SAP MODULE 1 – DETAILED STATISTICAL METHODOLOGY

Protocol EN3835-212; October 22, 2019
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A PHASE 2A, OPEN-LABEL STUDY TO ASSESS THE IMPACT OF CCH TREATMENT OF BUTTOCK AND THIGH CELLULITE IN ADULT FEMALES USING PHOTONUMERIC SCALES, MAGNETIC RESONANCE IMAGING, AND HISTOPATHOLOGY

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[redacted]

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate transaminase
ATC	Anatomical therapeutic chemical
AUX-I	Clostridial class I collagenase
AUX-II	Clostridial class II collagenase
BMI	Body mass index
BUN	Blood urea nitrogen
CRF	Case report form
CR-PCSS	Clinician-reported Photonumeric Cellulite Severity Scale
CSS	Cellulite Severity Scale
ECG	Electrocardiogram
eCRF	Electronic case report form
EFP	Edematous fibrosclerotic panniculopathy
FDA	United States Food and Drug Administration
HBsAg	Hepatitis B surface antigen
HBcAb	Hepatitis B core antibody
HIV	Human immunodeficiency virus
IEC	Independent ethics committee
IRB	Institutional review board
MedDRA	Medical Dictionary for Regulatory Activities
Max	Maximum
Min	Minimum
MRI	Magnetic resonance imaging
PCI	Potentially clinically important
PR-PCSS	Patient-reported Photonumeric Cellulite Severity Scale
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SOC	System organ class
TEAE	Treatment-emergent adverse event
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the planned analyses to assess the impact of CCH treatment on buttock and thigh cellulite using photonumeric scales, magnetic resonance imaging (MRI), and histopathology in adult women.

Specific information about the study is described in the EN3835-212 protocol.

2. STUDY OBJECTIVES AND ENDPOINTS

The primary, secondary, and tertiary objectives and corresponding endpoints are outlined in Table 1 below.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the subject reported impact of CCH in the treatment of cellulite in adult females.	• The change from baseline (screening) in Patient-reported Photonumeric Cellulite Severity Scale (PR-PCSS) at Day 71.
Secondary	
• To assess the subject and clinician reported impact of CCH in the treatment of cellulite in adult females.	• The change from baseline (screening) in PR-PCSS at Days 22 and 43. • The change from baseline (screening) in Clinician-reported Photonumeric Cellulite Severity Scale (CR-PCSS) at Days 22, 43, and 71. • The change from baseline (screening) in Hexsel Cellulite Severity Scale (CSS) at Days 22, 43, and 71.
• To radiologically assess the impact of treatment with CCH in adult females with cellulite.	• Comparison of baseline (screening) MRI tissue morphology and septae under the treatment areas to images taken at Day 71.
• To evaluate tissue histopathology to assess the impact of treatment with CCH in adult females with cellulite.	• Comparison of baseline (screening) histopathology to the histopathology of samples taken at Day 71.
• To assess the safety of CCH treatment of cellulite in adult females.	• The proportion of subjects reporting each adverse event (AE), treatment-emergent adverse event (TEAE), adverse event of special interest (AESI), and serious adverse event (SAE).

Objectives	Endpoints
	• The change from baseline in vital signs and clinical laboratory parameters at each visit where these parameters are measured. • The change from baseline in anti-AUX-I and anti-AUX-II antibodies and neutralizing antibodies at each visit where these parameters are measured.
Tertiary	
• To assess the complete loss of patient reported impact after CCH treatment in adult females with cellulite.	• The proportion of subjects with no change (or worsening) from baseline (screening) in PR-PCSS rating at Day 161 and at Day 251.
• To assess the complete loss of clinician reported impact after CCH treatment in adult females with cellulite.	• The proportion of subjects with no change (or worsening) from baseline (screening) in CR-PCSS rating at Day 161 and at Day 251. • The proportion of subjects with no change (or worsening) from baseline (screening) in Hexsel CSS total score at Day 161 and at Day 251.
• To radiologically assess the long-term impact of treatment with CCH in adult females with cellulite.	• Comparison of baseline (screening) MRI tissue morphology and septae under the treatment areas to images taken at Day 251.
• To evaluate tissue histopathology to assess the long-term impact of treatment with CCH in adult females with cellulite.	• Comparison of baseline (screening) histopathology to the histopathology of samples taken at Day 251.

3. STUDY DESIGN AND MEASURES

3.1. Study Design

This is a single center, open-label, Phase 2a study to assess the safety and efficacy of CCH in adult women with moderate or severe edematous fibrosclerotic panniculopathy (EFP) of the buttocks or thighs using photonumeric scales, MRI, and histopathology of tissues from the treated area. Approximately 18 subjects will be screened in order to dose approximately 12 subjects. Every attempt will be made to enroll an equal number of subjects across the 2 severity levels in both buttocks and thighs (eg, 3 subjects with moderate buttock cellulite, 3 subjects with severe buttock cellulite, 3 subjects with moderate thigh cellulite, and 3 subjects with severe thigh cellulite).

Following a screening period of approximately 35 days, qualified subjects will receive 0.84 mg of CCH per treatment area (buttock or thigh) for a total dose of 1.68 mg in both buttocks or both thighs per treatment session for 3 sessions. Treatment sessions will occur approximately 21 days apart (Day 1, Day 22, and Day 43). Following treatment and assessments at Day 71, subjects will be assessed and followed for an additional 194 days.

Subjects will have MRIs and double punch biopsies of 3 selected target dimples 3 times during the study (Screening, Day 71, and Day 251).

Subjects will participate in the study for up to approximately 305 days (approximately 10 months). The duration of the study from first subject first visit to last subject last visit will be dependent upon the ability of the site to identify and enroll subjects. The entire study is expected to require approximately 12 months to complete.

Table 2 below describes the schedule of activities and assessments performed during screening, the treatment phase, and the extension phase of the study.

Table 2: Schedule of Activities

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

Table 2: Schedule of Activities (Continued)

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

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

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

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

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

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

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

[g] Screening MRIs will be performed after all other screening assessments (except the biopsy) have been completed.

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

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

[j] The Day 71 and Day 251 imaging for efficacy, PR-PCSS, and CR-PCSS must be completed prior to the biopsy sample collection required at those visits. The Day 251/Early Termination biopsy is not required for subjects who withdraw from the study (early termination).

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

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

3.2. Eligibility Criteria for Subject Selection

3.2.1. Inclusion Criteria

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

1. Be female and ≥18 and ≤50 years of age at the time of consent.
2. Have both buttocks or both posterolateral thighs with:
   a. A score of 3 or 4 (moderate or severe) as reported by the investigator using the CR-PCSS.
   b. A Hexsel Cellulite Severity Scale (CSS) total score of ≤13.
   c. A Hexsel CSS Subsection A "Number of Evident Depressions" score of >0.
   d. A Hexsel CSS Subsection B "Depth of Depressions" score of 2 (medium depth depressions) or 3 (deep depressions).
3. Have a body mass index (BMI) score between 18.5 kg/m^2 to 29.9 kg/m^2 and intends to maintain stable body weight throughout the duration of the study (from the Screening Visit through the Day 251/Early Termination Visit). A variation of ≤10% from the Day 1 Visit weight is permitted.
4. Be willing and consent to undergo human immunodeficiency virus (HIV) and hepatitis B testing, as well as double punch biopsy and MRI procedures.
5. Have a minimum of 2 well defined and isolated cellulite dimples that are considered moderate or deep in depth in each treatment area (each thigh or each buttock, for a total of 4 such dimples), of which 3 will be selected for MRI and biopsy procedures.
6. Be willing to apply sunscreen to the treatment area before each exposure to the sun for the duration of the study (from the Screening Visit through the Day 251/Early Termination Visit).
7. Be judged by the investigator to be in good health, based upon the results of a medical history, physical examination, electrocardiogram (ECG), and laboratory profile at screening.
8. Be of nonchildbearing potential (history of hysterectomy, bilateral oophorectomy, bilateral tubal ligation, or postmenopausal with no history of menstrual flow in the 12 months prior to the Screening Visit); or, if of childbearing potential, be nonpregnant, nonlactating, and agree to use effective contraception when with a male partner at least 1 menstrual cycle prior to the first dose of study treatment through the Day 251/Early Termination Visit. Acceptable forms of contraception include hormonal measures (oral contraceptive pills, contraceptive patch, contraceptive ring, injections, etc), intrauterine devices, double barrier methods (condom plus diaphragm, condom or diaphragm plus spermicidal gel or foam), surgical sterilization of the male partner, and abstinence.
9. Have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy prior to dosing at each treatment session and prior to the Day 71 and Day 251 MRIs.

10. Be willing and able to comply with all protocol required visits and assessments.
11. Be able to read, understand, and independently complete patient reported outcome instruments in English.
12. Be adequately informed and understand the nature and risks of the study and be able to provide consent as per Institutional Review Board (IRB)/Independent Ethics Committee (IEC).
13. Must have evaluable MRI images of Dimples 1, 2, and 3 at screening. An evaluable MRI is defined as an image that adheres to the protocol scanning parameters and is free from artifacts that could affect the analysis.

3.2.2. Exclusion Criteria

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

1. Is from a vulnerable population, as defined by the US Code of Federal Regulations (CFR) Title 45, Part 46, Section 46.111(b) and other local and national regulations, including but not limited to, employees (temporary, part-time, full time, etc) or a family member of the research staff conducting the study, or of the sponsor, or of the contract research organization, or of the IRB/IEC.
2. Has a history of sensitivity or allergy to collagenase or any other excipient of CCH.
3. Has any of the following systemic conditions:
    a. Coagulation disorder.
    b. Evidence or history of malignancy (other than excised basal-cell carcinoma) unless there had been no recurrence in at least 5 years.
    c. History of keloidal scarring or abnormal wound healing.
    d. Concurrent diseases or conditions that might interfere with the conduct of the study, confound the interpretation of the study results, or endanger the subject's well-being. Any questions about concurrent diseases will be discussed with the Medical Monitor.
    e. Evidence of clinically significant abnormalities on physical examination, vital signs, ECG, or clinical laboratory values.
4. Has any of the following local conditions in the areas to be treated (both buttocks or both thighs):
    a. History of lower extremity thrombosis, deep vein thrombosis, or post-thrombosis syndrome.
    b. Vascular disorder (eg, varicose veins, telangiectasia).
    c. Inflammation or active infection.
    d. Active cutaneous alteration including rash, eczema, or psoriasis.
    e. A tattoo or other artificially inflicted body marker.
    f. A mole located within 2 cm of any injection site.

5. Has a Hexsel CSS Subsection D "Grade of Laxity, Flaccidity, or Sagging Skin" score of ≥2 or has linear undulations that can be effaced by lifting the skin in the areas to be treated (each buttock or each thigh).
6. Requires anticoagulant or antiplatelet medication during the study or has received anticoagulant or antiplatelet medication (except for ≤150 mg aspirin daily) within 7 days before injection of study treatment.
7. Has used any of the following for the treatment of EFP on either thigh or either buttock within the timelines identified below or intends to use any of the following at any time during the course of the study:
   a. Liposuction during the 12-month period before injection of study treatment.
   b. Injections (eg, mesotherapy, dermal fillers, biostimulatory fillers); radiofrequency
   c. device treatments; laser treatment; buttock or thigh implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision) during the 12-month period before injection of study treatment.
   d. Any investigational treatment for EFP on a buttock or thigh during the 12-month period before the injection of study treatment.
   e. Endermologie or similar treatments during the 6 month period before injection of study treatment.
   f. Massage therapy during the 3-month period before injection of study treatment.
   g. Creams (eg, Celluvera™, TriLastin®) and/or home therapies to prevent or mitigate EFP during the 2-week period before injection of study treatment.
8. Has used any form of artificial tanning (sprays, lotions, tanning booth, etc) within the 30 days prior to the first dose of study treatment or plans to use any form of artificial tanning during the study (through the Day 251/Early Termination Visit).
9. Has a positive HIV test and/or a positive hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb) test at screening.
10. Has had any surgery, invasive procedure (eg, liposuction), injectable treatment (eg, KYBELLA®) or any similar treatment that could have destroyed fat cells and/or removed 1fat deposits in the treatment area.
11. Has a history of keloids, hypertrophied scars, and/or other complications following biopsy.
12. Has any contraindications for MRI including, but not limited to:
    a. Has an implant containing metal including but not limited to intracranial aneurysm clips, cochlear implants, prosthetic devices containing metal, implanted drug infusion pumps, neurostimulators, bone-growth stimulators, intrauterine contraceptive devices containing metal, or any other type of iron-based metal implants.
    b. Has an internal metallic object such as bullets or shrapnel, as well as surgical clips, pins, plates, screws, metal sutures, or wire mesh.
    c. Has any tattoo or permanent cosmetics/make-up including, but not limited to, permanent lip liner or permanent eye liner.

d. Has severe claustrophobia.
e. Has experienced "ceremonial" syncope (fainting while standing still).
f. Has extremely low blood pressure, epilepsy, asthma, anemia, or sickle cell disease.

13. Has received any collagenase treatments at any time prior to treatment in this study and/or has received EN3835 or CCH in a previous investigational study for cellulite.
14. Has previously received treatment with CCH in this clinical study.
15. Has received treatment with an investigational product within 30 days (or 5 half-lives, whichever is longer) of the Screening Visit.
16. Is pregnant and/or is providing breast milk or plans to become pregnant and/or to provide breast milk during the course of the study.
17. Intends to initiate an intensive sport or exercise program during the study.
18. Intends to initiate an intensive weight reduction program during the study.
19. Has any other condition(s) that, in the investigator's opinion, might indicate the subject to be unsuitable for the study.

3.3. Treatment Region

Treatment region is defined as both buttocks or both thighs. Approximately 12 subjects will be dosed in this study, thus 6 subjects will be treated in the buttocks and 6 subjects will be treated in the thighs.

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

3.4. Selection and Marking of Dimples

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

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

3.5. Study Drug Administration

Each qualified subject will receive up to 24 subcutaneous injections (up to 12 injections per buttock or thigh) for a maximum total of 1.68 mg (0.84 mg per treatment area) at each treatment

session. Each subject will receive study drug on Day 1, Day 22, and Day 43. The maximum cumulative CCH dose will be 5.04 mg for each subject who completes the 3 treatment visits (total maximum dose of 1.68 mg per treatment session × 3 treatment sessions).

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

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

The injection volume and concentration for each treatment area are outlined in Table 3 below.

Table 3: Study Treatment

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

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

3.6. Determination of Sample Size

The sample size for this study is not based on a formal sample size calculation. A total of 12 subjects are considered sufficient to determine if biopsy will demonstrate changes in histopathology associated with CCH treatment while exposing the minimum number of subjects possible to the associated risks.

3.7. Blinding and Randomization

This is an open-label and non-randomized study. Treatment blinding and randomization are not applicable to this study.

3.8. Medical, Surgical and EFP History

The medical, surgical, and EFP history of the subjects will be taken at screening. Medical history will include relevant diagnoses and/or procedures/therapies with onset/resolutions dates. Historical and current medical conditions including date of last menstrual period will be recorded.

If onset date is unknown, then whether it occurred within 5 years or more than 5 years ago will be recorded on the electronic case report form (eCRF).

Surgical history will include a review of all surgical procedures completed in the prior 5 years and any surgery during the study.

EFP history will be obtained from the subject at screening. EFP history will include the following:

- Family history of cellulite (answered as yes, no, or unknown).
- Onset date of EFP symptoms.
- Previous treatments used for EFP.

3.9. Alcohol/Tobacco Use

History of tobacco and alcohol use will also be obtained at screening and the following information will be recorded:

- Type of substance (Alcohol/Tobacco).
- History of usage (Never/Currently/Former).
- Number of years the product was used (for current or former users).
- Stop date of using the product (for former users).

3.10. Prior/Concomitant Medications and Procedures

Any prior medications taken within the 90 days prior to the Screening Visit or any concomitant medications taken from the Screening Visit through the Day 265 Visit and nondrug therapies (eg, blood transfusions, oxygen supplementation, physical therapy, etc) will be recorded.

In addition, all prior treatments (including medications and procedures) for EFP will be recorded with start and stop date; and, where appropriate dose, unit, frequency and route of administration.

3.11. Prohibited Medications and Therapies

The following medications are prohibited for subjects during the study:

- Anticoagulants (warfarin, heparin, direct thrombin inhibitors, Factor X inhibitors) and antiplatelet agents (aspirin >150 mg/day and P2Y12 inhibitors, such as clopidogrel),

which can cause additional bruising. However, the use of aspirin at a dose level of ≤150 mg per day will be permitted during study.

The following procedures/treatments are not allowed in the selected treatment region (both buttocks or both thighs) during the course of the study (from the Screening Visit through the Day 265 Visit):

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

3.12. Efficacy Assessments

3.12.1. Imaging for Efficacy Assessments

The digital photographs are not direct efficacy measurements; however, digital photographs will be utilized in the assessment of certain efficacy measurements. At screening each of the 2 potential treatment areas (both buttocks and both thighs) will be photographed, using a Sponsor-supplied standardized digital camera in a standardized manner as per the Photography Manual. For subsequent visits, only the areas receiving treatment (both buttocks or both thighs) will be photographed. These photographs will be taken before and after marking of the treatment areas for dosing.

3.12.2. Subject and Investigator Cellulite Assessments

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

3.12.2.1. Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS)

The PR-PCSS-Buttock and PR-PCSS-Thigh will be used to assess the severity of cellulite of both treatment areas (each buttock and each thigh) independently.

The scale is a 5-level photonumeric scale developed specifically for patients and used by the subject to assess the severity of their cellulite in the buttocks or thighs by viewing digital images of each of their buttocks and/or thighs at Screening, Day 22, Day 43, Day 71, Day 161, and Day 251.

The ratings range from 0 (None) to 4 (Severe) with labels and descriptors to aid the subject in the assessments (Table 4).

Table 4: PR-PCSS for Buttocks or Thighs

Rating	Level of Severity	Description
0	None	No evident cellulite
1	Almost None	A few superficial dimples or ridges
2	Mild	Several dimples or ridges of which most are superficial
3	Moderate	Many dimples or ridges of which most are somewhat deep
4	Severe	A lot of dimples or ridges of which many are deep covering most of the skin area

3.12.2.2. Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)

The CR-PCSS-Buttock and CR-PCSS-Thigh will be used to assess the severity of cellulite of both treatment areas (each buttock and each thigh) independently.

The scale is a 5-level photonumeric scale developed specifically for clinicians and used by the investigator to assess the severity of the subject's cellulite in buttocks or thighs by live assessments at Screening, Day 22, Day 43, Day 71, Day 161, and Day 251.

The ratings range from 0 (None) to 4 (Severe) with labels and descriptors to aid the investigator in the assessments (Table 5).

Table 5: CR-PCSS for Buttocks or Thighs

Rating	Level of Severity	Description
0	None	No dimples or evident cellulite
1	Almost None	Few dimples that are mostly superficial in depth
2	Mild	Several dimples of which most are shallow in depth
3	Moderate	Many dimples of which most are moderate in depth
4	Severe	A lot of dimples with some of more severe depth

3.12.2.3. Hexsel Cellulite Severity Scale (CSS)

The Hexsel CSS (Hexsel et al, 2009; Nürnberger and Müller, 1978) is a photonumeric scale that looks at 5 key morphologic features of cellulite:

- A: Number of evident depressions.
- B: Depth of depressions.
- C: Morphological appearance of skin surface alterations.
- D: Laxity, flaccidity or sagging of skin.
- E: Current classification scale based on medical literature.

The investigator will access the cellulite using the Hexsel CSS for each buttock and each thigh, independently at Screening. For Day 22, Day 43, Day 71, Day 161, and Day 251, only the areas receiving treatment (each buttock or each thigh) will be assessed. This assessment should be made while the subject is in a standing position with relaxed gluteus muscles.

Each feature of the Hexsel CSS is evaluated on a 4-point scale, ranging from 0 to 3 as outlined in Table 6 below.

Table 6: Hexsel CSS

Morphologic Features	Severity Grade			
	0	1	2	3
Number of Evident Depressions	None/No depressions	A small amount: 1 – 4 depressions are visible	A moderate amount: 5 – 9 depressions are visible	A large amount: 10 or more depressions are visible
Depth of depressions	No depressions	Superficial depressions	Medium depth depressions	Deep depressions
Morphological Appearance of Skin Surface Alterations	No raised areas	Orange peel appearance	Cottage cheese appearance	Mattress appearance
Grade of Laxity, Flaccidity or Sagging Skin	Absence of laxity, flaccidity, or sagging skin	Slight draped appearance	Moderate draped appearance	Severe draped appearance
Classification Scale by Nurnberger and Muller	Zero grade	First grade	Second grade	Third grade

3.13. Safety Assessments

3.13.1. Adverse Events

Adverse events will be collected from the time of signing informed consent through the Day 265 Visit, or for 28 days after the last study treatment for subjects who terminate early.

3.13.1.1. Adverse Events

An AE is any unfavorable or unintended change in body structure (signs), body function (symptoms), laboratory result (eg, chemistry, ECG, X-ray, etc), or worsening of a preexisting condition associated temporally with the use of the study medication whether or not considered related to the study medication. AEs include:

- Changes in the general condition of the subject.
- Subjective symptoms offered by or elicited from the subject.
- Objective signs observed by the investigator or other study personnel.
- All concurrent diseases that occur after the start of the study, including any change in severity or frequency of preexisting disease.

- All clinically relevant laboratory abnormalities or physical findings that occur during the study.

3.13.1.2. Serious Adverse Events (SAEs)

Serious adverse events are those AEs that meet any of the following criteria:

- Results in death.
- Life-threatening event.
- Results in or prolongs an inpatient hospitalization.
- Results in permanent or substantial disability.
- Is a congenital anomaly or birth defect.
- Any important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

3.13.1.3. Adverse Events of Special Interest (AESI)

AEs such as bruising, ecchymosis, hematomas, and contusions that occur remote to the site of drug administration, or any hypersensitivity reactions, including anaphylaxis, will be recorded as AESIs.

In addition, local AEs associated with the injection site, including bruising, pain, nodules/mass, ulceration, erythema, pruritus, swelling, and/or induration will be recorded as AESIs.

3.13.2. Clinical Safety Laboratory Tests

Blood and urine samples will be collected for testing of the following clinical laboratory parameters during Screening, Day 71, and Day 251 (Table 7). Serology tests for HIV and hepatitis B will be performed at Screening.

Table 7: Clinical Safety Laboratory Parameters

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

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

Any clinically significant laboratory abnormality observed will be considered as an AE or SAE as appropriate. The clinical laboratory performing the testing will provide the reference ranges for all clinical laboratory parameters.

3.13.2.1. Pregnancy Test

All subjects of childbearing potential must have a negative pregnancy test at Screening and Day 1 to be enrolled in the study. All subjects of childbearing potential will undergo a serum pregnancy test at Screening and urine pregnancy tests at Day 1, Day 22, Day 43, Day 71, Day 161, and Day 251. Results must be available prior to study treatment and prior to MRIs. A subject who becomes pregnant must immediately be discontinued from study treatment and be withdrawn from the study.

3.13.3. Vital Signs

Vital signs (systolic and diastolic blood pressure, respiratory rate, pulse rate, body temperature) will be collected at Screening, Day 1, Day 22, Day 43, Day 71, Day 161, and Day 251, after the subject has been seated for 5 minutes (minimum).

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

Any clinically significant abnormality in vital sign observed, will be considered as an AE or SAE as appropriate.

3.13.4. 12-Lead Electrocardiogram (ECG)

A 12-lead ECG will be performed at Screening while the subject is in the supine position for at least 5 minutes.

The ECG recording should include a minimum of 5 heart cycles (beats). If the ECG report shows QT prolongation with QTc ≥ 450 ms, the investigator should repeat the ECG within 1 hour. If the initial findings are confirmed, the investigator should exclude the subject from study participation.

The ECG will be interpreted by the investigator and graded as:

- Normal.
- Abnormal, not clinically significant.
- Abnormal, clinically significant.

Any clinically significant abnormality in ECG observed, will be considered as an AE or SAE as appropriate.

3.13.5. Physical Examination

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

Physical examination findings will be recorded as normal or abnormal.

If physical examination findings meet the investigator's criteria for clinical significance, then it will be reported as an AE or SAE as appropriate.

3.13.6. Height and Weight

Height will be collected at Screening. Weight will be collected at Screening, Day 1, Day 22, Day 43, Day 71, Day 161, and Day 251. If change in subject weight from Screening to subsequent visits meets the investigator's criteria for clinical significance, then it will be reported as an AE or SAE as appropriate.

3.13.7. Fitzpatrick Skin Scale

The Fitzpatrick Skin Scale is used for assessment of skin color and propensity for tanning. Fitzpatrick skin type for all subjects will be determined at Screening.

The Fitzpatrick Skin Scale is a 6-level scale (Types I-VI) ranging from 1 to 6 as mentioned in Table 8 below.

Table 8: Fitzpatrick Skin Scale

Level	Description
1	Type I: Pale white skin, blue/hazel eyes, blond/red hair; Always burns, does not tan
2	Type II: Fair skin, blue eyes; Burns easily, tans poorly
3	Type III: Darker white skin; Tans after initial burn
4	Type IV: Light brown skin; Burns minimally, tans Easily
5	Type V: Brown Skin; Rarely burns, tans darkly easily
6	Type VI: Dark brown or black skin; Never burns, always tans darkly

3.13.8. Immunogenicity Samples

Immunogenicity variables include anti-AUX-I /anti-AUX-II (anti-drug antibodies) and neutralizing antibody results. Serum samples will be collected at Day 1 (prior to study treatment administration), Day 71, Day 161, and Day 251 for all subjects for the determination of serum anti-AUX-I and anti-AUX-II antibody levels and neutralizing antibodies to AUX-I and AUX-II.

3.13.9. Follow-up Biopsy

The investigator will examine the biopsy site for evidence of ongoing AEs related to the biopsy and will determine if the biopsy site has healed. The follow-up biopsy examination will be conducted at the Day 1, Day 85 and Day 265 visits. The investigator will examine and confirm sufficient healing of the biopsy site before dosing on Day 1.

3.14. Pharmacodynamics

Prior to the first MRI and biopsy, the investigator will select 3 dimples from the 2 treatment areas (both buttocks or both thighs) for MRI and biopsy evaluation from the 4 well-defined, isolated dimples that are considered moderate or deep in depth identified at Screening. The 3 selected dimples should be distributed across both regions of the treatment area (eg, 1 dimple on the left thigh [or buttock] and 2 dimples on the right thigh [or buttock], or vice versa). The investigator or designee will mark and label these 3 dimples for MRI and biopsies. The MRI technician or designee will locate the marked dimples and place an MRI coil appropriately on the dimple and photograph each dimple with the coil in place in a manner that will allow them to be relocated for subsequent MRIs.

3.14.1. MRI

MRI will be performed at Screening, Day 71 and Day 251. The Screening MRI will be performed after all other screening assessments, except the biopsy, are completed. Screening, Day 71, and Day 251 MRIs may be repeated as often as necessary to obtain an evaluable image. Repeat screening MRIs must take place within the screening window. The Day 71 and Day 251 MRI may be performed up to 7 days prior to the Day 71 and Day 251 visits respectively. The MRI must be completed before the biopsy at each visit. The Screening MRI will be done on all 3 selected dimples whereas the Day 71 and Day 251 MRI will be done on Dimple 2 & 3 and Dimple 3 respectively.

The Day 251/Early Termination MRI is not required for subjects who withdraw from the study (early termination).

3.14.2. Double Punch Biopsy

Biopsies will be performed at Screening, Day 71 and Day 251. The Screening biopsy will be performed on Dimple 1 after all other screening assessments, including MRI, are completed. The Screening biopsy will be performed at least 14 days prior to the Day 1 Visit.

The Day 71 biopsy will be performed on Dimple 2 and the Day 251 biopsy will be performed on Dimple 3 after completion of imaging for efficacy, PR-PCSS, and CR-PCSS at Day 71 and Day 251 respectively.

The Day 251/Early Termination biopsy is not required for subjects who withdraw from the study (early termination).

4. STUDY PARAMETERS

4.1. Subject Disposition

4.1.1. Discontinuation of Study Treatment

Subjects will be considered as completing the treatment phase if they complete Day 71 visit. Subjects discontinued from study treatment are those who discontinued the study at any time before completing all treatment phase visits. The date of, and reason for, study treatment discontinuation will be recorded in the eCRF.

If a subject becomes pregnant during the active treatment phase of the study (Day 1 through Day 43) then the study treatment will be permanently discontinued for that subject. Study treatment will also be discontinued if abnormal liver function is observed.

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

4.1.2. Subject Withdrawal from the Study

Subjects will be considered as completing the study if they complete the Day 265 visit. Withdrawn subjects are those who withdrew the study at any time before study end. The withdrawal date and reason will be recorded in the eCRF.

Subjects who withdrew from the study should undergo all early termination assessments. A subject who becomes pregnant at any time during the study will be permanently withdrawn. Subjects who have been withdrawn from the study will not be replaced.

The reason for early discontinuation will be recorded in the eCRF for the subjects who do not complete the study. The reason for screen failure will also be recorded in the eCRF for subjects who are not enrolled and are considered screen failures.

4.2. Protocol Deviations

Potential deviations will be identified and documented prior to database lock. Protocol deviations will be derived from the eCRF data, electronic vendor data, and will be obtained from the clinical monitoring reports. All deviations from these sources will be reconciled and duplicate deviations will be removed.

Possible deviations include, but are not restricted to the following deviation types:

- Ineligible subject/study entry criteria not satisfied.
- Informed consent not completed correctly.
- Non-compliance with study treatment.
- Prohibited medications/procedure.
- Visit/procedure missing or out of window.
- The Endo study team will approve all final protocol deviation assignments and classify them as either major or minor during ongoing protocol deviation review meetings, with the final meeting held prior to the database lock.

4.3. Prior/Concomitant Medications and Procedures

All medications will be coded using the World Health Organization (WHO) Drug Dictionary by active ingredient and anatomical therapeutic chemical (ATC) classification of ingredients. The dictionary version used is defined in the Data Management Plan.

Any medications/procedures within 90 days prior to the Screening Visit will be classified as prior medications/procedures.

Any medications/procedures from the Screening Visit through the Day 265 Visit will be classified as concomitant medications/procedures.

4.4. Prior EFP Treatment

Prior EFP treatment will be obtained from the prior/concomitant medication and/or prior/concomitant procedure pages of the eCRF. If on either of these pages a medication or procedure is reported with the indication 'EFP/Cellulite' and the start date is prior to the Screening Visit, then the medication or procedure will be considered a prior EFP treatment.

All medications will be classified as EFP Drug. All procedures will be classified into one of the following groups:

- Liposuction.
- Laser.
- Massage.
- Radiofrequency.
- Mesotherapy.
- Cream.

- Other.

The classification will be reviewed and approved by the study medical monitor. Any EFP treatment used after the Day 1 visit will be noted and reported as a protocol violation.

4.5. Efficacy Parameters

Cellulite assessments using the PR-PCSS, CR-PCSS and Hexsel CSS will be performed at Screening, Days 22, 43, 71, 161, and 251.

4.5.1. Change from Baseline in PR-PCSS Rating (Primary Endpoint)

To assess the subject reported impact of CCH in the treatment of cellulite in adult females, the change from Baseline (Screening) in PR-PCSS will be determined for treatment region (both buttocks or both thighs) on Day 71.

4.5.2. Change from Baseline in PR-PCSS Rating (Secondary Endpoint)

To assess the subject reported impact of CCH in the treatment of cellulite in adult females, the change from Baseline (Screening) in PR-PCSS will be determined for treatment region (both buttocks or both thighs) on Days 22 and 43.

4.5.3. Change from Baseline in CR-PCSS Rating (Secondary Endpoint)

To assess the clinician reported impact of CCH in the treatment of cellulite in adult females, the change from Baseline (Screening) in CR-PCSS will be determined for treatment region (both buttocks or both thighs) on Days 22, 43, and 71.

4.5.4. Change from Baseline in Hexsel CSS Total Score (Secondary Endpoint)

To assess the clinician reported impact of CCH in the treatment of cellulite in adult females, the change from Baseline (Screening) in Hexsel CSS total score will be determined for treatment region (both buttocks or both thighs) on Days 22, 43, and 71.

4.5.5. Proportion of Subjects with No Change (or Worsening) from Baseline (Tertiary Endpoints)

Complete loss of Response at Days 161 and 251 is defined as worsening of cellulite severity improvement on PR-PCSS/CR-PCSS /Hexsel CSS total score ratings at Days 161 and 251 compared to the score at Day 71, where cellulite severity returns to baseline levels or worse.

Tertiary endpoints will be analyzed for each scale separately.

4.6. Safety Parameters

4.6.1. Adverse Events

AE verbatim terms as reported by the investigator will be mapped to system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). The dictionary version is defined in the Data Management Plan.

4.6.1.1. Treatment Emergent Adverse Events

TEAEs are defined as any AEs that occur or worsen (increase in severity) on the same day or after the study drug administration on Day 1.

Refer to Section 6.3.1.2 to identify TEAE status when start date of an AE is unknown.

4.6.1.2. Intensity of Adverse Events

Intensity (or severity) of AEs will be graded as "Mild", "Moderate" or "Severe". For AEs with missing severity, the most severe assessment will be imputed for analyses, following worst case principle. If the intensity of an AE changes, then the most severe intensity during the continuous episode will be recorded.

4.6.1.3. Relationship to Study Drug

Causal relationship of an AE with study drug will be classified by the investigator and will be reported as "Not related", "Unlikely related", "Probably related" or "Possibly related". The sponsor will classify "Probably related" and "Possibly related" causality assessments as positive causality and "Not related" and "Unlikely related" causality assessments as negative causality.

Any missing relationship of an AE to study drug will be considered as related to study drug for the analyses, following worst case principle.

4.6.2. Potentially Clinically Important Laboratory Values

Potentially clinically important (PCI) laboratory values are presented in Table 9 below.

Table 9: Potentially Clinically Important Laboratory Criteria

Parameter	PCI Low: Less than or equal to	PCI High: Greater than or equal to
Hemoglobin (g/L)	100	190
Hematocrit	0.3	0.6
Platelets (10^9/L)	100	650
ALT (U/L)		3×ULN
AST (U/L)		3×ULN
Creatinine (µmol/L)		300
BUN (mmol/L)		12

ALT=Alanine Aminotransferase; AST=Aspartate Aminotransferase; BUN=Blood urea nitrogen; ULN=Upper limit of normal

4.6.3. Potentially Clinically Important Vital Sign Values

Vital sign values are PCI if they meet either or both of the observed value criteria and the change from baseline criteria. The PCI vital sign values are presented in Table 10 below.

Table 10: Potentially Clinically Important Vital Sign Criteria

Parameter	PCI Low	PCI High
Systolic Blood Pressure	≤90 mmHg and/or decrease≥20 mmHg from baseline	≥180 mmHg and/or increase≥20 mmHg from baseline
Diastolic Blood Pressure	≤50 mmHg and/or decrease≥15 mmHg from baseline	≥105 mmHg and/or increase≥15 mmHg from baseline
Pulse Rate	≤50 bpm and/or decrease ≥15 bpm from baseline	≥120 bpm and/or increase≥15 bpm from baseline
Respiratory Rate	≤8 brpm and/or decrease≥7 brpm from baseline	≥25 brpm and/or increase ≥7 brpm from baseline
Temperature		≥38.3°C and/or increase ≥1.1°C from baseline

bpm=Beats per minute; brpm=Breaths per minute

4.6.4. Immunogenicity

Serum samples will be collected and will be tested for binding anti-AUX-I and anti-AUX-II antibodies. When immunogenicity samples are required on Day 1, the samples will be collected prior to study treatment administration. The samples also will be tested for neutralizing antibodies at times to be determined by the sponsor.

4.7. Pharmacodynamics

4.7.1. Comparison of Baseline (Screening) MRI Tissue Morphology and Septae

To radiologically assess the impact of treatment with CCH in adult females with cellulite, Baseline (Screening) MRI tissue morphology and septae will be compared to images taken at Day 71.

The long-term impact of treatment with CCH in adult females with cellulite will be assessed by comparing the changes in MRI tissue morphology and septae at Day 251 to Baseline (Screening).

4.7.2. Comparison of Baseline (Screening) Histopathology

The evaluation of tissue histopathology in assessing the impact of treatment with CCH in adult females with cellulite will be done by comparing Baseline (Screening) histopathology to the sample taken at Day 71.

The evaluation of tissue histopathology in assessing the long-term impact of treatment with CCH in adult females with cellulite will be done by comparing Baseline (Screening) histopathology to the sample taken at Day 251.

5. ANALYSIS POPULATIONS

The study will use the following analysis populations for data summarization.

Table 11: Analysis Population

Population	Definition	Displays
Safety Population	The Safety Population will include all subjects who have undergone any MRI or biopsy at Screening.	All demographic and baseline characteristics as well as safety parameters will be summarized based on this population.
Evaluable Population	The Evaluable Population will include all subjects in the Safety Population who have a baseline and at least 1 post-injection PR-PCSS evaluation.	All efficacy analyses will be based on this population.

6. STATISTICAL METHODS

6.1. General Methodology

All statistical analysis, summary tables and data listings will be prepared using version 9.3 or later of SAS® software.

All statistical tests of efficacy parameters will be 2-sided with a significance level of α=0.05, unless specified otherwise.

Continuous data will be summarized using descriptive statistics (number of subjects [n], mean, standard deviation [SD] or standard error [SE], median, minimum [min], and maximum [max]) and discrete data will be summarized using frequency counts and percentages, the denominator will be based on the number of subjects in the appropriate population. For the purpose of display, the summary results will be rounded as follows:

- Min and max: same number of decimal places as the raw data.
- Mean and median: 1 more decimal place than the raw data.
- SD/SE: 2 more decimal places than the raw data.
- Percentages will be displayed with 1 decimal precision. A zero count will not have the associated percentage presented on the table (ie, no 0%).
- The standard form of a percentage change variable is 0 decimal places.

For categorical variables with missing values, a category documenting the frequency of missing values will be displayed in the summary tables.

Summary tables, subject listings and any supportive SAS output will include a "footer" of explanatory notes that will indicate, when applicable:

- Date of data extraction
- Date and time of output generation
- SAS program name, including the path, that generates the output

When calculating percentages, the denominator will be based on the number of subjects with non-missing values. If the denominator is expected to change over time, then the denominator used to calculate the percentage should be based on the number of subjects with non-missing values at each visit. Any subject removed from an analysis will be noted at the bottom of the table along with the reason the subject was removed.

Null summary tables will be presented with a note stating that "No Subjects Met Criteria".

Subject listings of all data from the eCRFs as well as any derived variables will be presented.

6.2. Derived Variables

Refer to Table 12 below for derived variables and their definitions for various study parameters.

Table 12: Derived Variables and Definition

Variable	Definition
Height (cm)	If height is recorded in inches, then height is equal to the recorded value multiplied by 2.54 and then rounded to 1 decimal place.
Weight (kg)	If weight is recorded in pounds, then weight is equal to the recorded value multiplied by 0.454 and then rounded to 1 decimal place.
Baseline	Baseline is defined as the last non-missing measurement/assessment prior to the CCH injections given at Day 1. Any assessments performed at an unscheduled visit will be considered in the calculation of baseline, if the unscheduled assessment is the closest value preceding the study drug injection.
Study Day	Study Day will be computed as Date of Assessment – Date of Day 1 + 1 for assessments on or after Day 1, else study day will be computed as Date of Assessment – Date of Day 1.
Change from Baseline	Change from baseline will be derived as post-baseline visit/time point value – the baseline value.
Last Date in the Study	Last date in study is defined as: • The date of Day 265 (Biopsy follow-up visit) if the subject completes the study • The date of early termination visit if the subject is terminated early from study at a non-scheduled visit • The date of the latest scheduled visit if the subject is terminated early from study at a scheduled visit or lost to follow-up.
Age (Years) at EFP Symptom Onset	Date of EFP symptoms reported – Date of Birth/365.25. See Section 6.3.1.3 for handling of partial or unknown EFP symptom onset dates.
Time (Years) Since Last EFP Treatment	Date of most recent EFP treatment – Date of informed consent/365.25. See Section 6.3.1.3 for handling of partial or unknown EFP treatment dates.
Duration (Minutes) of Exposure at Each Visit	Date/Time of Last Injection – Date/Time of First Injection
Duration of AE (Days)	AE end date – AE start date + 1
AE Onset Day	AE start date – Date of Day 1 + 1.

6.3. Handling of Missing Data

Subjects who discontinue the study any time after the initiation of the study drug will not be replaced and available data of these subjects until the point of discontinuation will be summarized. The missing baseline assessment will not be imputed.

For categorical variables with missing values, a category documenting the frequency of missing values will be displayed in the summary tables.

Subjects who discontinue early will be encouraged to complete all end of study (EOS) procedures and assessments at an early termination visit.

There will be no imputation of missing values for safety data, however missing relationship between AE and study drug will be considered as related to study drug following worst case principle. Missing severity of an AE will be summarized as a severe AE.

Immunogenicity samples with a positive titer value will undergo a log transformation for analyses. Samples with titer levels less than 1 will be assigned or imputed as a log transformed titer of 0 for analyses.

6.3.1. Imputation of Partial Dates

The following rules will apply in cases of partial dates in concomitant medications and procedures:

- If the start date is partial with month and year present, then missing day will be imputed with the first day of the month. Whereas if the end date is partial with month and year present then missing day will be imputed with the last day of the month.
- If only year is present in the start date, then missing day and month will be imputed with first day of January. Whereas if only year is present then missing day and month will be imputed with the last day of December.

6.3.1.1. Concomitant Status of Medication for Unknown Start Date

The following rules will apply in cases where the start date of a concomitant medication is completely unknown:

- If the medication onset date is unknown and the end date is on or after the Screening Visit date or medication is ongoing, then the medication will be considered as concomitant.
- If the medication onset date is unknown and the end date is before the Screening Visit date, then the medication will not be considered as concomitant.
- If both the start and end dates are unknown, then the medication will be considered as concomitant. This approach is considered to be the most conservative following the worst-case principle.
- If the medication onset date is partly present and month/year is before informed consent date, then the medication will not be considered as concomitant.

6.3.1.2. TEAE Status When Start Date Is Unknown

The following rules will apply in cases where start date of an AE is unknown:

- If the AE onset date is unknown and the end date is after the date of CCH injection on Day 1 or ongoing, then the AE will be considered a TEAE.
- If the AE onset date is unknown and the end date is before the date of CCH injection on Day 1, then the AE will not be considered a TEAE.
- If both the start date and end date are unknown (or ongoing), then the AE will be considered a TEAE, following the worst-case principle.

6.3.1.3. Missing EFP Onset Date

Missing EFP onset day will be imputed as the first day of the month and missing onset month will be imputed as January. If the EFP onset date is indicated as completely unknown but starting less than 5 years ago, the EFP onset date will be imputed as the informed consent date minus 5 years. If the EFP onset date is indicated as completely unknown but starting more than 5 years ago, the EFP onset date will not be imputed. Missing EFP medication/treatment end days will be imputed with the last day of the month and missing end months will be imputed with December, except if the end year is equal to the date of injection year and then the EFP medication/ treatment end date will be imputed with the first injection date.

6.4. Interim Analyses

An interim analysis will be conducted when all subjects have completed their Day 71 visit. Analysis of all primary and secondary endpoints will be included in the interim analysis.

The purpose of the interim analysis is to determine if changes in morphology and/or histology can be identified using MRI and biopsy. If the interim analysis does not indicate that such changes can be identified, subsequent or additional MRIs or biopsies will not be done in this study.

7. STATISTICAL ANALYSES

7.1. Subject Disposition

The number of subjects included in each study population will be summarized by treatment region (ie, buttocks, thighs) and overall. Subjects excluded from the Safety Population or Evaluable Population will be listed.

The frequency counts and percentages of subjects screened, screen failed, treated, not treated completed, and discontinued from study treatment and/or withdrawn from the study, as well as the reason for discontinuation from study and reason for discontinuation of study drug will be summarized by treatment region and overall.

A listing of disposition for all subjects will be provided. Screen failure reasons will also be listed. In addition, a listing for inclusion/exclusion criteria will also be presented.

7.2. Protocol Deviations

A listing of all protocol deviations will be presented.

7.3. Demographics and Baseline Characteristics

Demographic and other baseline characteristics will be summarized by treatment region, not treated and overall using the Safety and Evaluable Population.

Age, height (at screening), body weight (at screening) and BMI in kg/m^2 will be summarized by treatment region and overall as continuous variables using descriptive statistics. Gender, race, ethnicity, skin category based on the Fitzpatrick scale assessment, PR-PCSS, CR-PCSS, Hexsel CSS total score and report of tobacco and alcohol use (never, current, and former) will be summarized by treatment region, not treated and overall as categorical variables using frequency counts and percentages.

All demographic and baseline characteristics will be presented in a listing for all subjects.

7.4. Medical and Surgical History

Medical history will be coded using the MedDRA dictionary (version is defined in the Data Management Plan). Medical, surgical and EFP history data will not be summarized; however, a subject listing will be provided for all subjects.

7.5. Prior/Concomitant Medications and Procedures

Prior and concomitant medications, procedures and EFP treatments will be summarized by treatment region, not treated and overall using frequency counts and percentages for subjects in the Safety Population, by active ingredient within each ATC, with ATC and active ingredients ordered alphabetically. Multiple use of the same medication by a subject will be counted only once.

A listing of prior and concomitant medications and procedures will be provided for all subjects. Similarly, a separate listing of medications and procedures for EFP/Cellulite will also be presented.

7.6. Efficacy Analyses

Efficacy parameters will be summarized by treatment area (left or right) and treatment region (buttock or thigh) using the Evaluable Population.

PR-PCSS, CR-PCSS and Hexsel CSS total score ratings and the level of change from baseline will be summarized as per below sections.

A listing for digital photography will be provided with date and time for photos taken and reasons for photos not taken per protocol.

Individual listings will be provided for PR-PCSS ratings, CR-PCSS ratings and Hexsel CSS ratings and total scores.

7.6.1. Primary Endpoint

7.6.1.1. Change from Baseline in PR-PCSS Rating at Day 71

The baseline PR-PCSS ratings and the level of change in PR-PCSS ratings from Baseline (Screening) at Day 71 will be summarized using frequency counts and percentages for each severity rating and with mean and SD.

To assess the impact of CCH at Day 71, the PR-PCSS ratings at Day 71 will be compared with Baseline ratings using paired *t* test. The normality assumption of the difference of assessment will be evaluated using Shapiro-Wilk test and Q-Q plot.

Two-sided *p* value with 5% level of significance will be used to check if normality is achieved or not. Normality will be concluded if the *p* value > 0.05.

In case normality assumption is not met then Wilcoxon Signed Rank Pratt Lehmann test (adjusted for the correction factor for ties and zeros, if present) will be used.

The result of the analysis will be presented as:

SAS appendix will be presented detailing the test of normality of differences in Day 71 and Baseline PR-PCSS ratings.

Paired *t* test: Mean difference between Baseline and Day 71 ratings and associated 95% CI, SE, and *p* value. The negative mean difference indicates improvement in cellulite severity at Day 71.

Wilcoxon Signed Rank Pratt Lehmann test: Sum of positive ranks, sum of negative ranks and *p* value will be presented. If the sum of the negative rank is greater than the sum of positive rank, then it indicates improvement in cellulite severity at Day 71.

7.6.2. Secondary Endpoints

7.6.2.1. Change from Baseline in PR-PCSS Rating at Days 22 and 43

The baseline PR-PCSS ratings and the level of change in PR-PCSS ratings from Baseline (Screening) at Day 22 and 43 will be summarized using frequency counts and percentages for each severity rating and with mean and SD.

In addition, the PR-PCSS ratings at Day 22 and 43 will be compared with Baseline ratings using similar analysis as mentioned for primary endpoint. Refer to Section 7.6.1.1 for more details.

7.6.2.2. Change from Baseline in CR-PCSS Rating at Days 22, 43, and 71

The baseline CR-PCSS ratings and the level of change in CR-PCSS ratings from Baseline (Screening) at Days 22, 43, and 71 will be summarized using frequency counts and percentages for each severity rating and with mean and SD.

In addition, the CR-PCSS ratings at Days 22, 43, and 71 will be compared with Baseline ratings using similar analysis as mentioned for primary endpoint. Refer to Section 7.6.1.1 for more details.

7.6.2.3. Changes in the Hexsel CSS Total Score from Baseline at Days 22, 43, and 71

The baseline Hexsel CSS scores and the level of change in Hexsel CSS scores from Baseline (Screening) at Days 22, 43, and 71 will be summarized using frequency counts and percentages for each severity scores and with mean and SD.

In addition, the Hexsel CSS total score ratings at Days 22, 43, and 71 will be compared with Baseline using similar analysis as mentioned for the primary endpoint. Refer to Section 7.6.1.1 for more details.

7.6.3. Tertiary Endpoints

7.6.3.1. Proportion of Subjects with No Change (or Worsening) from Baseline in PR-PCSS Rating on Days 161 and 251

The proportion of subjects with complete loss of response as provided in Section 4.5.5 in PR-PCSS rating will be summarized using frequency counts and percentages.

7.6.3.2. Proportion of Subjects with No Change (or Worsening) from Baseline in CR-PCSS Rating on Days 161 and 251

The proportion of subjects with complete loss of response as provided in Section 4.5.5 in CR-PCSS rating will be summarized using frequency counts and percentages.

7.6.3.3. Proportion of Subjects with No Change (or Worsening) from Baseline in Hexsel CSS Total Score on Days 161 and 251

The proportion of subjects with complete loss of response as provided in Section 4.5.5 in Hexsel CSS total score will be summarized using frequency counts and percentages.

7.7. Safety Analyses

Safety data will be summarized using the Safety Population.

7.7.1. Study Drug Exposure

The following will be summarized at each treatment session by treatment area for each treatment region using descriptive statistics:

- Number of injections given.
- Number of dimples treated.
- Average number of injections per dimple.
- Duration of exposure (refer to Table 12 for computation of exposure duration).
- Total dose administered.

The number of subjects treated at each treatment session will be summarized using frequency counts and percentages by treatment area for each treatment region.

A subject listing of overall exposure and injection status will be provided.

7.7.2. Adverse Events

All AE summary tables will include TEAEs and the AEs before the first injection.

AEs will be summarized by SOC and PT and by treatment region and overall as frequency counts and percentages of subjects with AEs and number of AEs (total events), unless otherwise specified.

A subject will only be counted once per SOC and PT.

For AEs by severity grade (mild, moderate, severe), if a subject has multiple events occurring in the same SOC or same PT, then the event with the maximum intensity (ie, severe) will be counted.

For AEs by relationship to study drug, if a subject has multiple events occurring in the same SOC or same PT, the event with the highest association (ie, related) to study drug will be summarized.

AEs will be presented in decreasing order of the incidences at SOC level and within each SOC, in decreasing order of the incidences at the PT level.

An overall summary of AEs and AEs related to study drug will be presented and will include:

- Any AE.
- Any mild, moderate and severe AE.
- Any study drug related AE.
- Any serious AEs.
- Any study drug related serious AE.
- Any AEs leading to study drug interruption/discontinuation.
- Any study drug related AEs leading to study drug interruption/discontinuation.
- Any AEs leading to study withdrawal.
- Any study drug related AEs leading to study withdrawal.
- Any AEs resulting in death.
- Any study drug related AEs resulting in death.
- Any AESIs.

The following summary tables will be presented by SOC and PT:

- All AEs.
- AEs by Severity.
- TEAEs by Relationship to Study Drug.
- Serious AEs.
- Serious study drug related TEAEs.
- TEAEs leading to study drug interruption/discontinuation.

- Study drug related TEAEs leading to study drug interruption/discontinuation.
- AEs leading to study withdrawal.
- Study drug related TEAEs leading to study withdrawal.
- AEs resulting in death.
- Study drug related TEAEs resulting in death.
- AESIs.

Most common non-serious AEs by order of frequency (most frequent, 2nd most frequent, and 3rd most frequent) will be summarized by PT. Most common non-serious AEs are any PT that at least 5% of the subjects reported at least once.

The following listings will be presented by subject:

- All AEs.
- Serious AEs.
- AEs resulting in drug interruption/discontinuation.
- AEs resulting in study withdrawal.
- AEs resulting in deaths.
- AESIs.

Refer to Table 12 for computation of duration of AEs.

7.7.3. Clinical Laboratory

Laboratory parameters (hematology and chemistry) results will be summarized by treatment region, not treated and overall using descriptive statistics for observed and change from baseline values at Baseline (Screening), Day 71, and Day 251.

PCI laboratory values will be summarized by frequency counts and percentages. Refer to Table 9 for PCI criteria.

Individual laboratory results including hematology, chemistry, urinalysis, blood serology, serum and urine pregnancy test results will be listed.

7.7.4. Vital Signs and Body Weight

Vital signs parameters (blood pressure, pulse rate, respiratory rate, and body temperature) and body weight will be summarized by treatment region, not treated and overall using descriptive statistics for observed and change from baseline values for all visits/time points.

PCI vital sign values will be summarized by frequency counts and percentages. Refer to Table 10 for PCI criteria.

Individual vital sign measurements including pulse rate, systolic blood pressure, diastolic blood pressure, respiratory rate, and body temperature will be listed.

7.7.5. 12-Lead ECG

A subject listing will be presented for the investigator interpretation.

7.7.6. Physical Examination

A subject listing will be presented for the physical examination (by body system) for Screening results.

7.7.7. Immunogenicity

Binding anti-AUX-I and anti-AUX-II antibody data will be summarized using the number of subjects with an immunogenicity sample, the frequency counts and percentages of subjects with a positive sample, and a descriptive summary of the average titer level of the positive samples at Day 1, Day 71, Day 161, and Day 251. The titer levels will be logarithmically transformed prior to being summarized descriptively.

The frequency counts and percentages of assayed serum samples that will detect the presence or absence of neutralizing antibodies (positive/negative) to AUX-I and AUX-II will be summarized by treatment region and overall using frequency counts and percentages at all visits.

Listings of immunogenicity data will be presented for all subjects.

7.8. Pharmacodynamics

Pharmacodynamic parameters, if available, will be summarized by treatment region (buttock or thigh) using the Safety Population.

7.8.1. Comparison of Baseline (Screening) MRI Tissue Morphology and Septae

A summary table and a listing will be provided based on Safety population if the data are available.

7.8.2. Comparison of Baseline (Screening) Histopathology

A summary table and a listing will be provided based on Safety population if the data are available.

8. CHANGE FROM PROTOCOL

This SAP is prepared primarily based on the study protocol; original version dated October 22, 2019 and protocol amendment 1 dated January 16, 2020.

9. REVISION HISTORY

This SAP is the first version.

10. REFERENCES

A Phase 2a Open-Label, Study to Assess the Impact of CCH Treatment of Buttock and Thigh Cellulite in Adult Females Using Photonumeric Scales, Magnetic Resonance Imaging, and Histopathology [EN3835-212 Clinical Study Protocol, Amendment 1]. Endo Pharmaceuticals Inc.; January 16, 2020.

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

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

11. TABLES, LISTINGS, AND GRAPH SHELLS

The layouts of the summary tables, subject listings, and graphs are presented in SAP Module 2.

These layouts incorporate all the appropriate table titles, table numbers, and footnotes.