptive statistics using the Evaluable Population.

Section 9.4 Interim Analysis

This section has been modified to indicate that the interim analysis will be conducted when at least 4 of the 12 subjects who received their first dose of study drug after 18 March 2020 have completed their Day 71 visit. For all subjects who received their first dose of study drug after 18 March 2020, analysis of all primary, secondary, and tertiary endpoints will be included in the interim analysis. For the subjects who received all three doses prior to 18 March 2020, their MRI and biopsy data, if available, will be assessed separately but included in interim analysis. The purpose of the interim analysis is to determine if changes in morphology and/or histology can be identified using MRI and biopsy. If the interim analysis does not indicate that such changes can be identified, subsequent or additional MRIs or biopsies will not be performed in this study.

Protocol Amendment 2: 04 March 2020

Amendment 2 was incorporated into the protocol on 04 March 2020. The major reason for this amendment is that a slower than expected enrollment rate has made it unlikely that all subjects will complete the Day 71 visits before the earliest enrolled subjects are scheduled for additional MRI and biopsies. Therefore, the interim analysis will be conducted when the first 6 subjects complete their Day 71 Visit, rather than when all subjects complete that visit. Additional minor changes that do not impact study conduct or participant safety were also made.

The major revision to the protocol is:

- The interim analysis will be done when at least 6 subjects have completed their Day 71 visit (Section 9.4).

Protocol Amendment 1: 16 January 2020

Amendment 1 was incorporated into the protocol on 16 January 2020. The major reason for this amendment is to allow more time to obtain evaluable MRI images at screening and to permit repetition of MRIs during screening. Additional minor changes that do not impact study conduct or participant safety were also made.

The major revisions to the protocol include:

- Increasing the window for screening from 28 to 35 days. The screening period is now Day -35 to Day -1. This increases the duration of subject participation from approximately 298 Days to approximately 305 days (Section 1.1 Synopsis, Section 1.2 Schedule of Activities, and Section 4.1 Overall Design).
- Increased the window for the Day 71 visit to 10 days (Section 1.2 Schedule of Activities).
- Adding an additional inclusion criteria (Section 5.1, #13) requiring subjects to have evaluable MRI images of Dimples 1, 2, and 3 at screening.
- Clarifying the wording in Section 5.4 Screen Failures to indicate that subjects can repeat any screening evaluation once with the exception of the Dimple 1, 2, and 3 MRIs which may be repeated until an evaluable image is obtained, and to allow rescreening of subjects who do not have evaluable MRIs during the screening period.
- As per Administrative Change Letter No. 1, the phrase “up to” was added to all references to the number of injections in Section 1.1 Synopsis, Section 6.2 Selecting and Marking Dimples for Treatment, and Table 2 Study Treatment.
- Permitting the repetition of MRIs on Day 71 and Day 251 as often necessary to obtain an evaluable image (Section 1.2, footnote h and Section 8.6.1).

TABLE OF CONTENTS

LIST OF TABLES

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 2a open-label, study to assess the impact of CCH treatment of buttock and thigh cellulite in adult females using photonumeric scales, magnetic resonance imaging, and histopathology

Lead Principal Investigator: Not applicable

Study Period:
Estimated date first subject enrolled: November 2019
Estimated date last subject completed: October 2021

Phase of Development: 2a

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To assess the subject reported impact of CCH in the treatment of cellulite in adult females.	• The change from baseline (screening) in Patient-reported Photonumeric Cellulite Severity Scale (PR-PCSS) at Day 71.
Secondary	
• To assess the subject and clinician reported impact of CCH in the treatment of cellulite in adult females.	• The change from baseline (screening) in PR-PCSS at Days 22 and 43. • The change from baseline (screening) in Clinician-reported Photonumeric Cellulite Severity Scale (CR-PCSS) at Days 22, 43, and 71. • The change from baseline (screening) in Hexsel Cellulite Severity Scale (CSS) at Days 22, 43, and 71.
• To radiologically assess the impact of treatment with CCH in adult females with cellulite.	• Comparison of baseline (screening) MRI tissue morphology and septae under the treatment areas to images taken at Day 71.
• To evaluate tissue histopathology to assess the impact of treatment with CCH in adult females with cellulite.	• Comparison of baseline (screening) histopathology to the histopathology of samples taken at Day 71.
• To assess the safety of CCH treatment of cellulite in adult females.	• The proportion of subjects reporting each adverse event, treatment-emergent adverse event, adverse event of special interest, and serious adverse event. • The change from baseline in vital signs and clinical laboratory parameters at each visit where these parameters are measured. • The change from baseline in anti-AUX-I and anti-AUX-II antibodies and neutralizing antibodies at each visit where these parameters are measured.

Name of Sponsor/Company: Endo Pharmaceuticals Inc.

Name of Investigational Product: CCH

Name of Active Ingredient: Collagenase clostridium histolyticum

Objectives	Endpoints
Tertiary	
• To assess the complete loss of patient reported impact after CCH treatment in adult females with cellulite.	• The proportion of subjects with no change (or worsening) from baseline (screening) in PR-PCSS rating at Day 161 and at Day 251.
• To assess the complete loss of clinician reported impact after CCH treatment in adult females with cellulite.	• The proportion of subjects with no change (or worsening) from baseline (screening) in CR-PCSS rating at Day 161 and at Day 251. • The proportion of subjects with no change (or worsening) from baseline (screening) in Hexsel CSS total score at Day 161 and at Day 251.
• To radiologically assess the long-term impact of treatment with CCH in adult females with cellulite.	• Comparison of baseline (screening) magnetic resonance imaging (MRI) tissue morphology and septae under the treatment areas to images taken at Day 251.
• To evaluate tissue histopathology to assess the long-term impact of treatment with CCH in adult females with cellulite.	• Comparison of baseline (screening) histopathology to the histopathology of samples taken at Day 251.

Overall Design:

This is a single-center, open-label, Phase 2a study to assess the photonumeric scale, morphological, and histopathological changes associated with CCH in adult women with moderate or severe edematous fibrosclerotic panniculopathy (EFP). Approximately 19 subjects with moderate or severe EFP in the posterolateral thighs will be dosed in this study.

This study was suspended due to the COVID-19 public health emergency on 18 March 2020. When the study re-opens, subjects who had received less than 3 doses of CCH prior to 18 March 2020 will be allowed to continue in the study and may receive any remaining doses with Sponsor approval. These subjects will complete all remaining visits and assessments EXCEPT biopsies and biopsy follow-up visits, if willing to do so. These subjects will be included in the safety assessments for the study, but will not be included in the efficacy assessments. Subjects who received less than 3 doses prior to 18 March 2020 may elect to remain in the study without receiving additional doses.

Subjects who received all 3 doses of CCH prior to 18 March 2020, will be allowed to continue in the study and complete all remaining visits and assessments (including biopsies and biopsy follow-up visits), if willing to do so. These subjects will be included in the safety assessments for the study, but will not be included in the efficacy assessments. Subjects who received all 3 doses of CCH prior to 18 March 2020 may elect to remain in the study without completing the biopsies and biopsy follow-up visits.

An additional 12 subjects will be dosed in the study. These subjects will be included in the safety assessments, and all efficacy assessments will be based on the data for these 12 subjects. For the 12 subjects who receive their first dose of study drug after 18 March 2020, every attempt will be made to enroll an equal number of subjects across the 2 severity levels in both buttocks and thighs (eg, 3 subjects with moderate buttock cellulite, 3 subjects with severe buttock cellulite, 3 subjects with moderate thigh cellulite, and 3 subjects with severe thigh cellulite).

Name of Sponsor/Company: Endo Pharmaceuticals Inc.
Name of Investigational Product: CCH
Name of Active Ingredient: Collagenase clostridium histolyticum
Following a screening period of up to 35 days, qualified subjects will receive 0.84 mg of CCH per treatment area (each buttock or each thigh) for a total dose of 1.68 mg in both buttocks or both thighs per treatment session × 3 treatment sessions (Day 1, Day 22, and Day 43). Buttock treated subjects will receive 0.84 mg of CCH administered as up to 12 injections (0.3 mL administered as three 0.1 mL aliquots per injection in each buttock). Thigh treated subjects will receive 0.84 mg of CCH administered as up to 12 injections (1.5 mL administered as five 0.3 mL aliquots per injection in each thigh). Subjects will have MRI and (except as noted above) double punch biopsies of 3 selected target dimples 3 times during the study. All subjects will be followed for 265 days after the first dose of study treatment. Subjects will participate in the study for approximately 305 days (10 months) plus any delays caused by the COVID-19 public health emergency. The duration of the study from first subject first visit to last subject last visit will be dependent upon the ability of the site to identify and enroll subjects. The entire study is expected to require about 24 months to complete.
Disclosure Statement: This is an open-label study.
Number of Subjects (planned): Approximately 19 subjects will receive study drug so that approximately 12 subjects who did not experience COVID-19 public health emergency interruption will complete the study.
Treatment Groups and Duration: Subjects will receive 3 treatment sessions 21 days apart and consisting of 0.84 mg of CCH in each treatment area (each buttock or each thigh for a total dose of 1.68 mg). The total amount of CCH to be administered per subject over the course of the study will not exceed 5.04 mg.
Data and Safety Monitoring Committee: No data and safety monitoring committee will be used for this study.

1.2. Schedule of Activities

Table 1: Schedule of Activities

Activities	Screening (Day -35 to Day -1)			Treatment Phase				Extension Phase			
	Before MRI	Before biopsy	Approximately Day -14	Day 1 Treatment Session I	Day 22 (± 3 Days) Treatment Session II	Day 43 (± 3 Days) Treatment Session III	Day 71 (+10 Days)	Day 85 (±5 Days)/ Biopsy Follow-up	Day 161 (± 15 Days)	Day 251 (±15 Days)/ Early Termination	Day 265 (±5 Days)/ Biopsy Follow- up
Informed consent[a]	X										
Inclusion/exclusion criteria review[b]	X			X							
Medical and surgical history	X										
EFP history	X										
Prior medications (including all prior medications for cellulite)	X										
Physical examination	X										
Height	X										
Weight	X			X	X	X	X		X	X	
Fitzpatrick Skin Type	X										
Vital signs	X			X[c]	X[c]	X[c]	X		X	X	
ECG	X										
Hematology, chemistry, and urinalysis	X						X			X	
Serum pregnancy test	X										
Urine pregnancy test				X	X	X	X[d]		X	X[d]	
HIV and Hepatitis B tests	X										
Immunogenicity sample collection				X			X		X	X	
Selection of treatment region (both buttocks or both thighs)	X										
Imaging for efficacy assessments (IntelliStudio)	X[e]			X[f]	X[f]	X[f]	X		X	X	
PR-PCSS	X[e]				X	X	X		X	X	
CR-PCSS	X[e]				X	X	X		X	X	
Hexsel CSS	X[e]				X	X	X		X	X	
Selection, marking, labeling, and/or photography of 3 dimples for MRI and Biopsy (Dimples 1, 2, and 3)		X									

Table 1: Schedule of Activities (Continued)

Activities	Screening (Day -35 to Day -1)			Treatment Phase				Extension Phase			
	Before MRI	Before biopsy	Approximately Day -14	Day 1 Treatment Session I	Day 22 (± 3 Days) Treatment Session II	Day 43 (± 3 Days) Treatment Session III	Day 71 (+10 Days)	Day 85 (±5 Days)/ Biopsy Follow-up	Day 161 (± 15 Days)	Day 251 (±15 Days)/ Early Termination	Day 265 (±5 Days)/ Biopsy Follow-up
MRI		X[g] Dimples 1, 2, and 3					X[h] Dimples 2 and 3			X[h] Dimple 3	
Biopsy sample collection			X[i] Dimple 1				X[j] Dimple 2			X[j] Dimple 3	
Biopsy follow-up examination				X				X[k]			X[k]
Select and mark up to 12 dimples for CCH injection in each treatment area (including Dimples 2 and 3)				X	X	X					
Study drug administration				X	X	X					
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Injections site reactions/local tolerability in areas treated				X	X	X	X		X	X	
All other AEs[l]	Monitored throughout the study										

[a] Performed prior to any study-required assessments, unless exceptions granted for standard of care procedures. A separate informed consent may be used for HIV testing and must be signed before the sample is collected, if required.

[b] Should be reassessed and verified prior to dosing.

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

[d] Urine pregnancy test should be completed prior to the MRI.

[e] At screening all 4 potential treatment areas (each buttock and each thigh) will be imaged; and CR-PCSS, PR-PCSS, and Hexsel CSS assessments will be done for each potential treatment area (each buttock and each thigh).

[f] Before and after marking dimples for treatment. No manipulation of the treatment area should be done prior to the "before" photographs.

[g] Screening MRIs will be performed after all other screening assessments (except the biopsy) have been completed. MRIs may be repeated within the screening window as often as necessary to obtain evaluable images.

[h] The Day 71 and Day 251 MRIs may be performed up to 7 days prior to the indicated visit. The MRI must be completed before the biopsy required for these visits. The Day 251/Early Termination MRI is not required for subjects who withdraw from the study (early termination). The Day 71 and Day 251 MRIs may be repeated as often as necessary to obtain an evaluable image.

Table 1: Schedule of Activities (Continued)

[i] The screening biopsy will be performed after all other screening assessments (including MRI) are completed. The screening biopsy will be performed at least 14 days prior to the Day 1 Treatment Visit. The investigator must examine and confirm sufficient healing of the biopsy site before dosing on Day 1. The timing of all subsequent visits will be based on the actual date that the first dose of CCH is administered.

[j] The Day 71 and Day 251 imaging for efficacy, PR-PCSS, and CR-PCSS must be completed prior to the biopsy sample collection required at those visits. The Day 251/Early Termination biopsy is not required for subjects who withdraw from the study (early termination). For subjects who received less than 3 doses of CCH prior to 18 March 2020, no Day 71 or Day 251 biopsy samples will be collected.

[k] Visit not required for subjects who had less than 3 doses of CCH prior to 18 March 2020.

[l] Adverse events (AE)/serious adverse events (SAE) will be captured from time of informed consent signature until the Day 265 Visit or until 28 days after last dose of study drug whichever is later. There is no time limit on collection of SAEs considered to be related to study treatment.

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

2. INTRODUCTION

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

2.1. Study Rationale

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

The efficacy of CCH treatment on cellulite has been demonstrated in previous clinical studies using validated photonumeric scales. This study will capture the change from baseline after CCH treatment using the validated photonumeric scales and explore tissue level changes in the treatment areas (buttocks and thigh), both from histopathology and radiology perspectives.

COVID-19 Public Health Emergency Impact

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

Endo initiated study EN3835-212 at a single investigational site in November of 2019. The first subject was dosed with CCH on 26 December 2019. On 18 March 2020, the investigational site suspended Study EN3835-212 due to the COVID-19 public health emergency. At that time, 7 subjects had received at least 1 dose of CCH in this study. Of those 7 subjects, 2 had completed the 3 doses required for the study and 1 subject had completed 2 doses. No subjects had completed all assessments required for the Day 71 Visit or beyond.

On 15 April 2020, all 7 subjects were more than 1 week outside of the visit window for their next dose or for the Day 71 visit and there was no indication that the site would be able to re-open within the following 2 weeks. In order to ensure subject safety and protect data integrity, Endo, in accordance with the *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency* (March 2020, updated 16 April 2020), decided to add additional subjects and modify the assessments required for current subjects when the investigational site re-opens as follows (and with subject consent):

- Subjects who were in screening for the study at the time of interruption (18 March 2020) but who had not been dosed with CCH will repeat all screening assessments to determine eligibility, if willing to do so. All screening assessments must be repeated within the screening window.

- Subjects who had received less than 3 doses of CCH prior to 18 March 2020 will be allowed to continue in the study and may receive any remaining doses with Sponsor approval. These subjects will complete all remaining visits and assessments EXCEPT biopsies and biopsy follow-up visits, if willing to do so. These subjects will be included in the safety assessments for the study, but will not be included in the efficacy assessments. Subjects who received less than 3 doses prior to 18 March 2020 may elect to remain in the study without receiving additional doses.
- Subjects who received all 3 doses of CCH prior to 18 March 2020, will be allowed to continue in the study and complete all remaining visits and assessments (including biopsies and biopsy follow-up visits), if willing to do so. These subjects will be included in the safety assessments for the study, but will not be included in the efficacy assessments. Subjects who received all 3 doses of CCH prior to 18 March 2020 may elect to remain in the study without completing the biopsies and biopsy follow-up visits.
- An additional 12 subjects will be dosed in the study. These subjects will be included in the safety assessments and all efficacy assessments will be based on the data for these 12 subjects.

2.2. Background

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

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

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

A number of therapies have been utilized in an attempt to treat cellulite, much of the evidence for their efficacy is anecdotal, subjective, or based only on patient self-assessment and many of the treatments have undesirable side effects (Avram, 2004; Collis et al, 1999; Khan et al, 2010; Hexsel and Mazzuco, 2000). Some of the historical treatments for EFP have included weight loss, pharmacological agents (eg, xanthines, retinoids, lactic acid, and herbals), Endermologie® or lipomassage, mesotherapy, radiofrequency, subcision (including powered subcision eg, Cellfina®), and laser (including Triactive® and CelluLaze™) (Boyce et al, 2005;

DiBernardo, 2011; Hexsel and Mazzuco, 2000; Khan et al, 2010). However, there remains an unmet need for safe and effective nonsurgical therapies to improve the aesthetic outcome in women with cellulite. CCH has the potential to effectively lyse the subdermally located fibrous septae, the underlying cause of the skin dimpling in women with cellulite, at the site of injection.

The results from previous studies have shown improvement in the severity of cellulite, as determined by both the investigator and the subject, in subjects treated with CCH administered at a dose of 0.84 mg per treatment area (1 buttock or 1 thigh) every 21 days for 3 sessions. Across all previous studies, CCH has demonstrated an acceptable safety and immunogenicity profile. The majority of AEs occurred at the site of injection, were mild to moderate in nature, and often resolved within 2 to 3 weeks without any sequelae.

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

The purpose of this study is to examine the impact of CCH on the tissue following administration of 0.84 mg per treatment area in the buttocks or thighs of adult women with EFP at 3 treatment sessions approximately 21 days apart using photonumeric scales, magnetic resonance imaging (MRI), and histopathology.

2.3. Risk/Benefit Assessment

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

The following AEs have been commonly observed in subjects treated with CCH for EFP: local injection site reactions including injection site bruising, injection site swelling, and injection site pain. These events are similar to events reported in the clinical trials of EN3835 for the approved indications. Postmarketing safety data are consistent with safety data reported in clinical trials.

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

Due to the use of the strong magnet, MRI cannot be performed on subjects with any implant containing metal or those who have other internal or external metallic objects as it may cause these objects to move. MRI may potentially increase the temperature of amniotic fluid, so should not be used in pregnant women. The risks associated with punch biopsies include local bleeding and bruising, pain, infection, allergic reaction to the numbing medicine used in the procedure, damage to the structures beneath the skin site (such as an artery or a nerve), and permanent scarring.

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

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the subject reported impact of CCH in the treatment of cellulite in adult females.	• The change from baseline (screening) in Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) at Day 71.
Secondary	
• To assess the subject and clinician reported impact of CCH in the treatment of cellulite in adult females.	• The change from baseline (screening) in PR-PCSS at Days 22 and 43. • The change from baseline (screening) in Clinician-reported Photonumeric Cellulite Severity Scale (CR-PCSS) at Days 22, 43, and 71. • The change from baseline (screening) in Hexsel Cellulite Severity Scale (CSS) at Days 22, 43, and 71.
• To radiologically assess the impact of treatment with CCH in adult females with cellulite.	• Comparison of baseline (screening) MRI tissue morphology and septae under the treatment areas to images taken at Day 71.
• To evaluate tissue histopathology to assess the impact of treatment with CCH in adult females with cellulite.	• Comparison of baseline (screening) histopathology to the histopathology of samples taken at Day 71.
• To assess the safety of CCH treatment of cellulite in adult females.	• The proportion of subjects reporting each AE, treatment-emergent adverse event (TEAE), adverse event of special interest (AESI), and serious adverse event (SAE). • The change from baseline in vital signs and clinical laboratory parameters at each visit where these parameters are measured. • The change from baseline in anti-AUX-I and anti-AUX-II antibodies and neutralizing antibodies at each visit where these parameters are measured.
Tertiary	
• To assess the complete loss of patient reported impact after CCH treatment in adult females with cellulite.	• The proportion of subjects with no change (or worsening) from baseline (screening) in PR-PCSS rating at Day 161 and at Day 251.
• To assess the complete loss of clinician reported impact after CCH treatment in adult females with cellulite.	• The proportion of subjects with no change (or worsening) from baseline (screening) in CR-PCSS rating at Day 161 and at Day 251. • The proportion of subjects with no change (or worsening) from baseline (screening) in Hexsel CSS total score at Day 161 and at Day 251.

Objectives	Endpoints
• To radiologically assess the long-term impact of treatment with CCH in adult females with cellulite.	• Comparison of baseline (screening) MRI tissue morphology and septae under the treatment areas to images taken at Day 251.
• To evaluate tissue histopathology to assess the long-term impact of treatment with CCH in adult females with cellulite.	• Comparison of baseline (screening) histopathology to the histopathology of samples taken at Day 251.

4. STUDY DESIGN

4.1. Overall Design

This is a single-center, open-label, Phase 2a study to assess the safety and efficacy of CCH in adult women with moderate or severe EFP of the buttocks or thighs using photonumeric scales, MRI, and histopathology of tissues from the treated area. Approximately 19 subjects will be dosed in this study.

This study was suspended due to the COVID-19 public health emergency on 18 March 2020. When the study re-opens, subjects who had received less than 3 doses of CCH prior to 18 March 2020 will be allowed to continue in the study and may receive any remaining doses with Sponsor approval. These subjects will complete all remaining visits and assessments EXCEPT biopsies and biopsy follow-up visits, if willing to do so. These subjects will be included in the safety assessments for the study, but will not be included in the efficacy assessments. Subjects who received less than 3 doses prior to 18 March 2020 may elect to remain in the study without receiving additional doses.

Subjects who received all 3 doses of CCH prior to 18 March 2020, will be allowed to continue in the study and complete all remaining visits and assessments (including biopsies and biopsy follow-up visits), if willing to do so. These subjects will be included in the safety assessments for the study, but will not be included in the efficacy assessments. Subjects who received all 3 doses of CCH prior to 18 March 2020 may elect to remain in the study without completing the biopsies and biopsy follow-up visits.

An additional 12 subjects will be dosed in the study. These subjects will be included in the safety assessments, and all efficacy assessments will be based on the data from these 12 subjects. For the 12 subjects who receive their first dose of study drug after 18 March 2020, every attempt will be made to enroll an equal number of subjects across the 2 severity levels in both buttocks and thighs (eg, 3 subjects with moderate buttock cellulite, 3 subjects with severe buttock cellulite, 3 subjects with moderate thigh cellulite, and 3 subjects with severe thigh cellulite).

Following a screening period of up to 35 days, qualified subjects will receive 0.84 mg of CCH per treatment area (each buttock or each thigh) for a total dose of 1.68 mg in both buttocks or both thighs per treatment session × 3 treatment sessions (Day 1, Day 22, and Day 43). Buttock treated subjects will receive 0.84 mg of CCH administered as up to 12 injections (0.3 mL administered as three 0.1 mL aliquots per injection in each buttock). Thigh treated subjects will receive 0.84 mg of CCH administered as up to 12 injections (1.5 mL administered as five 0.3 mL aliquots per injection in each thigh).

Subjects will have MRI and (except as noted above) double punch biopsies of 3 selected target dimples 3 times during the study. All subjects will be followed for 265 days after the first dose of study treatment.

Subjects will participate in the study for approximately 305 days (10 months) plus any delays caused by the COVID-19 public health emergency. The duration of the study from first subject first visit to last subject last visit will be dependent upon the ability of the site to identify and enroll subjects. The entire study is expected to require about 24 months to complete.

4.2. Scientific Rationale for the Study Design

Although the visual impact and efficacy of CCH treatment on cellulite dimples has been studied using photographic images of buttocks and thighs, the subdermal impact has not been characterized and/or visualized. This study will use MRI and histopathology to attempt to visualize and/or characterize changes in subdermal tissue after treatment with CCH and to better understand the mechanism of action of CCH.

4.3. Justification for Dose

The results from a Phase 2b study (EN3835-201) suggested that CCH 0.84 mg per treatment area (1 buttock or 1 thigh) × 3 treatment sessions is safe and effective. The Phase 3 studies (EN3835-302 and EN3835-303) showed efficacy when using the same treatment in the buttocks with a similar safety profile where most AEs were mild to moderate in severity and transient. The immunogenicity profile of CCH has been consistent across all clinical studies to date. Therefore, the dose of 0.84 mg per treatment area (buttock or thigh - with a total dose of 1.68 mg of CCH for 2 buttocks or 2 thighs) administered at 3 treatment sessions approximately 21 days apart will be used in this study.

4.4. End of Study Definition

A subject will be considered to have completed the study if the subject received their first dose of study drug after 18 March 2020 and completed the Day 265 visit. Subjects who received their first dose of study drug prior to 18 March 2020 and complete the Day 265 Visit (or the Day 251 Visit if they elect not to have biopsies) also will be considered to have completed the study.

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

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1. Subject Inclusion Criteria

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

1. Be female and ≥ 18 and ≤ 50 years of age at the time of consent.

2. Have both buttocks or both posterolateral thighs with:
    a. A score of 3 or 4 (moderate or severe) as reported by the investigator using the CR-PCSS.
    b. A Hexsel CSS total score of ≤ 13.
    c. A Hexsel CSS Subsection A "Number of Evident Depressions" score of > 0.
    d. A Hexsel CSS Subsection B "Depth of Depressions" score of 2 (medium depth depressions) or 3 (deep depressions).
3. Have a body mass index (BMI) score between 18.5 kg/m^2 to 29.9 kg/m^2 and intends to maintain stable body weight throughout the duration of the study (from the Screening Visit through the Day 251/Early Termination Visit). A variation of ≤ 10% from the Day 1 Visit weight is permitted.
4. Be willing and consent to undergo human immunodeficiency virus (HIV) and hepatitis B testing, as well as double punch biopsy and MRI procedures.
5. Have a minimum of 2 well defined and isolated cellulite dimples that are considered moderate or deep in depth in each treatment area (each thigh or each buttock, for a total of 4 such dimples), of which 3 (Dimples 1, 2 and 3) will be selected for MRI and biopsy procedures.
6. Be willing to apply sunscreen to the treatment area before each exposure to the sun for the duration of the study (from the Screening Visit through the Day 251/Early Termination Visit).
7. Be judged by the investigator to be in good health, based upon the results of a medical history, physical examination, electrocardiogram (ECG), and laboratory profile at screening.
8. 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 at least 1 menstrual cycle prior to the first dose of study treatment through the Day 251/Early Termination Visit. Acceptable forms of contraception include hormonal measures (oral contraceptive pills, contraceptive patch, contraceptive ring, injections, etc), intrauterine devices, double barrier methods (condom plus diaphragm, condom or diaphragm plus spermicidal gel or foam), surgical sterilization of the male partner, and abstinence.
9. Have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy prior to dosing at each treatment session and prior to the Day 71 and Day 251 MRIs.
10. Be willing and able to comply with all protocol required visits and assessments.
11. Be able to read, understand, and independently complete patient reported outcome instruments in English.
12. 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.

13. Must have evaluable MRI images of Dimples 1, 2, and 3 at screening. An evaluable MRI is defined as an image that adheres to the protocol scanning parameters and is free from artifacts that could affect the analysis.

5.2. Subject Exclusion Criteria

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

1. Is from a vulnerable population, as defined by the US Code of Federal Regulations (CFR) Title 45, Part 46, Section 46.111(b) and other local and national regulations, including but not limited to, employees (temporary, part-time, full-time, etc) or a family member of the research staff conducting the study, or of the sponsor, or of the contract research organization, or of the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).
2. Has a history of sensitivity or allergy to collagenase or any other excipient of CCH.
3. Has any of the following systemic conditions:
    a. Coagulation disorder.
    b. Evidence or history of malignancy (other than excised basal-cell carcinoma) unless there had been no recurrence in at least 5 years.
    c. History of keloidal scarring or abnormal wound healing.
    d. Concurrent diseases or conditions that might interfere with the conduct of the study, confound the interpretation of the study results, or endanger the subject's well-being. Any questions about concurrent diseases will be discussed with the Medical Monitor.
    e. Evidence of clinically significant abnormalities on physical examination, vital signs, ECG, or clinical laboratory values.
4. Has any of the following local conditions in the areas to be treated (both buttocks or both thighs):
    a. History of lower extremity thrombosis, deep vein thrombosis, or post-thrombosis syndrome.
    b. Vascular disorder (eg, varicose veins, telangiectasia).
    c. Inflammation or active infection.
    d. Active cutaneous alteration including rash, eczema, or psoriasis.
    e. A tattoo or other artificially inflicted body marker.
    f. A mole located within 2 cm of any injection site.
5. Has a Hexsel CSS Subsection D "Grade of Laxity, Flaccidity, or Sagging Skin" score of ≥2 or has linear undulations that can be effaced by lifting the skin in the areas to be treated (each buttock or each thigh).
6. Requires anticoagulant or antiplatelet medication during the study or has received anticoagulant or antiplatelet medication (except for ≤ 150 mg aspirin daily) within 7 days before injection of study treatment.

7. Has used any of the following for the treatment of EFP on either thigh or either buttock within the timelines identified below or intends to use any of the following at any time during the course of the study:
   a. Liposuction during the 12-month period before injection of study treatment.
   b. Injections (eg, mesotherapy, dermal fillers, biostimulatory fillers); radiofrequency device treatments; laser treatment; buttock or thigh implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision) during the 12-month period before injection of study treatment.
   c. Any investigational treatment for EFP on a buttock or thigh during the 12-month period before the injection of study treatment.
   d. Endermologie or similar treatments during the 6-month period before injection of study treatment.
   e. Massage therapy during the 3-month period before injection of study treatment.
   f. Creams (eg, Celluvera™, TriLastin®) and/or home therapies to prevent or mitigate EFP during the 2-week period before injection of study treatment.
8. Has used any form of artificial tanning (sprays, lotions, tanning booth, etc) within the 30 days prior to the first injection of study drug or during the study (through the Day 265/Early Termination Visit).
9. Has a positive HIV test and/or a positive Hepatitis B surface antigen (HBsAg) or Hepatitis B core antibody (HBcAb) test at screening.
10. Has had any surgery, invasive procedure (eg, liposuction), injectable treatment (eg, KYBELLA®) or any similar treatment that could have destroyed fat cells and/or removed fat deposits in the treatment area.
11. Has a history of keloids, hypertrophied scars, and/or other complications following biopsy.
12. Has any contraindications for MRI including, but not limited to:
    a. Has an implant containing metal including but not limited to intracranial aneurysm clips, cochlear implants, prosthetic devices containing metal, implanted drug infusion pumps, neurostimulators, bone-growth stimulators, intrauterine contraceptive devices containing metal, or any other type of iron-based metal implants.
    b. Has an internal metallic object such as bullets or shrapnel, as well as surgical clips, pins, plates, screws, metal sutures, or wire mesh.
    c. Has any tattoo or permanent cosmetics/make-up including, but not limited to, permanent lip liner or permanent eye liner.
    d. Has severe claustrophobia.
    e. Has experienced "ceremonial" syncope (fainting while standing still).
    f. Has extremely low blood pressure, epilepsy, asthma, anemia, or sickle cell disease.
13. Has received any collagenase treatments at any time prior to treatment in this study and/or has received EN3835 or CCH in a previous investigational study for cellulite.
14. Has previously received treatment with CCH in this clinical study.

15. Has received treatment with an investigational product within 30 days (or 5 half-lives, whichever is longer) of the Screening Visit.
16. Is pregnant and/or is providing breast milk or plans to become pregnant and/or to provide breast milk during the course of the study.
17. Intends to initiate an intensive sport or exercise program during the study.
18. Intends to initiate an intensive weight reduction program during the study.
19. Has any other condition(s) that, in the investigator's opinion, might indicate the subject to be unsuitable for the study.

5.3. Lifestyle Considerations

See Section 5.1 and Section 5.2. In addition, subjects should not donate blood while participating in this study and for 28 days after the last study treatment.

5.4. Screen Failures

Screen failures are defined as subjects who consent to participate in this study but are not subsequently treated.

Subjects will be allowed to repeat any screening assessment/procedure once; however, MRI(s) may be repeated as often as necessary to obtain an evaluable image, provided the repeat MRI(s) are within the screening window. The subject will not be considered a screen failure unless the repeat assessment/procedure result does not meet eligibility criteria. The period from the start of screening related procedures at the Screening Visit to the Day 1 Visit must not exceed 35 days, inclusive of any repeat screening procedures.

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

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

Subjects who were screened prior to 18 March 2020 for the study but had not been dosed with CCH may be rescreened. All screening assessments must be repeated within the screening window (35 days).

For subjects screened after 18 March 2020, a subject who is a screen failure may not be rescreened, unless the reason for screen failure is the inability to obtain evaluable MRI(s) during the screening period. These subjects must repeat all screening activities. The period from the start of rescreening related activities to the first injection of study drug must not exceed 35 days. Subjects may be rescreened only once.

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

Selection of the treatment region (both buttocks or both thighs) will be at the discretion of the investigator at screening and in accordance with the distribution required for the study. Approximately 19 subjects will be dosed in this study. For the 12 new subjects who receive their first dose of study drug after 18 March 2020, every attempt will be made to enroll an equal number of subjects across the 2 severity levels in both buttocks and thighs (eg, 3 subjects with moderate buttock cellulite, 3 subjects with severe buttock cellulite, 3 subjects with moderate thigh cellulite, and 3 subjects with severe thigh cellulite).

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

6.2. Selecting and Marking Dimples for Treatment

In each treatment area, cellulite dimples for CCH treatment will be selected at screening at the discretion of the investigator and must be well-defined, evident when the subject is standing, and suitable for treatment. An adequate number of dimples should be selected at each treatment area for administration of up to 12 subcutaneous CCH injections. The dimples selected for treatment must include Dimple 2 and Dimple 3 that were selected for MRI and biopsy and these dimples will be treated throughout the study (see Section 8.6). Dimple 1 will not be treated at any time during the study.

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

6.3. Treatment Administration

CCH is a sterile lyophilized powder that is reconstituted with a sterile diluent made of 0.6% sodium chloride and 0.03% calcium chloride dihydrate in water. Subjects who qualify for the study will be given a maximum dose of 0.84 mg of CCH per treatment area (each buttock or each thigh) per treatment visit (total dose of 1.68 mg per treatment session), administered as up to 12 subcutaneous injections per buttock or thigh at 3 treatment sessions approximately 21 days apart (Days 1, 22, and 43).

Buttock cellulite dimple injections will consist of administration of 0.3 mL of reconstituted CCH, administered in 3 aliquots of 0.1 mL each. For thighs, cellulite dimple injections will consist of 1.5 mL of reconstituted CCH, administered in 5 aliquots of 0.3 mL each (see Table 2).

In this study, the reconstitution volumes and angles of injection will be different for the buttocks and the posterolateral thighs. However, the total dose in each treatment area per treatment session will remain 0.84 mg of CCH.

Specific instructions for CCH reconstitution and administration, including the injection techniques, will be provided in the Pharmacy Manual.

Table 2: Study Treatment

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

Treatment will consist of up to 12 injections per treatment area (1 buttock or 1 thigh) for a total of up to 24 injections in 2 buttocks or in 2 thighs per treatment visit. With the exception of Dimples 1, 2, and 3 (see Section 6.2), and because the goal of treatment is to improve the aesthetic appearance of each entire treatment area, the investigator will select dimples that in his or her opinion would most improve the aesthetic appearance of each entire treatment area. Therefore, the same dimples within a treatment area (each buttock or each thigh) or different dimples within a treatment area may be treated at each treatment visit, but injections must be administered within the selected treatment area (buttocks or thighs) for each of the 3 treatment visits. Dimple 1 will not be treated at any time during this study. Dimples 2 and 3 must be treated at each treatment session.

Study treatment will be injected subcutaneously while the subject is in a prone position. Specific instructions outlining the injection techniques will be provided in the Pharmacy Manual.

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

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

6.4. Study Treatment Preparation/Handling/Storage/Accountability

CCH and its diluent will be supplied in bulk cartons of 10 vials each. Each vial of study treatment and diluent will minimally be labeled with contents, sponsor identification, storage, administration/use, and appropriate caution statements. CCH and the diluent must be stored in an appropriate, secure area. Study treatment must be kept in a temperature-monitored refrigerator (2°C to 8°C) with locked access until used or returned to Endo.

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

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

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

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

6.5. Measures to Minimize Bias

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

6.5.1. Interactive Response Technology

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

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

6.6. Study Treatment Compliance

All subjects will receive study treatment administered by the investigator at the study site. All dosing information will be recorded for each subject visit. Drug inventory will be maintained in the IRT system, 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 8.4).

6.7. Prior and Concomitant Medications and Procedures

The start and stop date, dose, unit, frequency, route of administration, and indication for all prior (taken within the 90 days prior to the Screening Visit) and concomitant (taken from the Screening Visit through the Day 265 Visit) medications and nondrug therapies (eg, blood transfusions, oxygen supplementation, physical therapy, etc) received will be recorded.

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

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 265 Visit):

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

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

7. DISCONTINUATION FROM STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

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

Permanent study treatment discontinuation is required for the following:

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

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

If a clinically significant cardiac finding is identified (including but not limited to changes from baseline in corrected QT [QTc] interval) 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.

All subjects dosed prior to 18 March 2020 will be replaced. Subjects who receive their first dose of study drug after 18 March 2020 and subsequently discontinue from study treatment will not be replaced.

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 tested and the investigator must document this in the site study records.

Withdrawal from the study is required for any subject who becomes pregnant at any time during the study.

A subject may also 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.

All subjects dosed prior to 18 March 2020 will be replaced. Subjects who receive their first dose of study drug after 18 March 2020 and subsequently withdraw from the study will not be replaced.

7.3. Lost to Follow-up

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

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

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

All subjects dosed prior to 18 March 2020 will be replaced. Subjects who receive their first dose of study drug after 18 March 2020 and are subsequently lost to follow-up will not be replaced.

8. STUDY ASSESSMENTS AND PROCEDURES

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

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

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

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

8.1. 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 Clinical Operations Study Manual.

8.1.1. Imaging for Efficacy Assessments

Although digital photographs are not direct efficacy measurements, digital photography will be utilized in the assessment of certain efficacy measurements (ie, to assess certain cellulite severity parameters at specific intervals-see Section 1.2). At screening, the investigator or qualified designee will photograph each of the 2 potential treatment areas (both buttocks and both thighs) independently using a sponsor-supplied standardized digital camera in a standardized manner. For subsequent visits, only the areas receiving treatment (both buttocks or both thighs) will be photographed. The subject will be standing in a consistent, relaxed standing pose (ie, standing position with relaxed gluteus muscles) for each photography session and will be wearing a standardized photographic garment as described in the Photography Manual. These photographs will be taken before and after marking of the treatment area for dosing.

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.

8.1.2. Subject and Investigator Cellulite Assessments

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

8.1.2.1. Patient-reported Photonumeric Cellulite Severity Scale

The PR-PCSS-Buttock and PR-PCSS-Thigh will be used to assess the severity of cellulite of both treatment areas (each buttock and each thigh, independently). The PR-PCSS-Buttock and PR-PCSS-Thigh are 5-level photonumeric scales developed specifically for patients and used by the subject to assess the severity of their cellulite in the buttocks and/or thighs by viewing digital images of each of their buttocks and/or thighs captured by photography at times outlined in the Schedule of Activities (Section 1.2). The ratings range from 0 (None) to 4 (Severe) with labels and descriptors to aid the subject in the assessments.

At screening, the subjects will use the appropriate PR-PCSS scale to assess the cellulite in all potential treatment areas (each buttock and each thigh) independently. For subsequent visits only the areas receiving treatment (each buttock or each thigh) will be assessed.

Subjects will be trained/retrained on the use of the PR-PCSS prior to each assessment.

8.1.2.2. Clinician-reported Photonumeric Cellulite Severity Scale

The CR-PCSS-Buttock and CR-PCSS-Thigh will be used to assess the severity of cellulite of both treatment areas (each buttock and each thigh, independently). The CR-PCSS-Buttock and CR-PCSS-Thigh are 5-level photonumeric scales developed specifically for clinicians and used by the investigator to assess the severity of the subject's cellulite in each buttock or each thigh by live assessments. The ratings range from 0 (None) to 4 (Severe) with labels and descriptors to aid the investigator in the assessments. This assessment should be made while the subject is in the standing position with relaxed gluteus muscles at times outlined in the Schedule of Activities (Section 1.2). Each treatment area (each buttock and/or each thigh) will be assessed independently.

At screening, an Investigator who is a physician will use the appropriate CR-PCSS scale to assess the cellulite in all potential treatment areas (each buttock and each thigh) independently For subsequent visits only the areas receiving treatment (each buttock or each thigh) will be assessed.

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

8.1.2.3. Hexsel Cellulite Severity Scale

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

At screening, an Investigator who is a physician will use the Hexsel CSS to assess the cellulite in all potential treatment areas (each buttock and each thigh) independently. For subsequent visits only the areas receiving treatment (each buttock or each thigh) will be assessed. This assessment should be made while the subject is in the standing position with relaxed gluteus muscles.

8.2. Safety Assessments

All safety assessments will be performed at the times outlined in the Schedule of Activities (Section 1.2). Additional (unscheduled) safety assessments may be performed as needed.

8.2.1. Medical and Surgical History

Medical and surgical history will be obtained at the Screening Visit. Medical history will include a review of the following systems: general, dermatological, respiratory, cardiovascular, gastrointestinal, genitourinary, gynecological, endocrine, musculoskeletal, hematological, neuropsychological, immune (allergies), and head, eyes, ears, nose, and throat. Historical and

current medical conditions including date of last menstrual period for female subjects will be recorded. History of tobacco and alcohol use (never, current, former) will also be collected.

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

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

8.2.2. Physical Examination

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

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

8.2.3. Height and Weight

Height will be collected at screening only. Weight will be collected as outlined in the Schedule of Activities (Section 1.2). 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).

8.2.4. Fitzpatrick Skin Scale

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

8.2.5. Vital Signs

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

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

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

8.2.6. 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 QT prolongation with QTc ≥ 450 ms, the investigator should repeat the ECG within 1 hour. If the initial findings are confirmed, the investigator should exclude the subject from study participation.

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

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

Clinical laboratory tests will be conducted according to the Schedule of Activities (Section 1.2). Required clinical laboratory tests are outlined in Section 10.2. Clinical laboratory tests will be performed by a designated central laboratory. The site will be provided with instructions for specimen collection, preparation, packaging and transport. The results of the tests will be returned to the investigational site.

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

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

8.2.8. 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 (Section 1.2). Results must be available prior to protocol mandated study treatment and prior to MRIs. 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 the study and will have the pregnancy reported as per Section 8.3.5.

For all female subjects of childbearing potential, the subject's agreement to use contraception throughout their study participation (Screening Visit through Day 265, or for a minimum of

28 days after the last dose of study treatment for subjects who early terminate) will be documented.

8.2.9. Biopsy Follow-up Examination

The investigator will examine the biopsy site for evidence of ongoing AEs related to the biopsy and to determine if the biopsy site has healed at times specified in the Schedule of Activities (Section 1.2). The Day 85 and Day 265 Biopsy Follow-up Visits are not required for subjects who had less than 3 doses of study drug prior to 18 March 2020.

8.3. 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, and medically significant laboratory values 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.

8.3.1. 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 265 visit or for 28 days after the last study treatment for those who early terminate. For subjects who undergo the screening biopsy and are not subsequently dosed, AEs will be followed for 28 days after the biopsy. 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, including all medically significant and grade 4 labs, 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.

8.3.2. 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.

8.3.3. 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.

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

An investigator who receives an investigator safety report describing and 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.

8.3.5. 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 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 Pregnancy Form. Monitoring of the pregnancy should continue with 1 or more Pregnancy Form(s) detailing progress, and a Two-Month Follow-up Pregnancy Report Form detailing the outcome, should be submitted.

Pregnancy itself is not regarded as an AE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not considered AEs. Any SAEs associated with pregnancy (eg, congenital abnormalities/birth defects, 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 and withdrawn from the study.

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

8.3.6. 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.

8.3.7. 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.

8.4. 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.

8.5. Pharmacokinetics

Not applicable.

8.6. Pharmacodynamics

Prior to the first MRI and biopsy, the investigator will select 3 dimples from the 2 treatment areas (both buttocks or both thighs) for MRI and biopsy evaluation from the 4 well-defined, isolated dimples that are considered moderate or deep in depth identified at screening (see Section 5.1, Item 5). The 3 selected dimples should be distributed across both regions of the treatment area (eg, 1 dimple on the left thigh [or buttock] and 2 dimples on the right thigh [or buttock], or vice versa). The investigator or designee will mark and label these 3 dimples in a manner that will allow them to be relocated for subsequent MRIs and biopsies (see the Clinical Operations Study Manual for specific instructions). To ensure proper healing, the dimple biopsied at screening (Dimple 1) will not receive treatment with CCH. Dimple 2 and Dimple 3 will receive the entire CCH treatment course in this study.

8.6.1. MRI

MRIs of each of the 3 dimples selected for MRI and biopsy (Dimples 1, 2, and 3) will be performed on all subjects at times outlined in the Schedule of Activities (Section 1.2). Screening, Day 71, and Day 251 MRIs may be repeated as often as necessary to obtain an evaluable image. Repeat screening MRIs must take place within the screening window. MRIs must be completed prior to the required biopsies. Specific instructions for the MRI procedures will be provided in the Clinical Operations Study Manual.

All MRIs 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.

8.6.2. Double Punch Biopsy

Subjects will have a total of three 8 mm double punch biopsies done, 1 in each of the 3 dimples selected for MRI and biopsy (Dimples 1, 2, and 3) at the times outlined in the Schedule of Activities (Section 1.2). Detailed directions of the collection, processing, storage, handling and shipment of the biopsy samples will be provided in the Clinical Operations Study Manual. The investigator must examine and confirm sufficient healing of the biopsy site before dosing on Day 1.

Subjects who received all 3 doses of study drug prior to 18 March 2020 will have Day 71 and 251 biopsies, if willing to do so. Subjects who received less than 3 doses of study drug prior to 18 March 2020 will not have the Day 71 and Day 251 biopsies performed.

De-identified biopsy samples may be stored for a maximum of 5 years (or according to local regulations) following the last sample collection from the last subject last visit for the study at a facility selected by the sponsor to enable further analysis including to 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 intervention.

8.7. Genetics

Not applicable

8.8. Biomarkers

8.8.1. Immunogenicity Assessments

Serum samples will be collected at times outlined in the Schedule of Activities (Section 1.2) and will be tested for binding anti-AUX-I and anti-AUX-II antibody testing. When immunogenicity samples are required on a Treatment Day, the sample will be collected prior to study treatment administration. The samples also will be tested for neutralizing antibodies at times to be determined by the sponsor.

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

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

8.9. Medical Resource Utilization and Health Economics

Not applicable

9. STATISTICAL CONSIDERATIONS AND METHODS

9.1. Sample Size Determination

There was no formal sample size calculation for this study. A total of 12 subjects is considered sufficient to determine if biopsy will demonstrate changes in histopathology associated with CCH treatment while exposing the minimum number of subjects possible to the risks associated with this invasive procedure.

9.2. Populations for Analysis

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

- The Safety Population will include all subjects who have undergone the first (screening) biopsy.
- The Evaluable Population will include all subjects in the Safety Population who received their first dose of CCH in this study after 18 March 2020 and who had a baseline and at least 1 postinjection PR-PCSS evaluation.

9.3. Statistical Hypotheses and Analyses

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

9.3.1. Efficacy Analysis

The primary endpoint of change from baseline in PR-PCSS at Day 71 will be summarized by treatment area (left or right) and region (buttock or thigh) using appropriate descriptive statistics using the Evaluable Population.

All secondary and tertiary PR-PCSS, CR-PCSS, and Hexsel efficacy endpoints will be summarized by treatment area (left or right) and region (buttock or thigh) using appropriate descriptive statistics using the Evaluable Population.

9.3.2. MRI and Biopsy Analyses

A descriptive summary of changes from baseline seen in MRI and biopsy results will be provided for the Evaluable Population.

9.3.3. Safety Analyses

All subjects who have undergone the first biopsy during screening will be included in the safety analyses.

9.3.3.1. Adverse Events

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

9.3.3.2. Vital Signs and Laboratory Evaluations

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

9.3.4. Other Analyses

Anti-AUX-I and anti-AUX-II antibody levels will be summarized using descriptive statistics for the actual value at the visit. Samples from Day 1, Day 71, Day 161, and Day 251 visits will be analyzed for anti-AUX-I and anti-AUX-II antibodies and a subset of samples will be analyzed for neutralizing antibodies. Neutralizing antibody results, if tested, will be summarized as percentage of positive/negative.

9.4. Interim Analysis

An interim analysis will be conducted when at least 4 of the 12 subjects who received their first dose of study drug after 18 March 2020 have completed their Day 71 visit. For all subjects who received their first dose of study drug after 18 March 2020, analysis of all primary, secondary,

and tertiary endpoints will be included in the interim analysis. For the subjects who received all three doses prior to 18 March 2020, their MRI and biopsy data, if available, will be assessed separately but included in interim analysis. The purpose of the interim analysis is to determine if changes in morphology and/or histology can be identified using MRI and biopsy. If the interim analysis does not indicate that such changes can be identified, subsequent or additional MRIs or biopsies will not be performed in 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 CFR parts 50, 54, 56 and 312.

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

Approval by the IRB/IEC prior to the start of the study will be the responsibility of the investigator. A copy of approval documentation will be supplied to Endo. along with a roster of IRB/IEC members that demonstrates appropriate composition or other documentation of assurance of appropriate composition per local and national regulations (eg, a Department of Health and Human Services [DHHS] Assurance Number will satisfy this requirement for IRBs in the United States).

The study protocol, the ICF, advertisements, materials being provided to subjects, and amendments (if any) will be approved to IRB/IECs at each study center in conformance with ICH E6, CFR Title 21 Part 56, and any other applicable local laws. The investigator is responsible for supplying the IRB/IEC with a copy of the current Investigator's Brochure, Package Insert, or Summary of Product Characteristics, as well as any updates issued during the study. During the course of the study, the investigator will provide timely and accurate reports to the IRB/IEC on the progress of the study, at intervals not exceeding 1 year (or as appropriate), and will notify the IRB/IEC of SAEs or other significant safety findings, per the policy of the IRB/IEC. At the conclusion of the study, the investigator will submit a final report or close out report to the IRB/IEC and provide a copy to Endo.

Any amendment to this protocol will be provided to the investigator in writing by Endo. No protocol amendment may be implemented (with the exceptions noted below) before it has been approved by the IRB/IEC and the signature page, signed by the investigator, has been received by Endo. Where the protocol is amended to eliminate or reduce the risk to the subject, the amendment may be implemented before IRB/IEC review and approval. However, the IRB/IEC

must be informed in writing of such an amendment and approval obtained within reasonable time limits. Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the subject, and must be immediately reported to Endo.

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

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

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

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

10.1.7. Data Quality Assurance

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

The sponsor or its designee will utilize qualified monitors to review and evaluate activities conducted at investigator sites.

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

The study will be monitored and/or audited at intervals to ensure that the clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the study protocol, ICH E6 consolidated guidelines, and other applicable regulations. The extent, nature, and frequency of monitoring and/or audits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity, and

enrollment rate. At the conclusion of a program, a compliance statement will be generated by the sponsor (or designee) listing all audit activities performed during the clinical study.

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

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

10.1.8. Source Documents

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

Source documents include but are not limited to original documents, data and records such as hospital/medical records (including electronic health records), clinic charts, lab results, subject diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, etc. At a minimum, all data required to be collected by the protocol should have supporting source documentation for entries in the eCRF, unless the protocol specifies that data can be recorded directly on/in the eCRF or other device.

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

10.1.9. Study and Site Closure

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

10.1.10. Publication Policy

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

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

10.2. Appendix 2: Clinical Laboratory Tests

Table 3: Clinical Laboratory Tests

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

[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 pre-existing 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 pre-existing disease.
- All clinically relevant laboratory abnormalities or physical findings that occur during the study.

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

A SAE is defined as an AE that:

- Results in death
- Is immediately life-threatening (there is an immediate risk of death from the AE as it occurred; this does not include an AE that had it occurred in a more serious form may have caused death)
- Results in or prolongs an inpatient hospitalization (Note: a hospitalization for elective or preplanned surgery, procedure, or drug therapy does not constitute an SAE)
- Results in permanent or substantial disability (permanent or substantial disruption of one's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect (in offspring of a subject using the study medication regardless of time to diagnosis)
- Is considered an important medical event

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

10.3.2. Relationship to Study Drug

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

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

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

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

10.3.3. Intensity Assessment

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

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

10.3.4. Reporting Adverse Events and Serious Adverse Events

10.3.4.1. Reporting Adverse Events

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

All AEs will be collected by the investigator from the time of signing the informed consent through the Day 265 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 265 Visit, or 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 Day 265 or 28 days after the last dose of study medication in subjects who early terminate. SAEs that occur within 28 days following study treatment discontinuation, or within 28 days following withdrawal 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 reported via email (safety@endo.com) or fax (610-968-7135).

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 Serious Adverse Event (SAE)/Reportable Event 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 8.2.8.

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
DHHS	Department of Health and Human Services
ECG	Electrocardiogram
eCRF	Electronic case report form
EFP	Edematous fibrosclerotic panniculopathy
EGAL	Endo Global Aesthetics Limited
FDA	Food and Drug Administration
GCP	Good clinical practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
ID	Identification
IEC	Independent ethics committee
IND	Investigational new drug
INR	International normalized ratio
IRB	Institutional review board
IRT	Interactive response technology
MRI	Magnetic resonance imaging
PR-PCSS	Patient-reported Photonumeric Cellulite Severity Scale
QTc	Corrected QT interval
SAE	Serious adverse event
SUSAR	Suspected unexpected serious adverse reaction
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/Printed Name of Investigator

12. REFERENCES

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

Boyce S, Pabby A, Chuchaltkaren P, Brazzini B, Goldman MP. Clinical Evaluation of a Device for the Treatment of Cellulite: Triactive. *Am J Cosmet Surg*. 2005;22(4):233-7.

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

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

Food and Drug Administration. Guidance for Industry, Investigators, and Institutional Review Boards. FDA Guidance on Conduct of Clinical Trials of Medical Products During COVID-10 Public Health Emergency. March 2020 (updated 16 April 2020). Available at https://www.fda.gov/media/136238/download. Accessed 16 April 2020.

Hexsel DM, Abreu M, Rodrigues TC, Soirefmann M, do Prado DZ, Gamboa MM. Side-by-side comparison of areas with and without cellulite depressions using magnetic resonance imaging. *Dermatol Surg*. 2009;35(10):1471-7.

Hexsel D, Dal'Forno T, Hexsel C, Schilling-Souza J, Naspolini Bastos F, Siega C. Magnetic Resonance Imaging of Cellulite Depressed Lesions Successfully Treated by Subcision. *Dermatol Surg*. 2016; 42(5):693-6.

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

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

Mirrashed F, Sharp JC, Krause V, Morgan J, Tomanek B. Pilot study of dermal subcutaneous fat structures by MRI in individuals who differ in gender, BMI, and cellulite grading. *Skin Res Technol*. 2004(3);10:161-8.

Nürnberger F, Müller G. So-called cellulite: an invented disease. *J Dermatol Surg Oncol*. 1978;4(3):221-9.

Piérard GE, Nizet JL, Piérard-Franchimont C. Cellulite: from standing fat herniation to hypodermal stretch marks. *Am J Dermatopath*. 2000;22(1):34-7.

Querleux B, Cornillon C, Jolivet O, Bittoun J. Anatomy and physiology of subcutaneous adipose tissue by in vivo magnetic resonance imaging and spectroscopy: relationships with sex and presence of cellulite. *Skin Res Technol*. 2002;8(2):118-24.

Rudolph C, Hladik C, Hamade H, Frank K, Kaminer MS, Hexsel D, at al. Structural Gender Dimorphism and the Biomechanics of the Gluteal Subcutaneous Tissue: Implications for the Pathophysiology of Cellulite. *Plast Reconstr Surg*. 2019;143(4):1077–1086. doi: 10.1097/PRS.0000000000005407