SAP MODULE 1 – DETAILED STATISTICAL METHODOLOGY

Protocol No. EN3835-224

A PHASE 2 MULTICENTER, OPEN-LABEL, RANDOMIZED, PARALLEL-GROUP, MULTIPLE-DOSE STUDY TO ASSESS THE EFFECTIVENESS, SAFETY AND SATISFACTION WITH COLLAGENASE CLOSTRIDIUM HISTOLYTICUM GRID TECHNIQUE INJECTIONS OF BUTTOCK OR THIGH CELLULITE WITH LAXITY IN ADULT FEMALES

Version 1.1

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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

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
BMI	Body mass index
BUN	Blood Urea Nitrogen
CCH	Collagenase clostridium histolyticum
CI	Confidence Interval
CR-PCSS	Clinician-reported Photonumeric Cellulite Severity Scale
CSS	Cellulite Severity Scale
ECG	Electrocardiogram
eCRF	Electronic case report form
ET	Early Termination
I-GAIS	Investigator Global Aesthetic Improvement Scale
S-GAIS	Subject Global Aesthetic Improvement Scale
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
MedDRA	Medical Dictionary for Regulatory Activities
PCI	Potentially Clinically Important
PT	Preferred Term
QTc	Corrected QT interval
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analyses to assess the safety and efficacy of collagenase clostridium histolyticum (CCH) in adult women with mild or moderate cellulite and moderate to severe dermal laxity.

General information about the study is described in the EN3835-224 Clinical Study Protocol, protocol amendment dated December 3, 2020.(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 for the treatment of cellulite in the presence of dermal laxity using the Investigator Global Aesthetic Improvement Scale (I-GAIS).	• Proportion of one-level responders (+1 or better score) on the I-GAIS for either buttock or either thigh at Day 180.
Secondary	
• To assess the efficacy of CCH for the treatment of cellulite in the presence of dermal laxity using the I-GAIS.	• Proportion of one-level responders (+1 or better score) on the I-GAIS for either buttock or either thigh at Study Days 28, 56, 84, 112, and 140. • I-GAIS ratings at Study Days 28, 56, 84, 112, 140, and 180.
• To assess the efficacy of CCH for the treatment of cellulite in the presence of dermal laxity using subject assessments.	• Proportion of one-level responders (+1 or better score) on the Subject Global Aesthetic Improvement Scale (S-GAIS) for either buttock or either thigh at Study Days 28, 56, 84, 112, 140, and 180. • The Change from baseline to Day 180 in the Body-Q Appraisal of the individual item cellulite scores and total score.
• To assess the effectiveness of CCH for the treatment of cellulite in the presence of dermal laxity using Subsection D of the Hexsel Cellulite Severity Scale (CSS).	• The Change from baseline to each Study Visit (Day 28 through the Day 180 Visit) in Hexsel CSS Subsection D severity score.
• To assess the safety and tolerability of CCH for the treatment of cellulite in the presence of dermal laxity.	• Proportion (incidence) of subjects reporting each adverse event (AE), treatment-emergent adverse event (TEAE), treatment-related AE, and adverse event of special interest (AESI). Change from baseline reported at each visit for vital signs, potentially clinically important vital signs, clinical laboratory tests, and potentially clinically important laboratory tests.

Table 1: Objectives and Endpoints (Continued)

Objectives	Endpoints
• To assess the immunogenicity of CCH in the treatment of cellulite in the presence of dermal laxity.	• Anti-Clostridial class I collagenase (AUX-I) and Anti-Clostridial class II collagenase (AUX-II) antibody levels. • Neutralizing antibodies to AUX-I and AUX-II.
[redacted]	
• [redacted]	• [redacted]
• [redacted]	• [redacted]
• [redacted]	• [redacted]

3. STUDY DESIGN AND MEASURES

3.1. Study Design

This is a Phase 2, open-label, randomized, parallel-group, multiple-dose, safety and effectiveness study designed to evaluate 2 different CCH dose concentrations and aliquot volumes delivered via uniform grid injection techniques in female subjects presenting with both mild to moderate cellulite and moderate to severe dermal laxity of the buttocks, or thighs, and with a body mass index 18 to < 29.9 kg/m^2 (normal or overweight).

Following determination of eligibility based on photography and Inclusion/Exclusion assessment, the investigator will propose each eligible subject for treatment of either both buttocks, or both thighs. A sponsor-designated reviewer will confirm subject eligibility for thighs or buttocks treatment based on review of screening images of areas to be treated. Prior to randomization, the sponsor will categorize the thighs or buttocks of each eligible subject for the following characteristics: mild cellulite with moderate dermal laxity, mild cellulite with severe dermal laxity, moderate cellulite with moderate dermal laxity and moderate cellulite with severe dermal laxity. This pre-randomization cohort management process is intended to try to ensure enrollment of the desired scope of study participants.

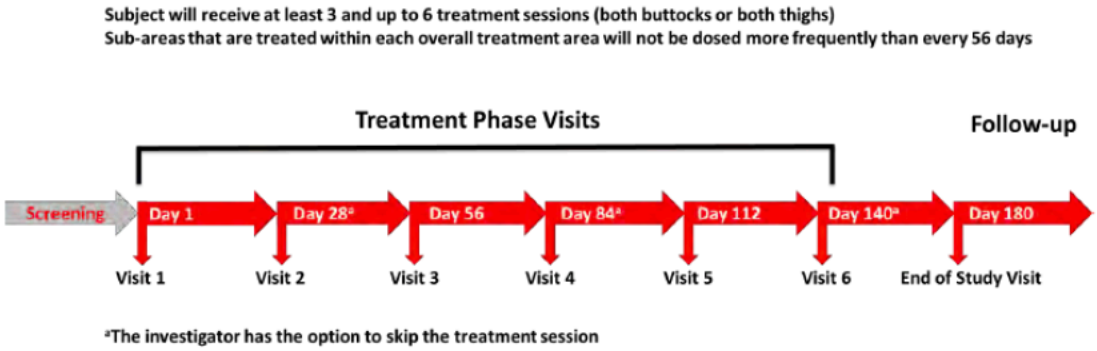
The study will enroll approximately 32 subjects such that approximately 24 subjects complete the study. Subjects will then be randomized to receive treatment in either treatment regimen A (Uniform 0.1-mL 1-Aliquot GRID injection technique) or treatment regimen B (Uniform 0.3-mL 2-Aliquot GRID injection technique) in a 1:1 ratio.

During the 6 scheduled Treatment Phase visits the investigator will determine the total number of treatments the subject will receive, and can incrementally treat new sub-areas at consecutive Treatment Phase visits. Specific injection sites (sub-areas) within the overall treatment area (entire buttock or entire thigh) will not be dosed more frequently than every 56 days. S[redacted]

[redacted]

Subjects will return to the study site for all 6 scheduled Treatment Phase visits to complete assessments, even if not receiving treatment during the visit.

The study is expected to enroll subjects over a period of approximately 3 months. Subjects will participate in the study for approximately 29 weeks, including a screening period of up to 28 days. The entire study is expected to require approximately 12 months to complete. However, the duration of the study may be changed due to possible COVID-19 impacts.



3.1.1. End-of-Study Definition

A subject is considered to have completed the study if the subject has completed the Day 180 Visit.

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

3.1.2. Schedule of Activities

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

Table 2: Schedule of Activities

Activities	Screening (Day -28 to Day -1)	Treatment Phase[a] Day 1 Visit 1	Day 28 (±3 day) Visit 2	Day 56 (±3 days) Visit 3	Day 84 (±3 days) Visit 4	Day 112 (±3 days) Visit 5	Day 140 (±3 days) Visit 6	Follow-up Day 180 End of Study/ Early Termination Visit (±10 days)
Informed consent[b]	X							
Inclusion/exclusion criteria review	X	X[c]						
[redacted]		X	X	X	X	X	X	X
Imaging for eligibility confirmation[d]	X							
Medical and cellulite history (including previous treatment)	X							
Physical examination	X							X
Height	X							
Weight	X	X						X
Fitzpatrick Skin type	X							
Vital signs[e]	X	X	X	X	X	X	X	X
12-lead ECG	X							X
Clinical safety laboratories	X							X
Anti-AUX-I/Anti-AUX-II antibody level sample		X						X
Serum pregnancy test	X							X
Urine Pregnancy Test		X	X	X	X	X	X	
CR-PCSS	X							
I-GAIS[f]			X	X	X	X	X	X
S-GAIS[f]			X	X	X	X	X	X
Body-Q		X						X
Hexsel CSS subsection D[g]	X[h]	X	X	X	X	X	X	X
[redacted]		[redacted]						

Table 2: Schedule of Activities (Continued)

Activities	Screening (Day -28 to Day -1)	Treatment Phase[a] Day 1 Visit 1	Day 28 (±3 day) Visit 2	Day 56 (±3 days) Visit 3	Day 84 (±3 days) Visit 4	Day 112 (±3 days) Visit 5	Day 140 (±3 days) Visit 6	Follow-up Day 180 End of Study/ Early Termination Visit (±10 days)
[redacted]		[redacted]						[redacted]
Assignment of treatment area (buttocks or thighs)	X							
Confirm eligibility		X						
Randomize treatment arm		X						
Digital photography[k]		X	X	X	X	X	X	X
Study intervention administration		X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	
Prior/Concomitant medications/ procedures	Collect throughout the study							
AEs	Collect throughout the study							

[a] During unscheduled visits the investigator or designee may perform any study procedure deemed 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 dosing.
[d] For these eligibility confirmation photographs the subject will be standing in a consistent, standardized relaxed standing pose (ie, standing position with relaxed gluteus muscles) and will be wearing a standardized photographic garment. Specific instructions for taking the eligibility confirmation photographs as well as for providing them to, and receiving confirmation (or lack thereof) from, the sponsor designated reviewer will be provided in the Study Operations Manual.
[e] On treatment phase visit days (Days 1, 28, 56, 84, 112, and 140) vital signs will be taken up to 4 hours prior to dosing and at 15 minutes and 30 minutes after dosing (body temperature is not required at the 15 minute postdose time point).
[f] These assessments, which will be based on digital photographs, are performed separately for each of 2 treatment areas and must be completed before study intervention administration on those visits. If at a treatment visit, use photographs taken before marking treatment area.
[g] [redacted]
[h] Subjects with Hexsel CSS Subsection D score greater than 3 at screening are excluded. A score greater than 3 is defined as an appearance significantly worse than exhibited in the Hexsel CSS Subsection D severe (score = 3) image.
[i] Collected after treatment on Study Day 1 and is assessed for the overall subject and not per treatment areas.
[j] [redacted]

[k] Photographs will be taken before and after marking the treatment areas. [redacted] For subjects not receiving treatment during a treatment phase visit a photograph will be taken but no marking will be done and no postmarking photograph will be taken. Please see the Photography Manual for details.

[l] Subjects will receive at least 3, and up to 6 treatment sessions. The investigator will determine the total number of treatments the subject will receive and can incrementally treat new sub-areas at consecutive treatment phase visits. Specific injection sites (sub-areas) within the overall treatment area will not be dosed more frequently than every 56 days. At the Treatment Phase visits after Day 1, the investigator has the option to skip treatment or proceed with a treatment session for a new sub-area. [redacted] fter treatment subjects will be provided with compression garments that they will be required to wear.

AE=Adverse event; CR-PCSS=Clinician-reported Photonumeric Cellulite Severity Scale; CSS= Cellulite Severity Scale; ECG=Electrocardiogram; I-GAIS=Investigator Global Aesthetic Improvement Scale; S-GAIS=Subject Global Aesthetic Improvement Scale.

3.2. Subject Inclusion Criteria

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

1. Be female ≥ 18 and ≤ 55 years of age at the time of consent.
2. Have a body mass index (BMI) of 18 to < 29.9 kg/m^2.
3. At the Screening Visit, have either both buttocks or both posterolateral thighs with:
   a. A score of 2 or 3 (mild or moderate cellulite) as reported by the investigator using the CR-PCSS, and
   b. a Hexsel CSS Subsection D "Grade of Laxity, Flaccidity, or Sagging Skin" score of 2 or 3 (moderate or severe) as determined by the investigator.
4. 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 and for 28 days after any active treatment period. Acceptable forms of contraception include hormonal measures (oral contraceptive pills, contraceptive patch, contraceptive ring, and 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.
5. Be willing and able to comply with all protocol required visits and assessments, including eligibility photographs of the mid-back to mid- posterolateral-thigh taken during screening that will be submitted to a sponsor designated reviewer to confirm eligibility.
6. 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/early termination [ET] Visit).
7. Be adequately informed and understand the nature and risks of the study and be able to provide consent.

3.3. Subject Exclusion Criteria

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

1. Has a history of hypersensitivity or allergy to collagenase or any other excipient of CCH. Has concurrent diseases that might interfere with the conduct of the study, confound the interpretation of the study results, or endanger the participant's well-being, (eg, evidence or history of malignancy, other than excised basal cell carcinoma and adequately treated squamous cell carcinoma of skin, unless there has been no recurrence in at least 5 years since treatment, or any significant hematological, endocrine, cardiovascular, respiratory, renal, hepatic, neurologic, psychiatric or gastrointestinal disease). If there is a history of such disease but the condition has been stable for more than 5 years and is judged by the

investigator not to interfere with the participant's participation in the study, the participant may be included, with the documented approval of the Medical Monitor.

2. At the Screening Visit has a CR-PCSS score of less than 2 or greater than 3 for the area to be treated (buttocks or thighs) and/or has a Hexsel CSS Subsection D "Grade of Laxity, Flaccidity, or Sagging Skin" score of less than 2 or greater than 3 (severe) for the area to be treated (buttocks or thighs).
3. Has a coagulation disorder which requires anticoagulant or antiplatelet medication during the study (except for ≤ 150 mg aspirin daily), or has taken anticoagulant or antiplatelet medication within 14 days before injection of study treatment (except for ≤ 150 mg aspirin daily).
4. Is a prisoner, an individual with impaired decision making capacity, employees (temporary, part-time, full-time, etc) or a family member of the research staff conducting the study, or of the sponsor, or of the contract research organization, or of the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), or in the judgment of the investigator the subject is disadvantaged and vulnerable to coercion due to lack of education, or due to poor economic circumstances.
5. Has participated in a previous investigational study of CCH, received any collagenase treatments at any time prior to treatment in this study and/or has received previous treatment with CCH for cellulite, or received treatment with an investigational product within 30 days (or 5 half-lives, whichever is longer) of the Screening Visit.
6. Is pregnant and/or is breast-feeding or plans to become pregnant and/or to breast-feed during the course of the study, or for 28 days after the last dose of study intervention.
7. Has a history of scarring due to keloids or abnormal wound healing.
8. 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, vasculitis, varicose veins, telangiectasia).
    c. Inflammation or active infection (including lesions that indicate an active infection).
    d. Active cutaneous alteration including but not limited to rash, eczema or psoriasis.
    e. A tattoo or other artificially inflicted body marker within 2 cm of any injection site.
    f. Has a mole located within 2 cm of any injection site.
9. Has history of drug or alcohol abuse within the 5 years prior to the Screening Visit.
10. Has evidence of clinically significant abnormalities, as judged by the investigator, in any of the following: physical examination findings, electrocardiogram (ECG), clinical laboratory values, or vital signs. The sponsor's medical monitor will be required to review the results for confirmation of eligibility in the case of any of the following: abnormalities in ECGs indicating corrected QT interval (QTc) prolongation of 470 ms or greater, abnormalities in clinical laboratory values involving elevations above the normal range for alanine aminotransferase, total bilirubin, and aspartate aminotransferase.

11. Has used any of the following for the treatment of cellulite on either thigh or either buttock within the specified timelines, 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); 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 cellulite 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 cellulite during the 2-week period before injection of study treatment.
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 participant to be unsuitable for the study.
15. For the subset of subjects participating in the collection of ultrasound data, the following exclusions will apply: subjects will be excluded who have: a history of a spinal laminectomy, a previous history or presence of vascular abnormalities (eg, deep vein thrombosis, thrombophlebitis), a healing fracture, an impaired sensation within, or near, the planned treatment area, or any implants within, or near, the planned treatment area.

3.4. Treatment Region and Treatment Area

Treatment region is defined as either 2 buttocks or 2 thighs. Treatment area is defined as each buttock or thigh. None of the subjects will be treated in both buttock and thigh areas.

3.5. Pre-Randomization of Samples into Four Groups

All subjects must have the following:

- a cellulite score of 2 (mild) or 3 (moderate) on the CR-PCSS assessment and
- a dermal laxity score of 2 (moderate) or 3 (severe) on the Hexsel CSS Subsection D assessment.

Once a subject's treatment areas are classified to the defined categories, pre-randomization will be performed with the interactive response technology (IRT) cohort management module. Pre-randomization will be used to manage recruitment such that approximately equivalent numbers of subjects are enrolled for treatment of buttocks vs thighs, mild vs moderate cellulite, and moderate vs severe dermal laxity.

This pre-randomization process will be used in an attempt to fill the desired categories as shown in Table 3 below.

Table 3: Intended Distribution of Subject Treatment Area Characteristics and Locations

Criteria	CR-PCSS 2 (mild cellulite)	CR-PCSS 3 (moderate cellulite)
Hexsel CSS Subsection D2 (moderate laxity)	8 Buttocks	8 Buttocks
	8 Thighs	8 Thighs
Hexsel CSS Subsection D3 (severe laxity)	8 Buttocks	8 Buttocks
	8 Thighs	8 Thighs
Total	32 Treatment Areas	32 Treatment Areas

Note: A total of 32 subjects are expected to contribute a total of 64 treatment areas. Each subject's 2 treatment areas may be allocated to different categories according to the severity of cellulite and severity of dermal laxity.

3.6. Study Drug Administration

CCH is a sterile lyophilized powder that is reconstituted with a sterile diluent made of 0.6% sodium chloride and 0.03% calcium chloride dihydrate in water.

Subjects who qualify for the study will be given a maximum dose of 1.68 mg of CCH inclusive of both treatment areas (2 buttocks or 2 thighs) per treatment visit (total maximum dose of 1.68 mg per treatment session during 6 treatment sessions [Days 1, 28 (±3), 56 (±3), 84 (±3), 112 (±3), and 140 (±3)] for a maximum total dose of 10.08 mg). Treatment Session y, where y denotes 1, 2, 3, 4, 5, 6 is not always associated with the same study visit. Treatment Session 1 will always start at Day 1 (study drug given), but the following treatment sessions are dependent on the treatment schedule of the subject. For example, Treatment Session 2 can start at Day 28 visit or Day 56 visit depending on the treatment schedule of the subject.

[redacted]

The injection volume and concentration for each treatment area are outlined in Table 4 below.

Table 4: Study Treatment

Regimen Name	A	B
Injection Technique	Uniform 0.1-mL 1-Aliquot GRID	Uniform 0.3-mL 2-Aliquot GRID
Product Name	CCH	CCH
Number of Subjects	N = 16 (8 buttocks and 8 thighs)[a]	N = 16 (8 buttocks and 8 thighs)[a]
Injection Volume (mL) × Aliquot(s) = Total Injection Volume	0.1 mL × 1 = 0.1 mL	0.3 mL × 2 = 0.6 mL
Concentration (mg/mL)	[redacted]	[redacted]
Maximum CCH Dose/ Treatment Area	1.68 mg (0.84 mg per buttock or thigh)	1.68 mg (0.84 mg per buttock or thigh)
Maximum Injection Volume/Visit	[redacted]	[redacted]
Maximum Number of Injection Sites/Subject/Visit	[redacted]	[redacted]
Cumulative CCH Dose 3 Treatment Visits 6 Treatment Visits	5.04 mg 10.08 mg	5.04 mg 10.08 mg

[a] Number of subjects shown for buttocks and thighs treatment represents the ideal distribution.

3.6.1. Determination of Sample Size

The sample size for this exploratory Phase 2 study was based on the minimum number of treatment area assessments (N=64 treatment areas, among 32 subjects) that could contribute to an initial clinical evaluation of tolerability and response to CCH treatment in a population of subjects with both mild to moderate cellulite and moderate to severe dermal laxity. This population will also allow a comparison across the 2 randomized treatment arms that utilize a grid pattern for dosing. This study is not statistically powered to detect a difference in response across the 2 treatment regimens.

3.6.2. Blinding and Randomization

This is an open-label study, blinding is not applicable. The specific treatment taken by each subject will be randomly assigned using IRT.

3.7. Efficacy Assessments

Efficacy assessments will be evaluated at times specified in the Schedule of Activities (Table 2). During any COVID-19 interruption, remote efficacy assessments (I-GAIS, S-GAIS, Hexsel CSS Subsection D, Body-Q Appraisal of Cellulite, CR-PCSS-Buttock, CR-PCSS-Thigh, and [redacted] are not allowed due to potential bias.

3.7.1. Subject and Investigator Cellulite Assessments

Investigator cellulite assessments are independent of the subject assessments. Therefore, all subject cellulite assessments must be completed before the investigator's cellulite assessments are initiated. Subject assessments will occur while the subject is alone with no study site

personnel in the room. Investigators will be instructed not to verbalize their ratings while in the presence of the subject and vice versa.

3.7.2. Subject Global Aesthetic Improvement Scale (S-GAIS)

The S-GAIS is a 7-level scale (Table 5) ranging from +3 (very much improved) to -3 (very much worse). Subjects will use the S-GAIS to determine the degree of improvement of each buttock or thigh by comparing the cellulite from the Day 1 pretreatment (baseline) image of each buttock or each thigh to the images taken at the subsequent visits (Days 28, 56, 84, 112, 140 and 180/ET) specified in the Schedule of Activities (Table 2).

S-GAIS assessments, which will be based on digital photographs and will be performed separately for each of 2 treatment areas and must be completed before study intervention administration on the scheduled visits. At treatment visits, the photographs taken before marking the treatment areas will be used.

Table 5: S-GAIS Scale

Rating	Response Option	Description
+3	Very much improved	My treated cellulite looks very much better.
+2	Much improved	My treated cellulite looks much better, but additional treatment would slightly improve the result.
+1	Improved	My treated cellulite looks better, but additional treatment is necessary.
0	No change	My treated cellulite looks essentially the same as it did originally.
-1	Worse	My treated cellulite looks worse than it did originally.
-2	Much worse	My treated cellulite looks much worse than it did originally.
-3	Very much worse	My treated cellulite looks very much worse than it did originally.

3.7.3. Investigator Global Aesthetic Improvement Scale (I-GAIS)

The I-GAIS is a 7-level scale (Table 6) ranging from +3 (very much improved) to -3 (very much worse). Investigators who are physicians will use the I-GAIS to determine the degree of improvement of each buttock or thigh by comparing the cellulite from the Day 1 pretreatment (baseline) image of each buttock or each thigh to the images taken at the subsequent visits (Days 28, 56, 84, 112, 140 and 180/ET) specified in the Schedule of Activities (Table 2).

The I-GAIS assessments will be based on digital photographs, are performed separately for each of 2 treatment areas and must be completed before study intervention administration on those visits. At treatment visits, the photographs taken before marking the treatment areas will be used.

Table 6: 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.

3.7.4. 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.(2) The Body-Q Appraisal of Cellulite in this study consists of 11 questions (see Table 7) 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 Day 1 and Day 180/ET Visits.

The Body-Q Appraisal of Cellulite will be completed prior to any investigator cellulite assessments (CR-PCSS, I-GAIS, [redacted]

Table 7: 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

3.7.5. Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) – Buttock

The CR-PCSS-Buttock will be used to assess the severity of cellulite of both buttocks (each buttock, independently) at Screening to determine study eligibility. 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 (Table 8). 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.

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

Table 8: 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.

3.7.6. Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) – Thigh

The CR-PCSS-Thigh will be used to assess the severity of cellulite of both thighs (each thigh, independently) at Screening to determine study eligibility. 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 (Table 9). 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.

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

Table 9: CR-PCSS - Thigh

Rating	Level of Severity	Description
0	None	No depressions or raised area.
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.

3.7.7. Hexsel Cellulite Severity Scale

The Hexsel CSS is a photonumeric scale that looks at 5 key morphologic features of cellulite (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 10). For this study, only "D- laxity, flaccidity or sagging of skin" will be assessed for eligibility.

The investigator or qualified designee will use the Hexsel CSS Subsection D to assess the severity of dermal laxity in each buttock or each thigh independently. This assessment should be made while the subject is in the standing position with relaxed gluteus muscles. This assessment will be conducted at the Screening Visit and all study visits (Table 2), and should be performed prior to the 3D digital photography assessments, if possible.

Table 10: Hexsel CSS (D) Laxity, Flaccidity or Sagging of Skin

Rating	Description
0	Absence of laxity, flaccidity, or sagging skin
1	Slight draped appearance
2	Moderate draped appearance
3	Severe draped appearance

Subjects with Hexsel CSS Subsection D score greater than 3 at screening are excluded. A score greater than 3 is defined as an appearance significantly worse than exhibited in the Hexsel CSS Subsection D severe (score = 3) image.

3.7.8. [redacted]

3.7.10. [redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
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[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

3.8. Medical and Cellulite History

A medical and cellulite 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.

3.9. Substance 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/Illegal Drug).
- 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 prior to the Screening Visit or any concomitant medications or nondrug therapies received from the Screening Visit through the End of Study (EOS) Visit will be recorded.

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

3.10.1. Prohibited Medications and Procedures

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 /ET 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 cellulite (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 cellulite.

3.11. Adverse Events

All AEs and serious adverse events (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 (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 preexisting condition associated temporally with the use of the study medication whether or not considered related to the study medication. AEs will be captured once a subject has signed the informed consent. AEs include:

- Changes in the general condition of the subject.
- Subjective symptoms offered by or elicited from the subject.
- Objective signs observed by the investigator or other study personnel.
- All concurrent diseases that occur after the start of the study, including any change in severity or frequency of pre-existing disease.
- 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.
- All clinically relevant laboratory abnormalities or physical findings that occur during the study.

3.11.2. Serious Adverse Events (SAE)

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.

3.11.3. Adverse Events of Special Interest (AESI)

AESIs for this study include:

- Bruising, ecchymosis, hematomas, and contusions that occur remote to the site of drug administration.
- Any hypersensitivity reactions.
- Local AEs associated with the injection site, including bruising, pain, nodules/mass, ulceration, erythema, pruritus, swelling, and/or induration.

These events will be reported as AEs in the eCRF. All AEs will be evaluated for seriousness and severity.

3.12. Clinical Safety Laboratory Tests

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

Table 14: Clinical Laboratory parameters

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

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

Any clinically significant laboratory abnormality observed will be considered as an AE or SAE as appropriate.

3.13. Pregnancy Test

All female subjects of childbearing 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 180/ET Visit and urine pregnancy tests at Days 1, 28, 56, 84, 112, and 140 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 Height, Body Weight and BMI

Height and body weight measurements will be taken at screening. Body weight will also be measured at the Days 1 and 180/ET Visits. BMI will be calculated using the height at screening and weight at respective visits. Refer to Table 19 for BMI derivation.

3.15. 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, Days 1, 28, 56, 84, 112, 140 and 180/ET Visits. On treatment visits (Days 1, 28, 56, 84, 112, and 140), vital signs will be assessed at 4 hours prior to, and at 15 and 30 minutes after study drug administration (body temperature is not required at the 15 minute postdose time point). The subject's vital signs must be stable, or repeated until stable before the subject can leave direct observation.

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

3.16. 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.

3.17. Physical Examination

The complete physical examination (by body system) will be performed at the Screening and Day 180/ET Visit. Physical examination will include: evaluation of the head, eyes, ears, nose, throat, neck (including thyroid), cardiovascular system (including assessment of heart, peripheral pulses, presence or absence of edema), lungs, abdomen (including liver and spleen, bowel sounds), lymph nodes, musculoskeletal system (including spine, joints, muscles), neurological system (including cranial nerves, reflexes, sensation, strength), skin, extremities, and other systems or organs 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 15: Fitzpatrick Scale

Level	Description
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

3.18. 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 the Day 1 Visit (prior to study treatment administration) and at the Day 180/ET Visit for the determination of serum anti-AUX-I and anti-AUX-II antibody levels and neutralizing antibodies to AUX-I and AUX-II.

4. STUDY PARAMETERS

4.1. Subject Disposition

A subject 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 ET 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.

Subjects who have been withdrawn from the study at any time after the first dose of study treatment will not be replaced. 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.

If implications from COVID-19 cause subjects to miss study visits during the Treatment Phase additional subjects may be enrolled, at the discretion of the sponsor, in order to obtain a minimum of 24 subjects with sufficient efficacy assessments for overall objective and endpoint analysis purposes.

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 substance use
  - Alcohol use (Never, Current, and Former).
  - Tobacco use (Never, Current, and Former).
  - Illegal Drug use (Never, Current, and Former).

4.3. Protocol Deviations

Protocol deviations will be identified and documented prior to database lock. Protocol deviations may 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.

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 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 prior to the Screening Visit.

A concomitant medication (or non-drug therapy) is any medication (or therapy) taken on or after the Screening Visit through the Day 180 Visit or the medication is reported as ongoing.

Please note that if a medication started prior to Screening and end date is after Screening/ongoing it will be counted as both prior and concomitant medication.

4.5. Prior Cellulite Treatment

Prior cellulite 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 cellulite treatment.

All cellulite treatment medications will be classified as cellulite Drug. All cellulite 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 cellulite 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 Ratings

The I-GAIS rating is directly obtained from the investigator's assessments at an analysis visit (Day 28, Day 56, Day 84, Day 112, Day 140, Day 180 and Last [see the definition of Last in Table 19]).

4.6.1.2. One-Level I-GAIS Responder

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

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 analysis 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 analysis visit.

4.6.2. S-GAIS

4.6.2.1. S-GAIS Ratings

The S-GAIS rating is directly obtained from the subject's assessments at an analysis visit (Day 28, Day 56, Day 84, Day 112, Day 140, Day 180, and Last).

4.6.2.2. One-Level S-GAIS Responder for Either Buttock or Either Thigh

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

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

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

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 each analysis visit (Day 1, Day 180, and Last). Change from baseline (Day 1) in each item score will be summarized for treated buttock or thigh subjects at Day 180 and Last.

4.6.3.2. Total Scores

Total score will be calculated for a treated buttock or thigh subject at each analysis visit (Day 1, Day 180, and Last). In case of missing responses for a subject, total score will be imputed as explained in Section 6.3. Change from baseline (Day 1) in Body-Q Appraisal of Cellulite for total score will be summarized for treated buttock or thigh subjects at Day 180 and Last.

Higher scores reflect a better outcome.

4.6.4. Hexsel CSS Subsection D Severity

To assess the effectiveness of CCH for the treatment of cellulite in the presence of dermal laxity in adult females, the observed score and change from baseline (Day 1) in Hexsel CSS Subsection D severity score will be determined for each treatment area (left buttock, right buttock, left thigh, or right thigh) at each analysis visit (Day 28, Day 56, Day 84, Day 112, Day 180, and Last).

4.6.5. Skin Surface Roughness

[redacted]

[redacted]

[redacted]

4.6.6. [redacted]

[redacted]

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.

[redacted]

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

4.7.1.4. Adverse Event Categorization by Treatment Session

The AEs will be associated with the treatment session based on the start date of the AE compared to date of treatment sessions, as below:

- Treatment session 1: First injection date until start of next treatment session or end of study visit if no treatment after treatment session 1.
- Treatment session 2: Date of second treatment session until start of next treatment session or end of study visit if no treatment after treatment session 2.
- Treatment session 3: Date of third treatment session until start of next treatment session or end of study visit if no treatment after treatment session 3.
- Treatment session 4: Date of fourth treatment session until start of next treatment session or end of study visit if no treatment after treatment session 4.
- Treatment session 5: Date of fifth treatment session until start of sixth treatment session or end of study visit if no treatment after treatment session 5.
- Treatment session 6: Sixth injection date until start of Day 180/ET Visit.

Note: For adverse events by treatment session, Treatment Session y, where y denotes 1, 2, 3, 4, 5, 6 refers to a period of time from the start date of the study drug given at that treatment session to the end of the day before the next treatment session, or the end of study if no study drug was given after Treatment Session y. Therefore, Treatment Session y varies among subjects in study.

4.7.2. Vital Signs and Clinical Laboratories

4.7.2.1. Laboratory Values

Clinical laboratory data (hematology and chemistry only) will be analyzed for observed value and change from baseline to Last. Refer to Table 19 for definition of baseline and Last.

In addition, subjects reporting any sponsor-defined Potentially Clinically Important (PCI) laboratory values during the study will be analyzed.

PCI laboratory values are presented in Table 16 below.

Table 16: Potentially Clinically Important Laboratory values

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. Vital Signs

Vital signs will be analyzed for observed value and change from baseline separately for vital signs on injection days and vital signs at each visit (excluding post injection time points on injection days). Refer to Table 19 for the definition of baseline.

In addition, subjects reporting any sponsor-defined PCI vital sign values during the study will be analyzed.

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 17 below.

Table 17: 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. 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.

5. ANALYSIS POPULATIONS

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

Table 18: Analysis Populations

Population	Definition	Analysis
Safety Population	Safety Population is defined as all enrolled participants who received at least 1 injection of CCH.	All demographic, baseline characteristics and safety parameters will be summarized based on this population.
Intent-to-Treat (ITT)	The Intent-to-Treat (ITT) Population is defined as all enrolled participants who received at least 1 injection of CCH.	
Modified Intent-to-Treat (mITT)	The Modified Intent-to-Treat (mITT) Population is defined as all ITT participants who have at least 1 valid I-GAIS assessment after an injection of CCH.	All efficacy/effectiveness 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 α=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 19 defines the derived variables for study parameters.

Table 19: Derived Variables and Definition

Variable	Definition
Age Group	18 – <35 years 5 – <45 years 45 – 55 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 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.
Baseline for Vital Signs on Injection Days	For vital signs on injection days, the baseline value will be the vital sign measure immediately prior to 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 (analysis)	Last is defined as the last non-missing measurement/assessment post the first dose of study drug.
Last Date in Study	Last date in study is defined as: • The date of Day 180 Visit if the subject completes the study. • The date of ET visit if the subject is terminated early from study at a non-scheduled visit. • The date of the latest scheduled visit if the subject is terminated early from study at a scheduled visit or lost to follow-up.
Age (Years) at cellulite Onset	(Date of cellulite symptoms reported – Date of Birth)/365.25. See Section 6.3.1.3 for handling of partial or unknown Cellulite symptom onset dates.
Time (Years) since last cellulite treatment	(Date of informed consent – Date of most recent cellulite treatment)/365.25. See Section 6.3.1.3 for handling of partial or unknown treatment dates.
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 Start Day	AE start date – Date of Day 1 + 1
AE Stop Day	AE end date – Date of Day 1 + 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 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. Also, if the missing data at a visit is more than 50% then for that subject raw sum score will be considered as missing.

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 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 Cellulite Onset Date

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

If the onset date is indicated as completely unknown but starting less than 5 years ago, the onset date will be imputed as the informed consent date minus 5 years.

If the onset date is indicated as completely unknown but starting more than 5 years ago, the onset date will not be imputed.

Missing cellulite 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 cellulite 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 Analysis

No interim analysis is planned for this study.

7. STATISTICAL ANALYSES

7.1. Subject Disposition

The number of subjects included in each study population will be summarized by treatment regimen and overall. Subjects excluded from the safety, ITT, or mITT populations will be listed.

The frequency counts and percentages of subjects screened, enrolled, completed, and/or withdrawn from the study, as well as the reason for withdrawal from study will be summarized by treatment regimen 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 summarized by deviation classification (major/minor), and by treatment regimen and overall. A listing of all protocol deviations will be presented.

7.3. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment regimen 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 19 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 substance use
  - Alcohol use (Never, Current or Former).
  - Tobacco use (Never, Current or Former).
  - Illegal Drug use (Never, Current or 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. Cellulite History

Cellulite history will be summarized by treatment regimen and overall using frequency counts and percentages which will include:

- Age (years) at cellulite symptom onset (summarized descriptively).
- Prior treatments for cellulite including liposuction, laser, massage, radiofrequency, drug, mesotherapy, cream, other, or none. Subjects can report more than 1 prior cellulite treatment.
- Number of prior cellulite treatments (0, 1, 2, or ≥3).
- Time (years) since most recent cellulite treatment (summarized descriptively).

Refer to Table 19 for computation of "age at cellulite onset" and "time since last cellulite treatment." Cellulite history will be listed.

7.6. Prior/Concomitant Medications and Procedures

Prior and concomitant medications will be summarized by treatment regimen 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 treatment regimen 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 cellulite will also be presented.

7.7. Efficacy Analyses

Efficacy parameters will be summarized for each treatment areas (buttock or thigh), treatment regimen and overall using the mITT Population.

7.7.1. Primary Efficacy Endpoint

7.7.1.1. One-level I-GAIS Responders

The 1-level I-GAIS responders will be summarized by treatment regimen and overall using frequency counts, proportion and corresponding 95% CI based on the Clopper-Pearson method for 1-level I-GAIS responders at Day 180 and Last for each treatment area and either buttock or either thigh.

The definition of a one-level responder is provided in Section 4.6.1.2.

7.7.2. Secondary Efficacy Endpoints

7.7.2.1. One-level I-GAIS Responders by Visit

The 1-level I-GAIS responders will also be summarized by treatment regimen and overall using frequency counts, proportion and corresponding 95% CI based on the Clopper-Pearson method for 1-level I-GAIS responders at Day 28, Day 56, Day 84, Day 112, Day 140, and Last for each treatment area and either buttock or either thigh.

Additionally, I-GAIS ratings will also be summarized at Day 28, Day 56, Day 84, Day 112, Day 140, Day 180, and Last for each treatment area.

7.7.2.2. One-level S-GAIS Responders by Visit

The 1-level S-GAIS responders will also be summarized by treatment regimen and overall using frequency counts, proportion and corresponding 95% CI based on the Clopper-Pearson method for 1-level S-GAIS responders at Day 28, Day 56, Day 84, Day 112, Day 140, Day 180 and Last for each treatment area and for either buttock or either thigh.

The definition of a one-level responder is provided in Section 4.6.2.2.

Additionally, S-GAIS ratings will also be summarized at Day 28, Day 56, Day 84, Day 112, Day 140, Day 180 and Last for each treatment area.

7.7.2.3. Change from baseline in Body-Q -Appraisal of Cellulite Total Score by Visit

The observed and change from baseline (Day 1) in Body-Q Appraisal of cellulite total score will be summarized at Day 180 and Last by treatment regimen and overall using descriptive statistics.

In addition to 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 180 and Last using frequency counts and percentages with mean and SD.

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

7.7.2.4. Change from baseline in Hexsel CSS Subsection D Score by Visit

The observed and change from baseline (Day 1) to each analysis visit (Day 28, Day 56, Day 84, Day 112, Day 140, Day 180, and Last) in Hexsel CSS Subsection D severity score will be summarized by treatment area and severity grades.

A listing of Hexsel CSS Subsection score will be provided.

7.7.3. [redacted]

7.7.3.1. [redacted]

[redacted]

7.7.3.2. [redacted]

[redacted]

7.8. Safety Analyses

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

7.8.1. Study Drug Exposure

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

- Total number of injections given.
- Number of sub-area under each treatment area treated.
- Number of additional sub-area under each treatment area treated.
- Number of treatment region treated.
- Average number of injections per sub-area under each treatment area.
- Duration of exposure (refer to Table 19 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 treatment region and treatment regimen.

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 (ie, related) to study drug will be summarized.

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.
- Study drug related TEAEs.
- TEAEs by severity.
- Study drug related TEAEs by severity.
- TEAEs by treatment session.
- Duration of study drug related TEAEs (1 – 7 days, 8 – 14 days, 15 – 21 days, >21 days).
- Serious TEAEs.
- TEAEs of special interest.
- TEAEs of special interest by severity.

The most common non-serious TEAEs by order of frequency (most frequent, 2nd most frequent, and 3rd most frequent) will be summarized by PT. The most common 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.
- Fatal AEs.
- Non-fatal serious AEs.
- Non-fatal non-serious AEs leading to study discontinuation.
- Non-fatal non-serious AEs resulting in drug interruption/withdrawn.

Refer to Table 19 for computation of duration of AEs.

7.8.3. Clinical Laboratory

Hematology and chemistry results will be summarized by treatment regimen and overall using descriptive statistics for observed and change from baseline to Last.

The PCI laboratory values will be summarized by treatment regimen and overall using frequency counts and percentages. Refer to Table 16 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 treatment regimen and overall and listed as baseline characteristics as mentioned in Section 7.3.

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

7.8.5. Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) will be summarized by treatment regimen 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 treatment regimen and overall for observed and change from baseline values for all time points 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 treatment regimen and overall using frequency counts and percentages. Refer to Table 17 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 treatment regimen 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 Last will be presented by treatment regimen and overall using frequency counts and percentages.

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

7.8.8. 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 and Last by total number of treatment sessions received. The titer levels will be logarithmically transformed prior to being summarized.

Neutralizing antibody results will be summarized by total number of treatment sessions as percentage of positive/negative.

A listing of immunogenicity results by subject will be provided.

Note: For immunogenicity table “x treatment sessions” presents a cohort of subjects who received a total of x treatment sessions during the study.

8. CHANGE FROM PROTOCOL

This SAP is prepared based on Protocol Amendment 1: December 3, 2020. Table 20 lists any significant changes in the SAP from what is proposed in the protocol.

Table 20: Changes from Protocol

Text in Protocol	Change in SAP	Justification
N/A		

9. REVISION HISTORY

Non-editorial changes made to any of the modules of this SAP will be recorded in Table 21.

Table 21: Revision History

Version	Date	Revision Author	Comments
1.0	09-Nov-2020	[redacted]	Original
1.1	24-Jun-2021	[redacted]	SAP updated as per Protocol Amendment 1

10. REFERENCES

1. Protocol Amendment 1: A Phase 2 Multicenter, Open-Label, Randomized, Parallel-Group, Multiple-Dose Study to Assess The Effectiveness, Safety And Satisfaction With Collagenase Clostridium Histolyticum Grid Technique Injections Of Buttock Or Thigh Cellulite With Laxity In Adult Females. Dated: December 3, 2020.
2. Scott AM, Pusic AL, Cano SJ, et al. The BODY-Q: A new patient reported outcome (PRO) measure for body contouring patients. *Qual Life Res*. 2012;20:74-5.
3. Hexsel DM, Dal'Forno T, Hexsel CL. A validated photonumeric cellulite severity scale. *J Eur Acad Dermatol Venereol*. 2009;23 (5):523-8.