# SAP MODULE 1 – DETAILED STATISTICAL METHODOLOGY

**Protocol No. EN3835-305**

# A REAL WORLD, MULTICENTER, OPEN-LABEL, MULTIPLE DOSE STUDY TO ASSESS THE EFFECTIVENESS OF, AND SATISFACTION WITH, CCH TREATMENT OF BUTTOCK OR THIGH CELLULITE IN ADULT FEMALES

**Version 2.0**

**July 22, 2020**

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[redacted]

The sponsor of the application is Endo Global Aesthetics Limited (EGAL); however, Endo Pharmaceuticals Inc. (Endo) is authorized to act and to communicate on behalf of EGAL. The sponsor is responsible for the conduct of the study, analysis of the data, and preparation of the clinical study report.

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# LIST OF ABBREVIATIONS AND DEFINITIONS

| Abbreviation | Definition |
|---|---|
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALT | Alanine transaminase |
| AST | Aspartate transaminase |
| ATC | Anatomical therapeutic chemical |
| AUX-I | Clostridial class I collagenase |
| AUX-II | Clostridial class II collagenase |
| BDDQ | Body Dysmorphic Disorder Questionnaire |
| BMI | Body mass index |
| bpm | Beats per minute |
| brpm | Breaths per minute |
| CCH | Collagenase clostridium histolyticum |
| CFR | Code of Federal Regulations |
| CI | Confidence Interval |
| CM | Centimeter |
| CR-PCSS | Clinician-reported Photonumeric Cellulite Severity Scale |
| CSS | Cellulite Severity Scale |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| EFP | Edematous fibrosclerotic panniculopathy |
| ET | Early Termination |
| FDA | Food and Drug Administration |
| I-GAIS | Investigator Global Aesthetic Improvement Scale |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| LOCF | Last Observation Carried Forward |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PCI | Potentially clinically important |
| PT | Preferred term |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SD | Standard deviation |
| SOC | System organ class |
| TEAE | Treatment-emergent adverse event |
| US | United States |
| WHO | World Health Organization |

# 1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analyses to assess the safety and efficacy of Collagenase clostridium histolyticum (CCH) in adult women with mild or moderate edematous fibrosclerotic panniculopathy (EFP), also known as cellulite.

Specific information about the study is described in the EN3835-305 Clinical Study Protocol.[1]

# 2. STUDY OBJECTIVES AND ENDPOINTS

The primary, secondary and exploratory objectives and corresponding endpoints are outlined in Table 1 below:

**Table 1: Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To assess the efficacy of CCH treatment of buttock or thigh cellulite at the Day 90 Visit in adult females. | • The proportion of subjects with improved (+1 or better) score on the Investigator Global Aesthetic Improvement Scale (I-GAIS) for either buttock or either thigh at the Day 90 Visit. |
| **Secondary** | |
| • To assess the efficacy of CCH in the treatment of buttock or thigh cellulite in adult females. | • The proportion of subjects with improved (+1 or better) score on I-GAIS for either buttock or either thigh at the Day 22, Day 43, and Day 180 Visits. |
| • To assess the effectiveness of CCH in the treatment of buttock cellulite in adult females. | • Mean change from baseline in CR-PCSS for each buttock at the Day 22, Day 43, Day 90, and Day 180 Visits. |
| • To assess subject satisfaction with CCH treatment of buttock or thigh cellulite in adult females. | • Mean change from baseline in Body-Q Appraisal of Cellulite for buttock or thigh treated subjects at the Day 90 and Day 180 Visits. |
| • To assess the safety and tolerability of CCH when administered to adult female subjects with buttock or thigh cellulite. | • Proportion of subjects reporting each treatment-emergent adverse events (TEAEs) and adverse events of special interest (AESIs).<br>• Actual and change from baseline at each visit for vital signs and for each clinical laboratory test parameter.<br>• Percentage of subjects with positive antibody titers for anti-AUX-I and anti-AUX-II and neutralizing antibodies. |
| **Exploratory** | |
| • [redacted] | [redacted] |

# 3. STUDY DESIGN AND MEASURES

## 3.1. Study Design

This is a real world, multicenter, open-label, multiple dose, 2 cohort, Phase 3b study to assess the safety and efficacy of CCH in adult women with mild or moderate EFP.

The study will screen approximately 200 subjects in order to dose approximately 150 subjects in 2 cohorts. Cohort 1 will include approximately 80 subjects with mild or moderate EFP in the posterolateral thighs and Cohort 2 will include approximately 70 subjects with mild or moderate EFP in the buttocks. No subjects will be treated in both the buttocks and the thighs during this study. Subjects who discontinue from study treatment at any time after the first dose of study drug will not be replaced.

Subjects who complete the study will participate for approximately 200 days (approximately 7 months) plus the length of any COVID-19 delay including Screening period up to 28-days, a 43-day Treatment period and a 137-day Follow-up period. Subjects will receive the study injections on Days 1, 22, and 43. Follow-up visits will be performed approximately 90 and 180 days after Day 1. The entire study is expected to require approximately 14 months to complete.

A subject who is a screen failure at the Screening Visit may be rescreened with approval from the sponsor. The subject must repeat all screening procedures. The period from the start of rescreening related procedures to the study treatment must not exceed 28 days. Subjects may be rescreened only once; however subjects whose rescreening process was interrupted by COVID-19 may be rescreened for a second time.

Qualified subjects will receive 0.84 mg of CCH per treatment area (each buttock or each thigh) for a total dose of 1.68 mg in both buttocks or both thighs per treatment session × 3 treatment sessions (Day 1, Day 22 [+7 days], and Day 43 [+14 days]).

[redacted]

Table 2 below describes the schedule of activities and assessments performed during Screening, Treatment visits, and Follow-up visits.

**Table 2: Schedule of Activities**

| Activities | Screening (Day-28 to Day -1) | Day 1 (Treatment Session I) | Day 22 (+7 days) (Treatment Session II) | Day 43 (+14 days) (Treatment Session III) | Day 90 (+14 days) | Day 180 (+14 days)/ Early Termination |
|---|---|---|---|---|---|---|
| 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)[b] | X | X | | | | |
| Physical examination | X | | | | X | X |
| Height | X | | | | | |
| Weight | X | X | X | X | X | X |
| Fitzpatrick skin type | X | | | | | |
| Hexsel CSS Subsection D[b] | X | | | | | |
| Vital signs | X | X[c] | X[c] | X[c] | X | X |
| ECG | X | | | | | |
| Hematology, chemistry, and urinalysis | X | | | | X | X |
| Serum pregnancy test | X | | | | | |
| Urine pregnancy test | | X | X | X | X | X |
| Immunogenicity sample collection | | X | | | X | X |
| Body-Q Appraisal of Cellulite[d] | X | | | | X | X |
| Body Dysmorphic Disorder Questionnaire | | | | | | X |
| Imaging for eligibility confirmation | X | | | | | |

**Table 2: Schedule of Activities (Continued)**

| Procedure | Screening (Day-28 to Day -1) | Day 1 (Treatment Session I) | Day 22 (+7 days) (Treatment Session II) | Day 43 (+14 days) (Treatment Session III) | Day 90 (+14 days) | Day 180 (+14 days)/ Early Termination |
|---|---|---|---|---|---|---|
| Eligibility confirmation[e] | X | | | | | |
| Selection of treatment region (both buttocks or both thighs) | X | | | | | |
| Imaging for outcome evaluations (IntelliStudio)[f] | X | X | X | X | X | X |
| Ultrasound[g] | | X | X | X | X | X |
| CR-PCSS[h] | X | X | X | X | X | X |
| I-GAIS[i] | | | X | X | X | X |
| Select and mark up to 12 target dimples for CCH injection in each treatment area (each buttock or each thigh) | | X | X | X | | |
| [redacted] | | X | X | X | X | X |
| Study drug administration | | X | X[j] | X[j] | | |
| [redacted] | | | | X | | |
| [redacted] | | | | | X | |
| Concomitant medications | X | X | X | X | X | X |
| Injection site reactions/local tolerability in areas treated | | 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.
[b] Should be reassessed and verified prior to dosing. In the event that any safety laboratory testing results are unavailable prior to the subject's first dosing visit, the investigator will notify the sponsor to discuss on a case-by-case basis, prior to administering any study treatment to the subject.
[c] 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] Assessment should be completed independently of, and prior to, any investigator cellulite assessments (CR-PCSS, I-GAIS, [redacted]).
[e] Provided by an evaluator designated by the sponsor.
[f] Before and after marking target dimples at treatment visits. No manipulation of the treatment area should be done prior to the "before" images.
[g] Performed at selected site(s) only.
[h] CR-PCSS-Buttock and CR-PCSS-Thigh will both be done at screening. Thereafter, only buttock treated subjects will be assessed by CR-PCSS-Buttock.
[i] I-GAIS will be completed after CR-PCSS when both are required at the same visit.
[j] Subjects receiving treatment to the thigh may receive dosing via an updated injection technique if their I-GAIS score has improved by at least +1. Refer to the pharmacy manual for all injection techniques.
[k] AEs/SAEs will be captured from the time of informed consent signature until the Day 180/Early Termination Visit or until 28 days after last dose of study drug whichever is later. There is no time limit on collection of SAEs felt 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).

**Rescheduling visits that were out of window due to the COVID-19 interruption (see COVID-19 Trial Impact Mitigation Instructions for EN3835 – 305 v1.0 - 13May2020 FINAL for details)**

Protocol deviations will be recorded for all subjects who had visits outside of the windows outlined in this Schedule of Activities, regardless of reason (including all subjects who experienced the COVID-19 interruption). The reason for out of window visits will be recorded.

Every effort will be made to conduct the Day 180 visit no more than 180 (+14) days after the first dose of CCH for all subjects. Those subjects who received any dose of CCH prior to the COVID-19 interruption (13 April 2020) will be allowed to remain in the study if willing to do so, and if they can abide by the following:

- Subjects who had completed only the Day 1 Visit and received their first dose of CCH prior to the COVID-19 interruption will have the Day 22 Visit scheduled at the earliest possible date upon the reopening of the site but no later than 100 days after their first dose of CCH. For these subjects, the Day 43 visit will be scheduled no less than 21 days after the Day 22 Visit and the Day 90 Visit will be scheduled for no less than 28 days after the Day 43 Visit but should not precede the Day 180 Visit by less than 45 days. The Day 180 Visit will remain scheduled for 180 (+14) days after the first dose of CCH.

- Subjects who had completed only the Day 1 and Day 22 Visits and received their first 2 doses of CCH prior to the COVID-19 interruption will have the Day 43 Visit scheduled at the earliest possible date upon the reopening of the site but no later than 121 days after their first dose of CCH. For these subjects, the Day 90 Visit will be scheduled for no less than 28 days after the Day 43 Visit and the Day 180 Visit will occur no less than 45 days after the Day 90 Visit.

- Subjects who had completed only the Day 1, 22, and 43 Visits and received all 3 doses of CCH prior to the COVID-19 interruption will have the Day 90 Visit scheduled at the earliest possible date upon the reopening of the site. For these subjects the Day 180 Visit will be scheduled for no less than 45 days after the Day 90 Visit and will remain scheduled for 180 (+14) days after the first dose of CCH.

## 3.2. Inclusion Criteria

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

1. Be female and ≥18 and ≤60 years of age at the time of consent.
2. Have both buttocks or both posterolateral thighs with:
   a. A score of 2 or 3 (mild or moderate) as reported by the investigator using the Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS).
   b. A Hexsel Cellulite Severity Scale (CSS) Subsection D "Grade of Laxity, Flaccidity, or Sagging Skin" score of 0 (absence of laxity, flaccidity, or sagging skin), or 1 (slightly draped appearance) at the Screening Visit only.
3. Have a body mass index (BMI) score between 18.0 kg/m$^2$ and 30.0 kg/m$^2$ and intends to maintain stable body weight (≤10% change from the Day 1 Visit weight) throughout the duration of the study (from the Screening Visit through the Day 180/ET Visit).
4. Be willing to apply sunscreen to the treatment areas before each exposure to the sun for the duration of the study (from the Screening Visit through the Day 180/ET Visit).
5. 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.
6. Be of nonchildbearing potential (history of hysterectomy, bilateral oophorectomy, bilateral tubal ligation, or postmenopausal with no history of menstrual flow in the 12 months prior to the Screening Visit); or, if of childbearing potential, be nonpregnant, nonlactating, and agree to use effective contraception when with a male partner for the duration of the study. Acceptable forms of contraception include hormonal measures (oral contraceptive pills, contraceptive patch, contraceptive ring, injections), intrauterine devices, double barrier method (condom plus diaphragm, condom or diaphragm plus spermicidal gel or foam), surgical sterilization of the male partner, and abstinence.
7. Have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test prior to dosing at each treatment session.
8. Be willing and able to comply with all protocol required visits and assessments.
9. Be able to read, understand, and independently complete patient reported outcome instruments in English.
10. Be adequately informed and understand the nature and risks of the study and 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).

## 3.3. Exclusion Criteria

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

1. Is from a vulnerable population, as defined by the United States (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 or post-thrombosis syndrome.
    b. A current 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. Has a mole located within 2 cm of any injection site.
5. Has skin laxity or linear undulations on the treatment region (both buttocks or both thighs) that can be effaced by lifting skin.
6. Has a Hexsel CSS Subsection D "Grade of laxity, flaccidity, or sagging skin" of 2 (moderate draped appearance) or 3 (severe draped appearance).
7. 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.
8. 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 dosing with study treatment.
    b. Injections (eg, mesotherapy, dermal fillers, biostimulatory fillers); radiofrequency device treatments; laser treatment; buttock or thigh implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision) during the 12-month period before injection of study treatment.

c. Any investigational treatment for EFP on a buttock or thigh during the 12-month period before the injection of study treatment.
d. Endermologie or similar treatments during the 6-month period before injection of study treatment.
e. Massage therapy during the 3-month period before injection of study treatment.
f. Creams (eg, Celluvera™, TriLastin®) and/or home therapies to prevent or mitigate EFP during the 2-week period before injection of study treatment.

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

## 3.4. Treatment Region and Treatment Area

Treatment region is defined as both buttocks or both thighs. Treatment area is defined as each buttock or each thigh. No subjects will be treated in both the buttocks and the thighs.

## 3.5. Selection and Marking of Dimples and Injection Sites During Treatment Visits

The investigator or qualified designee will select up to 12 dimples within each treatment area (each buttock or each thigh) that are well defined, evident when the subject is standing and suitable for treatment. These dimples will be designated as the target dimples, and will be treated at each treatment session (Days 1, 22, and 43) as long as they remain visible. If less than 12 target dimples are identified at the Day 1, Day 22, or Day 43 Visits, then the target dimples will be treated first, thereafter additional other dimples within the same treatment area may be treated at the discretion of the investigator as long as the maximum dose per treatment area (each buttock or each thigh) does not exceed 0.84 mg.

Injection sites within a dimple should be spaced approximately 2 cm apart, if a dimple requires more than 1 injection.

## 3.6. Study Drug Administration

Each qualified subject will receive up to 24 subcutaneous injections (12 injections per buttock or thigh) for a total of 1.68 mg (0.84 mg per treatment area) at each treatment session visit. Each subject will receive study drug on Day 1, Day 22, and Day 43 (treatment session). 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 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) | Up to 12 per buttock × 2 buttocks = up to 24 injections | Up to 0.84 mg per buttock × 2 buttocks = up to 1.68 mg (12 injections per buttock × 0.07 mg/injection × 2 buttocks) | Up to 3.6 mL per buttock × 2 buttocks = up to 7.2 mL (24 injections × 0.3 mL) | Maximum of 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) | Up to 12 per thigh × 2 thighs = up to 24 injections | Up to 0.84 mg per thigh × 2 thighs = up to 1.68 mg (12 injections per thigh × 0.07 mg/injection × 2 thighs) | Up to 18 mL per thigh × 2 thighs = up to 36 mL (24 injections × 1.5 mL) | Maximum of 5.04 mg (3 treatment visits × 0.84 mg per thigh × 2 thighs) |

### 3.6.1. Determination of Sample Size

The proposed sample size, 150 subjects (ie, 70 buttocks subjects [Cohort 2] and 80 thigh subjects [Cohort 1]) is based on the rate of I-GAIS responders defined as subjects with an I-GAIS rating of "Improved", "Much Improved", or "Very Much Improved" on Day 90.

The sample size calculation was based on the following assumptions: 1) the proportion of 1-level I-GAIS responders is 70% for buttocks and 60% for thighs (based on results from earlier studies of CCH in EFP), 2) the estimated proportion of 1-level I-GAIS responders in this study will be no less than 60% for buttocks and 50% for thighs with a 95% chance, and 3) the dropout rate will be approximately 10%.

Sample size may be increased based on the results from the interim analysis for cohort 1.

### 3.6.2. Blinding and Randomization

This is an open-label, nonrandomized study. Treatment blinding or randomization are not applicable to this study.

## 3.7. Efficacy Assessments

Efficacy assessments will be evaluated as per Schedule of Activities. All the virtual efficacy assessments (mentioned below) are not allowed due to the potential of bias.

### 3.7.1. Imaging for Outcome Assessments

Digital photographs are not direct efficacy measurements; however, digital photography will be utilized in the assessment of treatment effect. The investigator or qualified designee will take photographs prior to injections using a Sponsor-supplied standardized digital camera in a standardized manner per the Photography Manual as follows:

- At screening, the investigator or qualified designee will photograph each of the 2 potential treatment areas (both buttocks and both thighs).
- For subsequent visits only the areas receiving treatment (both buttocks or both thighs) will be photographed.

The subject will be standing in a consistent, relaxed standing pose (ie, standing position with relaxed gluteus muscles) for each photography session and will be wearing a standardized photographic garment as described in the Photography Manual. These photographs will be taken before and after marking of the treatment areas for dosing.

### 3.7.2. Subject and Investigator Cellulite Assessments

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

### 3.7.3. Body-Q Appraisal of Cellulite

The Body-Q Appraisal of Cellulite is a subset of questions from the Body-Q questionnaire that was developed to measure patient perceptions of weight loss and/or body contouring.[4] The Body-Q Appraisal of Cellulite in this study consists of 11 questions (see Table 4) which are based on how subjects are bothered by their cellulite, and the responses will be collected

using a 4 level scale. The ratings range from 1 (Extremely bothered) to 4 (Not at all bothered). Subjects will complete this questionnaire at Screening, Day 90 and Day 180 Visits.

The Body-Q – Appraisal of Cellulite will be completed prior to any investigator cellulite assessments (CR-PCSS, I-GAIS, Investigator Satisfaction with CCH Administration/Treatment).

**Table 4: Body-Q Appraisal of Cellulite Questions and Responses**

| | Extremely bothered | Moderately bothered | A little bothered | Not at all bothered |
|---|---|---|---|---|
| 1. Having to dress in a way to hide your cellulite? | 1 | 2 | 3 | 4 |
| 2. How deep the dimpling in your cellulite looks? | 1 | 2 | 3 | 4 |
| 3. Not being able to wear certain clothes because of your cellulite? | 1 | 2 | 3 | 4 |
| 4. How noticeable your cellulite is? | 1 | 2 | 3 | 4 |
| 5. How lumpy your cellulite looks? | 1 | 2 | 3 | 4 |
| 6. The amount of dimpling in your cellulite? | 1 | 2 | 3 | 4 |
| 7. The amount of cellulite you have? | 1 | 2 | 3 | 4 |
| 8. How the skin where you have cellulite looks (not as smooth as you would like)? | 1 | 2 | 3 | 4 |
| 9. People seeing your cellulite? | 1 | 2 | 3 | 4 |
| 10. How your cellulite looks up close? | 1 | 2 | 3 | 4 |
| 11.How your cellulite looks when you are naked? | 1 | 2 | 3 | 4 |

### 3.7.4. Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) - Buttock

The CR-PCSS - Buttock (Table 5) will be used to assess the severity of cellulite of both buttocks (each buttock, independently).

The CR-PCSS - Buttock is a 5-level photonumeric scale developed specifically for clinicians and used by the Investigator to assess the severity of the subject's cellulite in each buttock by live assessments at Screening, Day 1, Day 22, Day 43, Day 90, and Day 180 Visits.

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.

**Table 5: CR-PCSS -Buttock**

| 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 |

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

### 3.7.5. Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) - Thigh

The CR-PCSS - Thigh (Table 6) will be used to assess the severity of cellulite of both thighs (each thigh, independently).

The CR-PCSS - Thigh is a 5-level photonumeric scale developed specifically for clinicians and used by the Investigator to assess the severity of the subject's cellulite in each thigh by live assessments at the Screening Visit.

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.

**Table 6: CR-PCSS-Thigh**

| 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 |

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

### 3.7.6. Hexsel Cellulite Severity Scale

The 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.
- 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 (Table 7).

For this study, only "D- laxity, flaccidity or sagging of skin" will be assessed for eligibility.

**Table 7: Hexsel CSS (D) laxity, flaccidity or sagging of skin**

| Rating | Description |
|---|---|
| 0 | Absence |
| 1 | Slight |
| 2 | Moderate |
| 3 | Severe |

Investigators who are physicians will use the Hexsel CSS Section D (laxity, flaccidity or sagging of skin) to assess the severity of laxity in each buttock or each thigh at the Screening Visit. The assessment will be made while the subject is in the standing position with relaxed gluteus muscles.

### 3.7.7. Investigator Global Aesthetic Improvement Scale

Using the I-GAIS (Table 8), an investigator who is a physician will determine the degree of improvement of each buttock or thigh by comparing the cellulite from the Day 1 pretreatment (baseline) digital image of each buttock or thigh to the cellulite seen in a digital image captured on Day 22, Day 43, Day 90, and Day 180 Visits. The I-GAIS assessment will occur after the CR-PCSS assessment to avoid introducing potential bias to the static CR-PCSS assessment by the investigator.

**Table 8: I-GAIS Scale**

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

### 3.7.8. [redacted]

[redacted]

### 3.7.9. [redacted]

[redacted]

### 3.7.10. [redacted]

[redacted]

**Table 9:** [redacted]

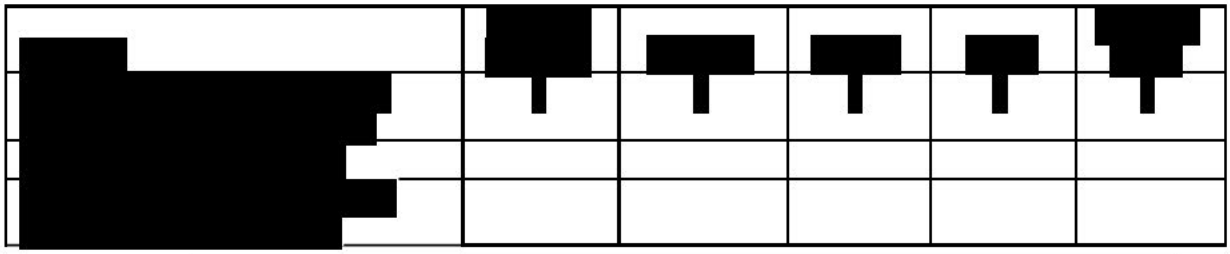
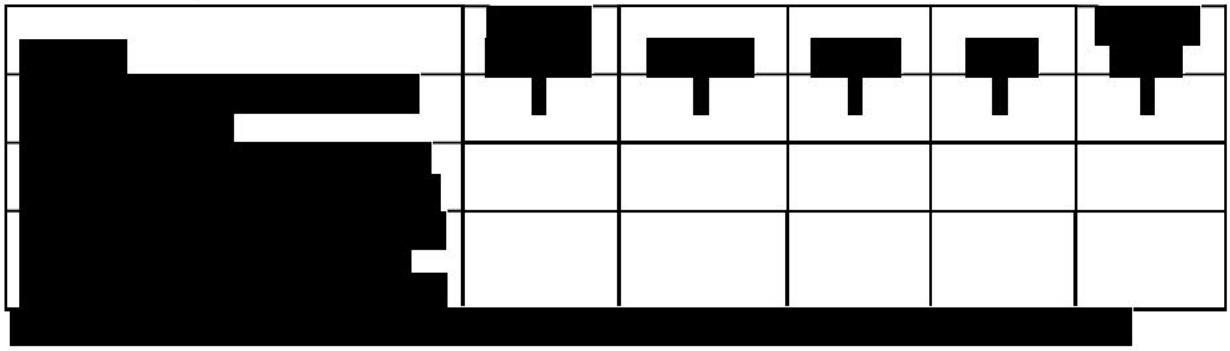


**Table 10:** [redacted]



## 3.8. Medical and Surgical History and EFP History

A medical, surgical, and EFP history of the subject will be taken during 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 of medical history 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 completed at any time in the treatment areas.

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.

## 3.9. Alcohol/Tobacco Use

History of tobacco and alcohol use will also be taken during the Screening period 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 medications and nondrug therapies (eg, blood transfusions, oxygen supplementation, physical therapy, etc.) taken within the 90 days prior to the Screening Visit or any concomitant medications or nondrug therapies received from the Screening Visit through the Day 180 Visit or for 28 days after the last study treatment for those who terminate early 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.

### 3.10.1. Prohibited Medications

The following medications and procedures are not allowed during the course of the study (from the Screening Visit through the Day 180 Visit):

- Anticoagulants (warfarin, heparin, direct thrombin inhibitors, Factor X inhibitors) and antiplatelet agents (aspirin >150 mg/day and P2Y12 inhibitors, such as clopidogrel), which can cause additional bruising. However, the use of aspirin at a dose level of ≤150 mg per day will be permitted during study.

The following procedures/treatments are not allowed in the selected treatment region (both buttocks or both thighs) during the course of the study (from the Screening Visit through the Day 180 End of Study/Early Termination Visit):

- Liposuction.
- Any injectable treatment (eg, KYBELLA) or any similar treatment that could destroy fat cells and/or remove fat deposits.
- Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; buttock implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision).
- Any investigational treatment for 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.

## 3.11. Adverse Events

All AEs and SAEs will be collected by the investigator from the time of signing the informed consent through the Day 180 Visit or for 28 days after the last study treatment for those who terminate early.

### 3.11.1. Adverse Events Definitions

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

- Changes in the general condition of the subject.
- Subjective symptoms offered by or elicited from the subject.
- Objective signs observed by the investigator or other study personnel.
- All concurrent diseases that occur after the start of the study, including any change in severity or frequency of pre-existing disease.
- Conditions present at baseline that worsen after initiation of study treatment will be captured as an AE; the onset date will be the date the event worsened.

### 3.11.2. Serious Adverse Events

Serious adverse events (SAEs) 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.

### 3.11.3. 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 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 as AEs of special interest.

## 3.12. Clinical Safety Laboratory Tests

Blood and urine samples will be collected for testing the following clinical laboratory parameters at Screening, Day 90, and the Day 180 Visit.

**Table 11: 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 |

**Table 11: Clinical Safety Laboratory Parameters (Continued)**

| Hematology | Biochemistry | Urinalysis |
|---|---|---|
| WBC Differential | Carbon dioxide (CO2) | 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 new clinically significant laboratory abnormality observed, will be considered as an AE or SAE as appropriate.

## 3.13. Pregnancy Test

Female subjects of child-bearing potential must have a 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 test at the Screening Visit and urine pregnancy tests at Day 1, Day 22, Day 43, Day 90, and Day 180/ET Visits. Any female subject that becomes pregnant during the study will be immediately withdrawn from treatment and will have the pregnancy reported.

## 3.14. Body Dysmorphic Disorder Questionnaire

The Body Dysmorphic Disorder Questionnaire (BDDQ) is validated, 4-question self-administered assessment tool used to screen for body dysmorphic disorder.[5]

The questionnaire will ask the subject about concerns with physical appearance. The responses will be binary in nature. The BDDQ will be administered to all subjects at the Day 180 Visit.

BDDQ assessment should be completed independently of, and prior to, any investigator cellulite assessments (CR-PCSS, I-GAIS).

**Table 12: Body Dysmorphic Disorder Questionnaire**

| Question No. | Question |
|---|---|
| 1 | Are you worried about how you look? (Yes/No)<br>• If yes: Do you think about your appearance problems a lot and wish you could think about them less? (Yes/No)<br>– If yes: List the body areas you don't like |
| 2 | Is your main concern with how you look that you aren't thin enough or that you might get too fat? (Yes/No) |
| 3 | How has this problem with how you look affected your life?<br>• Has it often upset you a lot? (Yes/No)<br>• Has it often gotten in the way of doing things with friends, dating, your relationships with people, or your social activities? (Yes/No)<br>– If yes: Describe how. |

**Table 12: Body Dysmorphic Disorder Questionnaire (Continued)**

| Question No. | Question |
|---|---|
| | • Has it caused you any problems with school, work, or other activities? (Yes/No)<br>– If yes: What are they?<br>• Are there things you avoid because of how you look? (Yes/No)<br>– If yes: What are they? |
| 4 | On an average day, how much time do you usually spend thinking about how you look?<br>• Less than 1 hour a day.<br>• 1-3 hours a day.<br>• More than 3 hours a day. |

## 3.15. Body Height, Body Weight, and BMI

Height and body weight measurements will be taken at screening. Body weight will also be measured at the Day 1, 22, 43, 90, and 180 Visits. BMI will be calculated using the height at screening and weight at respective visits. Refer to Table 18 for BMI derivation.

## 3.16. Vital Signs

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

Vital signs measurements will be taken at the Screening, Day 1, 22, 43, 90, and 180 Visits. 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.

The investigator will review all vital sign values for clinical significance. Any clinically significant abnormality in vital sign observed will be considered as an AE or SAE as appropriate.

## 3.17. 12-Lead Electrocardiogram

A 12-Lead ECG will be recorded during screening while the subject is in a 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 clinically significant abnormality in ECG observed will be considered as an AE or SAE as appropriate.

## 3.18. Physical Examination

A complete physical examination (by body system) will be performed at the Screening, Day 90 and 180/ET Visits. This 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 other conditions of note. Physical examination findings will be recorded as normal, abnormal or not done as not standard of care.

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

The subject's skin type and propensity for tanning will be assessed at screening using the Fitzpatrick scale (6-level scale [levels I-VI]) shown below:

**Table 13: 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 |

## 3.19. Immunogenicity

Immunogenicity variables include anti-AUX-I /anti-AUX-II binding antibodies (ie, anti-drug antibodies) and neutralizing antibody results. Serum samples will be collected at Day 1 (prior to study treatment administration) and at the Day 90 and Day 180 Visits for the determination of serum anti-AUX-I and anti-AUX-II antibody levels and neutralizing antibodies to AUX-I and AUX-II.

All safety assessments described above will be evaluated as per Schedule of Activities. Virtual visits are allowed to assess safety during any COVID-19 interruption.

# 4. STUDY PARAMETERS

## 4.1. Subject Disposition

Subjects will be considered to have completed the study if they complete the Day 180 Visit. Subjects who discontinue from study treatment or withdraw from the study for any reason after the Day 1 dosing will be encouraged to complete the remaining study visits and evaluations and provide any additional follow-up information as required by the study, unless the subject specifically indicates that they will not participate in any further evaluations.

If a subject withdraws from the study, all Early Termination procedures should be conducted as detailed in the Schedule of Activities. The reason and date for early withdrawal will be recorded in the eCRF for subjects who do not complete the study. If, however, a subject withdraws consent, no additional procedures are required except the collection of AE information. This information should be recorded in the source documentation and the eCRF. The reason for screen failure will also be recorded in eCRF for subjects who sign consent but do not receive any dose of study treatment.

## 4.2. Demographics and Baseline Characteristics

Demographics and baseline characteristics include the following parameters:

- Age.
- Height (at Screening).
- Body weight (at Screening).

- BMI in $kg/m^2$ (at Screening).
- Gender.
- Race.
- Ethnicity.
- Time since last menstrual period.
- CR-PCSS cellulite severity ratings for thigh and buttock at Screening.
- Hexsel CSS Section D (laxity, flaccidity or sagging of skin) scores at Screening.
- 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).

## 4.3. Protocol Deviations

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

Possible protocol deviations include, but are not restricted to the following 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.

## 4.4. Prior/Concomitant Medications

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

A prior medication is defined as any medication taken within the 90 days prior to the Screening Visit.

A concomitant medication is any medication taken between the Screening Visit and the Day 180 Visit or 28 days after the last study treatment for those who terminate early or the medication is reported as ongoing.

## 4.5. 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' prior to the Screening Visit, then the medication or procedure will be considered a prior EFP treatment.

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

- Liposuction.
- Surgery (including subcision and/or powered subcision).
- 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 deviation.

## 4.6. Efficacy Parameters

### 4.6.1. I-GAIS

#### 4.6.1.1. I-GAIS Rating

The I-GAIS rating is directly obtained from the investigator's assessments at an evaluation visit (Day 22, Day 43, Day 90, or Day 180).

In addition, the last observation carried forward (LOCF) will be used to impute any missing data at Day 90 Visit for the primary analysis.

#### 4.6.1.2. One-Level I-GAIS Responder for a Treatment Area

One-level I-GAIS Responder for a treatment area is defined as any subject with an improved (+1, +2 or +3) score on the I-GAIS at an evaluation visit for that treatment area.

#### 4.6.1.3. One-Level I-GAIS Responder for Either Buttock or Either Thigh

One-level I-GAIS Responder for either buttock is defined as any buttock-treated subject with an improved (+1, +2 or +3) score on the I-GAIS for at least one buttock at an evaluation visit.

One-level I-GAIS Responder for either thigh is defined as any thigh-treated subject with an improved (+1, +2 or +3) score on I-GAIS for at least one thigh at an evaluation visit.

### 4.6.2. CR-PCSS – Buttock

#### 4.6.2.1. CR-PCSS-Buttock Ratings

To assess the effect of CCH treatment on buttock cellulite in adult females, the mean change from baseline (Screening) in CR-PCSS will be determined for each buttock on Day 22, Day 43, Day 90, and Day 180 Visits as a secondary efficacy endpoint.

### 4.6.3. Body-Q Appraisal of Cellulite

#### 4.6.3.1. Individual Item Ratings

To assess the subject satisfaction with CCH treatment of buttock or thigh cellulite in adult females, the Body-Q Appraisal of Cellulite score for each of the 11 questions will be summarized for treated buttock or thigh subjects at Day 90 and Day 180 Visits.

To assess the improvement in subject satisfaction with CCH treatment of buttock or thigh cellulite in adult females, change from baseline in the Body-Q Appraisal of Cellulite score greater than or equal to +1 for each of the 11 questions will be summarized for treated buttock or thigh subjects at Day 90 and Day 180 Visits.

#### 4.6.3.2. Total Scores

Total score will be calculated for a subject at all visits. In case of missing responses for a subject, total score will be imputed as explained in Section 6.3. Mean change from baseline (Screening) in Body-Q Appraisal of Cellulite for total score will be assessed for treated buttock or thigh subjects at Day 90 and Day 180 Visits.

Higher scores reflect a better outcome.

#### 4.6.3.3. RASCH Transformed Score

Body-Q™ Appraisal of Cellulite RASCH Transformed Score is the total score converted into a score from 0 (worst) to 100 (best) based on responses for all 11 questions for a subject (Table 14). For a subject the minimum total score will be 11 and the maximum total score will be 44.

Mean change from baseline (Screening) in Body-Q Appraisal of Cellulite RASCH transformed score will be assessed for treated buttock or thigh subjects at Day 90 and Day 180 Visits.

**Table 14: BODY-Q- Appraisal of Cellulite Conversion Table**

| Sum Score | Equivalent RASCH Transformed Score (0-100) |
|---|---|
| 11 | 0 |
| 12 | 10 |
| 13 | 15 |
| 14 | 19 |
| 15 | 22 |
| 16 | 25 |
| 17 | 28 |
| 18 | 30 |
| 19 | 32 |
| 20 | 35 |
| 21 | 37 |

**Table 14: BODY-Q- Appraisal of Cellulite Conversion Table (Continued)**

| Sum Score | Equivalent RASCH Transformed Score (0-100) |
|---|---|
| 22 | 39 |
| 23 | 40 |
| 24 | 42 |
| 25 | 44 |
| 26 | 46 |
| 27 | 48 |
| 28 | 50 |
| 29 | 52 |
| 30 | 54 |
| 31 | 56 |
| 32 | 58 |
| 33 | 60 |
| 34 | 63 |
| 35 | 65 |
| 36 | 68 |
| 37 | 70 |
| 38 | 73 |
| 39 | 76 |
| 40 | 79 |
| 41 | 83 |
| 42 | 87 |
| 43 | 92 |
| 44 | 100 |

**4.6.4.** [redacted]

**4.6.5.** [redacted]

**4.6.5.4.** [redacted]

#### 4.6.6. Scores for Each Question on [redacted]

Scores for each question and total score on the [redacted] will be summarized at Day 43. Total score will be sum of scores from two individual questions.

#### 4.6.7. Scores for Each Question on [redacted]

Scores for each question and total score on the [redacted] will be summarized at Day 90. Total score will be sum of scores from two individual questions.

## 4.7. Safety Parameters

### 4.7.1. 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).

#### 4.7.1.1. 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 6.3.1.1 to identify TEAE status when start date of an AE is unknown.

#### 4.7.1.2. 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.

#### 4.7.1.3. Relationship to Study Drug

The causal relationship 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 not related.

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

### 4.7.2. Vital Signs and Clinical Laboratories

#### 4.7.2.1. Potentially Clinically Important Laboratory Values

Sponsor determined potentially clinically important (PCI) laboratory values are presented in Table 15 below:

**Table 15: 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.

#### 4.7.2.2. 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 sponsor determined PCI vital sign values are presented in Table 16 below:

**Table 16: 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 mm Hg 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.

## 4.8. Other Safety Parameters

### 4.8.1. 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.

### 4.8.2. Body Dysmorphic Disorder Questionnaire

Subject will be classified as Body Dysmorphic Disorder (BDD) if subject answered Yes to both parts of Q1, answered Yes to any one of the subpart questions for Q3 and answered >1 hour a day for Q4. BDDQ responses and BDD subjects will be summarized at Day 180.

# 5. ANALYSIS POPULATIONS

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

**Table 17: Analysis Populations**

| Population | Definition | Displays |
|---|---|---|
| Safety Population | The Safety Population will include all subjects who receive at least 1 injection of study medication. | 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 who receive at least 1 injection of study medication and have at least 1 I-GAIS evaluation. | 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 9.3 or higher.

All statistical tests will be performed with a significance level of $\alpha$=0.05, unless specified otherwise and will be supported by presenting estimates and 95% confidence intervals (CI).

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 evaluable 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 decimal place more than the raw data.
- Standard deviation (SD): Two decimal places more than the raw data.
- Percentages will be displayed with one decimal place precision.

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, which 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. Derived Variables

Table 18 defines the derived variables for study parameters:

**Table 18: Derived Variables and Definition**

| Variable | Definition |
|---|---|
| Age Group | 18 – <35 years<br>35 – <45 years<br>45 – <60 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 measured at screening and body weight measured at respective visits as, BMI ($kg/m^2$) = Weight (kg) / Height $(m)^2$ |
| 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 will be the screening value. The assessments made in unscheduled visits will be considered in calculation of baseline, if the unscheduled assessment is the closest value preceding the first dose of study drug. |
| Change from Baseline | Change from baseline will be derived as: post-baseline visit/time point value – the baseline value. |
| Last Date in Study | Last date in study is defined as:<br>• The date of Day 180 if the subject completes the study.<br>• The date of early termination visit if the subject is terminated early from study at a non-scheduled visit.<br>• 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. |
| Baseline CR-PCSS Buttock Score | Investigator baseline CR-PCSS scores for each buttock will be based on the investigator's CR-PCSS evaluation done at the Screening Visit. |
| Duration (Minutes) of Exposure at each visit | Date/Time of Last Injection – Date/Time of First Injection |
| Duration (Days) of AE | AE end date – AE start date + 1 |
| AE Onset Day | AE start date – Date of first injection + 1 |

## 6.3. Handling of Missing Data

Subjects who withdraw from the study after the initiation of the study drug will not be replaced and available data for these subjects until the point of withdrawal 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.

For I-GAIS, the LOCF will be used to impute the missing data at Day 90. For subjects who withdraw from study prior to Day 90, the last non missing assessment will be carried forward for Day 90 analysis (ie, LOCF Approach).

For Body Q- Appraisal of Cellulite, if missing data at a visit is less than 50% of the scale's items, the mean of the completed items multiplied by 11 will be used to determine total score. If the imputed value for total score is in decimals then the nearest integer will be considered to get the RASCH score, and the rounded value will be used for the summary and analysis. Also, if the missing data at a visit is more than 50% then for that subject raw sum score as well as transformed score will be considered as missing.

Subjects who withdraw early from study will be encouraged to have all Day 180 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. Duration of the AE is classified in the '>21 Days" category if an AE is ongoing for more than 21 days by the last visit of the subject in the study.

Immunogenicity samples with a positive titer value will undergo a log transformation for analyses. Samples with titer level less than 10 will be assigned or imputed as a log transformed titer of 1 for analyses.

### 6.3.1. Imputation of Partial Dates

#### 6.3.1.1. 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 on or 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.

#### 6.3.1.2. 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 the screening date but before the Day 180 visit date or 28 days after the last study treatment for those who terminate early or the 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 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 prior to the first injection date, then the medication will not be considered as concomitant.

#### 6.3.1.3. 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.

#### 6.3.1.4. Missing Last Menstrual Date

Missing date of last menstrual period will be imputed with the last day of the month and missing onset month will be imputed with December.

## 6.4. Interim Analyses

One interim analysis is planned to be conducted for this study. This interim analysis is primarily planned for sample size recalculation. The interim analysis will be performed when approximately the first 40 Cohort 1 (thigh) subjects complete their Day 90 assessments.

There will be no reduction in sample size as a result of the interim analysis; however, the sample size may be increased based on the results of interim analysis.

Based on the data of Day 90 assessments of the first 40 Cohort 1 subjects (approximately) the following parameters will be calculated:

1. Proportion of subjects with improved [+1 or better] score on I-GAIS for either thigh at Day 90.
2. Mean change from baseline in Body-Q Appraisal of Cellulite at Day 90 for thigh treated subjects.

The sample size for thigh-treated subjects may be adjusted if the proportion of subjects with an improved [+1 or better] score on I-GAIS for either thigh at Day 90 is less than 50%.

# 7. STATISTICAL ANALYSES

## 7.1. Subject Disposition

The number of subjects included in each study population will be summarized by cohort and overall. Subjects excluded from the safety or evaluable populations will be listed.

The number and percentages of subjects screened, enrolled, completed, and discontinued from study treatment and/or withdrawn from the study, as well as the reason for withdrawal from study and reason for discontinuation of study drug will be summarized by cohort and overall.

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

## 7.2. Protocol Deviations

Protocol deviations will be divided in categories and severity (major/minor) and summarized by category, severity (major/minor), and cohort/overall. A listing of all protocol deviations will be presented.

## 7.3. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by cohort and overall using the Safety Population. Age, height (at Screening), body weight (at Screening), BMI in $kg/m^2$ (at Screening) and time since last menstrual period 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 18 for descriptions of age categories.

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

- CR-PCSS cellulite severity ratings for thigh and buttock at screening (mean and SD will also be provided).
- Hexsel CSS Section D (laxity, flaccidity or sagging of skin) 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. 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 cohort and overall using frequency 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 18 for computation of "age at EFP onset" and "time since last EFP treatment." EFP history will be listed.

## 7.6. Prior/Concomitant Medications and Procedures

Prior and concomitant medications will be summarized by cohort and overall using frequency counts and percentages by active ingredient within each ATC, with ATC and active ingredients ordered alphabetically. Prior and concomitant procedures (nondrug therapies) will be summarized by cohort and overall using frequency counts and percentages with name of the procedures ordered alphabetically. Multiple uses of the same medication/procedure by a subject will be counted only once.

A subject listing of medications indicating prior and concomitant 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 for each cohort (treatment region) and overall using the Evaluable Population.

### 7.7.1. Primary Efficacy Endpoint

#### 7.7.1.1. One-level I-GAIS Responders for Treatment Area and Either Buttock or Either Thigh at Day 90 Visit

The l-level I-GAIS responders will be summarized by cohort and overall using frequency counts, proportion and corresponding 95% CI based on the Wilson (Score) for 1-level I-GAIS responders at Day 90, and Day 90 (LOCF) Visits for treatment area and either buttock or either thigh. The definition of a 1-level responder is provided in Section 4.6.1.

A listing of I-GAIS ratings will be provided.

### 7.7.2. Secondary Efficacy Endpoints

#### 7.7.2.1. One-level I-GAIS Responders for Treatment Area and Either Buttock or Either Thigh by Visit

The I-GAIS ratings as well as 1-level I-GAIS responders will also be summarized by cohort and overall using frequency counts, proportion and corresponding 95% CI based on the Wilson (Score) for 1-level I-GAIS responders at Day 22, Day 43, Day 90, Day 90 (LOCF), and Day 180 Visits for each treatment area and either buttock or either

#### 7.7.2.2. Change from Baseline in CR-PCSS for Each Buttock by Visit

The observed and change from baseline in CR-PCSS will be summarized using frequency counts and percentages and with mean and SD for each study visit/day (Day 22, Day 43, Day 90, and Day 180) and for each buttock and overall.

A listing of CR-PCSS ratings will be provided.

#### 7.7.2.3. Change from Baseline in Body-Q -Appraisal of Cellulite Total Score for Buttock or Thigh Treated Subjects by Visit

The observed and change from baseline in Body-Q Appraisal of cellulite total score and RASCH transformed score will be summarized by cohort and overall using descriptive statistics for each study visit/day (Day 90 and Day 180). In addition, Body-Q Appraisal of Cellulite score, change from baseline and subjects that improved (change from baseline >=+1) for each of individual 11 items will be summarized for treated buttock or thigh subjects at Day 90 and Day 180 using frequency counts and percentages with mean and SD.

A listing of Body-Q™ ratings will be provided.

### 7.7.3. [redacted]

### 7.7.4. Other Efficacy Measurement

A listing of digital photography (were digital photography taken, date/time/timepoint of photo taken, corresponding laterality/location and whether imaging done per protocol and if no, then reason) will be provided.

## 7.8. Safety Analyses

Safety data will be summarized by cohort and overall using the Safety Population.

### 7.8.1. Study Drug Exposure

The following will be summarized at each treatment visit by treatment area (left or right) for each cohort (thigh or buttock) using descriptive statistics:

- Total number of injections given.
- Number of target dimples treated.
- Number of additional dimples treated.
- Average number of injections per dimple.
- Duration of exposure (refer to Table 18 for computation of exposure duration).

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

A subject listing of drug exposure information will be provided.

### 7.8.2. Adverse Events

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

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

For TEAEs 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 TEAEs 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 (i.e. related) to study drug will be summarized.

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

An overall summary of TEAEs and TEAEs 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 TEAEs of special interest.
- Subjects with any TEAE.
- Subjects with any TEAE of special interest.
- 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/discontinuation.
- Subjects with any TEAEs leading to withdrawal from study.
- Subjects with any TEAEs resulting in death.

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

- All TEAEs.
- TEAEs by severity.
- All study drug related TEAEs.
- Study drug related TEAEs by severity.
- Duration of study drug related TEAEs (1 – 4 days, 5 – 7 days, 8 – 14 days, 15 – 21 days and >21 days).
- TEAEs of special interest.

The most common serious and non-serious TEAEs by order of frequency (most frequent, 2nd most frequent, and 3rd most frequent) will be summarized by PT. The most common serious and non-serious AEs are those with 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 death.
- AEs of special interest.

Refer to Table 18 for computation of duration of AEs.

### 7.8.3. Clinical Laboratory

Hematology and chemistry results will be summarized by cohort and overall using descriptive statistics for observed and change from baseline values at Day 90 and Day 180.

The PCI laboratory values will be summarized by cohort and overall using frequency counts and percentages. Refer to Table 15 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. Body Height, Body Weight and BMI

Body height, weight and BMI at Screening will be summarized by cohort and overall and listed as baseline characteristics as mentioned in Section 7.3.

Body weight will be summarized by cohort and overall using descriptive statistics for observed and change from baseline values for all visits.

### 7.8.5. Vital Signs

By-visit vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) will be summarized by cohort and overall using descriptive statistics for observed and change from baseline values for all assessments visits. Baseline (study baseline) will be the vital sign value taken at Day 1 predose for the by-visit analyses.

Vital signs will additionally be summarized by cohort and overall for observed and change from baseline values on each injection day. For each injection day, baseline (injection day baseline) will be a predose value taken on that day.

The PCI vital signs values will be summarized by cohort and overall using frequency counts and percentages. Refer to Table 16 for PCI criteria.

A subject listing will be presented for vital sign results.

### 7.8.6. 12-Lead ECG

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

A subject listing will be presented for the investigator interpretation with other details.

### 7.8.7. Physical Examination

Physical examination results (by body system) at baseline and post baseline study visits will be presented by cohort and overall using frequency counts and percentages.

A subject listing will be presented for the physical examination result (by body system) at Screening, Day 90, and Day 180 Visits.

## 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 percentage of subjects with a positive sample, and the average titer level of the positive

samples at Day 1, Day 90, and Day 180 Visits along with summary statistics if antibody assays are conducted. The titer levels will be logarithmically transformed prior to being summarized.

Samples from Day 1, Day 90, and Day 180 Visits will be analyzed for anti-AUX-I and anti-AUX-II antibodies and a subset of samples will be analyzed for neutralizing antibodies. Neutralizing antibody results will be summarized as percentage of positive/negative.

A listing of immunogenicity results by subject will be provided.

### 7.9.2. Body Dysmorphic Disorder Questionnaire

BDDQ responses and BDD subjects will be summarized by cohort and overall using frequency counts and percentages.

A listing of BDDQ responses by subject will be provided.

## 8. CHANGE FROM/ PROTOCOL

This SAP is prepared based on study protocol amendment 3 dated June 1, 2020.

Table 19 lists any significant changes in the SAP from what is proposed in the protocol.

**Table 19: Changes from Protocol**

| Text in Protocol | Change in SAP | Justification |
|---|---|---|
| | None | |
| | | |
| | | |
| | | |

## 9. REVISION HISTORY

Non-editorial changes made to any of the modules of this SAP will be recorded in Table 20.

**Table 20: Revision History**

| Version | Date | Revision Author | Comments |
|---|---|---|---|
| 1.0 | 4-Jan-2020 | [redacted] | Original final version |
| 2.0 | 22-Jul-2020 | | Updated SAP as per protocol amendment 2, 3 |
| | | | |

## 10. REFERENCES


1. Clinical Study Protocol Amendment 3: A real world, multicenter, open-label, multiple dose study to assess the effectiveness of, and satisfaction with, CCH treatment of buttock or thigh cellulite in adult females. Dated: June 01, 2020.
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):221-9.
4. Scott AM, Pusic AL, Cano SJ, Johnson J, Lawson J, Wildgoose P, et al. The BODY-Q: A new patient reported outcome (PRO) measure for body contouring patients. *Qual Life Res*. 2012;20:74-5.

5. Phillips K. The broken mirror: understanding and treating body dysmorphic disorder. New York, NY:Oxford University Press;2005.

# 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.