SAP MODULE 1 - DETAILED STATISTICAL METHODOLOGY

Protocol No. EN3835-213

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

Statistical Analysis Plan

Prepared for:

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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

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
AUX-I	Clostridial class I collagenase
AUX-II	Clostridial class II collagenase
B-HCG	Human chorionic gonadotropin
BMI	Body mass index
bpm	Beats per minute
brpm	Breaths per minute
C	Celsius
CBC	Complete blood count
CCH	Collagenase clostridium histolyticum
CFR	Code of Federal Regulations
cm	Centimeter
DMP	Data Management Plan
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of study
ET	Early termination
IEC	Independent Ethics Committee
IRB	Institutional Review Board
kg	Kilogram
m	Meter
Max	Maximum
Min	Minimum
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
mmHg	Millimeter of mercury
PCI	Potentially clinically important
PT	Preferred term

Abbreviation	Definition
PT/PTT	Prothrombin time/partial thromboplastin time
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
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 immunogenicity profile in response to treatment with collagenase clostridium histolyticum (CCH) in subjects undergoing elective abdominoplasty surgery.

The general information about the study is detailed in the EN3835-213 Clinical Study Protocol, A Phase 2b, Open-label Study to Explore Tissue Histopathology Following Subcutaneous Injection of Collagenase Clostridium Histolyticum Using an Abdominoplasty Model, Amendment 4, dated May 1, 2020.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of this study is to evaluate the histopathology and immunohistochemistry of subcutaneous tissue isolated after single and multiple CCH doses with both a [redacted] single injection technique and [redacted] (relative to control, non-dosed tissue) in adult female subjects undergoing abdominoplasty.

2.2. Secondary Objective

The secondary objectives of this study are:

- To compare the histopathology and immunohistochemistry of tissue from treatment areas dosed with CCH in adult women undergoing elective abdominoplasty surgery.
  - Multiple doses versus single dose with a [redacted] single injection technique.
  - Multiple doses versus single dose with a [redacted].
  - Multiple doses with a [redacted] versus multiple doses with a [redacted] single injection technique.
  - Single dosing with a [redacted] versus single dosing with a [redacted] single injection technique.
- To assess the safety and immunogenicity of CCH injected in adult women undergoing an elective abdominoplasty surgery.

3. STUDY DESIGN AND MEASURES

3.1. Study Design

This is a Phase 2b, open-label, exploratory study of the mechanism of action of bruising and safety of CCH subcutaneously administered in subjects undergoing elective abdominoplasty surgery.

Approximately 8 subjects (1 or 2 subjects per group) were originally expected to enroll and complete the study (on Day 28). An additional 2 subjects will be enrolled to replace (for overall

objective and endpoint analysis purposes) subjects whose abdominoplasty surgeries were delayed due to COVID-19 restrictions. The 2 subjects whose surgeries were delayed due to COVID-19 can still undergo planned abdominoplasty surgery at a time convenient to both the investigator and the subject, and complete the study, but will be excluded from the non-safety analysis population. Subjects who are considered screen failures due to logistic/timing purposes surrounding the subject's availability for surgery (excluding any other inclusion/exclusion criteria reasons) and/or COVID-19 restrictions, may be rescreened. Subjects who undergo elective abdominoplasty surgery and are willing to receive injections of CCH and have their tissue donated for evaluation (otherwise discarded post-surgery) will be eligible, provided all inclusion/exclusion criteria are met. The subjects will be assigned to 1 of 6 groups after the screening period of up to 28 days. Each subject will have 2 marked areas (Area 1 and Area 2) of the abdomen dosed with CCH (single or multiple doses) plus a marked non-dosed control area for comparison. The control area will be located between the 2 treatment areas. Subjects in each group will receive up to 3 CCH doses (each dose as either a [redacted] single injection technique or a [redacted] e) across 2 treatment areas. Total study duration for each subject is approximately 50 to 71 days depending on the group assigned (not including the screening period of up to 28 days). The duration of the study from first subject first visit to last subject last visit will depend on the ability of the investigative site to identify and enroll eligible 10 subjects.

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

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

Subjects in each group will receive up to 3 CCH doses across 2 treatment areas at the following dosing visits:

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

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

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

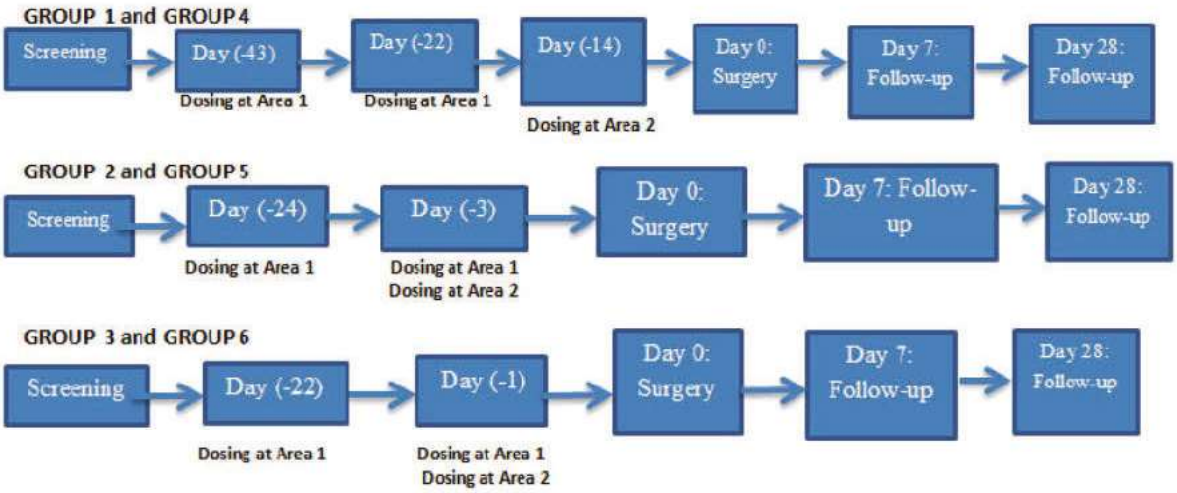
Treatment areas of each subject group will be marked: Treatment Area 1 and Treatment Area 2.

By the end of the dosing phase:

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

The study schema displayed below provides additional details of the flow of study.

Figure 1: Study Schema



The complete Schedule of Activities is provided in Table 1.

Table 1: Schedule of Activities

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

Table 1: Schedule of Activities (Continued)

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

Note: AUX-I = Clostridial class I collagenase, AUX-II = Clostridial class II collagenase, ECG = Electrocardiogram, EOS = End of Study
Note: Unless otherwise stated above or outlined below (and with the exception of injection site reactions/local tolerability in the area treated), all assessments should be completed prior to study treatment administration on Treatment Days.

[a] Performed prior to any study-required assessments.

[b] Laboratory safety testing will be performed at the investigative site or designated laboratory, as part of the standard of care (hematology, biochemistry, ECG, etc) of the subject's preparation for elective abdominoplasty as deemed required by the investigator. These testing results will be assessed for inclusion/exclusion criteria by the investigator. All inclusion/exclusion criteria should be reassessed and verified prior to the first dose of study treatment. In the event that any safety laboratory testing results are unavailable prior to the subject's first dosing visit, the investigator will notify the sponsor to discuss on a case-by-case basis, prior to administering any study treatment to the subject.

[c] Physical examination performed prior to surgery.

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

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

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

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

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

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

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

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

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

3.2. Eligibility Criteria for Subject Selection

3.2.1. Inclusion Criteria

In order to be eligible to participate in the study, subjects must meet all of the following inclusion criteria:

1. Be adequately informed and understand the nature and risks of the study and be able to provide consent.
2. Be undergoing planned elective abdominoplasty.
3. Be willing to have their tissue donated for evaluation.
4. Be female and ≥18 years of age and ≤ 55 years of age at time of informed consent.
5. Have a body mass index (BMI) between ≥ 20.0 and ≤ 35.0 kg/m^2.
6. Be willing to apply sunscreen to the abdomen before each exposure to the sun while participating in the study (ie, Screening through Day 28 End of Study [EOS]/Early Termination [ET] Visit).
7. Be judged to be in good health, based upon the results of a medical history, physical examination, and any standard of care laboratory profile available at Screening.
8. Be postmenopausal (of nonchildbearing potential) with no history of menstrual flow in the 12 months prior to the Screening Visit); or, if of childbearing potential, be nonpregnant, nonlactating and agree to use effective contraception when with a male partner for the duration of the study. Acceptable forms of contraception include hormonal measures (oral contraceptive pills, contraceptive patch, contraceptive ring, or injections), intrauterine devices, double barrier method (condom plus diaphragm, condom or diaphragm plus spermicidal gel or foam), surgical sterilization of the male partner, and abstinence.
9. Have a negative serum pregnancy test at screening and a negative urine pregnancy prior to the first dose of study drug.
10. Be willing and able to cooperate with the requirements of the study.

3.2.2. Exclusion Criteria

In order to be eligible to participate in the study, subjects must not meet any of the following exclusion criteria:

1. Is from a vulnerable population, as defined by the US Code of Federal Regulations (CFR) Title 45, Part 46, Section 46.111(b) and other local and national regulations, including but not limited to, employees (temporary, part-time, full time, etc) or a family member of the research staff conducting the study, or of the sponsor, or of the contract research organization, or of the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).
2. Has any of the following systemic conditions:
   a. Coagulation disorder.

b. Evidence or history of malignancy (other than excised basal-cell carcinoma) unless there has been no recurrence in at least 5 years.
c. History of keloidal scarring or abnormal wound healing.
d. Concurrent diseases or conditions that might interfere with the conduct of the study, confound the interpretation of the study results, or endanger the subject's well-being. Any questions about concurrent diseases should be discussed with the Sponsor Medical Monitor.
e. Evidence of clinically significant abnormalities observed/recorded on physical examination, vital signs, clinical laboratory values at screening and/or during presurgery preparation at site (including electrocardiogram [ECG], laboratory, etc).

3. Has any of the following local conditions in the areas to be treated:
   a. History of lower extremity thrombosis or post-thrombosis syndrome.
   b. Vascular disorder (eg, telangiectasia) in area to be treated.
   c. Inflammation or active infection.
   d. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer within last 5 years.
   e. Has a tattoo and/or a mole located within 2 cm of the site of injection.
4. Requires the following concomitant medications before or during participation in the trial:
   a. Anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication 7 days prior to injection with study drug (CCH) (except for ≤ 150 mg aspirin daily, permitted only within a window-specific timeframe as determined by the investigator prior to abdominoplasty surgery).
5. Has history of any abdominal surgery, including but not limited to liposuction, caesarean section, appendectomy, cholecystectomy, or umbilical hernia repair.
6. Has used any of the following within the timelines as identified below OR has used/intends to use any of the following:
   a. Injections (eg. mesotherapy), radiofrequency device treatments, laser treatment cryolipolysis, or surgery (including subcision and/or powered subcision) within the abdominal area during the 18-month period before injection of study drug.
   b. Any investigational treatment in the abdominal area during the 12-month period before injection of study drug.
   c. CoolSculpting® or similar treatments of the abdomen during the 18-month period before injection of study drug.
   d. Deep massage therapy (such as Endermologie™) or similar therapy, within the abdominal area during the 6-month period before injection of study drug.
   e. Creams (eg, Celluvera™, TriLastin®) and/or home therapies within the abdominal area during the 2-week period before injection of study drug and at any time during the course of the study.

f. Bath/shower salts or sugar/salt scrubs, lotions, loofahs, or other exfoliating products on the abdominal area during the 2-week period prior to injection of study drug and at any time during the course of the study.

7. Is presently nursing or providing breast milk in any manner.
8. Intends to become pregnant during the study.
9. Intends to initiate an intensive sport or exercise program regimen during the study.
10. Intends to use any tanning spray or tanning booths during the study.
11. Has received any investigational drug or treatment within 30 days prior to first injection of study drug.
12. Has a known systemic allergy to collagenase or any other excipient of study drug.
13. Has received any collagenase treatment at any time prior to treatment in this study.
14. Has a medical history of being treated with (or received) CCH or XIAFLEX®.
15. Has been known to have syncope.
16. Any other condition(s) that, in the investigator's opinion, might indicate the subject to be unsuitable for the study.

3.3. Selecting and Marking Treatment Area

For each subject, there will be 2 marked areas (Area 1 and Area 2) of the abdomen selected for injection with CCH plus a marked non-injected control area for comparison. The control area will be located between the two treatment areas. Treatment areas of each subject group will be marked as Treatment Area 1 and Treatment Area 2 respectively with the non-injected area marked as control.

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

3.4. Study Drug Administration

Subjects who qualify for the study will be given a maximum total dose of approximately 0.21 mg CCH over the course of the study, which will be administered as 3 doses of 0.07 mg CCH each, approximately, during 2 or 3 dosing sessions.

The dosing detail, volume and concentration is explained in Table 2 below.

Table 2: Study Treatment (All Subjects)

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

[a] [redacted] mL of the 1.5 mL dilution will be remaining and returned to Endo.

3.5. Determination of Sample Size

As this an exploratory study, no formal sample size calculation is required.

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

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

Completion of 8 subjects with abdominoplasty surgeries completed within the allowable timeframe per protocol (not due to COVID-19 delay) will provide data to meet the primary objective. The 2 subjects whose surgery was delayed due to COVID-19 will not be included for the specific objective but will be analyzed separately.

3.6. Blinding and Randomization

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

3.7. Gross Pathology, Histopathology, and Immunohistochemistry

Digital photography will be conducted so that the photographs of the treatment area can assist the histopathologist/evaluator in assessing the gross pathology and histopathology of the excised tissues.

The subjects will be photographed after marking the treatment areas and the injection sites with a surgical marker (but prior to CCH injection) at each dosing visit, while the subject is in a consistent, standardized relaxed standing pose.

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

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

Histopathology and immunohistochemistry of the excised abdominal tissue will be performed at the central pathology laboratory.

Histopathology and immunohistochemistry findings in the excised abdominal tissues injected with CCH will be compared to histopathology and immunohistochemistry findings in noninjected control tissue. Comparisons will also be made between tissues dosed twice with CCH versus tissue dosed only once, and tissue dosed using the [redacted] technique versus the [redacted].

3.8. Medical Clearance

Medical clearance for surgery will be obtained at the Screening Visit and also prior to the Surgery Visit (Day -30 through Day -1). Information related to whether or not medical clearance was provided, along with the date of medical clearance will be collected.

3.9. Abdominoplasty Procedure

Following administration of 3 doses of CCH, abdominoplasty and collection of the excised abdominal tissue will occur on Day 0 (Surgery Visit). Information on details of the abdominoplasty surgery along with the date of surgery and whether the tissue excision was performed and shipped will be collected. If abdominoplasty surgery is not performed, or if tissue was not excised, or if the tissue was excised and not shipped, the date and reason for these events will be collected and presented in a listing.

3.10. Medical/Surgical History

Medical and surgical history will be obtained at the Screening Visit and will include previous medications, procedures, surgery, and obstetrics details. Historical and current medical conditions including date of last menstrual period will be recorded. History of tobacco and alcohol use (never, current, former) will also be collected.

Surgical history will include a review of all surgical procedures completed in the prior 5 years and any surgery completed at any time in the treatment areas.

3.11. Prior/Concomitant Medications and Procedures

Any medications taken within the 90 days prior to the Screening Visit or taken from the Screening Visit through the Day 28 Post-surgery follow-up visit/EOS/ET Visit will be recorded.

Any diagnostic, therapeutic, surgical procedure or nondrug therapies (eg, blood transfusions, oxygen supplementation, physical therapy, etc) performed for the above said periods will be recorded.

3.11.1. Prohibited Medications and Procedures

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

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

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

3.12. Safety Assessments

3.12.1. Adverse Events (AEs)

All AEs occurring after signing the informed consent are to be recorded on the AE pages of the electronic case report form (eCRF). A condition present at baseline that worsens after initiation of study treatment will be captured as an AE; the onset date will be the date the event worsened.

Adverse Events (AEs)

An AE is any unfavorable or unintended change in body structure (signs), body function (symptoms), laboratory result (eg, chemistry, 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. This would include AEs resulting from concurrent illness, reactions to concurrent medication use, or progression of disease states. AEs include:

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

Serious Adverse Events (SAEs)

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 patient or may require medical intervention to prevent one of the outcomes listed above

Adverse Events of Special Interest (AESI)

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

Adverse Events Related to Abdominoplasty

As with any surgical procedure, abdominoplasty can also have procedure-related AEs and/or complications. Most common local complications observed include (but are not limited to) seroma, haematoma, infection, skin necrosis, suture extrusions, umbilical anomalies, hypertrophic scars, keloids, poor wound healing, and changes in skin sensation. Systemic complications, though rare, that could be serious and sometimes fatal are deep venous thrombosis and pulmonary thromboembolism, respiratory distress, and even death.

3.12.2. Clinical Safety Laboratory Tests

Laboratory safety testing will be performed as part of the standard of care of the subject's preparation for elective abdominoplasty as deemed required by the investigator at Screening, and prior to surgery on Day 0.

Laboratory safety testing will be performed at the investigative site or designated laboratory. These test results will be assessed for inclusion/exclusion criteria by the investigator. All inclusion/exclusion criteria should be reassessed and verified prior to the first dose of study treatment.

In the event that any safety laboratory testing results are unavailable prior to the subject's first dosing visit, the investigator will notify the sponsor to discuss on a case-by-case basis, prior to administering any study treatment to the subject.

Any clinical post-operative laboratory testing may be performed post-surgery through Day 28 Post-surgery follow-up visit/EOS/ET Visit as deemed necessary by the investigator.

Subjects in Group 1 and Group 4 may undergo additional clinical laboratory safety testing as standard of care (hematology, biochemistry) as part of additional preparation for abdominoplasty surgery.

Clinical laboratory parameters may include, but not be limited to, the following:

- Complete blood count with differential count (CBC W/DIFF).
- Prothrombin time/partial thromboplastin time (PT/PTT).

- Chemistry panel (CHEM PROFILE).
- Human chorionic gonadotropin (B-HCG) qualitative.

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

3.12.3. Pregnancy Test

Female subjects of child bearing potential must have a negative serum pregnancy test at the Screening Visit prior to the first dose of study treatment to be enrolled in the study. Female subjects of childbearing potential will undergo a serum pregnancy at the Screening Visit and urine pregnancy tests at each dosing visit, at the Surgery Visit (Day 0) and the Day 28 Post-surgery follow-up visit/EOS/ET Visit.

3.12.4. Vital Signs

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

Vital signs (blood pressure, respiratory rate, pulse rate, and body temperature) will be collected on dosing visits up to 2 hours prior to dosing, at 30 minutes after dosing, and 15 minutes after dosing (without body temperature at this time point) on Days -43, -24, -22, -14, -3 and -1. Vital sign measurements will also be collected at Day -30 through Day -1, Surgery Visit (Day 0), Day 7 Post-surgery follow-up visit and, Day 28 Post-surgery follow-up visit/EOS/ET Visit. Pulse and blood pressure should be taken after the subject has been sitting for 5 minutes.

The vital signs of the subject must be stable before the subject can leave direct observation. Height and body weight measurements will be collected at the Screening Visit only, in order to calculate BMI.

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

3.12.5. 12-Lead Electrocardiogram (ECG)

An ECG will be performed as part of preoperative assessments as per standard-of-care and interpreted by the investigator. The investigator will review the ECG and other preoperative assessment results for clinical significance.

Any ECG result meeting the investigator's or sponsor's criteria for clinical significance will be considered as an AE or SAE as appropriate.

3.12.6. Physical Examination

The complete physical examination will follow the investigative site's standard of care and may include evaluation of the head, eyes, ears, nose, throat, neck (including thyroid), cardiovascular (including assessment of heart, peripheral pulses, presence or absence of edema), lungs, abdomen (including liver and spleen, bowel sounds), lymph nodes, musculoskeletal system (including spine, joints, muscles), neurological system (including cranial nerves, reflexes, sensation, strength), skin, extremities, and other conditions of note.

Complete physical examination (by body system) on each subject will be performed at the Screening Visit, Surgery Visit (prior to surgery), Day 7 Post-surgery follow-up visit, and at the Day 28 Post-surgery follow-up visit/EOS/ET Visit.

3.12.7. Immunogenicity Samples

Serum samples will be collected at the Screening Visit, Surgery Visit Day 0, and Day 28 Post-surgery follow-up visit/EOS/ET Visit for all subjects for the determination of serum anti-AUX-I and anti-AUX-II antibody levels. Neutralizing antibodies will only be tested from anti-drug antibody (ADA) positive samples from the Day 0 and Day 28 visits.

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

4. STUDY PARAMETERS

4.1. Subject Disposition

Subjects will be considered to have completed the study if they complete the Day 28 Post-surgical follow-up visit. The end of the study is defined as the completion of the final assessment for the last subject enrolled in the trial. Discontinued subjects are those subjects who discontinued the study at any time before the study ends.

For any subject who discontinues the study prematurely, the discontinuation date and reason of early discontinuation will be recorded in eCRF.

Any subject who prematurely withdraws from the study should undergo all ET assessments.

The reason of screen failure will also be recorded in eCRF for subjects who are not enrolled and are considered screen failures.

A subject may be discontinued from the study for the following medical or administrative reasons:

- Withdrawal by subject (reason must be specified).
- An AE.
- Death.
- A protocol violation (reason must be specified, for example: lack of compliance, use of a prohibited concomitant medication, etc).
- The subject was lost to follow-up.
- Other reasons (reason must be specified, for example: the subject moved, pregnancy, investigator decision, sponsor decision to terminate trial, etc).

4.2. Protocol Deviations

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

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

- Ineligible subject/study entry criteria not satisfied
- Informed consent not completed correctly
- Prohibited medications/procedure

4.3. Prior/Concomitant Medications

All medications will be coded using the World Health Organization (WHO) Drug Dictionary. The version of the dictionary will be defined in the Data Management Plan (DMP).

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

A concomitant medication is defined as any medication taken from the Screening Visit through the Day 28 Post-surgery follow-up visit/EOS/ET Visit or the medication is reported as ongoing.

4.4. Safety Parameters

4.4.1. Adverse Events

AE verbatim terms as reported by the investigator will be mapped to system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). The MedDRA version to be used in this study will be defined in the DMP.

4.4.1.1. Treatment-Emergent Adverse Events (TEAEs)

A TEAE is any condition that was not present prior to treatment with study medication but appeared following treatment, was present at treatment initiation but worsened during treatment, or was present at treatment initiation but resolved and then reappeared while the individual was on treatment (regardless of the intensity of the AE when the treatment was initiated).

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

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

Refer to Section 6.3.1.1 to identify TEAE status when start date of an AE is unknown.

4.4.1.2. Intensity of Adverse Events

Intensity (or severity) of AEs will be graded as "Mild", "Moderate" or "Severe". For AEs with missing severity, the most severe assessment will be imputed for analyses, following worst case principle.

4.4.1.3. Relationship to Study Drug

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

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

Related AEs are AEs with the relationship described by the investigators as "probably related" or "possibly related". "Not related" or "Unlikely related" causality assessments are considered as negative causality.

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

4.4.2. Potentially Clinically Important (PCI) Vital Sign Values

The PCI vital sign values are presented in Table 3 below.

Table 3: Potentially Clinically Important Criteria

Parameter	PCI Low	PCI High
Systolic Blood Pressure	≤ 90 mmHg and decrease ≥ 20 mmHg from baseline	≥ 140 mmHg and increase ≥ 20 mmHg from baseline
Diastolic Blood Pressure	≤ 60 mmHg and decrease ≥ 15 mmHg from baseline	≥ 100 mmHg and increase ≥ 15 mmHg from baseline
Pulse Rate	≤ 50 bpm and decrease ≥ 15 bpm from baseline	≥ 125 bpm and increase ≥ 15 bpm from baseline
Respiratory Rate	≤ 12 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

5. ANALYSIS POPULATIONS

The study will use the following analyses population for data summarization:

Table 4: Analysis Population

Population	Definition	Displays
Evaluable Population	The Evaluable Population is defined as all subjects who receive at least 1 injection of study drug and have histopathology and immunohistochemistry results. The histopathology data of the 2 subjects whose abdominoplasty surgery was delayed due to COVID-19, will be analyzed separately.	This population will be used for summarization of demographic and baseline characteristics.
Safety Population	The Safety Population is defined as all subjects who receive at least 1 injection of study drug.	This population will be used for all analyses of subject disposition, demographic and baseline characteristics and safety data listings.

6. STATISTICAL METHODS

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

6.1. General Methodology

All summary tables and data listings will be prepared using version 9.3 or later of SAS® software (SAS Institute, Cary, NC).

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

- Min and max: same number of decimal places as the raw data.
- Mean and median: one more decimal place than the raw data.
- SD: two more decimal places than the raw data.
- Percentages will be displayed with one decimal precision. For zero count, count and percentages will be displayed as "0 (0.0)".
- The standard form of a percentage change variable is 1 decimal place.

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

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

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

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

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

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

6.2. Derived Variables

Refer to Table 5 below for a list of derived variables and their definitions for study parameters.

Table 5: Derived Variables and Definitions

Variable	Definition
Height (cm)	If height is recorded in inches, then height is equal to the recorded value multiplied by 2.54 and then rounded to 1 decimal point.
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 point.
Body Mass Index (BMI)	BMI will be computed using height and body weight measured at screening as, BMI (kg/m^2) = Weight (kg) / Height $(m)^2$.
Study Day	Study Day will be computed as, Date of Assessment – Date of Day 0 (Surgery Visit).
Baseline	Baseline is defined as the last non-missing measurement/assessment 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 Date in Study	Last date in study is defined as: • The date of Day 28 if the subject completes the study. • The date of early termination 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.
Time in Study	Last date in study - Date of ICF signed in study + 1.
Duration of AE	AE end date – AE start date + 1.
AE Onset Day	AE start date – Date of Day 0 (Surgery Visit) + 1.

ICF=Informed consent

6.3. Handling of Missing Data

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

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

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 one (1) for analyses.

6.3.1. Imputation of Partial Dates

6.3.1.1. TEAE Status When Start Date and Time Is Unknown

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

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

6.3.1.2. Concomitant Status of Medication for Completely/Partial Unknown Start Date

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

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

7. STATISTICAL ANALYSES

7.1. Subject Disposition

The number and percent of subjects screened, screen failed and enrolled will be summarized. The numbers and percentages of subjects who complete and discontinue from the study will be summarized for overall subjects. For subjects who discontinue from the study, the reason for discontinuation will be tabulated. The number of subjects included in each study population and in each group will be summarized for overall as well.

Subjects excluded from the Safety Population or Evaluable Population will be listed.

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

7.2. Protocol Deviations

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

7.3. Demographics and Baseline Characteristics

Demographic and baseline characteristics, including age, sex, race, height, weight, and BMI will be summarized using appropriate descriptive statistics in Safety Population and Evaluable Population. If both the populations are identical, duplicate tables will not be produced.

Age, height (at screening), body weight (at screening) and BMI in kg/m^2 will be summarized as continuous variables using descriptive statistics.

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

History of tobacco and alcohol use will be summarized using frequency count and percent as:

- Alcohol use (Never, Current or Former)
- Tobacco use (Never, Current or Former)

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

7.4. Medical History

Medical history will be recorded for each subject and will be coded using MedDRA. All medical and surgical history will be presented in a listing for all subjects.

7.5. Prior and Concomitant Medications/Procedures

All medications will be coded using the World Health Organization (WHO) Drug Dictionary. Listings of prior and concomitant medications/procedures will be presented for all subjects.

7.6. Abdominoplasty Procedure

Listings with details of the abdominoplasty surgery and date of surgery will be presented for all subjects. The histopathology data of the 2 subjects whose abdominoplasty surgery was delayed due to COVID-19 will be flagged in the listing.

7.7. Digital Photography

Subject listings will be presented with date of digital photographs taken, start time of photo session, and reasons if the digital photographs were not done per protocol.

7.8. Medical Clearance for Surgery

Listings with details of the medical clearance test for surgery (ie, whether pre-op testing was completed, and whether medical clearance was given to proceed with abdominoplasty surgery) and date of medical clearance will be presented for all subjects.

7.9. Safety Analyses

Safety data listings will be presented using the Safety Population.

7.9.1. Study Drug Exposure

A listing of CCH administration with details of start/end date/time of CCH administration along with the reasons for injections not given per protocol will be provided.

7.9.2. Adverse Events

Subject listings of all AEs, SAEs, AEs leading to study discontinuation, AEs resulting in drug interruption/withdrawn, AEs resulting in death, AESIs and AEs related to abdominoplasty will be provided.

7.9.3. Clinical Laboratory

A listing (including urinalysis results) will be presented for all laboratory parameters. In addition, serum and urine pregnancy test results will be listed by subject for the Safety Population.

7.9.4. Vital Signs

A listing will be presented for all vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate and body temperature) results including PCI values.

7.9.5. Physical Examination

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

7.9.6. Immunogenicity

Samples from Screening will be analyzed for anti-AUX-I and anti-AUX-II antibodies. Samples from Day 0 and Day 28 will be analyzed for anti-AUX-I antibodies, anti-AUX-II antibodies, and neutralizing antibodies. Neutralizing antibodies will only be tested from ADA positive samples.

A subject listing will be presented for anti-AUX-I and anti-AUX-II antibody levels, and neutralizing antibody results (positive/negative).

8. CHANGE FROM PROTOCOL

This SAP is prepared primarily based on the study protocol; original version dated September 19, 2019 and Protocol Amendment 4 dated May 1, 2020. There are no planned changes either in the conduct of the study or planned analysis at the time of preparing this SAP.

9. REVISION HISTORY

Non-editorial changes made to any of the modules of this SAP will be recorded in Table 6 below.

Table 6: Revision [redacted]

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

10. REFERENCES

1. Clinical Study Protocol: A Phase 2b, Open-label Study to Explore Tissue Histopathology Following Subcutaneous Injection of Collagenase Clostridium Histolyticum Using an Abdominoplasty Model, Amendment 4. May 1, 2020.

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.