SAP MODULE 1 – DETAILED STATISTICAL METHODOLOGY

Study EN3835-209

A PHASE 2A, OPEN-LABEL STUDY EVALUATING THE SAFETY AND DIFFERENT INJECTION TECHNIQUES OF COLLAGENASE CLOSTRIDIUM HISTOLYTICUM FOR THE TREATMENT OF EDEMATOUS FIBROSCLEROTIC PANNICULOPATHY

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
AE	Adverse event
AOI	Area of Interest
ATC	Anatomical therapeutic chemical
AUX-I	Clostridial class I collagenase
AUX-II	Clostridial class II collagenase
BMI	Body mass index
bpm	Beats per minute
brpm	Breaths per minute
CCH	Collagenase clostridium histolyticum
CI	Confidence interval
cm	Centimeter
CR-PCSS	Clinician-Reported Photonumeric Cellulite Severity Scale
CSS	Cellulite Severity Scale
DMP	Data Management Plan
3-D	Three dimensional
ECG	Electrocardiogram
EDC	Electronic data capture
EOS	End of study
eCRF	Electronic case report form
eCrCl	Creatinine clearance (estimated)
EFP	Edematous fibrosclerotic panniculopathy
Hexsel CSS	Hexsel Cellulite Severity Scale
IAT	Image Analysis Technician
IEC	Independent Ethics Committee
IRB	Institutional Review Board
kg	Kilogram
m	Meter
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
N	Number of subjects
OTC	Over the counter
PCI	Potentially clinically important
PT	Preferred term

Abbreviation	Definition
SAE	Serious adverse event
SAP	Statistical analysis plan
SCr	Serum creatinine
SD	Standard deviation
SOC	System organ class
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analyses to evaluate the safety and effectiveness of different injection techniques of collagenase clostridium histolyticum (CCH) in adult women with mild, moderate or severe edematous fibrosclerotic panniculopathy (EFP)/cellulite.

The general information about the study is detailed in the EN3835-209 protocol amendment 1, dated August 29, 2018.(1)

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of this study is to assess the treatment effects of CCH when administered by different injection techniques in subjects with EFP.

2.2. Secondary Objective

The secondary objective of this study is to assess the safety of CCH when administered using different injection techniques in subjects with EFP.

2.3. Exploratory Objectives

The exploratory objectives include:

- To assess the immunogenicity of CCH in the treatment of EFP
- To assess the usefulness of 3-D photography in evaluating outcomes of treatment for EFP

3. STUDY DESIGN AND MEASURES

3.1. Study Design

This is a Phase 2a, open-label, multicenter, exploratory study to evaluate the safety and effectiveness of different injection techniques of CCH for the treatment of adult women with EFP. This study will be performed at approximately 5 sites in the United States (US).

Subjects having the evidence of cellulite in 2 buttocks or 2 thighs (treatment area) at the Screening Visit will be enrolled if they satisfy the criteria below:

- Have a CR-PCSS score of 2 (mild), 3 (moderate) or 4 (severe) as reported by the Investigator in 2 treatment areas (two thighs or two buttocks)
- Have at least 2 dimples from each treatment area that:
  - are isolated and separated by at least 5 cm from any other dimples

- score 2 or 3 on the Hexsel depression scale
- have dimple width: length ratio ≥ 0.5

If both buttocks and both thighs meet entry criteria for a single subject, then the thighs will be treated. No subject will be treated for EFP in both the buttocks and the thighs during this study.

The study will enroll approximately 60 subjects; 30 subjects with 2 eligible buttocks (to be dosed in the buttocks) and 30 subjects with 2 eligible thighs (to be dosed in the thighs). The 30 subjects in each treatment region (buttocks or thighs) will be assigned sequentially to 1 of 5 injection technique treatment arms on Day 1 (ie, 6 subjects per region per treatment arm). No control groups will be employed. Subjects who discontinue from the study will not be replaced.

Subjects who complete the study will participate for approximately 92 days including a 21-day of screening period, a 43-day treatment period and a 28-day follow-up period. Subjects will receive the study injections on Days 1, 22, and 43. Additional scheduled assessments will be performed on Days 4, 8, 15, and 71.

Table 1 below describes the schedule of events and assessments performed during screening, treatment visits, and assessment visits.

Table 1: Schedule of Events

Procedure	Screening (Day-21 to Day -1)	Day 1	Day 4 (± 1 day)	Day 8 (± 1 day)	Day 15 (± 2 days)	Day 22 (± 2 days)	Day 43 (± 2 days)	End of Study/ Early Termination/ Day 71 (± 3 days)	Unscheduled Clinic Visit[a]
Informed consent[b]	X								
Inclusion/exclusion criteria review	X	X[c]							
Demographic data	X								
3-D Photography	X	X[d,e]	X	X	X	X[d,e]	X[d,e]	X	
Medical/surgical/EFP history (including previous treatment)	X								
Prior/concomitant medications/procedures	X	X[e]	X	X	X	X	X	X	X
Physical Examination	X							X	X
Height	X								
Weight	X	X[e]						X	X
Fitzpatrick skin type	X								
Vital signs	X	X[f]				X[f]	X[f]	X	X
12-lead ECG	X								
Safety Laboratory Tests	X							X	X
Anti-AUX-1/anti-AUX-II antibody level sample		X[e]						X	
Serum pregnancy test	X								
Urine pregnancy test		X[e]				X[e]	X[e]	X	X
Assignment of treatment area (buttocks or thighs)	X								
Selection of 2 dimples within each treatment area for volumetric assessment		X[e]							
CR-PCSS	X								
Hexsel Depression Depth Scale	X					X	X	X	
Assign Treatment Arm (dosing injection technique)		X[e]							
Mark the dimple injection sites		X[e]				X[e]	X[e]		

Table 1: Schedule of Events (Continued)

Procedure	Screening (Day-21 to Day -1)	Day 1	Day 4 (± 1 day)	Day 8 (± 1 day)	Day 15 (± 2 days)	Day 22 (± 2 days)	Day 43 (± 2 days)	End of Study/ Early Termination/ Day 71 (± 3 days)	Unscheduled Clinic Visit[a]
Study drug administration		X				X	X		
Injection site reactions/local tolerability in the treated areas		X	X	X	X	X	X	X	X
All other adverse events	←----------X----------→								

[a] During unscheduled visits the investigator or designee may perform any study procedure that they deem clinically necessary (eg, vital signs, clinical laboratory assessments, pregnancy test, etc).
[b] Performed prior to any study-required assessments.
[c] Should be reassessed and verified prior to study drug administration.
[d] Complete before and after marking injection sites.
[e] Complete prior to study drug administration.
[f] Vital signs will be collected up to 4 hours prior to, and at 15 and 30 minutes after study drug administration on Days 1, 22, and 43.

3.2. Inclusion Criteria

No subject will be assigned to treatment until all eligibility criteria have been satisfied. To qualify for the study a subject must:

1. Be able to provide voluntary written informed consent prior to the initiation of any study specific procedures per the policy of the governing Institutional Review Board (IRB)/ Independent Ethics Committee (IEC).
2. Be female and at least 18 years of age at the time of consent.
3. Have evidence of cellulite in 2 bilateral treatment areas (defined as right and left buttocks OR right and left posterolateral thighs) as assessed by the Investigator at the Screening visit, and fulfills the following requirements:
   a. has a score of 2 (mild), 3 (moderate) or 4 (severe) as reported by the Investigator (CR-PCSS) in 2 treatment areas (two thighs or two buttocks) at the Screening Visit.
   b. has at least 2 dimples from each treatment area that:
      - are isolated and separated by at least 5 cm from any other dimples
      - score 2 or 3 on the Hexsel depression scale
      - have dimple width: length ratio ≥ 0.5
4. Be willing to apply sunscreen to the dosing areas before each exposure to the sun while participating in the study (ie, screening through end of study).
5. Be judged to be in good health, based upon the results of a medical history, physical examination, and laboratory profile at screening.
6. Have a negative serum pregnancy test at the Screening Visit and negative urine pregnancy at Day 1 (before injection of study drug), be using an effective contraception method (eg, abstinence, intrauterine device, hormonal [estrogen/progestin] contraceptives, or double barrier control) for at least 1 menstrual cycle prior to study enrollment and through Day 71; or be menopausal defined as at least 12 months of amenorrhea in the absence of other biological or physiological causes (as determined by the Investigator), or be post-menopausal for at least 1 year, or be surgically sterile (hysterectomy, bilateral oophorectomy, bilateral tubal ligation).
7. Be willing and able to comply with all protocol required study visits and assessments.

3.3. Exclusion Criteria

A subject will be excluded from study participation if she:

1. Is pregnant or is intending to become pregnant during the study.
2. Is presently nursing/breastfeeding or providing breast milk.
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 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 Medical Monitor.
e. Evidence of clinically significant abnormalities on physical examination, vital signs, electrocardiogram (ECG), or clinical laboratory values.

4. 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, varicose veins, telangiectasia).
   c. Inflammation or active infection.
   d. Severe skin laxity, flaccidity, and/or sagging.
   e. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer.

5. Has a tattoo located within 2 cm of the site of injection.

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 drug.

7. Has used any of the following for the treatment of EFP on the area to be treated within the timelines identified below or intends to use any of the following at any time during the course of the study:

   a. Liposuction within the treatment areas during the 12-month period before injection of study drug.
   b. Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; or surgery (including subcision and/or powered subcision) within the treatment areas during the 12-month period before injection of study drug.
   c. Any investigational treatment for EFP/cellulite on treatment areas during the 12-month period before the injection of study drug.
   d. Endermologie® or similar treatments within the treatment areas during the 6-month period before injection of study drug.
   e. Massage therapy within the treatment areas during the 3-month period before injection of study drug.
   f. Creams (eg, Celluvera™, TriLastin®) to prevent or mitigate EFP within the treatment areas during the 2-week period before injection of study drug.

8. Has received an investigational drug or treatment within 30 days before injection of study drug.

9. Has a known systemic allergy to collagenase or any other excipient of study drug.

10. Has a history of drug or alcohol abuse.

11. Intends to initiate an intensive sport or exercise program during the study.

12. Intends to initiate a weight reduction program during the study.

13. Intends to use tanning spray or tanning booths during the study.

14. Has previously received any collagenase treatments (eg, Santyl® ointment and/or XIAFLEX/XIAPEX®).
15. Was a subject in a previous cellulite clinical trial of CCH: AUX-CC-830, AUX-CC-831, EN3835-102, EN3835-104, EN3835-201, EN3835-202, EN3835-205, EN3835-302, or EN3835-303.
16. Any other condition(s) that, in the Investigator's opinion, might indicate the subject is unsuitable for the study.

3.4. Treatment Region and Area

Treatment region is defined as buttocks OR posterolateral thighs. A subject will have two treatment areas defined as both buttocks (left and right buttocks) OR both thighs (left and right posterolateral thighs).

3.5. Selection of Dimples and Injection Sites During Treatment Visits

3.5.1. Selecting and Marking the Dimples

The investigator will select dimples in the treatment areas (left and right buttocks OR left and right posterolateral thighs) that are well defined, evident when the subject is standing in a consistent relaxed pose (without the use of any manipulation such as skin pinching or muscle contraction), and suitable for treatment. If both buttocks and both thighs meet entry criteria for a single subject, then the thighs will be treated. No subject will be treated for EFP in both the buttocks and the thighs during this study.

The Investigator will identify at least two (2) dimples per treatment area which should be spaced out by at least 5 cm from other dimples and score 2 or 3 on the Hexsel depression scale (see Table 6 for Question B on Hexsel score).

3.6. Study Drug Administration

Each subject will receive 24 injections for a total of 1.68 mg (0.84 mg per treatment area) at each treatment visit. The cumulative CCH dose will be 5.04 mg for each subject who completes the 3 treatment visits.

Each subject will receive study drug on Day 1, Day 22 and Day 43 (treatment visits) unless the treatment area is dimple-free at Treatment Visit 2 (Day 22) and/or Treatment Visit 3 (Day 43). A dimple-free buttock or thigh at Treatment Visit 1 (Day1) is precluded by the eligibility criteria. A dimple-free buttock or thigh at Treatment Visit 2 (Day 22) and/or Treatment Visit 3 (Day 43) does not preclude treatment of the contralateral buttock or thigh unless it is also dimple-free.

The study drug, CCH, will be administered using 1 of 5 injection techniques. Each of the injection techniques are referred to as a treatment arm (I - V). Subjects will be sequentially assigned to a treatment arm at Day 1. Injection techniques differ from each other in, concentration of the CCH injectate, angle of injection, depth of injection, volume of injection and study drug administration at injection site.

At every treatment visit, irrespective of the treatment arm (injection technique) assigned, all eligible subjects will receive the same amount of study drug (CCH, 0.84mg) injected in each

assigned treatment area. All eligible subjects with dimples (in each buttock or thigh) that require treatment to improve the aesthetic appearance will receive full treatment course with CCH injections. Across all treatment arms, study drug will be administered subcutaneously while subject is in a prone position.

The injection volume and concentration for each treatment arm are outlined in Table 2 below.

Table 2: Volume and Concentration of Injections

Treatment	Number of Subjects/Area	Dose/ Injection	Volume/Injection	Drug Concentration/ Injection	Total Volume/ Treatment Visit
Treatment I: Shallow injection, 3 aliquots	6 (buttocks) 6 (thighs)	0.07 mg	0.3 mL (given as 3 - 0.1 mL aliquots)	0.23 mg/mL	7.2 mL (12 injections/ treatment area x 2 treatment areas x 0.3 mL)
Treatment II: Shallow injection, 1 aliquot	6 (buttocks) 6 (thighs)	0.07 mg	0.3 mL (given as 1 - 0.3 mL aliquot)	0.23 mg/mL	7.2 mL (12 injections/ treatment area x 2 treatment areas x 0.3 mL)
Treatment III: Deep injection, 1 aliquot	6 (buttocks) 6 (thighs)	0.07 mg	0.3 mL(given as 1 - 0.3 mL aliquot)	0.23 mg/mL	7.2 mL (12 injections/ treatment area x 2 treatment areas x 0.3 mL)
Treatment IV: Deep and shallow injections, 5 aliquots	6 (buttocks) 6 (thighs)	0.07 mg	1.5 mL (given as 5 - 0.3 aliquots)	0.047 mg/mL	36 mL (12 injections/ treatment area x 2 treatment areas x 1.5 mL)
Treatment V: Shallow injection, 4 aliquots	6 (buttocks) 6 (thighs)	0.07 mg	1.2 mL (given as 4 - 0.3 mL aliquots)	0.060 mg/mL	28.8 mL (12 injections/ treatment area x 2 treatment areas x 1.2 mL)

3.6.1. Determination of Sample Size

A sample size of 60 subjects (30 with two eligible buttocks and 30 with two eligible thighs) was chosen empirically based on the pragmatic criteria and published data of previous studies.

3.6.2. Blinding and Randomization

This is an open-label study. Subjects will be sequentially assigned to a treatment arm at Day 1.

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

The CR-PCSS - Buttock (Table 3) and the CR-PCSS - Thigh (Table 4) will be used to assess the severity of cellulite of both treatment areas respectively at Screening (each buttock or each thigh independently).

These ratings will be marked on the source documentation and then entered into the Electronic Data Capture (EDC) system.

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 each buttock or thigh by live assessments.

The ratings range from 0 (None) to 4 (Severe) with labels and descriptors to aid the Investigator in the assessments. This assessment should be made while the subject is in the standing position with relaxed gluteus muscles. See chart below for details.

Table 3: CR-PCSS Buttock Scale

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

Table 4: CR-PCSS Thigh Scale

Rating	Level of Severity	Description
0	None	No depressions or raised areas
1	Almost None	A few depressions or undulations that are mostly superficial in depth
2	Mild	Several undulations that are shallow in depth with areas of slight protuberances
3	Moderate	Many undulations with alternating areas of protuberances and depressions, of which most are moderate in depth
4	Severe	A lot of undulations with alternating areas of protuberances and depressions, some of more severe depth.

The investigator will go through a training process and will need to pass a qualifying exercise prior to using the CR-PCSS.

3.8. 3-D Photography

The 3-D photographs are not direct efficacy measurements; however, 3-D photography will be utilized in the assessment of treatment effect. The investigator or qualified designee will photograph each treatment area (both buttocks and both thighs) prior to injections using a Sponsor-supplied standardized digital camera in a standardized manner as per 3-D photography manual, at the following time points:

- Before and after marking dimples and injection sites on treatment Days 1, 22, and 43
- Single set of photographs will be taken at screening and all other visits

The 3-D photographs taken at Days 4, 8, 15, 22, 43, and 71 [End of Study (EOS)/Early termination) will be assessed by a central assessor blinded to the treatment arm and study visit day. The central assessor will complete a 5-point Likert Scale to gauge the level of aesthetic improvement achieved (from baseline) in each treatment area (ie, scoring from worse to very much improved, for aesthetic improvement).

The labels and descriptions associated with each level of aesthetic improvement achieved of Likert Scale are shown in Table 5 below:

Table 5: Likert Scale of Level of Aesthetic Improvement

Rating	Description
-1	Worse (The treated area appearance is worse than before treatment)
0	No change (The treated area appearance is essentially the same as before treatment)
1	Improved (Obvious improvement in the treated area appearance from before treatment, but additional treatment is indicated)
2	Much Improved (Marked improvement in the treated area appearance from before treatment, but not completely optimal)
3	Very much improved (Optimal cosmetic result from treatment of the treated dimples)

3.9. Dimple Analysis

The Image Analysis Technician (IAT) will use the Day 1-Post marking image as a reference to determine the location of the target dimple on the Day 1-Pre marking image.

A tracing will be made around the border of concavity of the dimple on the Day 1-Pre marking.

The dimple tracing will be transposed on to the Day 22-Pre Marking, Day 43-Pre marking, and Day 71/ET images.

This tracing will be used to measure the:

- Max length, the largest straight line distance across the dimple
- Max width, the largest straight line distance perpendicular to the max length measurement
- Surface area of the dimple
- Volume between the base of the dimple and the interpolated surface

3.10. Bruise Analysis

The IAT will trace the bruise on the Day 4 image in addition to an area of normal skin. The bruise tracing and normal tissue tracing will be transposed onto the Day 1-Pre Marking, Day 8, and Day 15 images.

A pair of numerical values of the mean lab color (number) value of bruised area and normal skin color value will be collected from the 3-D photographs at each imaging evaluation visit for bruising.

Bruise analysis will consist of two L*A*B* color measurements. L*A*B* color values will be measured within the bruised tissue and normal tissue area of interest (AOI).

3.11. Hexsel Depression Depth Scale

The Hexsel Cellulite Severity Scale (Hexsel CSS) is a photonumeric scale that looks at 5 key morphologic features of cellulite (2,3):

- A - number of evident depressions
- B - depth of depressions
- C - morphological appearance of skin surface alterations
- D - laxity, flaccidity or sagging of skin, and
- E - current classification scale based on medical literature

Each of these features is evaluated on a 4-point scale from a low of 0 to a high of 3. For this study, only "B - depth of depressions" will be assessed.

The investigator or qualified designee will use the Hexsel CSS (B) depth of depressions to assess the severity of EFP in each buttock or each thigh. The assessment will be made while the subject is in the standing position with relaxed gluteus muscles at the following visits:

- Screening visit
- Days 22, 43, and 71(EOS/ Early termination)

The labels and descriptions associated with each level of depth of depression of Hexsel CSS (B) are shown in Table 6 below.

Table 6: Hexsel CSS (B) Depth of Depressions

Rating	Description
0	No depressions
1	Superficial depressions
2	Medium depth depressions
3	Deep depressions

3.12. Medical and Surgical History

A medical and surgical history of the subject will be taken during the screening period. Medical history will include relevant diagnoses and/or procedures/therapies with onset/resolutions dates.

If onset date is unknown, then condition whether it occurred within 5 years or more than 5 years will be recorded on the eCRF.

3.13. Edematous Fibrosclerotic Panniculopathy Disease (EFP) History

EFP disease history will be obtained from the subject during the screening period. The EFP disease 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

3.14. Substance Use

History of tobacco and alcohol use will be taken during the screening period and 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)

3.15. Prior/Concomitant Medications and Procedures

Any medications (including OTC medication) taken during the study or within 90 days prior to Day 1 will be recorded.

Any diagnostic, therapeutic, or surgical procedure performed before the study or during the study, including the treatment of EFP will be recorded.

3.16. Prohibited Medications

The following medications and procedures 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.
- Liposuction within the treatment areas.
- Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; or surgery (including subcision and/or powered subcision).
- Any investigational treatment for EFP/cellulite on treatment areas or any other investigational drug or treatment.
- Endermologie or similar treatments within the treatment areas.

- Massage therapy within the treatment areas during the 3-month period before injection of study drug.
- Creams (eg, Celluvera, TriLastin) within the treatment areas.

3.17. Adverse Events

All Adverse Events (AE) occurring after signing the informed consent and through 28 days after last dose are to be recorded on the AE pages of the eCRF. Conditions existing prior to screening will be recorded as part of subject's medical history.

3.17.1. Adverse Events (AE)

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. This would include AEs resulting from concurrent illness, reactions to concurrent medication use, or progression of disease states (excluding the disease under study). A condition present at baseline that worsens after initiation of study treatment will be captured as an AE; the onset date will be the date the event worsened.

3.17.2. Serious Adverse Events (SAEs)

Serious adverse event 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 subject or may require medical intervention to prevent one of the outcomes listed above

3.17.3. Adverse Events of Special Interest

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 an AE of special interest and reported as an AE or SAE as appropriate.

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

3.18. Clinical Safety Laboratory Tests

Blood and urine samples will be collected for testing the following clinical laboratory parameters during the screening period and at EOS.

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*
	Creatinine clearance	Leukocytes*
	Aspartate transaminase (AST)	
	Alanine transaminase (ALT)	
	Gamma-glutamyl transferase (GGT)	
	Total bilirubin (TBL) (direct bilirubin reflex if elevated)	
	Albumin	
	Alkaline phosphatase (ALP)	
	Uric acid	

*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.

3.19. Pregnancy Test

Female subjects of child bearing potential must have negative pregnancy test at Screening and Day 1 to be enrolled in the study. Female subjects of child bearing potential will undergo a serum pregnancy at the Screening Visit and urine pregnancy tests at Days 1, 22, and 43 prior to study drug administration and at Day 71 (EOS). Additional urine pregnancy tests will be performed at the discretion of the Investigator when required.

3.20. Vital Signs

Vital signs measurements will be taken at Screening, Day 1, 22, 43, and at the EOS visit. On treatment visits (Days 1, 22, and 43), vital signs will be assessed at 4 hours prior to, and at 15 and 30 minutes after study drug administration.

Vital signs measurements include: systolic and diastolic blood pressure, respiratory rate, pulse rate, body temperature, height, and body weight.

Height and body weight measurements will be taken at Screening. Body weight will also be measured at Day 1 and at EOS visit.

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

3.21. 12-Lead Electrocardiogram (ECG)

A 12-Lead ECG will be recorded during the screening period while the subject is in supine position for at least 5 minutes before the recording is conducted.

ECGs will be assessed by the Investigator and graded as:

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

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

3.22. Physical Examination

A complete physical examination (by body system) on each subject will be performed at screening. This evaluation will include an examination of head, eyes, ears, nose and throat, skin, neck, chest, heart, lungs, breasts, lymph nodes, abdomen, back, extremities, musculoskeletal system, and central nervous system. Physical examination findings will be recorded as normal, abnormal or not done as not standard of care.

Any abnormality in physical examination observed, will be considered as an AE or SAE as appropriate.

The subject's skin type will be assessed at screening using the Fitzpatrick scale shown below.

Table 8: Fitzpatrick Scale

I	Pale white skin, blue/hazel eyes, blond/red hair	Always burns, does not tan
II	Fair skin, blue eyes	Burns easily, tans poorly
III	Darker white skin	Tans after initial burn
IV	Light brown skin	Burns minimally, tans easily
V	Brown skin	Rarely burns, tans darkly easily
VI	Dark brown or black skin	Never burns, always tans darkly

3.23. Immunogenicity

Immunogenicity variables include anti-AUX-I/anti-AUX-II binding (ie, anti-drug) and neutralizing antibody results. Serum samples will be collected at Day 1 (before injection) and at the Day 71 (EOS) visit for the determination of serum anti-AUX-I and anti-AUX-II antibody levels and neutralizing antibodies to AUX-I and AUX-II. A subset (based on every other sample from the Day 71 upper and lower quartiles of all positive binding antibody titers) of subject samples will be tested for neutralizing antibodies from the Day 1 and Day 71 visits; additional samples will be retained.

4. STUDY PARAMETERS

4.1. Subject Disposition

Subjects will be considered as completing the study if they complete all the scheduled treatment and the Day 71/EOS visit. A premature discontinuation will occur if subjects discontinue treatment and/or participation in the study. Subjects who discontinue early for any reason, will be

encouraged to have all Day 71/EOS procedures and assessments completed at an early termination visit.

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

4.2. Protocol Deviations

Protocol deviations will be identified and documented prior to database lock. Protocol deviations will be derived from the eCRF data and will be obtained from the clinical monitoring reports. All deviations from these two sources will be reconciled and duplicate deviations will be removed. When a deviation is both found in the database and in clinical monitoring reports, in most cases the text of the deviation from the database will be retained. The exception to this rule will occur if the deviation from the monitoring report provides important information not found in the database. In that case, the information will be reconciled in the database.

Possible protocol 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 of 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 a protocol deviation review meeting held prior to the database lock.

4.3. Prior Concomitant and Follow-up Medications

All medications will be coded using World Health Organization (WHO) Drug Dictionary - Global B3 format 2018, by active ingredient and WHO anatomical therapeutic chemical (ATC) classification of ingredients.

A prior medication is defined as any medication taken prior to the first injection of the study drug.

A concomitant medication is any medication taken between the date of first injection of the study drug and the date of last injection of study drug or the medication is reported as ongoing. Any medications started after the last injection of the study drug will be considered as follow-up medications.

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' with a start date prior to the first injection of study drug, 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

4.5.1. Improvement in Aesthetic Appearance using 3-D Photographic Image

Improvement from baseline in aesthetic appearance of the treatment area will be assessed by a blinded central assessor using a 5-point Likert Scale in each treatment area (ie, from worse to very much improved, for aesthetic improvement) at Day 22, 43 and 71. The efficacy will be evaluated at Day 22, 43 and 71.

4.5.2. Change in Dimple Analysis Parameters using 3-D Photographic Image

Dimple analysis parameters, max length, max width, surface area and volume between the dimple base and interpolated surface, will be assessed by IAT in each treatment area at Day 1, Day 22, 43, and 71/ET. The change in these parameters from Day 1 will be evaluated at Day 22, 43, and 71/ET.

4.5.3. Change from Baseline in Dimple Depth Depression by Hexsel CSS (B)

Dimple depth depression will be assessed by Investigator at the Screening visit, Day 22, 43, and 71 using Hexsel CSS (B) depth of depressions scale and graded as; No depressions (0), Superficial depressions (1), Medium depth depressions (2) and Deep depressions (3).

The change from baseline at each post baseline visits will be analyzed and summarized for Hexsel CSS (B) depth of depressions scale score of each treatment area.

4.6. Safety Parameters

4.6.1. Adverse Events

Adverse Event verbatim terms as reported by the investigator of adverse event will be mapped to System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The version to be used will be defined in Data Management Plan (DMP).

4.6.1.1. Treatment Emergent Adverse Events (TEAEs)

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

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

- If the AE onset date is prior to first injection on Day 1, then the AE will not be considered a TEAE.
- If the AE onset date or date of AE worsening is equal to or later than first injection on Day 1, then the AE will be considered a TEAE.

Refer to section 6.4.1.1 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.

4.6.1.3. Relationship to Study Drug

Causal relationship of AE with study drug will be classified by the Investigator and will be reported as follows:

- Not related
- Unlikely related
- Possibly related
- Probably related

Related adverse events are AEs with the relationship described by the investigator as "probably related" or "possibly related". "Not related" or "Unlikely related" causality assessments are considered 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. Vital Signs and Clinical Laboratories

4.6.2.1. 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 (%)	30	60
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 transaminase; AST=Aspartate transaminase; BUN=Blood urea nitrogen; ULN=Upper limit of normal

4.6.2.2. Potentially Clinically Important Vital Sign Values

Vital sign values are PCI if they meet both 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 decrease ≥20 mmHg from baseline	≥180 mmHg and increase ≥20 mmHg from baseline
Diastolic Blood Pressure	≤50 mmHg and decrease ≥15 mmHg from baseline	≥105 mmHg and increase ≥15 mmHg from baseline
Pulse Rate	≤50 bpm and decrease ≥15 bpm from baseline	≥120 bpm and increase ≥15 bpm from baseline
Respiratory Rate	≤8 brpm and decrease ≥7 brpm from baseline	≥25 brpm and increase ≥7 brpm from baseline
Temperature		≥38.3°C and increase ≥1.1°C from baseline

bpm=Beats per minute; brpm=Breaths per minute

4.6.3. Bruise Analysis using L*A*B* Coordinates

Bruised tissue and normal tissue will be assessed using two L*A*B* color measurements at Day 1, 4, 8, and 15. The change in visual perception between two colors, ie, ΔE will be computed as follows:

Bruised Tissue vs. Normal Tissue at Day 1, 4, 8, and 15

$$\Delta E \text{ (Bruised vs. Normal)} = [(L^*_B - L^*_N)^2 + (A^*_B - A^*_N)^2 + (B^*_B - B^*_N)^2]^{1/2}$$

Where, ΔE = Color difference between Bruised Tissue vs. Normal Tissue)

L^*_B = Bruised Tissue L*
L^*_N = Normal Tissue L*
A^*_B = Bruised Tissue A*
A^*_N = Normal Tissue A*
B^*_B = Bruised Tissue B*
B^*_N = Normal Tissue B*

Normal Tissue of Follow-up Visits vs. Normal Tissue of Day 1

$$\Delta E \text{ (Normal – Day 1 vs. Follow-up)} = [(L^*_F - L^*_{D1})^2 + (A^*_F - A^*_{D1})^2 + (B^*_F - B^*_{D1})^2]^{1/2}$$

Where, ΔE = Color difference between Normal Tissue at Follow-up visits vs. Normal Tissue at Day 1

L^*_F = Normal Tissue L* at Follow-up visit
L^*_{D1} = Normal Tissue L* at Day 1
A^*_F = Normal Tissue A* at Follow-up visit
A^*_{D1} = Normal Tissue A* at Day 1
B^*_F = Normal Tissue B* at Follow-up visit
B^*_{D1} = Normal Tissue B* at Day 1

4.7. Other Safety Parameters

4.7.1. Immunogenicity

Seropositivity and titer levels for both anti-AUX-I and anti-AUX-II antibodies will be obtained from each analyzed sample. Samples with a positive titer value will undergo a log transformation for analyses. Samples with titer level less than 1 will be assigned or imputed as a log transformed titer of zero (0) for analyses.

All samples with seropositive antibodies will be tested for neutralizing antibodies on Day 1 and Day 71. Samples will be classified as positive or negative for neutralizing antibodies based on the results of these analyses.

5. ANALYSIS POPULATIONS

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

Table 11: Analysis Populations

Population	Definition	Displays
Safety Population	The Safety Population will include all subjects who have at least 1 injection of study medication.	All demographic, baseline characteristics and safety parameters will be summarized based on this population.
Evaluable Population	The Evaluable Population will include all subjects in the Safety Population who have completed screening procedures and at least 1 post baseline assessment of the Likert Scale score of aesthetic appearance improvement.	All efficacy analysis will be based on this population.

6. STATISTICAL METHODS

6.1. General Methodology

All statistical tests, summary tables and data listings will be prepared using SAS version 9.4

All statistical tests of efficacy parameters will be two-sided with a significance level of α=0.05, unless specified otherwise. Statistical tests will be supported by presenting estimates and 95% confidence intervals (CI) for the respective treatment effects. These estimates and CI will be based on the linear regression model.

Continuous data will be summarized using descriptive statistics. 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:

- Minimum and maximum: same number of decimal places as the raw data.
- Mean and Median: one more decimal place than the raw data.
- SD: Two more decimal places than the raw data.
- Percentages will be displayed with one decimal place precision. A zero count will be left blank.
- The standard form of a percentage change variable is 0 decimal place.

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, graphs and any supportive SAS output will include footnotes that will indicate:

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

Empty 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. Adjustments for Covariates

Not applicable.

6.3. Derived Variables

Table 12 defines the derived variables for study parameters.

Table 12: Derived Variables and Definition

Variable	Definition
Age Group	<35 years 35 – <45 years 45 – <65 years ≥65 years
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.
Body Mass Index (BMI)	BMI will be computed using height and body weight measured at screening as, BMI (kg/m^2) = Weight (kg) / Height $(m)^2$
BMI Group	Underweight (<18.5 kg/m2) Normal Weight (18.5 – <25.0 kg/m2) Overweight (25.0 – <30.0 kg/m2) Obese (≥30.0 kg/m2)
Relative Day	The day of first injection of study drug will be considered as relative day 1
Study Day (for assessment on or after Day 1)	Study Day will be computed as, Date of Assessment – Date of Day 1 + 1
Study Day (for assessment before Day 1)	Study Day will be computed as, Date of Assessment – Date of Day 1
Baseline	Baseline is defined as the last non-missing measurement/assessment prior to the first dose of study drug. For vital signs, the baseline will be the Day 1 pre-dose values. For clinical laboratories this could be the screening value, or it could be an unscheduled lab, if the unscheduled lab is the closest value preceding the first injection.
Change from Baseline	Change from baseline will be derived as, post-baseline visit/time point value – the baseline value.
Last Date in Study	• The date of Day 71 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 at EFP Symptom Onset	Date of EFP symptoms reported – Date of Birth/365.25. See section 6.4.1.3 for handling of partial or unknown EFP symptom onset dates.
Time Since Last EFP Treatment	Date of most recent EFP treatment – Date of informed consent)/365.25. See section 6.4.1.3 for handling of partial or unknown EFP treatment dates.
Baseline CR-PCSS Score	Investigator baseline CR-PCSS scores for each treatment area will be based on the investigator's CR-PCSS evaluation done at the Screening visit.
Baseline for Hexsel Depression Depth Scale	The investigator assessment performed at Screening for each treatment area will be considered as Baseline.
Duration of Exposure at Each Visit	Date/Time of Last Injection – Date/Time of First Injection
Duration of AE	AE end date – AE start date + 1
AE Onset Day	AE start date - Date of first injection + 1

6.4. Handling of Missing Data

Subjects who discontinue the study prior to or after the initiation of the study drug will not be replaced and available data for 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 have all Day 71 procedures and assessments completed 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 level less than 1 will be assigned or imputed as a log transformed titer of zero (0) for analyses.

6.4.1. Imputation of Partial Dates

6.4.1.1. TEAE Status for Completely Unknown Start Date

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

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

If the AE onset date is partly present and month/year is prior to the first injection date then the AE will not be considered a TEAE.

6.4.1.2. Concomitant Status of Medication for Completely Unknown Start Date

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

- If the medication onset date is unknown and the end date is after first injection on Day 1 but before the last injection 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 first injection on Day 1, 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 prior to the first injection date, then the medication will not be considered as concomitant.

6.4.1.3. Missing EFP Onset Date

Missing EFP onset days will be imputed with the first day of the month and missing onset month will be imputed with 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.

6.5. Interim Analyses

No interim analysis is planned in this study.

7. STATISTICAL ANALYSES

7.1. Subject Disposition

The number of subjects included in each study population will be summarized by treatment arm and by treatment region (ie, Buttocks, Thighs, and Overall). Subjects excluded from the safety or evaluable populations will be listed.

The number and percentages of subjects screened, completed, and discontinued during the study and study treatment, as well as the reason for discontinuation from study and reason for discontinuation of study drug will be summarized by treatment arm.

A listing of disposition data will be provided. Screen failure reasons will also be presented.

7.2. Protocol Deviation

Protocol deviation will not be summarized. A listing of all protocol deviations will be presented.

7.3. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment arm and by treatment region (ie, Buttocks, Thighs, and Overall) using the Safety Population. Age, height (at screening), body weight (at screening) and body mass index (BMI) in kg/m^2 will be summarized as continuous variables using descriptive statistics.

Gender, race and ethnicity will be summarized as categorical variables using frequency counts and percentages.

Refer to Table 12 for descriptions of age categories and BMI groups.

The following baseline characteristics will be summarized using frequency counts and percentages:

- CR-PCSS cellulite severity ratings at screening (Mean and SD will also be provided)
- Hexsel CSS (B) depression depth scale scores at screening (Mean and SD will also be provided)
- Skin category based on Fitzpatrick scale assessment
- Report of tobacco and alcohol use
  - Alcohol use (Never, Current, and Former)
  - Tobacco use (Never, Current, and Former)

All demographic and baseline characteristics will be presented in subject listings.

7.4. Medical and Surgical History

Medical history will be coded using MedDRA dictionary. The version to be used will be defined in DMP. Medical and surgical history data will not be summarized; however, a subject listing will be provided.

7.5. EFP History

EFP history will be summarized by treatment arm and by treatment region (ie, Buttocks, Thighs, and Overall) using counts and percentages which will include:

- Family history of cellulite (Yes/No)
- Age (years) at EFP symptom onset (summarized descriptively)
- Prior treatments for EFP including liposuction, laser, massage, radiofrequency, drug, mesotherapy, cream, other, or none. Subjects can report more than 1 prior EFP treatment.
- Number of prior EFP treatments (0, 1, 2, or ≥3)
- Time (years) since most recent EFP treatment (summarized descriptively)

Refer to Table 12 for computation of "age at EFP onset" and "time since last EFP treatment." EFP history will be listed.

7.6. Concomitant Medications and Procedures

The prior, concomitant and follow-up medication will be summarized by treatment arm and by treatment region (ie, Buttocks, Thighs, and Overall) using frequency counts and percentages 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 subject listing of medications indicating prior, concomitant and follow-up medications and procedures will be provided. Similarly a separate listing of medications and procedures for EFP/ Cellulite will also be presented.

7.7. Efficacy Analyses

Efficacy parameters will be summarized and analyzed for each treatment area by treatment arm using the Evaluable Population.

7.7.1. Improvement in Aesthetic Appearance using 3-D Photographic Images

7.7.1.1. Analysis of Treatment Region and Area

The Likert Scale score of improvement in aesthetic appearance from baseline will be analyzed using a linear mixed model with treatment arm, study visit, interaction of treatment arm and study visit as fixed effects. The fixed effect estimates and 95% CIs for interaction effect of treatment arm and study visit will be presented. This model will be fitted using the response for each treatment area (ie, left buttock, right buttock, left thigh, and right thigh) and for the average of left and right of treatment area (ie, average of left buttock and right buttock; average of left thigh and right thigh).

The Likert Scale rating of improvement in aesthetic appearance from baseline will also be summarized using count and percentage by treatment arm and study visit/day (Day 22, 43, and 71) for each treatment area and with mean and SD.

A listing of Likert Scale scores will be provided.

7.7.2. Change in Dimple Analysis Parameters using 3-D Photographic Image

The observed and change from Day 1 pre-marking image in dimple analysis parameters, max length, max width, surface area, and volume between the dimple base and interpolated surface, will be summarized at Day 22, 43, and 71/ET by treatment area and treatment arm using descriptive statistics.

In addition, the volume and depth data will be analyzed using the linear mixed effect model described in Section 7.7.1.1.

A listing of dimple analysis parameters will be provided.

7.7.3. Change from Baseline in Dimple Depth Depression by Hexsel CSS (B)

The change from baseline in the Hexsel CSS (B) depression depth scale for each treatment area at Days 22, 43, and 71 will be analyzed and summarized as described in Section 7.7.1.1.

In addition, a shift table of Hexsel CSS (B) depression depth evaluation at baseline and post baseline study visit/day will be presented using counts and percentages.

A listing of Hexsel CSS (B) values will be provided.

7.8. Safety Analyses

Safety data will be summarized by treatment arm and by treatment region (ie, Buttocks, Thighs, and Overall) using the Safety Population.

7.8.1. Study Drug Exposure

The number of injections of study drug given on Days 1, 22, and 43, will be summarized per treatment area and by treatment arm using counts and percentages as:

- Subjects who received 12 injections per treatment area
- Subjects who received less than 12 injections per treatment area along with reason

The following will be summarized at each treatment visit by treatment area and treatment arm 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)

The number of subjects treated at each treatment visit will be summarized using frequency count and percentage by treatment area and treatment arm.

A subject listing of overall exposure, and injection status will be provided along with the reasons for receiving less than 12 injections per treatment area.

7.8.2. Adverse Events

All AE summary tables will include only TEAEs, unless otherwise specified.

AEs will be summarized by SOC and PT. 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 AE and AE related to study drug will be presented and will include:

- Total number of TEAEs reported
- Total number of TEAEs reported by severity
- Total number of AEs of special interest
- Subjects with any TEAE
- Subjects with any special interest AE
- Subjects with any serious TEAE
- Subjects with any severe TEAE

- Subjects with no severe TEAEs, but at least one moderate TEAE
- Subjects with no severe TEAEs, but at least one mild TEAE
- Subjects with any TEAEs leading to drug interruption/withdrawn
- Subjects with any TEAEs leading to study discontinuation
- Subjects with any TEAEs resulting in death

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

- All TEAEs
- TEAEs by severity
- TEAEs by relationship to study drug
- All non-study drug related TEAEs
- All study drug related TEAEs
- Study drug related TEAEs by severity
- Serious TEAEs
- Serious study drug related TEAEs
- Duration of study drug related TEAEs (<14 days, 14 – 21 days and >21 days)
- TEAEs leading to drug interruption/withdrawn
- Study drug related TEAEs leading to drug interruption/withdrawn
- TEAEs leading to study discontinuation
- Study drug related TEAE leading to study discontinuation
- TEAEs resulting in death
- Study drug related TEAEs resulting in death
- AEs of special interest

Serious and most common non-serious TEAE 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 preferred term 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/withdrawn
- AEs resulting in study discontinuation
- AEs resulting in deaths
- AEs of special interest

Refer to Table 12 for computation of duration of AEs.

7.8.3. Clinical Laboratory

Laboratory results (hematology and biochemistry) will be summarized using descriptive statistics for observed and change from baseline values at baseline and Day 71.

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

A subject listing (including urinalysis results) will be presented for all laboratory parameters. Serum and urine pregnancy test results will also be listed.

7.8.4. Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and body weight) will be summarized using descriptive statistics for observed and change from baseline values for all assessments visits.

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

A subject listing will be presented for vital signs results.

7.8.5. 12-Lead ECG

The investigator interpretation of ECG results (normal, abnormal not clinically significant or abnormal clinically significant) will be summarized using frequency counts and percentages.

A subject listing will be presented for investigator interpretation.

7.8.6. Physical Examination

A subject listing will be presented for the physical examination (by body system) screening and Day 71 (EOS) results.

7.8.7. Bruise Analysis using L*A*B* Coordinates

Color difference (ie, ΔE) between bruised tissues vs. normal tissues will be summarized at each visit (ie, Day 1 – Pre-Marking, Day 4, 8, and 15) by treatment area and treatment arm using descriptive statistics.

Color difference (ie, ΔE) in normal tissues at Day 4, 8, and 15 from normal tissues at Day 1 – Pre Marking will be summarized at each visit (ie, Day 4, 8, and 15) by treatment region and treatment arm using descriptive statistics.

The L*A*B color values measured within the bruised tissue and normal tissue AOI will also be summarized by treatment region and treatment arm using descriptive statistics.

A listing of color difference and L*A*B color values will be provided.

7.9. Other Safety Parameters

7.9.1. Immunogenicity

The immunogenicity analysis of binding and neutralizing anti-AUX-I and anti-AUX-II antibodies will summarize the number of subjects with an immunogenicity sample, the percentages of subjects with a positive sample, and the average titer level of the positive samples at Day 1 and EOS along with summary statistics if antibody assays are conducted. The titer levels will be logarithmically transformed prior to being summarized.

The number and percentage 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 antidrug antibody quartiles using frequency count and percentage at Day 1 and EOS.

A listing of immunogenicity results by subject will be provided.

8. CHANGE FROM PROTOCOL

This SAP is prepared based on the original study protocol dated June 27, 2018 and the amended protocol dated August 29, 2018 .There are no planned changes either in the conduct of the study or planned analysis at the time of preparing this SAP.

Table 13 lists any significant changes in the SAP from what is proposed in the protocol.

Table 13: Changes from Protocol

Text in Protocol	Change in SAP	Justification
a linear mixed model will be utilized to fit change from baseline of each endpoint with treatment arm, cellulite dimples, and study visit as fixed effects, subject as random effect, and assessments across study visits as repeated measure. The fixed effect estimates and the corresponding 95% confidence intervals will be presented for each endpoint.	The Likert Scale score of improvement in aesthetic appearance from baseline will be analyzed using a linear mixed model with treatment arm, study visit, interaction of treatment arm and study visit as fixed effects. The fixed effect estimates and 95% CIs for interaction effect of treatment arm and study visit will be presented. This model will be fitted using the response for each treatment area (ie, left buttock, right buttock, left thigh, and right thigh) and for the average of left and right of treatment area (ie, average of left buttock and right buttock; average of left thigh and right thigh).	Clarify the same model will fit to the response for each treatment area. Remove the covariate of cellulite dimples from the model as the number of dimples treated is not play an role

9. REVISION HISTORY

Non-editorial changes made to any of the modules of this SAP are recorded in Table 14.

Table 14: Revision History

Version	Date	Revision Author	Comments
1.0	23-Oct-2018	Endo Pharmaceuticals Inc.	Published version
2.0	11-Feb-2019	[redacted]	Updated for image analysis

10. REFERENCES

1. Clinical Study Protocol: A Phase 2a, Open-Label Study Evaluating the Safety and Different Injections Techniques of CCH for the Treatment of Edematous Fibrosclerotic Panniculopathy, Amendment 1: 29 August 2018.
2. Hexsel DM, Dal'Forno T, Hexsel CL. A validated photonumeric cellulite severity scale. *J Eur Acad Dermatol Venereol.* 2009; 23 (5):523-8.
3. Nürnberger F, Müller G. So-called cellulite: an invented disease. *J Dermatol Surg Oncol.* 1978;4(3):221-229.

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.