SAP MODULE 1 – DETAILED STATISTICAL METHODOLOGY

STUDY EN3835-205

A PHASE 2 OPEN-LABEL STUDY OF EN3835 IN THE TREATMENT OF EDEMATOUS FIBROSCLEROTIC PANNICULOPATHY

Version 1.0

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Endo Pharmaceuticals Inc.
1400 Atwater Drive
Malvern, PA 19355
USA

Confidentiality Statement

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
AE	Adverse Event
ALT	Alanine Transaminase
ALP	Alkaline Phosphatase
AST	Aspartate Transaminase
AUX-I	Clostridial Class I Collagenase
AUX-II	Clostridial Class II Collagenase
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CCH	Collagenase Clostridium Histolyticum
CR-PCSS	Clinician Reported Photonumeric Cellulite Severity Scale
CSS	Cellulite Severity Scale
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EFP	Edematous Fibrosclerotic Panniculopathy
GGT	Gamma-glutamyl Transferase
IUD	Intrauterine Device
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
PCI	Potentially Clinically Important
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TBL	Total Bilirubin
ULN	Upper Limit of Normal
WBC	White Blood Cell

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for Protocol EN3835-205 (Version 1.0, dated August 31, 2017).

2. STUDY OBJECTIVES

The primary objective of this study is to assess the safety of EN3835 in the treatment of edematous fibrosclerotic panniculopathy (EFP) commonly known as cellulite in adult women. The secondary objective of this study is to assess the effectiveness of EN3835 in the treatment of EFP.

3. STUDY DESIGN AND MEASURES

3.1. Study Design

This study is a Phase 2, open-label study of safety and effectiveness of EN3835 in the treatment of EFP in adult women. Subjects will be screened for study eligibility within 14 days prior to enrolling in this study. Subjects with at least 2 bilateral treatment areas (bilateral buttocks or bilateral posterolateral thighs) (also referred to as a region) (eg, their left and right buttocks or left and right posterolateral thighs) with mild, moderate or severe levels of cellulite as assessed by the Investigator using the Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) and a Hexsel Cellulite Severity Scale (CSS) no greater than 13 will be eligible. If both their left and right buttocks AND left and right posterolateral thighs are eligible, one pair will be randomly selected as the assigned treatment region.

Subjects will receive an open-label treatment course which consists of up to 3 treatment visits (ie, Day 1, Day 22, and Day 43). Each treatment visit will consist of 12 injections (0.3 mL per injection of EN3835 0.07 mg/injection) in each of the treatment areas of the region for a total volume of 7.2 mL (1.68 mg). Selection of dimples to be treated in the assigned treatment areas will be at the discretion of the Investigator. End-of-study will occur at study Day 180.

At each treatment visit, the Investigator will first conduct a live assessment of each treatment area of the assigned region using the CR-PCSS. The Investigator will then select and mark the dimples to be treated within each treatment area. All the assessments must be done before marking the dimples for injection.

At Day 180 (End of Study/Early Termination), the Investigator will conduct live assessments of each treatment area using the CR-PCSS. The subject will complete the Subject Satisfaction with Cellulite Treatment assessment.

In a photographic sub-study at two sites, subjects will return to the site to have their treated areas photographed at 1, 3, 6, and 13 days after each treatment visit to assess local site reactions post-injection.

The complete schedule of events is provided in Table 1.

Table 1: Schedule of Events

Procedures	Day -14 to -1 Screening	Day 1 (Baseline)	Post-Injection Day 1	Post-Injection Day 3	Post-Injection Day 6	Post-Injection Day 13	Day 22 (±3 d)	Post-Injection Day 1	Post-Injection Day 3	Post-Injection Day 6	Post-Injection Day 13	Day 43 (± 3 d)	Post-Injection Day 1	Post-Injection Day 3	Post-Injection Day 6	Post-Injection Day 13	Day 90 (± 7d)	Day 180 (+ 7 d) EOS/ET	Unsched. Visit
Informed Consent	X																		
Inclusion/Exclusion	X																		
Medical history/EFP history including previous treatments	X																		
Prior/concomitant medications/ procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination:	X																		
• Body weight	X						X[a]					X[a]					X	X	X
• Height	X																		
• Fitzpatrick skin type	X																		
Vital signs	X	X[b]					X[b]					X[b]					X	X	X
12-lead ECG	X																		
Digital Photography[c]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Medical status follow-up			X	X	X	X		X	X	X	X		X	X	X	X			
Laboratory Assessments																			
• Clinical laboratory	X																	X	X
• Anti-AUX-I/anti-AUX-II antibody level		X[a]					X[a]					X[a]					X	X	
• Pregnancy testing	X[f]	X[a,f]					X[a,f]					X[a,f]					X[f]	X[f]	X
Subject Cellulite Assessments																			
• Subject Satisfaction With Cellulite Treatment Assessment																		X[e]	
Investigator Cellulite Assessments																			
• Selection and marking of dimples to be treated within both assigned treatment areas		X[a]					X[a]					X[a]							
• Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)	X						X[a,e]					X[a,e]					X[e]	X[e]	
• Hexsel Cellulite Severity Scale (CSS)	X[d]																		

Table 1: Schedule of Events (Continued)

Procedures	Day -14 to -1 Screening	Day 1 (Baseline)	Post-Injection Day 1	Post-Injection Day 3	Post-Injection Day 6	Post-Injection Day 13	Day 22 (±3 d)	Post-Injection Day 1	Post-Injection Day 3	Post-Injection Day 6	Post-Injection Day 13	Day 43 (± 3 d)	Post-Injection Day 1	Post-Injection Day 3	Post-Injection Day 6	Post-Injection Day 13	Day 90 (± 7d)	Day 180 (+ 7 d) EOS/ET	Unsched. Visit
• Confirm Eligibility																			
• Assign Region	X																		
• Study drug administration		X					X					X							
• Injection site reactions/local tolerability in assigned treatment areas		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
• Adverse events	Monitored Throughout Study																		

[a] Before injection.
[b] Up to 4 hours before injection; approximately 15 and 30 minutes after injection. Pulse and BP to be taken after subject has been sitting for 5 minutes. Vital signs must be stable before the subject is discharged.
[c] Applies only to sites participating in the photography sub-study. Photos are to be obtained before and after dimple marking on treatment visits.
[d] Initial Hexsel CSS at Screening must be ≤13 on at least 2 bilateral treatment areas, and confirmed at Day 1 visit.
[e] Assessment of each of the two assigned treatment areas only.
[f] Serum pregnancy test on Screening and Day 180/EOS/ET, and any Unscheduled Visits; urine pregnancy test on Day 1, Day 22, Day 43, and Day 90 visits
BP=Blood pressure; d=Days; ECG=Electrocardiogram; EFP=Edematous fibrosclerotic panniculopathy; EOS=End of study; ET=Early termination

3.1.1. Inclusion Criteria

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

1. Voluntarily sign and date an informed consent agreement
2. Be a female ≥18 years of age
3. At Screening visit, have at least 2 bilateral treatment areas with each treatment area having:
    a. a score of 2 (mild) or greater as reported by the Investigator (CR-PCSS), and
    b. a Hexsel CSS score no greater than 13
4. Be willing to apply sunscreen to the selected treatment areas before each exposure to the sun while participating in the study (ie, Screening through end-of-study)
5. Be judged to be in good health, based upon the results of a medical history, physical examination, and laboratory profile at Screening
6. Have a negative serum pregnancy test at Screening and a negative urine pregnancy test before injection of study drug and be using a stable and effective contraception method (eg, abstinence, intrauterine device [IUD], hormonal [estrogen/progestin] contraceptives, or double barrier method) for at least 1 menstrual cycle prior to study enrollment and for the duration of the study; or be menopausal defined as 12 months of amenorrhea in the absence of other biological or physiological causes, as determined by the Investigator; or post-menopausal for at least 1 year; or be surgically sterile
7. Be willing and able to cooperate with the requirements of the study
8. Be able to read, complete, and understand the patient-reported outcomes rating instruments in English

3.1.2. Exclusion Criteria

Subjects who meet any of the following criteria will not be eligible to participate in the study:

1. Has any of the following systemic conditions:
    a. Coagulation disorder
    b. Evidence or history of malignancy (other than excised basal-cell carcinoma) unless there has been no recurrence in at least 5 years
    c. History of keloidal scarring or abnormal wound healing
    d. Concurrent diseases or conditions that might interfere with the conduct of the study, confound the interpretation of the study results, or endanger the subject's well-being. Any questions about concurrent diseases should be discussed with the Medical Monitor.
    e. Evidence of clinically significant abnormalities on physical examination, vital signs, electrocardiogram (ECG), or clinical laboratory values
2. Has any of the following local conditions in the area to be treated:
    a. History of lower extremity thrombosis or post-thrombosis syndrome
    b. Vascular disorder (eg, varicose veins, telangiectasia) in area to be treated

   c. Inflammation or active infection
   d. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer
   e. Has a tattoo and/or a mole located within 2 cm of the site of injection

3. Requires the following concomitant medications before or during participation in the trial:
   a. Anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication (except for ≤150 mg aspirin daily) within 7 days before injection of study drug
4. Has used any of the following for the treatment of EFP on the legs or buttocks within the timelines identified below or intends to use any of the following at any time during the course of the study:
   a. Liposuction in the areas of the body selected for treatment during the 12-month period before injection of study drug
   b. Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; buttock and/or thigh implant treatment; or surgery (including subcision and/or powered subcision) within the assigned treatment areas during the 12-month period before injection of study drug
   c. Endermologie, cryolipolysis or similar treatments within the assigned treatment areas during the 6-month period before injection of study drug
   d. Massage therapy within the assigned treatment areas during the 3-month period before injection of study drug
   e. Creams (eg, Celluvera™, TriLastin®) to prevent or mitigate EFP within the assigned treatment areas during the 2-week period before injection of study drug
5. Is presently nursing a baby or providing breast milk
6. Intends to become pregnant during the study
7. Intends to initiate an intensive sport or exercise program during the study
8. Intends to initiate a weight reduction program during the study
9. Intends to use tanning spray or tanning booths during the study
10. Has received an investigational drug or treatment within 30 days before injection of study drug
11. Has a known systemic allergy to collagenase or any other excipient of study drug
12. Has received any collagenase treatments at any time prior to treatment
13. Was a subject in a previous cellulite clinical trial of collagenase clostridium histolyticum (CCH): AUX-CC-830, AUX-CC-831, EN3835-102, EN3835-104, EN3835-201, and/or EN3835-202
14. Any other condition(s) that, in the Investigator's opinion, might indicate the subject to be unsuitable for the study

3.1.3. Randomization and Study Drug Administration

3.1.3.1. Randomization

This is a single-arm open-label study. There is no randomization for treatment assignment. Each subject will have one or two regions (bilateral buttocks and/or thighs) eligible for treatment. If two regions are eligible, the interactive web response system (IWRS) will randomly assign a treatment region.

3.1.3.2. Study Drug Administration

A dose of 0.84 mg of EN3835 per treatment area will be administered as 12 subcutaneous injections (0.3-mL injection administered as three 0.1-mL aliquots per injection) in each of two treatment areas for a total dose of 1.68 mg and a total volume of 7.2 mL (3.6 mL per treatment area). Total number of injections will be 24 injections per treatment visit into the assigned region (left and right buttocks or left and right posterolateral thighs). There will be 3 treatment visits at 21-day intervals, ie, treatments on Days 1, 22, and 43 will be administered.

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

The CR-PCSS will be conducted for the purpose of assessing the severity of cellulite in the buttock or thigh; there are separate scales for buttocks or thighs. The scales are 5-level photonumeric scales developed specifically for clinicians and used by the Investigator to assess the severity of the subject's cellulite in each treatment area by live assessments; the ratings range from 0 (None) to 4 (Severe) with labels and descriptors to aid the Investigator in the assessments.

The Investigator will determine severity of cellulite of each of the 4 treatment areas at the Screening visit, and evaluate each of the two assigned treatment areas before injections on treatment visits Day 1, Day 22, and Day 43, and on visit Day 90 and Day 180 (EOS/ET) using the CR-PCSS. If the buttocks are the treated region, the Investigator will use the CR-PCSS for the buttock to make his/her evaluation; if the thighs are the treated region, the Investigator will use the CR-PCSS for the thigh to make his/her evaluation.

The following labels and descriptions are associated with each level of severity on the CR-PCSS Buttock scale:

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

The following labels and descriptions are associated with each level of severity on the CR-PCSS Thigh scale:

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

3.1.5. Subject Satisfaction with Cellulite Treatment Assessment

At the Day 180 visit, subjects will be instructed to answer a question related to their treated region. Subjects will be given one list of region-specific responses based on which region was treated and they will provide a rating from those below that best represents their answer.

- +2 - Very Satisfied
- +1 - Satisfied
- 0 - Neither Dissatisfied nor Satisfied
- -1 - Dissatisfied
- -2 - Very Dissatisfied

3.1.6. Hexsel Cellulite Severity Scale

During the Screening Visit, the Hexsel CSS will be administered. The Hexsel CSS is a 5-item questionnaire; each item is answered on a 4-point scale from 0 (least severe) to 3 (most severe). The total CSS score can range from 0 to 15, with higher scores indicating more severe cellulite. Total scores from 0 to 5 indicate mild cellulite, total scores from 6 to 10 indicate moderate cellulite, and total scores from 11 to 15 indicate severe cellulite.

The 5 morphological features measured on the CSS and the response options are shown in Table 2.

Table 2: Hexsel Cellulite Severity Scale

A	Number of evident depressions	0=none/no depressions 1=a small amount: 1-4 depressions are visible 2=a moderate amount: 5-9 depressions are visible 3=a large amount: 10 or more depressions are visible
B	Depth of depressions	0=no depressions 1=superficial depressions 2=medium depth depressions 3=deep depressions
C	Morphological appearance of skin surface alterations	0=no raised areas 1='orange peel' appearance 2='cottage cheese' appearance 3='mattress' appearance
D	Grade of laxity, flaccidity, or sagging skin	0=absence of laxity, flaccidity, or sagging skin 1=slight draped appearance 2=moderate draped appearance 3=severe draped appearance
E	Classification scale by Nürnberger and Müller	0 = zero grade = Grade or Stage 0 = There is no alteration of the skin surface. 1 = first grade = Grade or Stage I = The skin of the affected area is smooth while the subject is standing or lying, but the alterations to the skin surface can be seen by pinching the skin or with muscle contraction. 2= second grade = Grade or Stage II = The orange skin or mattress appearance is evident when standing, without the use of any manipulation (skin pinching or muscle contraction). 3= third grade = Grade or Stage III = The alterations described in Grade or Stage II, are present together with raised areas and nodules.

3.1.7. Skin Assessment (Fitzpatrick Scale)

At the Screening Visit, subject skin type will be evaluated using the Fitzpatrick Scale, shown in Table 3.

Table 3: 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

3.1.8. Weight, Height, and Body Mass Index

At the Screening Visit, height and weight measurements will be taken. Baseline BMI will be computed from these measurements as weight (in kilograms)/height^2 (in meters). Body weight will also be measured at Day 22, Day 43, Day 90, and Day 180 (EOS/ET) visits (see Table 1).

3.1.9. Adverse Events

Medically significant changes that occur after enrollment into this study are recorded as adverse events (AEs).

The following information is collected for all AEs:

- Verbatim description
- Date of Onset
- Date of Resolution /or Ongoing
- Severity (Mild, Moderate, Severe)
- Relationship to Study Drug (Not Related, Unlikely related, Possibly related, Probably related)
- Action taken with study drug (None, Drug Interrupted, Drug Withdrawn)
- Outcome (Recovered/Resolved, Recovered/Resolved w/Sequelae, Recovering/Resolving, Not Recovered/Not Resolved, Fatal, Unknown)
- Whether the AE led to study discontinuation
- Whether or not a concomitant medication or procedure was required
- Classified as a serious adverse event (SAE) or not
- SAE Code (Death, Life-threatening, Inpatient or prolonged hospitalization, Persistent or significant disability/incapacity, Congenital anomaly or birth defect, Other medically important event)
- Adverse event of special interest (Yes/No)

3.1.10. Medical History

A medical history of the subject will be taken during the screening period. The onset and resolution date or ongoing will be recorded for each condition reported. If no part (including year) of the onset or resolution date is known, then the condition will be reported as occurring less than 5 years ago or more than or equal to 5 years ago.

Medical history will also include a report of tobacco and alcohol use. For each item subjects are to report whether they never used, are currently using, or have formerly used. If subjects are a current or former user, they are to indicate the number of years they used the product, and former users are to indicate the stop date of using the product.

3.1.11. EFP Disease History

During the screening period an EFP disease history will be obtained from the subject. The EFP disease history will include onset date of EFP symptoms, previous treatments used for EFP, and family history of cellulite, answered as yes, no, or unknown for any family relation.

3.1.12. Physical Examination

During the screening period, the investigator will perform a physical examination (by body system) on each subject. Any abnormalities will be described.

3.1.13. Vital Signs

Blood pressure (systolic/diastolic), respiratory rate, pulse rate, and body temperature will be assessed at each study visit. On injection days (Day 1, Day 22, and Day 43), blood pressure, respiratory rate, and pulse rate will be measured prior to the injections (up to 4 hours prior to the injection), and at 15 and 30 minutes after the injection. On injection days, body temperature will be taken only prior to the injection, and at the 30-minute post-dose measurement. On injection days, the time vital signs are taken will also be recorded.

3.1.14. 12-Lead Electrocardiogram

During the screening period, subjects will have a resting 12-lead ECG. A qualified physician will assess the ECG to normal, abnormal not clinically significant, or abnormal clinically significant. The investigator will be able to record any comments regarding the ECG, such as explaining any abnormal findings or providing details if the ECG was not done per protocol.

3.1.15. Clinical Laboratory

Blood and urine samples will be collected for testing the following clinical laboratory parameters during the screening period and on the Day 180 (EOS/ET) visit. The analytes listed in Table 4 will be obtained.

Table 4: Clinical 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	CO_2	Bilirubin
	Inorganic phosphate	Urobilinogen
	Blood urea nitrogen Nitrite	Blood[a]
	Creatinine	Leukocytes[a]
	Creatinine clearance (estimated)	
	Aspartate transaminase (AST)	
	Alanine transaminase (ALT)	
	Gamma-glutamyl transferase (GGT)	
	Total bilirubin (TBL) (direct bilirubin reflex if elevated)	
	Albumin	
	Alkaline phosphatase (ALP)	
	Uric acid	

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

For all subjects, urine pregnancy tests are done on Day 1, Day 22, Day 43 and Day 90; serum pregnancy tests are done at Screening, and Day 180 (EOS/ET).

A certified laboratory will process specimens and provide results for each subject.

3.1.16. Immunogenicity Samples

Blood samples to be analyzed for anti-AUX-I and anti-AUX-II antibodies will be drawn before the injections on the Day 1, Day 22, and Day 43 visits, and on the Day 90 and Day 180 (EOS/ET) visits. A subset [redacted] of subject samples will be tested for neutralizing antibodies from Day 1 and Day 180 (EOS/ET) visits. The neutralizing antibodies results will be recorded as either positive or negative.

A certified laboratory will process specimens and provide results for each subject.

3.1.17. Prior and Concomitant Medications

Any medications (prescription or over-the-counter) used during the study or within 90 days prior to Day 1 will be recorded. Any prior medications used for EFP/Cellulite should be reported. Included will be:

- Verbatim name of medication
- Medication start date
- Medication end date or ongoing

- Dose, units, frequency, and route of medication
- Reason for medication (medical history, AE, prophylaxis, health maintenance, EFP/Cellulite, birth control, or other)

Additional space is available for comments regarding reason for medication, units, route, and frequency.

3.1.18. Concomitant Procedures/Therapies

Any procedures or therapies used during the study will be recorded. Any prior procedures for EFP/Cellulite or birth control should be reported. Included will be:

- Verbatim description of the procedure
- Start date
- End date or ongoing
- Reason for procedure (medical history, AE, prophylaxis, health maintenance, EFP/Cellulite, birth control, or other)

Additional space is available for comments regarding reason for procedure.

3.2. STUDY PARAMETERS

3.2.1. Subject Disposition

Subjects will be considered as completing the study if they complete the last scheduled visit. Subjects who do not complete the study will report their reason for early discontinuation. Time in the study will be computed as: Last date in study – Date of first injection + 1.

3.2.2. Number of Treatment Sessions

Subjects who receive at least one injection of study medication on Day 1, Day 22, or Day 43 will be counted as having a treatment session. Subjects will be classified into cohorts based on the number of injection sessions and the treatment areas they have. The reason why a treatment session was not done will be obtained and classified into one of the following:

- Early termination prior to visit
- Visit not done
- Visit done but no injections given due to other reasons

If a treatment session was done, subjects are classified into one of the following per treatment sessions:

- 24 injections given
- Less than 24 injections given due to other reasons

Within a treatment session, subjects are also classified into one of the following per treatment area (ie, right side or left side of treatment region):

- 12 injections given
- Less than 12 injections given due to other reasons

3.2.3. Treatment Groups

There is only one treatment group EN3835 1.68 mg total dose (0.84 mg per treatment area) in this study.

3.2.4. Protocol Deviations

A listing of protocol deviations will be provided. Before database lock, the statistical team will programmatically check against the prespecified criteria provided in a separate document ie, Protocol Deviation Checklist, and produce a subject list outputs under each criteria. The data review team will review the outputs and the protocol deviation tracker obtained during the study conduct, and then determine the major/minor category for each deviation. If any data points or subjects are excluded from the analysis, they will be documented in the data review meeting minutes and also be presented in a data listing.

3.2.5. Effectiveness Parameters

3.2.5.1. Baseline CR-PCSS Score

Baseline CR-PCSS scores for the assigned region will be based on the investigator's CR-PCSS evaluation done at the Screening visit.

3.2.5.2. Change from Baseline in CR-PCSS Score

The change from baseline in CR-PCSS score will be the CR-PCSS score at each visit minus the baseline score. The more negative the change from baseline indicates a greater improvement of cellulite severity in the assigned region.

3.2.5.3. Clinician Responder

A 2-level clinician responder for a treatment area is defined as a subject with an improvement in the CR-PCSS rating of at least 2 levels from baseline (ie, change from baseline in CR-PCSS rating of -2, -3, or -4) on that treatment area. A 1-level clinician responder for a treatment area is defined as a subject with an improvement in the CR-PCSS rating of at least 1 level from baseline (ie, change from baseline in CR-PCSS rating of -1, -2, -3, or -4) on that treatment area.

3.2.5.4. Subject Satisfaction with Cellulite Treatment

The subject satisfaction response is one of the five ratings (+2, +1, 0, -1, and -2) for the region treated, assessed at visit Day 180 (EOS/ET).

3.2.6. Safety Parameters

3.2.6.1. Adverse Events

Adverse events will be mapped to preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), Version 19.0. Treatment-emergent AEs are any AEs with a start date equal to or after the date of the first injection. Treatment-related AEs are any AEs with a relationship of possibly or probably related to study medication or AEs with a missing relationship.

3.2.6.1.1. Adverse Event Treatment Session

An AE's association with a treatment session will be based on the start date of AEs compared to the date of the injection. Adverse events with a start date between the Day 1 visit date and the day prior to the Day 22 visit date will be associated with Treatment Session 1. AEs with a start date between the Day 22 visit date and the day prior to the Day 43 visit date will be associated with Treatment Session 2. AEs with a start date between the Day 43 visit date and the Day 180 (EOS/ET) visit date will be associated with Treatment Session 3.

3.2.6.1.2. Adverse Event Duration

Duration of AEs will be the AE end date minus the AE start date + 1. Adverse event duration will be computed within each treatment session. Adverse events still ongoing at the end of the study or containing partial start or stop dates will not be included in the analysis of AE duration.

The duration of AEs will be used to determine the categories of AE durations (≥ 1 to ≤ 4 days, > 4 to ≤ 7 days, > 7 to ≤ 14 days, ≥ 15 to ≤ 21 days, and >21 days). For ongoing AEs, the category of AE duration will be missing unless those events have an onset date 21 days prior to the subject's last visit in the study. In this case, the category of the AE duration will be classified as "> 21 days".

3.2.6.2. Vital Signs and Clinical Laboratories

3.2.6.2.1. Baseline Values and Change from Baseline Values

The baseline values for vital signs and clinical laboratories will be the last available measurement prior to the first dose of study medication. 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. For vital signs, baseline will be Day 1 pre-dose for the by visit analyses.

Vital signs will additionally be analyzed on each injection day. For the first treatment session, baseline will be the last available measurement prior to the injection (Day 1 pre-dose). For Day 22 and Day 43, baseline will be the last available pre-injection measurement taken on that day.

Change from baseline will be the visit/time point value minus the baseline value.

3.2.6.2.2. Sponsor-Defined Potentially Clinically Important Vital Sign Values

Table 5 presents the criteria for determining potentially clinically important (PCI) vital sign values.

Table 5: Sponsor-Defined Potentially Clinically Important Vital Sign Criteria

Parameter	PCI Low	PCI High
Systolic blood pressure	≤ 90 mmHg and decrease ≥ 20 mmHg from baseline	≥ 180 mmHg and increase ≥ 20 mmHg from baseline
Diastolic blood pressure	≤ 50 mmHg and decrease ≥ 15 mmHg from baseline	≥ 105 mmHg and increase ≥ 15 mmHg from baseline
Pulse rate	≤ 50 bpm and decrease ≥ 15 bpm from baseline	≥ 120 bpm and increase ≥ 15 bpm from baseline
Respiratory rate	≤ 8 brpm and decrease ≥ 7 brpm from baseline	≥ 25 brpm and increase ≥ 7 brpm from baseline
Temperature		≥ 38.3°C and increase ≥ 1.1°C from baseline

3.2.6.2.3. Sponsor-Defined Potentially Clinically Important Laboratory Values

Table 6 presents the criteria for determining PCI laboratory values.

Table 6: Sponsor-Defined 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)		3xULN[a]
AST (U/L)		3xULN[a]
Creatinine (μmol/L)		300
BUN (mmol/L)		12

[a] ULN=Upper limit of normal.

3.2.6.3. 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 that are less than 1 titer will be analyzed with a log transformed titer of 0.

A subset of samples from Day 1 and Day 180 (EOS/ET) will be analyzed for neutralizing antibodies.

3.2.6.4. Medical History

Medical history will be mapped to preferred term using MedDRA, Version 19.0. Subjects with medical histories of Dupuytren's Disease, Ledderhose's Disease, Knuckle Pads, Diabetes, and

Epilepsy will be summarized. Subjects will be coded as having these disorders based on the preferred term of their reported medical histories. Knuckle pads will also include the preferred term of 'Garrod pads'. Ledderhose's disease will also include the preferred term of 'Fibromatosis'. Epilepsy will also include the preferred term of 'Convulsion'. Diabetes will include the preferred terms of 'Diabetes mellitus', 'Type 1 diabetes mellitus', or 'Type 2 diabetes mellitus'. Diabetes will not include subjects who report 'Glucose tolerance impaired' (borderline diabetes or pre-diabetes), 'Diabetic vascular disorder' or 'Blood glucose increased'. All medical history terms will be reviewed by the study medical monitor to determine if any other terms should be included in the summary.

Age at EFP symptoms onset will be computed as the date of the EFP symptoms reported on the medical history page minus the date of birth divided by 365.25. If the date of EFP symptom onset is incomplete, the date will be imputed according to the rules set up in section 3.5.3.

3.2.6.5. Prior and Concomitant Medications

All medications will be coded with the WHO drug dictionary, Version 01 MAR2016. A concomitant medication is any medication with a stop date on or after the date of the first injection or the medication is reported as ongoing. A prior medication is any medication with a start date prior to the date of the first injection.

3.2.6.6. Prior EFP Treatment

Prior EFP treatment will be obtained from the prior/concomitant medication and prior/concomitant procedure pages of the electronic Case Report Form (eCRF). If on either of these pages a medication or treatment is reported with the indication 'EFP/Cellulite' with a start date prior to the first dose of study medication, 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.

Time since the last EFP treatment will be computed as the date of the most recent EFP treatment minus the date the informed consent was signed divided by 365.25. If the date of any EFP treatments is incomplete, the date will be imputed according to the rules set up in section 3.5.3.

3.3. ANALYSIS POPULATIONS

The following populations are considered in the statistical analysis of the study: safety population and effectiveness population.

3.3.1. Safety Population

The safety population is defined as all enrolled subjects who have at least one injection of study medication. All safety parameters will be summarized based on this population.

3.3.2. Effectiveness Population

The effectiveness population is defined as all subjects in safety population with a baseline and at least 1 post-injection evaluation of the Investigator CR-PCSS in at least one treatment area.

All evaluations of effectiveness will be based on the effectiveness population.

3.4. STATISTICAL METHODS

3.4.1. General Consideration

In general, descriptive statistics for continuous variables may include number of subjects (n), mean, standard deviation, median, minimum and maximum values. Analysis of categorical variables will include frequency and percentage.

3.4.2. Subject Disposition

The total number of patients will be summarized for the following categories: those who were screened and those who screen failed.

The number and percentage of patients within each assigned region (buttock or thigh) and overall treatment group will be presented by the following categories: enrolled, completed the study, discontinued from the study (and reasons), and those who are included in safety population, effectiveness population, and photographic sub-study. The percentages are based on the number of the subjects who were enrolled into the study.

The descriptive statistics of time in the study (days) including number of subjects (n), mean, standard deviation, median, minimum and maximum values will also be provided.

The number and percentage of subjects by investigational site will also be summarized by assigned region (buttock or thigh) and overall treatment group.

Listing of all discontinued subjects and listing of subjects excluded from analysis populations will be generated.

3.4.3. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by assigned region (buttock or thigh) and overall for safety population, and will include:

- Age
- Age category (≥ 18 to < 35 years, ≥ 35 to < 45 years, ≥ 45 to < 55 years, ≥ 55 to < 65 years, ≥ 65 years)

- Gender
- Race
- Ethnicity
- Weight (in kg)
- Height (in cm)
- BMI (in kg/m^2)
- BMI group (underweight [< 18.5 kg/m^2], normal weight [≥ 18.5 to < 25.0 kg/m^2], overweight [≥ 25.0 to < 30.0 kg/m^2], obese [≥ 30.0 kg/m^2])
- Skin category based on Fitzpatrick scale rating
- Alcohol use
- Tobacco use

Individual subject listing of all demographic and baseline characteristics will be generated.

3.4.4. EFP Risk Factors and EFP History

EFP risk factors and EFP history characteristics will be summarized by assigned region (buttock or thigh) and overall for both the safety population and effectiveness population, and will include:

- Family history of cellulite
- Medical history of Dupuytren's disease, knuckle pads, Ledderhose's disease, diabetes, epilepsy (see section 3.2.6.4)
- Age at EFP symptom onset (in years)
- Prior treatments for EFP including Liposuction, Laser, Massage, Radiofrequency, Drug, Mesotherapy, Cream, Other or None. Subjects can report more than one prior EFP treatment.
- Number of prior EFP treatments (0, 1, 2, or ≥ 3)
- Time since most recent EFP treatment (in years)

3.4.5. EFP Baseline Severity

EFP baseline severity variable characteristics (including CR-PCSS rating and Hexsel CSS total score from Screening Visit) will be summarized by assigned region (buttock or thigh) and overall in the safety population.

Individual subject listing of all Hexsel CSS results will be generated.

3.4.6. Effectiveness Evaluation

All analyses for effectiveness evaluation will be conducted in the effectiveness population.

3.4.6.1. CR-PCSS

3.4.6.1.1. CR-PCSS Rating Summaries

The investigator CR-PCSS ratings will be summarized by assigned region (buttock or thigh) and overall at baseline (prior to Day 1), Day 22, Day 43, Day 90, and Day 180 (EOS/ET) with counts and percentages at each severity rating and with means and standard deviation. The change from baseline in CR-PCSS score will be summarized by assigned region (buttock or thigh) and overall at Day 22, Day 43, Day 90, and Day 180 (EOS/ET) with counts at each change score and with means and standard deviation. The change from baseline score can vary from -4 (change from severe to none) to +2 (change from mild to severe).

Individual subject listing of CR-PCSS ratings will be generated.

3.4.6.1.2. Responder Summaries

The investigator CR-PCSS responder classification will be summarized by assigned region (buttock or thigh) and overall (buttock and thigh) at Day 22, Day 43, Day 90, Day 180 (EOS/ET) with counts and percentages for both two-level responders and the one-level responders.

3.4.6.2. Subject Satisfaction with Cellulite Treatment Assessment

Subject satisfaction with cellulite treatment will be summarized by assigned region (buttock or thigh) and overall with counts and percentages for each response level. Additionally the mean and standard deviation of responses within each assigned region and overall will be presented. Subject satisfaction scores include +2 (Very Satisfied), +1 (Satisfied), 0 (Neither Dissatisfied nor Satisfied), -1 (Dissatisfied), and -2 (Very Dissatisfied).

Individual subject listing of subject satisfaction with cellulite treatment will be generated.

3.4.7. Safety Analysis

All analyses for safety will be conducted in the safety population.

3.4.7.1. Adverse Events

The following listings will be provided based on all AEs:

- Listing of AEs
- Listing of deaths
- Listing of SAEs
- Listing of AEs leading to discontinuation

The following summary tables of AEs will be presented by assigned region (buttock or thigh) and overall:

- Treatment-Emergent AEs
  - Overall summary
  - By preferred term

  - By preferred term and severity
  - By frequency for SAEs
  - By frequency for most common non-serious AEs
- Treatment-Related AEs
  - Overall summary
  - By preferred term
  - By preferred term and severity
  - By preferred term and treatment session
  - Duration of AEs

The overall summary will consist of the following items:

- Total number of AEs
  - All AEs
  - Mild AEs
  - Moderate AEs
  - Severe AEs
- Total number of subjects with
  - At least one AE
  - At least one SAE
  - At least one severe AE
  - At least one AE leading to discontinuation
- Total number of subjects who died (Treatment-emergent only)

Percentages for the total number of mild, moderate, and severe AEs will be based on the total number of all AEs in the corresponding assigned region and overall.

The by frequency summaries will also include the total number of occurrences the AE preferred term was reported as well the number of subjects with at least one report of the AE. Most common non-serious AEs are any preferred term AE that at least 5% of the subjects report at least once.

3.4.7.1.1. Adverse Event Conventions

The following conventions will be followed:

- Table by preferred term - If an AE preferred term occurred multiple times within a body system for the same subject, the preferred term will only be counted once for the subject for the summary of preferred terms. If an AE body system occurred multiple times for the same subject, the body system will only be counted once for the subject

for the summary of body systems. If a subject has any AE, the subject will be counted once in the summary of subjects with at least one AE.

- Table by preferred term and severity - If an AE preferred term occurred multiple times within a body system for the same subject, only the most severe one will be used. If the most severe preferred term of an AE occurred multiple times within a body system for the same subject, only one will be counted. In addition, this summary will also contain the total number of subjects with at least one mild, one moderate, or one severe. If a subject has at least one severe AE, then the subject will be counted in the severe category. If the subject has no severe AEs, but at least one moderate AE, then the subject will be counted in the moderate category, and if the subject has no severe and no moderate AEs, but has at least one mild AE, then the subject will be counted in the mild category.
- Table by preferred term and treatment session – If an AE preferred term occurred multiple times with a body system for the same subject within a treatment session, the preferred term will only be counted once for the subject in the treatment session for the summary of preferred terms. If an AE preferred term occurred multiple times within a body system for the same subject in different treatment sessions, the preferred term will be counted at each treatment session. If an AE body system occurred multiple times for the same subject within a treatment session, the body system will only be counted once for the subject in the treatment session for the summary of body systems. If an AE body system occurred multiple times for the same subject in different treatment sessions, the body system will be counted at each treatment session for the summary of body systems. If a subject has any AE within a treatment session, the subject will be counted once in the treatment session in the summary of subjects with at least one AE. If a subject has any AE in different treatment sessions, the subject will be counted in each treatment session in the summary of subjects with at least one AE.
- Table by duration of treated-related TEAE and treatment session – For each subject within each treatment session, every event will have its duration calculated. The multiple events for the same SOC and the same PT will be combined together for the sum of duration. Therefore for each SOC/PT in each treatment session, each subject will only have at most one (sum) duration which will be classified into one of the duration categories (≥ 1 to ≤ 4 days, > 4 to ≤ 7 days, > 7 to ≤ 14 days, ≥ 15 to ≤ 21 days, and >21 days).
- For ongoing AEs, the category of AE duration will be missing unless those events have an onset date 21 days prior to the subject's last visit in the study. In this case, the category of the AE duration will be classified as "> 21 days".
- Table of frequency of preferred terms – Preferred terms will be ordered by their descending frequency in the overall safety population. If 2 or more preferred terms are tied in their frequency, then the preferred terms will be ordered alphabetically.

3.4.7.1.2. Adverse Event of Special Interest

Adverse events of special interest will also be summarized by assigned region (buttock or thigh) and overall.

3.4.7.2. Study Drug Exposure

The exposure summary will be summarized by assigned region (buttock or thigh) and overall, and will include:

- number of treatment sessions
- whether all 24 injections were completed within each treatment session
- reason that treatment session was not done
- number of injections within each treatment session
- number of dimples treated within each treatment session
- average number of injections per dimple within each treatment session

A listing of subjects who did not receive all 3 treatment sessions and a listing of subjects who did not receive all 24 injections at each treatment session will be generated.

The similar analyses will be done for each treatment area (ie, right side or left side of treatment region) within treatment session. The number of injections should be 12 for a treatment area.

3.4.7.3. Body Weight

Body weight at baseline and post-baseline visits ie, Day 22, Day 43, Day 90, and Day 180 (EOS/ET) will be summarized by assigned region (buttock or thigh) and overall. The summary of change from baseline at postbaseline visits will also be provided.

3.4.7.4. Vital Signs

Vital signs at baseline (Day 1 pre-injection), all study visits (Day 22 pre-injection, Day 43 pre-injection, Day 90, and Day 180 (EOS/ET)), and change from baseline will be summarized by assigned region (buttock or thigh) and overall.

Vital signs on injection days will be summarized at baseline (pre-injection on that day), all postinjection time points (15 minutes and 30 minutes) and change from baseline. The baseline value will be based on the pre-injection measurement at each treatment session.

The incidence of subjects with sponsor-defined potentially clinically importance (PCI), vital sign values (see Table 5) at any time during the study (including post-30 minute measurements) will be summarized by assigned region (buttock or thigh) and overall. For vital signs PCI calculation, the baseline refers to the latest vital sign assessment values before the first injection on Day 1. Any subject with at least one PCI vital sign value will have all vital sign values listed.

3.4.7.5. Clinical Laboratory

Clinical laboratory results (hematology and chemistry only) at baseline, Day 180 (EOS/ET), and change from baseline will be summarized. Any hematology or chemistry lab results not reported as a continuous value will not be included in the summaries. All post-injection laboratory values

(Day 180 (EOS/ET) and unscheduled labs (taken on Day 1 or later) will be used to determine the incidence of PCI laboratory values.

The incidence of subjects with sponsor-defined PCI laboratory values (see Table 6) will be presented. Any subject with at least one PCI laboratory value will have all the values for that analyte listed. Individual subject listing of all lab results will be generated.

3.4.7.6. Immunogenicity

Anti-AUX-I and anti-AUX-II titer levels will be summarized at Day 1, Day 22, Day 43, Day 90, and Day 180 (EOS/ET) by assigned region (buttock or thigh) and overall using appropriate descriptive statistics. In addition, a subset of these immunogenicity samples will be analyzed for neutralizing antibodies by calculating the frequency count of the positive samples and the negative samples and the percentage of samples in each category.

Individual subject listing of all immunogenicity results will be generated.

3.4.7.7. Prior and Concomitant Medications

Prior and Concomitant medications will be summarized for preferred term (generic name from WHO dictionary) by assigned region (buttock or thigh) and overall. If two medications are coded to the same preferred term, it will be counted only once for a subject. Medications will be ordered alphabetically by drug class and preferred term within drug class.

Individual subject listing of prior and concomitant medications will be generated.

3.5. DERIVED VARIABLES

3.5.1. Subject Level Variables

The following variables will be determined for each subject (see Table 7).

Table 7: Subject Level Derived Dataset Variables

Variable	Definition
Age Group	≥ 18 to < 35 years ≥ 35 to < 45 years ≥ 45 to < 55 years ≥ 55 to < 65 years ≥ 65 years
Height (cm)	If height unit is inches, then height is equal to the recorded value multiplied by 2.54. And then rounded to 1 decimal point.
Weight (kg)	If weight unit is pounds, then weight is equal to the recorded value multiplied by 0.454. And then rounded to 1 decimal point.
BMI (kg/m^2)	$Weight/(Height)^2$
BMI Group	Underweight (< 18.5 kg/m^2) Normal Weight (≥ 18.5 to < 25.0 kg/m^2) Overweight (≥ 25.0 to <30.0 kg/m^2) Obese (≥ 30.0 kg/m^2)
Date of First Injection	Day 1 visit date
Last date in study	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 minus Date of first injection + 1
Age at EFP Symptom Onset	(Start date of EFP symptom onset (from medical history) – Date of Birth)/365.25, truncated to integer value. See section 3.5.3 for handling of partial or unknown EFP symptom onset dates.

3.5.2. Safety Variables

Adverse events will be organized in two different ways: by event and by subject. The by event dataset will include all the characteristics of the event obtained on the eCRF plus the derived variables presented in Table 8. A second by event dataset will be created for the AE duration analysis, where AEs with the same preferred terms within a treatment session for a subject are combined and the duration is the sum duration described in section 3.2.6.1.2. This duration dataset will contain only the subject number, treatment session, body system classification, preferred term, and total duration.

Table 8: Adverse Event Variables by Event

Variable	Values/Definition
Treatment-Emergent	AEs with a start date after the first dose of study medication
Treatment-Related	If relationship to study medication is reported as possible, probable or missing
Onset Day	AE start date minus date of first injection + 1
Duration	AE stop date minus AE start date + 1
Treatment Session	The number of the treatment session immediately preceding the AE onset date

The by-subject dataset will summarize all the AE events for a subject and will include the variables presented in Table 9. The same variables will be computed for treatment-emergent AEs and treatment related AEs.

Table 9: Adverse Event Variables by Subject

Variable	Values/Definition
Total AEs	Sum of Number of AEs the subject reported
Total Mild AEs	Sum of Number of mild AEs the subject reported
Total Moderate AEs	Sum of Number of moderate AEs the subject reported
Total Severe AEs	Sum of Number of severe AEs the subject reported
Had AE	Flag (Y/N) to indicate subject had at least one AE
Had Severe AE	Flag (Y/N) to indicate subject had at least one AE of moderate or severe severity
Had SAE	Flag (Y/N) to indicate subject had at least one serious AE
Had AE Leading to Discontinuation	Flag (Y/N) to indicate subject had at least one AE that lead to discontinuation from the study

3.5.3. Imputation of Partial Dates

Study visit dates, birthdates, informed consent date, injection dates/times, all assessment dates, all lab dates, and date of completion/last contact date must be complete dates; no imputations will be done. No imputations will be done for partial medical history onset/resolution dates (except EFP onset date), partial alcohol/tobacco stop dates, partial AEs onset/end dates and partial concomitant medication start/stop dates. All AEs with a missing onset day will be considered treatment emergent except if the onset month/year is prior to the first injection date. All medications with a missing onset and stop day will be considered concomitant except if the stop month/year is prior to the first injection date.

For EFP onset date and prior EFP medications/treatment dates, missing EFP onset dates or missing prior EFP medication/treatment start dates will be imputed with the 1st day of the month and missing onset month will be imputed with January. If the EFP onset date is indicated as completely unknown but starting less than 5 years ago, the EFP onset date will be imputed as the informed consent date minus 5 years. If the EFP onset date is indicated as completely unknown but starting more than 5 years ago, the EFP onset date will not be imputed. Missing EFP medication/ treatment end days will be imputed with the last day of the month and missing end

months will be imputed with December, except if the end year is equal to the date of injection year and then the EFP medication/treatment end date will be imputed with the first injection date.

All the missing date imputation will be used for the summary tables only; no imputation will be applied for the subject listings.

3.5.4. Relative Study Day/Treatment Session Study Day

Relative study day will be computed for each visit and for each AE. For visits or events occurring on or after the Day 1 visit, relative study day will be date of visit (event) − date of first injection + 1. For visits or events that occur prior to the Day 1 visit, the relative study day will be the date of visit (event) − date of first injection.

3.5.5. Conventions and Algorithms

3.5.5.1. Summary Tables/Subject Listings Conventions

Summary tables, subject listings, graphs 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 that generated the output

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

All summary tables involving percentages will round the percentages off to 1 decimal place. All summary tables involving descriptive statistics of continuous variables will round the mean and median to 1 decimal place more than the variable's standard form and round the standard deviation to 2 decimal places more than the variable's standard form. The standard form of a percent change variable is 0 decimal places.

When summarizing AEs, potentially clinically important laboratory, and potentially clinically important vital signs, subjects with multiple occurrences of an event will be counted only once in the summary. When AEs are summarized by severity, if the subject has multiple occurrences of the same AE, the most severe will be used for the summary.

Individual subject listings will be provided as support for summary tables and serve as a data source substitute when a summary table is deemed either inappropriate or unnecessary. All subject listings will be sorted by subject number. When applicable, the subject listings will include the visit date, and days relative to the start of first treatment and start of treatment session.

3.6. INTERIM ANALYSES

No interim analysis is planned for this study.

3.7. SAMPLE SIZE CALCULATION

To have a sufficient safety database of subjects establishing safety following exposure to EN3835, up to 150 subjects will be enrolled and monitored for 6 months in accordance with International Conference on Harmonisation (ICH) guidance.

3.8. TABLES, LISTINGS, AND GRAPHS SHELLS

The layouts of the summary tables, subject listings, and graphs are presented in SAP Module 2. These layouts incorporate all the appropriate table/listing/graph titles, numbers, and footnotes.