Endo Pharmaceuticals Inc.
1400 Atwater Drive
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EN3835-213

A PHASE 2B, OPEN-LABEL STUDY TO EXPLORE TISSUE HISTOPATHOLOGY FOLLOWING SUBCUTANEOUS INJECTION OF COLLAGENASE CLOSTRIDIUM HISTOLYTICUM USING AN ABDOMINOPLASTY MODEL

Sponsor Name: Endo Pharmaceuticals Inc.

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

Regulatory Agency Identifier Number: IND 110077

Original Protocol: September 10, 2019

Protocol Amendment 1: October 14, 2019

Protocol Amendment 2: December 2, 2019

Protocol Amendment 3: January 16, 2020

Protocol Amendment 4: May 01, 2020

Confidentiality Statement

[redacted]

The sponsor of the application 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.

PROTOCOL AMENDMENT 4 SUMMARY OF CHANGES – CHANGES RELATED TO COVID-19 (MAY 01, 2020)

Amendment 4 was incorporated into the protocol on 01 May 2020. The major reason for this amendment was to modify the protocol due to the interruption of study conduct caused by the Coronavirus Disease 2019 (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 the primary concern. In addition, the integrity of data obtained from clinical trials must be ensured.

Endo initiated Study EN3835-213 enrolling the first subject in December 2019 with a total of 8 subjects. While 6 subjects completed the CCH dosing and planned abdominoplasty surgeries, 2 subjects in this study received their final CCH doses, but were not able to undergo surgery during the allowable surgery window determined by the sponsor (45 days from last CCH dose) due to COVID-19 delays in elective surgeries. The latest allowable surgery dates for these subjects were 27 April 2020 and 02 May 2020, however, surgeries were not able to be scheduled within this timeline.

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 enroll 2 additional subjects to replace the 2 subjects above (for overall objective and endpoint analysis purposes). The 2 subjects whose surgeries were delayed due to COVID-19 can, however, still undergo planned abdominoplasty surgery at a time convenient to both the investigator and the subject, and complete the study, but will be excluded from the non-safety analysis population. Subjects who are considered screen failures due to logistic/timing purposes surrounding the subject's availability for surgery (not including any other Inclusion/Exclusion criteria reasons) and/or COVID-19 restrictions, may be rescreened. Screening assessments and/or safety laboratory tests done within 28 days prior to (or as mandated in the protocol) the Day 1 Visit can be considered for screening purposes. In the case of subjects who have more than 28 days between initial screening and the Day 1 Visit, all screening assessments and/or safety labs will be repeated to confirm subject eligibility.

The specific sections of the protocol that are affected are outlined below:

1. Section 1.1 Synopsis, Study Period: Text "Estimated date first subject enrolled" changed from "Oct 2019" to "December 2019" and "The estimated date of the last subject completion" has been changed from "March 2020" and is now estimated for "September 2020."
2. Section 1.1 Synopsis, Overall Design: Text added "An additional 2 subjects will be enrolled to replace (for overall objective and endpoint analysis purposes) subjects whose abdominoplasty surgeries were delayed due to COVID-19 restrictions."
3. Section 1.1 Synopsis, Number of Subjects (planned): Text added: "Due to COVID-19 restrictions and impacts, an additional 2 subjects will be enrolled to replace (for overall objective and endpoint analysis purposes) subjects whose abdominoplasty surgeries were delayed due to COVID-19 restrictions. The 2 subjects whose surgeries were delayed due

to COVID-19 are still planned to complete the study. While the safety data of these subjects will be considered for safety analysis, the histopathology data of their abdominoplasty tissue specimens would be analyzed separately."

4. Section 1.1 Synopsis, Treatment Groups and Duration: Text changed from "~~8 subjects. The study is expected to enroll subjects over a 3 month period~~" changed to: "10 subjects." The following text was also added "With the addition of 2 replacement subjects the approximate duration of the study has been increased and is to be determined due to COVID-19 impacts."

5. Section 1.1 Synopsis, Treatment Groups and Duration and Section 4.1 Overall Design: Length of screening period changed from up to 14 days to up to 28 days.

6. Section 2.1 COVID-19 Public Health Emergency Impact, Text added "Endo initiated Study EN3835-213 enrolling the first subject in December 2019 with a total of 8 subjects. While 6 subjects completed the CCH dosing and planned abdominoplasty surgeries, 2 subjects in this study received their final CCH doses but were not able to undergo abdominoplasty surgery during the allowable surgery window as determined by the sponsor (45 days from last CCH dose) due to COVID-19 delays in elective surgeries. The latest allowable surgery dates for these subjects were 27 April 2020 and 02 May 2020.

   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 enroll 2 additional subjects to replace the 2 subjects above (for overall objective and endpoint analysis purposes). The 2 subjects whose surgeries were delayed due to COVID-19 can, however, still undergo planned abdominoplasty surgery at a time convenient to both the investigator and the subject, and complete the study. These 2 subjects will be included in safety analysis and the histopathology data of their tissue specimen will be analyzed separately."

7. Section 4.1 Overall Design, paragraphs 1 and 6: Text added "An additional 2 subjects will be enrolled to replace (for overall objective and endpoint analysis purposes) subjects whose abdominoplasty surgeries were delayed due to COVID-19 restrictions."

8. Section 4.1 Overall Design: Text added "Screening assessments and/or safety laboratory tests done within 28 days prior to (or as mandated in the protocol) the Day 1 Visit can be considered for screening purposes. In the case of subjects who have more than 28 days between initial screening and the Day 1 Visit, all screening assessments and/or safety labs will be repeated to confirm subject eligibility."

9. Section 5.4 Screen Failures, Text changed from "Subjects who are considered screen failures may not be rescreened." To "Subjects who are considered screen failures due to logistic/timing purposes surrounding the subject's availability for surgery (not including any other Inclusion/Exclusion criteria reasons) and/or COVID-19 restrictions, may be rescreened.

10. Section 5.4 Screen Failures, Text added "Screening assessments and/or safety laboratory tests done within 28 days prior to (or as mandated in the protocol) the Day 1 Visit can be considered for screening purposes. In the case of subjects who have more than 28 days

between initial screening and the Day 1 Visit, all screening assessments and/or safety labs will be repeated to confirm subject eligibility."

11. Section 9.1 Sample Size Determination, Text deleted "~~Approximately 15 subjects may be screened with 8 subjects being enrolled to receive CCH injection and undergo elective abdominoplasty.~~" Text changed from "Approximately 8 subjects will be enrolled in this study; namely, at least 1 subject each will be enrolled in Group 2…" changed to "Approximately 10 subjects will be enrolled to receive CCH injection and undergo elective abdominoplasty in this study, with at least 1 subject enrolled in Group 2…." Additional text added "An additional 2 subjects will be enrolled to replace (for overall objective and endpoint analysis purposes) subjects whose abdominoplasty surgeries were delayed due to COVID-19 restrictions."
12. Section 9.2 Populations for Analysis, Text added "The histopathology data of the 2 subjects whose abdominoplasty surgery was delayed due to COVID-19, will be analyzed separately."
13. Overall Changes: Other minor edits were made to correct punctuation and grammar.

PROTOCOL AMENDMENT 3 SUMMARY OF CHANGES (JANUARY 16, 2020)

The major reasons for this amendment were to: extend the screening period to allow for additional safety assessments, update version of investigator's brochure referenced, clarify how subjects are to be handled if safety laboratory results are unavailable prior to first dose of study treatment, revise handling temperature of study drug, clarify the handling of any remaining unused reconstituted study drug, clarify that providing breast milk in any form is not permitted, revise text to indicate more than 1 investigational site will be used, indicate that vital signs must be stable before the subject can leave direct observation following dosing, and revise the definition of adverse events.

1. Section 1.1, Synopsis, Treatment Groups and Duration. Text changed from "Total study duration for each subject is approximately 50 to 71 days depending on the group assigned (not including the screening period of up to 14 days)" to "Total study duration for each subject is approximately 50 to 71 days depending on the group assigned (not including the screening period of up to ~~14~~ **28** days)."
2. Section 1.1, Synopsis, Overall Design. Text changed from "Following a screening period of approximately 28 days, subjects will be assigned to 1 of 6 groups" to "Following a screening period of ~~approximately 14~~ **up to 28** days, subjects will be assigned to 1 of 6 groups."
3. Section 1.1, Synopsis, Treatment Groups and Duration. Text changed from "The duration of the study from first subject first visit to last subject last visit will be dependent on the ability of the site to identify and enroll eligible 8 subjects" to "The duration of the study from first subject first visit to last subject last visit will be dependent on the ability of the **investigative** sites to identify and enroll eligible 8 subjects."
4. Section 1.3, Schedule of Activities. Heading changed from "Screening Visit (14 Days)" to "Screening Visit (~~14~~ **28** days)."
5. Section 1.3, Schedule of Activities. Footnote b changed to include the following statement "**In the event that any safety laboratory testing results are unavailable prior to the subject's first dosing visit, the investigator will notify the sponsor to discuss on a case-by-case basis, prior to administering any study treatment to the subject.**"
6. Section 1.3, Schedule of Activities. Footnote a was added to Inclusion/exclusion criteria review. Footnote b was added to Clinical laboratory testing to reflect correct procedure.
7. Section 2.4.1, Product Background, Section 2.5, Risk/Benefit Assessment, and Section 12. Reference to Investigator Brochure updated from 2017 to the **2019** version.
8. Section 4.1, Overall Design. Text changed from "Subjects will be screened for study eligibility within 14 days prior to enrolling in this 6-group, multiple dose study" to "Subjects will be screened for study eligibility within ~~14~~ **28** days prior to enrolling in this 6-group, multiple dose study."

9. Section 4.1, Overall Design. Text changed from "Following a screening period of approximately 14 days, subjects will be assigned to 1 of 6 groups" to "Following a screening period of ~~approximately 14~~ **up to 28** days, subjects will be assigned to 1 of 6 groups."

10. Section 4.1, Overall Design. Text changed from "The duration of the study from first subject first visit to last subject last visit will be dependent on the ability of the site to identify and enroll eligible 8 subjects." to "The duration of the study from first subject first visit to last subject last visit will be dependent on the ability of the **investigative** sites to identify and enroll eligible 8 subjects."

11. Section 4.1, Overall Design. Text changed from "Total study duration for each subject is approximately 50 to 71 days depending on the group assigned (not including the screening period of up to 14 days)" to "Total study duration for each subject is approximately 50 to 71 days depending on the group assigned (not including the screening period of up to ~~14~~ **28** days)."

12. Section 5.1, Subject Inclusion Criteria. Text changed from "Be of nonchildbearing potential (history of hysterectomy, bilateral oophorectomy, bilateral tubal ligation, or postmenopausal with no history of menstrual flow in the 12 months prior to the Screening Visit); or, if of childbearing potential, be nonpregnant, nonlactating and agree to use effective contraception when with a male partner for the duration of the study" to "Be ~~of nonchildbearing potential (history of hysterectomy, bilateral oophorectomy, bilateral tubal ligation, or~~ postmenopausal **(of nonchildbearing potential)** with no history of menstrual flow in the 12 months prior to the Screening Visit); or, if of childbearing potential, be nonpregnant, nonlactating and agree to use effective contraception when with a male partner for the duration of the study."

13. Section 5.2 , Subject Exclusion Criteria. Text changed from "Is presently nursing or providing breast milk" to "Is presently nursing or providing breast milk **in any manner**."

14. Section 5.4, Screen Failures. Text changed from "The period from the start of screening related procedures at the Screening Visit to the first Dosing Visit must not exceed 14 days, inclusive of any repeat screening procedures" to "The period from the start of screening related procedures at the Screening Visit to the first Dosing Visit must not exceed ~~14~~ **28** days, inclusive of any repeat screening procedures."

15. Section 6.2, Study Drug Administration. Text changed from "The subject's vital signs should be stable before the subject can leave direct observation" to "The subject's vital signs ~~should~~ **must** be stable before the subject can leave direct observation."

16. Section 6.3, Study Treatment Preparation/Handling/Storage/Accountability. Text changed from "The investigator or designee will confirm that appropriate temperature control conditions have been maintained during transit for all study treatments received…" to "The investigator or designee will confirm that appropriate temperature control conditions have been maintained ~~during transit~~ for all study treatments received..."

Text changed from "Aliquots remaining from the hexagonal grid will be stored and returned to Endo or designee" to "~~Aliquots~~ **Any** remaining ~~from the hexagonal grid~~

~~technique~~ **unused reconstituted study drug** will be stored and returned to Endo or designee."

17. Section 8.1.6, Clinical Laboratory Determinations. Added the following text "**In the event that any safety laboratory testing results are unavailable prior to the subject's first dosing visit, the investigator will notify the sponsor to discuss on a case-by-case basis, prior to administering any study treatment to the subject.**"
18. Section 8.2, Adverse Events and Serious Adverse Events. Text changed from "This would include AEs resulting from concurrent illness, reactions to concurrent medication use, or progression of disease states (excluding the disease under study)" to "This would include AEs resulting from concurrent illness, reactions to concurrent medication use, or progression of disease states ~~(excluding the disease under study)~~."
19. Other minor edits were made to correct punctuation and grammar.

PROTOCOL AMENDMENT 2 SUMMARY OF CHANGES (DECEMBER 2, 2019)

The major reasons for this amendment were to 1) modify the study inclusion criteria to better reflect the abdominoplasty population and 2) to ensure that vital signs were collected after the subject had been sitting for at least 5 minutes.

1. Section 5.1 Subject Inclusion Criteria, revised Item 5, from "Have a body mass index (BMI) between $\geq$ 20.0 and $\leq$ 32.0 kg/m^2" to "Have a body mass index (BMI) $\geq$ 20.0 and $\leq$ 35.0 kg/m^2".
2. Section 1.3 Schedule of Activities- Footnote "d" and Section 8.1.4, Vital Signs - Added clarification that vital sign measurements should be taken after the subject has been sitting for 5 minutes.

   [d] Vital signs (blood pressure, respiratory rate, pulse rate, and body temperature) will be collected up to **2 hours prior** to dosing, at **30 minutes after** dosing, and also at **15 minutes after dosing (without body temperature)** on Days -43, -24, -22, -14, -3 and -1 at dosing visits. **All vital sign measurements should be taken after the subject has been sitting for 5 minutes.** Vital signs **must be stable** before the subject is discharged.

PROTOCOL AMENDMENT 1 SUMMARY OF CHANGES (OCTOBER 14, 2019)

Changes were made in the following sections of the original protocol to clarify entry criteria and make minor clarifications to the schedule of activities. The changes are as follows:

1. Section 1.3, Schedule of Activities, removed footnote 'e' from column heading for Day -30 through Day -1.
2. Section 1.3, Schedule of Activities, a new footnote (l) for anti-AUX-I/anti-AUX-II sample collection (Surgery Visit only) was added. The footnote reads:

   [1] Day 0 samples for anti-AUX-I, anti-AUX-II, and neutralizing antibodies may be collected as part of the standard of care presurgical visit that is nearest to the scheduled date of the abdominoplasty procedure (after dosing visits are completed).
3. Section 5.1 Subject Inclusion Criteria, revised Item 4, from "Be female and ≥18 years of age and ≤ 40 years of age at time of informed consent," to "Be female and ≥18 years of age and ≤ 55 years of age at time of informed consent."
4. Section 5.1 Subject Inclusion Criteria, revised Item 5, from "Have a body mass index (BMI) ≥ 20.0 to 32.0 kg/m^2," to "Have a body mass index (BMI) between ≥ 20.0 and ≤ 32.0 kg/m^2."
5. Section 6.1 Selecting and Marking of Treatment Area, revised the time of treatment area marking and photography from each dosing visit and Day 0 (Day of surgery) to each dosing visit.
6. Section 6.1 Selecting and Marking of Treatment Area, revised the description of marking of the treatment area to include a temporary tattoo, ie, changed "…after marking the treatment area and the injection site with a surgical marker (but prior to CCH dosing or the abdominoplasty procedure)…" to "…after marking the treatment area and the injection site with a surgical marker and a temporary tattoo (but prior to CCH dosing or the abdominoplasty procedure)…"
7. Section 6.1 Selecting and Marking of Treatment Area, added a second sentence to the second paragraph:

   On Day of Surgery (Day 0), prior to abdominoplasty procedure, the borders of the treatment area will be marked with a surgical marker. Following marking, the treatment areas will then be photographed while the subject is in a standing pose (as previously described).

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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 2b, Open-Label Study to Explore Tissue Histopathology Following Subcutaneous Injection of Collagenase Clostridium Histolyticum Using an Abdominoplasty Model	
Lead Principal Investigator: Not applicable	
Study period: Estimated date first subject enrolled: December 2019 Estimated date last subject completed: September 2020	**Phase of development:** 2b

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the histopathology and immunohistochemistry of subcutaneous tissue isolated after single and multiple CCH doses with both a [redacted] single injection technique and [redacted] (relative to control, non-dosed tissue) in adult female subjects undergoing abdominoplasty.	• The primary endpoint will be the change in histopathology and immunohistochemistry of tissue dosed with CCH relative to control tissue (tissue not dosed with CCH). ○ [redacted] single injection technique: ▪ Area 1 tissue relative to control for all groups. ▪ Area 2 tissue relative to control for all groups. ○ [redacted]: ▪ Area 1 tissue relative to control for all groups. ▪ Area 2 tissue relative to control for all groups.
Secondary	
• To compare the histopathology and immunohistochemistry of tissue from treatment areas dosed with CCH in adult women undergoing elective abdominoplasty surgery. ○ Multiple doses versus single dose with a [redacted] single injection technique.	• The change in histopathology and immunohistochemistry of tissue samples dosed with CCH multiple times relative to tissues dosed with CCH a single time with a [redacted] injection technique. ○ Area 1 tissues relative to Area 2 for all groups.

○ Multiple doses versus single dose with a [redacted]. ○ Multiple doses with a [redacted] versus multiple doses with a [redacted] single injection technique. ○ Single dosing with a [redacted] versus single dosing with a [redacted] single injection technique.	• The change in histopathology and immunohistochemistry of tissue samples dosed with CCH multiple times relative to tissue dosed with CCH a single time with a [redacted] injection technique. ○ Area 1 tissues relative to Area 2 for all groups. • The change in histopathology and immunohistochemistry of tissue samples dosed with CCH multiple times with a [redacted] single injection technique relative to tissues dosed with CCH multiple times with a [redacted] technique. • The change in histopathology and immunohistochemistry of tissue samples dosed with CCH a single time with a [redacted] single injection technique relative to tissues dosed with CCH a single time with a [redacted] technique.
• To assess the safety and immunogenicity of CCH injected in adult women undergoing an elective abdominoplasty surgery.	• Treatment-emergent adverse events (TEAEs). • Adverse events of special interest (AESI). • Anti-AUX-I antibodies, anti-AUX-II antibodies, and neutralizing antibodies analysis.

Overall Design:

This study is a Phase 2b, open-label, exploratory study of the mechanism of action of bruising and safety of CCH subcutaneously administered in subjects undergoing elective abdominoplasty surgery. Subjects will be screened for study eligibility within 28 days prior to enrolling in this 6-group, multiple dose study. Approximately 8 subjects (1 or 2 subjects per group) are expected to enroll and complete the study (on Day 28). An additional 2 subjects will be enrolled to replace (for overall objective and endpoint analysis purposes) subjects whose abdominoplasty surgeries were delayed due to COVID-19 restrictions. Subjects who undergo elective abdominoplasty surgery and are willing to receive injections of CCH and have their tissue donated for evaluation (otherwise discarded post-surgery) will be eligible, provided all inclusion/exclusion criteria are met.

The study will be conducted in adherence to 3 main activities as follows:

1. Dosing: CCH injections as defined in this protocol.
2. Abdominoplasty: Aesthetic surgery for the permanent removal/excision of abdominal tissue.
3. Histopathology and immunohistochemistry of the excised abdominal tissue.

Following a screening period of up to 28 days, subjects will be assigned to 1 of 6 groups. Each subject will have 2 marked areas (Area 1 and Area 2) of the abdomen dosed with CCH (single or multiple doses) plus a marked non-dosed control area for comparison. The control area will be located between the 2 treatment areas. By the end of the dosing phase, Treatment Area 1 will receive a total of 2 doses (referred to as multiple doses in the objectives) at specified study visits for the group assigned, and Treatment Area 2 will receive a total of 1 dose (referred to as single dose in the objectives) at specified study visits for the group assigned. Refer to the study schema in Section 1.2 for additional details.

Disclosure Statement: This is an open-label exploratory study with 6 dosing arms. The pathologist reporting the results will be blinded to the dosing schedule.

Number of Subjects (planned):

It was originally planned that 8 subjects (1 or 2 subjects per group) enroll and complete the study. Due to COVID-19 restrictions and impacts, an additional 2 subjects will be enrolled to replace (for overall objective and endpoint analysis purposes) subjects whose abdominoplasty surgeries were delayed due to COVID-19 restrictions. The 2 subjects whose surgeries were delayed due to COVID-19 are still planned to complete the study. While the safety data of these subjects will be considered for safety analysis, the histopathology data of their abdominoplasty tissue specimens would be analyzed separately.

Treatment Groups and Duration:

Subjects in each group will receive up to 3 CCH doses (each dose as either a [redacted] single injection technique or a [redacted]) across 2 treatment areas at the following dosing visits:

Group 1 and Group 4 (n = 2 subjects/group): Dosing on Days -43 and -22, and -14.

Group 2 and Group 5 (n = 1 subject/group): Dosing on Days -24 and -3.

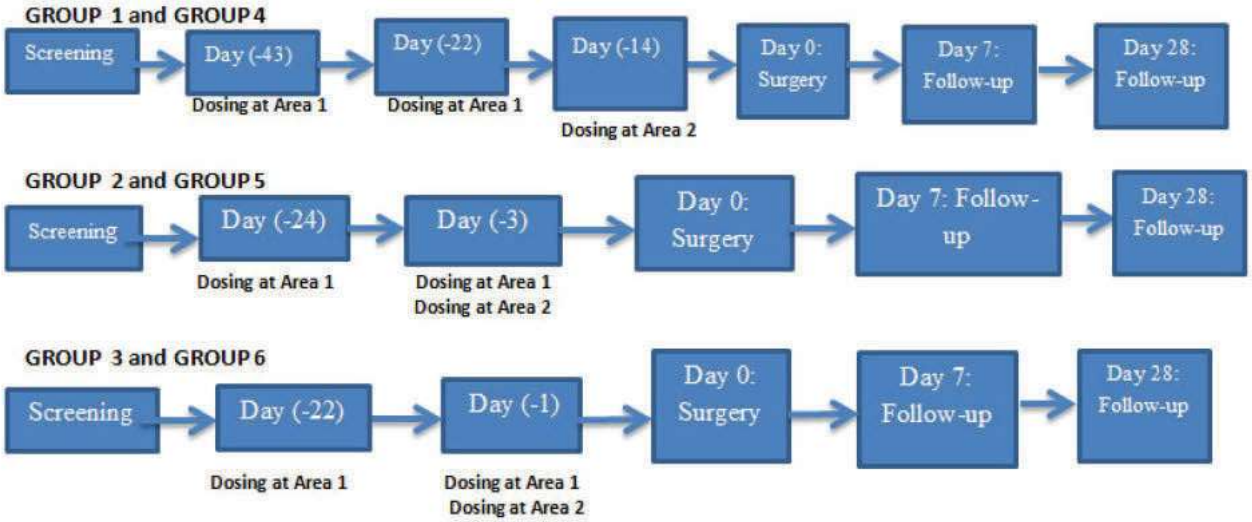
Group 3 and Group 6 (n = 1 subject/group): Dosing on Days -22 and -1.

At each dosing visit, the CCH injection dose administered per treatment area (Area 1 or Area 2) is approximately 0.07 mg CCH/0.3 mL (administered subcutaneously as [redacted] of [redacted] mL each in a single injection technique in Group 1, Group 2, and Group 3) or approximately 0.07 mg CCH/1.5 mL (administered subcutaneously as [redacted] of approximately [redacted] mL each in a [redacted] in Group 4, Group 5, and Group 6). Following administration of 3 doses of CCH, abdominoplasty and collection of the excised abdominal tissue will occur on Day 0. Subjects will be followed for safety until 28 days post-surgery.

The duration of the study from first subject first visit to last subject last visit will be dependent on the ability of the investigative sites to identify and enroll eligible 10 subjects. Total study duration for each subject is approximately 50 to 71 days depending on the group assigned (not including the screening period of up to 28 days). With the addition of 2 replacement subjects due to COVID-19, the approximate duration of the study has been increased and is to be determined due to COVID-19 impacts.

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

1.2. Study Schema



Group 1 and Group 4: Dosing on Days -43 and -22, and -14.

Group 2 and Group 5: Dosing on Days -24 and -3.

Group 3 and Group 6: Dosing on Days -22 and -1.

Treatment areas of each subject group will be marked: Treatment Area 1 and Treatment Area 2.

By the end of the dosing phase:

- Treatment Area 1 will receive a total of 2 doses (referred to as multiple doses in the objectives) at specified study visits for the group assigned.
- Treatment Area 2 will receive a total of 1 dose (referred to as single dose in the objectives) at specified study visits for the group assigned.

1.3. Schedule of Activities

Procedures	Screening Visit (28 days)	*Dosing Visit* Groups 1 and 4: Day -43, Day -22 (±2 days) Groups 2 and 5: Day -24 (±2 days) Groups 3 and 6: Day -22 (±2 days)	*Dosing Visit* Groups 1 and 4: Day -14 (±2 days) Groups 2 and 5: Day -3 (-2 days) Group 3 and 6: Day -1 (-1 day)	Day -30 through Day -1	*Surgery Visit* All Groups: Day 0 (Day of Abdominoplasty)	All Groups: Day 7 Post-surgery follow-up visit (±3 day)	All Groups: Day 28 Post-surgery follow-up visit/ EOS/Early Termination visit (±3 days)
Informed consent[a]	X						
Inclusion/exclusion criteria review[a,b]	X	X	X	X			
Medical history (including previous medications/ procedures/surgery/obstetrics)	X						
Prior/concomitant medications/procedures	X	X	X	X	X	X	X
Physical Examination	X				X[c]	X	X
Height, weight, BMI confirmation	X						
Vital signs	X	X[d]	X[d]	X	X	X	X
Clinical laboratory testing[b,e]	X			X[f]			
Anti-AUX-I/anti-AUX-II antibody level sample collection and processing[g]	X				X[i]		X
Medical clearance for surgery	X			X			
Serum pregnancy testing	X[h]						
Urine pregnancy testing		X	X		X		X

Procedures	Screening Visit (28 days)	*Dosing Visit* Groups 1 and 4: Day -43, Day -22 (±2 days) Groups 2 and 5: Day -24 (±2 days) Groups 3 and 6: Day -22 (±2 days)	*Dosing Visit* Groups 1 and 4: Day -14 (±2 days) Groups 2 and 5: Day -3 (-2 days) Group 3 and 6: Day -1 (-1 day)	Day -30 through Day -1	*Surgery Visit* All Groups: Day 0 (Day of Abdominoplasty)	All Groups: Day 7 Post-surgery follow-up visit (±3 day)	All Groups: Day 28 Post-surgery follow-up visit/ EOS/Early Termination visit (±3 days)
Marking and labeling the site of injection (treatment and control) with surgical marker (Treatment Area 1, Non-injected Control Area, and Treatment Area 2)		X	X		X		
Digital Photography[i]		X	X		X		
CCH injection (approximately 0.07 mg) at Area 1		X[j]	X[j]				
CCH injection (approximately 0.07 mg) at Area 2			X[j]				
Abdominoplasty procedure					X		
Tissue excision and handling procedures for shipment					X		
Injection site evaluation (ie, adverse reactions/local tolerability in treatment areas)[k]		X	X		X		
All other adverse events	X	Monitored Throughout Study					

Note: AUX-I = Clostridial class I collagenase, AUX-II = Clostridial class II collagenase, ECG = Electrocardiogram, EOS = End of Study
Note: Unless otherwise stated above or outlined below (and with the exception of injection site reactions/local tolerability in the area treated), all assessments should be completed **prior** to study treatment administration on Treatment Days.
[a] Performed prior to any study-required assessments.
[b] Laboratory safety testing will be performed at the investigative site or designated laboratory, as part of the standard of care (hematology, biochemistry, ECG, etc) of the subject's preparation for elective abdominoplasty as deemed required by the investigator. These testing results will be assessed for inclusion/exclusion

criteria by the investigator. All inclusion/exclusion criteria should be reassessed and verified **prior** to the first dose of study treatment. In the event that any safety laboratory testing results are unavailable prior to the subject's first dosing visit, the investigator will notify the sponsor to discuss on a case-by-case basis, prior to administering any study treatment to the subject.

[c] Physical examination performed prior to surgery.

[d] Vital signs (blood pressure, respiratory rate, pulse rate, and body temperature) will be collected up to **2 hours prior** to dosing, at **30 minutes after** dosing, and also at **15 minutes after dosing (without body temperature)** on Days -43, -24, -22, -14, -3, and -1 at dosing visits. **All vital sign measurements should be taken after the subject has been sitting for 5 minutes**. Vital signs **must be stable** before the subject is discharged.

[e] Any clinical post-operative laboratory testing may be performed post-surgery through Day 28 as deemed necessary by the investigator.

[f] Subjects in **Group 1 and Group 4** may undergo additional clinical laboratory safety testing as standard of care (hematology, biochemistry, ECG, etc) as part of additional preparation for abdominoplasty surgery (as well as any additional subjects, as deemed necessary, by the investigator).

[g] Samples from Screening will be analyzed for anti-AUX-I and anti-AUX-II antibodies; samples from Day 0 and Day 28 Follow-up (EOS/Early Termination) visits will be analyzed for anti-AUX-I antibodies, anti-AUX-II antibodies, and neutralizing antibodies.

[h] Serum pregnancy testing results must be reviewed by the investigator **prior** to the first dose of study treatment.

[i] All photographs should be taken after marking the treatment and control areas with a surgical marker, but prior to CCH injection or abdominoplasty surgery. No manipulation of the treatment or control areas should be done prior to the photographs being taken.

[j] Treatment Area 1 in Group 1 and Group 4 will receive the first treatment on Day -43 and the second treatment on Day -22 (Note: for Group 1 and Group 4, treatment on Day -14 will occur in Treatment Area 2 NOT in Treatment Area 1). (Please see **Study Schema Section** 1.2).

[k] Local AEs associated with the injection site, including acute (eg, erythema, bruising, pain, nodules/mass, ulceration, blistering, pruritus, swelling, and/or induration) and/or chronic (eg, skin thickening, fibrosclerosis, and peau d'orange changes) cutaneous AEs, will be recorded and evaluated for seriousness and severity.

[l] Day 0 samples for anti-AUX-I, anti-AUX-II, and neutralizing antibodies may be collected as part of the standard of care presurgical visit that is nearest to the scheduled date of the abdominoplasty procedure (after dosing visits are completed).

2. INTRODUCTION

2.1. COVID-19 Public Health Emergency Impact

Endo initiated Study EN3835-213 enrolling the first subject in December 2019 with a total of 8 subjects. While 6 subjects completed the CCH dosing and planned abdominoplasty surgeries, 2 subjects in this study received their final CCH doses but were not able to undergo abdominoplasty surgery during the allowable surgery window as determined by the sponsor (45 days from last CCH dose) due to COVID-19 delays in elective surgeries. The latest allowable surgery dates for these subjects were 27 April 2020 and 02 May 2020.

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 enroll 2 additional subjects to replace the 2 subjects above (for overall objective and endpoint analysis purposes). The 2 subjects whose surgeries were delayed due to COVID-19 can, however, still undergo planned abdominoplasty surgery at a time convenient to both the investigator and the subject and complete the study. These 2 subjects will be included in safety analysis and the histopathology data of their tissue specimen will be analyzed separately.

2.2. Introduction to Study

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.

2.3. Study Rationale

CCH dose administration in buttocks or thighs with cellulite has shown to deliver an aesthetic improvement in the treated area. Endo studied the safety and efficacy of CCH 0.84 mg dose per treatment area (1 buttock or 1 thigh) in multiple Phase 2 and Phase 3 studies. In these studies, up to 12 cellulite dimples per treatment area (1 buttock or 1 thigh) were injected in each subject in 1 treatment session, and the approximate dose per dimple was 0.07 mg CCH. The efficacy results from these studies, based on improvement in cellulite severity as determined by the investigator and the subject, have consistently shown that CCH 0.84 mg dose per treatment area is an effective treatment for cellulite in buttocks or thighs. In addition, the safety and immunogenicity profile of CCH has been consistent across all these studies.

The majority of adverse events (AEs) occurred at the site of injection and resolved before the next scheduled treatment in these studies. Among the injection site reactions observed across these studies, the most common was injection site bruising. Injection site bruising observed in the clinical studies was self-limiting and predominately mild-to-moderate in severity. However, there was no histopathology examination of the injection site bruise area.

Tissue samples isolated from subjects undergoing an elective abdominoplasty procedure offer an opportunity to observe histopathological structure changes of tissues post treatment with CCH.

The histostain or microscopic examination of biological tissues may reveal the appearance of tissues in greater detail and bring better understanding of CCH treatment effect on tissue structure.

This study (EN3835-213) is an exploratory investigation to learn and compare the histopathology and immunohistochemistry changes, if any, in the subcutaneous tissue and surrounding area after single and multiple CCH injections of the abdomen across different time points. The abdominal area injected with CCH will be within the area targeted for excision during abdominoplasty.

2.4. Background

2.4.1. Product 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 edematous fibrosclerotic panniculopathy (EFP), commonly known as cellulite, Endo Pharmaceuticals Inc. (Endo) has developed a novel formulation of EN3835, referred to hereafter as CCH, with a different concentration and volume than the approved EN3835 formulation.

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

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

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

all previous studies, CCH has demonstrated an acceptable safety and immunogenicity profile. The majority of AEs occurred at the site of injection, were mild to moderate in nature, and often resolved within 2 to 3 weeks without any sequelae.

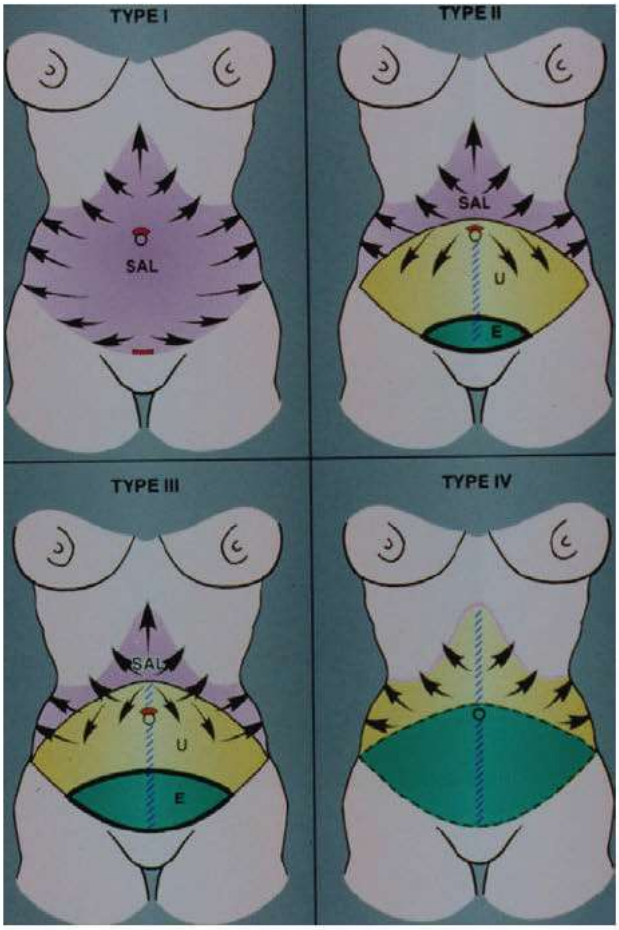
A detailed description of the chemistry, pharmacology, efficacy, and safety of CCH is provided in the Investigational Brochure (IB) (Endo, 2019).

2.4.2. Medical Procedure Background

The origins of abdominal and body contouring procedures emanate from the earliest awareness of self. In the late 1800s, abdominal wall surgeries were performed to address disfigurements and deformities of skin, fat, and the musculofascial system, which were attributed to scars, injuries, or defects. However, the modern history of abdominoplasty can be traced to the late 1960s and 1970s when it was accepted as an aesthetic procedure commonly performed to eliminate excess skin and fat accumulation in the abdominal area (Matarasso, 1991).

Suction-assisted lipectomy was developed in the 1980s, and subsequently a collective group of abdomen contour procedures, referred as abdominolipoplasty, which combined the liposuction with modifications in traditional abdominoplasty techniques became available. In 1989, Matarasso came up with general guideline to organize an approach to abdominolipoplasty surgeries based on the evaluation of skin, fat and, the musculofascial system (diagramed in Figure 1). In 2018, more than 130,000 abdominoplasty procedures were performed in the United States, making abdominoplasty among the top 5 cosmetic surgery procedures in the United States. Compared to the approximately 62,000 procedures performed in 2000, abdominoplasty has increased in popularity by 107 percent (ASPS, 2019).

Figure 1: The Abdominolipoplasty System of Classification and Treatment



- Type I: Liposuction alone
- Type II: Mini abdominoplasty
- Type III: Modified abdominoplasty
- Type IV: Full standard abdominoplasty with or without liposuction

Abbreviations: SAL, suction-assisted lipectomy.
Pink arrows = liposuction; yellow = undermining; green = excision; cross-hatching = fascial plication.
Matarasso, 2010.

2.5. 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. AEs reported to date in the completed Phase 3 trials of CCH for the treatment of EFP in the buttocks have been consistent with previously reported AEs in the studies to date.

More detailed information about the known and expected benefit, risks, and reasonably expected AEs can be found in the IB (Endo, 2019).

All procedures and activities in this study (except for CCH study drug administration, digital photography, and immunogenicity testing) are generally accepted as standard-of-care for patients undergoing abdominoplasty and do not present any increased risk to the subjects.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the histopathology and immunohistochemistry of subcutaneous tissue isolated after single and multiple CCH doses with both a [redacted] single injection technique and [redacted] (relative to control, non-dosed tissue) in adult female subjects undergoing abdominoplasty.	• The primary endpoint will be the change in histopathology and immunohistochemistry of tissue dosed with CCH relative to control tissue (tissue not dosed with CCH). o [redacted] single injection technique: ▪ Area 1 tissue relative to control for all groups. ▪ Area 2 tissue relative to control for all groups. o [redacted] ▪ Area 1 tissue relative to control for all groups. ▪ Area 2 tissue relative to control for all groups.
Secondary	
• To compare the histopathology and immunohistochemistry of tissue from treatment areas dosed with CCH in adult women undergoing elective abdominoplasty surgery. o Multiple doses versus single dose with a [redacted] single injection technique.	• The change in histopathology and immunohistochemistry of tissue samples dosed with CCH multiple times relative to tissues dosed with CCH a single time with a [redacted] injection technique. o Area 1 tissues relative to Area 2 for all groups.

○ Multiple doses versus single dose with a [redacted]. ○ Multiple doses with a [redacted] versus multiple dose with a [redacted] single injection technique. ○ Single dosing with a [redacted] versus single dosing with a [redacted] single injection technique.	• The change in histopathology and immunohistochemistry of tissue samples dosed with CCH multiple times relative to tissue dosed with CCH a single time with a [redacted] injection technique. ○ Area 1 tissues relative to Area 2 for all groups. • The change in histopathology and immunohistochemistry of tissue samples dosed with CCH multiple times with a [redacted] single injection technique relative to tissues dosed with CCH multiple times with a [redacted] technique. • The change in histopathology and immunohistochemistry of tissue samples dosed with CCH a single time with a [redacted] single injection technique relative to tissues dosed with CCH a single time with a [redacted] technique.
• To assess the safety and immunogenicity of CCH injected in adult women undergoing an elective abdominoplasty surgery.	• Treatment-emergent adverse events (TEAEs). • Adverse events of special interest (AESI). • Anti-AUX-I antibodies, anti-AUX-II antibodies, and neutralizing antibodies analysis.

The primary objective will be met if histopathology and immunohistochemistry findings in the excised abdominal tissues dosed with CCH demonstrate change from histopathology and immunohistochemistry findings in non-dosed control tissue.

4. STUDY DESIGN

4.1. Overall Design

This study is a Phase 2b, open-label, exploratory study of the mechanism of action of bruising and safety of CCH subcutaneously administered in subjects undergoing elective abdominoplasty surgery. Subjects will be screened for study eligibility within 28 days prior to enrolling in this 6-group, multiple dose study. Approximately 8 subjects (1 or 2 subjects per group) were originally expected to enroll and complete the study (on Day 28). An additional 2 subjects will

be enrolled to replace (for overall objective and endpoint analysis purposes) subjects whose abdominoplasty surgeries were delayed due to COVID-19 restrictions. Subjects who undergo elective abdominoplasty surgery and are willing to receive injections of CCH and have their tissue donated for evaluation (otherwise discarded post-surgery) will be eligible, provided all inclusion/exclusion criteria are met. Screening assessments and/or safety laboratory tests done within 28 days prior to (or as mandated in the protocol) the Day 1 Visit can be considered for screening purposes. In the case of subjects who have more than 28 days between initial screening and the Day 1 Visit, all screening assessments and/or safety labs will be repeated to confirm subject eligibility.

The study will be conducted in adherence to 3 main activities as follows:

1. Dosing: CCH injections as defined in this protocol.
2. Abdominoplasty: Aesthetic surgery for the permanent removal/excision of abdominal tissue.
3. Histopathology and immunohistochemistry of the excised abdominal tissue.

Following a screening period of up to 28 days, subjects will be assigned to 1 of 6 groups. An additional 2 subjects will be enrolled to replace (for overall objective and endpoint analysis purposes) subjects whose abdominoplasty surgeries were delayed due to COVID-19 restrictions. Each subject will have 2 marked areas (Area 1 and Area 2) of the abdomen dosed with CCH (single or multiple doses) plus a marked non-dosed control area for comparison. The control area will be located between the 2 treatment areas. By the end of the dosing phase, Treatment Area 1 will receive a total of 2 doses (referred to as "multiple doses" in the objectives) at specified study visits for the group assigned, and Treatment Area 2 will receive a total of 1 dose (referred to as "single dose" in the objectives) at specified study visits for the group assigned. Refer to the study schema in Section 1.2 for additional details.

Subjects in each group will receive up to 3 CCH doses (each dose as either a [redacted] single injection technique or a [redacted] across 2 treatment areas at the following dosing visits:

Group 1 and Group 4 (n = 2 subjects/group): Dosing on Days -43 and -22, and -14.

Group 2 and Group 5 (n = 1 subject/group): Dosing on Days -24 and -3.

Group 3 and Group 6 (n = 1 subject/group): Dosing on Days -22 and -1.

At each dosing visit, the CCH injection dose administered per treatment area (Area 1 or Area 2) is approximately 0.07 mg CCH/0.3 mL (administered subcutaneously as 3 aliquots of [redacted] mL each in a single injection technique in Group 1, Group 2, and Group 3) or approximately 0.07 mg CCH/1.5 mL (administered subcutaneously as [redacted] of approximately [redacted] mL each in a [redacted] in Group 4, Group 5, and Group 6). Following administration of 3 doses of CCH, abdominoplasty and collection of the excised abdominal tissue will occur on Day 0. Subjects will be followed for safety until 28 days post-surgery.

The duration of the study from first subject first visit to last subject last visit will be dependent on the ability of the investigative sites to identify and enroll eligible 10 subjects. Total study duration for each subject is approximately 50 to 71 days depending on the group assigned (not including the screening period of up to 28 days). With the addition of 2 replacement subjects due

to COVID-19, the approximate duration of the study has been increased and is to be determined due to COVID-19 impacts.

4.2. Scientific Rationale for the Study Design

This is an open-label exploratory study to support ongoing clinical research of CCH in EFP.

Subjects undergoing an abdominoplasty procedure are ideal for this clinical study as it facilitates the histopathological evaluation of the excised tissue previously exposed to the investigational product via histopathology assessment.

4.3. Justification for Dose

The results from the Phase 2b study (EN3835-201) suggested that CCH 0.84 mg per treatment area (1 buttock or 1 thigh) is safe and effective. The Phase 3 studies (EN3835-302 and EN3835-303) showed a similar safety profile with most AEs being mild to moderate in severity and transient. Across all previous studies, CCH has demonstrated an acceptable safety and immunogenicity profile. In these studies, up to 12 cellulite dimples per treatment area (1 buttock or 1 thigh) were injected in each subject in one treatment session, and the approximate dose per dimple was 0.07 mg CCH. Therefore, approximately 0.07 mg per dose will be used in this study.

4.4. End of Study Definition

A subject is considered to have completed the study if the subject has completed the Day 28 post-surgical follow-up visit.

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

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1. Subject Inclusion Criteria

In order to be eligible to participate in the study, at the Screening Visit and each Dosing Visit (according to the Schedule of Activities), subjects must:

1. 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.
2. Be undergoing planned elective abdominoplasty.
3. Be willing to have their tissue donated for evaluation.
4. Be female and $\geq$ 18 years of age and $\leq$ 55 years of age at time of informed consent.
5. Have a body mass index (BMI) between $\geq$ 20.0 and $\leq$ 35.0 kg/m^2.
6. Be willing to apply sunscreen to the abdomen before each exposure to the sun while participating in the study (ie, Screening through Day 28 End of Study/Early Termination Visit).

7. Be judged to be in good health, based upon the results of a medical history, physical examination, and any standard of care laboratory profile available at Screening.
8. Be postmenopausal (of nonchildbearing potential) with no history of menstrual flow in the 12 months prior to the Screening Visit); or, if of childbearing potential, be nonpregnant, nonlactating and agree to use effective contraception when with a male partner for the duration of the study. Acceptable forms of contraception include hormonal measures (oral contraceptive pills, contraceptive patch, contraceptive ring, or injections), intrauterine devices, double barrier method (condom plus diaphragm, condom or diaphragm plus spermicidal gel or foam), surgical sterilization of the male partner, and abstinence.
9. Have a negative serum pregnancy test at screening and a negative urine pregnancy prior to the first dose of study drug.
10. Be willing and able to cooperate with the requirements of the study.

5.2. Subject Exclusion Criteria

A subject is ineligible for study participation if, at the Screening Visit and prior to injection of study drug, 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 any of the following systemic conditions:
    a. Coagulation disorder.
    b. Evidence or history of malignancy (other than excised basal-cell carcinoma) unless there has been no recurrence in at least 5 years.
    c. History of keloidal scarring or abnormal wound healing.
    d. Concurrent diseases or conditions that might interfere with the conduct of the study, confound the interpretation of the study results, or endanger the subject's well-being. Any questions about concurrent diseases should be discussed with the Sponsor Medical Monitor.
    e. Evidence of clinically significant abnormalities observed/recorded on physical examination, vital signs, clinical laboratory values at screening and/or during pre-surgery preparation at site (including electrocardiogram [ECG], laboratory, etc).
3. Has any of the following local conditions in the areas to be treated:
    a. History of lower extremity thrombosis or post-thrombosis syndrome.
    b. Vascular disorder (eg, telangiectasia) in area to be treated.
    c. Inflammation or active infection.
    d. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer within last 5 years.

e. Has a tattoo and/or a mole located within 2 cm of the site of injection.

4. Requires the following concomitant medications before or during participation in the trial:
   a. Anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication 7 days prior to injection with study drug (CCH) (except for ≤ 150 mg aspirin daily, permitted only within a window-specific timeframe as determined by the investigator prior to abdominoplasty surgery).
5. Has history of any abdominal surgery, including but not limited to: liposuction, caesarean section, appendectomy, cholecystectomy, or umbilical hernia repair.
6. Has used any of the following within the timelines as identified below OR has used/intends to use any of the following:
   a. Injections (eg, mesotherapy), radiofrequency device treatments, laser treatment, cryolipolysis, or surgery (including subcision and/or powered subcision) within the abdominal area during the 18-month period before injection of study drug.
   b. Any investigational treatment in the abdominal area during the 12-month period before injection of study drug.
   c. CoolSculpting® or similar treatments of the abdomen during the 18-month period before injection of study drug.
   d. Deep massage therapy (such as Endermologie™) or similar therapy, within the abdominal area during the 6 month period before injection of study drug.
   e. Creams (eg, Celluvera™, TriLastin®) and/or home therapies within the abdominal area during the 2-week period before injection of study drug and at any time during the course of the study.
   f. Bath/shower salts or sugar/salt scrubs, lotions, loofahs, or other exfoliating products on the abdominal area during the 2 week period prior to injection of study drug and at any time during the course of the study.
7. Is presently nursing or providing breast milk in any manner.
8. Intends to become pregnant during the study.
9. Intends to initiate an intensive sport or exercise program regimen during the study.
10. Intends to use any tanning spray or tanning booths during the study.
11. Has received any investigational drug or treatment within 30 days prior to first injection of study drug.
12. Has a known systemic allergy to collagenase or any other excipient of study drug.
13. Has received any collagenase treatment at any time prior to treatment in this study.
14. Has a medical history of being treated with (or has received) CCH or XIAFLEX®.
15. Has been known to have syncope.
16. 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 exclusion criteria (Section 5.2).

5.4. Screen Failures

Screen failures are defined as subjects who consent to participate in this study but are not subsequently treated or who do not meet the eligibility criteria.

Subjects will be allowed to repeat any single screening assessment/procedure examination and/or vitals once, if necessary, if it is within the screening window. The subject will not be considered a screen failure unless the repeat assessment/procedure result does not meet eligibility criteria. The period from the start of screening related procedures at the Screening Visit to the first Dosing Visit must not exceed 28 days, inclusive of any repeat screening procedures. Subjects who are considered screen failures due to logistic/timing purposes surrounding the subject's availability for surgery (not including any other inclusion/exclusion criteria reasons) and/or COVID-19 restrictions, may be rescreened. Screening assessments and/or safety laboratory tests done within 28 days prior to (or as mandated in the protocol) the Day 1 Visit can be considered for screening purposes. In the case of subjects who have more than 28 days between initial screening and the Day 1 Visit, all screening assessments and/or safety labs will be repeated to confirm subject eligibility.

Subjects who do not meet all of the eligibility criteria at the Screening or first Dosing Visit 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 AE or serious adverse event (SAE) experienced by the subject.

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 and Marking Treatment Area

Each subject will have 2 marked areas (Area 1 and Area 2) of the abdomen selected for injection with CCH plus a marked non-injected control area for comparison (Figure 2). The control area will be located between the two treatment areas. Treatment areas of each subject group will be marked: Treatment Area 1 and Treatment Area 2 with the noninjected area marked as Control.

At each dosing visit, the treatment areas of each selected subject will be photographed **after marking the treatment area and the injection site with a surgical marker and a temporary tattoo (but prior to CCH dosing or the abdominoplasty procedure)**, while the subject is in a consistent, standardized relaxed standing pose. On Day of Surgery (Day 0), prior to abdominoplasty procedure, the borders of the treatment area will be marked with a surgical

marker. Following marking, the treatment areas will then be photographed while the subject is in a standing pose (as previously described). Additional instructions will be provided in the Clinical Operations Manual.

Figure 2: Diagram of Treatment Areas

6.2. Study Drug 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 total dose of approximately 0.21 mg CCH over the course of the study, which will be administered as 3 doses of 0.07 mg CCH each, approximately, during 2 or 3 dosing sessions. Refer to the study schema in Section 1.2 for the dosing sessions. There are 2 treatment areas. Group 1, Group 2, and Group 3 will have 2 dosings with the single injection technique in Treatment Area 1 and 1 dosing with the single injection technique in Treatment Area 2 at specified study visits. Group 4, Group 5, and Group 6 will have 2 dosings with the [redacted] in Treatment Area 1 and 1 dosing with the [redacted] in Treatment Area 2 at specified study visits. The maximum study dose per treatment area is approximately 0.14 mg CCH and the minimum dose per treatment area is approximately 0.07 mg CCH. See Table 1 for details.

At each dosing visit, the CCH injection dose administered per treatment area (Area 1 or Area 2) in Group 1, Group 2, and Group 3 is 0.07 mg CCH/0.3 mL administered subcutaneously as [redacted] of [redacted] mL with a single injection technique, or in Group 4, Group 5, and Group 6 is approximately 0.07 mg CCH/1.5 mL administered subcutaneously as [redacted] of [redacted] mL with a [redacted] see Table 1).

Specific instructions for CCH reconstitution and administration, including the injection techniques, will be provided in the Pharmacy Manual. Study treatment will be injected subcutaneously while the subject is in a supine position. Specific instructions outlining the injection techniques will be provided in the Clinical Operations Manual.

Table 1: Study Treatment (All Subjects)

Group	Injection Technique	Dose per Each Administration	Volume per Each Dose	Number of Doses	Dose (mg) at Each Treatment Area	Cumulative Study Dose
1, 2, 3	Single injection	CCH 0.07 mg	0.3 mL (given as three [redacted] mL aliquots)	2 doses in Treatment Area 1 and 1 dose in Treatment Area 2	0.14 mg in Treatment Area 1 and 0.07 mg in Treatment Area 2	0.21 mg
4, 5, 6	[redacted]	CCH 0.0653 mg	1.4 mL[a] (given as [redacted])	2 doses in Treatment Area 1 and 1 dose in Treatment Area 2	0.13 mg in Treatment Area 1 and 0.0653 mg in Treatment Area 2	0.196 mg

[a] [redacted] mL of the 1.5 mL dilution will be remaining and returned to Endo as described in Section 6.3.

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 with the investigator and site staff must be familiar with their use. To evaluate the subject for possible immediate immunological AEs, the subject will remain in direct observation of medical personnel who are skilled in the management of an allergic reaction for 30 minutes after receiving the injections of study treatment and until the subject exhibits no sign of an immunological or other clinically significant systemic or local AE. The subject's vital signs must be stable before the subject can leave direct observation.

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.

6.3. Study Treatment Preparation/Handling/Storage/Accountability

CCH and its diluent will be supplied in bulk. 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 or designee.

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

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

Any remaining unused reconstituted study drug will be stored and returned to Endo or designee.

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 of study treatment and administration syringes, as well as, handling, storage, and accountability of study treatment.

6.4. Measures to Minimize Bias

This is an open label, nonrandomized study. The pathologist, who is blinded to the dosing schedule, will report any observed tissue differences from the control area (not injected).

6.5. 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 an accountability record at the study site, and all original containers of used and unused study treatment and diluent will be returned to the sponsor (or designee) at the end of the study.

Accidental or intentional overdoses should be reported to the sponsor/designee promptly (see Section 8.3).

6.6. Prior and Concomitant Medications and Procedures

The investigators will provide the sponsor with a listing of the standard of care medications routinely given to subjects undergoing pre-planned, elective abdominoplasty surgery. These standard medications, when used prophylactically (such as antibiotics), and as part of routine surgical administration (such as oxygen supplementation, standard intravenous fluids, medications used in anesthesia, and blood products), are not required to be recorded via the electronic case report form (eCRF)/electronic data capture (EDC) system. In the event that any of these medications cause or are used to treat an AE that occurs during presurgery preparation, or during surgery or postsurgery, the corresponding AE and the medication will be recorded.

For all other medications, the start and stop date, dose, unit(s), 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 28 End of Study/Early Termination Visit) medications will be recorded. Nondrug therapies (eg, blood transfusions, physical therapy, and occupational therapy) received will also be recorded.

6.6.1. 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 the study.

The following procedures are not allowed in the abdominal area during the course of the study (from the Screening Visit through Day 0):

- Injections (eg, mesotherapy), radiofrequency device treatments, laser treatment, cryolipolysis, or surgery (including subcision and/or powered subcision).
- Any investigational treatment in the abdominal area.
- CoolSculpting® or similar treatments of the abdomen during the 18-month period before injection of study drug.
- Deep massage therapy (such as Endermologie™) or similar therapy, within the abdominal area.
- Creams (eg, Celluvera™, TriLastin®) and/or home therapies within the abdominal area.
- Bath/shower salts or sugar/salt scrubs, lotions, loofahs, or other exfoliating products on the abdominal area.

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

7. DISCONTINUATION FROM STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

Subjects who discontinue or are withdrawn from study treatment for any reason, 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 (Screening through Day 0).

If a clinically significant cardiac finding is identified (including, but not limited to, changes from baseline in QT 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.

Subjects who discontinue from study treatment for any reason after the first dose of study treatment may be replaced at the discretion of the sponsor to ensure the appropriate number of subjects complete the study.

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 of the subject 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 in writing destruction of any samples taken and the desire that these samples not be tested. The investigator must document this in the site study records.

A subject may be discontinued 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 Schedule of Activities. The date a subject discontinues and the reason for discontinuation will be recorded in the source documentation and eCRF. If, however, a subject withdraws consent, no additional procedures are required except the collection of AE information. This information should be recorded in the source documentation and the eCRF.

Subjects who have been withdrawn from the study at any time after the first dose of study drug may be replaced at the discretion of the sponsor to ensure the appropriate number of subjects complete the study.

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 of a subject fails to return for a required study visit:

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

Subjects who are lost to follow-up in the study for any reason after the first dose of study treatment may be replaced at the discretion of the sponsor to ensure the appropriate number of subjects complete the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Activities (Section 1.3). Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct. Protocol waivers or exemptions are not allowed. The details of activities outlined in the Clinical Operations Manual must be followed or will result in a protocol deviation.

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

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

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

8.1. Safety Assessments

All safety assessments will be performed at the time outlined in the Schedule of Activities. Additional (unscheduled) safety assessments may be performed as needed or as determined by the investigator. Detailed instructions for completing the assessment (and any required forms, questionnaires, etc) will be provided in the Clinical Operations/Study Laboratory Manuals.

8.1.1. Medical and Surgical History

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

Surgical history will include a review of all surgical procedures completed in the prior 5 years and any surgery completed at any time in the treatment area. Refer to Section 5.2 for excluded medical/surgical histories and/or conditions.

8.1.2. Physical Examination

The complete physical examination will follow the site's standard of care and may include evaluation of the head, eyes, ears, nose, throat, neck (including thyroid), cardiovascular system (including assessment of heart, peripheral pulses, presence or absence of edema), lungs,

abdomen (including liver and spleen, bowel sounds), lymph nodes, musculoskeletal system (including spine, joints, muscles), neurological system (including cranial nerves, reflexes, sensation, strength), skin, 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.

8.1.3. Height and Weight

Height and weight will be collected at Screening only for BMI calculation.

8.1.4. Vital Signs

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

Vital signs (blood pressure, respiratory rate, pulse rate, and body temperature) will be collected on dosing visits up to 2 hours prior to dosing, at 15 minutes after dosing (no body temperature at this time point), and at 30 minutes after dosing on Days -43, -24, -22, -14, -3, and -1. All vital sign measurements should be taken after the subject has been sitting for 5 minutes.

Vital signs must be stable before the subject is discharged from any visit. If vital signs are not stable, they must be repeated until the subject is stable and able to be discharged.

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).

8.1.5. Preoperative Standard of Care Assessments

ECG and all other preoperative assessments will be performed as per standard-of-care and interpreted by the investigator.

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

8.1.6. Clinical Laboratory Determinations

Clinical laboratory tests will be conducted according to the Schedule of Activities and per standard-of-care in preparation for the abdominoplasty procedure as determined by the investigator. Clinical laboratory tests will be performed by the site at their local laboratory as part of standard-of-care pre-surgery testing. In the event that any safety laboratory testing results are unavailable prior to the subject's first dosing visit, the investigator will notify the sponsor to discuss on a case-by-case basis, prior to administering any study treatment to the subject.

Samples for laboratory testing may be collected under fasted or nonfasted conditions as determined by the investigator. 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 to the sponsor as AEs (or SAEs, if appropriate) as determined by the investigator as part of standard-of-care preparation for abdominoplasty.

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 if needed to ensure subject safety.

8.1.7. Gross Pathology, Histopathology, and Immunohistochemistry

Digital photography will be conducted so that the photographs of the treatment area can assist the histopathologist/evaluator in assessing the gross pathology and histopathology of the excised tissues. Refer to the Clinical Operations Manual for the length of time of tissue storage.

At each dosing visit, the treatment areas of each selected subject will be photographed after marking the treatment area and the injection site with a surgical marker (but prior to CCH injection), while the subject is in a consistent, standardized relaxed standing pose.

At Day 0 (Day of Surgery), the treatment areas will be again photographed after marking the treatment area but prior to the abdominoplasty procedure, while the subject is in a consistent, standardized relaxed standing pose.

No manipulation of the treatment or control areas should be done prior to the photographs being taken.

The marked and photographed abdominal tissue that is isolated and excised during the abdominoplasty procedure will be shipped to a pathology laboratory for analysis according to instructions in the Clinical Operations Manual. All tissue samples will be handled by the pathologist according to instructions in the Histopathology Manual.

Histopathology and immunohistochemistry of the excised abdominal tissue will be performed at the central pathology laboratory. The pathologist, who is blinded to the dosing schedule, will report any observed tissue differences from the control area (not injected).

8.1.8. Immunogenicity Assessments

Serum samples (4 mL) will be collected at the time points outlined in the Schedule of Activities and will be tested for determination of binding and neutralizing anti-AUX-I and anti-AUX-II antibody presence and/or levels (Section 9.3.2.3).

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 antibodies, anti-AUX-II antibodies, and neutralizing antibodies. Specific instructions for the collection, processing, storage, handling and shipment of the immunogenicity samples will be provided in the Clinical Operations Manual.

De-identified immunogenicity samples may be stored for a maximum of 2 years (or according to local regulations) following the last subject's last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to study treatment; develop methods,

assays, prognostics and/or companion diagnostics related to specify the intervention target, disease process, pathways associated with disease state, and/or mechanism of action of the study treatment.

8.1.9. Pregnancy Testing

All female subjects of childbearing potential will have serum and urine pregnancy tests at the time points outlined in the Schedule of Activities. Results must be available prior to protocol mandated study treatment/first injection of study drug. Subjects with positive results at the Screening or first dosing visit will be ineligible for study entry. Any female subject that becomes pregnant during the study will be immediately withdrawn from treatment and will have the pregnancy reported as per Section 8.2.5.

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

8.2. Adverse Events and Serious Adverse Events

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

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

8.2.1. 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 28/End of Study Visit or for 28 days after the last study treatment for those who early terminate. This will include any AEs that are ongoing at the time of completion/termination of the study. All ongoing AEs must be followed until resolution or for 28 days after the subject's last study treatment, whichever comes first. Injection site reactions will be considered resolved when the surgery is done due to surgical removal of the area.

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 at least possibly related to the study treatment or study participation, the investigator must promptly notify the sponsor.

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

8.2.2. 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.

8.2.3. 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 AEs of special interest (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.

8.2.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

8.2.5. Pregnancy

Any uncomplicated pregnancy that occurs in a subject during this clinical study will be reported. 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 Initial Pregnancy Report Form. Monitoring of the pregnancy should continue until conclusion of the pregnancy; 1 or more Follow-up Pregnancy Report Form(s) detailing progress, and a Two-Month Follow-up Pregnancy Report Form detailing the outcome, should be submitted.

Pregnancy itself is not regarded as an AE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not considered AEs. Any SAEs associated with pregnancy (eg, congenital abnormalities/birth defects, or any other serious events) must additionally be reported as such using the Serious Adverse Even (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 be discontinued from study treatment. Attempts to obtain the pregnancy follow-up and pregnancy outcome information detailed above are necessary even if a subject withdraws from the study because of pregnancy.

8.2.6. 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 the Endo Pharmacovigilance and Risk Management Department (when the nonsubject agrees) on the Serious Adverse Even (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.

8.2.7. 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, including anaphylaxis.
- 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.

8.2.8. Adverse Events Related to Abdominoplasty

As with any surgical procedure, abdominoplasty can also have procedure-related AEs and/or complications. A review of the literature, including published case series, reveals that following abdominoplasty surgery local complications are considerably more common than complications with systemic repercussions (fewer than 1%). Most common local complications observed in the literature include (but are not limited to) seroma, hematoma, infection, skin necrosis, suture extrusions, umbilical anomalies, hypertrophic scars, keloids, poor wound healing, and changes in skin sensation. Systemic complications, though rare, that could be serious and sometimes fatal

are deep venous thrombosis and pulmonary thromboembolism, respiratory distress, and even death.

8.3. 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.

8.3.1. Treatment Abuse/Misuse

Not applicable.

8.4. Pharmacokinetics

Not applicable.

8.5. Pharmacodynamics

Not applicable.

8.6. Genetics

Not applicable.

8.7. Biomarkers

Not applicable.

8.8. Medical Resource Utilization and Health Economics

Not applicable.

9. STATISTICAL CONSIDERATIONS AND METHODS

9.1. Sample Size Determination

No formal sample size calculations were performed. Completion of 8 subjects will provide minimal data to meet the primary objective.

This is an exploratory study, and a sample size calculation is not required.

Approximately 10 subjects will be enrolled to receive CCH injection and undergo elective abdominoplasty in this study, with at least 1 subject enrolled in Group 2, Group 3, Group 5, and Group 6, and at least 2 subjects each will be enrolled in Group 1 and Group 4.

An additional 2 subjects will be enrolled to replace (for overall objective and endpoint analysis purposes) subjects whose abdominoplasty surgeries were delayed due to COVID-19 restrictions.

9.2. Populations for Analysis

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

- Evaluable Population: the Evaluable Population will include all subjects who receive at least 1 injection of study drug and have a histopathology and an immunohistochemistry report. The histopathology data of the 2 subjects whose abdominoplasty surgery was delayed due to COVID-19, will be analyzed separately.
- Safety Population: The Safety Population will include all subjects who receive at least 1 injection of study drug.

9.3. Statistical Hypotheses and Analyses

No statistical hypotheses and analyses are planned for the study. Subject narratives will be developed based on the histopathology and immunohistochemistry reports and safety data listings.

9.3.1. Histopathology and Immunohistochemistry

Histopathology and immunohistochemistry findings in the excised abdominal tissues injected with CCH will be compared to histopathology and immunohistochemistry findings in non-injected control tissue. Also, histopathology and immunohistochemistry findings in the excised abdominal tissues dosed twice with CCH will be compared to histopathology and immunohistochemistry findings in excised abdominal tissues dosed only once with CCH.

The pathologist, blind to the dosing schedule, will report any observed tissue differences from the control area (not injected).

9.3.2. Safety

All subjects who receive at least 1 dose of study drug will be included in the safety analyses. Subjects will be included in the safety analyses based on the actual treatment received.

9.3.2.1. Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities (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. By-subject listings of AEs will be provided.

9.3.2.2. Vital Signs

By-subject listings of vital signs will be provided.

9.3.2.3. Immunogenicity

Samples from Screening will be analyzed for anti-AUX-I and anti-AUX-II antibodies. Samples from Day 0 and Follow-up/End of Study visits will be analyzed for anti-AUX-I antibodies, anti-AUX-II antibodies, and neutralizing antibodies. Neutralizing antibodies will only be tested from anti-drug antibody (ADA) positive subjects. By-subject listings of anti-AUX-I and anti-AUX-II antibody levels, and neutralizing antibody results (positive/negative) will be provided.

9.4. Interim Analysis

No interim analysis is planned for this study.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

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

At the Screening Visit (and at other times 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, subject initials, date of birth, and no other identifiable information.

The subject must be informed that 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 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 site(s) 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 study 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

Clinical laboratory parameters will be measured as per standard-of-care for abdominoplasty and may include, but not be limited to, the following:

- Complete blood count with differential count (CBC W/DIFF).
- Prothrombin time/partial thromboplastin time (PT/PTT).
- Chemistry panel (CHEM PROFILE).
- Human chorionic gonadotropin (B-HCG) qualitative.

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 28/EOS Visit, or for 28 days after the last study treatment in subjects who terminate early. All ongoing AEs must be followed until resolution or for 28 days after the subject's last study visit, 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 28 days after the last dose of study medication. SAEs that occur within 28 days, following cessation of the study treatment, or within 28 days, following premature discontinuation from the study for any reason, must also be reported within the same timeframe. Any SAE that is felt by the investigator to be related to the study medication must be reported regardless of the amount of time since the last dose received. Follow-up information collected for any initial report of an SAE must also be reported to the sponsor within 24 hours of receipt by the investigator.

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

All SAEs should be sent [redacted]

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

10.3.4.3. Follow-up Procedures for Serious Adverse Events

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

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

See Section 5, Section 8.1.9, and Section 8.2.5.

10.5. Appendix 5: Genetics

Not applicable.

10.6. Appendix 6: Medical Device Incidents

Not applicable.

10.7. Appendix 7: Country-specific Requirements

Not applicable.

10.8. Appendix 8: Abbreviations

Abbreviation	Explanation
AE	Adverse event
AESI	Adverse events of special interest
AUX-I	Clostridial class I collagenase
AUX-II	Clostridial class II collagenase
BMI	Body mass index
CFR	Code of Federal Regulations
ECG	Electrocardiogram
eCRF	Electronic case report form
EFP	Edematous fibrosclerotic panniculopathy
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigational Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event

11. INVESTIGATOR'S STATEMENT

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

_____ _____/_____/_____

Investigator's Signature Date

_____

Typed Name of Investigator

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