SAP MODULE 1 - DETAILED STATISTICAL METHODOLOGY

Protocol No. EN835-304 Amendment 3; January 14, 2021

A PHASE 3B, OPEN-LABEL, LONG-TERM STUDY TO EVALUATE THE SAFETY AND TEMPORAL PATTERN OF RESPONSE OF COLLAGENASE CLOSTRIDIUM HISTOLYTICUM IN THE TREATMENT OF EDEMATOUS FIBROSCLEROTIC PANNICULOPATHY

Version 2.0

May 25, 2021

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ATC	Anatomical therapeutic chemical
AST	Aspartate transaminase
AUX-I	Clostridial class I collagenase
AUX-II	Clostridial class II collagenase
BMI	Body mass index
bpm	Beats per minute
brpm	Breaths per minute
BLA	Biologics License Application
BUN	Blood urea nitrogen
CCH	Collagenase clostridium histolyticum
CI	Confidence Interval
CO_2	Carbon dioxide
CRF	Case report form
CR-PCSS	Clinician-Reported Photonumeric Cellulite Severity Scale
CSS	Cellulite Severity Scale
DB	Double blind
DMP	Data management plan
ECG	Electrocardiogram
EOS	End of study
eCRF	Electronic case report form
EFP	Edematous fibrosclerotic panniculopathy
GGT	Gamma-glutamyl transferase
ICF	Informed consent form
IUD	Intrauterine device
MedDRA	Medical Dictionary for Regulatory Activities
n	Number of subjects
OLR	Open-label retreated
OLNR	Open-label not retreated
OTC	Over the counter
PCI	Potentially clinically important
PR-CIS	Patient Reported Cellulite Impact Scale
PR-PCSS	Patient Reported Photonumeric Cellulite Severity Scale
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis software
SD	Standard deviation

Abbreviation	Definition
SE	Standard error
S-GAIS	Subject Global Aesthetic Improvement Scale
SOC	System organ class
SSRS	Subject Self-Rating Scale
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TRR	Time to reduction of response
TX	Treatment
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analyses to assess the safety, long-term immunogenicity profile, and time to reduction of response of Collagenase Clostridium Histolyticum (CCH) in the treatment of edematous fibrosclerotic panniculopathy (EFP) in adult women.

The general information about the study is detailed in the EN3835-304 protocol, Original version dated 31-Jan-2018, Amendment 1 dated 19-Apr-2018, Amendment 2 dated 01-Nov-2018 and Amendment 3 dated 14-Jan-2021.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objectives of this study are to assess:

- The long-term safety of CCH in the treatment of EFP commonly known as cellulite in adult women
- The safety of CCH when used for retreatment in the treatment of EFP commonly known as cellulite in adult women
- The long-term immunogenicity profile of CCH following treatment of EFP commonly known as cellulite in adult women

2.2. Secondary Objective

The secondary objective of this study is to assess the time to reduction of response (TRR) to CCH in the treatment of EFP in adult women.

3. STUDY DESIGN AND MEASURES

3.1. Study Design

This is a Phase 3b, long-term open-label extension study to be performed at multiple centers in the United States (US), the study will enroll the subjects who participated in, and completed the previous double-blind, placebo-controlled Phase 3 cellulite studies EN3835-302 or EN3835-303. The objectives of this open-label extension study are to evaluate safety, immunogenicity profile, and temporal pattern of response of CCH in the treatment of EFP.

This study will initially enroll up to approximately 840 subjects until the double-blind studies are unblinded, after which only subjects who received active EN3835 will remain in observation in the current study.

The eligibility of the subjects for this study will be assessed during the Day 71 visit of the respective double-blind trial in which the subject participated. Subjects will be offered enrollment into this trial to observe and record continued evaluation of response to CCH and/or safety for a period of up to 3 years after their Day 71 visit in the double-blind study EN3835-302

or EN3835-303. The assessments made within 14 days of the subject's Day 71/End of Study (EOS) of the double-blind study, will serve as initial screening for the current open-label extension study. If the EN3835-304 screening visit is performed greater than 14 days after the subject's Day 71 of the double-blind study, then only the unique Screening Visit assessments will be performed (informed consent, inclusion and exclusion criteria evaluation, height, weight, and physical examination) separately for the open-label study as mentioned in schedule of events Table 1. No subject will be allowed to enroll in the study if the Screening Visit does not occur within 180 days after Day 71 of Study EN3835-302/303.

At the time of entry into the open-label study and at Visit 1 (Day 180) of study EN3835-304 (approximately 6 months after Day 71 of study EN3835-302/303), the subjects, Investigators and site personnel will remain blinded to the study drug received in the double-blind studies. Even if the EN3835-302/303 study drug blind is broken by the Sponsor; subjects, Investigators and site personnel in study EN3835-304 will remain blinded until after Day 180 safety and cellulite severity assessments of each treatment area are completed.

Upon completion and unblinding of the double-blind studies EN3835-302/303 (see Figure 1), subjects who received placebo during the double-blind studies will be discontinued, and subjects who received active CCH will be classified into one of three Categories:

- Category I: 1-Level Composite Responders
- Category II: 2-Level Composite Responders
- Category III: Non-Composite Responders

Composite response will be assessed using both the subject PR-PCSS (Patient Reported Photonumeric Cellulite Severity Scale) responder classification and investigator CR-PCSS (Clinician-Reported Photonumeric Cellulite Severity Scale) responder classification, where same level of improvement is observed by both the scales in the same buttock (eg, for 2 level composite improvement – the improvement in response of at least 2-level should be observed in both PR-PCSS and CR-PCSS for the same buttock).

3.1.1. Category I

- Subjects should have not received any collagenase treatments since the completion of the double-blind study.
- Subjects in which the maximum composite response was ONLY a 1-level composite improvement in cellulite severity at Day 71 as assessed by the PR-PCSS and CR-PCSS in either (or both) buttock(s) in the double-blind study. In cases where improvement was in both buttocks, the composite improvement of 1-level must have occurred in the same buttock (ie, the PR-PCSS and CR-PCSS improvement observed in the same buttock).
- Subjects who showed a 2-level improvement in one scale but only a 1-level improvement in the other scale, provided the composite improvement of 1-level was within the same buttock.
- Only buttocks with a composite 1-level improvement or less will be retreated.

- These subjects will be observed for time to reduction of response (defined in section 4.4.1) and safety approximately every 6 months for 2 years and will be observed annually for up to 3 years (Day 1080) from Day 71 of the double-blind study.

3.1.2. Category II

Subjects should have not received any collagenase treatments since the completion of double-blind study.

Subjects who showed an improvement in cellulite severity of at least two levels in at least one buttock in both the PR-PCSS and the CR-PCSS (ie, 2-level composite responder) in the double-blind study.

These subjects will be observed for time to reduction of response (defined in section 4.4.1) and safety approximately every 6 months for 2 years and will be observed annually for up to 3 years (Day 1080) from Day 71 of the double-blind study.

- Category II subjects must have at least 1-level composite response reduction (ie, reduction of response by at least 1-level in the PR-PCSS and CR-PCSS ratings) compared to Day 71 of the double-blind study (EN3835-302/303) AND no longer maintain 2-level composite response compared to baseline in the EN3835-302/303 study on either or both buttocks to be eligible for a retreatment course. If there is a composite worsening of cellulite severity, the confirmation of loss of response will be established during a follow-up visit ~2 weeks after the loss of response is detected at Day 180, if the loss of response is not confirmed then the subject will not be eligible for retreatment in this study.

One and only one retreatment course in up to 2 qualifying buttocks concurrently will be offered to eligible Category I and Category II subjects during this 3-year study. The subjects in Category I and/or eligible Category II subjects will receive a retreatment course consisting of 3 treatment sessions separated by 21 days (Day 1, 22, and 43). Each treatment session will consist of 12 injections (0.07 mg/0.3 mL per injection) of CCH for a dose of 0.84 mg and volume of 3.6 mL (identical to the treatment course administered in the double-blind study), in each qualifying buttock (see

Table 5) in up to two buttocks treated concurrently.

After initiation of retreatment, the safety and cellulite severity will be assessed on Days 22, 43, and 71. The Category I and Category II subjects who received retreatment will have safety assessment completed during the observational visits at Months 12, 18, 24, and 36 from Day 71 of the double-blind study.

The Category II subjects that have not shown at least 1-level composite reduction AND/OR have a buttock that has maintained at least a 2-level composite response (ie, have maintained a successful response), and/or Category I and/or Category II subjects who are eligible for a retreatment course but opted not to receive retreatment will have cellulite assessments at Months 12, 18, 24, and 36 from Day 71 of the double-blind study. If the subject's buttock(s) become eligible for retreatment based on the ratings during an observational visit and if they have not already received a course of retreatment in this study, then they will be offered one course of retreatment for the eligible buttock(s); one course of concurrent treatment for up to two eligible buttocks.

If a treatment period overlaps a scheduled observational visit, the observational visit will be skipped, and the subject will re-enter the observational schedule at the next interval visit. For example, if a subject initiated retreatment on Day 351 (which would then be Treatment Visit 1), the treatment period would proceed for approximately 71 days until Day 421 (Treatment Visit 4) and the Observational Visit at Day 360 would be skipped; the subject's next observational visit would be Day 540.

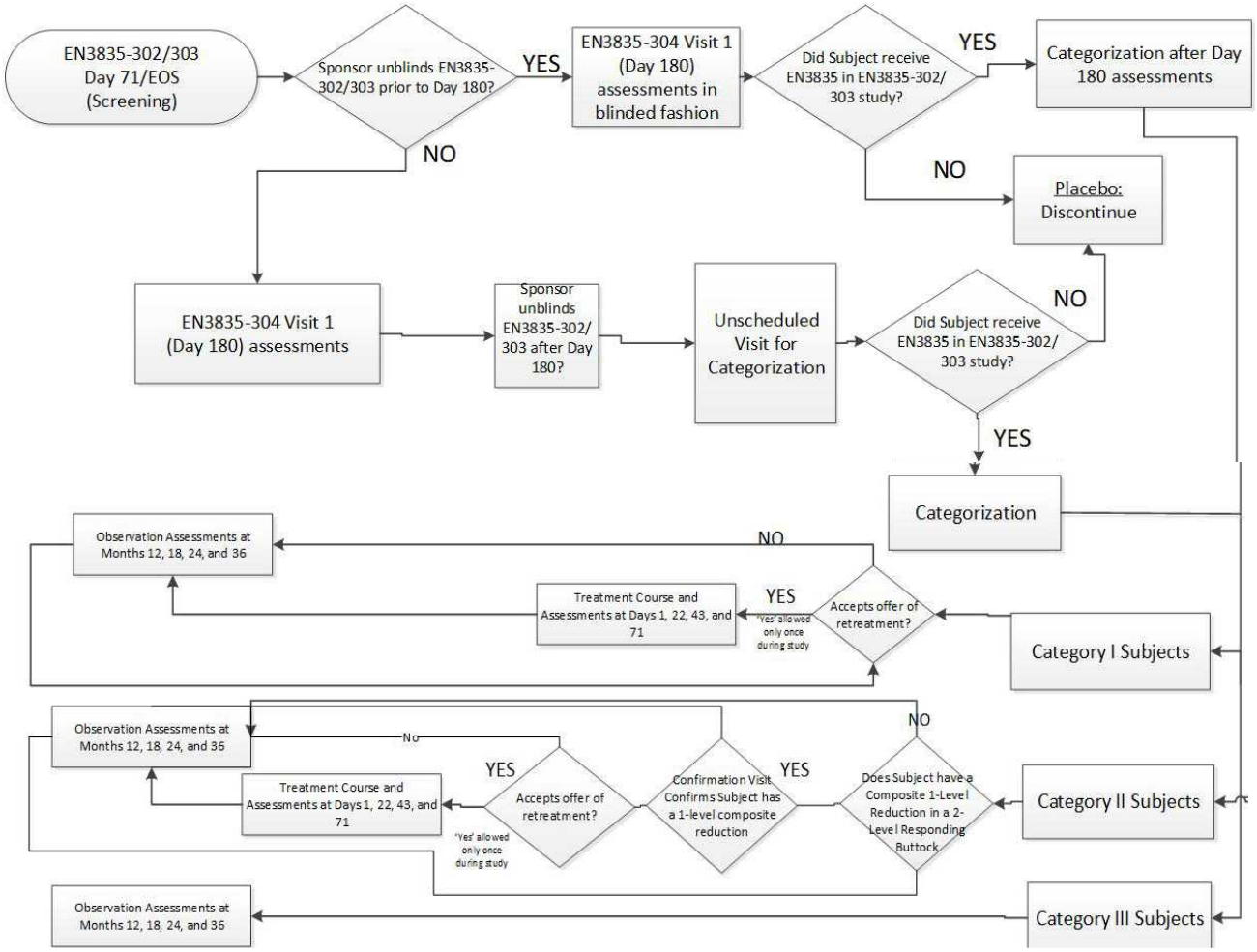
3.1.3. Category III

- Subjects who received active study drug in study EN3835-302 or EN3835-303 but did not meet criteria to be included in Category I or II (ie, non-composite responders).
- Category III subjects will not be eligible for retreatment in this study.

Assessment of open-label efficacy following retreatment will be determined up to Treatment Visit 4 (Day 71 + 5 days), after which all subjects (including the subjects who did not accept the offer of re-treatment) will be observed for safety every 6 months for 2 years and annually for up to 3 years (Day 1080) after Day 71 of the double-blind study.

The study schema is provided in Figure 1 below:

Figure 1: Study Design



The Schedule of Events for all subjects up through 180 days following the double-blind studies is provided in Table 1.

Table 1: Schedule of Events Up to 180 Days

Procedures[a]	**Screening A**[b] **(≥Day 71 Visit of Double-blind Study) (+14 days)**	**Visit 1 Day 180**[c] **(±14 days) M6/Early Termination**	**Durability Confirmation Visit**[d]
Unblinding of Investigator, subject and site to subjects' treatments in EN3835-302/303[e]		X	
Informed consent[f]	X	X	
Inclusion/exclusion	X		
Digital photography	X	X	X
Prior/concomitant medications/procedures[g]	X	X	
Physical examination:	X		
• Body weight	X	X	
• Height	X		
Vital signs	X	X	
Collection of Samples			
• Clinical laboratory	X	X	
• Anti-AUX-I/anti-AUX-II antibody level	X		
• Pregnancy testing[h]	X	X	
Subject Cellulite Assessments			
• Review assessments' training and use materials	X	X	X
• Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) [i,j]	X	X	X
• Subject Global Aesthetic Improvement (S-GAIS) [i]	X	X	
• Patient Reported Cellulite Impact Scale (PR-CIS)	X	X	
• Subject Satisfaction With Cellulite Treatment Assessment	X	X	
• Subject Self-Rating Scale (SSRS)	X	X	
Investigator Cellulite Assessments			
• Review assessment's training and use materials	X	X	X
• Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) [k]	X	X	X
Assignment of Subject to Category I, II, or III[l]		X	
Local safety assessments[m]	X	X	X
Adverse events[n]	Monitored throughout study		

Table 1: Schedule of Events Up to 180 Days (Continued)

FOOTNOTES:

[a] Unscheduled visits may be done as deemed necessary at any time during the study to ensure subject safety; assessments done at unscheduled visits are at the discretion of the investigator. No photographs or cellulite severity assessments will be done at unscheduled visits.

[b] Day 71 Visit is in double-blind study (EN3835-302/303).

[c] Visit 1 Day 180 is in study EN3835-304; approximately 180 days after Day 71 of double-blind study. A subject who terminates study participation between Day 71 and Day 180 will have an Early Termination Visit that includes the Assessments listed for Visit 1 Day 180.

[d] If the composite (CR-PCSS and PR-PCSS) ratings worsen by at least 1-level composite response ratings at Day 180 Visit or at a subsequent unscheduled unblindig visit for a subject that had a 2-level composite improvement at Day 71 of the double-blind study, an additional visit should be scheduled 14 days (± 5 days) later to confirm reduction of response, via re-assessment with the CR-PCSS and PR-PCSS.

[e] Depending on the date of unblinding of subject's treatment in EN3835-302/303; investigators, subjects, and site personnel may be unblinded at Day 180 Visit AFTER all assessments have been performed or at a time thereafter during an unscheduled visit. If database lock occurs prior to Day 180, the investigator, subjects, and site personnel will be remained blinded until the Day 180 Visit.

[f] Informed consent at Screening will address activities up through Day 180 Visit. Informed consent at Day 180 Visit will address the classification of subjects into Categories I, II, and III and activities and assessments that they will undergo.

[g] Including XIAFLEX as a concomitant medication; the use of the word 'prior' refers to the period between the last visit from the previous Phase 3 clinical study through the signing of informed consent in the EN3835-304 study; not applicable to subjects who sign consent for this study on the same day that they complete the EN3835-302/303 study.

[h] Serum pregnancy test occurs on Screening visit (carried over from Day 71/EOS visit of EN3835-302/303); urine pregnancy test on Day 180 Visit and, if deemed necessary, at an Unscheduled Visit.

[i] Subject assessments should be completed independently and prior to Investigator assessments at each visit.

[j] Assessment made via photographs.

[k] Assessment of each of the 2 buttocks independently.

[l] Assignment of subjects to Categories will occur after unblinding of investigators, subject and site personnel to subjects' treatment in EN3835-302/303 and will depend on treatment and Day 71 cellulite severity improvements. Depending on the date of the database lock of the double-blind studies, assignments may occur at Day 180 Visit after assessments are completed or at a time thereafter during an unscheduled visit.

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

[n] Any AE that occurs between the completion of studies EN3835-302/303 and the Day 180 Visit will be reported and evaluated.

EFP=Edematous fibrosclerotic panniculopathy; EOS=End of study; M=Month(s).

The Schedule of Events beyond Day 180 for Category I and II and who are eligible and opted to receive retreatment is provided in Table 2.

Table 2: Schedule of Events: Eligible Category I/II Subjects – Treatment Session Assessments

Procedures[a]	**Screening B**[b] **(Day -14 to -1 relative to Tx Visit 1)**	**Tx Visit 1 Tx Session 1 Day 1**	**Tx Visit 2 Tx Session 2 Day 22 (±3 days)**	**Tx Visit 3 Tx Session 3 Day 43 (±3 days)**	**Tx Visit 4 End of Treatment Day 71 (+5 days)** [c]
Informed consent[d]	X				
Inclusion/exclusion	X				
Digital photography[e]	X	X[f]	X[f]	X[f]	X
Prior/concomitant medications/procedures[g]	X	X	X	X	X
Physical examination:	X				
• Body weight	X		X[h]	X[h]	X
• Height	X				
Vital signs	X	X[i]	X[i]	X[i]	X
ECG[j]	X				
Collection of Samples					
• Clinical laboratory	X				X
• Anti-AUX-I/anti-AUX-II antibody level	X		X	X	X
• Pregnancy testing[k]	X	X[h]	X[h]	X[h]	X
Subject Cellulite Assessments					
• Review assessments' training and use materials	X	X	X	X	X
• Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS)[l,m]	X	X	X	X	X
• Subject Global Aesthetic Improvement Scale (S-GAIS) [l]	X				X
• Patient Reported Cellulite Impact Scale (PR-CIS)[l]	X				X
• Subject Satisfaction With Cellulite Treatment Assessment[l]	X				X
• Subject Self-Rating Scale (SSRS)[l]	X				X
Investigator Cellulite Assessments					
• Review assessment's training and use materials	X	X	X	X	X
• Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)	X	X	X	X	X
Selection of dimples to be treated		X	X	X	
Marking the dimples and injection sites to be treated within the buttocks		X	X	X	

Table 2: Schedule of Events: Eligible Category I/II Subjects – Treatment Session Assessments (Continued)

Procedures[a]	Screening B[b] (Day -14 to -1 relative to Tx Visit 1)	Tx Visit 1 Tx Session 1 Day 1	Tx Visit 2 Tx Session 2 Day 22 (±3 days)	Tx Visit 3 Tx Session 3 Day 43 (±3 days)	Tx Visit 4 End of Treatment Day 71 (+5 days) [c]
Confirm eligibility of buttocks for retreatment[n]	X				
Study drug administration		X	X	X	
Injection site reactions/local tolerability in the buttocks[o]		X	X	X	X
Adverse events	Monitored throughout study				

FOOTNOTES:

[a] Unscheduled visits may be done as deemed necessary at any time during the study to ensure subject safety; assessments done at unscheduled visits are at the discretion of the investigator. No photographs or cellulite severity assessments will be done at unscheduled visits.

[b] After the study drug treatment blind is broken in study EN3835-302/303 and subjects have been classified based on Day 71 composite responses in study EN3835-302/303, Category I and Category II subjects that qualify for treatment may elect to receive one and only one course of EN3835 retreatment (ie, 3 treatment sessions) in up to 2 buttocks. If a subject does not qualify to for treatment at that time, she may undergo another Screening B at a later time, if still eligible for treatment.

[c] Upon completion of treatment, subject will be followed at intervals as described in Table 3; if the 71-day treatment period overlaps with an Observation Visit in Table 3 for a subject, that particular Observation visit will be skipped, and the subject will be assessed at the next scheduled Observation Visit in Table 3.

[d] Informed consent for Category I and eligible Category II subjects who opt to receive retreatment.

[e] Photographs of both left and right buttocks should be taken.

[f] Before and after marking dimples and injection sites.

[g] Including XIAFLEX as a concomitant medication; the use of the word 'prior' refers to the period between the last visit from the previous Phase 3 clinical study through the signing of informed consent in the EN3835-304 study; not applicable to subjects who sign consent for this study on the same day that they complete the EN3835-302/303 study.

[h] Before injection.

[i] Up to 4 hours before injection; approximately 15 and 30 minutes after injection. Pulse and blood pressure to be taken after subject has been sitting for 5 minutes. Vital signs must be stable before the subject is discharged. Refer to section 14.9 of Protocol Amendment 3.

[j] Do not conduct if Screening B visit date is within 12 months of obtaining an ECG during the double-blind study (EN3835-302/303).

[k] Serum pregnancy test on Screening visit and Day 71/EOS visit; urine pregnancy test on Day 1, Day 22, and Day 43 visits and Unscheduled Visit.

[l] Assessment made via photographs (if treatment visit, use photographs taken before marking dimples and injection sites).

[m] Subject assessments should be completed independently and prior to investigator assessments at each visit. Includes bot buttocks regardless of treatment, each buttock should be assessed independently.

[n] At least one of the Category I subject's buttocks must have scores/ratings of at least 2 in both the CR-PCSS and PR-PCSS to be eligible to receive treatment. Category II subjects must have at least a 1-level composite response reduction compared to Day 71 of the EN3835-302/303 study AND no longer maintain a 2-level composite response compared to baseline in the EN3835-302/303 study on either or both buttocks.

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

ECG=Electrocardiogram; EFP=Edematous fibrosclerotic panniculopathy; EOS=End of study; Tx=Treatment.

The Schedule of Events beyond Day 180 for subjects in Category I and II who are eligible and opted to receive retreatment, for the subjects in Category II who are not eligible for retreatment, and Category I and II subjects who are eligible but opted not to have retreatment is provided in Table 3.

Table 3: Schedule of Events: Category I/II Subjects – Observation Assessments

Procedures[a]	OBS Visit 2 Day 360 (±30 d) (M12)	OBS Visit 3 Day 540 (±30 d) (M18)	OBS Visit 4 Day 720 (±30 d) (M24)	OBS Visit 5 Day 1080/EOS/Early Termination (±30 d) (M36)	Durability Confirmation Visit[b]
Verification of informed consent	X				
Inclusion/exclusion	X				
Digital photography	X	X	X	X	X
Prior/concomitant medications/procedures[c]	X	X	X	X	
Anti-AUX-I/anti-AUX-II antibody level	X	X	X	X	
Subject Cellulite Assessments					
• Review assessments' training and use materials	X	X	X	X	X
• Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) [d,e]	X	X	X	X	X
• Subject Global Aesthetic Improvement Scale (S-GAIS) [d]	X	X	X	X	
• Patient Reported Cellulite Impact Scale (PR-CIS) [d]	X	X	X	X	
• Subject Satisfaction With Cellulite Treatment Assessment[d]	X	X	X	X	
• Subject Self-Rating Scale (SSRS)	X	X	X	X	
Investigator Cellulite Assessments					
• Review assessment's training and use materials	X	X	X	X	X
• Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) [e]	X	X	X	X	X
Local safety assessments[f]	X	X	X	X	X
Adverse events	Monitored throughout study				

FOOTNOTES:

[a] Unscheduled visits may be done as deemed necessary at any time during the study to ensure subject safety; assessments done at unscheduled visits are at the discretion of the investigator. No photographs or cellulite severity assessments will be done at unscheduled visits.

[b] If the composite (CR-PCSS and PR-PCSS) ratings worsen by at least 1-level composite response ratings for a subject, an additional visit should be scheduled 14 days (± 5 days) later to confirm reduction of response, via re-assessment with the CR-PCSS and PR-PCSS. If reduction of response is confirmed, subjects will be offered one course of retreatment (one and only one course of retreatment in up to 2 buttocks concurrently will be offered to an individual subject during this open-label study from Visit 1 to Visit 5 (approximately 6 to 36 months after Day 71 of the double-blind study, respectively). The Sponsor has

Table 3: Schedule of Events: Category I/II Subjects – Observation Assessments (Continued)

decided to terminate the EN3835-304 clinical trial at the completion of 3-year time point (Day 1080) and will offer voucher(s) for commercially approved Qwo redeemable only for those trial participant(s) who will miss their potential retreatment opportunity due to this decision. Retreatment will only be offered following confirmation of eligibility through cellulite assessments performed at the Day 1080 visit for those participants, and a confirmation visit (as applicable).

[c] Including XIAFLEX as a concomitant medication; the use of the word 'prior' refers to the period between the last visit from the previous Phase 3 clinical study through the signing of informed consent in the EN3835-304 study; not applicable to subjects who sign consent for this study on the same day that they complete the EN3835-302/303 study.

[d] Assessment made via photographs.

[e] Subject assessments should be completed independently and prior to Investigator assessments at each visit. Assessment of each of the 2 buttocks is to be made independently.

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

d=Days; EFP=Edematous fibrosclerotic panniculopathy; EOS=End of study; M=Month(s); OBS=Observation.

The Schedule of Events for Category III subjects is shown in Table 4.

Table 4: Schedule of Events: Category III Subjects – Assessments

Procedures[a]	OBS Visit 2 Day 360 (±30 d) (M12)	OBS Visit 3 Day 540 (±30 d) (M18)	OBS Visit 4 Day 720 (±30 d) (M24)	OBS Visit 5 Day 1080/EOS/Early Termination (±30 d) (M36)
Verification of informed consent	X			
Inclusion/exclusion	X			
Prior/concomitant medications/procedures[b]	X	X	X	X
• Anti-AUX-I/anti-AUX-II antibody level	X	X	X	X
Local safety assessments[c]	X	X	X	X
Adverse events	Monitored throughout study			

FOOTNOTES:

[a] Unscheduled visits may be done as deemed necessary at any time during the study to ensure subject safety; assessments done at unscheduled visits are at the discretion of the investigator. No photographs or cellulite severity assessments will be done at unscheduled visits.

[b] Including XIAFLEX as a concomitant medication; the use of the word 'prior' refers to the period between the last visit from the previous Phase 3 clinical study through the signing of informed consent in the EN3835-304 study; not applicable to subjects who sign consent for this study on the same day that they complete the EN3835-302/303 study.

[c] Local adverse events associated with the injection site from the 302/303 studies, including acute (eg, erythema, bruising, pain, nodules/mass, ulceration, blistering, pruritus, swelling, and/or induration) and/or chronic (eg, skin thickening, fibrosclerosis, peau d'orange changes) cutaneous adverse events, will be recorded and evaluated for seriousness and severity.

d=Days; EOS=End of study; M=Month; OBS=Observation.

3.2. Eligibility Criteria for Subject Selection

3.2.1. Inclusion Criteria

3.2.1.1. All Subjects (Through Day 180)

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

1. Voluntarily sign and date an informed consent agreement.
2. Have participated in and completed the double-blind Phase 3 study EN3835-302 or EN3835-303 (ie, assessed safety and obtained PR-PCSS and CR-PCSS ratings at Day 71/EOS of the double-blind study; does not include early termination subjects).
3. Be willing to apply sunscreen to both buttocks before each exposure to the sun and/or tanning booths while participating in the study during this period.
4. Be judged to be in good health, based upon the results of a physical examination and laboratory profile at Screening.
5. Be willing and able to cooperate with the requirements of the study.
6. Be able to read, complete and understand the patient reported outcomes rating instruments in English.

For each category of subjects, the following inclusion criteria apply beyond the day that the investigator, subject, and site personnel are unblinded:

3.2.1.2. Category I Subjects (Post Unblinding of EN3835-302/303)

1. Voluntarily sign and date an informed consent agreement.
2. Have received active EN3835 in study EN3835-302 or EN3835-303.
3. Have had a maximum composite response at Day 71 in either or both buttocks in double-blind study EN3835-302 or EN3835-303 that was ONLY a 1-level improvement on CR-PCSS/PR-PCSS.
4. Be willing to apply sunscreen to the buttocks before each exposure to the sun.
5. Be judged to be in good health, based upon the results of a physical examination and laboratory profile at Screening.
6. Be willing and able to cooperate with the requirements of the study.
7. Be able to read, complete and understand the patient reported outcomes rating instruments in English.

3.2.1.3. Category II Subjects (Post Unblinding of EN3835-302/303)

1. Voluntarily sign and date an informed consent agreement.
2. Have received active EN3835 in study EN3835-302 or EN3835-303.

3. Have had a composite response at Day 71 in either or both buttocks in double-blind study EN3835-302 or EN3835-303 that was at least a 2-level composite improvement on CR-PCSS/ PR-PCSS.
4. Be willing to apply sunscreen to the buttocks before each exposure to the sun.
5. Be judged to be in good health, based upon the results of a physical examination, and laboratory profile at Screening.
6. Be willing and able to cooperate with the requirements of the study
7. Be able to read, complete and understand the patient reported outcomes rating instruments in English

3.2.1.4. Category III Subjects (Post Unblinding of EN3835-302/303)

1. Voluntarily sign and date an informed consent agreement.
2. Have received active EN3835 in study EN3835-302 or EN3835-303 but did not meet eligibility criteria for Category I or Category II status.
3. Be willing and able to cooperate with the requirements of the study.

3.2.1.5. Retreatment Subjects (Post Unblinding of EN3835-302/303)

Subjects in Category I and Category II who opt for retreatment must meet the following additional inclusion criteria to be eligible for retreatment. These subjects must:

1. Voluntarily sign and date an informed consent agreement for retreatment.
2. Be willing to apply sunscreen to the buttocks before each exposure to the sun while participating in the retreatment portion of the study (ie, Treatment Visit 1 through Treatment Visit 4).
3. Be judged to be in good health, based upon the results of a physical examination, and laboratory profile at Screening.
4. 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.
5. Category II subjects must have at least a 1-level composite response reduction compared to Day 71 of the EN3835-302/303 study AND no longer maintain a 2-level composite response compared to baseline in the EN3835-302/303 study on either or both buttocks that is confirmed at a Confirmation Visit.

3.2.2. Exclusion Criteria

3.2.2.1. All Subjects (Through Day 180)

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

A subject will be excluded from study participation if she:

1. Intends to or has used any of the following for the treatment of EFP on a buttock at any time during the time period from Day 71 of double-blind study EN3835-302 or EN3835-303 through Day 180 Visit in study EN3835-304 (approximately 6 months after Day 71 of study EN3835-302 or EN3835-303), including (but not limited to):
    a. Liposuction in a buttock
    b. Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; buttock implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision) within a buttock
    c. Any investigational drug or treatment for EFP on a buttock (other than treatment in study EN3835-302/303)
    d. Endermologie or similar treatments within a buttock
    e. Massage therapy within a buttock during the 3-month period before observational visit
    f. Creams (eg, Celluvera, TriLastin) and/or home therapies to prevent or mitigate EFP within a buttock during the 2-week period before observational visit
2. Intends to use tanning spray or tanning booths during this period.
3. Any other condition(s) that, in the Investigator's opinion, might indicate the subject to be unsuitable for the study.

3.2.2.2. Category I and II Subjects (Post Unblinding of EN3835-302/303)

A Category I or Category II subject will be excluded from study participation if she:

1. Intends to or has used any of the following for the treatment of EFP on a buttock at anytime during the course of the study:
    a. Liposuction in a buttock.
    b. Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; buttock implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision) within a buttock.
    c. Any investigational drug or treatment for EFP on a buttock (other than treatment in study EN3835-302/303).
    d. Endermologie or similar treatments within a buttock.
    e. Massage therapy within a buttock during the 3-month period before observational visit.
    f. Creams (eg, Celluvera, TriLastin) and/or home therapies to prevent or mitigate EFP within a buttock during the 2-week period before observational visit.
2. Has received any collagenase treatments at any time since completion of the double-blind study

3. Any other condition(s) that, in the Investigator's opinion, might indicate that the subject is unsuitable for the study.

3.2.2.3. Category III Subjects (Post Unblinding of EN3835-302/303)

There is no exclusion criteria defined in the protocol for category III subjects.

3.2.2.4. Retreatment Subjects (Eligible Subjects who opted to Receive Retreatment)

A Category I or Category II subject will be excluded from retreatment if she:

1. Has any of the following systemic conditions:
    a. Coagulation disorder.
    b. Evidence or history of malignancy (other than excised basal-cell or squamous-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 areas 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. Severe skin laxity, flaccidity, and/or sagging
    e. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer
    f. 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 retreatment portion the trial:
    a. Anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication (except for ≤150 mg aspirin daily) within 7 days before or 7 days after injection of study drug.
4. Is nursing or providing breast milk during the course of retreatment (Treatment Visit 1 through Treatment Visit 4).
5. Is pregnant or intends to become pregnant during the course of retreatment (Treatment Visit 1 through Treatment Visit 4).
6. Intends to use tanning spray or tanning booths in the 30 days prior to and during the course of retreatment (Treatment Visit 1 through Treatment Visit 4).
7. Has a known systemic allergy to collagenase or any other excipient of study drug.
8. Any other condition(s) that, in the Investigator's opinion, might indicate the subject to be unsuitable for retreatment.

3.3. Treatment Area

The treatment area is defined as eligible buttock(s). A subject will be eligible for treatment in either or both buttocks (ie, left and/or right buttock). All cellulite assessments will be performed on each individual treatment area. Treatment areas will be evaluated separately.

3.4. Selection and Marking of Dimples During Treatment Visits

The investigator will select the dimples within each buttock 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 treatment. Investigator will select the dimples for Category I and II subjects who are eligible for retreatment.

The same dimples within a buttock or different dimples within a buttock will be retreated at the designated treatment visits, but injections must be all within the buttocks (12 injections per buttock) for all the treatment visits. The Category I subjects and Category II subjects eligible for retreatment will receive study drug in 3 retreatment visits unless the buttock has no treatable EFP dimples and Investigator rates a buttock with a score of 0 on the CR-PCSS at Treatment Visit 1, Treatment Visit 2 and/or Treatment Visit 3. During each retreatment visit, the buttock(s) to be treated will be photographed before and after marking dimples and injection sites while the subject is standing in a consistent, standardized relaxed pose as per the Photography Manual.

If no injections in a particular buttock (right/left) are given at a treatment visit (for example, a treatment visit eg, Treatment Visit 2), subjects will still be assessed for retreatment in the contralateral buttock at that visit (Treatment Visit 2) if the buttock was treated during Treatment Visit 1. When the subject returns for Treatment Visit 3, each of the buttocks will again be evaluated by the subject (using PR-PCSS) and Investigator (using CR-PCSS). If the Investigator rates cellulite severity greater than 0 using the CR-PCSS in the eligible buttock(s), then injections will be given.

3.5. Study Drug Administration

The retreatment course of Category I and eligible Category II subjects will consist of 3 treatment sessions separated by 21 days (Day 1, 22, and 43) unless the buttock has no treatable EFP dimples ie, the Investigator rates a score of 0 on the CR-PCSS at Treatment Visit 1, 2 and/or Treatment Visit 3.

Each Category I and eligible Category II subject will receive 12 skin injections (0.07 mg/0.3 mL per injection) for a dose of 0.84 mg and volume of 3.6 mL, in each qualifying buttock in up to two buttocks treated concurrently.

The dosing detail, volume and concentration is explained in Table 5.

Table 5: Study Retreatment (Category I Subjects and Eligible Category II Subjects Only)

Dose per Each Injection [a]	Injection Volume per Each Injection	Number of Injections at Each Treatment Visit	Dose (mg) at Each Treatment Visit	Injection Volume (mL) per Each Treatment Visit	Cumulative EFP Dose
CCH 0.07 mg	0.3 mL	12 per buttock × up to 2 buttocks = up to 24 injections	0.84 mg per buttock × up to 2 buttocks = 1.68 mg (12 injections per buttock × 0.07 mg/injection × up to 2 buttocks)	3.6 mL per buttock × up to 2 buttocks = up to 7.2 mL (24 injections × 0.3 mL)	5.04 mg (3 treatment visits × 0.84 mg per buttock × up to 2 buttocks)

[a] Each injection of study drug is 0.3 mL administered as three 0.1 mL aliquots.

3.6. Determination of Sample Size

The study will rollover subjects who completed the respective double-blind studies and are willing to participate in the current study until the double-blind studies are unblinded, after which only active subjects (approximately 420 subjects who received CCH in the double-blind study) will remain in observation in this study. The sample size of approximately 420 should be adequate to determine long-term safety and time to reduction of response to CCH.

3.7. Blinding and Randomization

At the time of entry into the open-label study and at Visit 1 (Day 180) of study EN3835-304 (approximately 6 months after Day 71 of study EN3835-302/303), the subjects, Investigators and site personnel will remain blinded to the study drug received in the double-blind study. Even if the EN3835-302/303 study drug blind is broken by the Sponsor; subjects, Investigators and site personnel in study EN3835-304 will remain blinded until after Day 180 safety and cellulite severity assessments of each treatment area are completed.

3.8. Efficacy Measurements

3.8.1. Digital Photography

The digital photographs are not direct efficacy measurements; however, digital photographs will be utilized in the assessment of certain efficacy measurements. Each buttock will be photographed, using a Sponsor-supplied standardized digital camera in a standardized manner as per the Photography Manual, at the following time points for each of the two buttocks:

- Screening, Day 180, and Confirmation Visits (no markings of dimples or injection sites) for all subjects
- Before and after marking dimples and injection sites (prior to injections) during Treatment Visits (Day 1, 22, and 43) for Category I and/or eligible Category II subjects
- During the Day 71 visit (End of Treatment/Early Termination), Observation Assessments Visits [Day 360, 540, 720, and 1080/End of Study (EOS)], and Confirmation Visits (no dimple or injection site markings)

After the Day 180 Visit and unblinding of the double-blind studies EN3835-302/303, photography will be limited to Category I and Category II subjects.

3.8.2. Subject and Investigator Cellulite Assessments

Investigator cellulite assessments are independent of the subject assessments. All subject cellulite assessments must be completed before the Investigator's cellulite assessments are initiated.

The cellulite assessments will be performed at Screening (Day 71 of double-blind study) and Day 180 for all subjects, and then at all observational visits and treatment visits including Day 71/End of Retreatment for eligible Category I and/or Category II subjects.

3.8.2.1. Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS)

The subjects will rate the severity of the cellulite using the PR-PCSS for each buttock at Screening, and at the beginning of each visit where digital photography will be performed.

The PR-PCSS is a photonumeric scale ranging from 0 to 4 as mentioned in Table 6 below:

Table 6: PR-PCSS for Buttock

Severity Grade	Severity Labels	Description
0	None	No evident cellulite
1	Almost None	A few superficial dimples or ridges
2	Mild	Several dimples or ridges of which most are superficial
3	Moderate	Many dimples or ridges of which most are somewhat deep
4	Severe	A lot of dimples or ridges of which many are deep covering most of the skin area

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

The Investigator will rate the severity of the cellulite using the CR-PCSS for each buttock at Screening, and at the beginning of each visit after the subject has completed her self-assessment using the PR-PCSS.

The CR-PCSS is a photonumeric scale ranging from 0 to 4 as mentioned in Table 7 below:

Table 7: 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

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

Subjects will complete the S-GAIS for each of the buttocks at Screening (within 14 days after Day 71/EOS of double-blind study), Day 180, Retreatment Phase [Screening B and Day 71 (End of Treatment/Early Termination)], and Observation Assessments Visits [Day 360, 540, 720, and 1080/EOS] after they complete the PR-PCSS assessment at the respective visits. The subject will use pretreatment Day 1 digital images (Baseline) from the double-blind studies for comparison.

The subjects will rate the appearance of their treated cellulite a mentioned in Table 8 below. The subject will provide a rating that best represents their answer for each treated buttock.

Table 8: Subject Global Aesthetic Improvement Scale (S-GAIS)

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

The S-GAIS assessment will be occur after the subject has completed the PR-PCSS assessment to avoid introducing potential bias to the static PR-PCSS assessment.

3.8.2.4. Patient Reported Cellulite Impact Scale (PR-CIS)

Subjects will answer the PR-CIS at Screening (within 14 days after Day 71/EOS of double-blind study), Day 180, Retreatment Phase [Screening B and Day 71 (End of Treatment/Early Termination)], and Observation Assessments Visits [Day 360, 540, 720, and 1080/EOS].

The PR-CIS is a 6-item static questionnaire assessing the visual and emotional impact of cellulite (happy, bothered, self-conscious, embarrassed, looking older or looking overweight or out of shape); each item is answered by the subject on an 11-level numerical rating scale from 0 (not at all) to 10 (extremely) while viewing digital images of their buttocks. This assessment is of both the left and right buttock together rather than each individual buttock separately.

A PR-CIS total score and an abbreviated PR-CIS score (excluding question 5) will be derived from 6 individual questions mentioned in Table 9 below:

Table 9: Patient Reported Cellulite Impact Scale (PR-CIS) Questions

Question No.	Question
1	Thinking about the areas selected for treatment, how happy are you with the appearance of your cellulite?
2	Thinking about the areas selected for treatment, how bothered are you by the appearance of your cellulite?
3	Thinking about the areas selected for treatment, how self-conscious are you about the appearance of your cellulite?
4	Thinking about the areas selected for treatment, how embarrassed are you about the appearance of your cellulite?
5	Thinking about the areas selected for treatment, how much older do you look because of your cellulite?
6	Thinking about the areas selected for treatment, how overweight or out of shape do you look because of your cellulite?

3.8.2.5. Subject Satisfaction with Cellulite Treatment Assessment

The subjects will rate their overall satisfaction with the cellulite treatment on both buttocks at Screening (within 14 days after Day 71/EOS of double-blind study), Day 180, Retreatment Phase [Screening B and Day 71 (End of Treatment/Early Termination)], and Observation Assessments

Visits [Day 360, 540, 720, and 1080/EOS] while reviewing digital images of their buttocks. Subjects will provide a rating that best represents their answer. This assessment is of both the left and right buttock rather than each individual buttock separately.

The subjects will rate their *satisfaction level of the results of the cellulite treatment* as mentioned in Table 10 below:

Table 10: Subject Satisfaction with Cellulite Treatment Assessment – Buttocks

Rating	Description
+2	I am very satisfied with the cellulite treatment on my buttocks.
+1	I am satisfied with the cellulite treatment on my buttocks.
0	I am neither dissatisfied nor satisfied with the cellulite treatment on my buttocks.
-1	I am dissatisfied with the cellulite treatment on my buttocks.
-2	I am very dissatisfied with the cellulite treatment on my buttocks.

3.8.2.6. Subject Self-Rating Scale (SSRS)

Subject satisfaction with their appearance in association with cellulite on the buttocks will be assessed using the SSRS at Screening (within 14 days after Day 71/EOS of double-blind study), Day 180, Retreatment Phase [Screening B and Day 71 (End of Treatment/Early Termination)], and Observation Assessments Visits [Day 360, 540, 720, and 1080/EOS]. The SSRS scale ranges from 0 (extremely dissatisfied) to 6 (extremely satisfied).

No photographs or reference to previous ratings or evaluations will be used. Subjects will be given a list of response options and they will provide a rating that best represents their answer. This assessment is of both the left and right buttock rather than each individual buttock separately.

The subjects will answer their satisfaction level of the appearance of the buttocks at the present time whether or not in their judgement it is due entirely to EN3835 treatment as mentioned in Table 11 below:

Table 11: Subject Self-Rating Scale (SSRS)

Rating	Response Option
6	Extremely satisfied
5	Satisfied
4	Slightly satisfied
3	Neither satisfied nor dissatisfied
2	Slightly dissatisfied
1	Dissatisfied
0	Extremely dissatisfied

3.9. Medical History

The medical history of the subjects was collected in the respective double-blind study; however only newly discovered medical history (events/procedures that occurred prior to enrollment in study EN3835-302/303).

3.10. Prior/Concomitant Medications and Procedures

Any medications (including Over-the-counter (OTC) medication) taken from the last visit of the double-blind will be recorded.

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

3.10.1. Prohibited Medications and Procedures

For Category I subjects and eligible Category II subjects who opted for retreatment, the following medications are prohibited during the retreatment phase of the study:

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

Procedures listed in exclusion criterion #1 for all subjects up through the Day 180 Visit, and exclusion criterion #1 for Category I and Category II subjects are prohibited for all subjects up through the Day 180 visit, Category I and Category II subjects during the study, respectively.

For Category I, Category II, and Category III subjects, the use of creams, procedures, etc. as outlined in the exclusion criteria (section 3.2.2) is prohibited during the study.

3.11. Safety Assessments

3.11.1. Adverse Events (AE)

All Adverse Events (AE) occurring after signing the informed consent are to be recorded on the AE pages of the case report form (CRF). This includes any new signs, symptoms, injury or illness, including increased severity of previous existing signs, symptoms, injury, or illness. Any medical conditions occurring between completion of the double-blind studies and the screening visit of this study will be considered AE and will be recorded and evaluated for seriousness. The ongoing AE's from EN3835 302/303 studies at the time screening of this study will also be imported.

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)

Serious adverse event are those AEs 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 bruising, ecchymosis, hematomas, and contusions that occur remote to the site of drug administration, or any hypersensitivity reactions, including anaphylaxis, will be recorded as an AE of special interest and reported as an AE or SAE as appropriate.

In addition, local AEs associated with the injection site (whether the site was injected in the double-blind study (EN3835-302/303) or in this open-label study (EN3835-304)), including acute (eg, erythema, bruising, pain, nodules/mass, ulceration, erythema, pruritus, swelling, and/or induration) and/or chronic (eg, skin thickening, fibrosclerosis, peau d'orange changes), cutaneous adverse events, will be recorded.

3.11.2. Clinical Safety Laboratory Tests

Blood and urine samples will be collected for testing the following clinical laboratory parameters during the Screening (Day 71 of double-blind study), Day 180, and during the Retreatment Phase [Screening B and Day 71 (End of Treatment/Early Termination)].

Table 12: 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 (CO_2)	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 or SAE as appropriate.

3.11.2.1. Pregnancy Test

For women of child bearing potential, a serum pregnancy test will be performed at Day 71 of the double-blind studies, the results of which will transferred to the Screening Visit of this open-label study. Additionally, a serum pregnancy test will be performed at the Screening B visit of any Category I and/or eligible Category II subject for the Treatment phase of the study.

Urine pregnancy tests will be performed at Day 180 for all subjects and during Treatment Visits (Day 1, 22, and 43) for subjects who received retreatment (Category I, eligible Category II subjects). Additional urine pregnancy tests will be performed at the discretion of the Investigator when required.

3.11.3. Vital Signs

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

Vital signs measurements (except height and body weight) will be taken at Screening (Day 71 of double-blind study), Day 180, and during Retreatment Phase [Screening B, Day 1, 22, 43, and 71 (End of Treatment/Early Termination]. On the day of treatment (Day 1, 22, and 43), vital signs (except body temperature) will be measured up to 4 hours prior to study drug administration and at 15 and 30 minutes after the last injection; body temperature will be measured at 4 hours prior to study drug administration and at 30 minutes after the last injection.

Height and body weight measurements will be taken at Screening (Day 71 of double-blind study) for all subjects. Additionally, body weight will be measured at Day 180 and during treatment visits [Day 22, 43 and 71 (End of Treatment/Early Termination] before injection.

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

3.11.4. 12-Lead Electrocardiogram (ECG)

A 12-Lead ECG will be performed during the Screening B Visit if Screening B is performed greater than 12 months of an ECG obtained during the double-blind study. During the ECG measurement, the subject will be in a resting position.

ECG result will be interpreted by the Investigators and graded as:

- Normal
- Abnormal, not clinically significant OR
- Abnormal, clinically significant

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

3.11.5. Physical Examination

A complete physical examination (by body system) will be performed at Screening (Day 71 of double-blind study) for all subjects. If the Screening Visit is performed greater than 14 days after the subject's Day 71 of the double-blind study, then an additional evaluation will be conducted at Screening B during the retreatment phase.

This evaluation will include an examination of general appearance, head, eyes, ears, nose and throat, skin, neck, chest, heart, lungs, breasts, abdomen, back, extremities, skin (excluding cellulite), genitalia, lymph nodes, central nervous system, and musculoskeletal system. 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.

3.11.6. Immunogenicity Samples

Immunogenicity variables include anti-AUX-I/anti-AUX-II binding (ie, anti-drug) and neutralizing antibody results. Serum samples will be collected at Screening (Day 71 of double-blind study), Treatment visits (Day 22, 43, and 71), and Observation Visits (Day 360, 540, 720, and 1080/EOS) for all subjects for the determination of serum anti-AUX-I and anti-AUX-II antibody levels.

For Category I subjects and/or eligible Category II subjects receiving retreatment, a subset (based on every other sample from the Treatment Visit 4 upper and lower quartiles of binding antibody titers) of subject samples will be tested for neutralizing antibodies from these visits.

4. STUDY PARAMETERS

4.1. Subject Disposition

Subjects will be considered as completing the study if they complete all the safety assessment visits up to 3 years (1080 days) after completing Day 71 of the double-blind studies (EN3835-302 or EN3835-303). Subjects will be considered as completing the retreatment phase of the study if they complete all the treatment sessions and the Day 71 Visit of the retreatment course (if they are eligible for retreatment).

A subject can discontinue the study prematurely; the discontinuation date and reason of early discontinuation will be recorded in eCRF. If a subject discontinues early from the study, then all EOS procedures will be conducted on the day of discontinuation. If, however, a subject withdraws consent, no EOS procedures and assessments are required (but are encouraged to reduce missing information) except the collection of adverse events (AE) information. Discontinued from the retreatment phase, are the subjects who discontinued the treatment prior to the completion of all the treatment session (unless the investigator assessed the buttock(s) as dimple free) or the Day 71 visit of the retreatment course.

The subjects may screen fail after signing informed consent form (ICF) and prior to Day 180, the reason of screen failure prior to Day 180 will also be recorded in eCRF.

The disposition data will also be evaluated at each time period as:

- Day 71/EOS Phase 3 – Day 180 (M6)
- Day 180 (M6) – Day 360 (M12)
- Day 360 (M12) – Day 540 (M18)
- Day 540 (M18) – Day 720 (M24)
- Day 720 (M24) – Day 1080 (M36)

The subjects will be considered as completing a particular time period if they complete study assessments as per protocol schedule of events. Discontinued subjects are those subjects who discontinued the study prior to the time period.

4.2. Protocol Deviations

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

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

- Ineligible subject/study entry criteria not satisfied
- Informed consent not completed correctly
- Non-compliance with study treatment
- Prohibited medications/procedure
- Visit/procedure missing or out of window

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 prior medication is defined as any medication taken from the last visit of the double-blind study through the signing of informed consent form at Screening A in this study. A concomitant medication is any medication starting on or after the informed consent form at Screening A is signed for this study.

4.4. Efficacy Parameters

Cellulite assessments using the PR-PCSS, CR-PCSS, S-GAIS, PR-CIS, Subject satisfaction with cellulite treatment assessment, and SSRS will be performed on the eligible buttock(s).

If both the buttocks are eligible then the assessments using the PR-PCSS, CR-PCSS, and S-GAIS will be evaluated separately for each buttock, and assessments using PR-CIS, Subject satisfaction with cellulite treatment assessment, and SSRS will be evaluated for two buttocks.

4.4.1. Change from Baseline in Cellulite Severity Scale (PR-PCSS and CR-PCSS)

The change from Day 1 of the double-blind study for PR-PCSS and CR-PCSS is defined as PR-PCSS and CR-PCSS score at respective visit minus PR-PCSS and CR-PCSS score at Day 1 of the double-blind study.

The change from Day 71/EOS of the double-blind study for PR-PCSS and CR-PCSS is defined as PR-PCSS and CR-PCSS score at respective visit minus PR-PCSS and CR-PCSS score at Day 71/EOS of the double-blind study.

The change from Day 1 of retreatment period of this study for PR-PCSS and CR-PCSS is defined as PR-PCSS and CR-PCSS score at respective visit minus PR-PCSS and CR-PCSS score at Day 1 of retreatment period of this study.

4.4.2. Reduction / Improvement of Response in Cellulite Severity Scale (PR-PCSS and CR-PCSS)

Reduction of Response will be assessed separately for prior to retreatment (including Through Day 180 Observational Period) and after retreatment. Refer below Table 13 for definitions of reduction of response:

Table 13: Reduction of Response

Variables	Prior to Retreatment (including Through Day 180 Observational Period)	After Retreatment
Reduction of Response	Worsening of cellulite severity improvement on PR-PCSS or CR-PCSS ratings in this study prior to retreatment compared to the score at Day 71/EOS (or Day 1) in the double-blind study. This reduction is also referred as a Partial Loss of Response.	Worsening of cellulite severity improvement on PR-PCSS or CR-PCSS ratings during the observation phase after retreatment compared to the score at Day 71/End of Treatment Session in the open-label treatment phase.
2-level Reduction	Worsening of cellulite severity improvement at least by 2-level on PR-PCSS or CR-PCSS ratings in this study prior to retreatment, compared to the score at Day 71/EOS (or Day 1) in the double-blind study (ie, change from baseline PR-PCSS and/or CR-PCSS rating of 2, 3, or 4)	Worsening of cellulite severity improvement at least by 2-level on PR-PCSS or CR-PCSS ratings during the observation phase after retreatment compared to the score at Day 71/End of Treatment Session in the open-label treatment phase (ie, change from baseline PR-PCSS and/or CR-PCSS rating of 2, 3, or 4)
1-level Reduction	Worsening of cellulite severity improvement by only 1-level on PR-PCSS or CR-PCSS ratings in this study after retreatment compared to the score at Day 71/EOS (or Day 1) in the double-blind study (ie, change from baseline PR-PCSS and/or CR-PCSS rating of 1)	Worsening of cellulite severity improvement only by 1-level on PR-PCSS or CR-PCSS ratings during the observation phase after retreatment compared to the score at Day 71/End of Treatment Session in the open-label treatment phase (ie, change from baseline PR-PCSS and/or CR-PCSS rating of 1)
Composite Reduction	Composite Reduction will be assessed using both the subject PR-PCSS responder classification and investigator CR-PCSS responder, where both the scales have same level of reduction. If the classification is missing for 1 or both components (ie, the PR-PCSS component or the CR-PCSS component), then the composite responder classification is missing for that visit.	
2-level Composite Reduction	Worsening of cellulite severity improvement by at least 2-level on both PR-PCSS and CR-PCSS ratings compared to the score at Day 71/EOS (or Day 1) in the double-blind study.	Worsening of cellulite severity improvement by at least 2-level on both PR-PCSS and CR-PCSS ratings compared to the score at Day 71/End of Treatment Session in the open-label treatment phase.
1-level Composite Reduction	Worsening of cellulite severity improvement by only 1-level on both PR-PCSS and CR-PCSS ratings compared to the score at Day 71/EOS (or Day 1) in the double-blind study.	Worsening of cellulite severity improvement by only 1-level on both PR-PCSS and CR-PCSS ratings compared to the score at Day 71/End of Treatment Session in the open-label treatment phase.
Time to Composite Reduction of Response by 2-level	Number of days from the time of assessing composite improvement in cellulite severity on PR-PCSS and CR-PCSS at Day 71/EOS (or Day 1) in the double-blind study to the study visit prior to retreatment at which at least 2 level of worsening of response in both PR-PCSS and CR-PCSS ratings is observed for the first time.	Number of days from the time of assessing composite improvement in cellulite severity on PR-PCSS and CR-PCSS at Day 71/End of Treatment Session in the open-label treatment phase to the study visit during observation phase after retreatment at which at least 2 level of worsening of response in both PR-PCSS and CR-PCSS ratings is observed for the first time.
Time to Composite Reduction of Response by 1-level	Number of days from the time of assessing composite improvement in cellulite severity on PR-PCSS and CR-PCSS at Day 71/EOS (or Day 1) in the double-blind study to the study visit prior to retreatment at which only 1-level of worsening of response in both PR-PCSS and CR-PCSS ratings is observed for the first time.	Number of days from the time of assessing composite improvement in cellulite severity on PR-PCSS and CR-PCSS at Day 71/End of Treatment Session in the open-label treatment phase to the study visit during observation phase after retreatment at which only 1-level of worsening of response in both PR-PCSS and CR-PCSS ratings is observed for the first time.

Table 13: Reduction of Response (Continued)

Variables	Prior to Retreatment (including Through Day 180 Observational Period)	After Retreatment
Complete Loss of Response	Worsening of cellulite severity improvement on PR-PCSS and CR-PCSS ratings in this study prior to retreatment compared to the score at Day 71/EOS in the double-blind studies, where cellulite severity returns to baseline levels of the double-blind studies (ie, Day 1 of the double-blind studies) or worse.	Worsening of cellulite severity improvement on PR-PCSS and CR-PCSS ratings compared to the score at Day 71/End of Treatment Session in the open-label treatment phase, where cellulite severity returns to baseline levels of the retreatment phase (ie, Day 1 of the open-label retreatment phase) or worse.
Time to Complete Loss of Response	Number of days from the time of assessing composite improvement in cellulite severity on PR-PCSS and CR-PCSS at Day 71/EOS in the double-blind study to the study visit prior to retreatment at which the complete loss of response in both PR-PCSS and CR-PCSS is observed.	Number of days from the time of assessing composite improvement in cellulite severity on PR-PCSS and CR-PCSS at Day 71/End of Treatment Session in the open-label treatment phase to the study visit during observation phase after retreatment at which the complete loss of response in both PR-PCSS and CR-PCSS is observed.
2-level Improvement	Improvement in cellulite severity at least by 2 levels on PR-PCSS or CR-PCSS ratings from Day 1 of double-blind study (ie, change from baseline PR-PCSS and/or CR-PCSS rating of -2, or -3).	Improvement in cellulite severity at least by 2 levels on PR-PCSS or CR-PCSS ratings after receiving the retreatments compared to the corresponding rating at Day 1 of the Treatment Session of this study (ie, change from baseline PR-PCSS and/or CR-PCSS rating of -2, or -3).
1-level Improvement	Improvement in cellulite severity at least by 1 levels on PR-PCSS or CR-PCSS ratings from Day 1 of double-blind study (ie, change from baseline PR-PCSS and/or CR-PCSS rating of -2, or -3).	Improvement in cellulite severity at least by 1 levels on PR-PCSS or CR-PCSS ratings after receiving the retreatments compared to the corresponding rating at Day 1 of the Treatment Session of this study (ie, change from baseline PR-PCSS and/or CR-PCSS rating of -2, or -3).
2-level Responder	Improvement in the PR-PCSS or CR-PCSS ratings of at least 2 levels compared to the ratings at Day 1 of double-blind study.	Improvement in the PR-PCSS or CR-PCSS ratings of at least 2 levels compared to the ratings at Day 1 of the Treatment Session of this study.
1-level Responder	Improvement in the PR-PCSS or CR-PCSS ratings of at least 1 levels compared to the ratings at Day 1 of double-blind study.	Improvement in the PR-PCSS or CR-PCSS ratings of at least 1 levels compared to the ratings at Day 1 of the Treatment Session of this study.
2-level Composite Responder	Subject who is both 2-level PR-PCSS responder and a 2-level CR-PCSS responder.	
1-level Composite Responder	Subject who is both 1-level PR-PCSS responder and a 2-level CR-PCSS responder.	

Note: If the classification is missing for 1 or both components (ie, the PR-PCSS component or the CR-PCSS component), then the composite responder classification is missing for that visit.

4.4.3. Patient Reported Cellulite Impact Scale Total Score

A PR-CIS total score and an abbreviated PR-CIS score (excluding question 5) will be derived from 6 individual questions (refer to section 3.8.2.4) for a region, ie, two buttocks during evaluation.

The PR-CIS total score will be derived by adding the ratings of the 6 items on the scale. Item #1 on the PR-CIS asking – "how happy the subject is about their appearance of cellulite" will be reversed by subtracting the subject's reported assessment from 10 (ie, for purposes of the composite, scoring for the "happy" question is reversed (reflected) to make it directionally consistent with the other questions). In this manner, a higher number on 6 of the PR-CIS questions will reflect a more negative impact.

The PR-CIS total score will range from 0 to 60 with higher numbers reflecting more negative impact from the cellulite. If scores on two or less of the 6 items are missing, then the PR-CIS total score will be calibrated to 6 and computed as:

- Total PR-CIS Score = (Sum of the Scores ÷ Number of questions answered) x 6

If scores on three or more of the 6 items are missing, then the PR-CIS total score will be set to missing.

Similarly, the PR-CIS abbreviated total score will be derived by adding the sum of the five items (Items #1-4 and Item #6) on the scale (note that for the abbreviated total score Item #1 score should be replaced by the value generated by subtracting the item score from 10). The PR-CIS abbreviated total score will range from 0 to 50 with higher numbers reflecting more negative impact from the cellulite. If scores on two or less of the 5 items are missing, the PR-CIS abbreviated total score will be computed as:

- Abbreviated total PR-CIS Score = (Sum of the Scores ÷ Number of questions answered) x 5

If scores on three or more of the five items are missing, then the PR-CIS abbreviated total score will be set to missing.

4.4.3.1. Change from Baseline of PR-CIS Item or Total or Abbreviated Total Scores

The change from Day 1 of the double-blind study for PR-CIS is defined as PR-CIS score (item or total or abbreviated total) at respective visit minus PR-CIS score at Day 1 of the double-blind study.

The change from Day 71/EOS of the double-blind study for PR-CIS is defined as PR-CIS score (item or total or abbreviated total) at respective visit minus PR-CIS score at Day 71/EOS of the double-blind study.

The change from Day 1 of retreatment period for PR-CIS score (item or total or abbreviated total) will be the visit score minus the Day 1 of retreatment period score.

For Item #1, a more positive change in score indicates a greater improvement of impact of the cellulite on subject's happiness while for other items a more negative change in score indicates a greater reduction of impact of the cellulite on subject's life.

4.4.3.2. Responders based on Baseline PR-CIS Item or Total or Abbreviated Total Scores

A PR-CIS (item or total or abbreviated total) responder with respect to Day 1 of double-blind study is defined as a subject with a reduction in the PR-CIS score (item or total or abbreviated total) of at least 2 from Day 1 of double blind study at an evaluation time point.

A PR-CIS (item or total or abbreviated total) responder with respect to Day 71/EOS of double-blind study is defined as a subject with a reduction in the PR-CIS score (item or total) of at least 2 from Day 71/EOS of double blind study at an evaluation time point.

A PR-CIS (item or total or abbreviated total) responder with respect to Day 1 of retreatment period of this study is defined as a subject with a reduction in the PR-CIS score (item or total) of at least 2 from Day 1 of retreatment period of this study at an evaluation time point.

4.4.4. Subject Global Aesthetic Improvement Scale

The S-GAIS rating will be obtained from the subject's assessments of eligible buttock(s). If both the buttocks are eligible then S-GAIS will be evaluated separately for each buttock (left and right).

- **2-level S-GAIS Responder** is defined as a subject with S-GAIS rating of at least 2 (ie, 2, or 3) at an evaluation time point.
- **1-level S-GAIS Responder** is defined as a subject with S-GAIS rating of at least 1 (ie, 1, 2, or 3) at an evaluation time point.

4.4.5. Subject Satisfaction with Cellulite Treatment Assessment

The subject satisfaction with cellulite treatment rating will be obtained from the subject's assessments of eligible buttock(s). If both the buttocks are eligible then assessment will be evaluated for two buttocks.

- A responder is defined as subjects with a response of "Satisfied" or "Very Satisfied" in the subject satisfaction with cellulite treatment assessment during evaluation.

4.4.6. Subject Self-Rating Scale

The SSRS rating score is obtained from the subject's assessments of eligible buttock(s). If both the buttocks are eligible then assessment will be evaluated for two buttocks.

- A 1-Level SSRS responder is defined as a subject with at least slightly satisfied (ie, slightly satisfied [4], very satisfied [5] or extremely satisfied [6]) with her appearance of the cellulite on her buttocks during evaluation.
- A 2-Level SSRS responder is defined as a subject with at least very satisfied (ie, very satisfied [5] or extremely satisfied [6]) with her appearance of the cellulite on her buttocks during evaluation.

4.5. Safety Parameters

4.5.1. 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).

4.5.1.1. Adverse Events during 180 Day Observation Phase

All AEs recorded from the day of screening (on or after Day 71/EOS of double-blind study) until they attain the Open-label Period study visit and any ongoing AEs from EN3835-302/303 studies at the time of screening (on or after Day 71/EOS of double-blind study) will be summarized. All changes in medical history occurring between completion of study EN3835-302/303 and the Screening Visit of study EN3835-304 will be considered AEs.

4.5.1.2. Adverse Events during Open-label Period

Adverse Event Categorization Before Retreatment

The AEs will be associated with time periods in the open label study period based on the start date of the AE compared to time period start date, as below:

- Start of Open-label Period – <Day 360 (M12)
- ≥Day 360 (M12) – <Day 540 (M18)
- ≥Day 540 (M18) – <Day 720 (M24)
- ≥Day 720 (M24) – <Day 1080 (M36)

Adverse Event Categorization after Retreatment

An AE will be associated with a treatment session during the retreatment session based on the start date of the AE compared to the date of the injections.

- AEs (which occur or worsen) with a start date between the Day 1 visit date and the day prior to the next dose or, if no further dose, the Day 71 visit date, will be associated with Treatment Session 1.
- If study drug is administered at the Day 22 visit, AEs (which occur or worsen) with a start date between the Day 22 visit date and the day prior to the next dose or, if no further dose, the Day 71 visit date, will be associated with Treatment Session 2.
- If study drug is administered at the Day 43 visit, AEs (which occur or worsen) with a start date between the Day 43 visit date and the Day 71 visit date will be associated with Treatment Session 3.
- AEs with a start date on or after Day 71 of retreatment will be aligned with observational assessment visits as, AE occurring in time period:
  - ≥Day 71 of retreatment – <Day 360 (M12)
  - ≥Day 360 (M12) – <Day 540 (M18)
  - ≥Day 540 (M18) – <Day 720 (M24)
  - ≥Day 720 (M24) – <Day 1080 (M36)

Refer to section 6.3.1.1 to identify AE time period status when the start date of an AE is unknown.

4.5.1.3. Intensity of Adverse Events

Intensity (or severity) of AEs will be graded as “Mild”, “Moderate” or “Severe”. For AEs with missing severity, the most severe assessment will be imputed for analyses, following worst case principle. If the intensity of an AE changes, then the most severe intensity during the continuous episode will be recorded.

4.5.1.4. Relationship to Study Drug

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

- Not related

- Unlikely related
- Possibly related
- Probably related

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

The ongoing AE's from EN3835 302/303 studies at the time screening will be imported in the open label study and their relationship with study drug in EN3835 302/303 will also be classified as above.

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

4.5.2. Potentially Clinically Important Laboratory Values

Potentially clinically important (PCI) laboratory values are presented in Table 14 below:

Table 14: Potentially Clinically Important Laboratory Criteria

Parameter	PCI Low: Less than or equal to	PCI High: Greater than or equal to
Hemoglobin (g/L)	100	190
Hematocrit (%)	30	60
Platelets (10^9/L)	100	650
ALT (U/L)		3×ULN
AST (U/L)		3×ULN
Creatinine (µmol/L)		300
BUN (mmol/L)		12

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

4.5.3. 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 15 below:

Table 15: 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

4.5.4. 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.

5. ANALYSIS POPULATIONS

The study will use following analyses population for data summarization.

Table 16: Analysis Population

Population	Definition	Displays
Day-180 Observational Population	The Day-180 Observational Population includes all rollover subjects from studies EN3835-302/303.	The protocol deviations, demographic characteristics and safety analysis for the data obtained from Screening to Day 180 will be based on this population. The reduction of response, complete loss of response, and all cellulite assessments (ie, changes in CR-/PR-PCSS, PR-CIS, S-GAIS, SSRS, and subject satisfaction with cellulite treatment at Day 180 will be summarized.
Prior to Day 180 Population	Prior to Day 180 Population includes all subjects who did not meet inclusion criteria #2 or inclusion criteria #5 or those who withdrew from the study due to SAE/AE, or lost to follow-up prior to Day 180.	The protocol deviations, demographic characteristics and safety analysis for the data obtained from Screening to Day 180 will be based on this population.
Open Label Observation Population	The Open Label Observation Population includes all subjects who enter the open-label study and received active CCH in EN3835-302 or EN3835-303. This population will include all Category I, II, and III subjects including the subjects who received retreatment in the Open-label Period.	The protocol deviations, demographic characteristics and safety parameters for the open label period prior to retreatment will be summarized based on this population.
Time to Reduction of Response (TRR) Population Before Retreatment	The TRR Population Before Retreatment includes all subjects who have at least a 1-level or 2-level improvement in both CR-PCSS and PR-PCSS ratings during the double-blind study for either/both treated buttocks. This population will include Category I and II subjects. Reduction of response will be evaluated separately for subjects who have at least a 1-level and 2-level improvement in both CR-PCSS and PR-PCSS ratings during the double-blind study in each treated buttock. The reduction of response prior to retreatment will be analyzed using this population.	The analyses of cellulite assessments prior to retreatment, and demographic characteristics will be based on this population.

Table 16: Analysis Population (Continued)

Population	Definition	Displays
Open Label Retreated (OLR) Population	The OLR Population includes all subjects in TRR population who are retreated in the open label period of this study.	The analyses of cellulite assessments after retreatment ie, improvement of response during retreatment phase (Day 1 to Day 71+5 days of retreatment), study drug exposure during retreatment, Safety assessments after retreatment will be based on this population.
Open Label Not Retreated (OLNR) Population	The Open Label Not Retreated Population includes all subjects in TRR Population who are NOT retreated in the open label period of study.	All analyses for change from baseline in Day 1, or Day 71, and responder analysis based on this population will be performed
Time to Reduction of Response (TRR) Population After Retreatment	The TRR Population After Retreatment includes all subjects in OLR Population who have at least 1 level or 2-level improvement in both CR-PCSS and PR-PCSS ratings at Day 71/End of Treatment Session in the open label retreatment period. Reduction of response will be evaluated separately for subjects who have at least a 1-level and 2 level improvement in both CR-PCSS and PR-PCSS ratings during the open label treatment period in each treated buttock. The reduction of response after retreatment will be analyzed using this population.	The reduction of response in open label retreatment period compared to the score at Day 71 of retreatment period will be based on this population.

6. STATISTICAL METHODS

6.1. General Methodology

All summary tables and data listings will be prepared using version 9.4 or later of statistical analysis software (SAS®) software.

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

- Min and max: same number of decimal places as the raw data.
- Mean and median: one more decimal place than the raw data.
- SD/SE: two more decimal places than the raw data.
- Percentages will be displayed with one decimal precision. A zero count will not have the associated percentage presented on the table (ie, no 0%).
- The standard form of a percentage 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 "footer" of explanatory notes that will indicate, when applicable:

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

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

Null summary tables will be presented with a note stating that "No Subjects Met Criteria." Subject listings of all data from the CRFs as well as any derived variables will be presented.

6.2. Derived Variables

Refer to Table 17 below for the listing of the derived variables and their definitions for study parameters.

Table 17: 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 1 (retreatment phase)	The date of first injection of study drug during Open-label Period will be considered as relative Day 1 for Category I and II retreated subjects who took retreatment during current study.
Study Day (retreatment phase - for assessment on or after the Day 1)	Study Day will be computed as, Date of Assessment – Date of relative day 1 + 1
Study Day (retreatment phase - for assessment before Day 1)	Study Day will be computed as, Date of Assessment – Date of relative day 1
Relative Day 1 (overall study)	The date of Screening Visit (within 14 days after Day 71/EOS of double-blind study) in this study will be considered as relative Day 1
Study Day (overall study- for assessment on or after the Day 1)	Study Day will be computed as, Date of Assessment – Date of relative day 1 + 1
Baseline for Safety Parameters after Retreatment	For visits prior to/on first day of retreatment, Baseline is defined as the assessment values at Day 71/EOS visit in double-blind studies (EN3835-302/303). For visits after first day of retreatment, baseline is defined as the last non-missing measurement/assessment prior to/on the first dose date of retreatment. 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.

Table 17: Derived Variables and Definition (Continued)

Variable	Definition
Baseline for Safety parameters Before Retreatment	The measurements/assessment performed during Screening Visit of this study (within 14 days after/or Day 71/EOS Visit of double-blind period) will be considered as Baseline.
Baseline for Reduction of response and Improvement in Cellulite Severity (CR-PCSS and PR-PCSS)	**Improvement in Cellulite Severity**: The assessment performed at Day 1 during the retreatment phase will be used as baseline to evaluate improvement in cellulite severity at Day 71 in this study. **Reduction of Response Prior to Retreatment**: The assessment performed at Day 71/EOS visit in the double-blind phase will be used as baseline to evaluate reduction of response for any visits prior to/on first dose date of retreatment in this study. **Reduction of Response After Retreatment**: The assessment performed at Day 71/End of treatment Session in the retreatment phase will be used as baseline to evaluate reduction of response during the observation phase after retreatment.
Baseline for CR-PCSS, PR-PCSS and PR-CIS Score	**At 180 Day Evaluation**: The Screening assessment done within 14 days of Day 71/EOS of double-blind period will be used as baseline for 180 Day Evaluation period. **Before Retreatment**: The Screening assessment done within 14 days of Day 71/EOS of double-blind period will be used as baseline for open-label period for subjects in TRR population who are not retreated, and until the point prior to retreatment for the subjects who are retreated. **After Retreatment**: The assessments at Screening B/unscheduled assessment or Day 1 of the retreatment phase prior to/on the first dose date of retreatment in this study will be used as baseline.
Baseline for S-GAIS and Subject Satisfaction with Cellulite Treatment	The pretreatment Day 1 digital images from the double-blind study (EN3835-302/303) will be used as baseline.
Change from Baseline	Change from baseline will be derived as, post-baseline visit/time point value – the baseline value.
Time to reduction of response prior to retreatment (duration in days)	Date of visit where reduction is detected first – Date of Day 71/EOS of double-blinded studies 302/303
Time to reduction of response after retreatment (duration in days)	Date of visit where reduction is detected first – Date of Day 71/End of Treatment Session of open-label retreatment phase
Time to Complete Loss of Response prior to retreatment (duration in days)	Date of visit where complete loss of response reduction is detected first – Date of Day 71 of double-blinded studies 302/303 OR Date of Day 71/End of Treatment Session of open-label retreatment phase
Time to Complete Loss of Response after retreatment (duration in days)	Date of visit where complete loss of response reduction is detected first – Date of Day 71/End of Treatment Session of open-label retreatment phase
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.

Table 17: Derived Variables and Definition (Continued)

Variable	Definition
Time in Study	Last date in study – Date of Screening visit (relative day 1 overall study) + 1
Duration of AE	AE end date – AE start date + 1
AE Onset Day (retreatment phase)	AE start date - Date of first injection + 1
AE Onset Day (overall study)	AE start date - Date of Screening Visit (relative day 1 overall study) + 1

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 of these subjects until the point of discontinuation will be summarized. The missing baseline assessment will not be imputed.

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

Subjects who discontinue early will be requested to complete all EOS 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 worst case principle. Missing severity of an AE will be summarized as a severe AE.

Immunogenicity 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.

PR-CIS total score when scores are missing

If scores on at least two of the 6 items are missing, then PR-CIS total score will be calibrated to 6 and computed as:

- Total PR-CIS Score = (Sum of the Scores ÷ Number of question answered) x 6

If scores on three or more of the six items are missing, then the PR-CIS total score will be set to missing.

PR-CIS abbreviated total score when scores are missing

If scores on at least of the 5 items are missing, the PR-CIS abbreviated total score will be computed as:

- Abbreviated total PR-CIS Score = (Sum of the Scores ÷ Number of question answered) x 5

If scores on three or more of the five items are missing, then the PR-CIS abbreviated total score will be set to missing.

Composite response when PR-PCSS and/or CR-PCSS component missing

If the classification is missing for 1 or both components (ie, the PR-PCSS component or the CR-PCSS component), then the composite responder classification is missing for that visit.

6.3.1. Imputation of Partial Dates

6.3.1.1. Adverse Event Status for Completely Unknown AE Start Date

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

- If the AE onset date is unknown and the end date is on or after Day 71/EOS visit date of double-blind studies but before start of open-label period for the subjects who moved to open-label period OR end date is on or after Day 71/EOS visit date of double-blind studies for subjects who didn't enter open-label period, then the AE will be associated with 'Day 71/EOS Phase 3 – until start of open-label period.
- If the AE onset date is unknown and the end date is on or after start of Open-label period but before M12 assessment date, then the AE will be associated with 'Start of Open-label period – Day 360 (M12)' period.
- If the AE onset date is unknown and the end date is on or after M12 visit date but before M18 assessment date, then the AE will be associated with 'Day 360 (M12) – Day 540 (M18)' period.
- If the AE onset date is unknown and the end date is on or after M18 visit date but before M24 assessment date, then the AE will be associated with 'Day 540 (M18) – Day 720 (M24)' period.
- If the AE onset date is unknown and the end date is on or after M24 visit date but before M36 assessment date, then the AE will be associated with 'Day 720 (M24) – Day 1080 (M36)' period.

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

- If the AE onset date is unknown and the end date is on or after Day 1 visit date but before Day 22 visit date, then the AE will be associated with Treatment Session 1.
- If the AE onset date is unknown and the end date is on or after Day 22 visit date but before Day 43 visit date, then the AE will be associated with Treatment Session 2.
- If the AE onset date is unknown and the end date is on or after Day 43 visit date but before Day 71 visit date, then the AE will be associated with Treatment Session 3.
- If the AE onset date is unknown and the end date is on or after Day 71 or ongoing, then the AE will be associated with the observation assessment and will be imputed as:
  - If the AE onset date is unknown and the end date is on or after Day 71 visit date of retreatment session but before M12 assessment date, then the AE will be associated with 'Day 71 – Day 360 (M12)' period.
  - Remaining imputation of missing AE start date after retreatment is similar to the imputation outlined for 'before retreatment'
- If the AE onset date is partly present, month/year will be used to identify the treatment session and time period association.

6.3.1.2. Concomitant Status of Medication for Completely Unknown Start Date

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

- If the medication onset date is unknown and the end date is after the informed consent date or ongoing, then the medication will be considered as concomitant.
- If the medication onset date is unknown and the end date is before the informed consent, then the medication will not be considered as concomitant.
- If both the start and end dates are unknown (or medication 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 informed consent, then the medication will not be considered as concomitant.

6.4. Interim Analyses

As this is an observational study hence no formal interim analyses are planned. However, for Biologics License Application (BLA) submission an analysis for safety, reduction of response and complete loss of response analysis, and other cellulite assessments will be performed at Day 180 data cutoff and data cutoff for 4-month safety update after BLA-submission.

6.5. Treatment Groups and Summary Groups

One (1) retreatment course of CCH is comprised of three treatment sessions will be administered in up to 2 qualifying buttocks in this study.

For the Day-180 Observational Population and Prior to Day 180 Population, the summary tables will be presented by treatment arm (ie, CCH 1.68 mg, Placebo, and Overall) in double-blind studies (EN3835-302/303). For the Open Label Observation Population, the summary tables will be presented by Subject Category (ie, Category I, II, III, and Overall). The summary tables will be presented by Subject Category (ie, Category I, II, and Overall) in OLR Population, OLNR Population and TRR Population Before and After Retreatment.

7. STATISTICAL ANALYSES

7.1. Subject Disposition

The disposition summary table will include the disposition details of all the rollover subjects from the double-blind studies to this open-label extension study. The disposition data will be summarized by number and percentage of subjects for all the subjects in the 180 Day Observational Period and Open-label Period of the study.

For 180 Day Observational Period and Prior to Day 180 Population, the subject disposition summary table will include following information by treatment arm (CCH 1.68 mg, Placebo, and Overall) in the double-blind studies EN3835-302/303:

- Subjects screened
- Screen failure

- Subjects enrolled
- Completed up to Day 180 period
- Completed Day 180 and informed consent form signed for the 3 Year Observational Period
- Completed Day 180 and then Discontinued prior to Open-label Period
- Discontinued in Day 180 period
  - Reason of discontinuation (including subjects who received placebo in the double-blind studies)
- Subject Populations
  - Day 180 Observational Population
  - TRR Population Before Retreatment

For Open-label Period, the subject disposition summary table will include following information subject category (Category I, Category II, Category III, and Overall)

- Subjects entered Open-label Period
- Subject Populations
  - Open Label Observation Population
  - TRR Population Before Retreatment
  - OLR Population
  - OLNR Population
  - TRR Population After Retreatment
- Completed the study
- Discontinued the study
  - Reason of discontinuation
- Discontinued during the following time period
  - Start of Open-label Period– Day 360 (M12)
  - Day 360 (M12) – Day 540 (M18)
  - Day 540 (M18) – Day 720 (M24)
  - Day 720 (M24) – Day 1080 (M36)

In addition, time in the study will be summarized descriptively, this will include all Category I, II, and III subjects (see Table 17 for computation of time in study).

A listing of disposition from 180 Day Observational Period and disposition from Open-Label Period who entered the Open-Label Period will be provided separately. In addition, the discontinued subjects from the study and screen failures from study will also be listed.

A listing of subject excluded from different analysis population will be provided.

7.2. Protocol Deviations

A listing of all protocol deviations will be presented for All Subjects.

7.3. Demographics and Baseline Characteristics

Demographics characteristics will be summarized for the Day-180 Observational Population, Prior to Day 180 Population, Open-label Observation Population, TRR Population Before Retreatment, OLR Population, OLNR Population and TRR Population After Retreatment. For Day-180 Observational Population, the Demographics characteristics will be summarized by treatment arm (ie, CCH 1.68 mg, Placebo, and Overall) in the double-blinded studies (EN3835-302/303), for Open Label Observation Population the demographics characteristics will be summarized by Subject Category (ie, Category I, II, III, and Overall), and for TRR Population Before and After Retreatment and OLR Population the demographics characteristics will be summarized by Subject Category (ie, Category I, II, and Overall).

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.

Age category (<25, 25-34, 35-44, and ≥45 years of age), gender, race and ethnicity will be summarized as categorical variables using frequency counts and percentages.

All demographic characteristics will be presented in listing for All Subjects.

7.4. Medical History

Any newly discovered medical history (ie, events/procedures) that occurred prior to enrollment in study EN3835-302/303 and which was not reported earlier will be listed for all subjects and for Prior to Day 180 Observational Population will be presented separately.

7.5. Prior and Concomitant Medications/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.

Prior and concomitant medications will be summarized for the Day-180 Observational Population and Prior to Day 180 Population by treatment arm (ie, CCH 1.68 mg, Placebo, and Overall). Concomitant medications will be summarized for the Open-label Observation Population by Subject Category (ie, Category I, II, III, and Overall), and OLR Population by Subject Category (ie, Category I, II, and Overall).

The subject listings of prior and concomitant medications/procedures will be presented for All Subjects and for Prior to Day 180 Observational Population will be presented separately.

The separate listings of prior and concomitant medications/procedures and EFP/Cellulite will also be provided for All Subjects as well as for Prior to Day 180 Observational Population.

7.6. Efficacy Analyses

Efficacy parameters in 180 Day Observational Period will be summarized by subject category at treatment area (ie, left and/or right buttock separately) by treatment arm (ie, CCH 1.68 mg, Placebo, and Overall) for subjects in Day 180 Observational Population and Prior to Day 180 Population.

Efficacy parameters in Open Label Period will be summarized by subject category at treatment area (ie, left and/or right buttock separately) for subjects in the TRR Population Before Retreatment and TRR Population after Retreatment separately.

7.6.1. Changes in the PR-PCSS and CR-PCSS from Baseline

For Day 180 visit, the observed and change from Day 1 and Day 71/EOS of double blind study for PR-PCSS and CR-PCSS scores will be analyzed separately during using Day-180 Observational Population,

The PR-PCSS and CR-PCSS ratings and change from Day 1 and Day 71/EOS severity ratings (ie, Day 71/EOS of double-blind study) in Open-label Period will be summarized by treatment area (ie, separately for left and right buttock), assessment visits (baseline and all the post baseline observations) and subject category using counts and percentages at each severity rating and with mean and SD, for subjects in TRR Population Before Retreatment and OLNR Population.

For during and after retreatment period, the same analysis will be repeated using OLR Population.

7.6.2. Reduction of response using PR-PCSS and CR-PCSS Prior to Retreatment

The proportion of subjects or buttocks with reduction of response (refer to section 4.4.1) will be summarized using frequency counts and percentages using TRR Population Before Retreatment and OLNR Population subject category (ie, Category I and II, and Overall) and treatment area (ie, left and/or buttock) at the following visits prior to retreatment: Day 180, Month 12, 18, 24, and 36 where reduction of response is assessed.

The proportions will be computed based upon number of subjects within each category and treatment area remains not-retreated prior to that visit.

The following efficacy end points for reduction of response will be summarized:

- Proportion of subjects with 2-level composite reduction
- Proportion of subjects with 1-level composite reduction
- Proportion of subjects with complete loss of response

The time to composite reduction of response (ie, by 1-level and 2-level separately) and time to complete loss of response (refer to section 4.4.1 for derivation) will be summarized descriptively using TRR Population Before Retreatment and OLNR Population.

The listings of cellulite PR-PCSS and CR-PCSS severity ratings will be provided for All Subjects prior to retreatment.

7.6.3. Reduction of response using PR-PCSS and CR-PCSS after Retreatment

The proportion of subjects with reduction of response (refer to section 4.4.1) will be summarized using frequency counts and percentages using TRR Population after Retreatment by subject category (ie, Category I and II, and Overall) and treatment area (ie, left and/or buttock) at all observation visits after retreatment where cellulite assessments has been performed.

The proportions will be computed based upon number of subjects within each category and treatment area retreated prior to that visit.

The following efficacy end points for reduction of response will be summarized:

- Proportion of subjects with 2-level composite reduction
- Proportion of subjects with 1-level composite reduction
- Proportion of subjects with 2-level reduction on either scale
- Proportion of subjects with 1-level reduction on either scale
- Proportion of subjects with complete loss of response

The time to composite reduction of response (ie, by 1-level and 2-level separately), time to partial response and time to complete loss of response (refer to section 4.4.1 for derivation) will be summarized descriptively using TRR Population after Retreatment.

The listings of cellulite PR-PCSS and CR-PCSS severity ratings will be provided for subjects in OLR Population after Retreatment.

7.6.4. Improvement of Response using PR-PCSS and CR-PCSS

The improvement of response in cellulite severity is assessed in the open-label study for the subjects who received retreatment. The cellulite severity assessment during retreatment phase will be used for this analysis. The proportion of subjects with improvement in response compared to cellulite assessments at Day 1 prior to retreatment (refer to section **Error! Reference source not found.**) will be summarized using frequency counts and percentages using OLR Population by subject category (ie, Category I and II, and Overall) and treatment area (ie, separately for left and right buttock) at Day 22, 43, and 71 following retreatment:

- Proportion of 2-level composite responders
- Proportion of 1-level composite responders
- Proportion of 1-level and 2-level CR-PCSS responders
- Proportion of 1-level and 2-level PR-PCSS responders

The above responder analysis will be repeated considering Day 1 of double blinded study as reference.

The listings of cellulite PR-PCSS and CR-PCSS severity ratings will be provided for subjects in OLR Population after Retreatment.

7.6.5. Changes in the PR-CIS Scores from Baseline

The PR-CIS scores (Each item, total, and abbreviated) will be analyzed separately at Day 180 using Day-180 Observational Population and Prior to Day 180 Population, for the data before retreatment using TRR Population Before Retreatment, and OLNR Population and data for after retreatment using OLR Population.

At Day 180 Evaluation

The observed and/or change from baseline in PR-CIS item scores, total, and abbreviated scores (refer to section 4.4.3) of the subjects in 180 – Day Observational Population will be summarized descriptively by treatment arm (ie, CCH 1.68 mg, Placebo, and Overall) at overall treatment area

(ie, two buttocks). The Screening assessments done at Day 71/EOS visit in the double-blind studies will be used as baseline.

Also, the observed and/or change from Day 1 of double blind studies (302/303) in PR-CIS item scores, total, and abbreviated scores (refer to section 4.4.3) of the subjects up to Day 180 in 180–Day Observational Population and Prior to Day 180 Population will be summarized descriptively by treatment arm (ie, CCH 1.68 mg, Placebo, and Overall) at overall treatment area (ie, two buttocks).

Before Retreatment

The observed and/or change from baseline and change from Day 1 of double-blinded studies in PR-CIS item scores, total, and abbreviated scores (refer to section 4.4.3) of the subjects who did not receive retreatment and the data until the point prior to retreatment for the subjects who are retreated will be summarized descriptively using TRR Population Before Retreatment and OLNR Population by subject category (ie, Category I and II, and Overall) at overall treatment area (ie, two buttocks) and assessment visits: Day 180, Month 12, 18, 24, and 36.

The Screening assessments done at Day 71/EOS visit in the double-blind studies will be used as baseline.

Also, the observed and/or change from Day 1 of double blind studies (302/303) in PR-CIS item scores, total, and abbreviated scores (refer to section 4.4.3) of the subjects who did not receive retreatment and the data until the point prior to retreatment for the subjects in TRR Population and OLNR Population will be summarized descriptively by subject category (ie, Category I and II, and Overall) at overall treatment area (ie, two buttocks).

After Retreatment

The observed and/or change from baseline in PR-CIS item scores, total and abbreviated scores (refer to section 4.4.3) from Day 71 of the retreatment session and other observational visits of the subjects who are retreated in the open label study will be summarized descriptively using OLR Population by subject category (ie, Category I and II, and Overall) at overall treatment area (ie, two buttocks).

The Screening assessments (ie, Screening B) done during the retreatment phase in the open label study will be used as baseline.

The listings of PR-CIS scores for each item along with total and abbreviated scores will be provided separately for All Subjects prior to retreatment and for subjects in OLR Population after Retreatment.

7.6.6. Changes in the PR-CIS Scores from Day 71 Open-label Period

The PR-CIS scores (each item, total, and abbreviated) will also be analyzed for the observational period after retreatment using OLR Population.

The observed and/or change in PR-CIS item scores, total and abbreviated scores (refer to section 4.4.3) at observational visits after retreatment compared to Day 71/End of Treatment Session in open label retreatment phase will be summarized descriptively using OLR Population

by subject category (ie, Category I and II, and Overall) at overall treatment area (ie, two buttocks).

The listings of PR-CIS scores for each item along with total and abbreviated scores will be provided separately for subjects in OLR Population after retreatment.

7.6.7. Responder Analysis based on Baseline PR-CIS Scores

The PR-CIS responders (Each item, Total, and Abbreviated) will be analyzed separately at Day 180 using Day-180 Observational Population, for the data before retreatment using TRR Population Before Retreatment, and data after retreatment using OLR Population.

At Day 180 Evaluation

The proportion of PR-CIS responders based on item scores, total, and abbreviated scores (refer to section 4.4.3) of the subjects in 180 – Day Observational Population will be summarized using frequency counts and percentages by treatment arm (ie, CCH 1.68 mg, Placebo, and Overall) at overall treatment area (ie, two buttocks).

Before Retreatment

The proportion of PR-CIS responders based on item scores, total, and abbreviated scores (refer to section 4.4.3) of the subjects who did not receive retreatment and the data until the point prior to retreatment for the subjects who are retreated will be summarized using frequency counts and percentages for subjects in TRR Population Before Retreatment by subject category (ie, Category I and II, and Overall) at overall treatment area (ie, two buttocks) and assessment visits: Day 180, Month 12, 18, 24, and 36.

After Retreatment

The proportion of PR-CIS responders based on item scores, total and abbreviated scores (ie, based on scores as compared to baseline - refer to section 4.4.3) at Day 71 of the retreatment session and other observational visits of the subjects who are retreated in the open label study will be summarized using frequency counts and percentages for subjects in OLR Population by subject category (ie, Category I and II, and Overall) at overall treatment area (ie, two buttocks).

7.6.8. Responder Analysis based on Day 71 Open-label Period PR-CIS Scores

The proportion of PR-CIS responders based on item scores, total and abbreviated scores (ie, based on scores as compared to Day 71 of open-label period - refer to section 4.4.3) at observational visits after retreatment will be summarized using frequency counts and percentages for subjects in OLR Population by subject category (ie, Category I and II, and Overall) at overall treatment area (ie, two buttocks).

7.6.9. Responder Analysis at each level of improvement in the S-GAIS

The S-GAIS ratings and S-GAIS responders will be analyzed separately up to Day 180 using Day-180 Observational Population, for the data before retreatment using TRR Population Before Retreatment, and data after retreatment using OLR Population.

At Day 180 Evaluation

The proportion of S-GAIS responders (1-level and 2-level) and S-GAIS ratings (-3 to +3) (refer to section 4.4.4) of the subjects in 180 – Day Observational Population will be summarized using frequency counts and percentages by treatment arm (ie, CCH 1.68 mg and Placebo, and Overall) at treatment area (ie, separately for left and right buttock).

Before Retreatment

The S-GAIS response of the subjects who are not-retreated and until the point prior to retreatment for the subjects who are retreated will be evaluated.

The proportion of S-GAIS responders (1-level and 2-level) and S-GAIS ratings (-3 to +3) (refer to SAP section 4.4.4) will be summarized using frequency counts and percentages for subjects in TRR Population Before Retreatment by subject category (ie, Category I and II, and Overall) at treatment area (ie, separately for left and right buttock) and any visits in this study: Day 180, Month 12, 18, 24, and 36.

After Retreatment

The proportion of S-GAIS responders (1-level and 2-level) and S-GAIS ratings (-3 to +3) (refer to SAP section 4.4.4) at Day 71 and other observational visits of the subjects who are retreated in the open label study will be summarized using frequency counts and percentages for subjects in OLR population by subject category (ie, Category I and II, and Overall) at treatment area (ie, separately for left and right buttock).

The listings of subject response for S-GAIS assessments will be provided separately for All Subjects prior to retreatment and for subjects in OLR Population after retreatment.

7.6.10. Responder Analysis in Subject Satisfaction with Cellulite Treatment

The responders in subject satisfaction with cellulite treatment assessments and individual item ratings will be analyzed separately up to Day 180 using Day-180 Observational Population, for the data before retreatment using TRR Population Before Retreatment, and data after retreatment using OLR Population.

Up to Day 180 Evaluation

The proportion of responders in subject satisfaction with cellulite treatment assessments and individual item ratings (-2 to +2) (refer to section 4.4.5) of the subjects in 180 – Day Observational Population will be summarized using frequency counts and percentages by treatment arm (ie, CCH 1.68 mg and Placebo, and Overall) at overall treatment area (ie, two buttocks).

Before Retreatment

The response of the subjects who are not-retreated and until the point prior to retreatment for the subjects who are retreated will be evaluated.

The proportion of responders in subject satisfaction with cellulite treatment assessments and individual item ratings (-2 to +2) (refer to SAP section 4.4.5) will be summarized using frequency counts and percentages for subjects in TRR Population Before Retreatment by subject

category (ie, Category I and II, and Overall) at overall treatment area (ie, two buttocks) and any visits in this study: Day 180, Month 12, 18, 24, and 36.

After Retreatment

The proportion of responders in subject satisfaction with cellulite treatment assessments and individual item ratings (-2 to +2) (refer to SAP section 4.4.5) at Day 71 and other observational visits of the subjects who are retreated in the open label study will be summarized using frequency counts and percentages for subjects in OLR population by subject category (ie, Category I and II, and Overall) at overall treatment area (ie, two buttocks).

The listings of subject satisfaction with cellulite treatment assessments will be provided separately for All Subjects prior to retreatment and for subjects in OLR population after retreatment.

7.6.11. Proportion of subjects at each level of improvement in the SSRS

The SSRS responders and individual item ratings will be analyzed separately at Day 180 using Day-180 Observational Population, for the data before retreatment using TRR Population Before Retreatment, and data after retreatment using OLR Population.

At Day 180 Evaluation

The proportion of SSRS responders (1-level and 2-level) and individual item ratings (0 to 6) (refer to section 4.4.6) of the subjects in 180 – Day Observational Population will be summarized using frequency counts and percentages by treatment arm (ie, CCH 1.68 mg and Placebo, and Overall) at overall treatment area (ie, two buttocks).

Before Retreatment

The SSRS response of the subjects who are not-retreated and until the point prior to retreatment for the subjects who are retreated will be evaluated.

The proportion of SSRS responders (1-level and 2-level) and individual item ratings (0 to 6) (refer to SAP section 4.4.6) will be summarized using frequency counts and percentages for subjects in TRR Population Before Retreatment by subject category (ie, Category I and II, and Overall) at overall treatment area (ie, two buttocks) and any visits in this study: Day 180, Month 12, 18, 24, and 36.

After Retreatment

The proportion of SSRS responders (1-level and 2-level) and individual item ratings (0 to 6) (refer to SAP section 4.4.6) at Day 71 and other observational visits of the subjects who are retreated in the open-label study will be summarized using frequency counts and percentages for subjects in OLR population by subject category (ie, Category I and II, and Overall) at overall treatment area (ie, two buttocks).

The listings of subject response for SSRS assessments will be provided separately for All Subjects prior to retreatment and for subjects in OLR Population after retreatment.

7.7. Safety Analyses

Safety data for subjects who entered the Open-label Periodof the study will be summarized separately before retreatment using Open-label Observation Population, and after retreatment using OLR Population. Safety data from screening to Day 180 will be summarized using Day-180 Observational Population.

7.7.1. Study Drug Exposure

The exposure of study drug will be summarized for Category I and II subjects who received retreatment in this open-label study using OLR Population.

The number of injections of study drug given on Day 1, 22, and 43 during the retreatment phase, will be summarized using frequency counts and percentages by treatment sessions at treatment area (ie, left/right buttock) as:

- Number of subjects had treatment sessions
- Subjects received 12 injections per buttock
- Subjects received less than 12 injections per buttock
- Reason subject received less than 12 injections per buttock

The following will be summarized by treatment sessions at treatment area (ie, left/right buttock) 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 12 injections per treatment area and receiving less than 3 treatment sessions.

7.7.2. Adverse Events

AE 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.

AE 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.

All AE summary tables will include number of occurrences of the adverse events and the count of subjects experienced the AEs.

AEs during 180-Day Observation Session: The AEs recorded from day of screening (within 14 days after or on Day 71/EOS of double-blind study) until start of Open-label Periodand any

ongoing AEs from EN3835-302/303 studies at the time of screening of this study will be summarized by treatment arm (ie, CCH 1.68 mg, Placebo, and Overall) from double-blind studies (EN3835-302/303) using the Day-180 Observational Population and Prior to Day 180 Population.

An overall summary of AE will be presented and will include:

- Any AE
- Any ongoing AEs from EN3835 302/303
- Any AE of special interest
- Any serious AE
- Any mild, moderate and severe AE
- Any EN3835 302/303 study drug related AE
- Any AEs leading to study discontinuation
- Any AEs resulting in death

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

- All AEs
- Ongoing AEs from EN3835 302/303
- All 302/303 study drug related AEs
- AEs by Severity
- Serious AEs
- AEs leading to study discontinuation
- AEs resulting in death
- AEs of Special Interest

Serious and most common non-serious AE 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 preferred term that at least 5% of the subjects reported at least once.

Subject listings of all AEs, serious AEs, AEs leading to study discontinuation, AEs resulting in death and AEs of Special Interest will be provided for subjects in 180 Day Observational Population.

Subject listings of all AEs in 180 Day Observational Period for all screen failure subjects and Prior to Day 180 Population will also be provided.

AEs Before Retreatment: The new AEs recorded on or after Open-label Periodstarts but before retreatment in the open-label study will be summarized for subjects in Open-label Observation Population. This will include AEs of all Category I and II subjects recorded before retreatment and AEs of all Category III subjects.

An overall summary of new AE will be presented by subject category (ie, Category I, II, III, and Overall) and by time period as described in section 4.5.1.2, and will include:

- Any new AE
- Any new AE of special interest
- Any new serious AE

- Any new mild, moderate, and severe AE
- Any new AEs leading to study discontinuation
- Any new AEs resulting in death

The following summary tables will be presented by SOC and PT by subject category (ie, Category I, II, III, and Overall):

- All AEs
- AEs by Severity
- Serious AEs
- AEs leading to study discontinuation
- AEs resulting in death
- AEs of Special Interest

Serious and most common non-serious AE 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 preferred term that at least 5% of the subjects reported at least once.

Subject listings of all AEs, serious AEs, AEs leading to study discontinuation, AEs resulting in death and AEs of Special Interest will be provided.

AEs During and after Retreatment: The new AEs recorded on or after retreatment in the open label study will be summarized for subjects in OLR Population. This will include AEs of all Category I and II subjects recorded after retreatment.

An overall summary of new AE and new AE related to study drug recorded after retreatment will be presented for each subject category (ie, Category I, II and Overall) by treatment sessions and time period (ie, all study periods and each study period as described in section 4.5.1.2), and will include:

- Any new AE
- Any new AE of special interest
- Any new serious AE
- Any new mild, moderate, and severe AE
- Any new AEs leading to study drug withdrawn/interruption
- Any new AEs leading to study discontinuation
- Any new AEs resulting in death

The following summary tables will be presented by SOC and PT by subject category (ie, Category I, II, and overall) and each treatment sessions [TX1, TX2, TX3, and Total ('Total' includes AEs reported during Treatment Session 1, 2, and 3, and Observation Period post Day 71 of retreatment)]:

- All AEs
- AEs by causal relationship to study drug
- AEs by Severity
- Study drug related AEs by severity
- Serious AEs

- Serious study drug related AEs
- AEs leading to study drug withdrawn/interruption
- Study drug related AEs leading to study drug withdrawn/interruption
- AEs leading to study discontinuation
- Study drug related AEs leading to study discontinuation
- AEs resulting in death
- Study drug related AEs resulting in death
- AEs of Special Interest

Serious and most common non-serious AE 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 preferred term that at least 5% of the subjects reported at least once.

Subject listings of all AEs, serious AEs, AEs leading to study drug withdrawn/interruption, AEs leading to study discontinuation, AEs resulting in death and AEs of Special Interest will be provided.

Refer to Table 17 for computation of duration of AE.

7.7.3. Clinical Laboratory

For Day 180 Observational Population and Prior to Day 180 Population, laboratory assessments (hematology and biochemistry) at specific visits and change from baseline at corresponding post baseline visits through Day 180 visit will be summarized by treatment arm (ie, CCH 1.68 mg, Placebo, and Overall) in double-blind studies (EN3835-302/303).

For subjects in OLR Population after retreatment, laboratory assessments (hematology and biochemistry) at specific visits and change from baseline at corresponding post baseline visits after Day 180 visits and end of treatment session assessments (ie, Day 71) will be summarized by subject category (ie, Category I, II, and Overall) using descriptive statistics.

For Day 180 Observational Population and Prior to Day 180 Population, the Screening assessments done within 14 days of/or Day 71/EOS visit in the double-blind studies will be used as baseline. The same set of tables will be reproduced for change from baseline considering Day 1 of the double-blind studies will also be presented.

For subjects in OLR Population with after retreatment, the assessments at Screening B or unscheduled visits prior to/on the first dose date of retreatment in this study will be used as baseline.

The PCI laboratory values will be summarized by counts and percentages for Day 180 Observational Population and subjects in OLR Population after retreatment, separately. Refer to Table 14 for PCI criteria.

Subject listing (including urinalysis results) will be presented for all laboratory parameters for Day 180 Observational Population and for subjects in OLR Population after retreatment, separately. In addition, serum and urine pregnancy test results will be listed by subject for different populations as above.

7.7.4. Vital Signs

For Day 180 Observational Population, vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature and body weight) at specific visits and change from baseline at corresponding post baseline visits through Day 180 visit will be summarized using descriptive statistics by treatment arm (ie, CCH 1.68 mg, Placebo, and Overall) in double-blind studies (EN3835-302/303). The same set of tables will be reproduced for change from baseline considering Day 1 of the double-blind studies will also be presented.

For subjects in OLR Population after retreatment, vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature and body weight) at specific visits and change from baseline at corresponding post baseline visits after Day 180 visits through end of treatment session assessments will be summarized by subject category (ie, Category I, II, and Overall) using descriptive statistics.

For Day 180 Observational Population, the Screening assessments done within 14 days of/or Day 71/EOS visit in the double-blind studies will be used as baseline. For subjects in OLR Population after retreatment, the assessments at Screening B or unscheduled visits prior to/on the first dose date of retreatment in this study will be used as baseline.

The PCI vital signs values will be summarized by counts and percentages for Day 180 Observational Population and for subjects in OLR Population after retreatment, separately. Refer to Table 15 for PCI criteria.

A subject listing will be presented for all vital signs parameters for Day 180 Observational Population and for subjects in OLR Population with retreatment separately.

7.7.5. 12-Lead ECG

The investigator interpretation of ECG results (normal, abnormal not clinically significant or abnormal clinically significant) at Screening B (for Category I and II retreated subjects) will listed for OLR Population.

7.7.6. Physical Examination

Physical examination (body system) screening results will be presented separately for Day 180 Observational Population and for subjects in OLR Population separately.

7.7.7. Immunogenicity

The immunogenicity data for subjects who entered the Open-label Periodof the study will be summarized separately before retreatment using Open-label Observation Population, and after retreatment using OLR Population.

Immunogenicity Data Before Retreatment: The immunogenicity data at Screening (Day 71 of double-blind studies) and Observation Visits prior to retreatment will be summarized by Subject Category (ie, Category I, II, III, and Overall) for subjects in Open-label Observation Population.

Immunogenicity Data After Retreatment: The immunogenicity data at Screening B (screening during retreatment phase), Treatment Visits (TX2, TX3, and TX4) and Observation Visits after retreatment through end of study will be summarized for subjects in OLR Population.

The immunogenicity data of binding and neutralizing anti-AUX-I and anti-AUX-II antibodies will be summarized using 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 the assessment visits. The titer levels will be logarithmically transformed prior to being summarized descriptively.

The number and percentage of assayed serum samples that will detect the presence or absence of neutralizing antibodies (positive/negative) to AUX-I and AUX-II will be summarized by antidrug antibody quartiles for the retreated subjects using frequency counts and percentages at Day 71/End of Retreatment phase.

The listings of immunogenicity data will be presented separately for the All Subjects prior to retreatment and for subjects in OLR Population after retreatment.

8. CHANGE FROM PROTOCOL

This SAP is prepared based on the study protocol, original version dated 31-Jan-2018, Amendment 1 dated 19-Apr-2018, Amendment 2 dated 01-Nov-2018, and Amendment 3 dated 14-Jan-2021.

The changes in SAP from what is proposed in protocol is explained in Table 18 below:

Table 18: Changes from Protocol

Text in Protocol	Change in SAP	Justification
Overall Safety Population: All safety analyses will be based on this population. In addition, the safety data will be summarized by treatment period for those retreated subjects with EN3835.	Overall Safety Population is renamed as "Open-label Observation Population"	Safety profile in this study will be analyzed in two different phases, prior to retreatment phase and after retreatment phase. Hence these populations are defined. The data prior to retreatment will be summarized based on Open-label Observation Population, and data after retreatment will be summarized based on Open-label Retreated Population (Refer to section 5).
TRR Population: The TRR population is defined as all subjects who have at least a 1-level or 2-level improvement in both CR-PCSS and PR-PCSS ratings during the double-blind study for either/both treated buttocks. This population will include Category I and II subjects. TRR will be evaluated separately for subjects who had a 1-level and 2-level composite improvement in CR-PCSS and PR-PCSS during studies EN3835-302/303 in each buttock.	Instead of TRR Population, it is renamed as 'TRR Population Before Retreatment'	Reduction of Response will be assessed separately for prior to retreatment and after retreatment. Hence these populations are defined. TRR Population Before Retreatment will include the subjects who are not-retreated and until the point prior to retreatment for the subjects who are retreated (Refer to section 5). TRR Population After retreatment will only include the subjects who are retreated in this study and have at least 1 level or 2 level improvement in both CR-PCSS and PR-PCSS ratings at Day 71/End of Treatment Session in the open label retreatment phase (Refer to section 5).

9. REVISION HISTORY

Non-editorial changes made to any of the modules of this SAP are recorded in Table 19.

Table 19: Revision History

Version	Date	Revision Author	Comments
1.0	18-Jan-2019	Endo Pharmaceuticals Inc.	Published version
2.0	25-May-2021	[redacted]	As per Protocol Amendment 3 dated 14-Jan-2021

10. REFERENCES

1. Clinical Study Protocol Amendment 3: A Phase 3b, Open-Label, Long-Term Study to Evaluate the Safety and Temporal Pattern of Response of EN3835 in the Treatment of Edematous Fibrosclerotic Panniculopathy. Dated 14-Jan-2021.

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.