SAP MODULE 1 – DETAILED STATISTICAL METHODOLOGY

Protocol No. EN3835-103; 07Sep2018

A PHASE 1, OPEN-LABEL STUDY TO ASSESS THE SAFETY AND PHARMACOKINETICS OF A SINGLE DOSE OF COLLAGENASE CLOSTRIDIUM HISTOLYTICUM (3.36 MG) IN SUBJECTS WITH EDEMATOUS FIBROSCLEROTIC PANNICULOPATHY

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Confidentiality Statement

[redacted]

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
AE	Adverse event
ATC	Anatomical therapeutic chemical
$AUC_{0\text{-}inf}$	Area under the curve from time 0 to infinity
$AUC_{0\text{-}t}$	Area under the curve from time 0 to last time
AUX-I	Clostridial class I collagenase
AUX-II	Clostridial class II collagenase
BLQ	Below lower limit of quantification
BMI	Body mass index
bpm	Beats per minute
Brpm	Breaths per minute
CCH	Collagenase clostridium histolyticum
C_{max}	Maximum concentration
CRF	Case report form
CR-PCSS	Clinician-Reported Photonumeric Cellulite Severity Scale
CV	Coefficient of variation
DMP	Data Management Plan
ECG	Electrocardiogram
EDC	Electronic data capture
EOS	End of study
eCRF	Electronic case report form
eCrCl	Creatinine clearance (estimated)
EFP	Edematous fibrosclerotic panniculopathy
Kg	Kilogram
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
Ml	Milliliter
N	Number of subjects
NC	Not calculable
OTC	Over the counter
OPV	Outpatient visit
PCI	Potentially clinically important
PK	Pharmacokinetics
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
SQRT	Square root
TEAE	Treatment-emergent adverse event

Abbreviation	Definition
T_{max}	Time of maximum concentration
ULN	Upper limit of normal
US	United States
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analyses to assess the safety, pharmacokinetics (PK) and Immunogenicity of a single dose of Collagenase clostridium histolyticum (CCH) (3.36 mg) in female subjects with Edematous Fibrosclerotic Panniculopathy (EFP).

The general information about the study is detailed in the EN3835-103 protocol, dated September 07, 2018.

2. STUDY OBJECTIVE

The objectives of this study are to assess safety, and determine if there is systemic exposure, following a subcutaneous single dose of CCH (3.36 mg) provided via 12 injections per quadrant in 4 quadrants concurrently (0.84 mg per quadrant) in adult women with EFP.

3. STUDY DESIGN AND MEASURES

This is a Phase 1, open-label Pharmacokinetic (PK) study to be performed at a single center located in the United States (US) in adult female subjects with EFP.

Subjects will be screened for eligibility within 22 days prior to dosing in this study and subjects will be admitted to the clinical research unit on Day -1. Subjects will be dosed on Day 1 and will remain in the unit until after the 24-hour post-dose PK sample is collected on Day 2. Subjects will return to the unit for safety and PK assessments on Day 3, 8, and 22. The End of Study (EOS) visit occurs on Day 22.

The study will enroll 12 subjects. These subjects will receive a subcutaneous single dose of CCH (3.36 mg) study drug in 4 quadrants (ie, left buttock, right buttock, left posterolateral thigh, and right posterolateral thigh).

Table 1 provides the schedule of events and assessments of the study.

Table 1: Schedule of Study EN3835-103 Assessments

	Inpatient at the Research Unit				Follow-up Outpatient Visits (OPV)		
Event	**Screening**	**Admit to Clinic**	**Dose**	**Discharge from Clinic**	**OPV**	**OPV**	**OPV**
Study Day	**Day −22 to Day −2**	**Day −1**	**Day 1**	**Day 2 (24 hours post dose)**	**Day 3 (48 hours post dose)**	**Day 8 (168 hours post dose)**	**Day 22/ End of Study (504 hours post dose)**
Informed Consent[a]	X						
Inclusion/Exclusion[b]	X	X					
Medical History/EFP History Including Previous Treatments	X						
Prior Concomitant Medications/Procedures	X	X	X	X	X	X	X
Physical Examination:	X						
Body Weight	X						X
Height	X						
Fitzpatrick Skin Type	X						
Vital Signs[c]	X	X	X	X	X	X	X
12-Lead ECG	X						
Clinical Safety Laboratory Tests[d]	X						X
Pregnancy Test	X	X					
Urine Drug Screen[e]	X	X					
Alcohol Breath Test	X	X					
Investigator's Cellulite Assessment: Thigh/ Buttocks							
Investigator-Reported i cellulite Severity Scale (CR-PCSS)[f]	X						X
Select/Mark Dimples Within the Quadrants – Pre-dose			X				
Single Dose (48 injections)[g]			X				
Pharmacokinetic Blood Sampling[h]			X	X	X	X	X

Table 1: Schedule of Study EN3835-103 Assessments (Continued)

	Inpatient at the Research Unit				Follow-up Outpatient Visits (OPV)		
Event	**Screening**	**Admit to Clinic**	**Dose**	**Discharge from Clinic**	**OPV**	**OPV**	**OPV**
Study Day	**Day −22 to Day −2**	**Day −1**	**Day 1**	**Day 2 (24 hours post dose)**	**Day 3 (48 hours post dose)**	**Day 8 (168 hours post dose)**	**Day 22/ End of Study (504 hours post dose)**
Blood collection for possible Anti-AUX-I/ Anti-AUX-II Antibody Levels/Neutralizing Antibodies to AUX-I and AUX-II[i]			X				X
Assess Any Injection Site Reactions in the Areas that were Dosed			X	X	X	X	X
Adverse Events[j]	X	X	X	X	X	X	X

a Performed and signed prior to any study-required assessments.
b Should be reassessed and verified prior to dosing.
c Blood pressure (systolic/diastolic), respiratory rate, and radial pulse rate taken up to 4 hours pre-dose and 15 (± 3) and 30 (+10) minutes post dose. Oral temperature will be included at Screening, admission Day -1, on Day 1 pre-dose and at 30 (+10) minutes post dose, and on Day 2. All vital signs include oral temperature to be taken before blood sampling on the Day 3, 8 and 22 OPVs. Vital signs should be taken after the subject rests for at least 5 minutes.
d The list of clinical laboratory tests for safety is given in Table 5.
e Screen for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, opiates, and/or propoxyphene at the Screening visit and on Day −1. All tests must be negative.
f The Investigator's CR-PCSS assessment score must be a 2, 3, or 4 for study entry.
g The 24 subcutaneous injections (12 injections per quadrant in 2 quadrants concurrently) comprise the single dose.
h Blood collection (10 mL each) for pharmacokinetic measurement of plasma AUX-I and AUX-II concentrations are to be taken before dosing and at 5, 10, 20, and 30 minutes and 1, 2, 4, 8, 12, 24, 48, 168, and 504 hours after dosing. All blood samples are to be collected within 10% of the nominal time. The exact time of collection will be noted in the source document and eCRF.
i Collect blood for immunogenicity testing before injection on Day 1 prior to dosing and again on study Day 22 at approximately 504 hours after dosing. (Collect 1 × 5 mL of blood for immunogenicity testing at both time points.)
j AEs/SAEs will be captured from time of informed consent until study Day 22. There is no time limit on collection of SAEs felt to be related to study drug.

AE=Adverse event; eCRF=Electronic Case report form; CR-PCSS=Clinician-Reported Photonumeric Cellulite Severity Scale; ECG=Electrocardiogram; EFP=Edematous fibrosclerotic panniculopathy; EOS=End of study; OPV=Outpatient visit; SAE=Serious adverse event

3.1. Determination of Sample Size

A sample size of 12 subjects enrolled was chosen empirically based on the pragmatic criteria and published data of previous studies in order to have at least 10 subjects complete the study.

3.2. Blinding and Randomization

This is an open-label study. A single dose of CCH will be administered.

3.3. Selecting and Marking Dimples and Injection Sites

On Day 1, the investigator will select dimples within the quadrants that are well defined, evident when the subject is standing in a consistent relaxed pose (without the use of any manipulation such as skin pinching or muscle contraction), and suitable for dosing. The Investigator will choose 12 injection sites per quadrant (injection sites within a dimple should be spaced approximately 2 cm apart, if a dimple requires more than 1 injection) for a total of 48 injection sites.

3.4. Study Drug Administration

Each subject will be administered forty-eight (48) skin injections of 0.3 mL within the 4 quadrants (ie, 12 injections per quadrant) during the dosing session. The dosing detail, volume and concentration is explained in Table 2).

The total number of dimples treated, and the total number injections administered during dosing on Day 1 will be recorded in the electronic case report form (eCRF).

Table 2: Volume and Concentration of CCH Injections

	No. of injections	Dose/ Injection	Volume/Injection	Total Dose administered at the dosing session	Total injection volume administered at the dosing session
Overall	48 injections (4 × 12 injections)	0.07 mg	0.3 mL (administered as three - 0.1 mL aliquots)	3.36 mg (4 × 12 × 0.07 mg)	14.4 mL (4 × 12 × 0.3 mL)
Per Quadrant	12 injections	0.07 mg	0.3 mL (administered as three - 0.1 mL aliquots)	0.84 mg (12 × 0.07 mg)	3.6 mL (12 × 0.3 mL)

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

The investigator will rate the severity of the cellulite using the CR-PCSS for buttock and thigh at screening and EOS. These ratings will be marked on the source documentation and then entered into the Electronic Data Capture (EDC) system. The CR-PCSS is a photonumeric scale ranging from 0 to 4. Separate CR-PCSS scales will be used to evaluate the buttock and the thigh. Table 3 and Table 4 describe the CR-PCSS severity scale for buttock and thigh respectively.

Table 3: CR-PCSS for Buttock

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

Table 4: CR-PCSS for Thigh

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

3.6. Medical and Surgical History

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

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

3.7. EFP History

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

- Family history of cellulite (answered as yes, no, or unknown)
- Onset date of EFP symptoms
- Start year of EFP when unknown (year unknown - started >= 5 years ago/ started <5 years ago)
- Previous treatments used for EFP

3.8. Substance Use

History of tobacco and alcohol use will be taken during the screening period and the following information will be recorded:

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

3.9. Prior/Concomitant Medications and Procedures

Any medications (including OTC medication) taken during the study or within 3 months prior to the Screening visit will be recorded.

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

Prohibited Medications: Subjects are prohibited to take antiplatelet agents (aspirin>150 mg/day and P2Y12 inhibitors, such as clopidogrel) or anticoagulants (warfarin, heparin, direct thrombin inhibitors) within 7 days before and after the dosing administration.

3.10. Adverse Events

All Adverse Events (AE) occurring after signing the informed consent are to be recorded on the AE pages of the eCRF. This includes any new signs, symptoms, injury or illness, including increased severity of previous existing signs, symptoms, injury, or illness. Conditions existing prior to screening will be recorded as part of subject's medical history.

Adverse Events (AE)

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

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

Serious Adverse Events (SAEs)

Any untoward medical occurrence that meets 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

AEs such as [redacted]

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

3.11. Clinical Safety Laboratory Evaluations

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

Table 5: Clinical Safety Laboratory Parameters

Hematology	Biochemistry	Urinalysis
Hemoglobin	Glucose	Glucose
Hematocrit	Sodium	Protein
Red blood cell	Potassium	Specific gravity
White blood cell (WBC)	Calcium	pH
Platelets	Chloride	Ketones
WBC Differential	Carbon dioxide (CO2)	Bilirubin
	Inorganic phosphate	Urobilinogen
	Blood urea nitrogen (BUN)	Nitrite
	Creatinine	Blood*
	Creatinine clearance	Leukocytes*
	Aspartate transaminase (AST)	
	Alanine transaminase (ALT)	
	Gamma-glutamyl transferase (GGT)	
	Total bilirubin (TBL) (direct bilirubin reflex if elevated)	
	Albumin	
	Alkaline phosphatase (ALP)	
	Uric acid	

*Microscopic examination will be performed if blood or leukocytes are detected by dipstick.

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

3.11.1. Pregnancy Test

Female subjects of childbearing potential must have a negative pregnancy test to enter the study. Urine pregnancy (dipstick) or serum pregnancy test will be performed at screening and Day −1 for women of childbearing potential. If required, additional urine or serum pregnancy tests can be performed at any time during the study.

3.11.2. Urine Drug Screen

Subjects must be tested negative for all drugs of abuse. A urine drug screen will be done at screening and Day −1 for the following drugs of abuse: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, opiates, and propoxyphene.

3.11.3. Alcohol Breath Test

A breathalyzer test for the screening of alcohol will be done at screening and Day −1. Test must be negative before dose administration.

3.12. Vital Signs

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

Systolic and diastolic blood pressure, respiratory rate, and radial pulse rate will be collected up to 4 hours pre-dose and 15- and 30-minutes post dose. Oral body temperature will be included at Screening, Day -1, 4 hours pre-dose, 30 minutes post dose, and on Day 2. All vital signs measurements including oral temperature will be taken before blood sampling on the Day 3, 8, and at EOS (Day 22) outpatient visits (OPVs) after the subject has rested for at least 5 minutes.

Height and body weight measurements will be taken at Screening. Body weight will also be measured at Day 22.

Any vital sign values meeting the Investigator's criteria for clinical significance will be recorded as an AE or SAE as appropriate.

3.13. 12-Lead Electrocardiogram (ECG)

12-Lead ECG will be recorded during screening period while the subjects will be in resting position.

ECGs will be assessed by the Investigator and graded as:

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

If the ECG result meets the Investigator's criteria for clinical significance then it will reported as an AE or SAE as appropriate.

3.14. Physical Examination

A complete physical examination (by body system) will be performed at screening. The Investigator will assess the physical examination findings as normal or abnormal.

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

The subject's skin type will be assessed at screening using the Fitzpatrick Scale (Table 6).

Table 6: Fitzpatrick Scale

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

3.15. Immunogenicity Samples

Immunogenicity variables include anti-AUX-I/anti-AUX-II binding (ie, anti-drug) and neutralizing antibody results. Blood samples will be collected pre-dose on Day 1 and at EOS for the determination of serum anti-AUX-I and anti-AUX-II antibody levels and neutralizing antibodies to anti-AUX-I and anti-AUX-II. These samples will be assayed for antibody levels only if clinical findings and/or PK results warrant immunogenicity profiling.

3.16. Pharmacokinetic Samples

Blood samples will be collected for the determination of plasma AUX-I and AUX-II concentrations before dosing and at 5, 10, 20, and 30 minutes and 1, 2, 4, 8, 12, 24, 48, 168, and 504 hours after dosing. All blood samples are to be collected within 10% of the nominal time (eg, within 6 minutes for the 60-minute sample). The exact time of collection will be recorded in the source documentation and eCRF.

The plasma concentration data of AUX-I and AUX-II will be analyzed using a non-compartmental model using actual sample times of blood collection. The following PK parameters will be analyzed:

Table 7: Pharmacokinetic Parameters

PK Parameter	Definition
AUC_{0-t}	Area under the plasma concentration versus time curve from time 0 to the time of last quantifiable concentration (C_t), calculated by linear trapezoidal rule.
AUC_{0-inf}	Area under the plasma *c*oncentration versus time curve from time 0 to infinity calculated as $AUC_{0-t} + C_t/\lambda_n$
C_{max}	Observed maximum plasma concentration; the highest concentration observed during a dosage/application interval
T_{max}	The time at which C_{max} was observed
λ_n	Terminal rate constant calculated as the negative slope of the ln-linear portion of the terminal plasma concentration-time curve

4. STUDY PARAMETERS

4.1. Subject Disposition

Subjects will be considered as completing the study if they complete the Day 22 visit. The reason for early discontinuation will be recorded in eCRF for the subjects who do not complete the study.

4.2. Protocol Deviations

Potential 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 two sources will be reconciled and duplicate deviations will be removed. When a deviation is both found in the database and in clinical monitoring reports, in most cases the text of the deviation from the database will be retained. The exception to this rule will occur if the deviation from the monitoring report provides important information not found in the database. In that case, the information will be reconciled and included in the database.

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

- Ineligible subject/study entry criteria not satisfied
- Informed consent not completed correctly
- Non-compliance of dosing regimen
- Prohibited medications/procedure
- Visit/procedure missing or out of window
- PK blood sample drawn beyond 10% of the nominal time
- PK sample time points that were not collected

The protocol deviations will be detailed in a separate protocol deviation document. The Endo study team will approve all final protocol deviation assignments and classify them as either major or minor during a protocol deviation meeting held prior to the database lock. The decision to include the subjects with major protocol deviations into the study populations will be determined at the protocol deviation meeting.

4.3. 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 concomitant medication is defined as any medication given to the subject starting on or after the date of the first injection or the medication started prior to the date of the first injection but is reported as ongoing. A prior medication is any medication with a stop date prior to the date of the first injection.

4.4. Prior EFP Treatment

Prior EFP treatment will be obtained from the prior/concomitant medication and prior/concomitant procedure pages of the eCRF. If on either of these pages a medication or procedure is reported with the indication ‘EFP/cellulite’ with a start date prior to the first dose of study drug, then the medication or procedure will be considered a prior EFP treatment.

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

- Liposuction
- Laser
- Massage
- Radiofrequency
- Mesotherapy
- Cream
- Other

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

4.5. Cellulite Severity Variables

4.5.1. Clinician Responder

A responder is defined as a subject with an improvement in CR-PCSS rating from baseline (screening visit) to EOS.

- **2-point clinician responder**: with an improvement of 2 or more levels (ie, change from baseline CR-PCSS rating of -2, -3, or -4).
- **1-point clinician responder**: with an improvement of 1 or more levels (ie, change from baseline CR-PCSS rating of -1, -2, -3, or -4).

4.6. Safety Parameters

4.6.1. Adverse Events

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

Treatment Emergent Adverse Events (TEAEs)

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

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

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

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

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 the worst observation carried forward (WOCF) rule.

Relationship to Study Drug

Causal relationship to study drug will be classified by the Investigator and will be reported as one of the following:

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

Related adverse events 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 not related to treatment.

Any AE with a missing relationship to study drug will be considered to be related to study drug for the analyses following the WOCF rule.

4.6.2. Potentially Clinically Important Laboratory Values

Potentially clinically important (PCI) laboratory values are presented in Table 8 below:

Table 8: Potentially Clinically Important Laboratory Criteria

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

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

4.6.3. Potentially Clinically Important Vital Sign Values

Vital sign values are PCI if they meet both the observed value criteria and the change from baseline criteria. The PCI vital sign values are presented in Table 9 below:

Table 9: 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

4.7. Immunogenicity

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

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

The immunogenicity profiling will be performed only if clinical findings and/or PK results warrant immunogenicity profiling.

5. ANALYSIS POPULATIONS

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

Table 10: Analysis Populations

Population	Definition	Displays
Safety Population	The Safety Population includes all enrolled subjects who received at least one injection of CCH.	All demographic, baseline characteristics and safety parameters will be summarized based on this population.
Pharmacokinetic (PK) Population	The PK Population includes all enrolled subjects who received the full dose of CCH and have sufficient data from the 24-hour PK profile to determine key PK parameters such as C_{max} and AUC0-t.	The plasma concentration of AUX-I and AUX-II as well as PK parameters will be summarized based on this population.
Cellulite Severity Population	The Cellulite Severity Population consists of all enrolled subjects who receive at least one injection of CCH and have the screening and Day 22 CR-PCSS evaluation completed.	All summaries of cellulite severity, including changes from baseline, will be based on this population.

6. STATISTICAL METHODS

6.1. General Methodology

All summary tables and data listings will be prepared using SAS version 9.4.

Continuous data will be summarized using descriptive statistics. Discrete data will be summarized using frequency counts and percentages. The denominator will be based on the number of subjects. 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 precision to one decimal place. A zero count will not have the associated percentages presented on the table (ie, no 0%). It will be left blank.
- The standard form of a percent change variable is 0 decimal places.

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

Summary tables, subject listings, graphs and any supportive SAS output will include a footnote that will indicate, when applicable:

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

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

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

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

6.2. Derived Variables

Refer to Table 11 for the listing of the derived variables and their definitions for study parameters.

Table 11: Derived Variables and Definition

Variable	Definition
Height (cm)	If height is recorded in inches, then height is equal to the recorded value multiplied by 2.54 and then rounded to 1 decimal 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 $(m)^2$
Relative Day	The day of first injection of study drug will be considered as relative day 1
Study Day (for assessment on or after the Day 1)	Study Day will be computed as, Date of Assessment – Date of Day 1 + 1
Study Day (for assessment before Day 1)	Study Day will be computed as, Date of Assessment – Date of Day 1
Baseline	Baseline is defined as the last non-missing measurement/assessment prior to the first dose of study drug. For vital signs, the baseline will be the Day 1 pre-dose values. For clinical laboratories this could be the screening value, or it could be an unscheduled lab, if the unscheduled lab is the closest value preceding the first injection.
Change from Baseline	Change from baseline will be derived as, post-baseline visit/time point value – the baseline value.
Last Date in Study	End date of last visit where subject was seen by investigator. If subject was lost to follow-up, then last date of contact. If the subject had contact with the site after the final visit (eg, to follow-up on an AE), the last visit date will still be used as last date in the study.
Time in Study	Last date in study – Date of first injection + 1
Age at EFP Symptom Onset	Date of EFP symptoms reported – Date of Birth/365.25. See section 6.3.1.3 for handling of partial or unknown EFP symptom onset dates.
Time since last EFP treatment	Date of most recent EFP treatment – Date of informed consent)/365.25. See section 6.3.1.3 for handling of partial or unknown EFP treatment dates.
Baseline CR-PCSS Score	Investigator baseline CR-PCSS scores for each quadrant will be based on the investigator's CR-PCSS evaluation done at the Screening visit.
Change from Baseline CR-PCSS Score	The change from baseline CR-PCSS score at each quadrant will be the Day 22 score minus the baseline (Screening visit) score. A negative change indicates an improvement of cellulite severity in the treated quadrant.
Nominal time of PK blood sample collection	Pre-injection=0 hr, 5 min post injection=0.083 hrs, 10 min post injection=0.167 hrs etc.
Time difference of blood draw from last injection (hours)	Date/time of sample draw - Date/time of last injection
Duration of AE	AE end date – AE start date + 1
AE Onset Day	AE start date - Date of first injection + 1
Creatinine clearance (estimated) (eCrCl)	Creatinine clearance will be estimated by Endo using the Cockcroft-Gault formula (see [2]) as**:** **eCrCl (mL/min) = {[(140-age) × weight]/(72 × SCr)} × 0.85 for female** where, age is expressed in years (yrs), weight is expressed in kilograms (kg), and serum creatinine (SCr) is expressed in milligrams per deciliter (mg/dL).

6.3. Handling of Missing Data

Subjects who discontinue the study prior to or after the initiation of the study drug will not be replaced and available data for these subjects until the point of discontinuation will be summarized. Any missing baseline assessments will not be imputed.

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

Subjects who discontinue early will be requested to complete all Day 22 procedures and assessments at an early termination visit.

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

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

All plasma concentration values below the limit of quantification (BLQ) will be set to zero (0) in calculation of summary statistics. If the plasma concentration levels are BLQ for all subjects at a time point, then Not Calculable (NC) will be reported in the summary table. Any missing samples will be reported as 'Missing' and treated as missing for PK parameter and plasma concentration summary calculations. C_{max}, AUC_{0-t}, AUC_{0-inf} will be imputed as 0 and Terminal rate constant and T_{max} will be imputed as 'missing' when all plasma concentrations are below lower limit of quantifications.

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

If the medication onset date is partly present and month/year is prior to the first injection date, then the medication will not be considered as concomitant.

6.3.1.3. Missing EFP Onset Date

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

6.4. Interim Analyses

No interim analysis is planned for this study.

6.5. Treatment Groups

A single dose of CCH will be administered in this study. Subjects will be summarized overall as "CCH 3.36 mg."

7. STATISTICAL ANALYSES

7.1. Subject Disposition

The number of subjects included in each study population will be summarized. Subjects excluded from the Safety, PK, or Cellulite Severity Populations will be listed.

The number and percent of subjects screened, completed, and discontinued during the study, as well as the reason for discontinuation will be summarized. Subject time in the study will be summarized descriptively (See Table 11 for computation of time in the study). A listing of all subjects who discontinued the study will be provided.

7.2. Protocol Deviation

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

7.3. Demographics and Baseline Characteristics

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

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

Skin category based on Fitzpatrick scale rating will be summarized using frequency count 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 subject listings.

7.4. Medical and Surgical History

Medical history will be coded using the MedDRA dictionary (version defined in the DMP). A subject listing of medical history data will be provided.

7.5. EFP History

EFP history will be summarized using counts and percentages using the Safety Population, and will include:

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

Refer to Table 11 for computation of "age at EFP onset" and "time since last EFP treatment". EFP history will be listed.

7.6. Concomitant Medications and Procedures

Prior and concomitant medications will be summarized using frequency counts and percentages by active ingredient within each ATC, with ATC and active ingredients ordered alphabetically. Multiple use of the same medication by a subject will be counted only once.

A subject listing of prior and concomitant medications and procedures will be presented. A separate listing of prior and concomitant medications and procedures for EFP/Cellulite will also be presented.

7.7. Cellulite Severity Evaluations

The Cellulite Severity Population will be used for all the analyses.

The CR-PCSS ratings will be summarized at baseline. Change from baseline in severity will be summarized at EOS by quadrant using counts and percentages for each severity rating and with mean and SD. A shift table of CR-PCSS ratings at Baseline and EOS will be presented using counts and percentages.

The investigator CR-PCSS responder classification for 2-point responders and 1-point responders will be summarized using count and percentages at EOS by each quadrant.

A listing of cellulite severity ratings will be presented. If cellulite severity was not rated, the reason for the lack of assessment will be presented.

7.8. Pharmacokinetic Analyses

7.8.1. Plasma Concentration

Plasma concentrations of AUX-I and AUX-II will be summarized using descriptive statistics at each nominal sample time point. The number of samples above the lower limit of quantification and BLQ will be summarized. The handling of missing and BLQ data is described in section 6.3.

The listing will also include the actual time of the sample collection from the time of last injection.

Figures of mean (±SD) AUX-I and AUX-II plasma concentrations by time using nominal time will be presented on a linear and semi-logarithmic scale. Individual AUX-I and AUX-II plasma concentration actual time plots will also be presented using linear and semi-logarithmic scales.

The PK Population will be used for summary and plots.

7.8.2. Pharmacokinetic Parameters

$AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, C_{max} and T_{max} will be summarized using descriptive statistics for the PK Population. In addition, the geometric mean and coefficient of variation (CV) will be calculated and presented for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}. Geometric means and CV will be calculated for the log transformed parameters. The CV will be calculated as:

$$CV\ (\%) = SQRT[\exp(SD^2)-1]*100$$

The handling of missing and BLQ data is described in section 6.3. Individual AUX-I and AUX-II PK parameters will be listed.

7.9. Safety Analyses

Safety data will be summarized using the Safety Population.

7.9.1. Study Drug Exposure

The number of injections of study drug given on Day 1, will be summarized by counts and percentages for each quadrant:

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

Following will be summarized by each quadrant using descriptive statistics:

- number of injections given
- number of dimples treated
- average number of injections per dimple

A subject listing of overall exposure, and injection status will be provided along with the reasons for receiving less than 48 injections (12 injections per quadrant).

7.9.2. Adverse Events

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

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

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

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

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

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

- Total number of TEAEs reported
- Total number of TEAEs reported by severity
- Total number of AEs of special interest
- Subjects with any TEAE
- Subjects with any AE 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/withdrawn
- Subjects with any TEAEs leading to study discontinuation
- Subjects with any TEAEs resulting in death

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

- All TEAEs
- TEAEs by Severity
- All non-study drug related TEAEs
- All study drug related TEAEs
- Study drug related TEAEs by severity
- Serious TEAEs
- Duration of study drug related TEAEs (<14 days, 14 – 21 days and >21 days)
- AEs of Special Interest

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

The following listings will be presented by patient:

- All AEs
- Serious AEs
- AEs of special interest
- AEs resulting in drug interruption/withdrawn
- AEs resulting in study discontinuation
- AEs resulting in deaths

Refer to Table 11 for computation of duration of AE.

7.9.3. Clinical Laboratory

Laboratory results (hematology and biochemistry) will be summarized using descriptive statistics for observed and change from baseline values at baseline and Day 22.

The PCI laboratory values will be summarized by counts and percentages. Refer to Table 8 for PCI criteria.

A subject listing (including urinalysis results) will be presented for all laboratory parameters.

Serum and urine pregnancy test results, urine drug screen results and alcohol breath test results will be listed by subject.

7.9.4. Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and body weight) will be summarized using descriptive statistics for observed and change from baseline values for all assessments visits. The PCI vital signs values will be summarized by counts and percentages. Refer to Table 9 for PCI criteria.

A listing of vital signs by subject will be presented.

7.9.5. 12-Lead ECG

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

A listing of investigator interpretation of ECG results by subject will be presented.

7.9.6. Physical Examination

Physical examination (by body system) screening results by subject will be presented.

7.9.7. Immunogenicity

The immunogenicity profiling will be performed only if clinical findings and/or PK results warrant immunogenicity profiling.

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 a descriptive summary of the average titer level of the positive samples at Day 1 and EOS. The titer levels will be logarithmically transformed prior to being summarized.

A listing of immunogenicity results by subject will be provided.

8. CHANGE FROM PROTOCOL

This SAP is prepared based on the study protocol dated September 07, 2018 and there are no planned changes either in the conduct of the study or planned analysis at the time of preparing this SAP.

Table 12 lists any significant changes in the SAP from what is proposed in the protocol.

Table 12: Changes from Protocol

Text in Protocol	Change in SAP	Justification

9. REVISION HISTORY

The non-editorial changes made to any of the modules of this SAP will be recorded in Table 13.

Table 13: Revision History

Version	Date	Revision Author	Comments
1.0	27-Oct-2018	[redacted]	Original

10. REFERENCES

1. Clinical Study Protocol: A Phase I, Open-Label study to assess the Safety and Pharmacokinetics of a Single Dose of CCH (3.36 mg) in Subjects with Edematous Fibrosclerotic Panniculopathy. Dated 07-Sep-2018.

2. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31-41.

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.