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COLLAGENASE CLOSTRIDIUM HISTOLYTICUM (EN3835)

EN3835-202

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

IND 110077

Amendment 4

Date:

Original Protocol: June 20, 2016

Amendment 1: July 5, 2016

Amendment 2: October 25, 2016

Amendment 3: June 6, 2017

Amendment 4: October 2, 2017

Auxilium Pharmaceuticals, Inc. (Auxilium) was acquired by Endo International plc. in January 2015. The Sponsor of the application remains Auxilium; however, Endo Pharmaceuticals Inc. (Endo) is authorized to act and to communicate on behalf of Auxilium.

[redacted]

2. SUMMARY OF CHANGES

The EN3835-202 protocol amendments and amended informed consent forms (as necessary) have been reviewed and approved by the governing institutional review boards (IRBs) before implementation of the amendments at each study center.

Amendment 4 was incorporated into the protocol on October 2, 2017. The major reasons for this amendment are to include continuing durability assessments of subjects treated with active EN3835 in the EN3835-201 study, and remove provisions for direct data entry in the electronic data capture (EDC) system.

Section	Original Text	Revised Text
3 Sponsor Contact Information, Table 1, Medical Monitor	[redacted]	[redacted]
4 Synopsis, Objectives, Secondary 9.2 Secondary Objectives	ADDED TEXT	• To evaluate the long-term durability of response to EN3835 in EFP severity beyond 12 months post initial dosing of EN3835 in subjects previously receiving active treatment in study EN3835-201 using the PR-PCSS and the CR-PCSS.
4 Synopsis, Study Design	Subjects will be assessed for safety and cellulite severity assessments approximately every 3 months for a maximum of 1 year from their first exposure to EN3835 in each treated quadrant.	Subjects will be assessed for safety and cellulite severity assessments approximately every 3 months from their first exposure to EN3835 in each treated quadrant.
4 Synopsis, Study Design	After Day 71, they will be observed every 3 months from their first exposure to EN3835 up to a maximum of 1 year in each treated quadrant.	After Day 71, they will be observed every 3 months from their first exposure to EN3835 up to a maximum of 1 year in each treated quadrant (including both open-label and double-blind treated quadrants, if different quadrants were treated across both studies). Durability of open-label treatment with EN3835 will be assessed for up to 1 year (Day 360). Durability beyond Day 360 will be assessed in subjects who received active treatment in EN3835-201 and showed a composite improvement of at least 1 level on both the CR-PCSS and the PR-PCSS. In these subjects, the original quadrant treated in EN3835-201 will be assessed until the end of the current study, in addition to any treated quadrants occurring in the current study. Assessments of durability beyond Day 360 may also include subjects who opted not to receive additional treatments in EN3835-202.

Section	Original Text	Revised Text
4 Synopsis, Diagnosis and inclusion/exclusion criteria	ADDED TEXT	Qualification of Subjects Assessed For Durability Beyond Day 360 Inclusion criteria for observation: 1. Voluntarily sign and date an informed consent agreement 2. Has participated in and completed the double-blind study EN3835-201 3. Has received active EN3835 in the double-blind study EN3835-201 4. Achieved an improvement of at least 1 level on both the CR-PCSS and the PR-PCSS at the same visit on or before Day 71 in the double-blind study EN3835-201 5. Be willing to apply sunscreen to any treated quadrant before each exposure to the sun while participating in the study (ie, screening through end of study) Exclusion criteria for observation: 1. Treatment of the same quadrant in EN3835-202 and EN3835-201 2. Has used any of the following for the treatment of EFP on the thighs or buttocks since treatment in EN3835-201, or intends to use any of the following at any time during the course of the study: • Liposuction on the side of the body selected for treatment • Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; or surgery (including subcision and/or powered subcision) within the selected treatment quadrant • Endermologie or similar treatments within the selected treatment quadrant • Massage therapy within the selected treatment quadrant • Creams (eg, Celluvera™, TriLastin®) to prevent or mitigate EFP within the selected treatment quadrant

Section	Original Text	Revised Text
4 Synopsis, Investigational product, dosage and mode of administration	For the observational periods of this study, subjects will be assessed for safety and cellulite severity assessments at approximately 3-month intervals for a maximum of 1 year following their first exposure to EN3835 in each treated quadrant.	For the observational periods of this study, subjects will be assessed for safety and cellulite severity assessments at approximately 3-month intervals following their first exposure to EN3835 in each treated quadrant. Durability will be assessed for up to 24 months in subjects that received active EN3835 in the EN3835-201 study and showed at least a 1-level composite PR-PCSS/ CR-PCSS reduction in cellulite severity.
4 Synopsis, Duration of study	Twelve (12) months from first exposure to EN3835 in study EN3835-201 and 12 months from first exposure in any additional treated quadrants in the EN3835 202 study Screening Phase: Up to 14 days Observational Phase: Subjects will be assessed at visits that occur approximately every 3 months for a maximum of 1 year after the first exposure to EN3835 in each treated quadrant. Follow-up: Subjects will be assessed at visits that occur approximately every 3 months for a maximum of one year after the first exposure to EN3835 in each treated quadrant. For subjects treated with EN3835 in this study, subjects will be observed at treatment visits (Days 1, 22, and 43) and Day 71 after first injection. After Day 71, they will be observed every 3 months from their first exposure to EN3835 up to a maximum of one year in each treated quadrant.	A minimum of 12 months from first exposure to EN3835 in study EN3835-201 and 12 months from first exposure in any additional treated quadrants in the EN3835-202 study Screening Phase: Up to 14 days Observational Phase: Subjects will be assessed at visits that occur approximately every 3 months after the first exposure to EN3835 in each treated quadrant. Durability will be assessed for up to 24 months in subjects that received active EN3835 in the EN3835-201 study and showed at least a 1-level composite PR-PCSS/CR-PCSS reduction in cellulite severity. Follow-up: Subjects will be assessed at visits that occur approximately every 3 months after the first exposure to EN3835 in each treated quadrant. For subjects treated with EN3835 in this open-label study, subjects will be observed at treatment visits (Days 1, 22, and 43) and Day 71 after first injection. After Day 71, they will be observed every 3 months in each treated quadrant. Durability will be assessed for up to 24 months in subjects that received active EN3835 in the EN3835-201 study and showed at least a 1-level composite PR-PCSS/CR-PCSS reduction in cellulite severity.
4 Synopsis, Statistical methods, Analysis Populations	Observational population: The Observational population is defined as all subjects treated with EN3835 in study EN3835-201 who do not receive any treatment in the current study.	Observational population: The Observational population is defined as all subjects rolled over from study EN3835-201 who do not receive any treatment in the current study.
4 Synopsis, Statistical methods, Analysis Populations	ADDED TEXT	Durability Population: This population is defined as all active responders who have both CR-PCSS and PR-PCSS at 180 days or above. The active responders are subjects treated with EN3835 with improvements of 1 level or more on each scale (CR-PCSS and PR-PCSS) at Day 71 from the baseline.

Section	Original Text	Revised Text
4 Synopsis, Statistical methods, Efficacy Evaluations	ADDED TEXT	Durability of treatment effect will be based on the durability population.
5 Schedule of Events, Table 2, footnotes	ADDED TABLE FOOTNOTE	[f] For subjects treated with active EN3835 in the double-blind study and having a different quadrant treated in the open-label study, refer to Table 4 for continued assessments of the double-blind treated quadrant for durability beyond Day 360.
5 Schedule of Events, Table 4	ADDED TABLE	Added Table 4 Assessments for Durability (Beyond Day 360). Subsequent tables numbers have been increased.
8.3.1.4, Endo-Sponsored Phase 2b Study EN3835-201	Currently there is an ongoing Phase 2b study (EN3835-201) which is a double-blind, placebo-controlled study of 350 adult women randomized to EN3835 0.84 mg or placebo in a 1:1 ratio. Each subject can receive up to 3 treatment sessions of study drug separated by approximately 21 days; last visit is Day 71. Efficacy is being evaluated using a Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS), a Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS), the Hexsel Cellulite Severity Scale (CSS), Investigator Global Aesthetic Improvement Scale (I-GAIS), Subject Global Aesthetic Improvement Scale (S GAIS), and a subject satisfaction assessment. Subjects that complete study EN3835-201 will be offered the option of participating in study EN3835-202.	EN3835-201 was a double-blind, placebo-controlled study of 350 adult women randomized to EN3835 0.84 mg or placebo in a 1:1 ratio. Each subject received up to 3 treatment sessions of study drug separated by approximately 21 days; last visit was Day 71. Efficacy was evaluated using a Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS), a Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS), the Hexsel Cellulite Severity Scale (CSS), Investigator Global Aesthetic Improvement Scale (I-GAIS), Subject Global Aesthetic Improvement Scale (S GAIS), and a subject satisfaction assessment. Subjects that completed study EN3835-201 were offered the option of participating in study EN3835-202.
11.3, Durability of Treatment	ADDED TEXT	11.3. Durability of Treatment An assessment of treatment durability will include observations of up to 2 years in subjects who received active treatment in EN3835-201 and scored an improvement of at least 1 level on both the CR-PCSS and the PR-PCSS. For subjects who received active EN3835 in EN3835-201 and also received open-label EN3835 in EN3835-202, the original quadrant treated in EN3835-201 will be assessed until the end of the current study, *in addition* to any quadrants treated during the open-label study. The durability population may also include subjects who received active EN3835 in the double-blind study but opted not to receive additional treatments in EN3835-202. For subjects being assessed for

Section	Original Text	Revised Text
		durability beyond Day 360, the following eligibility criteria apply: 11.3.1. Subject Inclusion Criteria for Observation 1. Voluntarily sign and date an informed consent agreement 2. Has participated in and completed the double-blind study EN3835-201 3. Has received active EN3835 in the double-blind study EN3835-201 4. Achieved an improvement of at least 1 level on both the CR-PCSS and the PR-PCSS at the same visit on or before Day 71 in the double-blind study EN3835-201 5. Be willing to apply sunscreen to any treated quadrant before each exposure to the sun while participating in the study (ie, screening through end of study) 11.3.2. Exclusion Criteria for Observation 1. Treatment of the same quadrant in EN3835-202 and EN3835-201 2. Has used any of the following <u>for the treatment of EFP</u> on the thighs or buttocks since treatment in EN3835-201, or intends to use any of the following at any time during the course of the study: • Liposuction on the side of the body selected for treatment • Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; or surgery (including subcision and/or powered subcision) within the selected treatment quadrant • Endermologie or similar treatments within the selected treatment quadrant • Massage therapy within the selected treatment quadrant • Creams (eg, Celluvera™, TriLastin®) to prevent or mitigate EFP within the selected treatment quadrant

Section	Original Text	Revised Text
12.1.3.2, Durability Assessments	ADDED TEXT	12.1.3.2. Durability Assessments An assessment of treatment durability will include subjects treated with open label EN3835 in the current study as well as subjects that received active EN3835 in study EN3835-201 and showed a composite improvement of at least 1 level in the PR-PCSS and CR-PCSS. Similar to other EN3835-202 observational assessments, the first durability visit will be determined by the date of enrollment relative to the associated Schedule of Events. For subjects who were treated with active EN3835 in the double-blind study (Table 4), and who give written informed consent and meet all eligibility criteria, durability assessments of the quadrant treated in the double-blind study are to be conducted *in addition* to any assessments of the different quadrant treated in the open-label study. Subjects may complete assessments for durability of all treated quadrants (whether initiated in the double-blind and open-label study) at the same visits, where subject and site schedules permit.
13.1, Primary Efficacy Measurements	Digital Photography: Digital photography will be utilized to assess certain cellulite severity parameters at specific intervals (see Schedule of Events, Table 2) for subjects in the observation-only group as well as those electing to be re-treated or re-dosed with EN3835. At the Screening B visit for subjects electing to receive re-dosing or re-treatment, the Investigator or qualified designee will photograph each quadrant using a Sponsor-supplied standardized digital camera. The subject will be standing for each photography session and will be wearing a standardized photographic garment as described in the Photography Manual. The Investigator or qualified designee will photograph the selected quadrant as follows: Screening B (no dimple marking) Before and after dimple marking (prior to injections) on Days 1, 22, and 43 of each treatment course During the Day 71 visit (end of treatment phase/early termination) of each treatment course	Digital Photography: Digital photography will be utilized to assess certain cellulite severity parameters at specific intervals (see Schedule of Events, Table 2, Table 3, and Table 4) for subjects in the observation-only group as well as those electing to be re-treated or re-dosed with EN3835. At the Screening B visit for subjects electing to receive re-dosing or re-treatment, the Investigator or qualified designee will photograph each quadrant using a Sponsor-supplied standardized digital camera. The subject will be standing for each photography session and will be wearing a standardized photographic garment as described in the Photography Manual. The Investigator or qualified designee will photograph the selected quadrant as follows: • Screening B (no dimple marking) • Before and after dimple marking (prior to injections) on Days 1, 22, and 43 of each treatment course • During the Day 71 visit (end of treatment phase/early termination) of each treatment course • During the specified observation visits for assessments of durability (see Table 2 for durability up to Day 360, and Table 4 for durability beyond Day 360)

Section	Original Text	Revised Text
		All photographs from this study are the property of Endo and may be utilized for clinical development, scientific communication, marketing, regulatory purposes, and/or legal applications as required/desired by Endo.
13.1.1.1, Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS)	All subjects who enter the observation-only phase of the study will have the PR-PCSS evaluation at months 3, 6, 9, and 12 or at the end of study visit.	All subjects who enter the observation-only phase of the study will have the PR-PCSS evaluation at months 3, 6, 9, and 12 (and at specified visits in Table 4 for subjects originally treated with active in the double-blind study and being assessed for treatment durability beyond Day 360) or at the end of study visit.
13.1.1.4, Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS)	Investigators will have been trained on the use of the CR-PCSS. For observation-only subjects, the CR-PCSS will be done at 3, 6, 9, and 12 months or at the end of study visit.	Investigators will have been trained on the use of the CR-PCSS. For observation-only subjects, the CR-PCSS will be done at 3, 6, 9, and 12 months (and at visits specified in Table 4 for subjects participating in observation visits beyond Day 360) or at the end of study visit.
13.1.1.4, Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS) 13.1.1.5, Investigator Global Aesthetic Improvement Scale (I-GAIS) 13.1.1.6, Hexsel Cellulite Severity Scale 14.8, Vital Signs 14.10, Physical Examination	This variable may be entered directly into the EDC system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.	DELETED TEXT
14.7, Clinical Laboratory and Immunogenicity Determinations	Results of the urine pregnancy test may be entered directly into the EDC system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.	DELETED TEXT
14.9, Electro-cardiogram	The investigator's assessment may be entered directly into the EDC system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.	DELETED TEXT

Section	Original Text	Revised Text
17.2, Subject Cohorts and Subject Populations	All efficacy and safety analyses will be done within the classified cohort. Durability of treatment effects is defined as the time from onset of change from baseline of PR-PCSS and CR-PCSS in the quadrant treated in study EN3835-201 [redacted] where possible, in which the treated quadrant returns to baseline cellulite severity ratings of PR-PCSS and CR-PCSS in an EN3835-treated quadrant.	All efficacy and safety analyses will be done within the classified cohort. Durability of treatment effects is defined as the time from onset of change from baseline of PR-PCSS and CR-PCSS in the quadrant treated in study EN3835-201 [redacted] where possible, in which the treated quadrant returns to baseline cellulite severity ratings of PR-PCSS and CR-PCSS in an EN3835-treated quadrant. Durability will be determined for all subjects that were treated with EN3835 in either EN3835-202 or EN3835-201. If sequential visit [redacted] are not available for that quadrant due to retreatment or [redacted], then the singular time point at which ratings return to baseline will be the durability cessation date.
17.2.1, Observational Population	The Observational population includes all subjects treated with EN3835 in study EN3835-201 who do not receive any treatment in the current study. The durability of a treatment effect and long-term safety analyses for subjects who receive no treatment in the EN3835-2021 study will be performed using this population.	The Observational population includes all subjects rolled over from the study EN3835-201 who do not receive any treatment in the current study. Safety analyses for subjects who receive no treatment in the EN3835-202 study will be performed using this population.
17.2.4, Durability Populations	ADDED TEXT	17.2.4. Durability Populations Overall Durability Population: This population is defined as all active responders who have both CR-PCSS and PR-PCSS at 180 days or above. The active responders are subjects treated with EN3835 with improvements of at least 1level on each scale (CR-PCSS and PR-PCSS) from the baseline. 17.2.4.1. Durability Population for Double-blind Treated Subjects This population is defined as all subjects in the durability population who showed an improvement of at least 1 level on each scale (CR-PCSS and PR-PCSS) from the baseline for the quadrant treated with EN3835 in double-blind study EN3835-201 17.2.4.2. Durability Population for Open-label Treated Subjects This population is defined as all subjects in the durability population who showed an improvement of at least 1 level on both the CR-PCSS and the PR-PCSS from the baseline for the quadrant treated with EN3835 in the open-label study (current EN3835-202 study), and did not have the same quadrant treated in EN3835-201.

Section	Original Text	Revised Text
17.4, Demographics and Other Baseline Characteristics	Demographic and baseline characteristics, including age, race, and baseline values will be summarized for the Observational population, the Safety population, and the Effectiveness population using descriptive statistics.	Demographic and baseline characteristics, including age, race, and baseline values will be summarized for the Observational population, the Safety population, the Effectiveness population, and Durability Population using descriptive statistics.
17.5.2, Durability of Treatment Effect	ADDED TEXT	Durability of treatment effects will be presented as the number and percentage of treatment failure (or recurrence) among those active responders by follow-up time period, ie, 180 days, 360 days, 540 days, and 720 days. The treatment failure (recurrence) is defined as active reponders whose CR-PCSS and PR-PCSS return to the baseline in an EN3835-treated quadrant during a certain follow-up period.
19.1, Source Documents	Source documents include but are not limited to original documents, data and records such as hospital/medical records (including electronic health records), clinic charts, lab results, subject diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, etc. This study allows for direct data entry (DDE) for selected data points as outlined below: Inclusion/exclusion Vital signs including pre- and post-injection measurements Height and body weight CR-PCSS Hexsel CSS I-GAIS Physical examinations ECG results (if more than 1 year passed since ECG assessment) Urine pregnancy test Study drug administration All other data points, at a minimum, should have supporting source documentation for entries in the eCRF.	Source documents include but are not limited to original documents, data and records such as hospital/ medical records (including electronic health records), clinic charts, lab results, subject diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, etc. At a minimum, all data required to be collected by the protocol should have supporting source documentation for entries in the eCRF.

Section	Original Text	Revised Text
22.1, Data Collection	Study data will be collected by DDE or from source documents and entered into an eCRF within the EDC system. The Investigator will be responsible for ensuring the eCRFs are completed in a timely manner relative to the subject's visit. In addition to periodic monitoring occurring within the system by a Sponsor monitor, programmatic edit checks will be used to review EDC data for completeness, logic, and adherence to the study protocol. As a result of this monitoring and these checks, queries may be issued electronically to the clinical study sites and closed electronically by the monitor, data management staff or authorized staff at the study site. Additionally, the Investigator will review eCRFs, ensure all missing or corrected data is provided and will sign the eCRF pages with an electronic signature. An electronic audit trail will be maintained in the EDC system to track all changes made to data entered in the eCRF. Data will be retrievable in such a fashion that all information regarding each individual subject is attributable to that subject.	Study data will be collected from source documents and entered into an eCRF within the EDC system. The Investigator will be responsible for ensuring the eCRFs are completed in a timely manner relative to the subject's visit. In addition to periodic monitoring occurring within the system by a Sponsor monitor, programmatic edit checks will be used to review EDC data for completeness, logic, and adherence to the study protocol. As a result of this monitoring and these checks, queries may be issued electronically to the clinical study sites and closed electronically by the monitor, data management staff or authorized staff at the study site. Additionally, the Investigator will review eCRFs, ensure all missing or corrected data is provided and will sign the eCRF pages with an electronic signature. An electronic audit trail will be maintained in the EDC system to track all changes made to data entered in the eCRF. Data will be retrievable in such a fashion that all information regarding each individual subject is attributable to that subject. Unless otherwise indicated, all data captured in the eCRF must first be captured in source documents.

Amendment 3 was incorporated into the protocol on June 6, 2017. The major reasons for this amendment were to increase the number of subjects assessed at 12 months after their first exposure to EN3835 and to update the statistical methods.

Section	Original Text	Revised Text
3 Sponsor Contact Information, Table 1, Medical Monitor	[redacted]	[redacted]
4 Synopsis, Study Period	Estimated date last subject completed: Sep-2017	Estimated date last subject completed: Jun-2018

Section	Original Text	Revised Text
4 Synopsis, Study Design	Subjects will be assessed for safety and cellulite severity assessments approximately every 3 months for a maximum of 1 year from their first exposure to EN3835. Subjects with at least 1 quadrant with moderate or severe level of cellulite will be eligible for treatment with EN3835 after unblinding of study EN3835-201; a quadrant that was treated with EN3835 in the previous study EN3835-201 will only be eligible for retreatment if the cellulite severity in that quadrant is rated at levels of cellulite severity at baseline in study EN3835-201.	Subjects will be assessed for safety and cellulite severity assessments approximately every 3 months for a maximum of 1 year from their first exposure to EN3835 in each treated quadrant. Subjects with at least 1 quadrant with moderate or severe level of cellulite will be eligible for treatment with EN3835 after unblinding of study EN3835-201; a quadrant that was treated with EN3835 in the previous study EN3835-201 will only be eligible for retreatment if the cellulite severity in that quadrant is rated at levels of cellulite severity at baseline or greater in study EN3835-201.
4 Synopsis, Study Design	After Day 71, they will be observed every 3 months from their first exposure to EN3835 up to a maximum of 1 year. The study will terminate when at least 100 subjects have been assessed at 12 months after the first exposure to EN3835.	After Day 71, they will be observed every 3 months from their first exposure to EN3835 up to a maximum of 1 year in each treated quadrant.
4 Synopsis, Number of subjects (planned)	333	Approximately 350
4 Synopsis, Study center(s)	16 sites in the United States	15 sites in the United States
4 Synopsis, Investigational product, dosage and mode of administration	For the observational periods of this study, subjects will be assessed for safety and cellulite severity assessments at approximately 3-month intervals for a maximum of 1 year following their first exposure to EN3835.	For the observational periods of this study, subjects will be assessed for safety and cellulite severity assessments at approximately 3-month intervals for a maximum of 1 year following their first exposure to EN3835 in each treated quadrant.
4 Synopsis, Duration of study	Twelve (12) months from first exposure to EN3835 in study EN3835-201 or study EN3835 202	Twelve (12) months from first exposure to EN3835 in study EN3835-201 and 12 months from first exposure in any additional treated quadrants in the EN3835-202 study
4 Synopsis, Observational Phase	Subjects will be assessed at visits that occur approximately every 3 months for a maximum of 1 year after the first exposure to EN3835.	Subjects will be assessed at visits that occur approximately every 3 months for a maximum of 1 year after the first exposure to EN3835 in each treated quadrant.
4 Synopsis, Follow-up	Subjects will be assessed at visits that occur approximately every 3 months for a maximum of 1 year after the first exposure to EN3835. For subjects treated with EN3835 in this study, subjects will be observed at treatment visits (Days 1, 22, and 43) and Day 71 after first injection. After Day 71, they will be observed every 3 months from their first exposure to EN3835 up to a maximum of 1 year.	Subjects will be assessed at visits that occur approximately every 3 months for a maximum of 1 year after the first exposure to EN3835 in each treated quadrant. For subjects treated with EN3835 in this study, subjects will be observed at treatment visits (Days 1, 22, and 43) and Day 71 after first injection. After Day 71, they will be observed every 3 months from their first exposure to EN3835 up to a maximum of 1 year in each treated quadrant.

Section	Original Text	Revised Text
4 Synopsis, Statistical methods, Sample Size Consideration	The number of subjects (approximately 333) is intended to obtain additional subjects for adequate long-term safety data at the selected dose.	Approximately 350 subjects are planned to obtain adequate long-term safety data for this study.
4 Synopsis, Statistical methods, Analysis Populations	Safety population: The Safety population is defined as all enrolled subjects who received at least 1 injection of EN3835 in this study or in study EN38335-201. Intent-to-Treat (ITT) population: The ITT population is defined as all enrolled subjects in this study. Modified Intent-to-Treat (mITT) population: The mITT population is defined as ITT subjects who received at least 1 injection of EN3835 in this study with a baseline and 1 post-injection evaluation of both the CR-PCSS and PR-PCSS. All efficacy (cellulite assessments) analyses will be completed on this population. Per-Protocol population: The Per-Protocol population is defined as those subjects in the Safety population who have no major protocol deviations.	Safety population: The Safety population is defined as all enrolled subjects who received at least 1 injection of EN3835 in this study. Effectiveness population: This population is defined as all safety subjects who have a baseline and at least 1 post-injection evaluation of both the CR-PCSS and PR-PCSS.
4 Synopsis, Statistical methods, Efficacy Evaluations	The primary cellulite severity assessment endpoint, the proportion of composite responders with improvement of 2 or better on each scale (CR-PCSS and PR-PCSS) at Day 71, will be summarized as percentages and analyzed using a Cochran-Mantel-Haenszel test that compares the 2 treatment groups and adjusts for Investigator. The ITT population will be evaluated for the primary endpoint with any subjects not having a post-injection evaluation of either CR-PCSS or PR-PCSS classified as a non-responder. All secondary endpoints, except the Hexsel CSS total score, will be summarized as percentages. The dichotomous secondary endpoints (ie, responders endpoints) will be analyzed using a Cochran-Mantel-Haenszel test adjusted for investigator. Multiple-response endpoints (ie, scales) will be analyzed using the Mann-Whitney test. Change in Hexsel CSS total score will be summarized with descriptive statistics for continuous variable and will be analyzed using analysis of variance (ANOVA).	The composite endpoints for cellulite severity assessment, the proportions of composite responders with improvement of 2 (or 1) or better on each scale (CR-PCSS and PR-PCSS), will be summarized as numbers and percentages by study days (visit). The analysis will be based on Effectiveness population. All other endpoints including observational endpoints will be summarized by study days using appropriate descriptive statistics. The descriptive statistics will include the number and percentage for categorical response variables and number, mean, standard deviation, minimum, and maximum for continuous variables.

Section	Original Text	Revised Text
5 Schedule of Events, Table 2, Procedures	ADDED TEXT AND ROW	Prior/Concomitant Medications/Procedure Screening A: X Visit 1: X Visit 2: X Visit 3: X Visit 4: X
5 Schedule of Events, Table 2, footnotes	[b]Three (3)-month evaluation periods begin 90 days after Day 1 of the double-blind study (EN3835-201) (ie, within 20 days ±4 days of completion of double-blind study).	[b] Four (4) visits at 3-month periods begin 90 days after Day 1 of the double-blind study (EN3835-201) (ie, within 20 days ± 4 days of completion of double-blind study).
5 Schedule of Events, Table 3, Procedures	Informed Consent Screening B: X	DELETED TEXT AND ROW
9.2 Secondary Objectives	To assess safety and immunogenicity of re-treating or re-dosing a subject that had previously received treatment with EN3835	• To evaluate safety and immunogenicity of re-treating or re-dosing a subject that had previously received treatment with EN3835
10.1 Study Design	The study is planned to end when at least 100 subjects have 12 months after exposure ie 12 months after first treatment in study EN3835 201 or study EN3835-202.	DELETED TEXT
10.1 Study Design	Previously placebo-treated subjects will have the option to receive a second course of EN3835 in the same or different qualifying quadrant after at least 28 days following the end of the first treatment course (ie treatment of second quadrant could begin on Day 71 after treating the first quadrant). The selected quadrant can be re-treated or re-dosed.	Previously placebo-treated subjects will have the option to receive a second course of EN3835 in the same or different qualifying quadrant after at least 28 days following the end of the first treatment course (eg, the screening B visit of second quadrant could be performed on Day 71 after treating the first quadrant). The selected quadrant can be re-treated or re-dosed.
10.1 Study Design, table	N=333	DELETED TEXT
12.1.1 Subject Screening	Upon completion of Day 71 assessments in the double-blind study EN3835-201, a subject will be eligible to enter this open-label extension study. Investigators will be expected to maintain a Screening Log of all potential study subjects. This log will include limited information about the potential subject and the date and outcome of the screening process (eg, enrolled into the study, reason for ineligibility, or refused to participate). Investigators will provide information about the study to subjects who appear to meet the criteria for participation in the study.	Upon completion of Day 71 assessments in the double-blind study EN3835-201, a subject will be eligible to enter this open-label extension study. All potential subjects eligible for screening in EN3835-202 will be pre-populated in the electronic data capture (EDC) system. The status of all subjects (eg, screen fails) will also be kept in the EDC system.

Section	Original Text	Revised Text
12.1.3 Study Entry/Observational Assessments	ADDED TEXT	All subjects must complete Screening A and at least 1 Observation visit before Screening B can occur. Once the study blind was broken, the EN3835-201 placebo subjects were allowed to directly proceed to Screening B.
12.1.4.5 Follow-up Visits	Follow-up visits will continue until the study is terminated when at least 100 subjects have been assessed at 12 months after the first exposure to EN3835.	DELETED TEXT
12.5 End of Study	The end of study is when 100 subjects complete the 1-year safety and cellulite severity evaluations. At the time of study termination, ongoing subjects receiving treatment will be followed through the Day 71 visit. The remaining enrolled subjects (in excess of the first 100 subjects to complete 1 year) will undergo early termination procedures in accord with the Schedule of Events (section 5).	At the time of study termination, ongoing subjects receiving treatment will be followed through the Day 71 visit. The remaining enrolled subjects will undergo early termination procedures in accordance with the Schedule of Events (section 5).
13.1.1.4 Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS)	ADDED TEXT	This variable may be entered directly into the EDC system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.
13.1.1.5 Investigator Global Aesthetic Improvement Scale (I-GAIS)	The Investigator will circle the rating below that best represents their answer.	DELETED TEXT
13.1.1.5 Investigator Global Aesthetic Improvement Scale (I-GAIS)	ADDED TEXT	This variable may be entered directly into the EDC system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.
13.1.1.6 Hexsel Cellulite Severity Scale	ADDED TEXT	This variable may be entered directly into the EDC system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.
14.5.2 Reporting of Serious Adverse Events	Any SAE that is felt by the Investigator to be related to the study medication must be reported regardless of the amount of time since the last dose received.	Any SAE that is considered by the Investigator to be related to the study medication must be reported regardless of the amount of time since the last dose received.
14.7 Clinical Laboratory	ADDED TEXT	Results of the urine pregnancy test may be entered directly into the EDC system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.

Section	Original Text	Revised Text
14.7.1 Anti-AUX-I and Anti-AUX-II Antibodies	Serum samples will be collected and may be tested for binding and neutralizing anti-AUX-I and anti-AUX-II antibodies at visit 1 and visit 4.	Serum samples will be collected and may be tested for binding and neutralizing anti-AUX-I and anti-AUX-II antibodies at Visit 4 of the observation assessments.
14.8 Vital Signs	ADDED TEXT	The subject's vital signs should be stable, or repeated until stable before the subject can leave direct observation. This variable may be entered directly into the EDC system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.
14.9 Electro-cardiogram	ADDED TEXT	The investigator's assessment may be entered directly into the EDC system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.
14.10 Physical Examination	ADDED TEXT	This variable may be entered directly into the EDC system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.
17.1 Determination of Sample Size	It is estimated that approximately 95% of the 350 subjects randomized in study EN3835-201 will enroll in the current study for a sample size of 333. This sample size should be adequate to determine safety and cellulite assessments of EN3835 for subjects retreated in the same and in different quadrants.	Approximately 350 subjects that completed the EN3835-201study will enroll in the current study. This sample size should be adequate to determine long term safety and cellulite assessments of EN3835.
17.2 Subject Cohorts and Subject Populations	Durability of treatment effects defined as the time from onset of change from baseline of PR-PCSS and CR-PCSS in the quadrant treated in study EN3835-201 until the time that the treated quadrant return to baseline cellulite severity ratings of PR-PCSS and CR-PCSS in an EN3835-treated quadrant will be determined for all subjects that were treated with EN3835 in either this study or study EN3835-201.	Durability of treatment effects is defined as the time from onset of change from baseline of PR-PCSS and CR-PCSS in the quadrant treated until the time that the treated quadrant returns to baseline cellulite severity ratings of PR-PCSS and CR-PCSS in an EN3835-treated quadrant.
17.2.2 Safety Population	The Safety population will include all subjects who receive at least 1 dose of EN3835 in the current study or in study EN3835-201. All safety analyses will be performed using this population.	The Safety population will include all subjects who receive at least 1 dose of EN3835 in the current study. All safety analyses will be performed using this population.

Section	Original Text	Revised Text
17.2.3 Effectiveness Population	Intent-to-Treat Population The Intent-to-Treat (ITT) population includes all subjects who enroll in the current study.	Effectiveness Population The Effectiveness population includes all safety subjects who have a baseline and at least 1 post-baseline assessment on both the CR-PCSS and PR-PCSS on the quadrant selected for treatment in the current study. All analysis of effectiveness will be based on this population.
17.2.4 Modified Intent-to-Treat Population	17.2.4 Modified Intent-to-Treat Population The Modified Intent-to-Treat (mITT) population includes all subjects who receive at least 1 dose of EN3835 in the current study (EN3835-202) and have a baseline and at least 1 post-baseline assessment on both the CR-PCSS and PR-PCSS on the quadrant selected for treatment in the current study. All cellulite assessment analyses will be completed on this population.	DELETED TEXT
17.2.5 Per-Protocol Population	17.2.5 Per-Protocol Population The Per-Protocol population includes all subjects in the safety population who have no major protocol deviations. Major protocol deviations excluding subjects from this population will be determined at the protocol deviation assessment meeting prior to the database lock. If more than 10% of the safety population is excluded from the per-protocol population, then all safety and cellulite evaluations will be repeated using the per-protocol population.	DELETED TEXT
17.4 Demographics and Other Baseline Characteristics	Demographic and baseline characteristics, including age, race, and baseline values will be summarized for the Observational population, the Safety population, and the mITT population using descriptive statistics. The descriptive statistics will include frequency tables for all categorical response variables and number, mean, standard deviation, minimum, and maximum for all continuous variables.	Demographic and baseline characteristics, including age, race, and baseline values will be summarized for the Observational population, the Safety population, and the Effectiveness population using descriptive statistics. The descriptive statistics will include the number and percentage for categorical response variables and number, mean, standard deviation, minimum, and maximum for continuous variables.

Section	Original Text	Revised Text
17.5.1 Efficacy Analysis	The primary cellulite severity endpoint is the proportion of composite responders at Day 71 defined as subjects with an improvement in severity from baseline (Screening B visit) of at least 2 levels of severity in the CR-PCSS and an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS. The primary endpoint, the proportion of composite responders with improvement of 2 or better on each scale (CR-PCSS and PR-PCSS) will be summarized by region treated (buttock or thigh) and overall with percentages.	The composite endpoints for cellulite severity are the proportions of composite responders defined as subjects with an improvement in severity from baseline of at least 2 (or 1) levels of severity in the CR-PCSS and an improvement in severity from baseline of at least 2 (or 1) levels of severity in the PR-PCSS. These endpoints, will be summarized by treated quadrant and overall (buttocks and thighs) and by study day using appropriate descriptive statistics.
17.5.1 Efficacy Analysis	Secondary Efficacy Analysis	Other endpoints for treated quadrants include:
17.5.1 Efficacy Analysis	Proportion of composite responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS. (Day 71) Proportion at each level of improvement in the PR-PCSS (Day 71): Proportion of patient responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS Proportion of patient responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS Proportion at each level of improvement in the CR-PCSS (Day 71): Proportion of Investigator responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS (Investigator rated) Proportion of Investigator responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS (Investigator rated) Proportion of responders at each level of the I-GAIS (Day 71): Proportion of Investigator global responders defined as subjects with a response of 1 (improved) or better in the Investigator GAIS assessment Proportion of responders at each level of the S-GAIS (Day 71):	• Proportion at each level of improvement in the PR-PCSS: – Proportion of patient responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS – Proportion of patient responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS • Proportion at each level of improvement in the CR-PCSS: – Proportion of Investigator responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS (Investigator rated) – Proportion of Investigator responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS (Investigator rated) • Proportion of responders at each level of the I-GAIS: – Proportion of Investigator global responders defined as subjects with a response of 1 (improved) or better in the Investigator GAIS assessment • Proportion of responders at each level of the S-GAIS: – Proportion of subject global responders defined as subjects with a

Section	Original Text	Revised Text
	Proportion of subject global responders defined as subjects with a response of 1 (improved) or better in the subject GAIS assessment Proportion of responders at each level of the subject satisfaction with cellulite treatment (Day 71) Change in the Hexsel CSS total score from screening visit to Day 71 All secondary endpoints, except the Hexsel CSS total score, will be summarized by treated region (buttock or thigh) and overall using percentages. Change in Hexsel CSS total score will be summarized by treated region (buttock or thigh) and overall with descriptive statistics for continuous variables. Observational endpoints include: Proportion of 2-point composite responders as defined by responses in the quadrant treated in study EN3835-201 who either maintained response, lost response but did not return to the baseline of study EN3835-201, or returned to the baseline of study EN3835-201. Proportion of 1-point composite responders as defined by responses in the quadrant treated in study EN3835-201 who either maintained response, lost response but did not return to the baseline of study EN3835-201, or returned to the baseline of study EN3835-201. Proportion of 2-point CR-PCSS responders as defined by responses in the quadrant treated in study EN3835-201 who either maintained response, lost response but did not return to the baseline of study EN3835-201, or returned to the baseline of study EN3835-201. Proportion of 1-point CR-PCSS responders as defined by responses in the quadrant treated in study EN3835-201 who either maintained response, lost response but did not return to the baseline of study EN3835-201, or returned to the baseline of study EN3835-201. Proportion of 2-point PR-PCSS responders as defined by responses in the quadrant treated in study EN3835-201 who either maintained response, lost response but did not return to the baseline of study EN3835-201, or returned to the baseline of study EN3835-201. Proportion of 1-point PR-PCSS responders as defined by responses in the quadrant treated in study EN3835-201 who either maintained response, lost response but did not return to	response of 1 (improved) or better in the subject GAIS assessment • Proportion of responders at each level of the subject satisfaction with cellulite treatment • Change in the Hexsel CSS total score from screening visit All endpoints will be summarized by treated region (buttock or thigh) and overall and by study day using appropriate descriptive statistics. Observational endpoints include: • Proportions of composite responders defined as subjects with an improvement in severity from baseline of at least 2 (or 1) levels of severity in the CR-PCSS and an improvement in severity from baseline of at least 2 (or 1) levels of severity in the PR-PCSS. • Proportion at each level of improvement in the PR-PCSS: – Proportion of patient responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS – Proportion of patient responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS • Proportion at each level of improvement in the CR-PCSS: – Proportion of Investigator responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS (Investigator rated) – Proportion of Investigator responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS (Investigator rated) • Hexsel CSS total score changed from the study EN3835-201 baseline at Day 71 of study EN3835-201 and Day 360/end of study of the current study (EN3835-202). These endpoints will be summarized by treated region (buttock or thigh) and overall

Section	Original Text	Revised Text
	the baseline of study EN3835-201, or returned to the baseline of study EN3835-201. Duration of response as defined by the time from onset of change from baseline of PR-PCSS and CR-PCSS in the quadrant treated in study EN3835-201 until the time that the treated quadrant returned to the baseline PR-PCSS and CR-PCSS ratings from study EN3835-201. CR-PCSS change from the study EN3835-201 baseline at Day 71 of study EN3835-201, and Days 90, 180, 270, and 360/end of study of the current study (EN3835-202). PR-PCSS change from the study EN3835-201 baseline at Day 71 of study EN3835-201, and Days 90, 180, 270, and 360/end of study of the current study (EN3835-202). Hexsel CSS total score changed from the study EN3835-201 baseline at Day 71 of study EN3835-201 and Day 360/end of study of the current study (EN3835-202). Proportion of responses at each level of the I-GAIS (Day 360/end of study): Proportion of Investigator global responders defined as subjects with a response of 1 (improved) or better in the Investigator GAIS assessment Change in I-GAIS assessment from Day 71 of study EN3835-201 and Day 360/ end of study of the current study (EN3835-202 Proportion of responses at each level of the S-GAIS (Day 360/end of study): Proportion of subject global responders defined as subjects with a response of 1 (improved) or better in the subject GAIS assessment Proportion of 2-point PR-PCSS responders as defined by the responses in the quadrant treated in the current study who either maintained response, lost response but did not return to the study EN3835-202 baseline, or returned to the study EN3835-202 baseline. Proportion of 1-point PR-PCSS responders as defined by the responses in the quadrant treated in the current study who either maintained response, lost response but did not return to the study EN3835-202 baseline, or returned to the study EN3835-202 baseline. Change in S-GAIS assessment from Day 71 of study EN3835-201 and Day 360/ end of study of the current study (EN3835-202)	and by study day using appropriate descriptive statistics.

Section	Original Text	Revised Text
	Proportion of responses at each level of the subject satisfaction with cellulite treatment (Day 360/end of study) Change in subject satisfaction assessment from Day 71 of study EN3835-201 and Day 360/end of study of the current study (EN3835-202) For quadrants treated in the current study the following observational endpoints will be analyzed: Proportion of 2-point composite responders as defined by the responses in the quadrant treated in this current study (EN3835-202) who either maintained response, lost response but did not return to the study EN3835-202 baseline, or returned to the study EN3835-202 baseline. Proportion of 1-point composite responders as defined by the responses in the quadrant treated in the current study who either maintained response, lost response but did not return to the study EN3835-202 baseline, or returned to the study EN3835-202 baseline. Proportion of 2-point CR-PCSS responders as defined by the responses in the quadrant treated in this current study who either maintained response, lost response but did not return to the study EN3835-202 baseline, or returned to the study EN3835-202 baseline. Proportion of 1-point CR-PCSS responders as defined by the responses in the quadrant treated in the current study who either maintained response, lost response but did not return to the study EN3835-202 baseline, or returned to the study EN3835-202 baseline. CR-PCSS change from the study EN3835-202 baseline at Day 71, Day 90, Day 180, Day 270, and Day 360/end of study. PR-PCSS change from the study EN3835-202 baseline at Day 71, Day 90, Day 180, Day 270, and Day 360/end of study. Duration of response as defined by the time from onset of change from baseline of PR-PCSS and CR-PCSS in the quadrant treated in the current study until the time that the treated quadrant returned to the baseline PR-PCSS and CR-PCSS ratings from study EN3835-202.	

Section	Original Text	Revised Text
17.6.3 Measurement of Treatment Compliance	All doses are administered while the subjects are at the investigators' sites.	All doses are administered while the subjects are at the investigational site.
17.6.4 Adverse Events	The MedDRA will be used to code AEs. The version used in this study will be stated in the Data Management Plan. An AE (classified by preferred term) that started during the treatment period will be considered a TEAE if it was not present prior to the first dose of study drug, or was present prior to the first dose of study drug but increased in intensity during the treatment period. If more than 1 AE is reported prior to the first dose of study drug and coded to the same preferred term, then the AE with the greatest intensity will be used as the benchmark for comparison to the AEs occurring during the treatment period which were also coded to that preferred term. Any AE present prior to the first dose of study drug that increases in intensity during the treatment period will be re-entered with a new start date of the date of increased intensity. Descriptive statistics (the number and percentage) for subjects reporting TEAEs in each treatment group will be tabulated by system organ class and preferred term; by system organ class, preferred term, and severity; and by system organ class, preferred term, and relationship to study drug. If more than 1 AE is coded to the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to the study drug. SAEs and AEs leading to premature discontinuation of study drug will be summarized by preferred term and dose received. Listings will be presented for subjects with SAEs, subjects with AEs leading to discontinuation, and subjects who die (if any).	The MedDRA dictionary will be used to code AEs. The version used in this study will be stated in the Data Management Plan. Descriptive statistics (the number and percentage) for subjects reporting TEAEs will be tabulated by system organ class and preferred term; by system organ class, preferred term, and severity; and by system organ class, preferred term, and relationship to study drug. If more than 1 AE is coded to the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to the study drug. SAEs and AEs leading to premature discontinuation of study drug will be summarized. Listings will be presented for subjects with SAEs, subjects with AEs leading to discontinuation, and subjects who die (if any).
17.6.5 Vital Signs	Descriptive statistics for vital signs (eg, systolic and diastolic blood pressure, pulse rate, and body weight) and their changes from baseline at each visit and at the end of treatment visit will be presented.	Descriptive statistics for vital signs (eg, systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, and body weight) and their changes from baseline at each visit and at the end of treatment visit will be presented.

Section	Original Text	Revised Text
17.7 Immunogenicity Analyses	Binding antibody levels will be determined from samples collected on Days 1, 22, 43, and 71 during the treatment phase and Days 90, 180, 270 and 360 during the observational phase.	Binding antibody levels will be determined from samples collected on Days 1 and 71 during the treatment phase and Day 360 during the observational phase.
17.9 Interim Analysis	Two (2) interim analyses are planned. Following the breaking of the study drug blind in study EN3835-201, all follow-up safety data gathered prior to that time will be analyzed. The second interim analyses will occur following the Day 71 visit for all subjects treated with EN3835 in the current study. A preliminary data lock will be done on all treated quadrants and cellulite assessment and safety analyses will be done. The official database lock will occur after the last Day 360/end of study observational visit and all observational analyses on treated quadrants will be done.	Not applicable.
18.4 Study Drug Preparation	Refer to the Reconstitution Instructions in the Pharmacy Manual for detailed preparation instructions.	Refer to the Reconstitution Instructions for detailed preparation instructions.
18.4 Study Drug Preparation	Each vial of study drug powder for reconstitution will be diluted according to the instructions in the Pharmacy Manual.	Each vial of study drug powder for reconstitution will be diluted according to the Reconstitution Instructions.
19.1 Source Documents	Source documents include but are not limited to original documents, data and records such as hospital/ medical records (including electronic health records), clinic charts, lab results, subject diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, etc. At a minimum, all data required to be collected by the protocol should have supporting source documentation for entries in the eCRF, unless the protocol specifies that data can be recorded directly on/in the eCRF or other device.	This study allows for direct data entry (DDE) for selected data points as outlined below: • Inclusion/Exclusion • Vital signs including pre- and post-injection measurements • Height and body weight • CR-PCSS • Hexsel CSS • I-GAIS • Physical examinations • ECG results (if more than 1 year passed since ECG assessment) • Urine pregnancy test • Study drug administration All other data points, at a minimum, should have supporting source documentation for entries in the eCRF.
22.1 Data Collection	Study data will be collected from source documents and entered into an eCRF within the EDC system.	Study data will be collected by DDE or from source documents and entered into an eCRF within the EDC system.

Section	Original Text	Revised Text
22.1 Data Collection	Unless otherwise indicated, all data captured in the eCRF must first be captured in source documents. Data that can be directly recorded in the eCRF will be clearly identified in the section(s) of the protocol that describes the assessment(s).	DELETED TEXT
22.2 Study Documentation	Upon study completion, the Investigator will be provided with complete electronic copies of the CRF data for his/her files.	Upon study completion, the Investigator will be provided with complete electronic copies of the eCRF data for his/her files.

Amendment 2 was incorporated into the protocol on October 25, 2016. The major reasons for this amendment were to improve operational activities and clarifications, and optimize and reduce the number of blood sample collections needed to profile immunogenicity.

Section	Original Text	Revised Text
3 Sponsor Contact Information	[redacted]	[redacted]
3 Sponsor Contact Information	[redacted]	Medical Monitor email: [redacted]
3 Sponsor Contact Information	[redacted]	[redacted]
4 Synopsis, Study Period	Estimated date first subject enrolled: Jun-2016 Estimated date last subject completed: May-2017	Estimated date first subject enrolled: Oct-2016 Estimated date last subject completed: Sep-2017
4 Synopsis, Objectives, Secondary	To evaluate the durability of response to EN3835 in EFP severity over the 12-month post initial dosing of EN3835 in subjects previously receiving active treatment in study EN3835-201 using the Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS), the Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS), and the Hexsel Cellulite Severity Scale (CSS) To evaluate long-term response to EN3835 in assessments of EFP including subject satisfaction, Investigator Global Aesthetic Improvement Scale (I-GAIS), and Subject Global Aesthetic Improvement Scale (S-GAIS) To evaluate immunogenicity after exposure to EN3835	To assess safety and immunogenicity of re-treating or re-dosing a subject that had previously received treatment with EN3835 To evaluate the durability of response to EN3835 in EFP severity over the 12-month post initial dosing of EN3835 in subjects previously receiving active treatment in study EN3835-201 using the Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS) and the Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS) To evaluate long-term response to EN3835 in assessments of EFP including subject satisfaction, Investigator Global Aesthetic Improvement Scale (I-GAIS), and Subject Global Aesthetic Improvement Scale (S-GAIS) To assess cellulite severity assessments in quadrants treated in this study with EN3835.

Section	Original Text	Revised Text
		To evaluate immunogenicity after exposure to EN3835
4 Synopsis, Study Design	Treatments will be administered on days 1, 22, and 43; subjects will be assessed for safety on days 1, 22, 43, and 71 and for cellulite severity assessments on days 1, 43, and 71.	Treatments will be administered on Days 1, 22, and 43; subjects will be assessed for safety on Days 1, 22, 43, and 71 and for cellulite severity assessments at Screening visit and on Days 22, 43, and 71.
4 Synopsis, Diagnosis and inclusion/ exclusion criteria	**Qualification for the Open-label Treatment Phase of the Study** ***Inclusion criteria for treatment:*** Have participated in and completed the double-blind study EN3835-201 and all day 71 assessments	**Qualification for the Open-label Treatment Phase of the Study** ***Inclusion criteria for treatment:*** Have participated in and completed the double-blind study EN3835-201
4 Synopsis, Duration of study	**Follow-up**: For subjects treated with EN3835 in this study, subjects will be observed at treatment visits (Days 1, 22, and 43) and Day 71 after first injection.	**Follow-up**: For subjects treated with EN3835 in this study, subjects will be observed at treatment visits (Days 1, 22, and 43) and Day 71 after first injection. After Day 71, they will be observed every 3 months from their first exposure to EN3835 up to a maximum of 1 year.
5 Schedule of Events	NOTE: Observation visits (Table 2) in the open-label extension study begin after completion of double-blind study (day 71). Treatment sessions (Table 3), if elected, will begin when study drug blind is broken in study EN3835-201 while observation visits continue concurrently.	NOTE: Observation visits (Table 2) in the open-label extension study begin after completion of double-blind study (Day 71). Treatment sessions (Table 3), if elected, will begin after study drug blind is broken in study EN3835-201while observation visits continue concurrently.
5 Schedule of Events, Table 2, Collection of Samples: Anti-AUX-I/anti-AUX-II antibody level	Visit 1: X Visit 2: X Visit 3: X Visit 4: X	Visit 1: Visit 2: Visit 3: Visit 4: X
5 Schedule of Events, Table 3, Tx Visit 4 End of Treatment/Early Termination Day 71 …	Tx Visit 4 End of Treatment/ Early Termination Day 71 (±5 days)[b]	Tx Visit 4 End of Treatment/ Early Termination Day 71 (+5 days)[b]

Section	Original Text	Revised Text
5 Schedule of Events, Table 3, Procedures	Screening B[a]: Medical history/EFP history including previous treatments: X[k] Prior/Concomitant Medications/Procedures: X[k] Physical examination: Body weight: X Height: X Collection of samples: Clinical laboratory X Tx Visit 1: Prior/Concomitant Medications/Procedures: X	Screening B[a]: Medical history/EFP history including previous treatments: X[k,m] Prior/Concomitant Medications/Procedures: X[k,m] Physical examination: Body weight: X[m] Height: X[m] Collection of samples: Clinical laboratory: X[m] Tx Visit 1: Prior/Concomitant Medications/Procedures: X[m]
5 Schedule of Events, Table 3, Collection of Samples: Anti-AUX-I/anti-AUX-II antibody level	Tx Visit 1: X[e] Tx Visit 2: X[e] Tx Visit 3: X[e] Tx Visit 4: X	Tx Visit 1: X[e,m] Tx Visit 2: Tx Visit 3: Tx Visit 4: X
5 Schedule of Events, Table 3, footnotes	[a] Eligible subjects may choose additional treatment any time after the study drug blind is broken in study EN3835-201. Add	[a] After the study drug blind is broken in study EN3835-201, eligible subjects may elect to receive EN3835 treatments. [m] Do not conduct on subjects eligible and opting-in for a second course of treatment in the current study (EN3835-202) if Screening B visit or Day 1 visit for second treatment course is the same day as Day 71 of the first treatment course in this study or previous study EN3835-201.
9.2 Secondary Objectives	To assess safety and immunogenicity of re-treating or re-dosing a subject that had previously received treatment with EN3835 To evaluate the durability of response to EN3835 in EFP severity over the 12-month post initial dosing of EN3835 in subjects previously receiving active-treatment in study EN3835-201 using the PR-PCSS, the CR-PCSS, and the Hexsel CSS To evaluate long-term response to EN3835 in assessments of EFP including subject satisfaction, I-GAIS, and S-GAIS To assess cellulite severity assessments in quadrants treated in this study with EN3835	To assess safety and immunogenicity of re-treating or re-dosing a subject that had previously received treatment with EN3835 To evaluate the durability of response to EN3835 in EFP severity over the 12-month post initial dosing of EN3835 in subjects previously receiving active-treatment in study EN3835-201 using the PR-PCSS and the CR-PCSS To evaluate long-term response to EN3835 in assessments of EFP including subject satisfaction, I-GAIS, and S-GAIS To assess cellulite severity assessments in quadrants treated in this study with EN3835 To evaluate immunogenicity after exposure to EN3835

Section	Original Text	Revised Text
10.1 Study Design	Following the study drug blind being broken and communicated to centers, treatments of eligible subjects with EN3835 can begin at a visit at the discretion of the subject.	Following the study drug blind being broken and communicated to centers, eligible subjects may elect to receive EN3835 treatment.
11.1 Observation Phase	All subjects who have completed the double-blind study EN3835-201, including all day 71 assessments, and sign informed consent are eligible for enrollment in this open-label extension study and participation in the ongoing safety and cellulite evaluations.	All subjects who have completed the double-blind study EN3835-201 and sign the informed consent are eligible for enrollment in this open-label extension study and participation in the ongoing safety and cellulite evaluations.
11.2.1 Subject Inclusion Criteria for Treatment	Have participated in and completed the double-blind study EN3835-201 and all Day 71 assessments	Have participated in and completed the double-blind study EN3835-201
11.2.2 Subject Exclusion Criteria for Treatment	ADDED TEXT	Presence of any clinically relevant conditions, that in the opinion of the Investigator would interfere with completing the study including, but not limited to, visual problems, hearing problems, cognitive impairment or acute mental illness
12.1.3 Study Entry/ Observational Assessments	A subject who gives written informed consent and who satisfies all eligibility criteria (section 11) may be entered into the observational phase of the study and complete safety and cellulite severity assessments at 3-month intervals as detailed in Table 2.	A subject who gives written informed consent and who satisfies all eligibility criteria (section 11) may be entered into the observational phase of the study and complete safety and cellulite severity assessments at 3-month intervals as detailed in Table 2. The first visit will be determined by the date of enrollment in study EN3835-202 relative to the Schedule of Events for Study EN3835-202 (Table 2). For example, if a subject enrolls after the Day 90 visit window, the first observation visit for that subject would be Day 180.
12.1.4 Treatment Assessments (Optional)	If a subject received placebo in the double-blind study, she may be eligible for 2 treatments in the open-label study; if a subject received active drug in the double-blind study, she may be eligible for 1 additional treatment (3 treatment sessions) in the open-label study.	If a subject received placebo in the double-blind study, she may be eligible for 2 treatment courses in the open-label study; if a subject received active drug in the double-blind study, she may be eligible for 1 additional treatment course (3 treatment sessions) in the open-label study.
12.1.4 Treatment Assessments (Optional), Selection of Treatment Quadrant	The Investigator will then assess each of the 4 subject's quadrants live in real-time using the CR-PCSS.	The Investigator will then assess each of the subject's 4 quadrants live in real-time using the CR-PCSS.

Section	Original Text	Revised Text
12.1.4 Treatment Assessments (Optional), Selection of Treatment Quadrant	A subject who received placebo in the double-blind study may be treated in the same quadrant in the open-label study if the quadrant still meets all 3 criteria OR another qualifying quadrant may be selected for treatment by the Investigator and subject.	A subject who received placebo in the double-blind study may be treated in the same quadrant in the open-label study if the quadrant still meets all 3 criteria OR another qualifying quadrant may be selected for treatment by the subject.
12.1.4 Treatment Assessments (Optional), Selecting and Marking Dimples	The cellulite severity assessments using the PR-PCSS, CR-PCSS, and Hexsel CSS will be completed prior to dimple marking at treatment visits 2, 3, and 4/end of treatment.	The cellulite severity assessments using the PR-PCSS and CR-PCSS will be completed prior to dimple marking at treatment visits 2, 3, and 4/end of treatment.
12.1.4.1 Screening B (Days −14 to −1 Relative to Open-label Treatment Visit Day 1)	The Investigator will conduct live assessments of subject's cellulite severity of each quadrant using the CR-PCSS (section 13.1.1.4)	The Investigator will conduct independent live assessments of subject's cellulite severity of each quadrant using the CR-PCSS (section 13.1.1.4) after the subject completes her ratings and with no knowledge of the subject's ratings of her quadrants.
12.1.4.1 Screening B (Days −14 to −1 Relative to Open-label Treatment Visit Day 1)	Collection of samples for: Clinical laboratory testing including Anti-AUX-I and anti-AUX-II antibody testing (section 14.7) Urine pregnancy testing (section 14.7)	Collection of samples for: Clinical laboratory testing (section 14.7) Urine pregnancy testing (section 14.7)
12.1.4.2, Treatment Session 1 …	Treatment Session 1 (Visit 1B)	Treatment Session 1 (Treatment Visit 1)
12.1.4.2 Treatment Session 1 …, Pre-injection	Collection of samples for urine pregnancy testing (section 14.7)	Collection of samples for: anti-AUX-I and anti-AUX-II antibody testing (section 14.7.1) urine pregnancy testing (section 14.7)
12.1.4.3, Treatment Session 2 … and Treatment Session 3 …	Treatment Session 2 (Visit 2/Day 22 ± 3 Days) and Treatment Session 3 (Visit 3/Day 43 ± 3 Days)	Treatment Session 2 (Treatment Visit 2/ Day 22 ± 3 Days) and Treatment Session 3 (Treatment Visit 3/Day 43 ± 3 Days)
12.1.4.3 Treatment Session 2 … and Treatment Session 3 …, Pre-injection	Investigator live assessment of the severity of cellulite using the CR-PCSS (section 13.1.1.4)	Investigator will conduct an independent live assessment of the severity of cellulite using the CR-PCSS (section 13.1.1.4). The investigator will conduct the assessment of severity only after the subject has completed her rating of her quadrant and without knowledge of the subject's rating of her quadrant.

Section	Original Text	Revised Text
12.1.4.3 Treatment Session 2 … and Treatment Session 3 …	If no injections are given at treatment session 2, subjects will still return for the day 43 visit and the selected quadrant will again be evaluated by the subject (PR-PCSS) and Investigator (CR-PCSS).	If the Investigator rates the selected quadrant as 0, no injections will be given. If no injections are given at treatment session 2, subjects will still return for the Day 43 visit and the selected quadrant will again be evaluated by the subject (PR-PCSS) and Investigator (CR-PCSS).
12.1.4.4 Day 71 … End of Treatment/Early Termination	Day 71 (±5 Days) End of Treatment/Early Termination	Day 71 (+5 Days) End of Treatment/Early Termination
12.1.4.4 Day 71 … End of Treatment/Early Termination	Investigator cellulite assessments of selected quadrant using:	Investigator cellulite assessments of selected quadrant independently conducted; ie, with no knowledge of the subject's rating, using:
13.1.1.2 Subject Global Aesthetic Improvement Scale (S-GAIS)	The S-GAIS assessment will be done on day 71 of the treatment course and then at month 12 or the final study visit and compared back to the pre-dosing Screening B image (Baseline for treatment subjects) of the selected quadrant.	For subjects who elected to receive EN3835 treatment, the S-GAIS assessment will be done on Day 71 of the treatment course and then at month 12 or the final study visit and compared back to the pre-dosing Screening B image (Baseline for treatment subjects) of the selected quadrant.
13.1.1.6 Hexsel Cellulite Severity Scale	For subjects in the observation-only group, the Hexsel CSS will be done at month 3 and every 3 months thereafter and at the month 12 or the end of study visit. For subjects who elected to have EN3835 treatments, the Hexsel CSS will be done at 3-month intervals during the observation phase until the study drug blind is broken in study EN3835-201. The Hexsel CSS assessment will be done at Screening B visit and on day 71 of the treatment course and at month 12 or end of study visit. For the subjects electing treatment (re-treatment or re-dosing) with EN3835 the Investigator or qualified designee will use the Hexsel CSS to assess the severity of EFP in all quadrants at Screening B and the selected quadrant on day 71 of the course of treatment.	For subjects in the observation-only group, the Hexsel CSS will be done at the month 12 or the end of study visit. For the subjects electing treatment (re-treatment or re-dosing) with EN3835 the Investigator or qualified designee will independently use the Hexsel CSS to assess the severity of EFP in all quadrants at Screening B visit and the selected quadrant on Day 71 of the course of treatment and at month 12 or end of study visit.
14.6.1 Adverse Events of Special Interest	There are no AEs of special interest anticipated in this study. AEs such as bruising, ecchymosis, hematomas, and contusions that occur remote to the site of drug administration will be recorded as an AE or SAE as appropriate (see section 14.1.1, Adverse Events or section 14.1.2, Serious Adverse Events).	[redacted]

Section	Original Text	Revised Text
14.7 Clinical Laboratory and Immunogenicity Determinations	Urine pregnancy test kits will be supplied by the Sponsor.	DELETED TEXT
14.7.1 Anti-AUX-I and Anti-AUX-II Antibodies	Serum samples will be collected and may be tested for binding and neutralizing anti-AUX-I and anti-AUX-II antibodies at visit 1 through visit 4. Additionally, if a subject consents to treatment in the open-label study, serum samples for antibody testing will be collected before injection at treatment visits 1, 2, 3, and 4 of the open-label treatment period. A subset of subject samples will have neutralizing antibodies tested from day 1 and day 71 visits; additional samples may be analyzed if results or clinical signs warrant testing.	Serum samples will be collected and may be tested for binding and neutralizing anti-AUX-I and anti-AUX-II antibodies at visit 1 and visit 4. Additionally, if a subject consents to treatment in the open-label study, serum samples for antibody testing will be collected before injection at treatment visit 1 and at end of treatment/ early termination visit 4 of the open-label treatment period. A subset of subject samples may have neutralizing antibodies tested from Day 1 and Day 71 visits; additional samples may be analyzed if results or clinical signs warrant testing.
14.8 Vital Signs	These parameters include pulse rate, respiratory rate, systolic and diastolic blood pressure, and body weight.	These parameters include pulse rate, respiratory rate, systolic and diastolic blood pressure, and body temperature.
17.2 Subject Cohorts and Subject Populations	All efficacy and safety analyses will be done within the classified cohort. Durability of treatment effects defined as time period from injection to return to baseline cellulite severity ratings in a EN3835-treated quadrant will be determined for all subjects that were treated with EN3835 in either this study or study EN3835-201.	All efficacy and safety analyses will be done within the classified cohort. Durability of treatment effects defined as the time from onset of change from baseline of PR-PCSS and CR-PCSS in the quadrant treated in study EN3835-201 until the time that the treated quadrant return to baseline cellulite severity ratings of PR-PCSS and CR-PCSS in an EN3835-treated quadrant will be determined for all subjects that were treated with EN3835 in either this study or study EN3835-201.
17.6.1 Prior, Concomitant, and Follow-up Medication	The version used in this study will be stated in the Data Management Plan. Prior medication will be defined as any medication with a start date prior to the day 1 date and are collected at the screening visit and upon admission to the clinic on day −1.	The version used in this study will be stated in the Data Management Plan. Prior medication will be defined as any medication with a start date prior to the Day 1 date.
24.4 Use of Investigational Materials	The Investigator is responsible for monitoring subject's use of the study drug to ensure compliance with the protocol. All study supplies shall be returned to Endo Pharmaceuticals Inc. or its designee (this may include empty packaging such as bottles and blister cards). It is the Investigator's responsibility to ensure that subjects return their medication.	The Investigator is responsible for monitoring use of the study drug to ensure compliance with the protocol. All study supplies shall be returned to Endo Pharmaceuticals Inc. or its designee.

Section	Original Text	Revised Text
18.2 Study Drug Packaging and Labeling	Sterile vials of lyophilized EN3835 (formerly AA4500) and sterile diluent will be provided to the Investigator by Endo. Each kit will contain 1 vial each of EN3835 and sterile diluent.	Sterile vials of lyophilized EN3835 and sterile diluent will be provided to the Investigator by Endo. Each kit will contain 2 vials each of EN3835 and sterile diluent.
18.4 Study Drug Preparation	Designated study personnel will visually inspect the study drug vial to determine the integrity and acceptability of the lyophilized drug product for reconstitution.	Designated study personnel will visually inspect the study drug vials to determine the integrity and acceptability of the lyophilized drug product for reconstitution.
24.6 Subject Confidentiality	All subject records submitted to Endo Pharmaceuticals Inc. or its designee will be identified only by initials and code number.	All subject records submitted to Endo Pharmaceuticals Inc. or its designee will be identified only by initials and subject identification number.
24.6 Subject Confidentiality	The Investigator will adhere to all privacy laws to which she is subject.	The Investigator will adhere to all privacy laws to which he/she is subject.

Amendment 1 was incorporated into the protocol on July 5, 2016. The major reason for this amendment was to clarify that the investigators will conduct the assessment.

Section	Original Text	Revised Text
13.1.1.5 Investigator Global Aesthetic Improvement Scale (I-GAIS)	Subjects in the observation-only group will complete the I-GAIS as described below at the final study visit (month 12 or early termination) and a comparison back to the pre-treatment day 1 (Baseline) image of the assigned quadrant of the double-blind study.	Investigators will complete the I-GAIS on subjects in the observation-only group as described below at the final study visit (month 12 or early termination) and a comparison back to the pre-treatment Day 1 (Baseline) image of the assigned quadrant of the double-blind study.

3. SPONSOR CONTACT INFORMATION

Table 1: Sponsor Contact Information

Role in Study	Name	Telephone and Email Address
Clinical Research Scientist	[redacted]	[redacted]
Associate Director, Clinical Operations	[redacted]	[redacted]
Medical Monitor	[redacted]	[redacted]
SAE Reporting Pathway	Not applicable	[redacted]

A list of other key study personnel and vendors will be provided upon request separately for your reference.

4. SYNOPSIS

Name of Sponsor/Company: Endo Pharmaceuticals Inc.	
Name of Investigational Product: EN3835	
Name of Active Ingredient: Collagenase clostridium histolyticum	
Title of Study: A Phase 2, Open-label Extension Study of EN3835 in the Treatment of Edematous Fibrosclerotic Panniculopathy	
Lead Principal Investigator: To be determined	
Study period: Estimated date first subject enrolled: Oct-2016 Estimated date last subject completed: Jun-2018	**Phase of development:** Phase 2

Objectives:

Primary:

- The primary objective of this study is to assess long-term safety of EN3835 0.84 mg at scheduled intervals over 1 year (12 months) in all subjects with edematous fibrosclerotic panniculopathy (EFP) who elect to enroll in this open-label trial regardless of their decision to receive treatment (re-treatment or re-dosing) of open-label EN3835 or opt to receive no treatment.

Secondary:

- To evaluate safety and immunogenicity of re-treating or re-dosing a subject that had previously received treatment with EN3835
- To evaluate the durability of response to EN3835 in EFP severity over the 12-month post initial dosing of EN3835 in subjects previously receiving active treatment in study EN3835-201 using the Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS) and the Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS)
- To evaluate the durability of response to EN3835 in EFP severity beyond 12 months post initial dosing of EN3835 in subjects previously receiving active treatment in study EN3835-201 using the PR-PCSS and the CR-PCSS.
- To evaluate long-term response to EN3835 in assessments of EFP including subject satisfaction, Investigator Global Aesthetic Improvement Scale (I-GAIS), and Subject Global Aesthetic Improvement Scale (S-GAIS)
- To assess cellulite severity assessments in quadrants treated in this study with EN3835
- To evaluate immunogenicity after exposure to EN3835

Study Design: This study is a Phase 2 open-label study for the safety and efficacy of EN3835 in the treatment of EFP. To be eligible, a subject must have participated and completed the previous cellulite study EN3835-201. Subjects will be screened for study eligibility within 14 days prior to enrolling in this study (EN3835-202). Subjects will be assessed for safety and cellulite severity assessments approximately every 3 months from their first exposure to EN3835 in each treated quadrant. Subjects with at least 1 quadrant with moderate or severe level of cellulite will be eligible for treatment with EN3835 after unblinding of study EN3835-201; a quadrant that was treated with EN3835 in the previous study EN3835-201 will only be eligible for retreatment if the cellulite severity in that quadrant is rated at levels of cellulite severity at baseline or greater in study EN3835-201.

A treatment course will consist of 3 treatment sessions separated by 21 days. Treatment will be allowed in eligible subjects up to a maximum of 2 treatment courses including the treatment course in study

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EN3835-201 if subject was treated with EN3835. Each treatment session will consist of up to 12 injections (0.07 mg/0.3 mL per injection) of EN3835 for a dose of 0.84 mg and volume of 3.6 mL. Only a quadrant with moderate (rating of 3) or severe (rating 4) level of severity as assessed by the subject and investigator using the PR-PCSS and the CR-PCSS, respectively, will be eligible for treatment; if more than 1 eligible quadrant exists, the quadrant selected will be at the discretion of the subject. Treatments will be administered on Days 1, 22, and 43; subjects will be assessed for safety on Days 1, 22, 43, and 71 and for cellulite severity assessments at Screening visit and on Days 22, 43, and 71. After Day 71, they will be observed every 3 months in each treated quadrant (including both open-label and double-blind treated quadrants, if different quadrants were treated across both studies).

Durability of open-label treatment with EN3835 will be assessed for up to 1 year (Day 360). Durability beyond Day 360 will be assessed in subjects who received active treatment in EN3835-201 and showed a composite improvement of at least 1 level on both the CR-PCSS and the PR-PCSS. In these subjects, the original quadrant treated in EN3835-201 will be assessed until the end of the current study, in addition to any treated quadrants occurring in the current study. Assessments of durability beyond Day 360 may also include subjects who opted not to receive additional treatments in EN3835-202.

Number of subjects (planned): Approximately 350

Study center(s): 15 sites in the United States

Diagnosis and inclusion/exclusion criteria:

Qualification for the Open-label Observation Phase of the Study

Inclusion criteria for observation:

1. Voluntarily sign and date an informed consent agreement
2. Have participated in and completed the double-blind study EN3835-201
3. Be willing to apply sunscreen to any treated quadrant before each exposure to the sun while participating in the study (ie, screening through end of study)

Exclusion criteria for observation:

None

Qualification for the Open-label Treatment Phase of the Study

Inclusion criteria for treatment:

1. Voluntarily sign and date an informed consent agreement
2. Have participated in and completed the double-blind study EN3835-201
3. Be a female ≥18 years of age
4. At Screening B visit, have at least 1 quadrant with:
   a. a score of 3 or 4 (moderate or severe) as reported by the subject (PR-PCSS), and
   b. a score of 3 or 4 (moderate or severe) as reported by the Investigator (CR-PCSS), and
   c. a Hexsel Cellulite Severity Scale (CSS) score no greater than 13
5. Be willing to apply sunscreen to the selected treatment quadrant before each exposure to the sun while participating in the study (ie, Screening B through end of study)
6. Be judged to be in good health, based upon the results of a medical history, physical examination, and laboratory profile at Screening B
7. Have a negative urine pregnancy test at Screening B and before injection of study drug and be using an effective contraception method (eg, abstinence, intrauterine device [IUD], hormonal [estrogen/progestin] contraceptives, or double barrier method) for at least 1 menstrual cycle

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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

8. Be willing and able to cooperate with the requirements of the study
9. Be able to read, complete and understand the patient-reported outcomes rating instruments in English

***Exclusion criteria for treatment**:*

1. Has used any of the following for the treatment of EFP on the legs or buttock within the timelines identified below or intends to use any of the following at any time during the course of the study:
   - Liposuction on the side of the body selected for treatment during the 12-month period before injection of study drug
   - Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; or surgery (including subcision and/or powered subcision) within the selected treatment quadrant during the 12-month period before injection of study drug
   - Endermologie or similar treatments within the selected treatment quadrant during the
   - 6-month period before injection of study drug
   - Massage therapy within the selected treatment quadrant during the 3-month period before injection of study drug
   - Creams (eg, Celluvera™, TriLastin®) to prevent or mitigate EFP within the selected treatment quadrant during the 2-week period before injection of study drug
2. Is presently nursing a baby or providing breast milk for a baby
3. Intends to become pregnant during the study
4. Has received an investigational drug or treatment within 30 days before injection of study drug
5. Has a known systemic allergy to collagenase or any other excipient of study drug
6. Is currently receiving or plans to receive anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication (except for ≤150 mg aspirin daily) within 7 days before injection of study drug
7. Has a known recent history of stroke, bleeding, or other medical condition, which in the investigator's opinion would make the subject unsuitable for enrollment in this phase of the study
8. Presence of any clinically relevant conditions, that in the opinion of the Investigator would interfere with completing the study including, but not limited to, visual problems, hearing problems, cognitive impairment or acute mental illness

Qualification of Subjects Assessed for Durability Beyond Day 360

Inclusion criteria for observation:

1. Voluntarily sign and date an informed consent agreement
2. Participated in and completed the double-blind study EN3835-201
3. Received active EN3835 in the double-blind study EN3835-201
4. Achieved an improvement of at least 1 level on both the CR-PCSS and the PR-PCSS at the same visit on or before Day 71 in the double-blind study EN3835-201

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5. Be willing to apply sunscreen to the EN3835-201 treated quadrant before each exposure to the sun while participating in the study (ie, screening through end of study)

Exclusion criteria for observation:

1. Retreatment of the same quadrant in EN3835-202 and EN3835-201.
2. Has used any of the following for the treatment of EFP on the thighs or buttocks since treatment in EN3835-201, or intends to use any of the following at any time during the course of the study:
   - Liposuction on the side of the body selected for treatment
   - Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; or surgery (including subcision and/or powered subcision) within the selected treatment quadrant
   - Endermologie or similar treatments within the selected treatment quadrant
   - Massage therapy within the selected treatment quadrant
   - Creams (eg, Celluvera™, TriLastin®) to prevent or mitigate EFP within the selected treatment quadrant

Investigational product, dosage and mode of administration: EN3835, 0.84 mg, subcutaneous. A dose of 0.84 mg of EN3835 will be administered as up to 12 subcutaneous injections (0.3-mL injection administered as three 0.1-mL aliquots per injection, up to 12 injections per treatment session) for a maximum volume of 3.6 mL per treatment session. A treatment course will consist of 3 treatment sessions at 21 days intervals, ie, treatments on Days 1, 22, and 43 of each treatment course.

For the observational periods of this study, subjects will be assessed for safety and cellulite severity assessments at approximately 3-month intervals following their first exposure to EN3835 in each treated quadrant. Durability will be assessed for up to 24 months in subjects that received active EN3835 in the EN3835-201 study and showed at least a 1-level composite PR-PCSS/CR-PCSS reduction in cellulite severity.

Duration of study:

A minimum of 12 months from first exposure to EN3835 in study EN3835-201 and 12 months from first exposure in any additional treated quadrants in the EN3835-202 study

Screening Phase: Up to 14 days

Observational Phase: Subjects will be assessed at visits that occur approximately every 3 months after the first exposure to EN3835 in each treated quadrant. Durability will be assessed for up to 24 months in subjects that received active EN3835 in the EN3835-201 study and showed at least a 1-level composite PR-PCSS/CR-PCSS reduction in cellulite severity.

Follow-up: Subjects will be assessed at visits that occur approximately every 3 months after the first exposure to EN3835 in each treated quadrant. For subjects treated with EN3835 in this open-label study, subjects will be observed at treatment visits (Days 1, 22, and 43) and Day 71 after first injection. After Day 71, they will be observed every 3 months in each treated quadrant. Durability will be assessed for up to 24 months in subjects that received active EN3835 in the EN3835-201 study and showed at least a 1-level composite PR-PCSS/CR-PCSS reduction in cellulite severity.

Reference therapy, dosage and mode of administration: Not applicable

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Criteria for evaluation:

Efficacy:

- PR-PCSS while viewing digital images of the selected quadrant: 5-point scale ranging from 0 (no cellulite) to 4 (severe cellulite) (approximately every 3 months after initial injection [either an injection in previous study EN3835-201 or after an injection in this study]). If treatment is administered in this study, PR-PCSS will be obtained at Screening B (Baseline), Days 22, 43, and 71 after initial treatment within this study.
- Investigator using the CR-PCSS by live assessment: 5-point scale ranging from 0 (no cellulite) to 4 (severe cellulite) (every 3 months after initial injection [either an injection in previous study EN3835-201 or after an injection in this study]). If treatment is administered in this study, CR-PCSS will be obtained at Screening B (Baseline), Days 22, 43, and 71 after initial treatment within this study.
- Investigator rating of cellulite severity using the total score from the Hexsel CSS: scores can range from 0 (no cellulite) to 15 (extremely severe cellulite) (Day 360). If treatment is administered in this study, Hexsel CSS will be obtained in this study at Screening B (Baseline) and Day 71 after initial treatment within this study.
- I-GAIS: 7-point scale ranging from 3 (very much improved) to −3 (very much worse) (Day 71)
- S-GAIS: 7-point scale ranging from 3 (very much improved) to −3 (very much worse) (Day 71)
- Subject satisfaction with cellulite treatment assessment: 5-point scale ranging from 2 (very satisfied) to −2 (very dissatisfied) (Day 71)

Safety:

Safety will be assessed throughout the study through the recording of:

- Adverse events (AEs)
- Vital signs
- Clinical laboratory tests
- Immunogenicity assessment (ie, assessed through the determination of binding and neutralizing anti-AUX-I and anti-AUX-II antibody levels)

In addition, for subjects treated with EN3835 in this study, injection site reactions/local tolerability in treated quadrant (through subject and Investigator reporting) will be assessed.

Statistical methods:

Sample Size Consideration:

Approximately 350 subjects are planned to obtain adequate long-term safety data for this study.

Analysis Populations:

Observational population: The Observational population is defined as all subjects rolled over from study EN3835-201 who do not receive any treatment in the current study.

Safety population: The Safety population is defined as all enrolled subjects who received at least 1 injection of EN3835 in this study.

Effectiveness population: This population is defined as all safety subjects who have a baseline and at least 1 post-injection evaluation of both the CR-PCSS and PR-PCSS.

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Durability Population: This population is defined as all active responders who have both CR-PCSS and PR-PCSS at 180 days or above. The active responders are subjects treated with EN3835 with improvements of at least 1 level on each scale (CR-PCSS and PR-PCSS) from the baseline.

Efficacy Evaluations:

The composite endpoints for cellulite severity assessment, the proportions of composite responders with improvement of 2 (or 1) or better on each scale (CR-PCSS and PR-PCSS), will be summarized as numbers and percentages by study days (visit). The analysis will be based on the Effectiveness population.

All other endpoints including observational endpoints will be summarized by study days using appropriate descriptive statistics. The descriptive statistics will include the number and percentage for categorical response variables and number, mean, standard deviation, minimum, and maximum for continuous variables. Durability of treatment effect will be based on the durability populations.

Safety Analysis:

The following variables are safety endpoints:

- AEs: Mapped to preferred term using the Medical Dictionary for Regulatory Activities (MedDRA)
- Vital signs
- Clinical laboratory tests

AEs will be summarized by proportion of subjects reporting each event. Descriptive statistics will be presented for actual and change from baseline at each visit for vital signs and for each clinical laboratory test parameter.

Immunogenicity: Anti-AUX-I and anti-AUX-II antibody levels will be summarized using descriptive statistics for the actual value at the visit.

5. SCHEDULE OF EVENTS

NOTE: Observation visits (Table 2) in the open-label extension study begin after completion of double-blind study (Day 71). Treatment sessions (Table 3), if elected, will begin after study drug blind is broken in study EN3835-201while observation visits continue concurrently.

Table 2: Observation Assessments

Procedures	Screening A[a] (≥Day 71 Visit of Double-blind Study)	Visit 1 Day 90[b] (±7 days)	Visit 2 Day 180[b] (±7 days)	Visit 3 Day 270[b] (±7 days)	Visit 4 End of Study/ Early Termination Day 360[b,f] (±7 days)
Informed Consent	X				
Inclusion/Exclusion	X				
Digital photography		X[c]	X[c]	X[c]	X[c]
Prior/Concomitant Medications/Procedures	X	X	X	X	X
Body weight		X	X	X	X
Vital signs		X	X	X	X
Collection of samples:					
• Clinical laboratory					X
• Anti-AUX-I/anti-AUX-II antibody level					X
Subject cellulite assessments:					
• Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS)		X[d,e]	X[d,e]	X[d,e]	X[d,e]
• Subject Global Aesthetic Improvement (S-GAIS)					X[d,e]
• Subject satisfaction with cellulite treatment assessment					X[d,e]
Investigator cellulite assessments:					
• Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)		X[e]	X[e]	X[e]	X[e]
• Hexsel Cellulite Severity Scale (CSS)					X[e]
• Investigator Global Aesthetic Improvement (I-GAIS)					X[e]
Injection site reactions/local tolerability in assigned quadrant from EN3835-201 study		X	X	X	X
Adverse events	Monitored Throughout Study				

[a] Informed consent for open-label observation assessments and optional treatment election.
[b] Four (4) visits at 3-month periods begin 90 days after Day 1 of the double-blind study (EN3835-201) (ie, within 20 days ± 4 days of completion of double-blind study).
[c] Only the treated quadrant(s) is photographed. For subjects participating in observation-only visits, the quadrant treated in the double-blind study (EN3835-201) is photographed; for subjects with open-label treatment (treated with EN3835 in study EN3835-202), the treated quadrant is photographed.
[d] Assessment made via viewing digital image photograph.
[e] Assessment of treated quadrant(s) only.
[f] For subjects treated with active EN3835 in the double-blind study and having a different quadrant treated in the open-label study, refer to Table 4 for continued assessments of the double-blind treated quadrant for durability beyond Day 360.
NOTE: Subject cellulite assessments must be completed before the Investigator cellulite assessments are conducted at each visit.

Table 3: Treatment Session Assessments

Procedures	Screening B[a] (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/ Early Termination Day 71 (+5 days)[b]
Inclusion/Exclusion	X				
Digital photography	X[c]	X[c,d]	X[c,d]	X[c,d]	X[c]
Medical history/EFP history including previous treatments	X[k,m]				
Prior/Concomitant Medications/Procedures	X[k,m]	X[m]	X	X	X
Physical examination:	X				
• Body weight	X[m]		X[e]	X[e]	X
• Height	X[m]				
Vital signs	X	X[f]	X[f]	X[f]	X
12-lead ECG	X[l]				
Collection of samples:					
• Clinical laboratory	X[m]				X
• Anti-AUX-I/anti-AUX-II antibody level		X[e,m]			X
• Urine pregnancy testing	X	X[e]	X[e]	X[e]	
Subject cellulite assessments:					
• Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS)	X[g,h]		X[e,g,h]	X[e,g,h]	X[g,h]
• Subject Global Aesthetic Improvement (S-GAIS)					X[g,h]
• Subject satisfaction with cellulite treatment assessment					X[g,h]
Investigator cellulite assessments:					
• Selection of dimples to be treated within selected quadrant		X[e]	X[e]	X[e]	
• Marking the dimples to be treated within selected quadrant		X[e]	X[e]	X[e]	
• Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)	X[h]		X[e,h]	X[e,h]	X[h]
• Hexsel Cellulite Severity Scale (CSS)	X[h,i]				X[h]
• Investigator Global Aesthetic Improvement (I-GAIS)					X[h]
Confirm Eligibility	X	X[e]			
Select Quadrant	X[j]				
Study drug administration		X	X	X	
Injection site reactions/local tolerability in selected quadrant		X	X	X	X
Adverse events	Monitored Throughout Study				

[a] After the study drug blind is broken in study EN3835-201, eligible subjects may elect to receive EN3835 treatments.
[b] Upon completion of treatment, subject will be followed at 3-month intervals as in Table 2; if study terminates early, subject will be followed through Visit 4 (Day 71). If subject received placebo in the double-blind study (EN3835-201), she may be eligible for a total of 2 courses of treatment (a total of 6 treatment sessions) in this study.
[c] All 4 quadrants are photographed at screening; at other visits, the selected quadrant only is photographed.
[d] Before and after marking the dimples.
[e] Before injection.
[f] Up to 4 hours before injection; approximately 15 and 30 minutes after injection. Vital signs must be stable before the subject is discharged.
[g] Assessment made via photograph (if treatment session, use photograph taken before marking dimples).
[h] All 4 quadrants are assessed at the Screening B visit; at other visits, the selected quadrant only is assessed.
[i] Initial Hexsel CSS at screening must be ≤13 on selected quadrant (Appendix C).
[j] To qualify for treatment, the selected quadrant must have a score of 3 or 4 (moderate or severe) in both the CR-PCSS and PR-PCSS, and a Hexsel CSS score ≤13; to qualify a quadrant that had been previously treated with EN3835 in study EN3835-201, the quadrant must have CR-PCSS and PR-PCSS scores equal to or greater than study EN3835-201 baseline scores and a Hexsel CSS score ≤13.
[k] Medical history and prior medications will be based on EN3835-201 eCRF; only updates and concomitant medications need to be captured at Screening B visit.
[l] Do not conduct if Screening B visit date is within 12 months of obtaining an ECG during the double-blind study (EN3835-201).
[m] Do not conduct on subjects eligible and opting-in for a second course of treatment in the current study (EN3835-202) if Screening B visit or Day 1 visit for second treatment course is the same day as Day 71 of the first treatment course in this study or previous study EN3835-201.

ECG=Electrocardiogram; eCRF=Electronic case report form; EFP=Edematous fibrosclerotic panniculopathy; Tx=Treatment
NOTE: Subject cellulite assessments must be completed before the Investigator cellulite assessments are conducted at each visit.

Table 4: Assessments for Durability (Beyond Day 360)

Procedures	Long-term Durability Visit 1 Day 450[a] (±30 days)	Long-term Durability Visit 2 Day 540[a] (±30 days)	Long-term Durability Visit 3 Day 630[a] (±30 days)	End of Long-term Durability Study Day 720[a] or EOS/ET (±30 days)
Informed Consent	X			
Inclusion/Exclusion	X			
Digital photography	X	X	X	X
Medical history/EFP history including previous treatments	X[b]			
Prior/Concomitant Medications/Procedures	X[b]	X	X	X
Subject cellulite assessments:				
• Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS)	X[c,d]	X[c,d]	X[c,d]	X[c,d]
Investigator cellulite assessments:				
• Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)	X[d]	X[d]	X[d]	X[d]
• Hexsel Cellulite Severity Scale (CSS)	X[d]	X[d]	X[d]	X[d]
Adverse events	Monitored Throughout Study			

[a] Days listed reflect time from Day 1 visit in the double-blind study (EN3835-201).
[b] Only updates to medical history, prior medications, and concomitant medications need to be captured at this visit.
[c] Assessment made via photograph.
[d] Only the quadrant treated with active EN3835 in study EN3835-201 is assessed for subjects participating in durability assessments beyond Day 360.
EFP=Edematous fibrosclerotic panniculopathy; EOS=End of study; ET=Early termination

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7. LIST OF ABBREVIATIONS

The following abbreviations and specialist terms are used in this study protocol.

Table 5: Abbreviations and Specialist Terms

Abbreviation	Definition
AE	Adverse event
Assigned quadrant	Assigned quadrant (ie, left or right buttock, or the left or right posterolateral thigh) that was suitable for treatment and was randomly assigned in the double-blind study (EN3835-201). To be suitable for treatment the quadrant must have an Investigator CR-PCSS and subject PR-PCSS score of 3 or 4 and a Hexsel CSS score of no greater than 13 at Screening B visit and at Day 1 visit.
AUX-I	Clostridial class I collagenase
AUX-II	Clostridial class II collagenase
CFR	Code of Federal Regulations
CRF	Case report form
CR-PCSS	Clinician-Reported Photonumeric Cellulite Severity Scale
CSS	Cellulite Severity Scale
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EFP	Edematous fibrosclerotic panniculopathy
FDA	Food and Drug Administration
GCP	Good clinical practice
HREC	Human research ethics committee
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
I-GAIS	Investigator Global Aesthetic Improvement Scale
IND	Investigational new drug
IRB	Institutional review board
ITT	Intent-to-treat
kDa	Kilodalton
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
PCS	Potentially clinically significant
PR-PCSS	Patient-Reported Photonumeric Cellulite Severity Scale
Qualified designee	Qualified by education and training to perform the study procedure (eg, sub-Investigator, nurse)

Table 5: Abbreviations and Specialist Terms (Continued)

Abbreviation	Definition
SAE	Serious adverse event
SAP	Statistical Analysis Plan
Selected quadrant	Quadrant (ie, left or right buttock, or the left or right posterolateral thigh) that is suitable for treatment and is selected by patient and investigator for treatment. To be suitable for treatment the quadrant must have an Investigator CR-PCSS and subject PR-PCSS score of at least 3 or 4 and a Hexsel CSS score of no greater than 13 at Screening B visit.
S-GAIS	Subject Global Aesthetic Improvement Scale
TEAE	Treatment-emergent adverse event; adverse events that occur on or after the first injection of study drug

8. INTRODUCTION

8.1. Edematous Fibrosclerotic Panniculopathy

Edematous fibrosclerotic panniculopathy (EFP), commonly known as cellulite, has been defined as a local metabolic disorder of subcutaneous tissues that results in an alteration of skin topography.(1) The condition manifests as dimpled skin, described as an orange-peel, cottage cheese, or mattress texture, particularly in the gluteal-femoral region.(2,3) EFP is caused by herniation of subcutaneous fat lobules through the dermohypodermal junction. This creates an uneven surface with dimpling.(1) EFP is a medical condition resulting in a potentially cosmetically unacceptable alteration of the skin, and affects an estimated 85% to 98% of postpubertal women.(1,3)

The pathophysiology of EFP is not completely understood, but there are 3 main theories: edema resulting from excessive hydrophilia of the intercellular matrix, alteration of the regional microcirculation, and different anatomical conformation of collagenous subcutaneous tissues in women versus men.(4)

It is known that EFP is different from generalized obesity. In generalized obesity, adipocytes undergo hypertrophy and hyperplasia that are not limited to the pelvis, thighs, and abdomen.(1) In areas of EFP, adipocytes have physiologic and biochemical properties that differ from adipose tissue located elsewhere. Large, metabolically-stable adipocytes characterize EFP-prone areas; thus, the responsiveness to catecholamine-induced lipolysis is less in EFP tissues compared to visceral fat, which has the greatest responsiveness.(1)

Subcutaneous fat lobes are separated from one another by thin, usually rigid strands of collagenous connective tissues, which cross the fatty layers and connect the dermis to the underlying fascia. These septa stabilize the subcutis and divide the fat. In EFP, shortening of the collagen septa due to fibrosis provokes retraction at the insertion points of the trabeculae, causing the depressions that characterize EFP.(2) There are a higher percentage of thinner, perpendicular hypodermal septa in women with EFP than in men.(1) Weight gain makes EFP more noticeable, but it may be present even in thin subjects. Genetics may also play a role since EFP tends to run in families.

8.2. Current Edematous Fibrosclerotic Panniculopathy Treatments

There are therapies that have been utilized in an attempt to treat cellulite. Despite multiple therapeutic modalities, there is little scientific evidence that any of these treatments are beneficial. In fact, much of the evidence is anecdotal, subjective, or based only on patient self-assessment.(5) Some of the historical treatments for EFP have included:

- Weight loss: Weight loss generally decreases the severity of EFP but may only have a variable effect on EFP grades.(6)
- Pharmacological agents (eg, xanthines, retinoids, lactic acid, and herbals): Although there are numerous topical treatments that are available over the counter, there are no well-designed or large-scale studies demonstrating the effectiveness of any of these

therapies.(5) Additionally, ingredients in some of the topical treatments are unknown and may pose an increased risk for adverse effects.(5)

- Massage: Endermologie or lipomassage kneads the skin between rollers. This type of vigorous massage is posited to increase blood flow and reduce excess fluid in EFP prone areas. In a 12-week, randomized, controlled study of 52 women that examined the effectiveness of either endermologie or aminophylline versus a combination of both, there was no statistical difference in the thigh measurement between subjects.(7)
- Liposuction: Liposuction can reshape the body, but it does not typically correct cellulite as it does not interrupt collagen septae in a directed fashion. Additionally, liposuction is not a recommended treatment for cellulite given the potential for poor cosmetic outcome.(5,6)
- Mesotherapy: Mesotherapy involves injecting solutions containing various substances, eg, methylxanthines, to dissolve subcutaneous fat; however, this type of therapy often results in unwanted side effects, including infection, urticarial reactions, and bumpy or uneven skin contours.(6) To date, there are no regulatory approved mesotherapy mixtures for the treatment of EFP.
- Radiofrequency: Radiofrequency systems may temporarily improve the appearance of EFP after a series of treatments; but long-term efficacy has not been demonstrated.(6)
- Subcision: Subcision is an invasive surgical technique that severs the septa holding fat lobules that cause the skin dimpling associated with EFP. In a study conducted by Hexsel and Mazzuco, 232 subjects had subcision for the treatment of EFP.(8) Although 78% of subjects were satisfied after 1 treatment, there were no objective criteria by which to assess improvement, thereby limiting the value of this study. Additionally, side effects reported in this study included pain, bruising for 3 to 6 months, hyperpigmentation for 2 to 10 months, and skin puckering.(5,6) These effects are most likely due to the trauma from shearing the septa with a large gauge needle (eg, 16 or 18 gauge) or other cutting devices.
- Powered subcision: Powered subcision is a surgical technique utilizing a powered needle apparatus to sever the septa holding fat lobules that cause skin dimpling associated with EFP. The Cellfina® powered subcision device was recently approved by Food and Drug Administration (FDA; 2015) for the treatment of cellulite.
- Laser: Intense pulsed light has been investigated for the treatment of cellulite. Triactive® is an FDA-approved low-fluorescence 810-nm light source combined with a 915-nm laser. In a study of 16 female subjects who underwent 12 treatments with the Triactive, 21% had improvement (based on 5 blinded Investigators' analysis of photographs with respect to appearance of cellulite, skin tone, and texture) of their cellulite.(9) The CelluLaze™ system was used to treat cellulite on the thighs of 10 healthy women.(10) In this Investigator-initiated study, subjects received a single treatment with a 1440-nm laser. During the CelluLaze procedure, which is performed under a local tumescent and general anesthetic, the physician inserts a small cannula through the skin and the device technology directs controlled, laser thermal energy to

the treatment zones. The laser is designed to diminish the lumpy pockets of fat by melting the hypodermal fat; release the areas of skin depression through thermal subcision of the septal tissue; and increase the elasticity and thickness of the skin by melting the fat in the dermal invaginations. Subjective physician and subject evaluations indicated improvement in the appearance of cellulite and high patient satisfaction that persisted for a year. For both the Triactive and CelluLaze studies, there were no control groups and significance was not tested.

There remains an unmet medical need for safe and effective nonsurgical therapies to improve the esthetic outcome in women with cellulite. To effectively treat cellulite, a therapeutic approach may require disruption of the dermal septa, which are composed of collagen and cause the skin dimpling which is bothersome to many women.

8.3. EN3835 (Collagenase Clostridium Histolyticum)

Endo Pharmaceuticals Inc. (Endo) is developing EN3835 for the treatment of EFP. Because EN3835 is a proteinase that can hydrolyze the triple-helical region of collagen under physiological conditions, EN3835 has the potential to be effective in lysing subdermal collagen, such as those observed in the dermal septa, which are the underlying cause of the skin dimpling in women with EFP. EN3835 targets the collagenase structural matrix (eg, dermal septa) at the site of injection and does not require systemic exposure to be effective.

EN3835 is a parenteral lyophilized product comprised of 2 collagenases in an approximate 1:1 mass ratio, Collagenase I (AUX-I, Clostridial class I collagenase) and Collagenase II (AUX-II; Clostridial class II collagenase). These collagenases are isolated and purified from the fermentation of *Clostridium histolyticum*. Collagenase AUX-I is a single polypeptide chain containing approximately 1,000 amino acids of known sequence and with a molecular weight of 114 kDa. Collagenase AUX-II is also approximately 1,000 amino acids long and has a molecular weight of 113 kDa. These 2 collagenases are not immunologically cross-reactive and have different specificities, such that together they become synergistic, providing a very broad hydrolyzing reactivity toward collagen. Clostridial collagenases are proteinases that can hydrolyze the triple-helical region of collagen under physiological conditions.

EN3835 is currently approved for: 1) the treatment of adults with Dupuytren's contracture with a palpable cord and, 2) for the treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy.

8.3.1. Studies with EN3835 for the Treatment of Edematous Fibrosclerotic Panniculopathy

The studies summarized in this section are described in more detail in the Investigator's Brochure (IB).

8.3.1.1. Investigator-Initiated Proof-of-Concept Study

In an Investigator-initiated pilot study, 10 female subjects received EN3835 in the treatment of cellulite.(11) A 10×10-cm oval area was outlined on the posterolateral thigh and 0.58 mg EN3835 was injected using a template as 5 concurrent subcutaneous injections of 0.116 mg per injection. Subjects were followed up to 180 days after injection for reduction of the cellulite appearance in the injected area. At 1 month post injection, the area of cellulite (as measured from

photographs) was reduced 89% from baseline. Patient satisfaction score was 1.75 at month 6 (1=completely satisfied, 4=not satisfied). Side effects included the local events of injection area soreness, ecchymosis, and mild edema; these resolved within a mean of 18 days. The results from this study suggest that the collagen septa of EFP may be an appropriate substrate for lysis with injectable collagenase, and that treatment with collagenase appears to be tolerable and possibly effective. However, due to the paucity of the data, no conclusions could be drawn regarding dose, frequency, and injection technique.

8.3.1.2. Endo-Sponsored Phase 1b Dose-Escalation Study AUX-CC-830

A dose-ranging Phase 1b dose escalation study (AUX-CC-830) used a template arrangement of injections as was used in the Investigator-initiated pilot study but injected a matrix of doses, concentrations and injectate volumes to select doses for further development. This Phase 1b study showed efficacy results suggesting that collagenase clostridium histolyticum (CCH) may be effective in the treatment of EFP based on global aesthetic improvement at Day 90 with ratings of "improved" by 43.4% of Investigators and 52.5% of subjects. The majority of subjects (71.7%) were "quite satisfied" or "very satisfied" with treatment on Day 90. Adverse events (AEs) were local injection site events (bruising, pain, erythema, and edema) were mild or moderate and resolved within a period of 3 weeks.

8.3.1.3. Endo-Sponsored Phase 2a Dose-Ranging Study AUX-CC-831

The Phase 2a study (AUX-CC-831) was a double-blind, placebo-controlled, dose-ranging study of 150 women randomized to 0.06, 0.48, or 0.84 mg of CCH; or placebo in a 5:5:5:3 ratio. Each subject could receive up to 3 treatment sessions of study drug separated by approximately 21 days. Efficacy in this study was evaluated based on Investigator Global Aesthetic Improvement Scale (GAIS-I) and Subject Global Aesthetic Improvement Scale (GAIS-S) along with other measures of treatment efficacy. Improvements were observed in cellulite appearance based on the statistically significant changes in the appearance of cellulite based on both the GAIS-I and GAIS-S scores for the high and mid doses compared to placebo ($p<0.05$). The majority of the patients were either satisfied or very satisfied with the results of their cellulite treatment with the mid and high doses compared to placebo ($p<0.05$). Similar to the AEs reported in subjects in the previous study (AUX-CC-830) and subjects who received EN3835 for Dupuytren's contracture and Peyronie's disease, the majority of AEs occurred at the site of injection and resolved before the next scheduled treatment session.

8.3.1.4. Endo-Sponsored Phase 2b Study EN3835-201

EN3835-201 was a double-blind, placebo-controlled study of 350 adult women randomized to EN3835 0.84 mg or placebo in a 1:1 ratio. Each subject received up to 3 treatment sessions of study drug separated by approximately 21 days; last visit was Day 71. Efficacy was evaluated using a Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS), a Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS), the Hexsel Cellulite Severity Scale (CSS), Investigator Global Aesthetic Improvement Scale (I-GAIS), Subject Global Aesthetic Improvement Scale (S-GAIS), and a subject satisfaction assessment. Subjects that completed study EN3835-201 were offered the option of participating in study EN3835-202.

8.4. Summary of Nonclinical Studies

Nonclinical studies necessary to support clinical studies have been performed and are summarized in the IB. Nonclinical studies in the following areas were performed: toxicology, reprotoxicity, genotoxicity, and carcinogenicity.

8.5. Summary of Known Risks and Benefits

A summary of safety risks is provided in the IB. The following events have been commonly observed in prior studies: injection site AEs such as bruising, edema, erythema and pain.

There are previously generated potential clinical benefits associated with EN3835 in treating EFP, however, such potential benefits need further clinical evaluation. It is hoped that data from this clinical study will demonstrate a measurable sustained or durable clinical benefit of EN3835 in EFP as well as longer term safety.

8.6. Rationale

This study will allow an evaluation of longer term safety (over 12 months) following EN3835 treatment of subjects with EFP. Additionally, although uncontrolled, an assessment of cellulite assessments (efficacy) of EN3835 in the treatment of quadrants with moderate or severe cellulite will be conducted in subjects treated with placebo or EN3835 in the previous double-blind study (EN3835-201). The safety of re-dosing either in a previously treated quadrant (termed *re-treatment*) or in a naive quadrant (termed *re-dosing*) in subjects that previously received EN3835 treatment in study EN3835-201 will be assessed. Finally, the durability of improvement will be evaluated in enrolled subjects following EN3835 treatment in the double-blind study (EN3835-201) as well as those being treated with EN3835 in this open-label study (EN3835-202).

9. OBJECTIVES

9.1. Primary Objective

The primary objective of this study is to assess long-term safety of EN3835 0.84 mg at scheduled intervals over 1 year (12 months) or more in all subjects with EFP who elect to enroll in this open-label trial regardless of their decision to receive treatment (re-treatment or re-dosing) of open-label EN3835 or opt to receive no treatment.

9.2. Secondary Objectives

- To evaluate safety and immunogenicity of re-treating or re-dosing a subject that had previously received treatment with EN3835
- To evaluate the durability of response to EN3835 in EFP severity over the 12-month post initial dosing of EN3835 in subjects previously receiving active treatment in study EN3835-201 using the PR-PCSS and the CR-PCSS
- To evaluate the durability of response to EN3835 in EFP severity beyond 12 months post initial dosing of EN3835 in subjects previously receiving active treatment in study EN3835-201 using the PR-PCSS and the CR-PCSS
- To evaluate long-term response to EN3835 in assessments of EFP including subject satisfaction, I-GAIS, and S-GAIS
- To assess cellulite severity assessments in quadrants treated in this study with EN3835
- To evaluate immunogenicity after exposure to EN3835

9.3. Exploratory Objectives

There are no exploratory objectives for this open-label extension study.

10. INVESTIGATIONAL PLAN

10.1. Study Design

This open-label extension study will be performed at multiple centers currently participating in the double-blind, placebo-controlled, parent trial (EN3835-201) in the United States. The open-label extension study will enroll up to 350 subjects. Subjects who completed the entire double-blind study and sign an informed consent will be eligible to enter this open-label extension.

After the Sponsor has broken the EN3835-201 study drug blind, subjects enrolled in the open-label study will have the following options:

- To have no EN3835 treatments in study EN3835-202
- If received EN3835 in study EN3835-201, may elect to have a qualifying quadrant other than the one treated in study EN3835-201 treated with EN3835 (termed *re-dosing*)
- If received EN3835 in study EN3835-201 and the cellulite severity scores of the treated quadrant have returned to or are greater than EN3835-201 baseline scores, may elect to have the previously treated quadrant retreated with EN3835 (termed *re-treatment*)
- If received placebo in study EN3835-201, may elect to have a qualifying quadrant treated with EN3835; also may elect to have a second qualifying quadrant treated with EN3835 after completing the treatment course

Subjects enrolled in study EN3835-202 who elect to receive EN3835 treatment (either re-treatment, re-dosing, or a first treatment) must meet specific inclusion and exclusion criteria for eligibility during re-screening (Screening B) prior to EN3835 dosing.

Following completion of safety and cellulite assessments at Day 71 of the double-blind study (EN3835-201), subjects will be asked if they wish to continue in the open-label extension to the double-blind study (Screening A). At the time of entry into the open-label study, subjects and Investigators will remain blinded to study drug. Until the EN3835-201 study drug blind is broken by the Sponsor, subjects will undergo observation-only visits at 3-month intervals ± 7 days (relative to the initial dose in the double-blind study) where both safety and cellulite severity assessments of the treated quadrant will be made.

Following the study drug blind being broken and communicated to centers, eligible subjects may elect to receive EN3835 treatment. Subjects electing not to receive further EN3835 treatments (observation-only subjects) will continue to be followed for safety and cellulite severity assessments at 3-month intervals through month 12. Up to 14 days prior to initiating treatment injections of EN3835 on open-label treatment visit Day 1, subjects will undergo a screening evaluation (Screening B) to determine if they meet specified inclusion and exclusion criteria and to determine the quadrants, if any, that qualify for treatment.

During Screening B, photographs will be taken of each of the subject's 4 quadrants (left buttock, right buttock, left posterolateral thigh, and right posterolateral thigh). Subjects will again receive instructions for use of the PR-PCSS and will subsequently use the scale to rate the severity of

their cellulite in each of the 4 quadrants by comparing digital images of each of their quadrants displayed on standardized computer monitors with the PR-PCSS instrument. This independent self-assessment will take place in a private setting to minimize any potential bias from site personnel. The Investigator will then assess the subject's 4 quadrants live in real-time using the CR-PCSS. The Investigator will rate the 4 quadrants using the Hexsel CSS as described in section 13.1.1.6.(12) Subjects must have at least 1 quadrant that meets the following criteria for inclusion into the treatment phase of the study:

1. PR-PCSS score of 3 or 4, and
2. CR-PCSS score of 3 or 4, and
3. Hexsel CSS score of no greater than 13.

After the independent assessments are completed separately by the subject and the Investigator, the Investigator will review his/her assessments and the subject's assessment to determine which quadrants, if any, are eligible. The eligible quadrant chosen to receive treatment in the open-label study EN3835-202 will be at the discretion of the subject. A quadrant may be chosen for re-treatment if it was the quadrant treated in study EN3835-201 or a new quadrant may be chosen for re-dosing**. NOTE: For subjects who received active drug in the assigned quadrant in the double-blind study, the quadrant must have cellulite severity at (or greater) than the EN3835-201 baseline scores of PR-PCSS and CR-PCSS to qualify for re-treatment.**

Previously placebo-treated subjects will have the option to receive a second course of EN3835 in the same or different qualifying quadrant after at least 28 days following the end of the first treatment course (eg, the screening B visit of second quadrant could be performed on Day 71 after treating the first quadrant). The selected quadrant can be re-treated or re-dosed.

At each treatment session visit, Investigators will select the dimples within the chosen quadrant to be treated. Selection of dimples to be treated in the quadrant will be at the discretion of the Investigator. The selected EFP dimples in the selected quadrant must be well-defined and evident when the subject is standing in a consistent relaxed pose (without the use of any manipulation such as skin pinching or muscle contraction). The dimples selected to be treated will be circled with a surgical marker and injection site locations should be marked with a dot; if more than 1 injection per dimple is needed, the injection sites should be separated by approximately 2 cm. The selected quadrant will be photographed again after marking dimples. Subjects will be administered a maximum of EN3835 0.84 mg from a total of up to 12 injections. Up to 12 injections will be administered at each treatment session to treat the selected quadrant. Each of the injections will be administered as three 0.1-mL aliquots (total injection volume per injection is 0.3 mL; total injection volume per treatment session is 3.6 mL [12 injections × 0.3 mL], see table below).

Subjects will receive 3 treatment sessions (Day 1, Day 22, and Day 43) unless the chosen quadrant has no further treatable EFP dimples and the Investigator rates the quadrant a score of 0 on the CR-PCSS. The same dimples within a quadrant or different dimples within a quadrant may be treated at each session but injections must all be within the selected quadrant for all 3 sessions. Each treatment session will be separated by approximately 21 days.

Dose per Each Injection[a]	Injection Volume per Each Injection	Maximum Number of Injections per Each Treatment Session	Maximum Dose (mg) per Each Treatment Session	Maximum Injection Volume (mL) per Each Treatment Session	Maximum Cumulative EFP Dose
EN3835 0.07 mg	0.3 mL	12 injections	0.84 mg (12 injections × 0.07 mg)	3.6 mL (12 injections × 0.3 mL)	2.52 mg (3 treatment sessions × 0.84 mg)

[a] Each injection of EN3835 is 0.3 mL administered as three 0.1-mL aliquots.

The complete Schedule of Events is provided in section 5 (Table 2 and Table 3) and summarized in section 12.

10.2. Selection of Doses

Maximum possible doses of EN3835 employed will be the same as that administered in the double-blind, placebo-controlled, parent study (EN3835-201).

10.3. Study Drug Administration

Study drug in the form of sterile vials of lyophilized EN3835 (formerly AA4500) and sterile diluent will be provided by Endo. Study drug administration at each injection site is presented in section 12.1.4.2.

10.4. Discussion of Study Design, Including the Choice of Control Groups

The use of the open-label extension design allows for the following:

- Safety data over a 12-month period will be collected to assist in further defining the safety profile of EN3835 in this population,
- Safety data and immunogenicity after repeat exposure (re-treatment/re-dosing) and monitoring of previously active-treated subjects to EN3835 over a 12-month period,
- Previously placebo-treated subjects to have exposure to EN3835, and
- Durability of the response to EN3835 (cellulite severity assessments) will be assessed.

11. SELECTION AND WITHDRAWAL OF SUBJECTS

11.1. Observation Phase

All subjects who have completed the double-blind study EN3835-201 and sign the informed consent are eligible for enrollment in this open-label extension study and participation in the ongoing safety and cellulite evaluations.

11.1.1. Subject Inclusion Criteria for Observation

To qualify for this open-label observation study a subject must:

1. Voluntarily sign and date an informed consent agreement
2. Have participated in and completed the double-blind study EN3835-201
3. Be willing to apply sunscreen to any treated quadrant before each exposure to the sun while participating in the study (ie, screening through end of study)

11.1.2. Subject Exclusion Criteria for Observation

None

11.2. Treatment

Inclusion and exclusion criteria presented in section 11.2 apply only to those subjects in the open-label study who choose treatment.

At the time that the study drug blind is broken in the double-blind study EN3835-201, qualified subjects enrolled in the open-label study are eligible for treatment. A subject may participate in the observational period of this open-label study regardless of scoring of quadrant; however to receive treatment in this study, a subject must have at least 1 qualifying quadrant.

11.2.1. Subject Inclusion Criteria for Treatment

To qualify for treatment in the study a subject must:

1. Voluntarily sign and date an informed consent agreement
2. Have participated in and completed the double-blind study EN3835-201
3. Be a female ≥18 years of age
4. At Screening B visit, have at least 1 quadrant with:
   a. a score of 3 or 4 (moderate or severe) as reported by the subject (PR-PCSS), and
   b. a score of 3 or 4 (moderate or severe) as reported by the Investigator (CR-PCSS), and
   c. a Hexsel CSS score no greater than 13
5. Be willing to apply sunscreen to the selected treatment quadrant before each exposure to the sun while participating in the study (ie, Screening B through end of study)
6. Be judged to be in good health, based upon the results of a medical history, physical examination, and laboratory profile at Screening B

7. Have a negative urine pregnancy test at Screening B and before injection of study drug and be using an 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
8. Be willing and able to cooperate with the requirements of the study
9. Be able to read, complete and understand the patient-reported outcomes rating instruments in English

11.2.2. Subject Exclusion Criteria for Treatment

A subject will be **excluded from treatment** in the study (but not from the observation assessments) if she:

1. Has used any of the following for the treatment of EFP on the legs or buttock within the timelines identified below or intends to use any of the following at any time during the course of the study:
   - Liposuction on the side of the body selected for treatment during the 12-month period before injection of study drug
   - Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; or surgery (including subcision and/or powered subcision) within the selected treatment quadrant during the 12-month period before injection of study drug
   - Endermologie or similar treatments within the selected treatment quadrant during the 6-month period before injection of study drug
   - Massage therapy within the selected treatment quadrant during the 3-month period before injection of study drug
   - Creams (eg, Celluvera™, TriLastin®) to prevent or mitigate EFP within the selected treatment quadrant during the 2-week period before injection of study drug
2. Is presently nursing a baby or providing breast milk for a baby
3. Intends to become pregnant during the study
4. Has received an investigational drug or treatment within 30 days before injection of study drug
5. Has a known systemic allergy to collagenase or any other excipient of study drug
6. Is currently receiving or plans to receive anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication (except for ≤150 mg aspirin daily) within 7 days before injection of study drug
7. Has a known recent history of stroke, bleeding, or other medical condition, which in the investigator's opinion would make the subject unsuitable for enrollment in this phase of the study

8. Presence of any clinically relevant conditions, that in the opinion of the Investigator would interfere with completing the study including, but not limited to, visual problems, hearing problems, cognitive impairment or acute mental illness

11.3. Durability of Treatment

An assessment of treatment durability will include observations of up to 2 years in subjects who received active treatment in EN3835-201 and scored an improvement of at least 1 level on both the CR-PCSS and the PR-PCSS. For subjects who received active EN3835 in EN3835-201 and also received open-label EN3835 in EN3835-202, the original quadrant treated in EN3835-201 will be assessed until the end of the current study, *in addition* to any quadrants treated during the open-label study. The durability population may also include subjects who received active EN3835 in the double-blind study but opted not to receive additional treatments in EN3835-202. For subjects being assessed for durability beyond Day 360, the following eligibility criteria apply.

11.3.1. Subject Inclusion Criteria for Observation

1. Voluntarily sign and date an informed consent agreement
2. Participated in and completed the double-blind study EN3835-201
3. Received active EN3835 in the double-blind study EN3835-201
4. Achieved an improvement of at least 1 level on both the CR-PCSS and the PR-PCSS at the same visit on or before Day 71 in the double-blind study EN3835-201
5. Be willing to apply sunscreen to the EN3835-201 treated quadrant before each exposure to the sun while participating in the study (ie, screening through end of study)

11.3.2. Exclusion Criteria for Observation

1. Retreatment of the same quadrant in EN3835-202 and EN3835-201.
2. Has used any of the following <u>for the treatment of EFP</u> on the thighs or buttocks since treatment in EN3835-201, or intends to use any of the following at any time during the course of the study:
    - Liposuction on the side of the body selected for treatment during the EN3835-201 study
    - Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; or surgery (including subcision and/or powered subcision) within the selected treatment quadrant
    - Endermologie or similar treatments within the selected treatment quadrant
    - Massage therapy within the selected treatment quadrant
    - Creams (eg, Celluvera™, TriLastin®) to prevent or mitigate EFP within the selected treatment quadrant

11.4. Subject Discontinuation Criteria

A premature discontinuation will occur when a subject who signed informed consent ceases participation in the study, regardless of circumstances, prior to the completion of the protocol. Subjects can be prematurely discontinued from the study for one of the following reasons:

- An adverse event (AE)
- A protocol violation (reason must be specified, for example: lack of compliance, use of a prohibited concomitant medication, failure to meet inclusion/exclusion criteria after study entry, etc)
- Withdrawal by subject (reason must be specified)
- The subject was “lost to follow-up”
- Other reasons (reason must be specified, for example: the subject moved, pregnancy, investigator decision, Sponsor decision to terminate trial, etc)

If a subject discontinues from the study, all end-of-study procedures should be conducted as detailed in Schedule of Events. The date a subject discontinues and the reason for discontinuation will be recorded in the source documentation and Electronic Case Report Form (eCRF). If, however, a subject withdraws consent, no end-of-study procedures are required except the collection of AE information. This information should be recorded in the source documentation and the eCRF.

11.4.1. Replacement Procedures

Subjects who discontinue prematurely from the study will not be replaced.

12. PROCEDURES AND TREATMENTS

12.1. Study Visits

The Schedule of Events to be performed at each visit is shown in section 5. Provided below are further details where additional instruction about the assessments that will be performed is deemed to be needed.

12.1.1. Subject Screening

Upon completion of Day 71 assessments in the double-blind study EN3835-201, a subject will be eligible to enter this open-label extension study. All potential subjects eligible for screening in EN3835-202 will be pre-populated in the electronic data capture (EDC) system. The status of all subjects (eg, screen fails) will also be kept in the EDC system.

12.1.2. Screening Assessments

After obtaining informed consent, the full assessment of eligibility will be conducted and prior to study entry, screening assessments will be performed. Details about how the informed consent will be obtained and documented are provided in section 21.3, Subject Information and Consent. The subject may be entered into the observational phase of the study and complete safety and cellulite severity assessments at 3-month intervals as detailed in Table 2. In addition, once the study blind is broken in study EN3835-201, enrolled subjects will be asked if they wish to receive additional open-label treatments. If a subject elects to receive open-label treatment, study assessments will be conducted in accordance with Table 3.

12.1.3. Study Entry/Observational Assessments

A subject who gives written informed consent and who satisfies all eligibility criteria (section 11) may be entered into the observational phase of the study and complete safety and cellulite severity assessments at 3-month intervals as detailed in Table 2. The first visit will be determined by the date of enrollment in study EN3835-202 relative to the Schedule of Events for study EN3835-202 (Table 2). For example, if a subject enrolls after the Day 90 visit window, the first observation visit for that subject would be Day 180. In addition, once the study drug blind is broken in study EN3835-201, enrolled subjects will be asked if they wish to receive additional open-label treatments. If a subject elects to receive open-label treatment, study assessments will be conducted in accordance with Table 3. The subject identification number will be carried over from the double-blind, placebo-controlled study (EN3835-201). All subjects must complete Screening A and at least 1 Observation visit before Screening B can occur. Once the study blind was broken, the EN3835-201 placebo subjects were allowed to directly proceed to Screening B.

12.1.3.1. Three-Month Assessments

Subjects will return within 20 days (±4 days) of completion of the double-blind study for the first of 4 safety and cellulite severity evaluation visits. Assessments to be completed at these visits are detailed in Table 2. Subjects are to return at 3-month intervals until they have completed at least12 months from Day 1 of the double-blind study. At these visits, the quadrant previously treated with EN3835 in the EN3835-201 study or quadrants treated with EN3835 in the

open-label study will be evaluated. If the quadrant treated in study EN3835-201 is retreated in the open-label study, the 3-month assessments will reset to treatment visit 1/Day 1 of the open-label treatment and the study visits will continue as described in Table 3 followed by 3-month assessments as described in Table 2. If a different quadrant is treated in the open-label study, the 3-month assessments of both the quadrant treated in the double-blind study (EN3835-201) and the quadrant treated in the open-label study will continue.

12.1.3.2. Durability Assessments

An assessment of treatment durability will include subjects treated with open label EN3835 in the current study as well as subjects that received active EN3835 in study EN3835-201 and showed a composite improvement of at least 1 level in the PR-PCSS and CR-PCSS. Similar to other EN3835-202 observational assessments, the first durability visit will be determined by the date of enrollment relative to the associated Schedule of Events. For subjects who were treated with active EN3835 in the double-blind study (Table 4), and who give written informed consent and meet all eligibility criteria, durability assessments of the quadrant treated in the double-blind study are to be conducted *in addition* to any assessments of the different quadrant treated in the open-label study. Subjects may complete assessments for durability of all treated quadrants (whether initiated in the double-blind and open-label study) at the same visits, where subject and site schedules permit.

12.1.4. Treatment Assessments (Optional)

After unblinding of treatment assignment in the EN3835-201 study, subjects are eligible for optional treatment in the open-label study, provided they meet the inclusion and exclusion criteria detailed in section 11 and at least 1 quadrant meets the criteria for treatment. A subject may receive a maximum of 2 courses of treatment (6 treatment sessions) overall (total of treatments in double-blind and open-label study). If a subject received placebo in the double-blind study, she may be eligible for 2 treatment courses in the open-label study; if a subject received active drug in the double-blind study, she may be eligible for 1 additional treatment course (3 treatment sessions) in the open-label study.

Selection of Treatment Quadrant

During the Screening B visit, each subject will have photographs taken of the 4 targeted quadrants of the study (eg, their left and right buttocks and left and right posterolateral thighs). Subjects will receive instructions (Appendix D) for using the PR-PCSS and will use the scale to rate the severity of their cellulite in each of the 4 quadrants by comparing each of their digital image photographs with the PR-PCSS instrument. This self-assessment will take place in a private setting to minimize any potential bias from site personnel. The Investigator will then assess each of the subject's 4 quadrants live in real-time using the CR-PCSS. The Investigator will then examine each of the 4 quadrants live to assess the subject using the Hexsel CSS as described in section 13.1.1.6.(12) Subjects must have at least 1 quadrant that meets the following criteria for treatment in the study:

1. PR-PCSS score of 3 or 4, and
2. CR-PCSS score of 3 or 4, and
3. Hexsel CSS score no greater than 13.

After the independent assessments are completed separately by the subject and the Investigator, the Investigator will review his/her assessments and the subject's assessment to determine which quadrants, if any, are eligible. The eligible quadrants (must meet all 3 of the inclusion criteria (PR-PCSS, CR-PCSS, and Hexsel CSS scores), if any, for treatment will be determined by the Investigator after which the quadrant selected will be at the discretion of the subject. For subjects treated with EN3835 in the double-blind study, if the quadrant treated in the double-blind study (EN3835-201) has PR-PCSS and CR-PCSS ratings identical or more severe than the double-blind study (EN3835-201) PR-PCSS and CR-PCSS baseline ratings (Baseline is Day 1 of study EN3835-201), subjects can elect to have that same quadrant re-treated. Subjects who choose re-treatment of the previously treated quadrant will be classified in the re-treatment arm. If another quadrant besides the previously treated quadrant meets all 3 of the inclusion criteria, subjects can choose to be treated in the naive quadrant. Subjects who choose treatment into a naive quadrant will be classified in the re-dosing arm.

Assessments made with the PR-PCSS (from digital image), the CR-PCSS (live assessment), and the Hexsel CSS score during the open-label Screening B visit will be the baseline severity of EFP in the selected quadrant.

A subject who received placebo in the double-blind study may be treated in the same quadrant in the open-label study if the quadrant still meets all 3 criteria OR another qualifying quadrant may be selected for treatment by the subject. Following Day 71 of a treatment course (3 treatment sessions), subjects can choose to receive a second treatment session in either the same quadrant if it still meets qualification criteria or in a different quadrant that meets qualification criteria. For the first treatment course, these subjects will be considered in the treatment arm. For the second treatment course, if the same quadrant is treated, subjects will be in the re-treatment arm; if a different quadrant is treated, subjects will be considered in the re-dosing arm.

If no quadrant meets all 3 criteria, the subject may continue in the observation-only study with safety and cellulite severity evaluations performed at 3-month intervals but may not receive treatment in this study.

Selecting and Marking Dimples

Selection of dimples to be treated in the selected quadrant is at the discretion of the Investigator or qualified designee. Dimples must be well-defined and evident when the subject is standing in a consistent relaxed pose (without the use of any manipulation such as skin pinching or muscle contraction). Each subject will receive 3 treatment sessions of study drug in the selected quadrant. During each treatment session, the treatment quadrant will be photographed before and after dimple marking while the subject is standing in a consistent relaxed pose as described in the Photography Manual. The cellulite severity assessments using the PR-PCSS and CR-PCSS will be completed prior to dimple marking at treatment visits 2, 3, and 4/end of treatment.

12.1.4.1. Screening B (Days −14 to −1 Relative to Open-label Treatment Visit Day 1)

Subjects meeting the relevant criteria listed in section 11.2 may be eligible for treatment in the open-label study. The following procedures will be performed and documented during the screening period:

1. Evaluate eligibility based on inclusion/exclusion criteria (section 11.2)

2. Subject will have digital photographs taken of the 4 targeted quadrants of the study (left and right buttocks, and left and right posterolateral thighs) (section 13.1)
3. Subjects will get instruction on the use of the PR-PCSS (Appendix D)
4. Subjects will rate each quadrant using the PR-PCSS while viewing their digital images (section 13.1.1.1)
5. The Investigator will conduct independent live assessments of subject's cellulite severity of each quadrant using the CR-PCSS (section 13.1.1.4) after the subject completes her rating and with no knowledge of the subject's ratings of her quadrants.
6. The Investigator will conduct live cellulite evaluation of each quadrant using the Hexsel CSS (section 13.1.1.6).
7. If at least 1 quadrant qualifies based on PR-PCSS, CR-PCSS, and Hexsel CSS ratings, subject may return for treatment on treatment visit 1. If none of the 4 quadrants qualify, the subject may remain in the study and have safety and cellulite severity evaluations performed at 3-month intervals but is not eligible for treatment.
8. Subject will select an eligible quadrant (based on qualifying scores) to be treated at their discretion.
9. Medical history including EFP history. Medical history will be based on EN3835-201 eCRF; only updates to the history need to be captured at Screening B visit.
10. Record prior and concomitant medications/procedures. Prior medications will be based on EN3835-201 eCRF; only updates and concomitant medications need to be captured at Screening B visit (section 12.2).
11. Physical examination including measurement of body weight and height (section 14.10)
12. Vital sign measurements (section 14.8)
13. 12-lead electrocardiogram (ECG), not necessary if the date of the ECG obtained during the double-blind study (EN3835-201) is within 12 months of the date of the Screening B visit (section 14.9)
14. Collection of samples for:
    a. Clinical laboratory testing (section 14.7)
    b. Urine pregnancy testing (section 14.7)
15. Adverse events (section 14)

12.1.4.2. Treatment Session 1 (Treatment Visit 1)

Pre-injection

1. Confirm eligibility criteria (section 11)
2. Take digital photography of selected quadrant before dimple marking (section 13.1)
3. Record concomitant medications/procedures (section 12.2)
4. Vital sign measurements (section 14.8)

5. Collection of samples for:
    a. anti-AUX-I and anti-AUX-II antibody testing (section 14.7.1)
    b. urine pregnancy testing (section 14.7)
6. Select and mark dimples to be treated (section 12.1.4)
7. Take digital photograph of selected quadrant after dimple marking (section 13.1)

Injection

Administration of study drug in the prone position (see below)

Post-injection

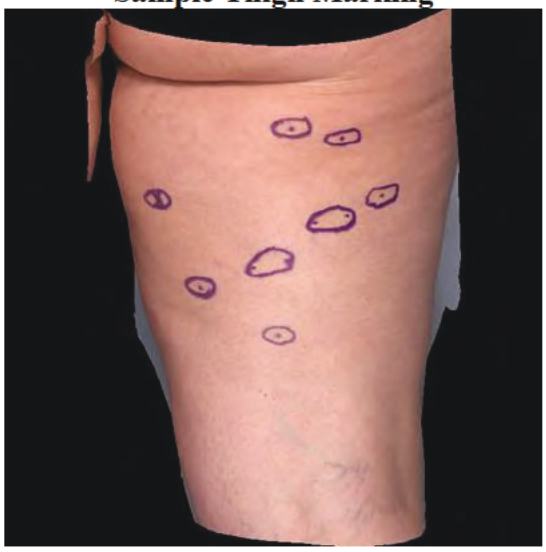
1. Record number of dimples treated and number of injections administered
2. Vital sign measurements (section 14.8)
3. Injection site reactions and local tolerability
4. Adverse events (section 14)

The selected quadrant will be photographed before and after dimple marking while the subject is standing in a consistent relaxed pose as described in the Photography Manual. Before injection at treatment session 1, the Investigator or qualified designee will begin the session by selecting dimples within the chosen quadrant that are well defined, evident when the subject is standing, and suitable for treatment; treatment consists of up to 12 injections per session. Because the goal of treatment is to improve the aesthetic appearance of the entire quadrant, the Investigator will be instructed to select dimples that in his or her opinion would most improve the aesthetic appearance of the entire quadrant. The same dimples within a quadrant or different dimples within a quadrant may be treated at each session but injections must all be within the selected quadrant for all 3 sessions.

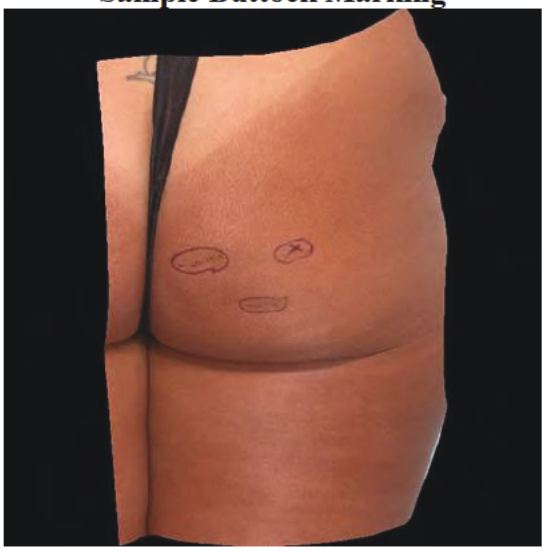
For each dimple selected for treatment, the Investigator or qualified designee will choose injection sites (injection sites within a dimple should be spaced approximately 2 cm apart, if a dimple requires more than 1 injection). Each injection site will be marked with a “dot” using a surgical marker. For round dimples, the “dot” will be placed in the center of the dimple; for elongated dimples, “dots” will be spaced out approximately 2 cm along the longer axis of the dimple. The Investigator or qualified designee will then use a surgical marker to circle each of the dimples selected for treatment. Circles in the selected quadrant should not overlap.

Examples of subject dimple marking:

Sample Thigh Marking



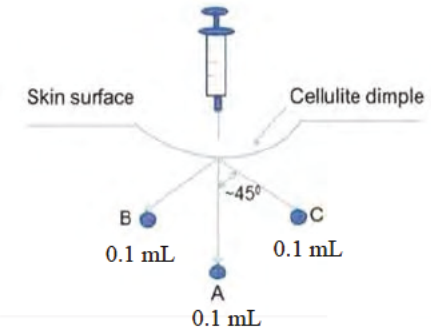
Sample Buttock Marking



Study Drug Administration at Each Injection Site

See section 18.4 for study drug preparation. Study drug will be injected subcutaneously while the subject is in a prone position using a syringe with a 30-gauge ½-inch needle. Each injection site will receive a single skin injection of study drug administered as three 0.1-mL aliquots to Positions A, B and C (for a total injection volume of 0.3 mL) as shown in the following figure. The depth of injection corresponds to the length of the treatment needle (0.5 inches) from the tip of the needle to the hub or base of the needle without downward pressure.

During each treatment session, the Investigator will be supplied with 4 syringes. Each syringe will contain 0.9 mL of study drug (ie, up to 3 injections in each syringe). Up to 12 skin injections of 0.3 mL per injection will be administered within the selected treatment quadrant during each treatment session.



- **Needle Tip Position A**: Position the needle at 90° angle perpendicular to the skin surface at the injection site and inject one 0.1-mL aliquot of study drug by gently pushing on the syringe plunger.
- **Needle Tip Position B**: Withdraw the needle slightly (but not so much as to remove from the injection site) and reposition approximately 45° (**but not more than 45°**) off

vertical and above the long axis of the dimple and inject one 0.1-mL aliquot of study drug) by gently pushing on the syringe plunger.

- **Needle Tip Position C**: Withdraw the needle slightly (but not so much as to remove from the injection site) and reposition approximately 45° (**but not more than 45°**) off vertical and below the long axis of the dimple and inject one 0.1-mL aliquot of study drug by gently pushing on the syringe plunger.
- Withdraw needle from the skin completely and move to the next identified injection site. Complete up to a total of three 0.3-mL injections (each administered as three 0.1-mL aliquots) and discard the first syringe appropriately. Use the second, third and fourth syringes to complete dosing in the quadrant (up to three 0.3-mL injections per syringe, each injection administered as three 0.1-mL aliquots). Up to 12 skin injections of 0.3 mL will be administered within the treated quadrant during each treatment session.
- After treatment the subject will remain prone for at least 5 minutes.

The total number of dimples treated and the total number of injections administered will be recorded during treatment sessions 1, 2, and 3.

NOTE: EN3835 is a foreign protein and Investigators must be prepared to address and manage an allergic reaction should it occur. At the time of each injection, a 1:1,000 solution of epinephrine for injection, 50-mg diphenhydramine injection or a suitable equivalent, and oxygen should be available and the Investigator and site staff must be familiar with their use.

Care Procedures After Injection

To evaluate the subject for possible immediate immunological AEs, the subject will remain in direct observation of medical personnel who are skilled in the management of an allergic reaction for 30 minutes after receiving the injection of study drug and until the subject exhibits no sign of an immunological or other clinically significant systemic or local AE. The subject's vital signs should be stable before the subject can leave direct observation (see section 14.8).

The Investigator or qualified designee will then apply a sterile dressing to the injection site with hypoallergenic tape. The subject will be instructed to remove the dressing in the evening.

12.1.4.3. Treatment Session 2 (Treatment Visit 2/Day 22 ± 3 Days) and Treatment Session 3 (Treatment Visit 3/Day 43 ± 3 Days)

Pre-injection

1. Record concomitant medications/procedures (section 12.2)
2. Body weight measurements
3. Vital sign measurements (section 14.8)
4. Collection of samples for urine pregnancy testing (section 14.7)
5. Digital photograph of selected quadrant before dimple marking (section 13.1)

6. Subject assessment of the severity of cellulite using photograph of the selected quadrant via PR-PCSS (section 13.1.1.1). NOTE: Complete the subject (PR-PCSS) assessment before the Investigator (CR-PCSS) assessment and before dimple marking.
7. Investigator will conduct an independent live assessment of the severity of cellulite using the CR-PCSS (section 13.1.1.4). The investigator will conduct the assessment of severity only after the subject has completed her rating of her quadrant and without knowledge of the subject's rating of her quadrant.
8. Selection and marking of dimples to be treated (section 12.1.4)
9. Digital photograph after dimple marking (section 13.1)

Injection

Administration of study drug in the prone position (section 12.1.4.2)

Post-injection

1. Record number of dimples treated and number of injections administered
2. Vital sign measurements (section 14.8)
3. Injection site reactions and local tolerability
4. AEs (section 14)

If the Investigator rates the selected quadrant as 0, no injections will be given. If no injections are given at treatment session 2, subjects will still return for the Day 43 visit and the selected quadrant will again be evaluated by the subject (PR-PCSS) and Investigator (CR-PCSS). If the Investigator rates the selected quadrant greater than 0 on the CR-PCSS, injections at treatment session 3 should be given.

Because the goal of treatment is to improve the aesthetic appearance of the entire quadrant, the Investigator will be instructed to select dimples that in his or her opinion would most improve the aesthetic appearance of the entire quadrant. The same dimples within a quadrant or different dimples within a quadrant may be treated at each session but injections must all be within the selected quadrant for all 3 sessions. Each subject will receive all 3 treatment sessions unless the selected quadrant has no treatable EFP dimples and the Investigator rates the quadrant a score of 0 on the CR-PCSS.

After the dimples are selected, the Investigator or qualified designee will again mark each injection site with a “dot,” and circle each dimple (circles should not overlap).

12.1.4.4. Day 71 (+5 Days) End of Treatment/Early Termination

The following procedures will be performed on Day 71:

1. Record concomitant medications/procedures (section 12.2)
2. Measurement of body weight
3. Vital sign measurements (section 14.8)

4. Collection of samples for:
    a. Clinical laboratory testing (section 14.7)
    b. Anti-AUX-I and anti-AUX-II antibody testing (section 14.7.1)
5. Digital photograph of selected quadrant (section 13.1)
6. Subject cellulite assessments of the selected quadrant using the photographic image (NOTE: complete subject cellulite assessments before Investigator cellulite assessments) using:
    a. PR-PCSS assessment (section 13.1.1.1)
    b. S-GAIS (section 13.1.1.2)
    c. Subject satisfaction with cellulite treatment assessment (section 13.1.1.3)
7. Investigator cellulite assessments of selected quadrant independently conducted; ie, with no knowledge of the subject's rating, using:
    a. CR-PCSS live assessment of subject (section 13.1.1.4)
    b. Hexsel CSS assessment of live subject while subject is standing in a relaxed position (section 13.1.1.6)
    c. I-GAIS (section 13.1.1.5)
8. Injection site reactions and local tolerability
9. AEs (section 14)

12.1.4.5. Follow-up Visits

Following the Day 71 visit, the quadrant(s) treated with EN3835 in the open label study will be evaluated every 3 months from the first exposure to EN3835 following the schedule in Table 2. The first follow-up visit will be approximately 20 days after the Day 71 visit (ie approximately Day 90 after treatment session 1).

12.2. Prior and Concomitant Medications and Procedures

All medications (including over-the-counter medications) taken by the subject at screening visit 1 through the end of the study must be recorded.

Additionally, any diagnostic, therapeutic or surgical procedures performed during the study period should be recorded including the date, indication for and description of the procedure.

12.2.1. Prohibited Medications

The following medications are prohibited for those subjects that elect to have treatment with study drug during the treatment 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 the treatment phase of the study. For those subjects in the observational-only phase of study, there are no prohibited medications.

Table 6: Concomitant Medication Restrictions for Subjects During the Treatment Phase of Study

Drug Class	Restrictions
Anticoagulants	Subjects who elect treatment cannot take antiplatelet agents or anticoagulants (except for ≤150 mg aspirin daily) within 7 days before and after the dosing administration.

12.2.2. Prohibited Procedures

The treatments and procedures listed in exclusion criteria are prohibited during the study.

12.3. Treatment Compliance

All subjects who elect to have treatment will receive study drug administered by a clinician at the investigator's site.

Accidental or intentional overdoses should be reported to the Sponsor/designee promptly (see section 14.6.2).

12.4. Blinding and Randomization

This study will be conducted as an open-label investigation; no blinding of assigned treatment will occur.

12.5. End of Study

At the time of study termination, ongoing subjects receiving treatment will be followed through the Day 71 visit. The remaining enrolled subjects will undergo early termination procedures in accordance with the Schedule of Events (section 5).

13. ASSESSMENT OF EFFICACY

13.1. Primary Efficacy Measurements

Although measures of efficacious drug effect (ie, durability of improvement) will be made during the observation phase before the study drug blind is broken in the double-blind study (EN3835-201), and thereafter to the end of study, emphasis is on the assessment of safety over 12 months after exposure to EN3835. Cellulite severity assessments will be made at scheduled intervals for both observation-only subjects (not receiving EN3835) as well as subjects who choose re-dosing or re-treatment with EN3835.

Digital Photography: Digital photography will be utilized to assess certain cellulite severity parameters at specific intervals (see Schedule of Events, Table 2, Table 3, and Table 4) for subjects in the observation-only group as well as those electing to be re-treated or re-dosed with EN3835. At the Screening B visit for subjects electing to receive re-dosing or re-treatment, the Investigator or qualified designee will photograph each quadrant using a Sponsor-supplied standardized digital camera. The subject will be standing for each photography session and will be wearing a standardized photographic garment as described in the Photography Manual. The Investigator or qualified designee will photograph the selected quadrant as follows:

- Screening B (no dimple marking)
- Before and after dimple marking (prior to injections) on Days 1, 22, and 43 of each treatment course
- During the Day 71 visit (end of treatment phase/early termination) of each treatment course
- During the specified observation visits for assessments of durability (see Table 2 for durability up to Day 360, and Table 4 for durability beyond Day 360)

All photographs from this study are the property of Endo and may be utilized for clinical development, scientific communication, marketing, regulatory purposes, and/or legal applications as required/desired by Endo.

13.1.1. Subject and Investigator Cellulite Assessments

As in the double-blind parent study, Investigator cellulite assessments are independent of the subject assessments. Therefore, all subject cellulite assessments must be completed before the Investigator's cellulite assessments are made. After both the subject's and investigator's assessments are completed, the subject's assessments will be revealed and compared to the clinician's assessments to determine eligible quadrants. If more than 1 quadrant is eligible, the subject will select one for treatment.

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

The PR-PCSS will be conducted for the purpose of assessing the severity of cellulite in the buttock or thigh; there are separate scales for buttocks or thighs. The scales are 5-level photonumeric scales developed specifically for patients and used by the subject to assess the severity of their cellulite in the quadrants by viewing digital images of each of their quadrants

captured by photography at the visit; the ratings range from 0 (None) to 4 (Severe) with labels and descriptors to aid the subject in the assessments.

All subjects who enter the observation-only phase of the study will have the PR-PCSS evaluation at months 3, 6, 9, and 12 (and at specified visits in Table 4 for subjects originally treated with active in the double-blind study and being assessed for treatment durability beyond Day 360) or at the end of study visit.

For subjects electing re-treatment or re-dosing after the study drug blind is broken in study EN3835-201, a Screening B visit (Baseline) within 14 days before dosing Day 1 will occur. Subjects will have digital photographs taken of all 4 quadrants as done in the double-blind trial for qualifying purposes. Subjects will then perform the PR-PCSS for both buttocks (Figure 1) and thighs (Figure 2) and will be reminded of their proper use (Appendix D).

At the beginning of visits on Days 22, 43, and 71 digital photographs of the selected quadrant will be taken. If the buttock is the treated region, subjects will be given the PR-PCSS for the buttock to use to make their evaluation; if the thigh is the treated region, subjects will be given the PR-PCSS for the thigh to make their evaluation.

Figure 1: Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS) for the Buttock

Figure 2: Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS) for the Thigh

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

Subjects in the observation-only group will complete the S-GAIS as described below at the final study visit (month 12 or early termination) using the pre-treatment Day 1 image (Baseline) of the assigned quadrant in the double-blind study for comparison.

For subjects who elected to receive EN3835 treatment, the S-GAIS assessment will be done on Day 71 of the treatment course and then at month 12 or the final study visit and compared back to the pre-dosing Screening B image (Baseline for treatment subjects) of the selected quadrant. All treated subjects will be instructed to answer the following question: *How would you rate the appearance of your treated cellulite after treatment?*

The S-GAIS assessment will occur after the subject has completed the PR-PCSS assessment to avoid introducing potential bias to the static PR-PCSS assessment. Each subject will view the pre-dosing Screening B visit digital image alongside their Day 71 treatment course visit and month 12 or end of study visit digital image of their selected quadrant to aid in the assessment (Table 7). Subjects will circle the rating below that best represents their answer.

Table 7: 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 originally.

13.1.1.3. Subject Satisfaction with Cellulite Treatment Assessment

For observation-only subjects (not receiving EN3835) the subjects will assess their satisfaction with cellulite treatment at the 12 month or end of study visit by being instructed to answer the following question: *Today, how satisfied are you with the results of the cellulite treatment you received on the specific area or areas on your buttocks or thighs that were treated?* Subjects will circle the rating in the below table that best represents their answer.

For subjects who have elected to receive EN3835 either through re-treatment or re-dosing, the subject satisfaction with the cellulite treatment (Table 8) with be done at the treatment course Day 71 and the month 12 visit or end of study visit. Subjects will be instructed to answer the following question: *Today, how satisfied are you with the results of the cellulite treatment you received on the specific area or areas on your buttocks or thighs that were treated?* Subjects will circle the rating below that best represents their answer.

Table 8: Subject Satisfaction with Cellulite Treatment Assessment

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

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

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

Investigators will have been trained on the use of the CR-PCSS. For observation-only subjects, the CR-PCSS will be done at 3, 6, 9, and 12 months (and at visits specified in Table 4 for subjects participating in observation visits beyond Day 360) or at the end of study visit.

For subjects who elected to receive EN3835 after the study drug blind is broken in study EN3835-201 as a re-treatment or re-dosing, the Investigator, at the Screening B visit (Baseline) will determine severity of cellulite of the 4 quadrants by assessing live subjects using the CR-PCSS for buttock (Figure 3) and thighs (Figure 4) after the subject has completed their self-assessment using the PR-PCSS. The eligible quadrant chosen for injection will be at the discretion of the subject. Before injections on treatment visit Days 22 and 43 and on visit Day 71; Investigators will evaluate the selected quadrant by live assessments. If the buttock is the treated region, the Investigator will use the CR-PCSS for the buttock to make his/her evaluation; if the thigh is the treated region, the Investigator will use the CR-PCSS for the thigh to make his/her evaluation. In each case, the Investigator will make his/her assessment independently and after the subject has conducted their self-assessment using the PR-PCSS.

Figure 3: Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS) for the Buttock

Figure 4: Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS) for the Thigh

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

Investigators will complete the I-GAIS on subjects in the observation-only group as described below at the final study visit (month 12 or early termination) and a comparison back to the pre-treatment Day 1 (Baseline) image of the assigned quadrant of the double-blind study.

On Day 71 of the treatment course and the 12 month or end of study visit, the Investigator will determine the degree of improvement from the Screening B digital image of the selected quadrant by comparing the cellulite in live assessment on Day 71 and at month 12 or study end to the Screening B pre-treatment (Baseline) image of the subject's selected quadrant (Table 9). The I-GAIS assessment will occur after the CR-PCSS assessment (section 13.1.1.4) to avoid introducing potential bias to the static CR-PCSS assessment by the Investigator at the site.

Table 9: Investigator Global Aesthetic Improvement Scale (I-GAIS)

Rating	Response Option	Description
+3	Very much improved	Optimal cosmetic result from treatment of the treated dimples
+2	Much improved	Marked improvement in the treated area appearance from before treatment, but not completely optimal
+1	Improved	Obvious improvement in the treated area appearance from before treatment, but additional treatment is indicated
0	No change	The treated area appearance is essentially the same as before treatment
−1	Worse	The treated area appearance is worse than before treatment
−2	Much worse	Marked worsening in appearance from the initial condition
−3	Very much worse	Obvious worsening in appearance from the initial condition

13.1.1.6. Hexsel Cellulite Severity Scale

The Hexsel Cellulite Severity Scale (referred to as the Hexsel CSS) is a photonumeric scale that looks at 5 key morphologic features of cellulite: (A) number of evident depressions, (B) depth of depressions, (C) morphological appearance of skin surface alterations, (D) laxity, flaccidity or sagging of skin, and (E) current classification scale based on medical literature including Nürnberger and Müller.(12,13) Each of these features is evaluated on a 4-point scale from a low of 0 to a high of 3 as described in Table 10 (see Appendix B). The total score is the summation of all 5 features.

For subjects in the observation-only group, the Hexsel CSS will be done at the month 12 or the end of study visit, and at months 15, 18, 21, and 24 for subjects originally treated with active EN3835 in the double-blind study that are being assessed for treatment durability beyond 1 year.

For the subjects electing treatment (re-treatment or re-dosing) with EN3835 the Investigator or qualified designee will independently use the Hexsel CSS to assess the severity of EFP in all quadrants at Screening B visit and the selected quadrant on Day 71 of the course of treatment and at month 12 or end of study visit. All cellulite assessments should be made while the subject is in the standing position with relaxed gluteus muscles. However, when evaluating the subject for Category E (classification scale by Nürnberger and Müller) (13) if the subject has no evident depressions, the subject should be asked to contract her gluteus muscles or the pinch test should

be applied (by pinching the skin between the thumb and index finger) so the Investigator or qualified designee can differentiate between scores/grades of zero (0) or I.

Table 10: Hexsel Cellulite Severity Scale

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

Source: Hexsel DM, Dal'Forno T, Hexsel CL. A validated photonumeric cellulite severity scale. *J Eur Acad Dermatol Venereol.* 2009;23(5):523-528.

[a] Subjects should be evaluated in the standing position with relaxed gluteus muscles. However, if the subject has no evident depressions, they should be asked to contract their gluteus muscles or the pinch test should be applied (by pinching the skin between the thumb and index finger) in order to differentiate between grade/stage of zero (0) or I.

14. ASSESSMENT OF SAFETY

14.1. Definitions

14.1.1. Adverse Event

An adverse event (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. AEs will be captured once a subject has signed the informed consent. AEs include:

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

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

All AEs, including both observed or volunteered problems, complaints, signs or symptoms must be recorded on the AE page of the eCRF, regardless of whether associated with the use of 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. The AE should be recorded in standard medical terminology when possible.

14.1.2. Serious Adverse Event

A serious adverse event (SAE) is defined as an AE that:

- Results in death
- Is immediately life-threatening (there is an immediate risk of death from the AE as it occurred; this does not include an AE that had it occurred in a more serious form may have caused death)
- Results in or prolongs an inpatient hospitalization (Note: a hospitalization for elective or pre-planned surgery, procedure, or drug therapy does not constitute an SAE)

- Results in permanent or substantial disability (permanent or substantial disruption of one's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect (in offspring of a subject using the study medication regardless of time to diagnosis)
- Is considered an important medical event

Important medical events are defined as events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the other serious outcomes. Examples of important medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

14.2. Monitoring Adverse Events

At each visit, subjects will be queried regarding any AEs that have occurred since the last visit. Subjects will be asked to volunteer information concerning AEs with a non-leading question such as, "How do you feel?" Study site personnel will then record all pertinent information in the source documents and the eCRF. The study drug compliance record should also be reviewed to detect potential overdoses (intentional/unintentional).

14.3. Relationship to Study Drug

The degree of "relatedness" of the AE to the study medication must be described using the following scale:

- **Not related** indicates that the AE is definitely not related to the study medication.
- **Unlikely related** indicates that there are other, more likely causes and study medication is not suspected as a cause.
- **Possibly related** indicates that a direct cause and effect relationship between study medication and the AE has not been demonstrated, but there is evidence to suggest there is a reasonable possibility that the event was caused by the study medication.
- **Probably related** indicates that there is evidence suggesting a direct cause and effect relationship between the AE and the study medication.

It is the Sponsor's policy to consider "Probably related" and "Possibly related" causality assessments as positive causality. "Not related" and "Unlikely related" causality assessments are considered as negative causality.

Assessments will be recorded on the eCRF and must indicate clearly the relationship being assessed. For example, an AE that appears during a placebo run-in phase would be assessed with respect to the placebo treatment received and/or study procedures conducted during this phase. If the AE continued into an active treatment phase, the relationship would be assessed for the active treatment phase only if the AE worsened.

14.4. Intensity Assessment

The intensity (or severity) of AEs is characterized as mild, moderate, or severe:

- **Mild** AEs are usually transient, requiring no special treatment, and do not interfere with the subject's daily activities.
- **Moderate** AEs introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.
- **Severe** AEs interrupt a subject's usual daily activity and typically require systemic drug therapy or other treatment.

When the intensity category of an AE changes, the greatest intensity during that continuous episode should be recorded.

14.5. Reporting Adverse Events and Serious Adverse Events

14.5.1. Reporting Adverse Events

Throughout the study, AEs will be documented on the source document and on the appropriate page of the eCRF whether or not considered treatment-related. This includes any new signs, symptoms, injury or illness, including increased severity of previously existing signs, symptoms, injury, or illness. Conditions existing prior to screening will be recorded as part of the subject's medical history. The Investigator is responsible for assessing the relationship of AEs to the study medication; relationship will be classified as not related, unlikely related, possibly related, or probably related.

All AEs will be collected by the Investigator from the time of signing the informed consent through 30 days after the last dose of study medication; this includes any AEs that are ongoing at the time of completion/termination of the study. All ongoing AEs must be followed until resolution or for 30 days after the subject's last study visit, whichever comes first.

14.5.2. Reporting Serious Adverse Events

Any SAE, including death resulting from any cause, which occurs to any subject participating in this study must be reported via email or fax by the Investigator using the Endo Clinical Trial Report Form for SAEs within 24 hours of first becoming aware of the SAE. SAEs will be collected by the Investigator from the time of signing the informed consent through 30 days after the last dose of study medication. SAEs that occur within 30 days, following cessation of the study treatment, or within 30 days, following premature discontinuation from the study for any reason, must also be reported within the same timeframe. Any SAE that is considered by the Investigator to be related to the study medication must be reported regardless of the amount of time since the last dose received. Follow-up information collected for any initial report of an SAE must also be reported to the Sponsor within 24 hours of receipt by the Investigator.

All SAEs will be followed until resolution, stabilization of condition, or until follow-up is no longer possible.

In the event discussion is necessary regarding treatment of a subject, call the Medical Monitor (see contact information in section 3).

All SAEs should be sent via the email address, or faxed to the fax number, provided in section 3.

The Sponsor will determine whether the SAE must be reported within 7 or 15 days to regulatory authorities in compliance with local and regional law. If so, the Sponsor (or the Sponsor's representative) will report the event to the appropriate regulatory authorities. The Investigator will report SAEs to the institutional review board (IRB) per their IRB policy.

14.5.2.1. Follow-up Procedures for Serious Adverse Events

To fully understand the nature of any SAE, obtaining follow-up information is important. Whenever possible, relevant medical records such as discharge summaries, medical consultations, and the like should be obtained. In the event of death, regardless of cause, all attempts should be made to obtain the death certificate and any autopsy report. These records should be reviewed in detail, and the Investigator should comment on any event, lab abnormality, or any other finding, noting whether it should be considered a serious or non-serious AE, or whether it should be considered as part of the subject's history. In addition, all events or other findings determined to be SAEs should be identified on the follow-up SAE form and the Investigator should consider whether the event is related or not related to study drug. All events determined to be nonserious should be reported on the eCRF.

14.6. Special Reporting Situations

14.6.1. Adverse Events of Special Interest

[redacted]

14.6.2. Overdose/Misuse/Abuse

Study drug overdose is any accidental or intentional use of study drug in an amount higher than the dose indicated by the protocol for that subject. Study drug compliance (see section 12.3) should be reviewed to detect potential instances of overdose (intentional or accidental).

Any study drug overdose during the study should be noted on the study medication eCRF.

An overdose is not an AE per se, however all AEs associated with an overdose should both be entered on the Adverse Event eCRF and reported using the procedures detailed in section 14.5.2, Reporting of Serious Adverse Events, even if the events do not meet seriousness criteria. If the AE associated with an overdose does not meet seriousness criteria, it must still be reported using the Endo Clinical Trial Report Form for SAEs and in an expedited manner, but should be noted as non-serious on the form and the Adverse Event eCRF.

14.6.3. Pregnancy

Any uncomplicated pregnancy that occurs in a subject during this clinical study will **be reported for tracking purposes only**. All subject pregnancies that are identified during or after this study, where the estimated date of conception is determined to have occurred during study drug therapy or within 30 days of the last dose of study medication need to be reported, followed to conclusion, and the outcome reported, even if the subject is discontinued from the study. The investigator should report all pregnancies within 24 hours using the Initial Pregnancy Report Form, and any pregnancy-associated SAE using the SAE report form, according to the usual timelines and directions for SAE reporting provided in section 14.5.2. Monitoring of the pregnancy should continue until conclusion of the pregnancy; 1 or more Follow-up Pregnancy Report Form(s) detailing progress, and a Two Month Follow-up Pregnancy Report Form detailing the outcome, should be submitted.

Pregnancy itself is not regarded as an AE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not considered AEs. Any SAEs associated with pregnancy (eg, congenital abnormalities/birth defects/spontaneous miscarriages or any other serious events) must additionally be reported as such using the SAE report form. Spontaneous miscarriages should also be reported and handled as SAEs.

Subjects should be instructed to immediately notify the investigator of any pregnancies.

Attempts to obtain the pregnancy follow-up and pregnancy outcome information detailed above are necessary even if a subject discontinues treatment because of pregnancy.

14.6.4. Adverse Events/Serious Adverse Events Experienced by Non-subjects Exposed to Study Medication

Non-subjects are persons who are not enrolled in the study but have been exposed to study medication, including instances of diversion of study medication. All such AEs/SAEs occurring in non-subjects from such exposure will be reported to the Endo Pharmacovigilance and Risk Management (PVRM) Department (when the non-subject agrees) on the departmental form for SAEs regardless of whether the event is serious or not. Instructions for completing the form for events experienced by non-subjects will be provided. SAEs occurring in non-subjects exposed to study medication will be processed within the same SAE reporting timelines as described in section 14.5.2, Serious Adverse Event Reporting. Additionally, the drug accountability source documentation at the site should reflect this occurrence.

14.7. Clinical Laboratory and Immunogenicity Determinations

Clinical laboratory tests will be conducted according to the Schedule of Events (section 5). Clinical laboratory tests will be performed by a designated central laboratory. Each site will be provided with instructions on specimen collection, preparation, packaging and transport. Refer to the central laboratory manual for further information regarding sample collection, handling, and labeling. The results of the tests will be returned to the investigational sites.

Clinical laboratory test data will be reviewed by the investigator, or designee, and additional clinical laboratory tests may be ordered at his/her discretion (eg, if the results of any clinical laboratory test falls outside the reference range or clinical symptoms necessitate additional

testing to ensure safety). Any additional testing will be performed by the designated central laboratory.

The investigator will review all abnormal lab results for clinical significance. Any abnormal clinical laboratory test result meeting the investigator's or Sponsor's criteria for clinical significance (refer to central laboratory manual) will be recorded as an AE or SAE as appropriate (see section 14.1.1, Adverse Events or section 14.1.2, Serious Adverse Events).

Laboratory results will be sent electronically to Endo for data management.

Clinical laboratory parameters that will be measured in this study are listed in Table 11.

Table 11: Clinical Laboratory Parameters

Hematology	Clinical Chemistry	Urinalysis
Hematocrit	Blood urea nitrogen	Specific gravity
Hemoglobin	Creatinine	Ketones
Red blood cell count	Total bilirubin	pH
Red blood cell morphology	Alanine aminotransferase (ALT)	Protein
White blood cell count	Aspartate aminotransferase (AST)	Blood
Neutrophils	Alkaline phosphatase	Glucose
Lymphocytes	Sodium	
Monocytes	Potassium	
Basophils	Calcium	
Eosinophils	Chloride	
Platelets	Phosphate	
	Serum bicarbonate	
	Uric acid	
	Total cholesterol	
	Total protein	
	Glucose	
	Triglycerides	
	Albumin	

Female subjects of childbearing potential must have a negative urine pregnancy test at Screening B and at treatment visits 1, 2, and 3 (section 5) to receive treatment in the study. If necessary, additional urine pregnancy tests can be performed at any time during the study at the discretion of the Investigator.

14.7.1. Anti-AUX-I and Anti-AUX-II Antibodies

Serum samples will be collected and may be tested for binding and neutralizing anti-AUX-I and anti-AUX-II antibodies at Visit 4 of the observation assessments. Additionally, if a subject consents to treatment in the open-label study, serum samples for antibody testing will be collected before injection at treatment visit 1 and at end of treatment/early termination visit 4 of the open-label treatment period. A subset of subject samples may have neutralizing antibodies tested from Day 1 and Day 71 visits; additional samples may be analyzed if results or clinical signs warrant testing.

The serum samples obtained will be processed, stored and then shipped on dry ice to the designated central clinical laboratory before forwarding to Endo's appointed laboratory for the determination of anti-AUX-I and anti-AUX-II antibodies according to the Laboratory Manual.

14.8. Vital Signs

Vital sign measurements will be documented as described in the Schedule of Events. These parameters include pulse rate, respiratory rate, systolic and diastolic blood pressure, and body temperature. Pulse and blood pressure readings will be taken after the subject has been sitting for 5 minutes. Height should only be recorded at Screening B.

The investigator will review all vital sign values for clinical significance. Any vital sign value meeting the investigator's or Sponsor's criteria for clinical significance will be recorded as an AE or SAE as appropriate (see section 14.1.1, Adverse Events, and section 14.1.2, Serious Adverse Events).

For subjects receiving treatment, vital signs will be assessed at the time points shown in Table 12 after the subject has rested for at least 5 minutes.

The subject's vital signs should be stable, or repeated until stable before the subject can leave direct observation.

Table 12: Vital Signs Measurements on Injection Day

Time Point Relative to Last Injection	Blood Pressure, Respiratory Rate, and Pulse Rate	Body Temperature
Up to 4 hours (before treatment)	X	X
Approximately 15 minutes after	X	
Approximately 30 minutes after	X	X

14.9. Electrocardiogram

Performing a 12-lead electrocardiogram (ECG) is not necessary if Screening B visit date is within 12 months of obtaining an ECG during the double-blind study (EN3835-201).

If the date of Screening B visit is later than 12 months since obtaining the ECG in study EN3835-201, subjects will have a resting 12-lead ECG performed during the Screening B visit. A qualified physician will interpret, sign, and date the ECGs. Electrocardiogram assessments must be "within normal limits" or interpreted as "abnormal, not clinically significant" for the subject to be included in the study.

Any ECG result meeting the investigator's or Sponsor's criteria for clinical significance will be recorded as an AE or SAE as appropriate (see section 14.1.1, Adverse Events and section 14.1.2, Serious Adverse Events).

14.10. Physical Examination

Body weight will be collected as described in the Schedule of Events (section 5). If a subject desires treatment in the open-label study, a complete physical examination will be performed at Screening B. All examinations will be performed by a physician or health professional listed on the Form FDA 1572 and licensed to perform physical examinations.

The investigator will review all physical exam findings for clinical significance. Any physical exam finding meeting the investigator's or Sponsor's criteria for clinical significance will be recorded as an AE or SAE as appropriate (see section 14.1.1, Adverse Events and section 14.1.2, Serious Adverse Events).

14.11. Other Safety Assessments

Not applicable.

15. ASSESSMENT OF PHARMACOKINETICS

Not applicable.

16. ASSESSMENT OF PHARMACODYNAMICS

Not applicable.

17. STATISTICAL CONSIDERATIONS AND METHODS

17.1. Determination of Sample Size

Approximately 350 subjects that completed the EN3835-201 study will enroll in the current study. This sample size should be adequate to determine long term safety and cellulite assessments of EN3835.

17.2. Subject Cohorts and Subject Populations

Subjects will be classified into 1 of 4 different cohorts depending on where they receive the treatment of EN3835 in relation to where they received treatment in study EN3835-201. The 4 cohorts are:

1. Observational subjects only - subjects who received EN3835 in study EN3835-201 but do not receive any injections in the current study.
2. Re-treatment subjects - subjects who received EN3835 in study EN3835-201 and receive EN3835 in the current study in the same quadrant that was treated in the EN3835-201 study. This will only be allowed for subjects who have baseline severity ratings in the current study at or worse than the baseline seen in study EN3835-201 for both the CR-PCSS and PR-PCSS of the quadrant.
3. Re-dosing subjects - subjects who received EN3835 in study EN3835-201 and receive EN3835 in the current study in a quadrant different than the EN3835-treated quadrant in study EN3835-201.
4. Initial treatment subjects - subjects who received placebo in study EN3835-201 and receive EN3835 in the current study.

All efficacy and safety analyses will be done within the classified cohort. Durability of treatment effects is defined as the time from onset of change from baseline of PR-PCSS and CR-PCSS in the quadrant treated in study EN3835-201 [redacted], where possible, in which the treated quadrant returns to baseline cellulite severity ratings of PR-PCSS and CR-PCSS in an EN3835-treated quadrant. Durability will be determined for all subjects that were treated with EN3835 in either EN3835-202 or EN3835-201. If sequential visit [redacted] are not available for that quadrant due to retreatment or [redacted], then the singular time point at which ratings return to baseline will be the durability cessation date.

17.2.1. Observational Population

The Observational population includes all subjects rolled over from the EN3835-201 study who do not receive any treatment in the current study. The safety analyses for subjects who received no EN3835 treatment in the current study will be performed using this population.

17.2.2. Safety Population

The Safety population will include all subjects who receive at least 1 dose of EN3835 in the current study. All safety analyses will be performed using this population.

17.2.3. Effectiveness Population

The Effectiveness population includes all safety subjects who have a baseline and at least 1 post-baseline assessment on both the CR-PCSS and PR-PCSS on the quadrant selected for treatment in the current study. All analysis of effectiveness will be based on this population.

17.2.4. Durability Populations

Overall Durability Population: This population is defined as all active responders who have both CR-PCSS and PR-PCSS at 180 days or above. The active responders are subjects treated with EN3835 with improvements of at least 1 level on each scale (CR-PCSS and PR-PCSS) from the baseline.

17.2.4.1. Durability Population for Double-blind Treated Subjects

This population is defined as all subjects in the durability population who showed an improvement of at least 1 level on each scale (CR-PCSS and PR-PCSS) from the baseline for the quadrant treated with EN3835 in double-blind study EN3835-201.

17.2.4.2. Durability Population for Open-label Treated Subjects

This population is defined as all subjects in the durability population who showed an improvement of at least 1 level on both the CR-PCSS and the PR-PCSS from the baseline for the quadrant treated with EN3835 in the open-label study (current EN3835-202 study) , and did not have the same quadrant treated in EN3835-201.

17.3. Subject Disposition

The number of subjects included in each study population will be summarized. The number and percentage of subjects completed and discontinued will be presented. Reasons for discontinuation as recorded on the eCRF will be summarized (number and percentage) for all subjects.

17.4. Demographics and Other Baseline Characteristics

Demographic and baseline characteristics, including age, race, and baseline values will be summarized for the Observational population, the Safety population, the Effectiveness population, and the Durability population using descriptive statistics. The descriptive statistics will include the number and percentage for categorical response variables and number, mean, standard deviation, minimum, and maximum for continuous variables.

17.5. Efficacy Analyses

Cellulite assessments (efficacy) include:

- PR-PCSS: 5-point scale ranging from 0 (no cellulite) to 4 (severe cellulite) (screening visit [Baseline], Days 22, 43, and 71). Also will be done at Day 90, Day 180, Day 270, and Day 360/end of study visits for observational assessments.

- CR-PCSS: 5-point scale ranging from 0 (no cellulite) to 4 (severe cellulite) (screening [Baseline], Days 22, 43, and 71). Also will be done at Day 90, Day 180, Day 270, and Day 360/end of study visits for observational assessments.
- Investigator rating of cellulite severity using the total scores from the Hexsel CSS scale: scores can range from 0 to 15 (screening [Baseline] and Day 71). Also will be done at Day 360/end of study visits for observational assessments.
- I-GAIS: 7-point scale ranging from 3 (very much improved) to −3 (very much worse) (Day 71). Also will be done at Day 360/end of study visit for observational assessments.
- S-GAIS: 7-point scale ranging from 3 (very much improved) to −3 (very much worse) (Day 71). Also will be done at Day 360/end of study visit for observational assessments.
- Subject satisfaction with cellulite treatment assessment: 5-point scale ranging from +2 (very much satisfied) to −2 (very much dissatisfied) (Day 71). Also will be done at Day 360/end of study visit for observational assessments.

All cellulite assessments will be done by treated quadrant. For initial treatment subjects who have 2 quadrants treated, each quadrant will be evaluated separately.

17.5.1. Efficacy Analysis

The composite endpoints for cellulite severity are the proportions of composite responders defined as subjects with an improvement in severity from baseline of at least 2 (or 1) levels of severity in the CR-PCSS and an improvement in severity from baseline of at least 2 (or 1) levels of severity in the PR-PCSS.

These endpoints, will be summarized by treated quadrant and overall (buttocks and thighs) and by study day using appropriate descriptive statistics.

Other endpoints for treated quadrants include:

- Proportion at each level of improvement in the PR-PCSS:
  - Proportion of patient responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS
  - Proportion of patient responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS
- Proportion at each level of improvement in the CR-PCSS:
  - Proportion of Investigator responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS (Investigator rated)
  - Proportion of Investigator responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS (Investigator rated)

- Proportion of responders at each level of the I-GAIS:
  - Proportion of Investigator global responders defined as subjects with a response of 1 (improved) or better in the Investigator GAIS assessment
- Proportion of responders at each level of the S-GAIS:
  - Proportion of subject global responders defined as subjects with a response of 1 (improved) or better in the subject GAIS assessment
- Proportion of responders at each level of the subject satisfaction with cellulite treatment
- Change in the Hexsel CSS total score from screening visit

All endpoints will be summarized by treated region (buttock or thigh) and overall and by study day using appropriate descriptive statistics.

Observational endpoints include:

- Proportions of composite responders defined as subjects with an improvement in severity from baseline of at least 2 (or 1) levels of severity in the CR-PCSS and an improvement in severity from baseline of at least 2 (or 1) levels of severity in the PR-PCSS.
- Proportion at each level of improvement in the PR-PCSS:
  - Proportion of patient responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS
  - Proportion of patient responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS
- Proportion at each level of improvement in the CR-PCSS:
  - Proportion of Investigator responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS (Investigator rated)
  - Proportion of Investigator responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS (Investigator rated)
- Hexsel CSS total score changed from the study EN3835-201 baseline at Day 71 of study EN3835-201 and Day 360/end of study of the current study (EN3835-202).

These endpoints will be summarized by treated region (buttock or thigh) and overall and by study day using appropriate descriptive statistics.

17.5.2. Durability of Treatment Effect

Durability of treatment effects will be presented as the number and percentage of treatment failure (or recurrence) among those active responders by follow-up time period, ie, 180 days, 360 days, 540 days, and 720 days. The treatment failure (recurrence) is defined as active

reponders whose CR-PCSS and PR-PCSS return to the baseline in an EN3835-treated quadrant during a certain follow-up period.

17.6. Safety Analyses

The following variables are safety endpoints.

- AEs: Mapped to preferred term using the Medical Dictionary for Regulatory Activities (MedDRA)
- Injection site reactions/local tolerability in selected quadrant (through subject and Investigator reporting)
- Vital signs
- Laboratory testing

AEs will be summarized by treatment group. AE duration will be summarized using descriptive statistics by treatment group.

Descriptive statistics will be presented for each clinical laboratory test for the actual and change from screening at each visit by treatment group and vital signs for the actual and change from Day 1 pre-injection for each injection day at each visit by treatment group.

17.6.1. Prior, Concomitant, and Follow-up Medication

The World Health Organization (WHO) Drug Dictionary will be used to classify prior and concomitant medications by therapeutic class. The version used in this study will be stated in the Data Management Plan. Prior medication will be defined as any medication with a start date prior to the Day 1 date. Concomitant medication is defined as any medication with a start date on or after the Day 1 date or reported as ongoing. Any medications started after the last dose of study drug will be considered as follow-up medications.

Prior and concomitant medication use will be summarized descriptively by the number and percentage of subjects receiving each medication within each therapeutic class. Multiple use of the same medication by a subject will be counted only once.

17.6.2. Study Drug Exposure

For those subjects that elect, are eligible, and do receive treatment, the number of injections will be summarized by counts and percentages. The number of dimples treated will be summarized with counts and percentages.

17.6.3. Measurement of Treatment Compliance

All doses are administered while the subjects are at the investigational site. Any dose that was not administered per protocol will recorded as a protocol deviation by the Investigator.

17.6.4. Adverse Events

The MedDRA dictionary will be used to code AEs. The version used in this study will be stated in the Data Management Plan.

Descriptive statistics (the number and percentage) for subjects reporting TEAEs will be tabulated by system organ class and preferred term; by system organ class, preferred term, and severity; and by system organ class, preferred term, and relationship to study drug. If more than 1 AE is coded to the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to the study drug.

SAEs and AEs leading to premature discontinuation of study drug will be summarized. Listings will be presented for subjects with SAEs, subjects with AEs leading to discontinuation, and subjects who die (if any).

17.6.5. Vital Signs

Descriptive statistics for vital signs (eg, systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, and body weight) and their changes from baseline at each visit and at the end of treatment visit will be presented.

Vital sign values are potentially clinically significant (PCS) if they meet both the observed value criteria and the change from baseline criteria. The criteria for PCS vital sign values will be detailed in the Statistical Analysis Plan (SAP). A listing of all AEs for subjects with PCS vital signs will also be provided.

17.6.6. Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values in International System of Units (SI units) and changes from baseline will be presented for each clinical laboratory parameter.

The number and percentage of subjects with PCS post-baseline clinical laboratory values will be tabulated. The criteria for PCS laboratory values will be detailed in the SAP. A listing of all AEs for subjects with PCS laboratory values will also be provided.

17.7. Immunogenicity Analyses

Immunogenicity variables include anti-AUX-I/anti-AUX-II binding antibody results. Binding antibody levels will be determined from samples collected on Days 1 and 71 during the treatment phase and Day 360 during the observational phase.

Descriptive statistics (percent of positive measurements and average antibody level) will be presented for anti-AUX-I and anti-AUX-II antibody levels at each time point by region treated and overall. Average antibody levels will be summarized on logarithmically transposed titer values.

17.8. Pharmacokinetic Analyses

Not applicable.

17.9. Interim Analysis

Not applicable.

17.10. Statistical Software

Statistical analyses will be performed using Version 9.3 (or higher) of SAS® (SAS Institute, Cary, North Carolina).

18. STUDY DRUG MATERIALS AND MANAGEMENT

18.1. Study Drug Identity

EN3835 is formerly known as AA4500; the 2 product names should be considered synonymous. The investigational product vials will be labeled as EN3835. The components of EN3835 are 0.9 mg of collagenase clostridium histolyticum, [redacted] n a lyophilized cake.

The components of EN3835 sterile diluent for reconstitution are 0.03% (2mM) calcium chloride ($CaCl_2$) in 0.9% (154mM) sodium chloride (NaCl) solution, pH 6.0 to 7.0. Diluent is supplied as a terminally-sterilized liquid at 3.0 mL per vial.

18.2. Study Drug Packaging and Labeling

Sterile vials of lyophilized EN3835 and sterile diluent will be provided to the Investigator by Endo. Each kit will contain 2 vials each of EN3835 and sterile diluent.

18.3. Study Drug Storage

All study drug will be provided by Endo. Study drug must be kept in a refrigerator (2°C-8°C) with locked access.

18.4. Study Drug Preparation

Refer to the Reconstitution Instructions for detailed preparation instructions.

Before reconstitution, remove the vials containing the lyophilized study drug powder and the vials containing the sterile diluent from the refrigerator and allow the vials to stand at room temperature for 15 minutes. Designated study personnel will visually inspect the study drug vials to determine the integrity and acceptability of the lyophilized drug product for reconstitution. The written procedures for inspection of the study drug vials will be provided to the site by Endo.

[redacted] The reconstituted study drug solution should be administered as soon as possible after reconstitution and further dilution. Each vial of study drug powder for reconstitution will be diluted according to the Reconstitution Instructions. Study personnel will maintain a record of the date and time of reconstitution.

18.5. Study Drug Accountability

Endo or its agent will maintain a master log of kits dispensed to the investigative sites. A drug inventory form must be kept current by the site staff designated to be responsible for reconstitution and must be made available to the clinical monitor, Endo employees, IRB/independent ethics committee (IEC), and regulatory agencies for routine inspection and accountability during monitoring visits. When instructed by Endo, the Investigator agrees to return all original containers of unused study drug to Endo or its designee.

18.5.1. Study Drug Handling and Disposal

The Investigator is responsible for recording the receipt and use of all drug supplied and for ensuring the supervision of the storage and allocation of these supplies. All unused study drug will be returned, and unit counts will be performed whenever medication is returned. The site must account for all study drug received. The Investigator agrees not to supply study drug to any person except to those subjects enrolled in the study. At the end of the study, all unused drug supplies will be returned to Endo as instructed by the clinical monitor.

19. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

19.1. Source Documents

Source documents include but are not limited to original documents, data and records such as hospital/ medical records (including electronic health records), clinic charts, lab results, subject diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, etc. At a minimum, all data required to be collected by the protocol should have supporting source documentation for entries in the eCRF.

19.2. Study Monitoring

A representative of Endo Pharmaceuticals Inc. will meet with the Investigator and his/her staff prior to the entrance of the first subject to review study procedures and methods of recording findings in the eCRF.

After enrollment of the first subject, an Endo Pharmaceuticals Inc. representative will be assigned to periodically monitor each Investigator site for study progress and to verify that standards of Good Clinical Practice (GCP) were followed. The Investigator is expected to prepare for the monitor visit, ensuring that all source documents, completed eCRFs, signed consent forms, and other study related documents are readily available for review.

19.3. Audits and Inspections

The Investigator shall permit audits and inspections by the Sponsor, its representatives and members of regulatory agencies. The investigator should immediately notify the Sponsor of an upcoming FDA or other regulatory agency inspection.

19.4. Institutional Review Board (IRB)

The Investigator shall permit members of the IRB/IEC to have direct access to source documents.

19.5. Data Recording and Documentation

All data recordings and source documentation (including electronic health records) must be made available to the Sponsor (or designee), FDA and any other regulatory agencies that request access to study records, including source documents, for inspection and copying, in keeping with federal and local regulations.

20. QUALITY CONTROL AND QUALITY ASSURANCE

Steps to assure the accuracy and reliability of data include the selection of qualified principal investigators and appropriate study centers, review of protocol procedures with the principal investigators and associated personnel prior to start of the study, and periodic monitoring visits conducted by the Sponsor or Sponsor representative. Significant and/or repeated non-compliance will be investigated and remedial action instituted when appropriate. Failure to comply with remedial actions may result in investigator site termination and regulatory authority notification.

The Sponsor or its designee will utilize qualified monitors to review and evaluate activities conducted at Investigator Sites.

The data will be entered into the clinical study database and verified for accuracy, following procedures defined by the Sponsor (or designee). Data will be processed and analyzed following procedures defined by the Sponsor (or designee).

The study will be monitored and/or audited at intervals to ensure that the clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the Study Protocol; International Conference on Harmonisation (ICH), E6 consolidated guidelines; and other applicable regulations. The extent, nature, and frequency of monitoring and/or audits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity, and enrollment rate. At the conclusion of a program, a compliance statement will be generated by the Sponsor (or designee) listing all audit activities performed during the clinical study.

21. ETHICS

21.1. Ethics Review

Approval by the IRB/IEC prior to the start of the study will be the responsibility of the Investigator. A copy of approval documentation will be supplied to Endo Pharmaceuticals Inc. along with a roster of IRB members that demonstrates appropriate composition (a Department of Health and Human Services [DHHS] Assurance Number will satisfy this requirement).

The study protocol, the informed consent form, advertisements, materials being provided to subjects and amendments (if any) will be approved to IRB/IECs at each study center in conformance with ICH E6, the Code of Federal Regulations (CFR), Title 21, Part 56 and any other applicable local laws. The Investigator is responsible for supplying the IRB/IEC with a copy of the current IB, Package Insert, or SPC as well as any updates issued during the study. During the course of the study, the Investigator will provide timely and accurate reports to the IRB/IEC on the progress of the study, at intervals not exceeding 1 year (or as appropriate), and will notify the IRB/IEC of SAEs or other significant safety findings, per the policy of the IRB/IEC. At the conclusion of the study, the Investigator will submit a final report or close out report to the IRB/IEC and provide a copy to Endo Pharmaceuticals Inc.

Any amendment to this protocol will be provided to the Investigator in writing by Endo Pharmaceuticals Inc. No protocol amendment may be implemented (with the exceptions noted below) before it has been approved by the IRB and the signature page, signed by the Investigator, has been received by Endo Pharmaceuticals Inc. Where the protocol is amended to eliminate or reduce the risk to the subject, the amendment may be implemented before IRB review and approval. However, the IRB must be informed in writing of such an amendment and approval obtained within reasonable time limits. Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the subject, and must be immediately reported to Endo Pharmaceuticals Inc.

The Investigator will be responsible for supplying updated safety and/or study information to study subjects as it becomes available.

21.2. Ethical Conduct of the Study

This clinical study is designed to comply with the ICH Guidance on General Considerations for Clinical Trials (62 FR 6611, December 17, 1997), Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (62 FR 62922, November 25, 1997), Good Clinical Practice: Consolidated Guidance (62 FR 25692, May 9, 1997) and 21 CFR parts 50, 54, 56, and 312.

The study will be conducted in full compliance with ICH E6, the FDA guidelines for GCP and in accordance with the ethical principles that have their origins in the Declaration of Helsinki defined in 21 CFR, 312.120.

21.3. Subject Information and Consent

Subjects, after having the study explained to them and an opportunity to have their questions answered sufficiently, will give voluntary and written informed consent (in compliance with ICH E6, 4.8 and 21 CFR Parts 50 and 312) before participating in any study-related procedures. The consent shall be written in a language understandable to the subject. Subjects unable to read (illiterate) shall have the consent process performed in the presence of an independent witness who shall also sign the consent. Each subject will read, assent understanding, and sign an instrument of informed consent after having had an opportunity to discuss the study and consent documents with the Investigator before signing, and will be made aware that she may withdraw from the study at any time.

In addition to obtaining informed consent, the Investigator is responsible for obtaining any additional documentation to demonstrate compliance with local privacy laws applicable to activities performed.

The consent process shall be recorded in source documents. Signed copies of the informed consent will be given to the Subject and originals will be placed in the Investigator study files.

A unique Subject identification number will be assigned according to section 12.1.3 at the time that the Subject signs the informed consent form.

22. DATA HANDLING AND RECORDINGKEEPING

22.1. Data Collection

Data collection will involve the use of an EDC system to which only authorized personnel will have access. The system will be secured to prevent unauthorized access to the data or the system. This will include the requirement for a user ID and password to enter or change data. The level of access to the EDC system will be dependent on the person's role in the study.

Study data will be collected from source documents and entered into an eCRF within the EDC system. The Investigator will be responsible for ensuring the eCRFs are completed in a timely manner relative to the subject's visit. In addition to periodic monitoring occurring within the system by a Sponsor monitor, programmatic edit checks will be used to review EDC data for completeness, logic, and adherence to the study protocol. As a result of this monitoring and these checks, queries may be issued electronically to the clinical study sites and closed electronically by the monitor, data management staff or authorized staff at the study site. Additionally, the Investigator will review eCRFs, ensure all missing or corrected data is provided and will sign the eCRF pages with an electronic signature.

An electronic audit trail will be maintained in the EDC system to track all changes made to data entered in the eCRF. Data will be retrievable in such a fashion that all information regarding each individual subject is attributable to that subject. Unless otherwise indicated, all data captured in the eCRF must first be captured in source documents.

In addition, any contact with the subject via telephone or other means that provide significant clinical information must be documented in source documents as described above.

22.2. Study Documentation

Upon study completion, the Investigator will be provided with complete electronic copies of the eCRF data for his/her files.

23. REPORTING AND PUBLICATION

All data generated in this study are the property of Endo. An integrated clinical and statistical report will be prepared at the completion of the study.

Publication of the results by the Investigator will be subject to mutual agreement between the Investigator and Endo.

24. INVESTIGATOR OBLIGATIONS

24.1. Regulatory Documents

The Investigator is responsible for creating and/or maintaining all study documentation required by 21CFR 50, 54, 56 and 312, ICH, E6 section 8, as well as any other documentation defined in the protocol or the Investigator Agreement. The Investigator must maintain the documentation relating to this study and permit Endo Pharmaceuticals Inc. or a member of a regulatory agency access to such records.

The Investigator must provide the following key documents to Endo Pharmaceuticals Inc. prior to the start of the study:

- A completed and signed Form FDA1572. If during the course of the study any information reported on the Form FDA 1572 changes, a revised Form FDA1572 must be completed and returned to Endo Pharmaceuticals Inc. for submission to the FDA. For studies executed outside the United States, documentation required by the governing regulatory authority may be substituted for the Form FDA 1572.
- A fully executed contract
- The Investigator's Statement page in this protocol signed and dated by the Investigator and any subsequent amendment signature pages
- The IB acknowledgment of receipt page
- Curricula vitae for the Principal Investigator and all Sub-Investigators listed on Form FDA 1572, including a copy of each physician's license (if applicable)
- A copy of the original IRB/IEC approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals or shorter intervals defined by the IRB/IEC. All subsequent modifications must be submitted and approved by the IRB, as described in section 21.1
- A copy of the IRB/IEC-approved informed consent form
- A list of IRB/IEC members or DHHS Assurance Number
- Laboratory certifications and normal ranges (if local labs are required by the protocol)
- A financial disclosure agreement completed and signed by the Investigator and all Sub-Investigators listed on Form FDA 1572. Investigator site staff that submitted an initial financial disclosure are also responsible for informing Endo Pharmaceuticals Inc. of any changes to their initial financial disclosure form 1 year after the completion of the study.

A complete list of required regulatory documents will be supplied by Endo Pharmaceuticals Inc. or its representative.

24.2. Delegation of Responsibilities and Adequate Resources

The Investigator should have adequate time to conduct the study properly and should have an adequate number of qualified staff to assist with the conduct of the study. The Investigator shall delegate tasks only to individuals qualified by education, training and experience to perform the delegated tasks. The Investigator shall have direct oversight of all delegated activities and shall document delegation of responsibilities. The Investigator is responsible for ensuring all delegated staff have been properly trained on the protocol and their assigned study responsibilities.

24.3. Medical Care of Study Subjects

The Investigator and/or a qualified sub-investigator shall be responsible for the subjects' medical care. Any unrelated medical condition discovered during the course of the study should be communicated to the subject so that they may seek appropriate medical care. The Investigator will report all AEs as required by the protocol (section 14.5). The Investigator will inform study subjects of new information regarding the study drug as it becomes available.

24.4. Use of Investigational Materials

The Investigator will acknowledge that the study drug supplies are investigational and as such must be used strictly in accordance with the protocol and only under the supervision of the Principal Investigator or Sub-Investigators listed on Form FDA1572 (or other regulatory document, depending on region). Study drug must be stored in a safe and secure location. At study initiation, a representative from Endo Pharmaceuticals Inc. will inventory the study drug at the site. The Investigator must maintain adequate records documenting the receipt and disposition of all study supplies. Endo Pharmaceuticals Inc. or its representative will supply forms to document total inventory as well as subject specific accountability. The Investigator is responsible for monitoring use of the study drug to ensure compliance with the protocol. All study supplies shall be returned to Endo Pharmaceuticals Inc. or its designee.

24.5. Retention of Records

Federal and local regulations require that the Investigator retain a copy of all regulatory documents and records that support the data for this study (eg, informed consents, laboratory reports, source documents, study drug dispensing records) for whichever of the following is the longest period of time:

- A period of 2 years following the final date of approval by the FDA or other regulatory agency of the study drug for the purposes that were the subject of the investigation; or
- A period of 5 years following the date on which the results of the investigation were submitted to the FDA or other regulatory agency in support of, or as part of, an application for a research or marketing permit for the study drug for the purposes that were the subject of the investigation

Endo will notify Investigators once one of the above 2 timeframes has been satisfied.

If the investigation does not result in the submission of the data in support of, or as part of, an application for a research or marketing permit, records must be retained for a period of 2 years

following notification by Endo Pharmaceuticals Inc. that the entire clinical investigation (not merely the Investigator's portion) is completed, terminated, or discontinued or 2 years following withdrawal of the Investigational New Drug application (IND).

If the Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. Endo must be notified in writing of the name and address of the new custodian. Study records should not be destroyed without consultation with Endo Pharmaceuticals Inc.

24.6. Subject Confidentiality

All subject records submitted to Endo Pharmaceuticals Inc. or its designee will be identified only by initials and subject identification number. Subjects' names are not to be transmitted to Endo Pharmaceuticals Inc. The Investigator will keep a Master Subject List on which the identification number and the full name, address, and telephone number of each subject are listed. It is the Investigators' responsibility to inform study subjects that representatives of the Sponsor, FDA, or other regulatory agencies may review all records that support their participation in the study. The Investigator will adhere to all privacy laws to which he/she is subject.

25. TERMINATION OF STUDY

The Sponsor has the right to suspend or terminate the study at any time. The study may be suspended or terminated for any reason.

26. INVESTIGATOR'S AGREEMENT

I agree to conduct the study in accordance with the protocol, and with all applicable government regulations and Good Clinical Practice guidance.

_____ _____/_____/_____

Investigator's Signature Date

_____

Typed Name of Investigator

27. REFERENCES

1. Khan MH, Victor F, Rao B, Sadick NS. Treatment of cellulite: Part I. Pathophysiology. *J Am Acad Dermatol* 2010;62(3):361-370.
2. Hexsel D, de Oliveira Dal'Forno T, Mazzuco R. Definition, clinical aspects, classifications, and diagnostic techniques. In: Goldman MP, Hexsel D, eds. *Cellulite: Pathophysiology and Treatment.* 2nd ed. New York, NY: Informa Healthcare; 2010:13-21.
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7. Collis N, Elliot LA, Sharpe C, Sharpe DT. Cellulite treatment: a myth or reality: a prospective randomized, controlled trial of two therapies, endermologie and aminophylline cream. *Plast Reconstr Surg*. 1999;104(4):1110-1114.
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LIST OF APPENDICES

APPENDIX A. DOCUMENTS REQUIRED PRIOR TO INITIATION OF THE STUDY

As a Sponsor of a clinical study, Endo Pharmaceuticals Inc. has an obligation to ensure that the study will be conducted by a qualified Investigator with sufficient resources of time, personnel, and physical facilities to conduct the study and to ensure that the Investigator understands and agrees to comply with the protocol, applicable regulations, policies, and procedures. The following documentation is required:

From the Principal Investigator

1. A signed agreement to perform the study per protocol (the signature page will suffice).
2. A signed Letter of Financial Agreement (including confidentiality statement).
3. Name(s) of the Principal Investigator and of all sub-Investigator(s)
4. All address(es) of the clinical site(s).
5. A current medical license valid where he/she practices and a current curriculum vitae for the Principal Investigator (signed and dated) and all sub-investigators, to contain at least the following elements:
   a. For physicians:
      i. Date of degree in Medicine
      ii. Name of the Institution granting the degree in Medicine.
      iii. Previous clinical postings with dates.
   b. For non-physician allowed by national law or regulations to act as clinical Investigators:
      i. Date and description of most advanced degree.
      ii. Name of the Institution granting the degree in number (i).
      iii. Other accreditation or qualifications relevant to the study.
      iv. Previous postings with dates.
      v. Name and qualification (see 5a above) of the physician or dentist in charge of study subjects.

   Note: If a non-physician is serving as Principal Investigator, then a qualified physician must be assigned as a sub-Investigator for the trial, to be responsible for all trial-related medical decisions.
6. Written notification of Institutional Review Board/Independent Ethics Committee/Human Research Ethics Committee (IRB/IEC/HREC) approval. The minimum requirements are as follows:
   a. Dated letter, including:
      i. The date on which the meeting for the review of the study protocol took place.
      ii. Study protocol/amendment number, and version date

iii. A clear statement of approval of the protocol and the informed consent text with version date, and authorization for the study to proceed.

iv. If the Investigator or any sub-Investigator is a part of the IRB/IEC/HREC Review Board, assurance that the Investigator abstained from voting at the meeting(s) when the study was discussed.

b. A dated list of the members and their occupations.

c. A specimen copy of the Committee-approved informed consent text to be used in the study.

7. Food and Drug Administration (FDA) Form 1572 (for studies submitted under a US Investigational New Drug application [IND]).

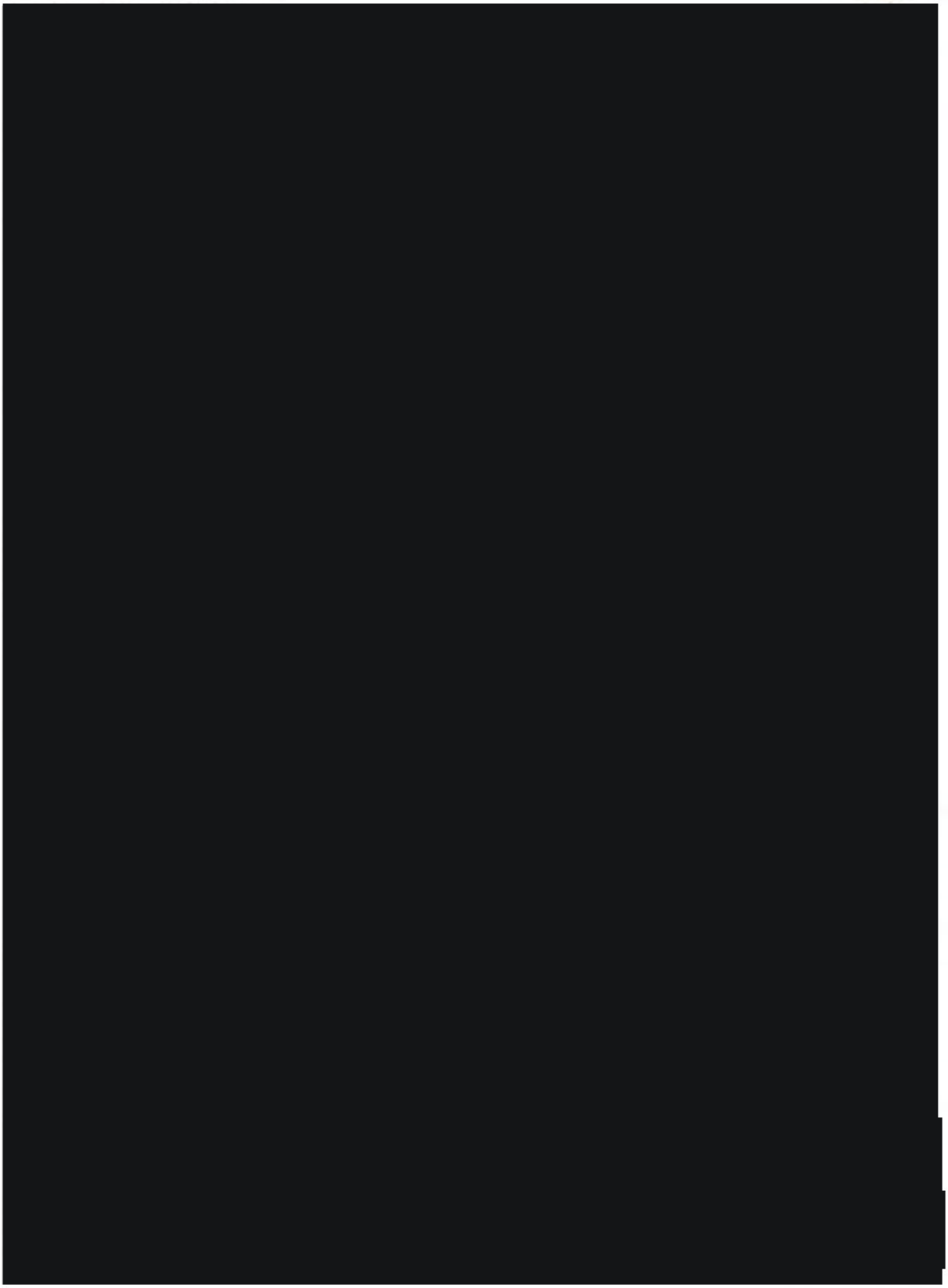
8. Financial Disclosure Certification or Certification of Non-Disclosure (for studies to be submitted for a US New Drug Application/Biologics License Application [NDA/BLA]).

Other

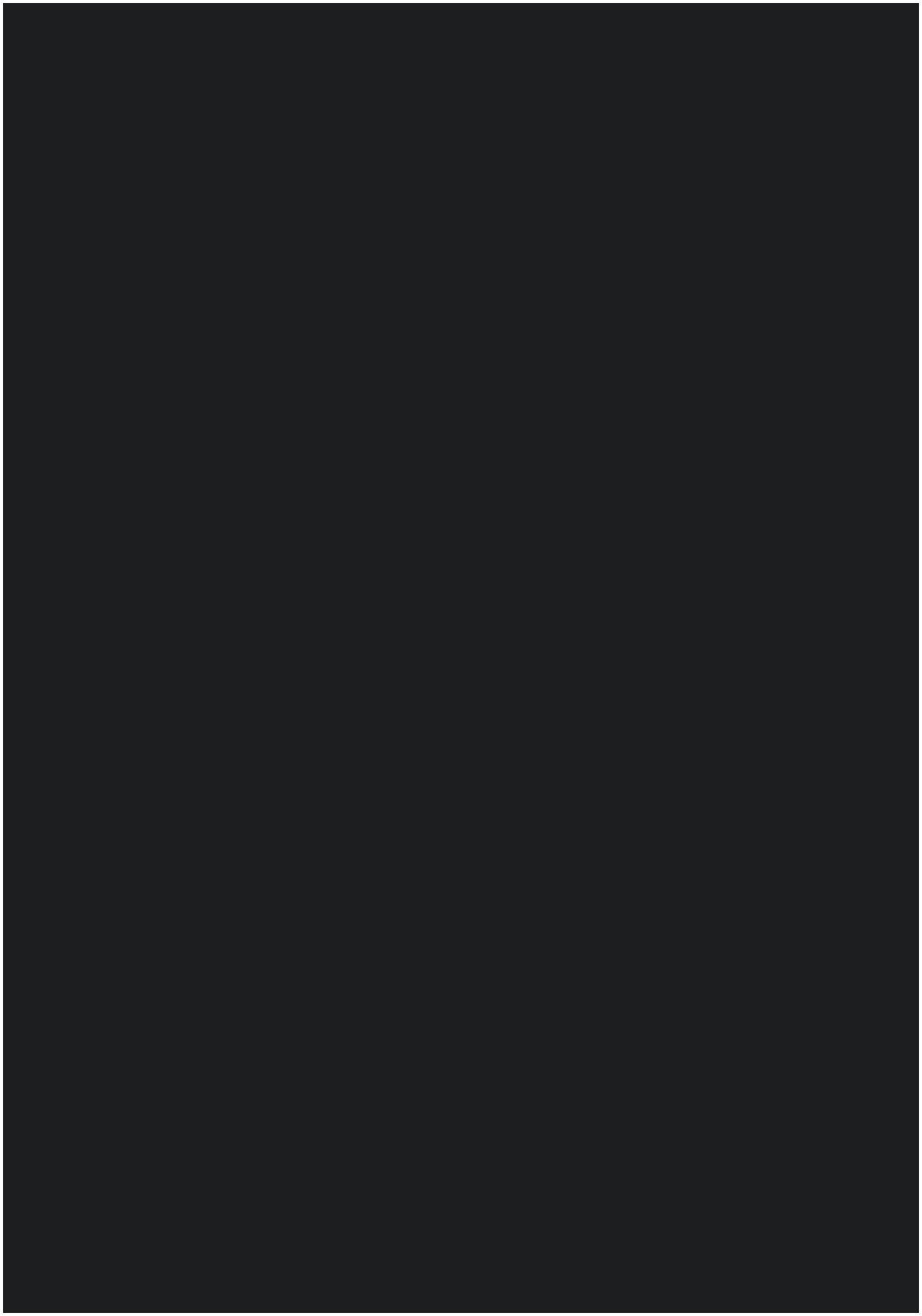
Any other documentation required by national law or regulations to be in the possession of the Sponsor or the Investigator for study participation or study initiation.

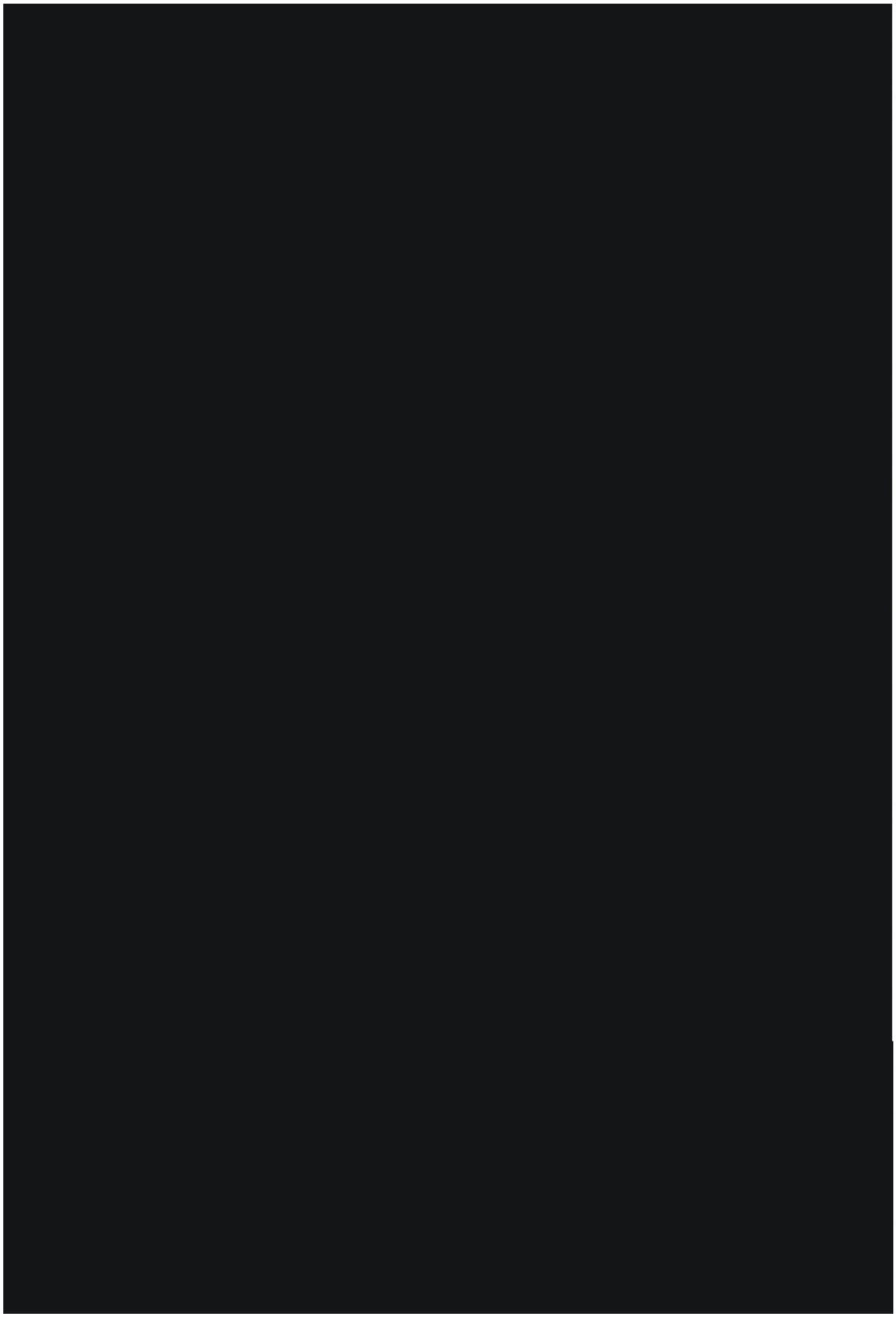
[redacted]

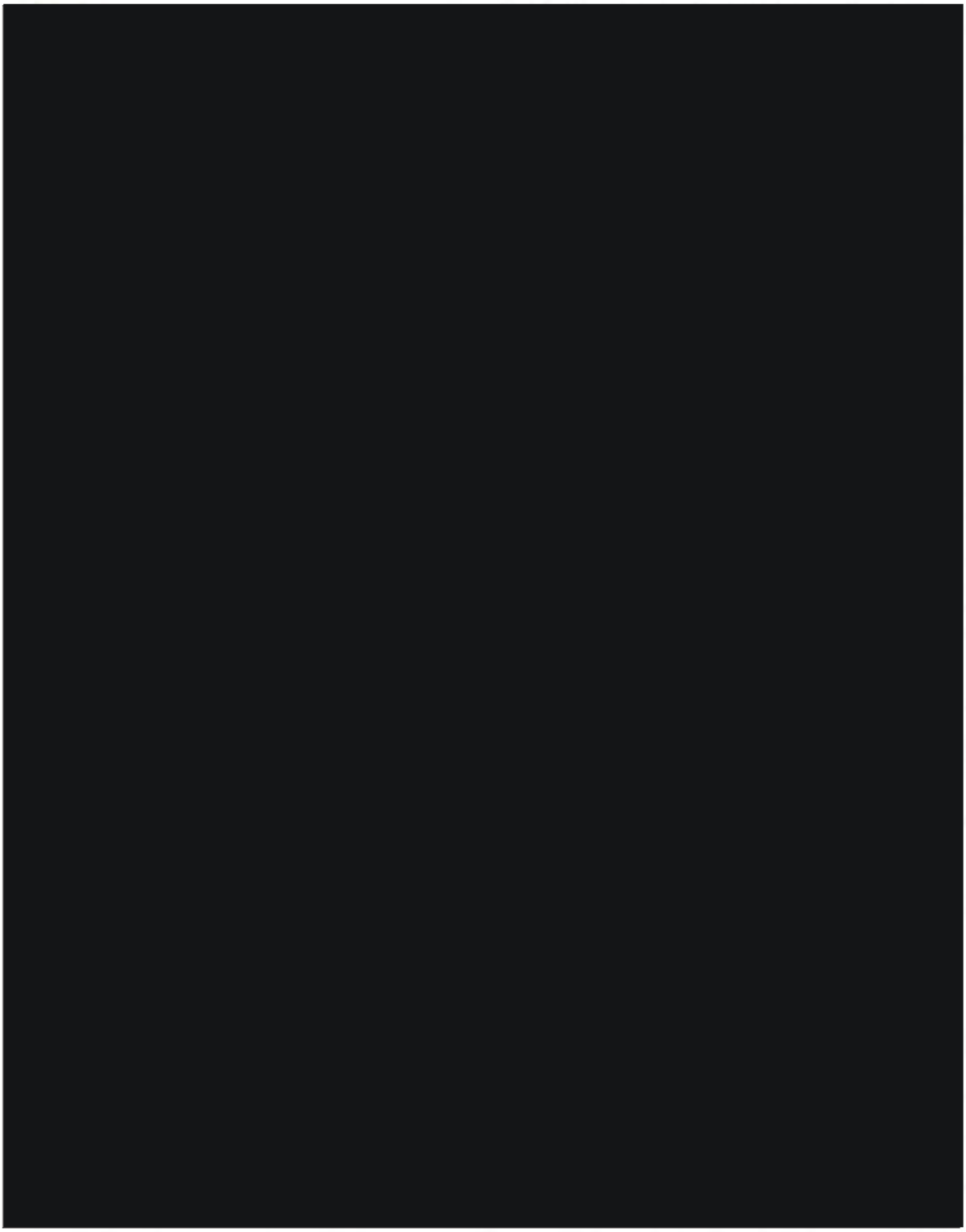
APPENDIX B. HEXSEL DM, DAL'FORNO T, HEXSEL CL. A VALIDATED PHOTONUMERIC CELLULITE SEVERITY SCALE. *J EUR ACAD DERMATOL VENEREOL*. 2009;23(5):523-528.



JEADV 2009, 23, 523–528





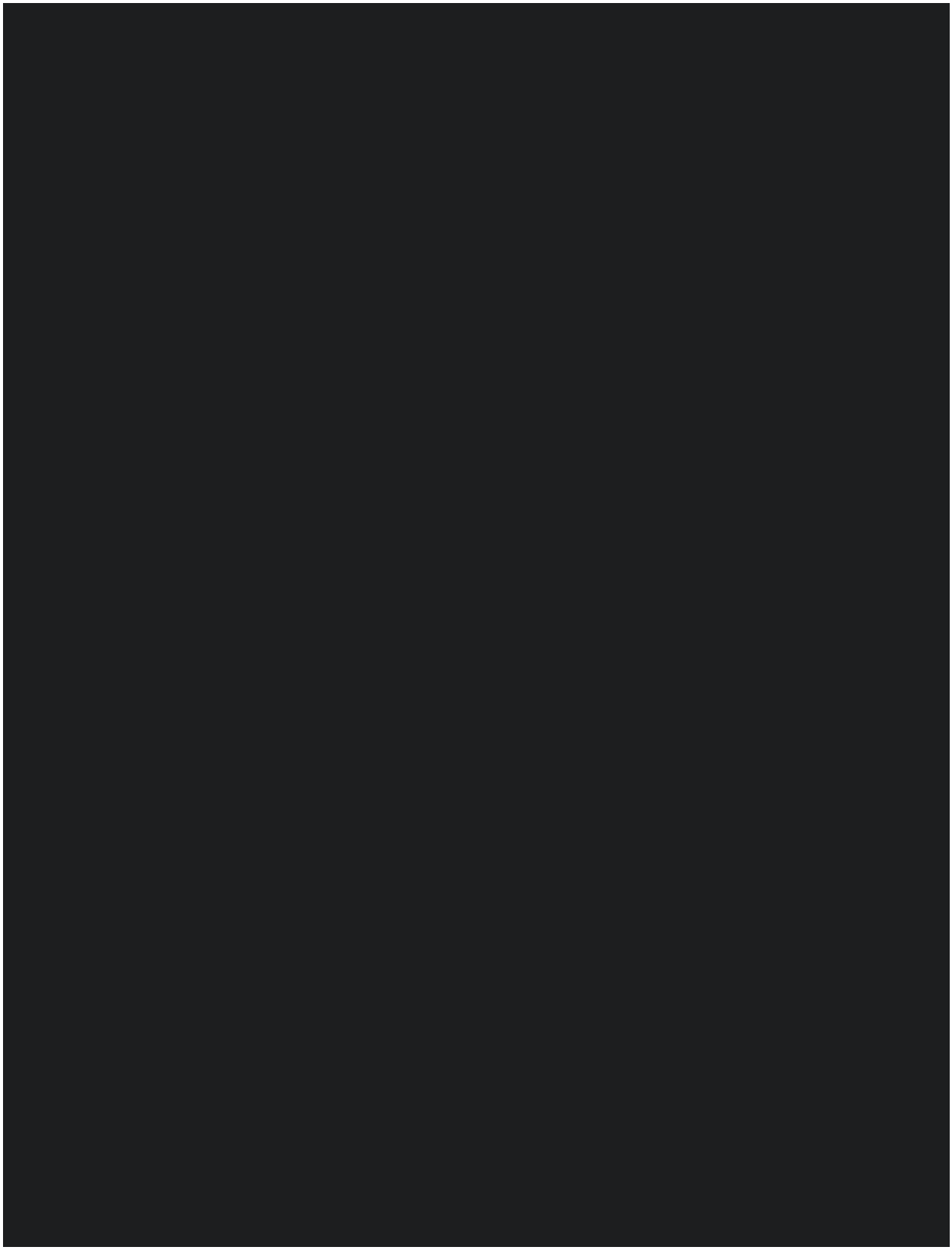


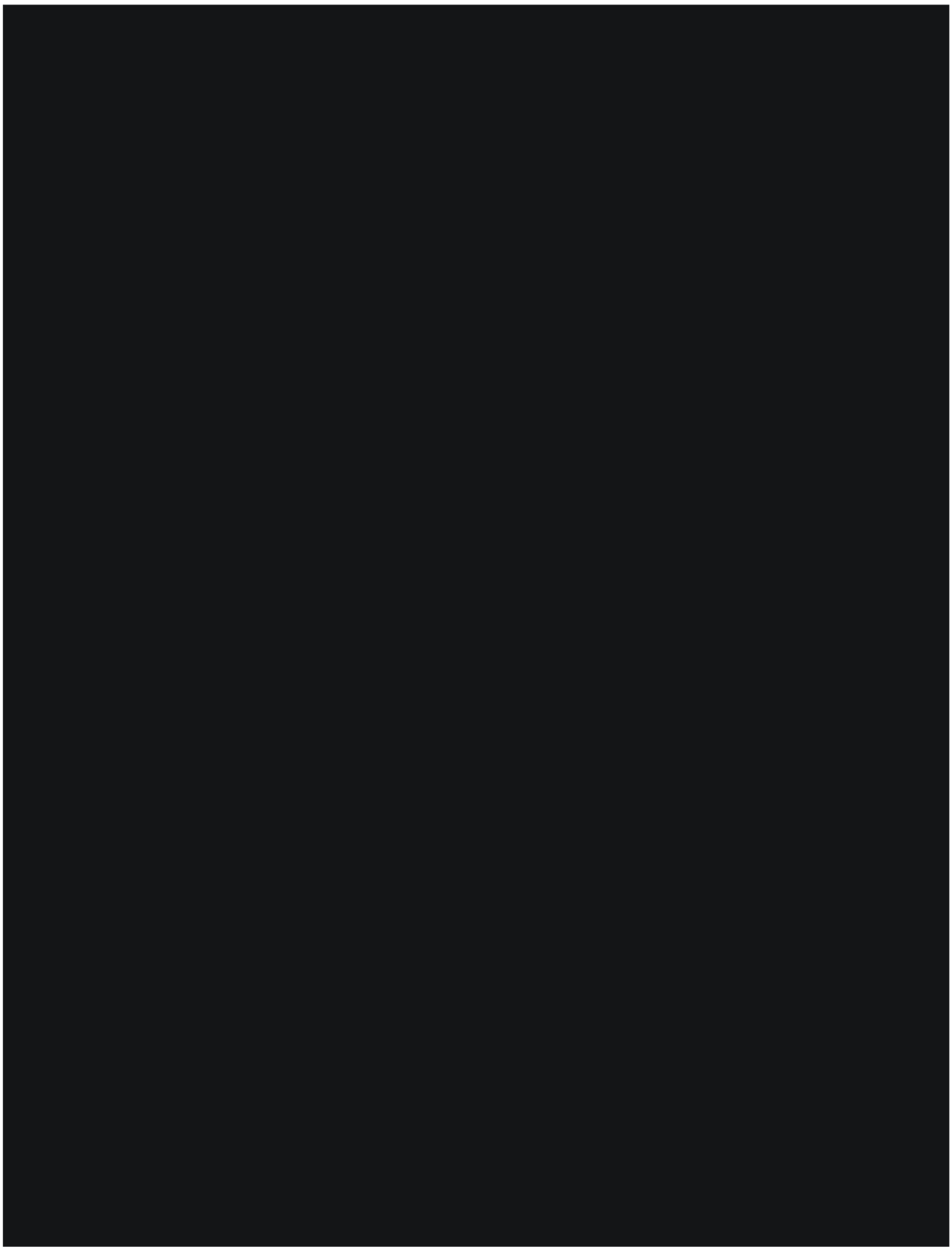
[redacted]

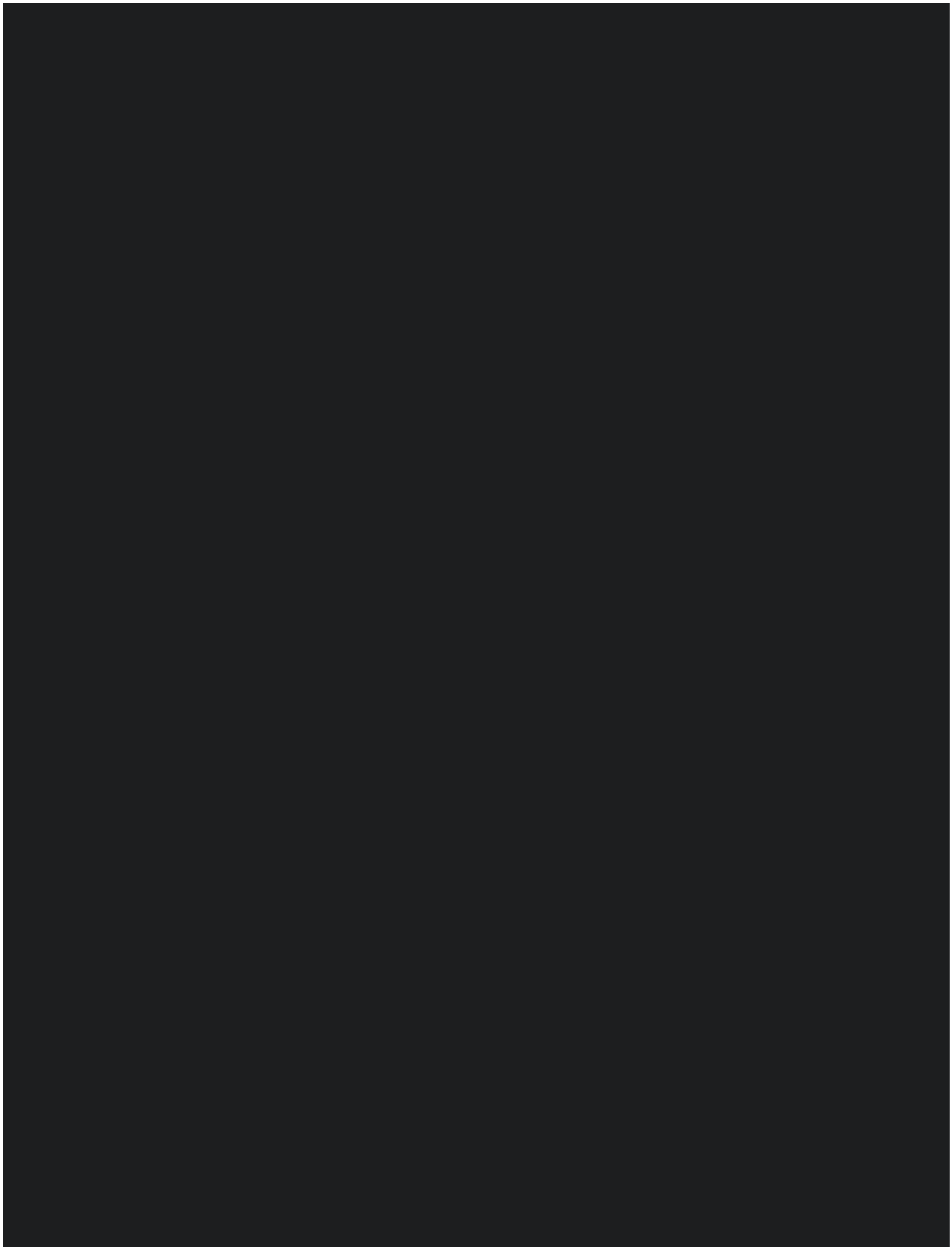
JEADV 2009, 23, 523–528

APPENDIX C. REFERENCE IMAGES FOR HEXSEL SEVERITY RATINGS

APPENDIX D. PATIENT INSTRUCTIONS FOR USE OF PATIENT-REPORTED PHOTONUMERIC CELLULITE SEVERITY SCALE (PR-PCSS)







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

COLLAGENASE CLOSTRIDIUM HISTOLYTICUM (EN3835)

EN3835-202

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

IND 110077

Amendment 3

Date:

Original Protocol: June 20, 2016

Amendment 1: July 5, 2016

Amendment 2: October 25, 2016

Amendment 3: June 6, 2017

Auxilium Pharmaceuticals, Inc. (Auxilium) was acquired by Endo International plc. in January 2015. The Sponsor of the application remains Auxilium; however, Endo Pharmaceuticals Inc. (Endo) is authorized to act and to communicate on behalf of Auxilium.

[redacted]

2. SUMMARY OF CHANGES

The EN3835-202 protocol amendments and amended informed consent forms (as necessary) have been reviewed and approved by the governing institutional review boards (IRBs) before implementation of the amendments at each study center.

Amendment 1 was incorporated into the protocol on July 5, 2016. The major reason for this amendment was to clarify that the investigators will conduct the assessment.

Section	Original Text	Revised Text
13.1.1.5 Investigator Global Aesthetic Improvement Scale (I-GAIS)	Subjects in the observation-only group will complete the I-GAIS as described below at the final study visit (month 12 or early termination) and a comparison back to the pre-treatment day 1 (Baseline) image of the assigned quadrant of the double-blind study.	Investigators will complete the I-GAIS on subjects in the observation-only group as described below at the final study visit (month 12 or early termination) and a comparison back to the pre-treatment Day 1 (Baseline) image of the assigned quadrant of the double-blind study.

Amendment 2 was incorporated into the protocol on October 25, 2016. The major reasons for this amendment were to improve operational activities and clarifications, and optimize and reduce the number of blood sample collections needed to profile immunogenicity.

Section	Original Text	Revised Text
3 Sponsor Contact Information	Clinical Trial Manager: [redacted]	Associate Director, Clinical Operations: [redacted]
3 Sponsor Contact Information	Medical Monitor email: [redacted]	Medical Monitor email: [redacted]
3 Sponsor Contact Information	[redacted]	[redacted]
4 Synopsis, Study Period	Estimated date first subject enrolled: Jun-2016 Estimated date last subject completed: May-2017	Estimated date first subject enrolled: Oct-2016 Estimated date last subject completed: Sep-2017
4 Synopsis, Objectives, Secondary	To evaluate the durability of response to EN3835 in EFP severity over the 12-month post initial dosing of EN3835 in subjects previously receiving active treatment in study EN3835-201 using the Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS), the Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS), and the Hexsel Cellulite Severity Scale (CSS) To evaluate long-term response to EN3835 in assessments of EFP including subject satisfaction, Investigator Global Aesthetic	To assess safety and immunogenicity of re-treating or re-dosing a subject that had previously received treatment with EN3835 To evaluate the durability of response to EN3835 in EFP severity over the 12-month post initial dosing of EN3835 in subjects previously receiving active treatment in study EN3835-201 using the Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS) and the Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS)

Section	Original Text	Revised Text
	Improvement Scale (I-GAIS), and Subject Global Aesthetic Improvement Scale (S-GAIS) To evaluate immunogenicity after exposure to EN3835	To evaluate long-term response to EN3835 in assessments of EFP including subject satisfaction, Investigator Global Aesthetic Improvement Scale (I-GAIS), and Subject Global Aesthetic Improvement Scale (S-GAIS) To assess cellulite severity assessments in quadrants treated in this study with EN3835. To evaluate immunogenicity after exposure to EN3835
4 Synopsis, Study Design	Treatments will be administered on days 1, 22, and 43; subjects will be assessed for safety on days 1, 22, 43, and 71 and for cellulite severity assessments on days 1, 43, and 71.	Treatments will be administered on Days 1, 22, and 43; subjects will be assessed for safety on Days 1, 22, 43, and 71 and for cellulite severity assessments at Screening visit and on Days 22, 43, and 71.
4 Synopsis, Diagnosis and inclusion/ exclusion criteria	**Qualification for the Open-Label Treatment Phase of the Study** ***Inclusion criteria for treatment:*** Have participated in and completed the double-blind study EN3835-201 and all day 71 assessments	**Qualification for the Open-Label Treatment Phase of the Study** ***Inclusion criteria for treatment:*** Have participated in and completed the double-blind study EN3835-201
4 Synopsis, Duration of study	**Follow-up**: For subjects treated with EN3835 in this study, subjects will be observed at treatment visits (Days 1, 22, and 43) and Day 71 after first injection.	**Follow-up**: For subjects treated with EN3835 in this study, subjects will be observed at treatment visits (Days 1, 22, and 43) and Day 71 after first injection. After Day 71, they will be observed every 3 months from their first exposure to EN3835 up to a maximum of 1 year.
5 Schedule of Events	NOTE: Observation visits (Table 2) in the open-label extension study begin after completion of double-blind study (day 71). Treatment sessions (Table 3), if elected, will begin when study drug blind is broken in study EN3835-201 while observation visits continue concurrently.	NOTE: Observation visits (Table 2) in the open-label extension study begin after completion of double-blind study (Day 71). Treatment sessions (Table 3), if elected, will begin after study drug blind is broken in study EN3835-201while observation visits continue concurrently.
5 Schedule of Events, Table 2, Collection of Samples: Anti-AUX-I/anti-AUX-II antibody level	Visit 1: X Visit 2: X Visit 3: X Visit 4: X	Visit 1: Visit 2: Visit 3: Visit 4: X
5 Schedule of Events, Table 3, Tx Visit 4 End of Treatment/Early Termination Day 71 …	Tx Visit 4 End of Treatment/ Early Termination Day 71 (±5 days)[b]	Tx Visit 4 End of Treatment/ Early Termination Day 71 (+5 days)[b]

Section	Original Text	Revised Text
5 Schedule of Events, Table 3, Procedures	Screening B[a]: Medical history/EFP history including previous treatments: X[k] Prior/Concomitant Medications/Procedures: X[k] Physical examination: Body weight: X Height: X Collection of samples: Clinical laboratory X Tx Visit 1: Prior/Concomitant Medications/Procedures: X	Screening B[a]: Medical history/EFP history including previous treatments: X[k,m] Prior/Concomitant Medications/Procedures: X[k,m] Physical examination: Body weight: X[m] Height: X[m] Collection of samples: Clinical laboratory: X[m] Tx Visit 1: Prior/Concomitant Medications/Procedures: X[m]
5 Schedule of Events, Table 3, Collection of Samples: Anti-AUX-I/anti-AUX-II antibody level	Tx Visit 1: X[e] Tx Visit 2: X[e] Tx Visit 3: X[e] Tx Visit 4: X	Tx Visit 1: X[e,m] Tx Visit 2: Tx Visit 3: Tx Visit 4: X
5 Schedule of Events, Table 3, footnotes	[a] Eligible subjects may choose additional treatment any time after the study drug blind is broken in study EN3835-201. Add	[a] After the study drug blind is broken in study EN3835-201, eligible subjects may elect to receive EN3835 treatments. [m] Do not conduct on subjects eligible and opting-in for a second course of treatment in the current study (EN3835-202) if Screening B visit or Day 1 visit for second treatment course is the same day as Day 71 of the first treatment course in this study or previous study EN3835-201.
9.2 Secondary Objectives	To assess safety and immunogenicity of re-treating or re-dosing a subject that had previously received treatment with EN3835 To evaluate the durability of response to EN3835 in EFP severity over the 12-month post initial dosing of EN3835 in subjects previously receiving active-treatment in study EN3835-201 using the PR-PCSS, the CR-PCSS, and the Hexsel CSS To evaluate long-term response to EN3835 in assessments of EFP including subject satisfaction, I-GAIS, and S-GAIS To assess cellulite severity assessments in quadrants treated in this study with EN3835	To assess safety and immunogenicity of re-treating or re-dosing a subject that had previously received treatment with EN3835 To evaluate the durability of response to EN3835 in EFP severity over the 12-month post initial dosing of EN3835 in subjects previously receiving active-treatment in study EN3835-201 using the PR-PCSS and the CR-PCSS To evaluate long-term response to EN3835 in assessments of EFP including subject satisfaction, I-GAIS, and S-GAIS To assess cellulite severity assessments in quadrants treated in this study with EN3835 To evaluate immunogenicity after exposure to EN3835

Section	Original Text	Revised Text
10.1 Study Design	Following the study drug blind being broken and communicated to centers, treatments of eligible subjects with EN3835 can begin at a visit at the discretion of the subject.	Following the study drug blind being broken and communicated to centers, eligible subjects may elect to receive EN3835 treatment.
11.1 Observation Phase	All subjects who have completed the double-blind study EN3835-201, including all day 71 assessments, and sign informed consent are eligible for enrollment in this open-label extension study and participation in the ongoing safety and cellulite evaluations.	All subjects who have completed the double-blind study EN3835-201 and sign the informed consent are eligible for enrollment in this open-label extension study and participation in the ongoing safety and cellulite evaluations.
11.2.1 Subject Inclusion Criteria for Treatment	Have participated in and completed the double-blind study EN3835-201 and all Day 71 assessments	Have participated in and completed the double-blind study EN3835-201
11.2.2 Subject Exclusion Criteria for Treatment	Add	Presence of any clinically relevant conditions, that in the opinion of the Investigator would interfere with completing the study including, but not limited to, visual problems, hearing problems, cognitive impairment or acute mental illness
12.1.3 Study Entry/ Observational Assessments	A subject who gives written informed consent and who satisfies all eligibility criteria (section 11) may be entered into the observational phase of the study and complete safety and cellulite severity assessments at 3-month intervals as detailed in Table 2.	A subject who gives written informed consent and who satisfies all eligibility criteria (section 11) may be entered into the observational phase of the study and complete safety and cellulite severity assessments at 3-month intervals as detailed in Table 2. The first visit will be determined by the date of enrollment in study EN3835-202 relative to the Schedule of Events for Study EN3835-202 (Table 2). For example, if a subject enrolls after the Day 90 visit window, the first observation visit for that subject would be Day 180.
12.1.4 Treatment Assessments (Optional)	If a subject received placebo in the double-blind study, she may be eligible for 2 treatments in the open-label study; if a subject received active drug in the double-blind study, she may be eligible for 1 additional treatment (3 treatment sessions) in the open-label study.	If a subject received placebo in the double-blind study, she may be eligible for 2 treatment courses in the open-label study; if a subject received active drug in the double-blind study, she may be eligible for 1 additional treatment course (3 treatment sessions) in the open-label study.
12.1.4 Treatment Assessments (Optional), Selection of Treatment Quadrant	The Investigator will then assess each of the 4 subject's quadrants live in real-time using the CR-PCSS.	The Investigator will then assess each of the subject's 4 quadrants live in real-time using the CR-PCSS.

Section	Original Text	Revised Text
12.1.4 Treatment Assessments (Optional), Selection of Treatment Quadrant	A subject who received placebo in the double-blind study may be treated in the same quadrant in the open-label study if the quadrant still meets all 3 criteria OR another qualifying quadrant may be selected for treatment by the Investigator and subject.	A subject who received placebo in the double-blind study may be treated in the same quadrant in the open-label study if the quadrant still meets all 3 criteria OR another qualifying quadrant may be selected for treatment by the subject.
12.1.4 Treatment Assessments (Optional), Selecting and Marking Dimples	The cellulite severity assessments using the PR-PCSS, CR-PCSS, and Hexsel CSS will be completed prior to dimple marking at treatment visits 2, 3, and 4/end of treatment.	The cellulite severity assessments using the PR-PCSS and CR-PCSS will be completed prior to dimple marking at treatment visits 2, 3, and 4/end of treatment.
12.1.4.1 Screening B (Days −14 to −1 Relative to Open-Label Treatment Visit Day 1)	The Investigator will conduct live assessments of subject's cellulite severity of each quadrant using the CR-PCSS (section 13.1.1.4)	The Investigator will conduct independent live assessments of subject's cellulite severity of each quadrant using the CR-PCSS (section 13.1.1.4) after the subject completes her ratings and with no knowledge of the subject's ratings of her quadrants.
12.1.4.1 Screening B (Days −14 to −1 Relative to Open-Label Treatment Visit Day 1)	Collection of samples for: Clinical laboratory testing including Anti-AUX-I and anti-AUX-II antibody testing (section 14.7) Urine pregnancy testing (section 14.7)	Collection of samples for: Clinical laboratory testing (section 14.7) Urine pregnancy testing (section 14.7)
12.1.4.2, Treatment Session 1 …	Treatment Session 1 (Visit 1B)	Treatment Session 1 (Treatment Visit 1)
12.1.4.2 Treatment Session 1 …, Pre-injection	Collection of samples for urine pregnancy testing (section 14.7)	Collection of samples for: anti-AUX-I and anti-AUX-II antibody testing (section 14.7.1) urine pregnancy testing (section 14.7)
12.1.4.3, Treatment Session 2 … and Treatment Session 3 …	Treatment Session 2 (Visit 2/Day 22 ± 3 Days) and Treatment Session 3 (Visit 3/Day 43 ± 3 Days)	Treatment Session 2 (Treatment Visit 2/ Day 22 ± 3 Days) and Treatment Session 3 (Treatment Visit 3/Day 43 ± 3 Days)
12.1.4.3 Treatment Session 2 … and Treatment Session 3 …, Pre-injection	Investigator live assessment of the severity of cellulite using the CR-PCSS (section 13.1.1.4)	Investigator will conduct an independent live assessment of the severity of cellulite using the CR-PCSS (section 13.1.1.4). The investigator will conduct the assessment of severity only after the subject has completed her rating of her quadrant and without knowledge of the subject's rating of her quadrant.

Section	Original Text	Revised Text
12.1.4.3 Treatment Session 2 … and Treatment Session 3 …	If no injections are given at treatment session 2, subjects will still return for the day 43 visit and the selected quadrant will again be evaluated by the subject (PR-PCSS) and Investigator (CR-PCSS).	If the Investigator rates the selected quadrant as 0, no injections will be given. If no injections are given at treatment session 2, subjects will still return for the Day 43 visit and the selected quadrant will again be evaluated by the subject (PR-PCSS) and Investigator (CR-PCSS).
12.1.4.4 Day 71 … End of Treatment/Early Termination	Day 71 (±5 Days) End of Treatment/Early Termination	Day 71 (+5 Days) End of Treatment/Early Termination
12.1.4.4 Day 71 … End of Treatment/Early Termination	Investigator cellulite assessments of selected quadrant using:	Investigator cellulite assessments of selected quadrant independently conducted; ie, with no knowledge of the subject's rating, using:
13.1.1.2 Subject Global Aesthetic Improvement Scale (S-GAIS)	The S-GAIS assessment will be done on day 71 of the treatment course and then at month 12 or the final study visit and compared back to the pre-dosing Screening B image (Baseline for treatment subjects) of the selected quadrant.	For subjects who elected to receive EN3835 treatment, the S-GAIS assessment will be done on Day 71 of the treatment course and then at month 12 or the final study visit and compared back to the pre-dosing Screening B image (Baseline for treatment subjects) of the selected quadrant.
13.1.1.6 Hexsel Cellulite Severity Scale	For subjects in the observation-only group, the Hexsel CSS will be done at month 3 and every 3 months thereafter and at the month 12 or the end of study visit. For subjects who elected to have EN3835 treatments, the Hexsel CSS will be done at 3-month intervals during the observation phase until the study drug blind is broken in study EN3835-201. The Hexsel CSS assessment will be done at Screening B visit and on day 71 of the treatment course and at month 12 or end of study visit. For the subjects electing treatment (re-treatment or re-dosing) with EN3835 the Investigator or qualified designee will use the Hexsel CSS to assess the severity of EFP in all quadrants at Screening B and the selected quadrant on day 71 of the course of treatment.	For subjects in the observation-only group, the Hexsel CSS will be done at the month 12 or the end of study visit. For the subjects electing treatment (re-treatment or re-dosing) with EN3835 the Investigator or qualified designee will independently use the Hexsel CSS to assess the severity of EFP in all quadrants at Screening B visit and the selected quadrant on Day 71 of the course of treatment and at month 12 or end of study visit.
14.6.1 Adverse Events of Special Interest	There are no AEs of special interest anticipated in this study. AEs such as bruising, ecchymosis, hematomas, and contusions that occur remote to the site of drug administration will be recorded as an AE or SAE as appropriate (see section 14.1.1, Adverse Events or section 14.1.2, Serious Adverse Events).	[redacted] (see section 14.1.1, Adverse Events or section 14.1.2, Serious Adverse Events).

Section	Original Text	Revised Text
14.7 Clinical Laboratory and Immunogenicity Determinations	Urine pregnancy test kits will be supplied by the Sponsor.	DELETED TEXT
14.7.1 Anti-AUX-I and Anti-AUX-II Antibodies	Serum samples will be collected and may be tested for binding and neutralizing anti-AUX-I and anti-AUX-II antibodies at visit 1 through visit 4. Additionally, if a subject consents to treatment in the open-label study, serum samples for antibody testing will be collected before injection at treatment visits 1, 2, 3, and 4 of the open-label treatment period. A subset of subject samples will have neutralizing antibodies tested from day 1 and day 71 visits; additional samples may be analyzed if results or clinical signs warrant testing.	Serum samples will be collected and may be tested for binding and neutralizing anti-AUX-I and anti-AUX-II antibodies at visit 1 and visit 4. Additionally, if a subject consents to treatment in the open-label study, serum samples for antibody testing will be collected before injection at treatment visit 1 and at end of treatment/ early termination visit 4 of the open-label treatment period. A subset of subject samples may have neutralizing antibodies tested from Day 1 and Day 71 visits; additional samples may be analyzed if results or clinical signs warrant testing.
14.8 Vital Signs	These parameters include pulse rate, respiratory rate, systolic and diastolic blood pressure, and body weight.	These parameters include pulse rate, respiratory rate, systolic and diastolic blood pressure, and body temperature.
17.2 Subject Cohorts and Subject Populations	All efficacy and safety analyses will be done within the classified cohort. Durability of treatment effects defined as time period from injection to return to baseline cellulite severity ratings in a EN3835-treated quadrant will be determined for all subjects that were treated with EN3835 in either this study or study EN3835-201.	All efficacy and safety analyses will be done within the classified cohort. Durability of treatment effects defined as the time from onset of change from baseline of PR-PCSS and CR-PCSS in the quadrant treated in study EN3835-201 until the time that the treated quadrant return to baseline cellulite severity ratings of PR-PCSS and CR-PCSS in an EN3835-treated quadrant will be determined for all subjects that were treated with EN3835 in either this study or study EN3835-201.
17.6.1 Prior, Concomitant, and Follow-up Medication	The version used in this study will be stated in the Data Management Plan. Prior medication will be defined as any medication with a start date prior to the day 1 date and are collected at the screening visit and upon admission to the clinic on day −1.	The version used in this study will be stated in the Data Management Plan. Prior medication will be defined as any medication with a start date prior to the Day 1 date.
24.4 Use of Investigational Materials	The Investigator is responsible for monitoring subject's use of the study drug to ensure compliance with the protocol. All study supplies shall be returned to Endo Pharmaceuticals Inc. or its designee (this may include empty packaging such as bottles and blister cards). It is the Investigator's responsibility to ensure that subjects return their medication.	The Investigator is responsible for monitoring use of the study drug to ensure compliance with the protocol. All study supplies shall be returned to Endo Pharmaceuticals Inc. or its designee.

Section	Original Text	Revised Text
18.2 Study Drug Packaging and Labeling	Sterile vials of lyophilized EN3835 (formerly AA4500) and sterile diluent will be provided to the Investigator by Endo. Each kit will contain 1 vial each of EN3835 and sterile diluent.	Sterile vials of lyophilized EN3835 and sterile diluent will be provided to the Investigator by Endo. Each kit will contain 2 vials each of EN3835 and sterile diluent.
18.4 Study Drug Preparation	Designated study personnel will visually inspect the study drug vial to determine the integrity and acceptability of the lyophilized drug product for reconstitution.	Designated study personnel will visually inspect the study drug vials to determine the integrity and acceptability of the lyophilized drug product for reconstitution.
24.6 Subject Confidentiality	All subject records submitted to Endo Pharmaceuticals Inc. or its designee will be identified only by initials and code number.	All subject records submitted to Endo Pharmaceuticals Inc. or its designee will be identified only by initials and subject identification number.
24.6 Subject Confidentiality	The Investigator will adhere to all privacy laws to which she is subject.	The Investigator will adhere to all privacy laws to which he/she is subject.

Amendment 3 was incorporated into the protocol on June 6, 2017. The major reasons for this amendment are to increase the number of subjects assessed at 12 months after their first exposure to EN3835 and to update the statistical methods.

Section	Original Text	Revised Text
3 Sponsor Contact Information, Table 1, Medical Monitor	[redacted]	[redacted]
4 Synopsis, Study Period	Estimated date last subject completed: Sep-2017	Estimated date last subject completed: Jun-2018
4 Synopsis, Study Design	Subjects will be assessed for safety and cellulite severity assessments approximately every 3 months for a maximum of 1 year from their first exposure to EN3835. Subjects with at least 1 quadrant with moderate or severe level of cellulite will be eligible for treatment with EN3835 after unblinding of study EN3835-201; a quadrant that was treated with EN3835 in the previous study EN3835-201 will only be eligible for retreatment if the cellulite severity in that quadrant is rated at levels of cellulite severity at baseline in study EN3835-201.	Subjects will be assessed for safety and cellulite severity assessments approximately every 3 months for a maximum of 1 year from their first exposure to EN3835 in each treated quadrant. Subjects with at least 1 quadrant with moderate or severe level of cellulite will be eligible for treatment with EN3835 after unblinding of study EN3835-201; a quadrant that was treated with EN3835 in the previous study EN3835-201 will only be eligible for retreatment if the cellulite severity in that quadrant is rated at levels of cellulite severity at baseline or greater in study EN3835-201.
4 Synopsis, Study Design	After Day 71, they will be observed every 3 months from their first exposure to EN3835 up to a maximum of 1 year. The study will terminate when at least 100 subjects have been assessed at 12 months after the first exposure to EN3835.	After Day 71, they will be observed every 3 months from their first exposure to EN3835 up to a maximum of 1 year in each treated quadrant.

Section	Original Text	Revised Text
4 Synopsis, Number of subjects (planned)	333	Approximately 350
4 Synopsis, Study center(s)	16 sites in the United States	15 sites in the United States
4 Synopsis, Investigational product, dosage and mode of administration	For the observational periods of this study, subjects will be assessed for safety and cellulite severity assessments at approximately 3-month intervals for a maximum of 1 year following their first exposure to EN3835.	For the observational periods of this study, subjects will be assessed for safety and cellulite severity assessments at approximately 3-month intervals for a maximum of 1 year following their first exposure to EN3835 in each treated quadrant.
4 Synopsis, Duration of study	Twelve (12) months from first exposure to EN3835 in study EN3835-201 or study EN3835 202	Twelve (12) months from first exposure to EN3835 in study EN3835-201 and 12 months from first exposure in any additional treated quadrants in the EN3835-202 study
4 Synopsis, Observational Phase	Subjects will be assessed at visits that occur approximately every 3 months for a maximum of 1 year after the first exposure to EN3835.	Subjects will be assessed at visits that occur approximately every 3 months for a maximum of 1 year after the first exposure to EN3835 in each treated quadrant.
4 Synopsis, Follow-up	Subjects will be assessed at visits that occur approximately every 3 months for a maximum of 1 year after the first exposure to EN3835. For subjects treated with EN3835 in this study, subjects will be observed at treatment visits (Days 1, 22, and 43) and Day 71 after first injection. After Day 71, they will be observed every 3 months from their first exposure to EN3835 up to a maximum of 1 year.	Subjects will be assessed at visits that occur approximately every 3 months for a maximum of 1 year after the first exposure to EN3835 in each treated quadrant. For subjects treated with EN3835 in this study, subjects will be observed at treatment visits (Days 1, 22, and 43) and Day 71 after first injection. After Day 71, they will be observed every 3 months from their first exposure to EN3835 up to a maximum of 1 year in each treated quadrant.
4 Synopsis, Statistical methods, Sample Size Consideration	The number of subjects (approximately 333) is intended to obtain additional subjects for adequate long-term safety data at the selected dose.	Approximately 350 subjects are planned to obtain adequate long-term safety data for this study.
4 Synopsis, Statistical methods, Analysis Populations	Safety population: The Safety population is defined as all enrolled subjects who received at least 1 injection of EN3835 in this study or in study EN38335-201. Intent-to-Treat (ITT) population: The ITT population is defined as all enrolled subjects in this study.	Safety population: The Safety population is defined as all enrolled subjects who received at least 1 injection of EN3835 in this study. Effectiveness population: This population is defined as all safety subjects who have a baseline and at least 1 post-injection evaluation of both the CR-PCSS and PR-PCSS.

Section	Original Text	Revised Text
	Modified Intent-to-Treat (mITT) population: The mITT population is defined as ITT subjects who received at least 1 injection of EN3835 in this study with a baseline and 1 post-injection evaluation of both the CR-PCSS and PR-PCSS. All efficacy (cellulite assessments) analyses will be completed on this population. Per-Protocol population: The Per-Protocol population is defined as those subjects in the Safety population who have no major protocol deviations.	
4 Synopsis, Statistical methods, Efficacy Evaluations	The primary cellulite severity assessment endpoint, the proportion of composite responders with improvement of 2 or better on each scale (CR-PCSS and PR-PCSS) at Day 71, will be summarized as percentages and analyzed using a Cochran-Mantel-Haenszel test that compares the 2 treatment groups and adjusts for Investigator. The ITT population will be evaluated for the primary endpoint with any subjects not having a post-injection evaluation of either CR-PCSS or PR-PCSS classified as a non-responder. All secondary endpoints, except the Hexsel CSS total score, will be summarized as percentages. The dichotomous secondary endpoints (ie, responders endpoints) will be analyzed using a Cochran-Mantel-Haenszel test adjusted for investigator. Multiple-response endpoints (ie, scales) will be analyzed using the Mann-Whitney test. Change in Hexsel CSS total score will be summarized with descriptive statistics for continuous variable and will be analyzed using analysis of variance (ANOVA).	The composite endpoints for cellulite severity assessment, the proportions of composite responders with improvement of 2 (or 1) or better on each scale (CR-PCSS and PR-PCSS), will be summarized as numbers and percentages by study days (visit). The analysis will be based on Effectiveness population. All other endpoints including observational endpoints will be summarized by study days using appropriate descriptive statistics. The descriptive statistics will include the number and percentage for categorical response variables and number, mean, standard deviation, minimum, and maximum for continuous variables.
5 Schedule of Events, Table 2, Procedures	ADDED TEXT AND ROW	Prior/Concomitant Medications/Procedure Screening A: X Visit 1: X Visit 2: X Visit 3: X Visit 4: X
5 Schedule of Events, Table 2, footnotes	[b]Three (3)-month evaluation periods begin 90 days after Day 1 of the double-blind study (EN3835-201) (ie, within 20 days ±4 days of completion of double-blind study).	[b] Four (4) visits at 3-month periods begin 90 days after Day 1 of the double-blind study (EN3835-201) (ie, within 20 days ± 4 days of completion of double-blind study).
5 Schedule of Events, Table 3, Procedures	Informed Consent Screening B: X	DELETED TEXT AND ROW

Section	Original Text	Revised Text
9.2 Secondary Objectives	To assess safety and immunogenicity of re-treating or re-dosing a subject that had previously received treatment with EN3835	• To evaluate safety and immunogenicity of re-treating or re-dosing a subject that had previously received treatment with EN3835
10.1 Study Design	The study is planned to end when at least 100 subjects have 12 months after exposure ie 12 months after first treatment in study EN3835 201 or study EN3835-202.	DELETED TEXT
10.1 Study Design	Previously placebo-treated subjects will have the option to receive a second course of EN3835 in the same or different qualifying quadrant after at least 28 days following the end of the first treatment course (ie treatment of second quadrant could begin on Day 71 after treating the first quadrant). The selected quadrant can be re-treated or re-dosed.	Previously placebo-treated subjects will have the option to receive a second course of EN3835 in the same or different qualifying quadrant after at least 28 days following the end of the first treatment course (eg, the screening B visit of second quadrant could be performed on Day 71 after treating the first quadrant). The selected quadrant can be re-treated or re-dosed.
10.1 Study Design, table	N=333	DELETED TEXT
12.1.1 Subject Screening	Upon completion of Day 71 assessments in the double-blind study EN3835-201, a subject will be eligible to enter this open-label extension study. Investigators will be expected to maintain a Screening Log of all potential study subjects. This log will include limited information about the potential subject and the date and outcome of the screening process (eg, enrolled into the study, reason for ineligibility, or refused to participate). Investigators will provide information about the study to subjects who appear to meet the criteria for participation in the study.	Upon completion of Day 71 assessments in the double-blind study EN3835-201, a subject will be eligible to enter this open-label extension study. All potential subjects eligible for screening in EN3835-202 will be pre-populated in the electronic data capture (EDC) system. The status of all subjects (eg, screen fails) will also be kept in the EDC system.
12.1.3 Study Entry/Observational Assessments	ADDED TEXT	All subjects must complete Screening A and at least 1 Observation visit before Screening B can occur. Once the study blind was broken, the EN3835-201 placebo subjects were allowed to directly proceed to Screening B.
12.1.4.5 Follow-up Visits	Follow-up visits will continue until the study is terminated when at least 100 subjects have been assessed at 12 months after the first exposure to EN3835.	DELETED TEXT

Section	Original Text	Revised Text
12.5 End of Study	The end of study is when 100 subjects complete the 1-year safety and cellulite severity evaluations. At the time of study termination, ongoing subjects receiving treatment will be followed through the Day 71 visit. The remaining enrolled subjects (in excess of the first 100 subjects to complete 1 year) will undergo early termination procedures in accord with the Schedule of Events (section 5).	At the time of study termination, ongoing subjects receiving treatment will be followed through the Day 71 visit. The remaining enrolled subjects will undergo early termination procedures in accordance with the Schedule of Events (section 5).
13.1.1.4 Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS)	ADDED TEXT	This variable may be entered directly into the EDC system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.
13.1.1.5 Investigator Global Aesthetic Improvement Scale (I-GAIS)	The Investigator will circle the rating below that best represents their answer.	DELETED TEXT
13.1.1.5 Investigator Global Aesthetic Improvement Scale (I-GAIS)	ADDED TEXT	This variable may be entered directly into the EDC system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.
13.1.1.6 Hexsel Cellulite Severity Scale	ADDED TEXT	This variable may be entered directly into the EDC system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.
14.5.2 Reporting of Serious Adverse Events	Any SAE that is felt by the Investigator to be related to the study medication must be reported regardless of the amount of time since the last dose received.	Any SAE that is considered by the Investigator to be related to the study medication must be reported regardless of the amount of time since the last dose received.
14.7 Clinical Laboratory	ADDED TEXT	Results of the urine pregnancy test may be entered directly into the EDC system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.
14.7.1 Anti-AUX-I and Anti-AUX-II Antibodies	Serum samples will be collected and may be tested for binding and neutralizing anti-AUX-I and anti-AUX-II antibodies at visit 1 and visit 4.	Serum samples will be collected and may be tested for binding and neutralizing anti-AUX-I and anti-AUX-II antibodies at Visit 4 of the observation assessments.

Section	Original Text	Revised Text
14.8 Vital Signs	ADDED TEXT	The subject's vital signs should be stable, or repeated until stable before the subject can leave direct observation. This variable may be entered directly into the EDC system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.
14.9 Electro-cardiogram	ADDED TEXT	The investigator's assessment may be entered directly into the EDC system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.
14.10 Physical Examination	ADDED TEXT	This variable may be entered directly into the EDC system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.
17.1 Determination of Sample Size	It is estimated that approximately 95% of the 350 subjects randomized in study EN3835-201 will enroll in the current study for a sample size of 333. This sample size should be adequate to determine safety and cellulite assessments of EN3835 for subjects retreated in the same and in different quadrants.	Approximately 350 subjects that completed the EN3835-201study will enroll in the current study. This sample size should be adequate to determine long term safety and cellulite assessments of EN3835.
17.2 Subject Cohorts and Subject Populations	Durability of treatment effects defined as the time from onset of change from baseline of PR-PCSS and CR-PCSS in the quadrant treated in study EN3835-201 until the time that the treated quadrant return to baseline cellulite severity ratings of PR-PCSS and CR-PCSS in an EN3835-treated quadrant will be determined for all subjects that were treated with EN3835 in either this study or study EN3835-201.	Durability of treatment effects is defined as the time from onset of change from baseline of PR-PCSS and CR-PCSS in the quadrant treated until the time that the treated quadrant returns to baseline cellulite severity ratings of PR-PCSS and CR-PCSS in an EN3835-treated quadrant.
17.2.2 Safety Population	The Safety population will include all subjects who receive at least 1 dose of EN3835 in the current study or in study EN3835-201. All safety analyses will be performed using this population.	The Safety population will include all subjects who receive at least 1 dose of EN3835 in the current study. All safety analyses will be performed using this population.
17.2.3 Effectiveness Population	Intent-to-Treat Population The Intent-to-Treat (ITT) population includes all subjects who enroll in the current study.	Effectiveness Population The Effectiveness population includes all safety subjects who have a baseline and at least 1 post-baseline assessment on both the CR-PCSS and PR-PCSS on the quadrant selected for treatment in the current study. All analysis of effectiveness will be based on this population.

Section	Original Text	Revised Text
17.2.4 Modified Intent-to-Treat Population	17.2.4 Modified Intent-to-Treat Population The Modified Intent-to-Treat (mITT) population includes all subjects who receive at least 1 dose of EN3835 in the current study (EN3835-202) and have a baseline and at least 1 post-baseline assessment on both the CR-PCSS and PR-PCSS on the quadrant selected for treatment in the current study. All cellulite assessment analyses will be completed on this population.	DELETED TEXT
17.2.5 Per-Protocol Population	17.2.5 Per-Protocol Population The Per-Protocol population includes all subjects in the safety population who have no major protocol deviations. Major protocol deviations excluding subjects from this population will be determined at the protocol deviation assessment meeting prior to the database lock. If more than 10% of the safety population is excluded from the per-protocol population, then all safety and cellulite evaluations will be repeated using the per-protocol population.	DELETED TEXT
17.4 Demographics and Other Baseline Characteristics	Demographic and baseline characteristics, including age, race, and baseline values will be summarized for the Observational population, the Safety population, and the mITT population using descriptive statistics. The descriptive statistics will include frequency tables for all categorical response variables and number, mean, standard deviation, minimum, and maximum for all continuous variables.	Demographic and baseline characteristics, including age, race, and baseline values will be summarized for the Observational population, the Safety population, and the Effectiveness population using descriptive statistics. The descriptive statistics will include the number and percentage for categorical response variables and number, mean, standard deviation, minimum, and maximum for continuous variables.
17.5.1 Efficacy Analysis	The primary cellulite severity endpoint is the proportion of composite responders at Day 71 defined as subjects with an improvement in severity from baseline (Screening B visit) of at least 2 levels of severity in the CR-PCSS and an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS. The primary endpoint, the proportion of composite responders with improvement of 2 or better on each scale (CR-PCSS and PR-PCSS) will be summarized by region treated (buttock or thigh) and overall with percentages.	The composite endpoints for cellulite severity are the proportions of composite responders defined as subjects with an improvement in severity from baseline of at least 2 (or 1) levels of severity in the CR-PCSS and an improvement in severity from baseline of at least 2 (or 1) levels of severity in the PR-PCSS. These endpoints, will be summarized by treated quadrant and overall (buttocks and thighs) and by study day using appropriate descriptive statistics.
17.5.1 Efficacy Analysis	Secondary Efficacy Analysis	Other endpoints for treated quadrants include:

Section	Original Text	Revised Text
17.5.1 Efficacy Analysis	Proportion of composite responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS. (Day 71) Proportion at each level of improvement in the PR-PCSS (Day 71): Proportion of patient responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS Proportion of patient responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS Proportion at each level of improvement in the CR-PCSS (Day 71): Proportion of Investigator responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS (Investigator rated) Proportion of Investigator responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS (Investigator rated) Proportion of responders at each level of the I-GAIS (Day 71): Proportion of Investigator global responders defined as subjects with a response of 1 (improved) or better in the Investigator GAIS assessment Proportion of responders at each level of the S-GAIS (Day 71): Proportion of subject global responders defined as subjects with a response of 1 (improved) or better in the subject GAIS assessment Proportion of responders at each level of the subject satisfaction with cellulite treatment (Day 71) Change in the Hexsel CSS total score from screening visit to Day 71 All secondary endpoints, except the Hexsel CSS total score, will be summarized by treated region (buttock or thigh) and overall using percentages. Change in Hexsel CSS total score will be summarized by treated region (buttock or thigh) and overall with descriptive statistics for continuous variables.	• Proportion at each level of improvement in the PR-PCSS: – Proportion of patient responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS – Proportion of patient responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS • Proportion at each level of improvement in the CR-PCSS: – Proportion of Investigator responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS (Investigator rated) – Proportion of Investigator responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS (Investigator rated) • Proportion of responders at each level of the I-GAIS: – Proportion of Investigator global responders defined as subjects with a response of 1 (improved) or better in the Investigator GAIS assessment • Proportion of responders at each level of the S-GAIS: – Proportion of subject global responders defined as subjects with a response of 1 (improved) or better in the subject GAIS assessment • Proportion of responders at each level of the subject satisfaction with cellulite treatment • Change in the Hexsel CSS total score from screening visit All endpoints will be summarized by treated region (buttock or thigh) and overall and by study day using appropriate descriptive statistics.

Section	Original Text	Revised Text
	Observational endpoints include: Proportion of 2-point composite responders as defined by responses in the quadrant treated in study EN3835-201 who either maintained response, lost response but did not return to the baseline of study EN3835-201, or returned to the baseline of study EN3835-201. Proportion of 1-point composite responders as defined by responses in the quadrant treated in study EN3835-201 who either maintained response, lost response but did not return to the baseline of study EN3835-201, or returned to the baseline of study EN3835-201. Proportion of 2-point CR-PCSS responders as defined by responses in the quadrant treated in study EN3835-201 who either maintained response, lost response but did not return to the baseline of study EN3835-201, or returned to the baseline of study EN3835-201. Proportion of 1-point CR-PCSS responders as defined by responses in the quadrant treated in study EN3835-201 who either maintained response, lost response but did not return to the baseline of study EN3835-201, or returned to the baseline of study EN3835-201. Proportion of 2-point PR-PCSS responders as defined by responses in the quadrant treated in study EN3835-201 who either maintained response, lost response but did not return to the baseline of study EN3835-201, or returned to the baseline of study EN3835-201. Proportion of 1-point PR-PCSS responders as defined by responses in the quadrant treated in study EN3835-201 who either maintained response, lost response but did not return to the baseline of study EN3835-201, or returned to the baseline of study EN3835-201. Duration of response as defined by the time from onset of change from baseline of PR-PCSS and CR-PCSS in the quadrant treated in study EN3835-201 until the time that the treated quadrant returned to the baseline PR-PCSS and CR-PCSS ratings from study EN3835-201. CR-PCSS change from the study EN3835-201 baseline at Day 71 of study EN3835-201, and Days 90, 180, 270, and 360/end of study of the current study (EN3835-202).	Observational endpoints include: • Proportions of composite responders defined as subjects with an improvement in severity from baseline of at least 2 (or 1) levels of severity in the CR-PCSS and an improvement in severity from baseline of at least 2 (or 1) levels of severity in the PR-PCSS. • Proportion at each level of improvement in the PR-PCSS: – Proportion of patient responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS – Proportion of patient responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS • Proportion at each level of improvement in the CR-PCSS: – Proportion of Investigator responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS (Investigator rated) – Proportion of Investigator responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS (Investigator rated) • Hexsel CSS total score changed from the study EN3835-201 baseline at Day 71 of study EN3835-201 and Day 360/end of study of the current study (EN3835-202). These endpoints will be summarized by treated region (buttock or thigh) and overall and by study day using appropriate descriptive statistics.

Section	Original Text	Revised Text
	PR-PCSS change from the study EN3835-201 baseline at Day 71 of study EN3835-201, and Days 90, 180, 270, and 360/end of study of the current study (EN3835-202). Hexsel CSS total score changed from the study EN3835-201 baseline at Day 71 of study EN3835-201 and Day 360/end of study of the current study (EN3835-202). Proportion of responses at each level of the I-GAIS (Day 360/end of study): Proportion of Investigator global responders defined as subjects with a response of 1 (improved) or better in the Investigator GAIS assessment Change in I-GAIS assessment from Day 71 of study EN3835-201 and Day 360/ end of study of the current study (EN3835-202 Proportion of responses at each level of the S-GAIS (Day 360/end of study): Proportion of subject global responders defined as subjects with a response of 1 (improved) or better in the subject GAIS assessment Proportion of 2-point PR-PCSS responders as defined by the responses in the quadrant treated in the current study who either maintained response, lost response but did not return to the study EN3835-202 baseline, or returned to the study EN3835-202 baseline. Proportion of 1-point PR-PCSS responders as defined by the responses in the quadrant treated in the current study who either maintained response, lost response but did not return to the study EN3835-202 baseline, or returned to the study EN3835-202 baseline. Change in S-GAIS assessment from Day 71 of study EN3835-201 and Day 360/ end of study of the current study (EN3835-202) Proportion of responses at each level of the subject satisfaction with cellulite treatment (Day 360/end of study) Change in subject satisfaction assessment from Day 71 of study EN3835-201 and Day 360/end of study of the current study (EN3835-202)	

Section	Original Text	Revised Text
	For quadrants treated in the current study the following observational endpoints will be analyzed: Proportion of 2-point composite responders as defined by the responses in the quadrant treated in this current study (EN3835-202) who either maintained response, lost response but did not return to the study EN3835-202 baseline, or returned to the study EN3835-202 baseline. Proportion of 1-point composite responders as defined by the responses in the quadrant treated in the current study who either maintained response, lost response but did not return to the study EN3835-202 baseline, or returned to the study EN3835-202 baseline. Proportion of 2-point CR-PCSS responders as defined by the responses in the quadrant treated in this current study who either maintained response, lost response but did not return to the study EN3835-202 baseline, or returned to the study EN3835-202 baseline. Proportion of 1-point CR-PCSS responders as defined by the responses in the quadrant treated in the current study who either maintained response, lost response but did not return to the study EN3835-202 baseline, or returned to the study EN3835-202 baseline. CR-PCSS change from the study EN3835-202 baseline at Day 71, Day 90, Day 180, Day 270, and Day 360/end of study. PR-PCSS change from the study EN3835-202 baseline at Day 71, Day 90, Day 180, Day 270, and Day 360/end of study. Duration of response as defined by the time from onset of change from baseline of PR-PCSS and CR-PCSS in the quadrant treated in the current study until the time that the treated quadrant returned to the baseline PR-PCSS and CR-PCSS ratings from study EN3835-202.	
17.6.3 Measurement of Treatment Compliance	All doses are administered while the subjects are at the investigators' sites.	All doses are administered while the subjects are at the investigational site.

Section	Original Text	Revised Text
17.6.4 Adverse Events	The MedDRA will be used to code AEs. The version used in this study will be stated in the Data Management Plan. An AE (classified by preferred term) that started during the treatment period will be considered a TEAE if it was not present prior to the first dose of study drug, or was present prior to the first dose of study drug but increased in intensity during the treatment period. If more than 1 AE is reported prior to the first dose of study drug and coded to the same preferred term, then the AE with the greatest intensity will be used as the benchmark for comparison to the AEs occurring during the treatment period which were also coded to that preferred term. Any AE present prior to the first dose of study drug that increases in intensity during the treatment period will be re-entered with a new start date of the date of increased intensity. Descriptive statistics (the number and percentage) for subjects reporting TEAEs in each treatment group will be tabulated by system organ class and preferred term; by system organ class, preferred term, and severity; and by system organ class, preferred term, and relationship to study drug. If more than 1 AE is coded to the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to the study drug. SAEs and AEs leading to premature discontinuation of study drug will be summarized by preferred term and dose received. Listings will be presented for subjects with SAEs, subjects with AEs leading to discontinuation, and subjects who die (if any).	The MedDRA dictionary will be used to code AEs. The version used in this study will be stated in the Data Management Plan. Descriptive statistics (the number and percentage) for subjects reporting TEAEs will be tabulated by system organ class and preferred term; by system organ class, preferred term, and severity; and by system organ class, preferred term, and relationship to study drug. If more than 1 AE is coded to the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to the study drug. SAEs and AEs leading to premature discontinuation of study drug will be summarized. Listings will be presented for subjects with SAEs, subjects with AEs leading to discontinuation, and subjects who die (if any).
17.6.5 Vital Signs	Descriptive statistics for vital signs (eg, systolic and diastolic blood pressure, pulse rate, and body weight) and their changes from baseline at each visit and at the end of treatment visit will be presented.	Descriptive statistics for vital signs (eg, systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, and body weight) and their changes from baseline at each visit and at the end of treatment visit will be presented.
17.7 Immunogenicity Analyses	Binding antibody levels will be determined from samples collected on Days 1, 22, 43, and 71 during the treatment phase and Days 90, 180, 270 and 360 during the observational phase.	Binding antibody levels will be determined from samples collected on Days 1 and 71 during the treatment phase and Day 360 during the observational phase.

Section	Original Text	Revised Text
17.9 Interim Analysis	Two (2) interim analyses are planned. Following the breaking of the study drug blind in study EN3835-201, all follow-up safety data gathered prior to that time will be analyzed. The second interim analyses will occur following the Day 71 visit for all subjects treated with EN3835 in the current study. A preliminary data lock will be done on all treated quadrants and cellulite assessment and safety analyses will be done. The official database lock will occur after the last Day 360/end of study observational visit and all observational analyses on treated quadrants will be done.	Not applicable.
18.4 Study Drug Preparation	Refer to the Reconstitution Instructions in the Pharmacy Manual for detailed preparation instructions.	Refer to the Reconstitution Instructions for detailed preparation instructions.
18.4 Study Drug Preparation	Each vial of study drug powder for reconstitution will be diluted according to the instructions in the Pharmacy Manual.	Each vial of study drug powder for reconstitution will be diluted according to the Reconstitution Instructions.
19.1 Source Documents	Source documents include but are not limited to original documents, data and records such as hospital/ medical records (including electronic health records), clinic charts, lab results, subject diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, etc. At a minimum, all data required to be collected by the protocol should have supporting source documentation for entries in the eCRF, unless the protocol specifies that data can be recorded directly on/in the eCRF or other device.	This study allows for direct data entry (DDE) for selected data points as outlined below: • Inclusion/Exclusion • Vital signs including pre- and post-injection measurements • Height and body weight • CR-PCSS • Hexsel CSS • I-GAIS • Physical examinations • ECG results (if more than 1 year passed since ECG assessment) • Urine pregnancy test • Study drug administration All other data points, at a minimum, should have supporting source documentation for entries in the eCRF.
22.1 Data Collection	Study data will be collected from source documents and entered into an eCRF within the EDC system.	Study data will be collected by DDE or from source documents and entered into an eCRF within the EDC system.
22.1 Data Collection	Unless otherwise indicated, all data captured in the eCRF must first be captured in source documents. Data that can be directly recorded in the eCRF will be clearly identified in the section(s) of the protocol that describes the assessment(s).	DELETED TEXT

Section	Original Text	Revised Text
22.2 Study Documentation	Upon study completion, the Investigator will be provided with complete electronic copies of the CRF data for his/her files.	Upon study completion, the Investigator will be provided with complete electronic copies of the eCRF data for his/her files.

3. SPONSOR CONTACT INFORMATION

Table 1: Sponsor Contact Information

Role in Study	Name	Telephone and Email Address
Clinical Research Scientist	[redacted]	[redacted]
Associate Director, Clinical Operations	[redacted]	[redacted]
Medical Monitor	[redacted]	[redacted]
SAE Reporting Pathway	Not applicable	[redacted]

A list of other key study personnel and vendors will be provided upon request separately for your reference.

4. SYNOPSIS

Name of Sponsor/Company: Endo Pharmaceuticals Inc.	
Name of Investigational Product: EN3835	
Name of Active Ingredient: Collagenase clostridium histolyticum	
Title of Study: A Phase 2, Open-Label Extension Study of EN3835 in the Treatment of Edematous Fibrosclerotic Panniculopathy	
Lead Principal Investigator: To be determined	
Study period: Estimated date first subject enrolled: Oct-2016 Estimated date last subject completed: Jun-2018	**Phase of development:** Phase 2

Objectives:

Primary:

- The primary objective of this study is to assess long-term safety of EN3835 0.84 mg at scheduled intervals over 1 year (12 months) in all subjects with edematous fibrosclerotic panniculopathy (EFP) who elect to enroll in this open-label trial regardless of their decision to receive treatment (re-treatment or re-dosing) of open-label EN3835 or opt to receive no treatment.

Secondary:

- To evaluate safety and immunogenicity of re-treating or re-dosing a subject that had previously received treatment with EN3835
- To evaluate the durability of response to EN3835 in EFP severity over the 12-month post initial dosing of EN3835 in subjects previously receiving active treatment in study EN3835-201 using the Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS) and the Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS)
- To evaluate long-term response to EN3835 in assessments of EFP including subject satisfaction, Investigator Global Aesthetic Improvement Scale (I-GAIS), and Subject Global Aesthetic Improvement Scale (S-GAIS)
- To assess cellulite severity assessments in quadrants treated in this study with EN3835
- To evaluate immunogenicity after exposure to EN3835

Study Design: This study is a Phase 2 open-label study for the safety and efficacy of EN3835 in the treatment of EFP. To be eligible, a subject must have participated and completed the previous cellulite study EN3835-201. Subjects will be screened for study eligibility within 14 days prior to enrolling in this study (EN3835-202). Subjects will be assessed for safety and cellulite severity assessments approximately every 3 months for a maximum of 1 year from their first exposure to EN3835 in each treated quadrant. Subjects with at least 1 quadrant with moderate or severe level of cellulite will be eligible for treatment with EN3835 after unblinding of study EN3835-201; a quadrant that was treated with EN3835 in the previous study EN3835-201 will only be eligible for retreatment if the cellulite severity in that quadrant is rated at levels of cellulite severity at baseline or greater in study EN3835-201.

A treatment course will consist of 3 treatment sessions separated by 21 days. Treatment will be allowed in eligible subjects up to a maximum of 2 treatment courses including the treatment course in study EN3835-201 if subject was treated with EN3835. Each treatment session will consist of up to 12 injections (0.07 mg/0.3 mL per injection) of EN3835 for a dose of 0.84 mg and volume of 3.6 mL.

Name of Sponsor/Company: Endo Pharmaceuticals Inc.

Name of Investigational Product: EN3835

Name of Active Ingredient: Collagenase clostridium histolyticum

Only a quadrant with moderate (rating of 3) or severe (rating 4) level of severity as assessed by the subject and investigator using the PR-PCSS and the CR-PCSS, respectively, will be eligible for treatment; if more than 1 eligible quadrant exists, the quadrant selected will be at the discretion of the subject. Treatments will be administered on Days 1, 22, and 43; subjects will be assessed for safety on Days 1, 22, 43, and 71 and for cellulite severity assessments at Screening visit and on Days 22, 43, and 71. After Day 71, they will be observed every 3 months from their first exposure to EN3835 up to a maximum of 1 year in each treated quadrant.

Number of subjects (planned): Approximately 350

Study center(s): 15 sites in the United States

Diagnosis and inclusion/exclusion criteria:

Qualification for the Open-Label Observation Phase of the Study

Inclusion criteria for observation:

1. Voluntarily sign and date an informed consent agreement
2. Have participated in and completed the double-blind study EN3835-201
3. Be willing to apply sunscreen to any treated quadrant before each exposure to the sun while participating in the study (ie, screening through end of study)

Exclusion criteria for observation:

None

Qualification for the Open-Label Treatment Phase of the Study

Inclusion criteria for treatment:

1. Voluntarily sign and date an informed consent agreement
2. Have participated in and completed the double-blind study EN3835-201
3. Be a female ≥18 years of age
4. At Screening B visit, have at least 1 quadrant with:
   a. a score of 3 or 4 (moderate or severe) as reported by the subject (PR-PCSS), and
   b. a score of 3 or 4 (moderate or severe) as reported by the Investigator (CR-PCSS), and
   c. a Hexsel Cellulite Severity Scale (CSS) score no greater than 13
5. Be willing to apply sunscreen to the selected treatment quadrant before each exposure to the sun while participating in the study (ie, Screening B through end of study)
6. Be judged to be in good health, based upon the results of a medical history, physical examination, and laboratory profile at Screening B
7. Have a negative urine pregnancy test at Screening B and before injection of study drug and be using an 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
8. Be willing and able to cooperate with the requirements of the study
9. Be able to read, complete and understand the patient-reported outcomes rating instruments in English

Name of Sponsor/Company: Endo Pharmaceuticals Inc.

Name of Investigational Product: EN3835

Name of Active Ingredient: Collagenase clostridium histolyticum

***Exclusion criteria for treatment**:*

1. Has used any of the following for the treatment of EFP on the legs or buttock within the timelines identified below or intends to use any of the following at any time during the course of the study:
   - Liposuction on the side of the body selected for treatment during the 12-month period before injection of study drug
   - Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; or surgery (including subcision and/or powered subcision) within the selected treatment quadrant during the 12-month period before injection of study drug
   - Endermologie or similar treatments within the selected treatment quadrant during the 6-month period before injection of study drug
   - Massage therapy within the selected treatment quadrant during the 3-month period before injection of study drug
   - Creams (eg, Celluvera™, TriLastin®) to prevent or mitigate EFP within the selected treatment quadrant during the 2-week period before injection of study drug
2. Is presently nursing a baby or providing breast milk for a baby
3. Intends to become pregnant during the study
4. Has received an investigational drug or treatment within 30 days before injection of study drug
5. Has a known systemic allergy to collagenase or any other excipient of study drug
6. Is currently receiving or plans to receive anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication (except for ≤150 mg aspirin daily) within 7 days before injection of study drug
7. Has a known recent history of stroke, bleeding, or other medical condition, which in the investigator's opinion would make the subject unsuitable for enrollment in this phase of the study
8. Presence of any clinically relevant conditions, that in the opinion of the Investigator would interfere with completing the study including, but not limited to, visual problems, hearing problems, cognitive impairment or acute mental illness

Investigational product, dosage and mode of administration: EN3835, 0.84 mg, subcutaneous. A dose of 0.84 mg of EN3835 will be administered as up to 12 subcutaneous injections (0.3-mL injection administered as three 0.1-mL aliquots per injection, up to 12 injections per treatment session) for a maximum volume of 3.6 mL per treatment session. A treatment course will consist of 3 treatment sessions at 21 days intervals, ie, treatments on Days 1, 22, and 43 of each treatment course.

For the observational periods of this study, subjects will be assessed for safety and cellulite severity assessments at approximately 3-month intervals for a maximum of 1 year following their first exposure to EN3835 in each treated quadrant.

Duration of study:

Twelve (12) months from first exposure to EN3835 in study EN3835-201 and 12 months from first exposure in any additional treated quadrants in the EN3835-202 study

Screening Phase: Up to 14 days

Observational Phase: Subjects will be assessed at visits that occur approximately every 3 months for a maximum of 1 year after the first exposure to EN3835 in each treated quadrant.

Name of Sponsor/Company: Endo Pharmaceuticals Inc.

Name of Investigational Product: EN3835

Name of Active Ingredient: Collagenase clostridium histolyticum

Follow-up: Subjects will be assessed at visits that occur approximately every 3 months for a maximum of 1 year after the first exposure to EN3835 in each treated quadrant. For subjects treated with EN3835 in this study, subjects will be observed at treatment visits (Days 1, 22, and 43) and Day 71 after first injection. After Day 71, they will be observed every 3 months from their first exposure to EN3835 up to a maximum of 1 year in each treated quadrant.

Reference therapy, dosage and mode of administration: Not applicable

Criteria for evaluation:

Efficacy:

- PR-PCSS while viewing digital images of the selected quadrant: 5-point scale ranging from 0 (no cellulite) to 4 (severe cellulite) (approximately every 3 months after initial injection [either an injection in previous study EN3835-201 or after an injection in this study]). If treatment is administered in this study, PR-PCSS will be obtained at Screening B (Baseline), Days 22, 43, and 71 after initial treatment within this study.
- Investigator using the CR-PCSS by live assessment: 5-point scale ranging from 0 (no cellulite) to 4 (severe cellulite) (every 3 months after initial injection [either an injection in previous study EN3835-201 or after an injection in this study]). If treatment is administered in this study, CR-PCSS will be obtained at Screening B (Baseline), Days 22, 43, and 71 after initial treatment within this study.
- Investigator rating of cellulite severity using the total score from the Hexsel CSS: scores can range from 0 (no cellulite) to 15 (extremely severe cellulite) (Day 360). If treatment is administered in this study, Hexsel CSS will be obtained in this study at Screening B (Baseline) and Day 71 after initial treatment within this study.
- I-GAIS: 7-point scale ranging from 3 (very much improved) to −3 (very much worse) (Day 71)
- S-GAIS: 7-point scale ranging from 3 (very much improved) to −3 (very much worse) (Day 71)
- Subject satisfaction with cellulite treatment assessment: 5-point scale ranging from 2 (very satisfied) to −2 (very dissatisfied) (Day 71)

Safety:

Safety will be assessed throughout the study through the recording of:

- Adverse events (AEs)
- Vital signs
- Clinical laboratory tests
- Immunogenicity assessment (ie, assessed through the determination of binding and neutralizing anti-AUX-I and anti-AUX-II antibody levels)

In addition, for subjects treated with EN3835 in this study, injection site reactions/local tolerability in treated quadrant (through subject and Investigator reporting) will be assessed.

Statistical methods:

Sample Size Consideration:

Approximately 350 subjects are planned to obtain adequate long-term safety data for this study.

Analysis Populations:

Observational population: The Observational population is defined as all subjects treated with EN3835 in study EN3835-201 who do not receive any treatment in the current study.

Name of Sponsor/Company: Endo Pharmaceuticals Inc.
Name of Investigational Product: EN3835
Name of Active Ingredient: Collagenase clostridium histolyticum

Safety population: The Safety population is defined as all enrolled subjects who received at least 1 injection of EN3835 in this study.

Effectiveness population: This population is defined as all safety subjects who have a baseline and at least 1 post-injection evaluation of both the CR-PCSS and PR-PCSS.

Efficacy Evaluations:

The composite endpoints for cellulite severity assessment, the proportions of composite responders with improvement of 2 (or 1) or better on each scale (CR-PCSS and PR-PCSS), will be summarized as numbers and percentages by study days (visit). The analysis will be based on Effectiveness population .

All other endpoints including observational endpoints will be summarized by study days using appropriate descriptive statistics. The descriptive statistics will include the number and percentage for categorical response variables and number, mean, standard deviation, minimum, and maximum for continuous variables.

Safety Analysis:

The following variables are safety endpoints:

- AEs: Mapped to preferred term using the Medical Dictionary for Regulatory Activities (MedDRA)
- Vital signs
- Clinical laboratory tests

AEs will be summarized by proportion of subjects reporting each event. Descriptive statistics will be presented for actual and change from baseline at each visit for vital signs and for each clinical laboratory test parameter.

Immunogenicity: Anti-AUX-I and anti-AUX-II antibody levels will be summarized using descriptive statistics for the actual value at the visit.

5. SCHEDULE OF EVENTS

NOTE: Observation visits (Table 2) in the open-label extension study begin after completion of double-blind study (Day 71). Treatment sessions (Table 3), if elected, will begin after study drug blind is broken in study EN3835-201while observation visits continue concurrently.

Table 2: Observation Assessments

Procedures	Screening A[a] (≥Day 71 Visit of Double-blind Study)	Visit 1 Day 90[b] (±7 days)	Visit 2 Day 180[b] (±7 days)	Visit 3 Day 270[b] (±7 days)	Visit 4 End of Study/ Early Termination Day 360[b] (±7 days)
Informed Consent	X				
Inclusion/Exclusion	X				
Digital photography		X[c]	X[c]	X[c]	X[c]
Prior/Concomitant Medications/Procedures	X	X	X	X	X
Body weight		X	X	X	X
Vital signs		X	X	X	X
Collection of samples:					
• Clinical laboratory					X
• Anti-AUX-I/anti-AUX-II antibody level					X
Subject cellulite assessments:					
• Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS)		X[d,e]	X[d,e]	X[d,e]	X[d,e]
• Subject Global Aesthetic Improvement (S-GAIS)					X[d,e]
• Subject satisfaction with cellulite treatment assessment					X[d,e]
Investigator cellulite assessments:					
• Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)		X[e]	X[e]	X[e]	X[e]
• Hexsel Cellulite Severity Scale (CSS)					X[e]
• Investigator Global Aesthetic Improvement (I-GAIS)					X[e]
Injection site reactions/local tolerability in assigned quadrant from EN3835-201 study		X	X	X	X
Adverse events	Monitored Throughout Study				

[a] Informed consent for open-label observation assessments and optional treatment election.

[b] Four (4) visits at 3-month periods begin 90 days after Day 1 of the double-blind study (EN3835-201) (ie, within 20 days ± 4 days of completion of double-blind study).

[c] Only the treated quadrant(s) is photographed. For subjects participating in observation-only visits, the quadrant treated in the double-blind study (EN3835-201) is photographed; for subjects with open-label treatment (treated with EN3835 in study EN3835-202), the treated quadrant is photographed.

[d] Assessment made via viewing digital image photograph.

[e] Assessment of treated quadrant(s) only.

NOTE: Subject cellulite assessments must be completed before the Investigator cellulite assessments are conducted at each visit.

Table 3: Treatment Session Assessments

Procedures	Screening B[a] (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/ Early Termination Day 71 (+5 days)[b]
Inclusion/Exclusion	X				
Digital photography	X[c]	X[c,d]	X[c,d]	X[c,d]	X[c]
Medical history/EFP history including previous treatments	X[k,m]				
Prior/Concomitant Medications/Procedures	X[k,m]	X[m]	X	X	X
Physical examination:	X				
• Body weight	X[m]		X[e]	X[e]	X
• Height	X[m]				
Vital signs	X	X[f]	X[f]	X[f]	X
12-lead ECG	X[l]				
Collection of samples:					
• Clinical laboratory	X[m]				X
• Anti-AUX-I/anti-AUX-II antibody level		X[e,m]			X
• Urine pregnancy testing	X	X[e]	X[e]	X[e]	
Subject cellulite assessments:					
• Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS)	X[g,h]		X[e,g,h]	X[e,g,h]	X[g,h]
• Subject Global Aesthetic Improvement (S-GAIS)					X[g,h]
• Subject satisfaction with cellulite treatment assessment					X[g,h]
Investigator cellulite assessments:					
• Selection of dimples to be treated within selected quadrant		X[e]	X[e]	X[e]	
• Marking the dimples to be treated within selected quadrant		X[e]	X[e]	X[e]	
• Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)	X[h]		X[e,h]	X[e,h]	X[h]
• Hexsel Cellulite Severity Scale (CSS)	X[h,i]				X[h]
• Investigator Global Aesthetic Improvement (I-GAIS)					X[h]
Confirm Eligibility	X	X[e]			
Select Quadrant	X[j]				
Study drug administration		X	X	X	
Injection site reactions/local tolerability in selected quadrant		X	X	X	X
Adverse events	Monitored Throughout Study				

[a] After the study drug blind is broken in study EN3835-201, eligible subjects may elect to receive EN3835 treatments.
[b] Upon completion of treatment, subject will be followed at 3-month intervals as in Table 2; if study terminates early, subject will be followed through Visit 4 (Day 71). If subject received placebo in the double-blind study (EN3835-201), she may be eligible for a total of 2 courses of treatment (a total of 6 treatment sessions) in this study.
[c] All 4 quadrants are photographed at screening; at other visits, the selected quadrant only is photographed.
[d] Before and after marking the dimples.
[e] Before injection.
[f] Up to 4 hours before injection; approximately 15 and 30 minutes after injection. Vital signs must be stable before the subject is discharged.
[g] Assessment made via photograph (if treatment session, use photograph taken before marking dimples).
[h] All 4 quadrants are assessed at the Screening B visit; at other visits, the selected quadrant only is assessed.
[i] Initial Hexsel CSS at screening must be ≤13 on selected quadrant (Appendix C).
[j] To qualify for treatment, the selected quadrant must have a score of 3 or 4 (moderate or severe) in both the CR-PCSS and PR-PCSS, and a Hexsel CSS score ≤13; to qualify a quadrant that had been previously treated with EN3835 in study EN3835-201, the quadrant must have CR-PCSS and PR-PCSS scores equal to or greater than study EN3835-201 baseline scores and a Hexsel CSS score ≤13.
[k] Medical history and prior medications will be based on EN3835-201 eCRF; only updates and concomitant medications need to be captured at Screening B visit.
[l] Do not conduct if Screening B visit date is within 12 months of obtaining an ECG during the double-blind study (EN3835-201).
[m] Do not conduct on subjects eligible and opting-in for a second course of treatment in the current study (EN3835-202) if Screening B visit or Day 1 visit for second treatment course is the same day as Day 71 of the first treatment course in this study or previous study EN3835-201.

ECG=Electrocardiogram; eCRF=Electronic case report form; EFP=Edematous fibrosclerotic panniculopathy; Tx=Treatment
NOTE: Subject cellulite assessments must be completed before the Investigator cellulite assessments are conducted at each visit.

6. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

[redacted]

LIST OF TABLES

LIST OF FIGURES

7. LIST OF ABBREVIATIONS

The following abbreviations and specialist terms are used in this study protocol.

Table 4: Abbreviations and Specialist Terms

Abbreviation	Definition
AE	Adverse event
Assigned quadrant	Assigned quadrant (ie, left or right buttock, or the left or right posterolateral thigh) that was suitable for treatment and was randomly assigned in the double-blind study (EN3835-201). To be suitable for treatment the quadrant must have an Investigator CR-PCSS and subject PR-PCSS score of 3 or 4 and a Hexsel CSS score of no greater than 13 at Screening B visit and at Day 1 visit.
AUX-I	Clostridial class I collagenase
AUX-II	Clostridial class II collagenase
CFR	Code of Federal Regulations
CRF	Case report form
CR-PCSS	Clinician-Reported Photonumeric Cellulite Severity Scale
CSS	Cellulite Severity Scale
DDE	Direct data entry
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EFP	Edematous fibrosclerotic panniculopathy
FDA	Food and Drug Administration
GCP	Good clinical practice
HREC	Human research ethics committee
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
I-GAIS	Investigator Global Aesthetic Improvement Scale
IND	Investigational new drug
IRB	Institutional review board
ITT	Intent-to-treat
kDa	Kilodalton
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
PCS	Potentially clinically significant
PR-PCSS	Patient-Reported Photonumeric Cellulite Severity Scale
Qualified designee	Qualified by education and training to perform the study procedure (eg, sub-Investigator, nurse)

Table 4: Abbreviations and Specialist Terms (Continued)

Abbreviation	Definition
SAE	Serious adverse event
SAP	Statistical Analysis Plan
Selected quadrant	Quadrant (ie, left or right buttock, or the left or right posterolateral thigh) that is suitable for treatment and is selected by patient and investigator for treatment. To be suitable for treatment the quadrant must have an Investigator CR-PCSS and subject PR-PCSS score of at least 3 or 4 and a Hexsel CSS score of no greater than 13 at Screening B visit.
S-GAIS	Subject Global Aesthetic Improvement Scale
TEAE	Treatment-emergent adverse event; adverse events that occur on or after the first injection of study drug

8. INTRODUCTION

8.1. Edematous Fibrosclerotic Panniculopathy

Edematous fibrosclerotic panniculopathy (EFP), commonly known as cellulite, has been defined as a local metabolic disorder of subcutaneous tissues that results in an alteration of skin topography.(1) The condition manifests as dimpled skin, described as an orange-peel, cottage cheese, or mattress texture, particularly in the gluteal-femoral region.(2,3) EFP is caused by herniation of subcutaneous fat lobules through the dermohypodermal junction. This creates an uneven surface with dimpling.(1) EFP is a medical condition resulting in a potentially cosmetically unacceptable alteration of the skin, and affects an estimated 85% to 98% of postpubertal women.(1,3)

The pathophysiology of EFP is not completely understood, but there are 3 main theories: edema resulting from excessive hydrophilia of the intercellular matrix, alteration of the regional microcirculation, and different anatomical conformation of collagenous subcutaneous tissues in women versus men.(4)

It is known that EFP is different from generalized obesity. In generalized obesity, adipocytes undergo hypertrophy and hyperplasia that are not limited to the pelvis, thighs, and abdomen.(1) In areas of EFP, adipocytes have physiologic and biochemical properties that differ from adipose tissue located elsewhere. Large, metabolically-stable adipocytes characterize EFP-prone areas; thus, the responsiveness to catecholamine-induced lipolysis is less in EFP tissues compared to visceral fat, which has the greatest responsiveness.(1)

Subcutaneous fat lobes are separated from one another by thin, usually rigid strands of collagenous connective tissues, which cross the fatty layers and connect the dermis to the underlying fascia. These septa stabilize the subcutis and divide the fat. In EFP, shortening of the collagen septa due to fibrosis provokes retraction at the insertion points of the trabeculae, causing the depressions that characterize EFP.(2) There are a higher percentage of thinner, perpendicular hypodermal septa in women with EFP than in men.(1) Weight gain makes EFP more noticeable, but it may be present even in thin subjects. Genetics may also play a role since EFP tends to run in families.

8.2. Current Edematous Fibrosclerotic Panniculopathy Treatments

There are therapies that have been utilized in an attempt to treat cellulite. Despite multiple therapeutic modalities, there is little scientific evidence that any of these treatments are beneficial. In fact, much of the evidence is anecdotal, subjective, or based only on patient self-assessment.(5) Some of the historical treatments for EFP have included:

- Weight loss: Weight loss generally decreases the severity of EFP but may only have a variable effect on EFP grades.(6)
- Pharmacological agents (eg, xanthines, retinoids, lactic acid, and herbals): Although there are numerous topical treatments that are available over the counter, there are no well-designed or large-scale studies demonstrating the effectiveness of any of these

therapies.(5) Additionally, ingredients in some of the topical treatments are unknown and may pose an increased risk for adverse effects.(5)

- Massage: Endermologie or lipomassage kneads the skin between rollers. This type of vigorous massage is posited to increase blood flow and reduce excess fluid in EFP prone areas. In a 12-week, randomized, controlled study of 52 women that examined the effectiveness of either endermologie or aminophylline versus a combination of both, there was no statistical difference in the thigh measurement between subjects.(7)
- Liposuction: Liposuction can reshape the body, but it does not typically correct cellulite as it does not interrupt collagen septae in a directed fashion. Additionally, liposuction is not a recommended treatment for cellulite given the potential for poor cosmetic outcome.(5,6)
- Mesotherapy: Mesotherapy involves injecting solutions containing various substances, eg, methylxanthines, to dissolve subcutaneous fat; however, this type of therapy often results in unwanted side effects, including infection, urticarial reactions, and bumpy or uneven skin contours.(6) To date, there are no regulatory approved mesotherapy mixtures for the treatment of EFP.
- Radiofrequency: Radiofrequency systems may temporarily improve the appearance of EFP after a series of treatments; but long-term efficacy has not been demonstrated.(6)
- Subcision: Subcision is an invasive surgical technique that severs the septa holding fat lobules that cause the skin dimpling associated with EFP. In a study conducted by Hexsel and Mazzuco, 232 subjects had subcision for the treatment of EFP.(8) Although 78% of subjects were satisfied after 1 treatment, there were no objective criteria by which to assess improvement, thereby limiting the value of this study. Additionally, side effects reported in this study included pain, bruising for 3 to 6 months, hyperpigmentation for 2 to 10 months, and skin puckering.(5,6) These effects are most likely due to the trauma from shearing the septa with a large gauge needle (eg, 16 or 18 gauge) or other cutting devices.
- Powered subcision: Powered subcision is a surgical technique utilizing a powered needle apparatus to sever the septa holding fat lobules that cause skin dimpling associated with EFP. The Cellfina® powered subcision device was recently approved by Food and Drug Administration (FDA; 2015) for the treatment of cellulite.
- Laser: Intense pulsed light has been investigated for the treatment of cellulite. Triactive® is an FDA-approved low-fluorescence 810-nm light source combined with a 915-nm laser. In a study of 16 female subjects who underwent 12 treatments with the Triactive, 21% had improvement (based on 5 blinded Investigators' analysis of photographs with respect to appearance of cellulite, skin tone, and texture) of their cellulite.(9) The CelluLaze™ system was used to treat cellulite on the thighs of 10 healthy women.(10) In this Investigator-initiated study, subjects received a single treatment with a 1440-nm laser. During the CelluLaze procedure, which is performed under a local tumescent and general anesthetic, the physician inserts a small cannula through the skin and the device technology directs controlled, laser thermal energy to

the treatment zones. The laser is designed to diminish the lumpy pockets of fat by melting the hypodermal fat; release the areas of skin depression through thermal subcision of the septal tissue; and increase the elasticity and thickness of the skin by melting the fat in the dermal invaginations. Subjective physician and subject evaluations indicated improvement in the appearance of cellulite and high patient satisfaction that persisted for a year. For both the Triactive and CelluLaze studies, there were no control groups and significance was not tested.

There remains an unmet medical need for safe and effective nonsurgical therapies to improve the esthetic outcome in women with cellulite. To effectively treat cellulite, a therapeutic approach may require disruption of the dermal septa, which are composed of collagen and cause the skin dimpling which is bothersome to many women.

8.3. EN3835 (Collagenase Clostridium Histolyticum)

Endo Pharmaceuticals Inc. (Endo) is developing EN3835 for the treatment of EFP. Because EN3835 is a proteinase that can hydrolyze the triple-helical region of collagen under physiological conditions, EN3835 has the potential to be effective in lysing subdermal collagen, such as those observed in the dermal septa, which are the underlying cause of the skin dimpling in women with EFP. EN3835 targets the collagenase structural matrix (eg, dermal septa) at the site of injection and does not require systemic exposure to be effective.

EN3835 is a parenteral lyophilized product comprised of 2 collagenases in an approximate 1:1 mass ratio, Collagenase I (AUX-I, Clostridial class I collagenase) and Collagenase II (AUX-II; Clostridial class II collagenase). These collagenases are isolated and purified from the fermentation of *Clostridium histolyticum*. Collagenase AUX-I is a single polypeptide chain containing approximately 1,000 amino acids of known sequence and with a molecular weight of 114 kDa. Collagenase AUX-II is also approximately 1,000 amino acids long and has a molecular weight of 113 kDa. These 2 collagenases are not immunologically cross-reactive and have different specificities, such that together they become synergistic, providing a very broad hydrolyzing reactivity toward collagen. Clostridial collagenases are proteinases that can hydrolyze the triple-helical region of collagen under physiological conditions.

EN3835 is currently approved for: 1) the treatment of adults with Dupuytren's contracture with a palpable cord and, 2) for the treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy.

8.3.1. Studies with EN3835 for the Treatment of Edematous Fibrosclerotic Panniculopathy

The studies summarized in this section are described in more detail in the Investigator's Brochure (IB).

8.3.1.1. Investigator-Initiated Proof-of-Concept Study

In an Investigator-initiated pilot study, 10 female subjects received EN3835 in the treatment of cellulite.(11) A 10×10-cm oval area was outlined on the posterolateral thigh and 0.58 mg EN3835 was injected using a template as 5 concurrent subcutaneous injections of 0.116 mg per injection. Subjects were followed up to 180 days after injection for reduction of the cellulite appearance in the injected area. At 1 month post injection, the area of cellulite (as measured from

photographs) was reduced 89% from baseline. Patient satisfaction score was 1.75 at month 6 (1=completely satisfied, 4=not satisfied). Side effects included the local events of injection area soreness, ecchymosis, and mild edema; these resolved within a mean of 18 days. The results from this study suggest that the collagen septa of EFP may be an appropriate substrate for lysis with injectable collagenase, and that treatment with collagenase appears to be tolerable and possibly effective. However, due to the paucity of the data, no conclusions could be drawn regarding dose, frequency, and injection technique.

8.3.1.2. Endo-Sponsored Phase 1b Dose-Escalation Study AUX-CC-830

A dose-ranging Phase 1b dose escalation study (AUX-CC-830) used a template arrangement of injections as was used in the Investigator-initiated pilot study but injected a matrix of doses, concentrations and injectate volumes to select doses for further development. This Phase 1b study showed efficacy results suggesting that collagenase clostridium histolyticum (CCH) may be effective in the treatment of EFP based on global aesthetic improvement at Day 90 with ratings of "improved" by 43.4% of Investigators and 52.5% of subjects. The majority of subjects (71.7%) were "quite satisfied" or "very satisfied" with treatment on Day 90. Adverse events (AEs) were local injection site events (bruising, pain, erythema, and edema) were mild or moderate and resolved within a period of 3 weeks.

8.3.1.3. Endo-Sponsored Phase 2a Dose-Ranging Study AUX-CC-831

The Phase 2a study (AUX-CC-831) was a double-blind, placebo-controlled, dose-ranging study of 150 women randomized to 0.06, 0.48, or 0.84 mg of CCH; or placebo in a 5:5:5:3 ratio. Each subject could receive up to 3 treatment sessions of study drug separated by approximately 21 days. Efficacy in this study was evaluated based on Investigator Global Aesthetic Improvement Scale (GAIS-I) and Subject Global Aesthetic Improvement Scale (GAIS-S) along with other measures of treatment efficacy. Improvements were observed in cellulite appearance based on the statistically significant changes in the appearance of cellulite based on both the GAIS-I and GAIS-S scores for the high and mid doses compared to placebo ($p<0.05$). The majority of the patients were either satisfied or very satisfied with the results of their cellulite treatment with the mid and high doses compared to placebo ($p<0.05$). Similar to the AEs reported in subjects in the previous study (AUX-CC-830) and subjects who received EN3835 for Dupuytren's contracture and Peyronie's disease, the majority of AEs occurred at the site of injection and resolved before the next scheduled treatment session.

8.3.1.4. Endo-Sponsored Phase 2b Study EN3835-201

Currently there is an ongoing Phase 2b study (EN3835-201) which is a double-blind, placebo-controlled study of 350 adult women randomized to EN3835 0.84 mg or placebo in a 1:1 ratio. Each subject can receive up to 3 treatment sessions of study drug separated by approximately 21 days; last visit is Day 71. Efficacy is being evaluated using a Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS), a Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS), the Hexsel Cellulite Severity Scale (CSS), Investigator Global Aesthetic Improvement Scale (I-GAIS), Subject Global Aesthetic Improvement Scale (S-GAIS), and a subject satisfaction assessment. Subjects that complete study EN3835-201 will be offered the option of participating in study EN3835-202.

8.4. Summary of Nonclinical Studies

Nonclinical studies necessary to support clinical studies have been performed and are summarized in the IB. Nonclinical studies in the following areas were performed: toxicology, reprotoxicity, genotoxicity, and carcinogenicity.

8.5. Summary of Known Risks and Benefits

A summary of safety risks is provided in the IB. The following events have been commonly observed in prior studies: injection site AEs such as bruising, edema, erythema and pain.

There are previously generated potential clinical benefits associated with EN3835 in treating EFP, however, such potential benefits need further clinical evaluation. It is hoped that data from this clinical study will demonstrate a measurable sustained or durable clinical benefit of EN3835 in EFP as well as longer term safety.

8.6. Rationale

This study will allow an evaluation of longer term safety (over 12 months) following EN3835 treatment of subjects with EFP. Additionally, although uncontrolled, an assessment of cellulite assessments (efficacy) of EN3835 in the treatment of quadrants with moderate or severe cellulite will be conducted in subjects treated with placebo or EN3835 in the previous double-blind study (EN3835-201). The safety of re-dosing either in a previously treated quadrant (termed *re-treatment*) or in a naive quadrant (termed *re-dosing*) in subjects that previously received EN3835 treatment in study EN3835-201 will be assessed. Finally, the durability of improvement will be evaluated in enrolled subjects following EN3835 treatment in the double-blind study (EN3835-201) as well as those being treated with EN3835 in this open-label study (EN3835-202).

9. OBJECTIVES

9.1. Primary Objective

The primary objective of this study is to assess long-term safety of EN3835 0.84 mg at scheduled intervals over 1 year (12 months) in all subjects with EFP who elect to enroll in this open-label trial regardless of their decision to receive treatment (re-treatment or re-dosing) of open-label EN3835 or opt to receive no treatment.

9.2. Secondary Objectives

- To evaluate safety and immunogenicity of re-treating or re-dosing a subject that had previously received treatment with EN3835
- To evaluate the durability of response to EN3835 in EFP severity over the 12-month post initial dosing of EN3835 in subjects previously receiving active treatment in study EN3835-201 using the PR-PCSS and the CR-PCSS
- To evaluate long-term response to EN3835 in assessments of EFP including subject satisfaction, I-GAIS, and S-GAIS
- To assess cellulite severity assessments in quadrants treated in this study with EN3835
- To evaluate immunogenicity after exposure to EN3835

9.3. Exploratory Objectives

There are no exploratory objectives for this open-label extension study.

10. INVESTIGATIONAL PLAN

10.1. Study Design

This open-label extension study will be performed at multiple centers currently participating in the double-blind, placebo-controlled, parent trial (EN3835-201) in the United States. The open-label extension study will enroll up to 350 subjects. Subjects who completed the entire double-blind study and sign an informed consent will be eligible to enter this open-label extension.

After the Sponsor has broken the EN3835-201 study drug blind, subjects enrolled in the open-label study will have the following options:

- To have no EN3835 treatments in study EN3835-202
- If received EN3835 in study EN3835-201, may elect to have a qualifying quadrant other than the one treated in study EN3835-201 treated with EN3835 (termed *re-dosing*)
- If received EN3835 in study EN3835-201 and the cellulite severity scores of the treated quadrant have returned to or are greater than EN3835-201 baseline scores, may elect to have the previously treated quadrant retreated with EN3835 (termed *re-treatment*)
- If received placebo in study EN3835-201, may elect to have a qualifying quadrant treated with EN3835; also may elect to have a second qualifying quadrant treated with EN3835 after completing the treatment course

Subjects enrolled in study EN3835-202 who elect to receive EN3835 treatment (either re-treatment, re-dosing, or a first treatment) must meet specific inclusion and exclusion criteria for eligibility during re-screening (Screening B) prior to EN3835 dosing.

Following completion of safety and cellulite assessments at Day 71 of the double-blind study (EN3835-201), subjects will be asked if they wish to continue in the open-label extension to the double-blind study (Screening A). At the time of entry into the open-label study, subjects and Investigators will remain blinded to study drug. Until the EN3835-201 study drug blind is broken by the Sponsor, subjects will undergo observation-only visits at 3-month intervals ± 7 days (relative to the initial dose in the double-blind study) where both safety and cellulite severity assessments of the treated quadrant will be made.

Following the study drug blind being broken and communicated to centers, eligible subjects may elect to receive EN3835 treatment. Subjects electing not to receive further EN3835 treatments (observation-only subjects) will continue to be followed for safety and cellulite severity assessments at 3-month intervals through month 12. Up to 14 days prior to initiating treatment injections of EN3835 on open-label treatment visit Day 1, subjects will undergo a screening evaluation (Screening B) to determine if they meet specified inclusion and exclusion criteria and to determine the quadrants, if any, that qualify for treatment.

During Screening B, photographs will be taken of each of the subject's 4 quadrants (left buttock, right buttock, left posterolateral thigh, and right posterolateral thigh). Subjects will again receive instructions for use of the PR-PCSS and will subsequently use the scale to rate the severity of

their cellulite in each of the 4 quadrants by comparing digital images of each of their quadrants displayed on standardized computer monitors with the PR-PCSS instrument. This independent self-assessment will take place in a private setting to minimize any potential bias from site personnel. The Investigator will then assess the subject's 4 quadrants live in real-time using the CR-PCSS. The Investigator will rate the 4 quadrants using the Hexsel CSS as described in section 13.1.1.6.(12) Subjects must have at least 1 quadrant that meets the following criteria for inclusion into the treatment phase of the study:

1. PR-PCSS score of 3 or 4, and
2. CR-PCSS score of 3 or 4, and
3. Hexsel CSS score of no greater than 13.

After the independent assessments are completed separately by the subject and the Investigator, the Investigator will review his/her assessments and the subject's assessment to determine which quadrants, if any, are eligible. The eligible quadrant chosen to receive treatment in the open-label study EN3835-202 will be at the discretion of the subject. A quadrant may be chosen for re-treatment if it was the quadrant treated in study EN3835-201 or a new quadrant may be chosen for re-dosing**. NOTE: For subjects who received active drug in the assigned quadrant in the double-blind study, the quadrant must have cellulite severity at (or greater) than the EN3835-201 baseline scores of PR-PCSS and CR-PCSS to qualify for re-treatment.**

Previously placebo-treated subjects will have the option to receive a second course of EN3835 in the same or different qualifying quadrant after at least 28 days following the end of the first treatment course (eg, the screening B visit of second quadrant could be performed on Day 71 after treating the first quadrant). The selected quadrant can be re-treated or re-dosed.

At each treatment session visit, Investigators will select the dimples within the chosen quadrant to be treated. Selection of dimples to be treated in the quadrant will be at the discretion of the Investigator. The selected EFP dimples in the selected quadrant must be well-defined and evident when the subject is standing in a consistent relaxed pose (without the use of any manipulation such as skin pinching or muscle contraction). The dimples selected to be treated will be circled with a surgical marker and injection site locations should be marked with a dot; if more than 1 injection per dimple is needed, the injection sites should be separated by approximately 2 cm. The selected quadrant will be photographed again after marking dimples. Subjects will be administered a maximum of EN3835 0.84 mg from a total of up to 12 injections. Up to 12 injections will be administered at each treatment session to treat the selected quadrant. Each of the injections will be administered as three 0.1-mL aliquots (total injection volume per injection is 0.3 mL; total injection volume per treatment session is 3.6 mL [12 injections × 0.3 mL], see table below).

Subjects will receive 3 treatment sessions (Day 1, Day 22, and Day 43) unless the chosen quadrant has no further treatable EFP dimples and the Investigator rates the quadrant a score of 0 on the CR-PCSS. The same dimples within a quadrant or different dimples within a quadrant may be treated at each session but injections must all be within the selected quadrant for all 3 sessions. Each treatment session will be separated by approximately 21 days.

Dose per Each Injection[a]	Injection Volume per Each Injection	Maximum Number of Injections per Each Treatment Session	Maximum Dose (mg) per Each Treatment Session	Maximum Injection Volume (mL) per Each Treatment Session	Maximum Cumulative EFP Dose
EN3835 0.07 mg	0.3 mL	12 injections	0.84 mg (12 injections × 0.07 mg)	3.6 mL (12 injections × 0.3 mL)	2.52 mg (3 treatment sessions × 0.84 mg)

[a] Each injection of EN3835 is 0.3 mL administered as three 0.1-mL aliquots.

The complete Schedule of Events is provided in section 5 (Table 2 and Table 3) and summarized in section 12.

10.2. Selection of Doses

Maximum possible doses of EN3835 employed will be the same as that administered in the double-blind, placebo-controlled, parent study (EN3835-201).

10.3. Study Drug Administration

Study drug in the form of sterile vials of lyophilized EN3835 (formerly AA4500) and sterile diluent will be provided by Endo. Study drug administration at each injection site is presented in section 12.1.4.2.

10.4. Discussion of Study Design, Including the Choice of Control Groups

The use of the open-label extension design allows for the following:

- Safety data over a 12-month period will be collected to assist in further defining the safety profile of EN3835 in this population,
- Safety data and immunogenicity after repeat exposure (re-treatment/re-dosing) and monitoring of previously active-treated subjects to EN3835 over a 12-month period,
- Previously placebo-treated subjects to have exposure to EN3835, and
- Durability of the response to EN3835 (cellulite severity assessments) will be assessed.

11. SELECTION AND WITHDRAWAL OF SUBJECTS

11.1. Observation Phase

All subjects who have completed the double-blind study EN3835-201 and sign the informed consent are eligible for enrollment in this open-label extension study and participation in the ongoing safety and cellulite evaluations.

11.1.1. Subject Inclusion Criteria for Observation

To qualify for this open-label observation study a subject must:

1. Voluntarily sign and date an informed consent agreement
2. Have participated in and completed the double-blind study EN3835-201
3. Be willing to apply sunscreen to any treated quadrant before each exposure to the sun while participating in the study (ie, screening through end of study)

11.1.2. Subject Exclusion Criteria for Observation

None

11.2. Treatment

Inclusion and exclusion criteria presented in section 11.2 apply only to those subjects in the open-label study who choose treatment.

At the time that the study drug blind is broken in the double-blind study EN3835-201, qualified subjects enrolled in the open-label study are eligible for treatment. A subject may participate in the observational period of this open-label study regardless of scoring of quadrant; however to receive treatment in this study, a subject must have at least 1 qualifying quadrant.

11.2.1. Subject Inclusion Criteria for Treatment

To qualify for treatment in the study a subject must:

1. Voluntarily sign and date an informed consent agreement
2. Have participated in and completed the double-blind study EN3835-201
3. Be a female ≥18 years of age
4. At Screening B visit, have at least 1 quadrant with:
   a. a score of 3 or 4 (moderate or severe) as reported by the subject (PR-PCSS), and
   b. a score of 3 or 4 (moderate or severe) as reported by the Investigator (CR-PCSS), and
   c. a Hexsel CSS score no greater than 13
5. Be willing to apply sunscreen to the selected treatment quadrant before each exposure to the sun while participating in the study (ie, Screening B through end of study)
6. Be judged to be in good health, based upon the results of a medical history, physical examination, and laboratory profile at Screening B

7. Have a negative urine pregnancy test at Screening B and before injection of study drug and be using an 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
8. Be willing and able to cooperate with the requirements of the study
9. Be able to read, complete and understand the patient-reported outcomes rating instruments in English

11.2.2. Subject Exclusion Criteria for Treatment

A subject will be **excluded from treatment** in the study (but not from the observation assessments) if she:

1. Has used any of the following for the treatment of EFP on the legs or buttock within the timelines identified below or intends to use any of the following at any time during the course of the study:
   - Liposuction on the side of the body selected for treatment during the 12-month period before injection of study drug
   - Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; or surgery (including subcision and/or powered subcision) within the selected treatment quadrant during the 12-month period before injection of study drug
   - Endermologie or similar treatments within the selected treatment quadrant during the 6-month period before injection of study drug
   - Massage therapy within the selected treatment quadrant during the 3-month period before injection of study drug
   - Creams (eg, Celluvera™, TriLastin®) to prevent or mitigate EFP within the selected treatment quadrant during the 2-week period before injection of study drug
2. Is presently nursing a baby or providing breast milk for a baby
3. Intends to become pregnant during the study
4. Has received an investigational drug or treatment within 30 days before injection of study drug
5. Has a known systemic allergy to collagenase or any other excipient of study drug
6. Is currently receiving or plans to receive anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication (except for ≤150 mg aspirin daily) within 7 days before injection of study drug
7. Has a known recent history of stroke, bleeding, or other medical condition, which in the investigator's opinion would make the subject unsuitable for enrollment in this phase of the study

8. Presence of any clinically relevant conditions, that in the opinion of the Investigator would interfere with completing the study including, but not limited to, visual problems, hearing problems, cognitive impairment or acute mental illness

11.3. Subject Discontinuation Criteria

A premature discontinuation will occur when a subject who signed informed consent ceases participation in the study, regardless of circumstances, prior to the completion of the protocol. Subjects can be prematurely discontinued from the study for one of the following reasons:

- An adverse event (AE)
- A protocol violation (reason must be specified, for example: lack of compliance, use of a prohibited concomitant medication, failure to meet inclusion/exclusion criteria after study entry, etc)
- Withdrawal by subject (reason must be specified)
- The subject was “lost to follow-up”
- Other reasons (reason must be specified, for example: the subject moved, pregnancy, investigator decision, Sponsor decision to terminate trial, etc)

If a subject discontinues from the study, all end-of-study procedures should be conducted as detailed in Schedule of Events. The date a subject discontinues and the reason for discontinuation will be recorded in the source documentation and Electronic Case Report Form (eCRF). If, however, a subject withdraws consent, no end-of-study procedures are required except the collection of AE information. This information should be recorded in the source documentation and the eCRF.

11.3.1. Replacement Procedures

Subjects who discontinue prematurely from the study will not be replaced.

12. PROCEDURES AND TREATMENTS

12.1. Study Visits

The Schedule of Events to be performed at each visit is shown in section 5. Provided below are further details where additional instruction about the assessments that will be performed is deemed to be needed.

12.1.1. Subject Screening

Upon completion of Day 71 assessments in the double-blind study EN3835-201, a subject will be eligible to enter this open-label extension study. All potential subjects eligible for screening in EN3835-202 will be pre-populated in the electronic data capture (EDC) system. The status of all subjects (eg, screen fails) will also be kept in the EDC system.

12.1.2. Screening Assessments

After obtaining informed consent, the full assessment of eligibility will be conducted and prior to study entry, screening assessments will be performed. Details about how the informed consent will be obtained and documented are provided in section 21.3, Subject Information and Consent. The subject may be entered into the observational phase of the study and complete safety and cellulite severity assessments at 3-month intervals as detailed in Table 2. In addition, once the study blind is broken in study EN3835-201, enrolled subjects will be asked if they wish to receive additional open-label treatments. If a subject elects to receive open-label treatment, study assessments will be conducted in accordance with Table 3.

12.1.3. Study Entry/Observational Assessments

A subject who gives written informed consent and who satisfies all eligibility criteria (section 11) may be entered into the observational phase of the study and complete safety and cellulite severity assessments at 3-month intervals as detailed in Table 2. The first visit will be determined by the date of enrollment in study EN3835-202 relative to the Schedule of Events for study EN3835-202 (Table 2). For example, if a subject enrolls after the Day 90 visit window, the first observation visit for that subject would be Day 180. In addition, once the study drug blind is broken in study EN3835-201, enrolled subjects will be asked if they wish to receive additional open-label treatments. If a subject elects to receive open-label treatment, study assessments will be conducted in accordance with Table 3. The subject identification number will be carried over from the double-blind, placebo-controlled study (EN3835-201). All subjects must complete Screening A and at least 1 Observation visit before Screening B can occur. Once the study blind was broken, the EN3835-201 placebo subjects were allowed to directly proceed to Screening B.

12.1.3.1. Three-Month Assessments

Subjects will return within 20 days (±4 days) of completion of the double-blind study for the first of 4 safety and cellulite severity evaluation visits. Assessments to be completed at these visits are detailed in Table 2. Subjects are to return at 3-month intervals until they have completed 12 months from Day 1 of the double-blind study. At these visits, the quadrant previously treated with EN3835 in the EN3835-201 study or quadrants treated with EN3835 in the open-label study

will be evaluated. If the quadrant treated in study EN3835-201 is retreated in the open-label study, the 3-month assessments will reset to treatment visit 1/Day 1 of the open-label treatment and the study visits will continue as described in Table 3 followed by 3-month assessments as described in Table 2. If a different quadrant is treated in the open-label study, the 3-month assessments of both the quadrant treated in the double-blind study (EN3835-201) and the quadrant treated in the open-label study will continue.

12.1.4. Treatment Assessments (Optional)

After unblinding of treatment assignment in the EN3835-201 study, subjects are eligible for optional treatment in the open-label study, provided they meet the inclusion and exclusion criteria detailed in section 11 and at least 1 quadrant meets the criteria for treatment. A subject may receive a maximum of 2 courses of treatment (6 treatment sessions) overall (total of treatments in double-blind and open-label study). If a subject received placebo in the double-blind study, she may be eligible for 2 treatment courses in the open-label study; if a subject received active drug in the double-blind study, she may be eligible for 1 additional treatment course (3 treatment sessions) in the open-label study.

Selection of Treatment Quadrant

During the Screening B visit, each subject will have photographs taken of the 4 targeted quadrants of the study (eg, their left and right buttocks and left and right posterolateral thighs). Subjects will receive instructions (Appendix D) for using the PR-PCSS and will use the scale to rate the severity of their cellulite in each of the 4 quadrants by comparing each of their digital image photographs with the PR-PCSS instrument. This self-assessment will take place in a private setting to minimize any potential bias from site personnel. The Investigator will then assess each of the subject's 4 quadrants live in real-time using the CR-PCSS. The Investigator will then examine each of the 4 quadrants live to assess the subject using the Hexsel CSS as described in section 13.1.1.6.(12) Subjects must have at least 1 quadrant that meets the following criteria for treatment in the study:

1. PR-PCSS score of 3 or 4, and
2. CR-PCSS score of 3 or 4, and
3. Hexsel CSS score no greater than 13.

After the independent assessments are completed separately by the subject and the Investigator, the Investigator will review his/her assessments and the subject's assessment to determine which quadrants, if any, are eligible. The eligible quadrants (must meet all 3 of the inclusion criteria (PR-PCSS, CR-PCSS, and Hexsel CSS scores), if any, for treatment will be determined by the Investigator after which the quadrant selected will be at the discretion of the subject. For subjects treated with EN3835 in the double-blind study, if the quadrant treated in the double-blind study (EN3835-201) has PR-PCSS and CR-PCSS ratings identical or more severe than the double-blind study (EN3835-201) PR-PCSS and CR-PCSS baseline ratings (Baseline is Day 1 of study EN3835-201), subjects can elect to have that same quadrant re-treated. Subjects who choose re-treatment of the previously treated quadrant will be classified in the re-treatment arm. If another quadrant besides the previously treated quadrant meets all 3 of the inclusion criteria, subjects can choose to be treated in the naive quadrant. Subjects who choose treatment into a naive quadrant will be classified in the re-dosing arm.

Assessments made with the PR-PCSS (from digital image), the CR-PCSS (live assessment), and the Hexsel CSS score during the open-label Screening B visit will be the baseline severity of EFP in the selected quadrant.

A subject who received placebo in the double-blind study may be treated in the same quadrant in the open-label study if the quadrant still meets all 3 criteria OR another qualifying quadrant may be selected for treatment by the subject. Following Day 71 of a treatment course (3 treatment sessions), subjects can choose to receive a second treatment session in either the same quadrant if it still meets qualification criteria or in a different quadrant that meets qualification criteria. For the first treatment course, these subjects will be considered in the treatment arm. For the second treatment course, if the same quadrant is treated, subjects will be in the re-treatment arm; if a different quadrant is treated, subjects will be considered in the re-dosing arm.

If no quadrant meets all 3 criteria, the subject may continue in the observation-only study with safety and cellulite severity evaluations performed at 3-month intervals but may not receive treatment in this study.

Selecting and Marking Dimples

Selection of dimples to be treated in the selected quadrant is at the discretion of the Investigator or qualified designee. Dimples must be well-defined and evident when the subject is standing in a consistent relaxed pose (without the use of any manipulation such as skin pinching or muscle contraction). Each subject will receive 3 treatment sessions of study drug in the selected quadrant. During each treatment session, the treatment quadrant will be photographed before and after dimple marking while the subject is standing in a consistent relaxed pose as described in the Photography Manual. The cellulite severity assessments using the PR-PCSS and CR-PCSS will be completed prior to dimple marking at treatment visits 2, 3, and 4/end of treatment.

12.1.4.1. Screening B (Days −14 to −1 Relative to Open-Label Treatment Visit Day 1)

Subjects meeting the relevant criteria listed in section 11.2 may be eligible for treatment in the open-label study. The following procedures will be performed and documented during the screening period:

1. Evaluate eligibility based on inclusion/exclusion criteria (section 11.2)
2. Subject will have digital photographs taken of the 4 targeted quadrants of the study (left and right buttocks, and left and right posterolateral thighs) (section 13.1)
3. Subjects will get instruction on the use of the PR-PCSS (Appendix D)
4. Subjects will rate each quadrant using the PR-PCSS while viewing their digital images (section 13.1.1.1)
5. The Investigator will conduct independent live assessments of subject's cellulite severity of each quadrant using the CR-PCSS (section 13.1.1.4) after the subject completes her rating and with no knowledge of the subject's ratings of her quadrants.
6. The Investigator will conduct live cellulite evaluation of each quadrant using the Hexsel CSS (section 13.1.1.6).

7. If at least 1 quadrant qualifies based on PR-PCSS, CR-PCSS, and Hexsel CSS ratings, subject may return for treatment on treatment visit 1. If none of the 4 quadrants qualify, the subject may remain in the study and have safety and cellulite severity evaluations performed at 3-month intervals but is not eligible for treatment.
8. Subject will select an eligible quadrant (based on qualifying scores) to be treated at their discretion.
9. Medical history including EFP history. Medical history will be based on EN3835-201 eCRF; only updates to the history need to be captured at Screening B visit.
10. Record prior and concomitant medications/procedures. Prior medications will be based on EN3835-201 eCRF; only updates and concomitant medications need to be captured at Screening B visit (section 12.2).
11. Physical examination including measurement of body weight and height (section 14.10)
12. Vital sign measurements (section 14.8)
13. 12-lead electrocardiogram (ECG), not necessary if the date of the ECG obtained during the double-blind study (EN3835-201) is within 12 months of the date of the Screening B visit (section 14.9)
14. Collection of samples for:
    a. Clinical laboratory testing (section 14.7)
    b. Urine pregnancy testing (section 14.7)
15. Adverse events (section 14)

12.1.4.2. Treatment Session 1 (Treatment Visit 1)

Pre-injection

1. Confirm eligibility criteria (section 11)
2. Take digital photography of selected quadrant before dimple marking (section 13.1)
3. Record concomitant medications/procedures (section 12.2)
4. Vital sign measurements (section 14.8)
5. Collection of samples for:
    a. anti-AUX-I and anti-AUX-II antibody testing (section 14.7.1)
    b. urine pregnancy testing (section 14.7)
6. Select and mark dimples to be treated (section 12.1.4)
7. Take digital photograph of selected quadrant after dimple marking (section 13.1)

Injection

Administration of study drug in the prone position (see below)

Post-injection

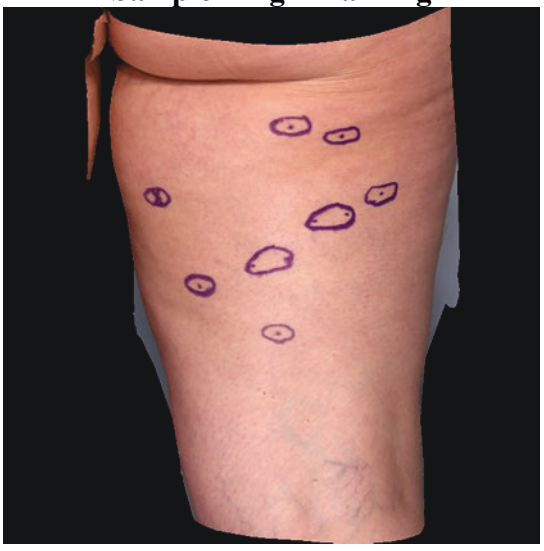
1. Record number of dimples treated and number of injections administered
2. Vital sign measurements (section 14.8)
3. Injection site reactions and local tolerability
4. Adverse events (section 14)

The selected quadrant will be photographed before and after dimple marking while the subject is standing in a consistent relaxed pose as described in the Photography Manual. Before injection at treatment session 1, the Investigator or qualified designee will begin the session by selecting dimples within the chosen quadrant that are well defined, evident when the subject is standing, and suitable for treatment; treatment consists of up to 12 injections per session. Because the goal of treatment is to improve the aesthetic appearance of the entire quadrant, the Investigator will be instructed to select dimples that in his or her opinion would most improve the aesthetic appearance of the entire quadrant. The same dimples within a quadrant or different dimples within a quadrant may be treated at each session but injections must all be within the selected quadrant for all 3 sessions.

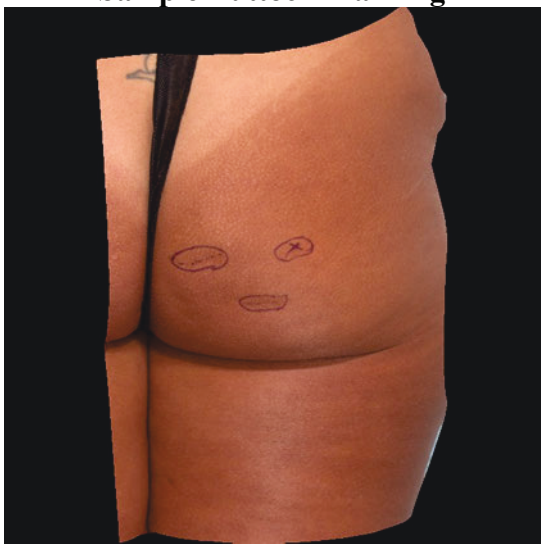
For each dimple selected for treatment, the Investigator or qualified designee will choose injection sites (injection sites within a dimple should be spaced approximately 2 cm apart, if a dimple requires more than 1 injection). Each injection site will be marked with a "dot" using a surgical marker. For round dimples, the "dot" will be placed in the center of the dimple; for elongated dimples, "dots" will be spaced out approximately 2 cm along the longer axis of the dimple. The Investigator or qualified designee will then use a surgical marker to circle each of the dimples selected for treatment. Circles in the selected quadrant should not overlap.

Examples of subject dimple marking:

Sample Thigh Marking



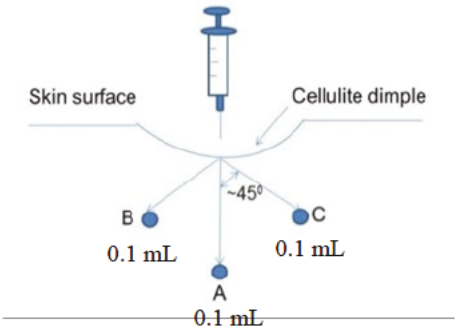
Sample Buttock Marking



Study Drug Administration at Each Injection Site

See section 18.4 for study drug preparation. Study drug will be injected subcutaneously while the subject is in a prone position using a syringe with a 30-gauge ½-inch needle. Each injection site will receive a single skin injection of study drug administered as three 0.1-mL aliquots to Positions A, B and C (for a total injection volume of 0.3 mL) as shown in the following figure. The depth of injection corresponds to the length of the treatment needle (0.5 inches) from the tip of the needle to the hub or base of the needle without downward pressure.

During each treatment session, the Investigator will be supplied with 4 syringes. Each syringe will contain 0.9 mL of study drug (ie, up to 3 injections in each syringe). Up to 12 skin injections of 0.3 mL per injection will be administered within the selected treatment quadrant during each treatment session.



- **Needle Tip Position A**: Position the needle at 90° angle perpendicular to the skin surface at the injection site and inject one 0.1-mL aliquot of study drug by gently pushing on the syringe plunger.
- **Needle Tip Position B**: Withdraw the needle slightly (but not so much as to remove from the injection site) and reposition approximately 45° (**but not more than 45°**) off vertical and above the long axis of the dimple and inject one 0.1-mL aliquot of study drug) by gently pushing on the syringe plunger.
- **Needle Tip Position C**: Withdraw the needle slightly (but not so much as to remove from the injection site) and reposition approximately 45° (**but not more than 45°**) off vertical and below the long axis of the dimple and inject one 0.1-mL aliquot of study drug by gently pushing on the syringe plunger.
- Withdraw needle from the skin completely and move to the next identified injection site. Complete up to a total of three 0.3-mL injections (each administered as three 0.1-mL aliquots) and discard the first syringe appropriately. Use the second, third and fourth syringes to complete dosing in the quadrant (up to three 0.3-mL injections per syringe, each injection administered as three 0.1-mL aliquots). Up to 12 skin injections of 0.3 mL will be administered within the treated quadrant during each treatment session.
- After treatment the subject will remain prone for at least 5 minutes.

The total number of dimples treated and the total number of injections administered will be recorded during treatment sessions 1, 2, and 3.

NOTE: EN3835 is a foreign protein and Investigators must be prepared to address and manage an allergic reaction should it occur. At the time of each injection, a 1:1,000 solution of epinephrine for injection, 50-mg diphenhydramine injection or a suitable equivalent, and oxygen should be available and the Investigator and site staff must be familiar with their use.

Care Procedures After Injection

To evaluate the subject for possible immediate immunological AEs, the subject will remain in direct observation of medical personnel who are skilled in the management of an allergic reaction for 30 minutes after receiving the injection of study drug and until the subject exhibits no sign of an immunological or other clinically significant systemic or local AE. The subject's vital signs should be stable before the subject can leave direct observation (see section 14.8).

The Investigator or qualified designee will then apply a sterile dressing to the injection site with hypoallergenic tape. The subject will be instructed to remove the dressing in the evening.

12.1.4.3. Treatment Session 2 (Treatment Visit 2/Day 22 ± 3 Days) and Treatment Session 3 (Treatment Visit 3/Day 43 ± 3 Days)

Pre-injection

1. Record concomitant medications/procedures (section 12.2)
2. Body weight measurements
3. Vital sign measurements (section 14.8)
4. Collection of samples for urine pregnancy testing (section 14.7)
5. Digital photograph of selected quadrant before dimple marking (section 13.1)
6. Subject assessment of the severity of cellulite using photograph of the selected quadrant via PR-PCSS (section 13.1.1.1). NOTE: Complete the subject (PR-PCSS) assessment before the Investigator (CR-PCSS) assessment and before dimple marking.
7. Investigator will conduct an independent live assessment of the severity of cellulite using the CR-PCSS (section 13.1.1.4). The investigator will conduct the assessment of severity only after the subject has completed her rating of her quadrant and without knowledge of the subject's rating of her quadrant.
8. Selection and marking of dimples to be treated (section 12.1.4)
9. Digital photograph after dimple marking (section 13.1)

Injection

Administration of study drug in the prone position (section 12.1.4.2)

Post-injection

1. Record number of dimples treated and number of injections administered
2. Vital sign measurements (section 14.8)

3. Injection site reactions and local tolerability
4. AEs (section 14)

If the Investigator rates the selected quadrant as 0, no injections will be given. If no injections are given at treatment session 2, subjects will still return for the Day 43 visit and the selected quadrant will again be evaluated by the subject (PR-PCSS) and Investigator (CR-PCSS). If the Investigator rates the selected quadrant greater than 0 on the CR-PCSS, injections at treatment session 3 should be given.

Because the goal of treatment is to improve the aesthetic appearance of the entire quadrant, the Investigator will be instructed to select dimples that in his or her opinion would most improve the aesthetic appearance of the entire quadrant. The same dimples within a quadrant or different dimples within a quadrant may be treated at each session but injections must all be within the selected quadrant for all 3 sessions. Each subject will receive all 3 treatment sessions unless the selected quadrant has no treatable EFP dimples and the Investigator rates the quadrant a score of 0 on the CR-PCSS.

After the dimples are selected, the Investigator or qualified designee will again mark each injection site with a "dot," and circle each dimple (circles should not overlap).

12.1.4.4. Day 71 (+5 Days) End of Treatment/Early Termination

The following procedures will be performed on Day 71:

1. Record concomitant medications/procedures (section 12.2)
2. Measurement of body weight
3. Vital sign measurements (section 14.8)
4. Collection of samples for:
   a. Clinical laboratory testing (section 14.7)
   b. Anti-AUX-I and anti-AUX-II antibody testing (section 14.7.1)
5. Digital photograph of selected quadrant (section 13.1)
6. Subject cellulite assessments of the selected quadrant using the photographic image (NOTE: complete subject cellulite assessments before Investigator cellulite assessments) using:
   a. PR-PCSS assessment (section 13.1.1.1)
   b. S-GAIS (section 13.1.1.2)
   c. Subject satisfaction with cellulite treatment assessment (section 13.1.1.3)
7. Investigator cellulite assessments of selected quadrant independently conducted; ie, with no knowledge of the subject's rating, using:
   a. CR-PCSS live assessment of subject (section 13.1.1.4)
   b. Hexsel CSS assessment of live subject while subject is standing in a relaxed position (section 13.1.1.6)

c. I-GAIS (section 13.1.1.5)

8. Injection site reactions and local tolerability
9. AEs (section 14)

12.1.4.5. Follow-up Visits

Following the Day 71 visit, the quadrant(s) treated with EN3835 in the open label study will be evaluated every 3 months from the first exposure to EN3835 following the schedule in Table 2. The first follow-up visit will be approximately 20 days after the Day 71 visit (ie approximately Day 90 after treatment session 1).

12.2. Prior and Concomitant Medications and Procedures

All medications (including over-the-counter medications) taken by the subject at screening visit 1 through the end of the study must be recorded.

Additionally, any diagnostic, therapeutic or surgical procedures performed during the study period should be recorded including the date, indication for and description of the procedure.

12.2.1. Prohibited Medications

The following medications are prohibited for those subjects that elect to have treatment with study drug during the treatment 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 the treatment phase of the study. For those subjects in the observational-only phase of study, there are no prohibited medications.

Table 5: Concomitant Medication Restrictions for Subjects During the Treatment Phase of Study

Drug Class	Restrictions
Anticoagulants	Subjects who elect treatment cannot take antiplatelet agents or anticoagulants (except for ≤150 mg aspirin daily) within 7 days before and after the dosing administration.

12.2.2. Prohibited Procedures

The treatments and procedures listed in exclusion criteria are prohibited during the study.

12.3. Treatment Compliance

All subjects who elect to have treatment will receive study drug administered by a clinician at the investigator's site.

Accidental or intentional overdoses should be reported to the Sponsor/designee promptly (see section 14.6.2).

12.4. Blinding and Randomization

This study will be conducted as an open-label investigation; no blinding of assigned treatment will occur.

12.5. End of Study

At the time of study termination, ongoing subjects receiving treatment will be followed through the Day 71 visit. The remaining enrolled subjects will undergo early termination procedures in accordance with the Schedule of Events (section 5).

13. ASSESSMENT OF EFFICACY

13.1. Primary Efficacy Measurements

Although measures of efficacious drug effect (ie, durability of improvement) will be made during the observation phase before the study drug blind is broken in the double-blind study (EN3835-201), and thereafter to the end of study, emphasis is on the assessment of safety over 12 months after exposure to EN3835. Cellulite severity assessments will be made at scheduled intervals for both observation-only subjects (not receiving EN3835) as well as subjects who choose re-dosing or re-treatment with EN3835.

Digital Photography: Digital photography will be utilized to assess certain cellulite severity parameters at specific intervals (see Schedule of Events, Table 2) for subjects in the observation-only group as well as those electing to be re-treated or re-dosed with EN3835. At the Screening B visit for subjects electing to receive re-dosing or re-treatment, the Investigator or qualified designee will photograph each quadrant using a Sponsor-supplied standardized digital camera. The subject will be standing for each photography session and will be wearing a standardized photographic garment as described in the Photography Manual. The Investigator or qualified designee will photograph the selected quadrant as follows:

- Screening B (no dimple marking)
- Before and after dimple marking (prior to injections) on Days 1, 22, and 43 of each treatment course
- During the Day 71 visit (end of treatment phase/early termination) of each treatment course

All photographs from this study are the property of Endo and may be utilized for clinical development, scientific communication, marketing, regulatory purposes, and/or legal applications as required/desired by Endo.

13.1.1. Subject and Investigator Cellulite Assessments

As in the double-blind parent study, Investigator cellulite assessments are independent of the subject assessments. Therefore, all subject cellulite assessments must be completed before the Investigator's cellulite assessments are made. After both the subject's and investigator's assessments are completed, the subject's assessments will be revealed and compared to the clinician's assessments to determine eligible quadrants. If more than 1 quadrant is eligible, the subject will select one for treatment.

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

The PR-PCSS will be conducted for the purpose of assessing the severity of cellulite in the buttock or thigh; there are separate scales for buttocks or thighs. The scales are 5-level photonumeric scales developed specifically for patients and used by the subject to assess the severity of their cellulite in the quadrants by viewing digital images of each of their quadrants captured by photography at the visit; the ratings range from 0 (None) to 4 (Severe) with labels and descriptors to aid the subject in the assessments.

All subjects who enter the observation-only phase of the study will have the PR-PCSS evaluation at months 3, 6, 9, and 12.

For subjects electing re-treatment or re-dosing after the study drug blind is broken in study EN3835-201, a Screening B visit (Baseline) within 14 days before dosing Day 1 will occur. Subjects will have digital photographs taken of all 4 quadrants as done in the double-blind trial for qualifying purposes. Subjects will then perform the PR-PCSS for both buttocks (Figure 1) and thighs (Figure 2) and will be reminded of their proper use (Appendix D).

At the beginning of visits on Days 22, 43, and 71; digital photographs of the selected quadrant will be taken. If the buttock is the treated region, subjects will be given the PR-PCSS for the buttock to use to make their evaluation; if the thigh is the treated region, subjects will be given the PR-PCSS for the thigh to make their evaluation.

Figure 1: Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS) for the Buttock

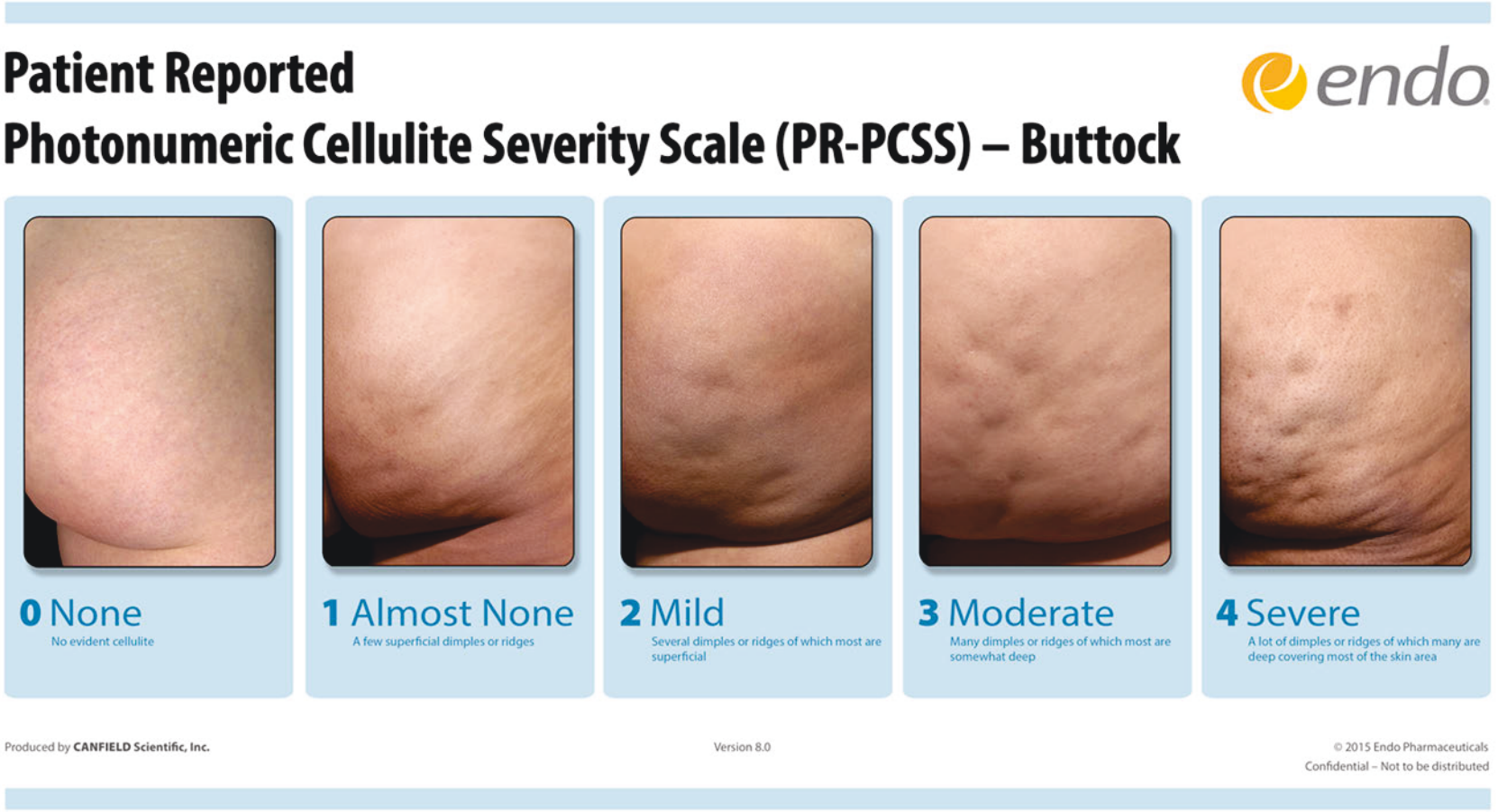


Figure 2: Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS) for the Thigh

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

Subjects in the observation-only group will complete the S-GAIS as described below at the final study visit (month 12 or early termination) using the pre-treatment Day 1 image (Baseline) of the assigned quadrant in the double-blind study for comparison.

For subjects who elected to receive EN3835 treatment, the S-GAIS assessment will be done on Day 71 of the treatment course and then at month 12 or the final study visit and compared back to the pre-dosing Screening B image (Baseline for treatment subjects) of the selected quadrant. All treated subjects will be instructed to answer the following question: *How would you rate the appearance of your treated cellulite after treatment?*

The S-GAIS assessment will occur after the subject has completed the PR-PCSS assessment to avoid introducing potential bias to the static PR-PCSS assessment. Each subject will view the pre-dosing Screening B visit digital image alongside their Day 71 treatment course visit and month 12 or end of study visit digital image of their selected quadrant to aid in the assessment (Table 6). Subjects will circle the rating below that best represents their answer.

Table 6: 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 originally.

13.1.1.3. Subject Satisfaction with Cellulite Treatment Assessment

For observation-only subjects (not receiving EN3835) the subjects will assess their satisfaction with cellulite treatment at the 12 month or end of study visit by being instructed to answer the following question: *Today, how satisfied are you with the results of the cellulite treatment you received on the specific area or areas on your buttocks or thighs that were treated?* Subjects will circle the rating in the below table that best represents their answer.

For subjects who have elected to receive EN3835 either through re-treatment or re-dosing, the subject satisfaction with the cellulite treatment (Table 7) with be done at the treatment course Day 71 and the month 12 visit or end of study visit. Subjects will be instructed to answer the following question: *Today, how satisfied are you with the results of the cellulite treatment you received on the specific area or areas on your buttocks or thighs that were treated?* Subjects will circle the rating below that best represents their answer.

Table 7: Subject Satisfaction with Cellulite Treatment Assessment

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

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

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

Investigators will have been trained on the use of the CR-PCSS. For observation-only subjects, the CR-PCSS will be done at 3, 6, 9, and 12 months or at the end of study visit.

For subjects who elected to receive EN3835 after the study drug blind is broken in study EN3835-201 as a re-treatment or re-dosing, the Investigator, at the Screening B visit (Baseline) will determine severity of cellulite of the 4 quadrants by assessing live subjects using the CR-PCSS for buttock (Figure 3) and thighs (Figure 4) after the subject has completed their self-assessment using the PR-PCSS. The eligible quadrant chosen for injection will be at the discretion of the subject. Before injections on treatment visit Days 22 and 43 and on visit Day 71; Investigators will evaluate the selected quadrant by live assessments. If the buttock is the treated region, the Investigator will use the CR-PCSS for the buttock to make his/her evaluation; if the thigh is the treated region, the Investigator will use the CR-PCSS for the thigh to make his/her evaluation. In each case, the Investigator will make his/her assessment independently and after the subject has conducted their self-assessment using the PR-PCSS.

This variable may be entered directly into the EDC system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.

Figure 3: Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS) for the Buttock

Figure 4: Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS) for the Thigh

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

Investigators will complete the I-GAIS on subjects in the observation-only group as described below at the final study visit (month 12 or early termination) and a comparison back to the pre-treatment Day 1 (Baseline) image of the assigned quadrant of the double-blind study.

On Day 71 of the treatment course and the 12 month or end of study visit, the Investigator will determine the degree of improvement from the Screening B digital image of the selected quadrant by comparing the cellulite in live assessment on Day 71 and at month 12 or study end to the Screening B pre-treatment (Baseline) image of the subject's selected quadrant (Table 8). The I-GAIS assessment will occur after the CR-PCSS assessment (section 13.1.1.4) to avoid introducing potential bias to the static CR-PCSS assessment by the Investigator at the site.

This variable may be entered directly into the EDC system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.

Table 8: Investigator Global Aesthetic Improvement Scale (I-GAIS)

Rating	Response Option	Description
+3	Very much improved	Optimal cosmetic result from treatment of the treated dimples
+2	Much improved	Marked improvement in the treated area appearance from before treatment, but not completely optimal
+1	Improved	Obvious improvement in the treated area appearance from before treatment, but additional treatment is indicated
0	No change	The treated area appearance is essentially the same as before treatment
−1	Worse	The treated area appearance is worse than before treatment
−2	Much worse	Marked worsening in appearance from the initial condition
−3	Very much worse	Obvious worsening in appearance from the initial condition

13.1.1.6. Hexsel Cellulite Severity Scale

The Hexsel Cellulite Severity Scale (referred to as the Hexsel CSS) is a photonumeric scale that looks at 5 key morphologic features of cellulite: (A) number of evident depressions, (B) depth of depressions, (C) morphological appearance of skin surface alterations, (D) laxity, flaccidity or sagging of skin, and (E) current classification scale based on medical literature including Nürnberger and Müller.(12,13) Each of these features is evaluated on a 4-point scale from a low of 0 to a high of 3 as described in Table 9 (see Appendix B). The total score is the summation of all 5 features.

For subjects in the observation-only group, the Hexsel CSS will be done at the month 12 or the end of study visit.

For the subjects electing treatment (re-treatment or re-dosing) with EN3835 the Investigator or qualified designee will independently use the Hexsel CSS to assess the severity of EFP in all quadrants at Screening B visit and the selected quadrant on Day 71 of the course of treatment and at month 12 or end of study visit. All cellulite assessments should be made while the subject is in the standing position with relaxed gluteus muscles. However, when evaluating the subject for Category E (classification scale by Nürnberger and Müller) (13) if the subject has no evident

depressions, the subject should be asked to contract her gluteus muscles or the pinch test should be applied (by pinching the skin between the thumb and index finger) so the Investigator or qualified designee can differentiate between scores/grades of zero (0) or I.

This variable may be entered directly into the EDC system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.

Table 9: Hexsel Cellulite Severity Scale

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

Source: Hexsel DM, Dal'Forno T, Hexsel CL. A validated photonumeric cellulite severity scale. *J Eur Acad Dermatol Venereol.* 2009;23(5):523-528.

[a] Subjects should be evaluated in the standing position with relaxed gluteus muscles. However, if the subject has no evident depressions, they should be asked to contract their gluteus muscles or the pinch test should be applied (by pinching the skin between the thumb and index finger) in order to differentiate between grade/stage of zero (0) or I.

14. ASSESSMENT OF SAFETY

14.1. Definitions

14.1.1. Adverse Event

An adverse event (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. AEs will be captured once a subject has signed the informed consent. AEs include:

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

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

All AEs, including both observed or volunteered problems, complaints, signs or symptoms must be recorded on the AE page of the eCRF, regardless of whether associated with the use of 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. The AE should be recorded in standard medical terminology when possible.

14.1.2. Serious Adverse Event

A serious adverse event (SAE) is defined as an AE that:

- Results in death
- Is immediately life-threatening (there is an immediate risk of death from the AE as it occurred; this does not include an AE that had it occurred in a more serious form may have caused death)
- Results in or prolongs an inpatient hospitalization (Note: a hospitalization for elective or pre-planned surgery, procedure, or drug therapy does not constitute an SAE)

- Results in permanent or substantial disability (permanent or substantial disruption of one's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect (in offspring of a subject using the study medication regardless of time to diagnosis)
- Is considered an important medical event

Important medical events are defined as events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the other serious outcomes. Examples of important medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

14.2. Monitoring Adverse Events

At each visit, subjects will be queried regarding any AEs that have occurred since the last visit. Subjects will be asked to volunteer information concerning AEs with a non-leading question such as, "How do you feel?" Study site personnel will then record all pertinent information in the source documents and the eCRF. The study drug compliance record should also be reviewed to detect potential overdoses (intentional/unintentional).

14.3. Relationship to Study Drug

The degree of "relatedness" of the AE to the study medication must be described using the following scale:

- **Not related** indicates that the AE is definitely not related to the study medication.
- **Unlikely related** indicates that there are other, more likely causes and study medication is not suspected as a cause.
- **Possibly related** indicates that a direct cause and effect relationship between study medication and the AE has not been demonstrated, but there is evidence to suggest there is a reasonable possibility that the event was caused by the study medication.
- **Probably related** indicates that there is evidence suggesting a direct cause and effect relationship between the AE and the study medication.

It is the Sponsor's policy to consider "Probably related" and "Possibly related" causality assessments as positive causality. "Not related" and "Unlikely related" causality assessments are considered as negative causality.

Assessments will be recorded on the eCRF and must indicate clearly the relationship being assessed. For example, an AE that appears during a placebo run-in phase would be assessed with respect to the placebo treatment received and/or study procedures conducted during this phase. If the AE continued into an active treatment phase, the relationship would be assessed for the active treatment phase only if the AE worsened.

14.4. Intensity Assessment

The intensity (or severity) of AEs is characterized as mild, moderate, or severe:

- **Mild** AEs are usually transient, requiring no special treatment, and do not interfere with the subject's daily activities.
- **Moderate** AEs introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.
- **Severe** AEs interrupt a subject's usual daily activity and typically require systemic drug therapy or other treatment.

When the intensity category of an AE changes, the greatest intensity during that continuous episode should be recorded.

14.5. Reporting Adverse Events and Serious Adverse Events

14.5.1. Reporting Adverse Events

Throughout the study, AEs will be documented on the source document and on the appropriate page of the eCRF whether or not considered treatment-related. This includes any new signs, symptoms, injury or illness, including increased severity of previously existing signs, symptoms, injury, or illness. Conditions existing prior to screening will be recorded as part of the subject's medical history. The Investigator is responsible for assessing the relationship of AEs to the study medication; relationship will be classified as not related, unlikely related, possibly related, or probably related.

All AEs will be collected by the Investigator from the time of signing the informed consent through 30 days after the last dose of study medication; this includes any AEs that are ongoing at the time of completion/termination of the study. All ongoing AEs must be followed until resolution or for 30 days after the subject's last study visit, whichever comes first.

14.5.2. Reporting Serious Adverse Events

Any SAE, including death resulting from any cause, which occurs to any subject participating in this study must be reported via email or fax by the Investigator using the Endo Clinical Trial Report Form for SAEs within 24 hours of first becoming aware of the SAE. SAEs will be collected by the Investigator from the time of signing the informed consent through 30 days after the last dose of study medication. SAEs that occur within 30 days, following cessation of the study treatment, or within 30 days, following premature discontinuation from the study for any reason, must also be reported within the same timeframe. Any SAE that is considered by the Investigator to be related to the study medication must be reported regardless of the amount of time since the last dose received. Follow-up information collected for any initial report of an SAE must also be reported to the Sponsor within 24 hours of receipt by the Investigator.

All SAEs will be followed until resolution, stabilization of condition, or until follow-up is no longer possible.

In the event discussion is necessary regarding treatment of a subject, call the Medical Monitor (see contact information in section 3).

All SAEs should be sent via the email address, or faxed to the fax number, provided in section 3.

The Sponsor will determine whether the SAE must be reported within 7 or 15 days to regulatory authorities in compliance with local and regional law. If so, the Sponsor (or the Sponsor's representative) will report the event to the appropriate regulatory authorities. The Investigator will report SAEs to the institutional review board (IRB) per their IRB policy.

14.5.2.1. Follow-up Procedures for Serious Adverse Events

To fully understand the nature of any SAE, obtaining follow-up information is important. Whenever possible, relevant medical records such as discharge summaries, medical consultations, and the like should be obtained. In the event of death, regardless of cause, all attempts should be made to obtain the death certificate and any autopsy report. These records should be reviewed in detail, and the Investigator should comment on any event, lab abnormality, or any other finding, noting whether it should be considered a serious or non-serious AE, or whether it should be considered as part of the subject's history. In addition, all events or other findings determined to be SAEs should be identified on the follow-up SAE form and the Investigator should consider whether the event is related or not related to study drug. All events determined to be nonserious should be reported on the eCRF.

14.6. Special Reporting Situations

14.6.1. Adverse Events of Special Interest

[redacted] (see section 14.1.1, Adverse Events or section 14.1.2, Serious Adverse Events).

14.6.2. Overdose/Misuse/Abuse

Study drug overdose is any accidental or intentional use of study drug in an amount higher than the dose indicated by the protocol for that subject. Study drug compliance (see section 12.3) should be reviewed to detect potential instances of overdose (intentional or accidental).

Any study drug overdose during the study should be noted on the study medication eCRF.

An overdose is not an AE per se, however all AEs associated with an overdose should both be entered on the Adverse Event eCRF and reported using the procedures detailed in section 14.5.2, Reporting of Serious Adverse Events, even if the events do not meet seriousness criteria. If the AE associated with an overdose does not meet seriousness criteria, it must still be reported using the Endo Clinical Trial Report Form for SAEs and in an expedited manner, but should be noted as non-serious on the form and the Adverse Event eCRF.

14.6.3. Pregnancy

Any uncomplicated pregnancy that occurs in a subject during this clinical study will **be reported for tracking purposes only**. All subject pregnancies that are identified during or after this study, where the estimated date of conception is determined to have occurred during study drug therapy or within 30 days of the last dose of study medication need to be reported, followed to conclusion, and the outcome reported, even if the subject is discontinued from the study. The investigator should report all pregnancies within 24 hours using the Initial Pregnancy Report Form, and any pregnancy-associated SAE using the SAE report form, according to the usual timelines and directions for SAE reporting provided in section 14.5.2. Monitoring of the pregnancy should continue until conclusion of the pregnancy; 1 or more Follow-up Pregnancy Report Form(s) detailing progress, and a Two Month Follow-up Pregnancy Report Form detailing the outcome, should be submitted.

Pregnancy itself is not regarded as an AE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not considered AEs. Any SAEs associated with pregnancy (eg, congenital abnormalities/birth defects/spontaneous miscarriages or any other serious events) must additionally be reported as such using the SAE report form. Spontaneous miscarriages should also be reported and handled as SAEs.

Subjects should be instructed to immediately notify the investigator of any pregnancies.

Attempts to obtain the pregnancy follow-up and pregnancy outcome information detailed above are necessary even if a subject discontinues treatment because of pregnancy.

14.6.4. Adverse Events/Serious Adverse Events Experienced by Non-subjects Exposed to Study Medication

Non-subjects are persons who are not enrolled in the study but have been exposed to study medication, including instances of diversion of study medication. All such AEs/SAEs occurring in non-subjects from such exposure will be reported to the Endo Pharmacovigilance and Risk Management (PVRM) Department (when the non-subject agrees) on the departmental form for SAEs regardless of whether the event is serious or not. Instructions for completing the form for events experienced by non-subjects will be provided. SAEs occurring in non-subjects exposed to study medication will be processed within the same SAE reporting timelines as described in section 14.5.2, Serious Adverse Event Reporting. Additionally, the drug accountability source documentation at the site should reflect this occurrence.

14.7. Clinical Laboratory and Immunogenicity Determinations

Clinical laboratory tests will be conducted according to the Schedule of Events (section 5). Clinical laboratory tests will be performed by a designated central laboratory. Each site will be provided with instructions on specimen collection, preparation, packaging and transport. Refer to the central laboratory manual for further information regarding sample collection, handling, and labeling. The results of the tests will be returned to the investigational sites.

Clinical laboratory test data will be reviewed by the investigator, or designee, and additional clinical laboratory tests may be ordered at his/her discretion (eg, if the results of any clinical laboratory test falls outside the reference range or clinical symptoms necessitate additional

testing to ensure safety). Any additional testing will be performed by the designated central laboratory.

The investigator will review all abnormal lab results for clinical significance. Any abnormal clinical laboratory test result meeting the investigator's or Sponsor's criteria for clinical significance (refer to central laboratory manual) will be recorded as an AE or SAE as appropriate (see section 14.1.1, Adverse Events or section 14.1.2, Serious Adverse Events).

Laboratory results will be sent electronically to Endo for data management.

Clinical laboratory parameters that will be measured in this study are listed in Table 10.

Table 10: Clinical Laboratory Parameters

Hematology	Clinical Chemistry	Urinalysis
Hematocrit	Blood urea nitrogen	Specific gravity
Hemoglobin	Creatinine	Ketones
Red blood cell count	Total bilirubin	pH
Red blood cell morphology	Alanine aminotransferase (ALT)	Protein
White blood cell count	Aspartate aminotransferase (AST)	Blood
Neutrophils	Alkaline phosphatase	Glucose
Lymphocytes	Sodium	
Monocytes	Potassium	
Basophils	Calcium	
Eosinophils	Chloride	
Platelets	Phosphate	
	Serum bicarbonate	
	Uric acid	
	Total cholesterol	
	Total protein	
	Glucose	
	Triglycerides	
	Albumin	

Female subjects of childbearing potential must have a negative urine pregnancy test at Screening B and at treatment visits 1, 2, and 3 (section 5) to receive treatment in the study. If necessary, additional urine pregnancy tests can be performed at any time during the study at the discretion of the Investigator.

Results of the urine pregnancy test may be entered directly into the EDC system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.

14.7.1. Anti-AUX-I and Anti-AUX-II Antibodies

Serum samples will be collected and may be tested for binding and neutralizing anti-AUX-I and anti-AUX-II antibodies at Visit 4 of the observation assessments. Additionally, if a subject consents to treatment in the open-label study, serum samples for antibody testing will be collected before injection at treatment visit 1 and at end of treatment/early termination visit 4 of the open-label treatment period. A subset of subject samples may have neutralizing antibodies

tested from Day 1 and Day 71 visits; additional samples may be analyzed if results or clinical signs warrant testing.

The serum samples obtained will be processed, stored and then shipped on dry ice to the designated central clinical laboratory before forwarding to Endo's appointed laboratory for the determination of anti-AUX-I and anti-AUX-II antibodies according to the Laboratory Manual.

14.8. Vital Signs

Vital sign measurements will be documented as described in the Schedule of Events. These parameters include pulse rate, respiratory rate, systolic and diastolic blood pressure, and body temperature. Pulse and blood pressure readings will be taken after the subject has been sitting for 5 minutes. Height should only be recorded at Screening B.

The investigator will review all vital sign values for clinical significance. Any vital sign value meeting the investigator's or Sponsor's criteria for clinical significance will be recorded as an AE or SAE as appropriate (see section 14.1.1, Adverse Events, and section 14.1.2, Serious Adverse Events).

For subjects receiving treatment, vital signs will be assessed at the time points shown in Table 11 after the subject has rested for at least 5 minutes.

The subject's vital signs should be stable, or repeated until stable before the subject can leave direct observation.

This variable may be entered directly into the EDC system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.

Table 11: Vital Signs Measurements on Injection Day

Time Point Relative to Last Injection	Blood Pressure, Respiratory Rate, and Pulse Rate	Body Temperature
Up to 4 hours (before treatment)	X	X
Approximately 15 minutes after	X	
Approximately 30 minutes after	X	X

14.9. Electrocardiogram

Performing a 12-lead electrocardiogram (ECG) is not necessary if Screening B visit date is within 12 months of obtaining an ECG during the double-blind study (EN3835-201).

If the date of Screening B visit is later than 12 months since obtaining the ECG in study EN3835-201, subjects will have a resting 12-lead ECG performed during the Screening B visit. A qualified physician will interpret, sign, and date the ECGs. Electrocardiogram assessments must be "within normal limits" or interpreted as "abnormal, not clinically significant" for the subject to be included in the study.

Any ECG result meeting the investigator's or Sponsor's criteria for clinical significance will be recorded as an AE or SAE as appropriate (see section 14.1.1, Adverse Events and section 14.1.2, Serious Adverse Events).

The investigator's assessment may be entered directly into the EDC system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.

14.10. Physical Examination

Body weight will be collected as described in the Schedule of Events (section 5). If a subject desires treatment in the open-label study, a complete physical examination will be performed at Screening B. All examinations will be performed by a physician or health professional listed on the Form FDA 1572 and licensed to perform physical examinations.

The investigator will review all physical exam findings for clinical significance. Any physical exam finding meeting the investigator's or Sponsor's criteria for clinical significance will be recorded as an AE or SAE as appropriate (see section 14.1.1, Adverse Events and section 14.1.2, Serious Adverse Events).

This variable may be entered directly into the EDC system, thus the electronic database will serve as the direct point of data capture and will serve as source for this variable.

14.11. Other Safety Assessments

Not applicable.

15. ASSESSMENT OF PHARMACOKINETICS

Not applicable.

16. ASSESSMENT OF PHARMACODYNAMICS

Not applicable.

17. STATISTICAL CONSIDERATIONS AND METHODS

17.1. Determination of Sample Size

Approximately 350 subjects that completed the EN3835-201 study will enroll in the current study. This sample size should be adequate to determine long term safety and cellulite assessments of EN3835.

17.2. Subject Cohorts and Subject Populations

Subjects will be classified into 1 of 4 different cohorts depending on where they receive the treatment of EN3835 in relation to where they received treatment in study EN3835-201. The 4 cohorts are:

1. Observational subjects only - subjects who received EN3835 in study EN3835-201 but do not receive any injections in the current study.
2. Re-treatment subjects - subjects who received EN3835 in study EN3835-201 and receive EN3835 in the current study in the same quadrant that was treated in the EN3835-201 study. This will only be allowed for subjects who have baseline severity ratings in the current study at or worse than the baseline seen in study EN3835-201 for both the CR-PCSS and PR-PCSS of the quadrant.
3. Re-dosing subjects - subjects who received EN3835 in study EN3835-201 and receive EN3835 in the current study in a quadrant different than the EN3835-treated quadrant in study EN3835-201.
4. Initial treatment subjects - subjects who received placebo in study EN3835-201 and receive EN3835 in the current study.

All efficacy and safety analyses will be done within the classified cohort. Durability of treatment effects is defined as the time from onset of change from baseline of PR-PCSS and CR-PCSS in the quadrant treated until the time that the treated quadrant returns to baseline cellulite severity ratings of PR-PCSS and CR-PCSS in an EN3835-treated quadrant.

17.2.1. Observational Population

The Observational population includes all subjects treated with EN3835 in study EN3835-201 who do not receive any treatment in the current study. The durability of a treatment effect and long-term safety analyses for subjects who receive no treatment in the EN3835-201 study will be performed using this population.

17.2.2. Safety Population

The Safety population will include all subjects who receive at least 1 dose of EN3835 in the current study. All safety analyses will be performed using this population.

17.2.3. Effectiveness Population

The Effectiveness population includes all safety subjects who have a baseline and at least 1 post-baseline assessment on both the CR-PCSS and PR-PCSS on the quadrant selected for treatment in the current study. All analysis of effectiveness will be based on this population.

17.3. Subject Disposition

The number of subjects included in each study population will be summarized. The number and percentage of subjects completed and discontinued will be presented. Reasons for discontinuation as recorded on the eCRF will be summarized (number and percentage) for all subjects.

17.4. Demographics and Other Baseline Characteristics

Demographic and baseline characteristics, including age, race, and baseline values will be summarized for the Observational population, the Safety population, and the Effectiveness population using descriptive statistics. The descriptive statistics will include the number and percentage for categorical response variables and number, mean, standard deviation, minimum, and maximum for continuous variables.

17.5. Efficacy Analyses

Cellulite assessments (efficacy) include:

- PR-PCSS: 5-point scale ranging from 0 (no cellulite) to 4 (severe cellulite) (screening visit [Baseline], Days 22, 43, and 71). Also will be done at Day 90, Day 180, Day 270, and Day 360/end of study visits for observational assessments.
- CR-PCSS: 5-point scale ranging from 0 (no cellulite) to 4 (severe cellulite) (screening [Baseline], Days 22, 43, and 71). Also will be done at Day 90, Day 180, Day 270, and Day 360/end of study visits for observational assessments.
- Investigator rating of cellulite severity using the total scores from the Hexsel CSS scale: scores can range from 0 to 15 (screening [Baseline] and Day 71). Also will be done at Day 360/end of study visits for observational assessments.
- I-GAIS: 7-point scale ranging from 3 (very much improved) to −3 (very much worse) (Day 71). Also will be done at Day 360/end of study visit for observational assessments.
- S-GAIS: 7-point scale ranging from 3 (very much improved) to −3 (very much worse) (Day 71). Also will be done at Day 360/end of study visit for observational assessments.
- Subject satisfaction with cellulite treatment assessment: 5-point scale ranging from +2 (very much satisfied) to −2 (very much dissatisfied) (Day 71). Also will be done at Day 360/end of study visit for observational assessments.

All cellulite assessments will be done by treated quadrant. For initial treatment subjects who have 2 quadrants treated, each quadrant will be evaluated separately.

17.5.1. Efficacy Analysis

The composite endpoints for cellulite severity are the proportions of composite responders defined as subjects with an improvement in severity from baseline of at least 2 (or 1) levels of severity in the CR-PCSS and an improvement in severity from baseline of at least 2 (or 1) levels of severity in the PR-PCSS.

These endpoints, will be summarized by treated quadrant and overall (buttocks and thighs) and by study day using appropriate descriptive statistics.

Other endpoints for treated quadrants include:

- Proportion at each level of improvement in the PR-PCSS:
  - Proportion of patient responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS
  - Proportion of patient responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS
- Proportion at each level of improvement in the CR-PCSS:
  - Proportion of Investigator responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS (Investigator rated)
  - Proportion of Investigator responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS (Investigator rated)
- Proportion of responders at each level of the I-GAIS:
  - Proportion of Investigator global responders defined as subjects with a response of 1 (improved) or better in the Investigator GAIS assessment
- Proportion of responders at each level of the S-GAIS:
  - Proportion of subject global responders defined as subjects with a response of 1 (improved) or better in the subject GAIS assessment
- Proportion of responders at each level of the subject satisfaction with cellulite treatment
- Change in the Hexsel CSS total score from screening visit

All endpoints will be summarized by treated region (buttock or thigh) and overall and by study day using appropriate descriptive statistics.

Observational endpoints include:

- Proportions of composite responders defined as subjects with an improvement in severity from baseline of at least 2 (or 1) levels of severity in the CR-PCSS and an improvement in severity from baseline of at least 2 (or 1) levels of severity in the PR-PCSS.

- Proportion at each level of improvement in the PR-PCSS:
  - Proportion of patient responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS
  - Proportion of patient responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS
- Proportion at each level of improvement in the CR-PCSS:
  - Proportion of Investigator responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS (Investigator rated)
  - Proportion of Investigator responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS (Investigator rated)
- Hexsel CSS total score changed from the study EN3835-201 baseline at Day 71 of study EN3835-201 and Day 360/end of study of the current study (EN3835-202).

These endpoints will be summarized by treated region (buttock or thigh) and overall and by study day using appropriate descriptive statistics.

17.6. Safety Analyses

The following variables are safety endpoints.

- AEs: Mapped to preferred term using the Medical Dictionary for Regulatory Activities (MedDRA)
- Injection site reactions/local tolerability in selected quadrant (through subject and Investigator reporting)
- Vital signs
- Laboratory testing

AEs will be summarized by treatment group. AE duration will be summarized using descriptive statistics by treatment group.

Descriptive statistics will be presented for each clinical laboratory test for the actual and change from screening at each visit by treatment group and vital signs for the actual and change from Day 1 pre-injection for each injection day at each visit by treatment group.

17.6.1. Prior, Concomitant, and Follow-up Medication

The World Health Organization (WHO) Drug Dictionary will be used to classify prior and concomitant medications by therapeutic class. The version used in this study will be stated in the Data Management Plan. Prior medication will be defined as any medication with a start date prior to the Day 1 date. Concomitant medication is defined as any medication with a start date on or after the Day 1 date or reported as ongoing. Any medications started after the last dose of study drug will be considered as follow-up medications.

Prior and concomitant medication use will be summarized descriptively by the number and percentage of subjects receiving each medication within each therapeutic class. Multiple use of the same medication by a subject will be counted only once.

17.6.2. Study Drug Exposure

For those subjects that elect, are eligible, and do receive treatment, the number of injections will be summarized by counts and percentages. The number of dimples treated will be summarized with counts and percentages.

17.6.3. Measurement of Treatment Compliance

All doses are administered while the subjects are at the investigational site. Any dose that was not administered per protocol will recorded as a protocol deviation by the Investigator.

17.6.4. Adverse Events

The MedDRA dictionary will be used to code AEs. The version used in this study will be stated in the Data Management Plan.

Descriptive statistics (the number and percentage) for subjects reporting TEAEs will be tabulated by system organ class and preferred term; by system organ class, preferred term, and severity; and by system organ class, preferred term, and relationship to study drug. If more than 1 AE is coded to the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to the study drug.

SAEs and AEs leading to premature discontinuation of study drug will be summarized. Listings will be presented for subjects with SAEs, subjects with AEs leading to discontinuation, and subjects who die (if any).

17.6.5. Vital Signs

Descriptive statistics for vital signs (eg, systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, and body weight) and their changes from baseline at each visit and at the end of treatment visit will be presented.

Vital sign values are potentially clinically significant (PCS) if they meet both the observed value criteria and the change from baseline criteria. The criteria for PCS vital sign values will be detailed in the Statistical Analysis Plan (SAP). A listing of all AEs for subjects with PCS vital signs will also be provided.

17.6.6. Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values in International System of Units (SI units) and changes from baseline will be presented for each clinical laboratory parameter.

The number and percentage of subjects with PCS post-baseline clinical laboratory values will be tabulated. The criteria for PCS laboratory values will be detailed in the SAP. A listing of all AEs for subjects with PCS laboratory values will also be provided.

17.7. Immunogenicity Analyses

Immunogenicity variables include anti-AUX-I/anti-AUX-II binding antibody results. Binding antibody levels will be determined from samples collected on Days 1 and 71 during the treatment phase and Day 360 during the observational phase.

Descriptive statistics (percent of positive measurements and average antibody level) will be presented for anti-AUX-I and anti-AUX-II antibody levels at each time point by region treated and overall. Average antibody levels will be summarized on logarithmically transposed titer values.

17.8. Pharmacokinetic Analyses

Not applicable.

17.9. Interim Analysis

Not applicable.

17.10. Statistical Software

Statistical analyses will be performed using Version 9.3 (or higher) of SAS® (SAS Institute, Cary, North Carolina).

18. STUDY DRUG MATERIALS AND MANAGEMENT

18.1. Study Drug Identity

EN3835 is formerly known as AA4500; the 2 product names should be considered synonymous. The investigational product vials will be labeled as EN3835. The components of EN3835 are 0.9 mg of collagenase clostridium histolyticum, [redacted] a lyophilized cake.

The components of EN3835 sterile diluent for reconstitution are 0.03% (2mM) calcium chloride ($CaCl_2$) in 0.9% (154mM) sodium chloride (NaCl) solution, pH 6.0 to 7.0. Diluent is supplied as a terminally-sterilized liquid at 3.0 mL per vial.

18.2. Study Drug Packaging and Labeling

Sterile vials of lyophilized EN3835 and sterile diluent will be provided to the Investigator by Endo. Each kit will contain 2 vials each of EN3835 and sterile diluent.

18.3. Study Drug Storage

All study drug will be provided by Endo. Study drug must be kept in a refrigerator (2°C-8°C) with locked access.

18.4. Study Drug Preparation

Refer to the Reconstitution Instructions for detailed preparation instructions.

Before reconstitution, remove the vials containing the lyophilized study drug powder and the vials containing the sterile diluent from the refrigerator and allow the vials to stand at room temperature for 15 minutes. Designated study personnel will visually inspect the study drug vials to determine the integrity and acceptability of the lyophilized drug product for reconstitution. The written procedures for inspection of the study drug vials will be provided to the site by Endo.

After reconstitution with the sterile diluent, the study drug solution can be kept at room temperature [redacted] he reconstituted study drug solution should be administered as soon as possible after reconstitution and further dilution. Each vial of study drug powder for reconstitution will be diluted according to the Reconstitution Instructions. Study personnel will maintain a record of the date and time of reconstitution.

18.5. Study Drug Accountability

Endo or its agent will maintain a master log of kits dispensed to the investigative sites. A drug inventory form must be kept current by the site staff designated to be responsible for reconstitution and must be made available to the clinical monitor, Endo employees, IRB/independent ethics committee (IEC), and regulatory agencies for routine inspection and accountability during monitoring visits. When instructed by Endo, the Investigator agrees to return all original containers of unused study drug to Endo or its designee.

18.5.1. Study Drug Handling and Disposal

The Investigator is responsible for recording the receipt and use of all drug supplied and for ensuring the supervision of the storage and allocation of these supplies. All unused study drug will be returned, and unit counts will be performed whenever medication is returned. The site must account for all study drug received. The Investigator agrees not to supply study drug to any person except to those subjects enrolled in the study. At the end of the study, all unused drug supplies will be returned to Endo as instructed by the clinical monitor.

19. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

19.1. Source Documents

Source documents include but are not limited to original documents, data and records such as hospital/medical records (including electronic health records), clinic charts, lab results, subject diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, etc. This study allows for direct data entry (DDE) for selected data points as outlined below:

- Inclusion/exclusion
- Vital signs including pre- and post-injection measurements
- Height and body weight
- CR-PCSS
- Hexsel CSS
- I-GAIS
- Physical examinations
- ECG results (if more than 1 year passed since ECG assessment)
- Urine pregnancy test
- Study drug administration

All other data points, at a minimum, should have supporting source documentation for entries in the eCRF.

19.2. Study Monitoring

A representative of Endo Pharmaceuticals Inc. will meet with the Investigator and his/her staff prior to the entrance of the first subject to review study procedures and methods of recording findings in the eCRF.

After enrollment of the first subject, an Endo Pharmaceuticals Inc. representative will be assigned to periodically monitor each Investigator site for study progress and to verify that standards of Good Clinical Practice (GCP) were followed. The Investigator is expected to prepare for the monitor visit, ensuring that all source documents, completed eCRFs, signed consent forms, and other study related documents are readily available for review.

19.3. Audits and Inspections

The Investigator shall permit audits and inspections by the Sponsor, its representatives and members of regulatory agencies. The investigator should immediately notify the Sponsor of an upcoming FDA or other regulatory agency inspection.

19.4. Institutional Review Board (IRB)

The Investigator shall permit members of the IRB/IEC to have direct access to source documents.

19.5. Data Recording and Documentation

All data recordings and source documentation (including electronic health records) must be made available to the Sponsor (or designee), FDA and any other regulatory agencies that request access to study records, including source documents, for inspection and copying, in keeping with federal and local regulations.

20. QUALITY CONTROL AND QUALITY ASSURANCE

Steps to assure the accuracy and reliability of data include the selection of qualified principal investigators and appropriate study centers, review of protocol procedures with the principal investigators and associated personnel prior to start of the study, and periodic monitoring visits conducted by the Sponsor or Sponsor representative. Significant and/or repeated non-compliance will be investigated and remedial action instituted when appropriate. Failure to comply with remedial actions may result in investigator site termination and regulatory authority notification.

The Sponsor or its designee will utilize qualified monitors to review and evaluate activities conducted at Investigator Sites.

The data will be entered into the clinical study database and verified for accuracy, following procedures defined by the Sponsor (or designee). Data will be processed and analyzed following procedures defined by the Sponsor (or designee).

The study will be monitored and/or audited at intervals to ensure that the clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the Study Protocol; International Conference on Harmonisation (ICH), E6 consolidated guidelines; and other applicable regulations. The extent, nature, and frequency of monitoring and/or audits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity, and enrollment rate. At the conclusion of a program, a compliance statement will be generated by the Sponsor (or designee) listing all audit activities performed during the clinical study.

21. ETHICS

21.1. Ethics Review

Approval by the IRB/IEC prior to the start of the study will be the responsibility of the Investigator. A copy of approval documentation will be supplied to Endo Pharmaceuticals Inc. along with a roster of IRB members that demonstrates appropriate composition (a Department of Health and Human Services [DHHS] Assurance Number will satisfy this requirement).

The study protocol, the informed consent form, advertisements, materials being provided to subjects and amendments (if any) will be approved to IRB/IECs at each study center in conformance with ICH E6, the Code of Federal Regulations (CFR), Title 21, Part 56 and any other applicable local laws. The Investigator is responsible for supplying the IRB/IEC with a copy of the current IB, Package Insert, or SPC as well as any updates issued during the study. During the course of the study, the Investigator will provide timely and accurate reports to the IRB/IEC on the progress of the study, at intervals not exceeding 1 year (or as appropriate), and will notify the IRB/IEC of SAEs or other significant safety findings, per the policy of the IRB/IEC. At the conclusion of the study, the Investigator will submit a final report or close out report to the IRB/IEC and provide a copy to Endo Pharmaceuticals Inc.

Any amendment to this protocol will be provided to the Investigator in writing by Endo Pharmaceuticals Inc. No protocol amendment may be implemented (with the exceptions noted below) before it has been approved by the IRB and the signature page, signed by the Investigator, has been received by Endo Pharmaceuticals Inc. Where the protocol is amended to eliminate or reduce the risk to the subject, the amendment may be implemented before IRB review and approval. However, the IRB must be informed in writing of such an amendment and approval obtained within reasonable time limits. Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the subject, and must be immediately reported to Endo Pharmaceuticals Inc.

The Investigator will be responsible for supplying updated safety and/or study information to study subjects as it becomes available.

21.2. Ethical Conduct of the Study

This clinical study is designed to comply with the ICH Guidance on General Considerations for Clinical Trials (62 FR 6611, December 17, 1997), Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (62 FR 62922, November 25, 1997), Good Clinical Practice: Consolidated Guidance (62 FR 25692, May 9, 1997) and 21 CFR parts 50, 54, 56, and 312.

The study will be conducted in full compliance with ICH E6, the FDA guidelines for GCP and in accordance with the ethical principles that have their origins in the Declaration of Helsinki defined in 21 CFR, 312.120.

21.3. Subject Information and Consent

Subjects, after having the study explained to them and an opportunity to have their questions answered sufficiently, will give voluntary and written informed consent (in compliance with ICH E6, 4.8 and 21 CFR Parts 50 and 312) before participating in any study-related procedures. The consent shall be written in a language understandable to the subject. Subjects unable to read (illiterate) shall have the consent process performed in the presence of an independent witness who shall also sign the consent. Each subject will read, assent understanding, and sign an instrument of informed consent after having had an opportunity to discuss the study and consent documents with the Investigator before signing, and will be made aware that she may withdraw from the study at any time.

In addition to obtaining informed consent, the Investigator is responsible for obtaining any additional documentation to demonstrate compliance with local privacy laws applicable to activities performed.

The consent process shall be recorded in source documents. Signed copies of the informed consent will be given to the Subject and originals will be placed in the Investigator study files.

A unique Subject identification number will be assigned according to section 12.1.3 at the time that the Subject signs the informed consent form.

22. DATA HANDLING AND RECORDINGKEEPING

22.1. Data Collection

Data collection will involve the use of an EDC system to which only authorized personnel will have access. The system will be secured to prevent unauthorized access to the data or the system. This will include the requirement for a user ID and password to enter or change data. The level of access to the EDC system will be dependent on the person's role in the study.

Study data will be collected by DDE or from source documents and entered into an eCRF within the EDC system. The Investigator will be responsible for ensuring the eCRFs are completed in a timely manner relative to the subject's visit. In addition to periodic monitoring occurring within the system by a Sponsor monitor, programmatic edit checks will be used to review EDC data for completeness, logic, and adherence to the study protocol. As a result of this monitoring and these checks, queries may be issued electronically to the clinical study sites and closed electronically by the monitor, data management staff or authorized staff at the study site. Additionally, the Investigator will review eCRFs, ensure all missing or corrected data is provided and will sign the eCRF pages with an electronic signature.

An electronic audit trail will be maintained in the EDC system to track all changes made to data entered in the eCRF. Data will be retrievable in such a fashion that all information regarding each individual subject is attributable to that subject.

In addition, any contact with the subject via telephone or other means that provide significant clinical information must be documented in source documents as described above.

22.2. Study Documentation

Upon study completion, the Investigator will be provided with complete electronic copies of the eCRF data for his/her files.

23. REPORTING AND PUBLICATION

All data generated in this study are the property of Endo. An integrated clinical and statistical report will be prepared at the completion of the study.

Publication of the results by the Investigator will be subject to mutual agreement between the Investigator and Endo.

24. INVESTIGATOR OBLIGATIONS

24.1. Regulatory Documents

The Investigator is responsible for creating and/or maintaining all study documentation required by 21CFR 50, 54, 56 and 312, ICH, E6 section 8, as well as any other documentation defined in the protocol or the Investigator Agreement. The Investigator must maintain the documentation relating to this study and permit Endo Pharmaceuticals Inc. or a member of a regulatory agency access to such records.

The Investigator must provide the following key documents to Endo Pharmaceuticals Inc. prior to the start of the study:

- A completed and signed Form FDA1572. If during the course of the study any information reported on the Form FDA 1572 changes, a revised Form FDA1572 must be completed and returned to Endo Pharmaceuticals Inc. for submission to the FDA. For studies executed outside the United States, documentation required by the governing regulatory authority may be substituted for the Form FDA 1572.
- A fully executed contract
- The Investigator's Statement page in this protocol signed and dated by the Investigator and any subsequent amendment signature pages
- The IB acknowledgment of receipt page
- Curricula vitae for the Principal Investigator and all Sub-Investigators listed on Form FDA 1572, including a copy of each physician's license (if applicable)
- A copy of the original IRB/IEC approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals or shorter intervals defined by the IRB/IEC. All subsequent modifications must be submitted and approved by the IRB, as described in section 21.1
- A copy of the IRB/IEC-approved informed consent form
- A list of IRB/IEC members or DHHS Assurance Number
- Laboratory certifications and normal ranges (if local labs are required by the protocol)
- A financial disclosure agreement completed and signed by the Investigator and all Sub-Investigators listed on Form FDA 1572. Investigator site staff that submitted an initial financial disclosure are also responsible for informing Endo Pharmaceuticals Inc. of any changes to their initial financial disclosure form 1 year after the completion of the study.

A complete list of required regulatory documents will be supplied by Endo Pharmaceuticals Inc. or its representative.

24.2. Delegation of Responsibilities and Adequate Resources

The Investigator should have adequate time to conduct the study properly and should have an adequate number of qualified staff to assist with the conduct of the study. The Investigator shall delegate tasks only to individuals qualified by education, training and experience to perform the delegated tasks. The Investigator shall have direct oversight of all delegated activities and shall document delegation of responsibilities. The Investigator is responsible for ensuring all delegated staff have been properly trained on the protocol and their assigned study responsibilities.

24.3. Medical Care of Study Subjects

The Investigator and/or a qualified sub-investigator shall be responsible for the subjects' medical care. Any unrelated medical condition discovered during the course of the study should be communicated to the subject so that they may seek appropriate medical care. The Investigator will report all AEs as required by the protocol (section 14.5). The Investigator will inform study subjects of new information regarding the study drug as it becomes available.

24.4. Use of Investigational Materials

The Investigator will acknowledge that the study drug supplies are investigational and as such must be used strictly in accordance with the protocol and only under the supervision of the Principal Investigator or Sub-Investigators listed on Form FDA1572 (or other regulatory document, depending on region). Study drug must be stored in a safe and secure location. At study initiation, a representative from Endo Pharmaceuticals Inc. will inventory the study drug at the site. The Investigator must maintain adequate records documenting the receipt and disposition of all study supplies. Endo Pharmaceuticals Inc. or its representative will supply forms to document total inventory as well as subject specific accountability. The Investigator is responsible for monitoring use of the study drug to ensure compliance with the protocol. All study supplies shall be returned to Endo Pharmaceuticals Inc. or its designee.

24.5. Retention of Records

Federal and local regulations require that the Investigator retain a copy of all regulatory documents and records that support the data for this study (eg, informed consents, laboratory reports, source documents, study drug dispensing records) for whichever of the following is the longest period of time:

- A period of 2 years following the final date of approval by the FDA or other regulatory agency of the study drug for the purposes that were the subject of the investigation; or
- A period of 5 years following the date on which the results of the investigation were submitted to the FDA or other regulatory agency in support of, or as part of, an application for a research or marketing permit for the study drug for the purposes that were the subject of the investigation

Endo will notify Investigators once one of the above 2 timeframes has been satisfied.

If the investigation does not result in the submission of the data in support of, or as part of, an application for a research or marketing permit, records must be retained for a period of 2 years

following notification by Endo Pharmaceuticals Inc. that the entire clinical investigation (not merely the Investigator's portion) is completed, terminated, or discontinued or 2 years following withdrawal of the Investigational New Drug application (IND).

If the Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. Endo must be notified in writing of the name and address of the new custodian. Study records should not be destroyed without consultation with Endo Pharmaceuticals Inc.

24.6. Subject Confidentiality

All subject records submitted to Endo Pharmaceuticals Inc. or its designee will be identified only by initials and subject identification number. Subjects' names are not to be transmitted to Endo Pharmaceuticals Inc. The Investigator will keep a Master Subject List on which the identification number and the full name, address, and telephone number of each subject are listed. It is the Investigators' responsibility to inform study subjects that representatives of the Sponsor, FDA, or other regulatory agencies may review all records that support their participation in the study. The Investigator will adhere to all privacy laws to which he/she is subject.

25. TERMINATION OF STUDY

The Sponsor has the right to suspend or terminate the study at any time. The study may be suspended or terminated for any reason.

26. INVESTIGATOR'S AGREEMENT

I agree to conduct the study in accordance with the protocol, and with all applicable government regulations and Good Clinical Practice guidance.

_____ _____/_____/_____

Investigator's Signature Date

_____

Typed Name of Investigator

27. REFERENCES

1. Khan MH, Victor F, Rao B, Sadick NS. Treatment of cellulite: Part I. Pathophysiology. *J Am Acad Dermatol* 2010;62(3):361-370.
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[redacted]

LIST OF APPENDICES

APPENDIX A. DOCUMENTS REQUIRED PRIOR TO INITIATION OF THE STUDY

As a Sponsor of a clinical study, Endo Pharmaceuticals Inc. has an obligation to ensure that the study will be conducted by a qualified Investigator with sufficient resources of time, personnel, and physical facilities to conduct the study and to ensure that the Investigator understands and agrees to comply with the protocol, applicable regulations, policies, and procedures. The following documentation is required:

From the Principal Investigator

1. A signed agreement to perform the study per protocol (the signature page will suffice).
2. A signed Letter of Financial Agreement (including confidentiality statement).
3. Name(s) of the Principal Investigator and of all sub-Investigator(s)
4. All address(es) of the clinical site(s).
5. A current medical license valid where he/she practices and a current curriculum vitae for the Principal Investigator (signed and dated) and all sub-investigators, to contain at least the following elements:
   a. For physicians:
      i. Date of degree in Medicine
      ii. Name of the Institution granting the degree in Medicine.
      iii. Previous clinical postings with dates.
   b. For non-physician allowed by national law or regulations to act as clinical Investigators:
      i. Date and description of most advanced degree.
      ii. Name of the Institution granting the degree in number (i).
      iii. Other accreditation or qualifications relevant to the study.
      iv. Previous postings with dates.
      v. Name and qualification (see 5a above) of the physician or dentist in charge of study subjects.

   Note: If a non-physician is serving as Principal Investigator, then a qualified physician must be assigned as a sub-Investigator for the trial, to be responsible for all trial-related medical decisions.
6. Written notification of Institutional Review Board/Independent Ethics Committee/Human Research Ethics Committee (IRB/IEC/HREC) approval. The minimum requirements are as follows:
   a. Dated letter, including:
      i. The date on which the meeting for the review of the study protocol took place.
      ii. Study protocol/amendment number, and version date

iii. A clear statement of approval of the protocol and the informed consent text with version date, and authorization for the study to proceed.

iv. If the Investigator or any sub-Investigator is a part of the IRB/IEC/HREC Review Board, assurance that the Investigator abstained from voting at the meeting(s) when the study was discussed.

b. A dated list of the members and their occupations.

c. A specimen copy of the Committee-approved informed consent text to be used in the study.

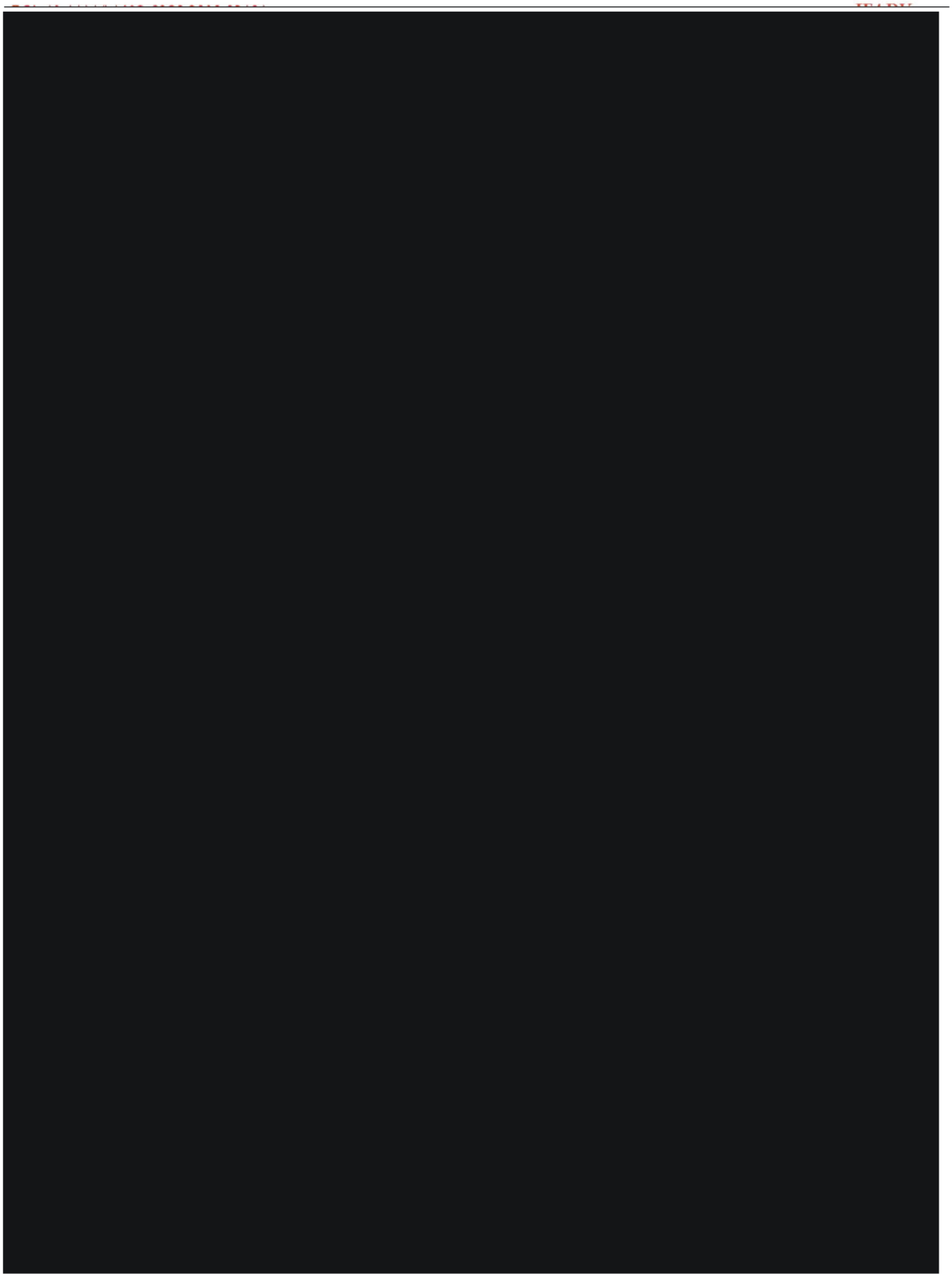
7. Food and Drug Administration (FDA) Form 1572 (for studies submitted under a US Investigational New Drug application [IND]).

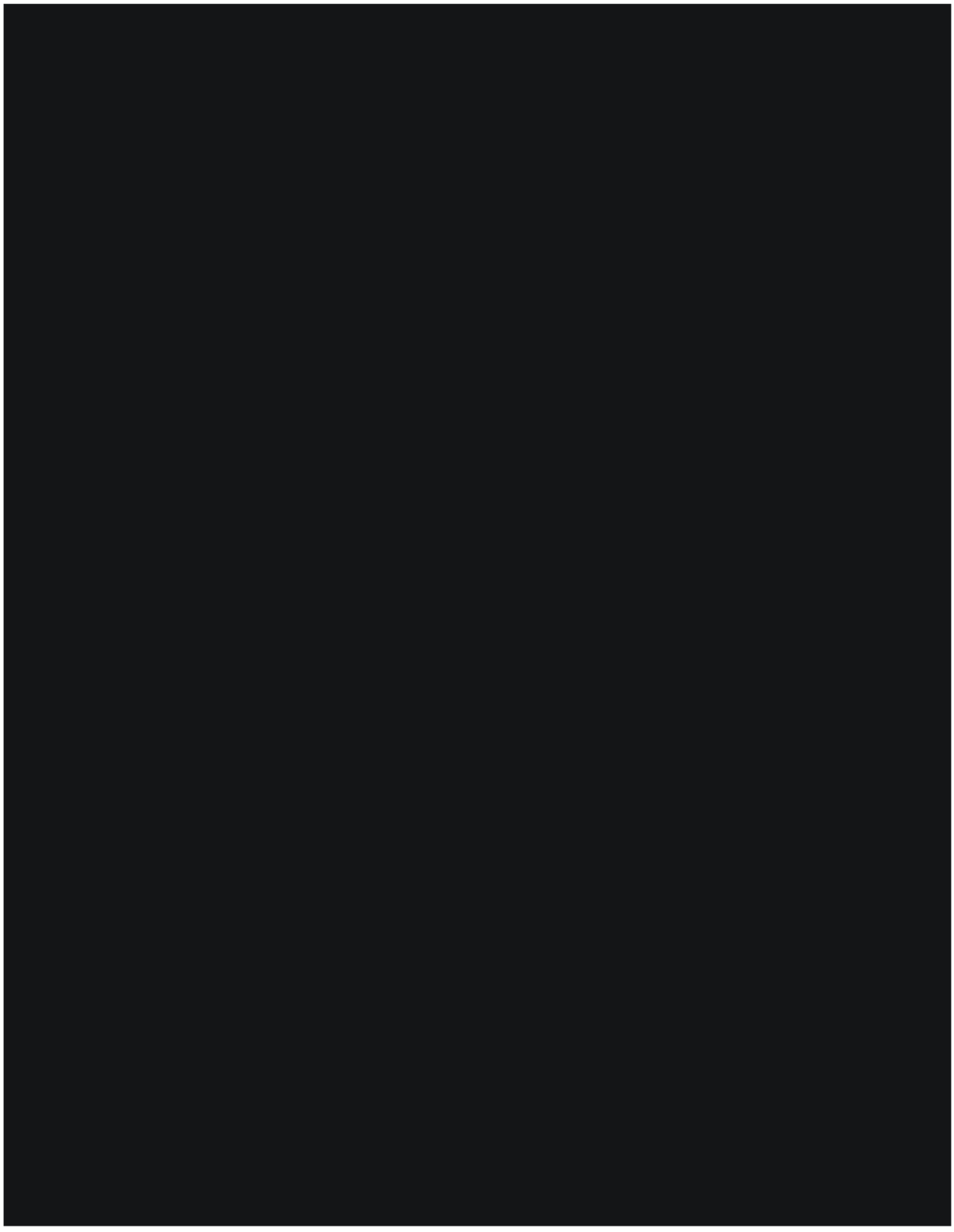
8. Financial Disclosure Certification or Certification of Non-Disclosure (for studies to be submitted for a US New Drug Application/Biologics License Application [NDA/BLA]).

Other

Any other documentation required by national law or regulations to be in the possession of the Sponsor or the Investigator for study participation or study initiation.

APPENDIX B. HEXSEL DM, DAL'FORNO T, HEXSEL CL. A VALIDATED PHOTONUMERIC CELLULITE SEVERITY SCALE. *J EUR ACAD DERMATOL VENEREOL*. 2009;23(5):523-528.





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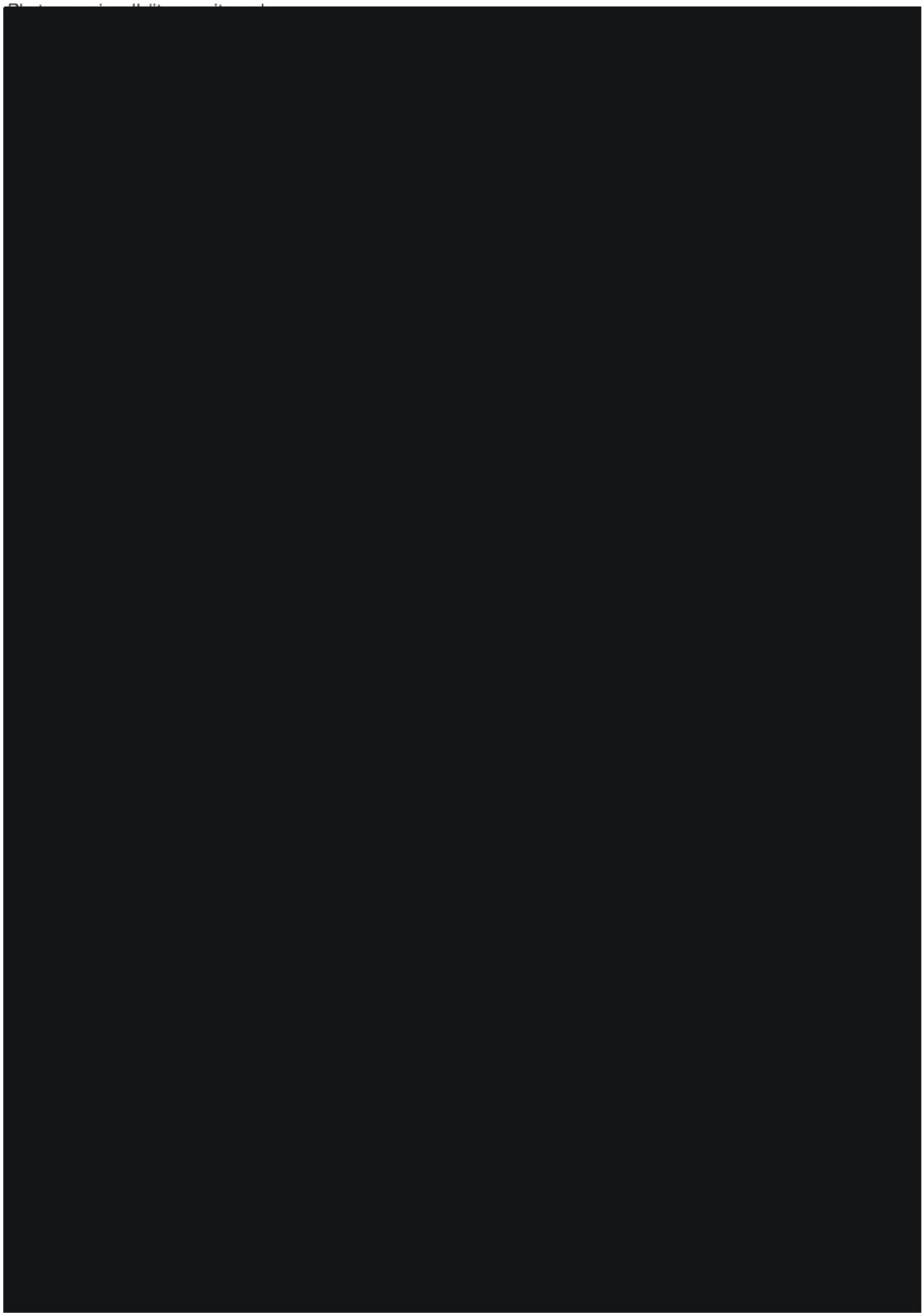

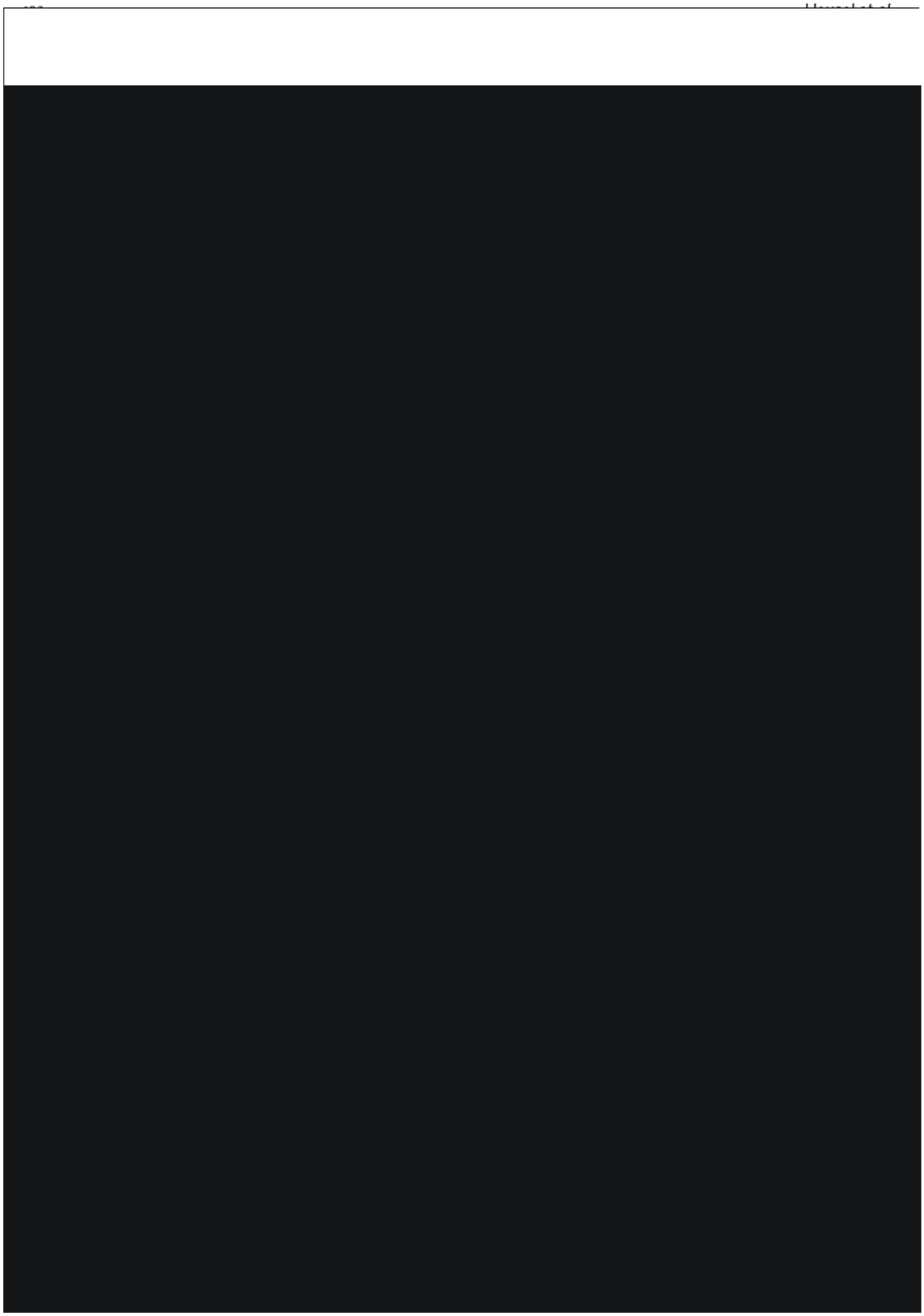

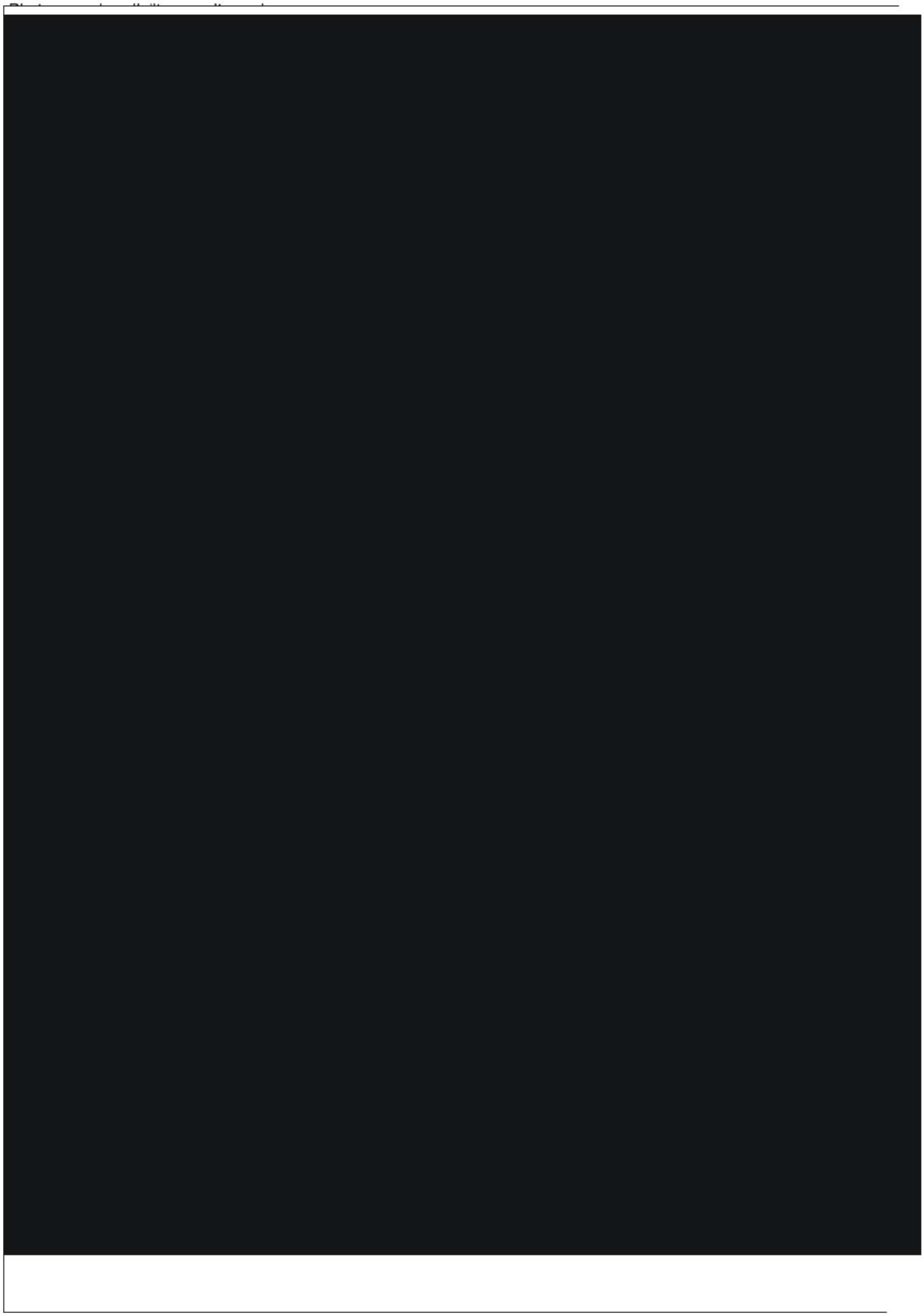

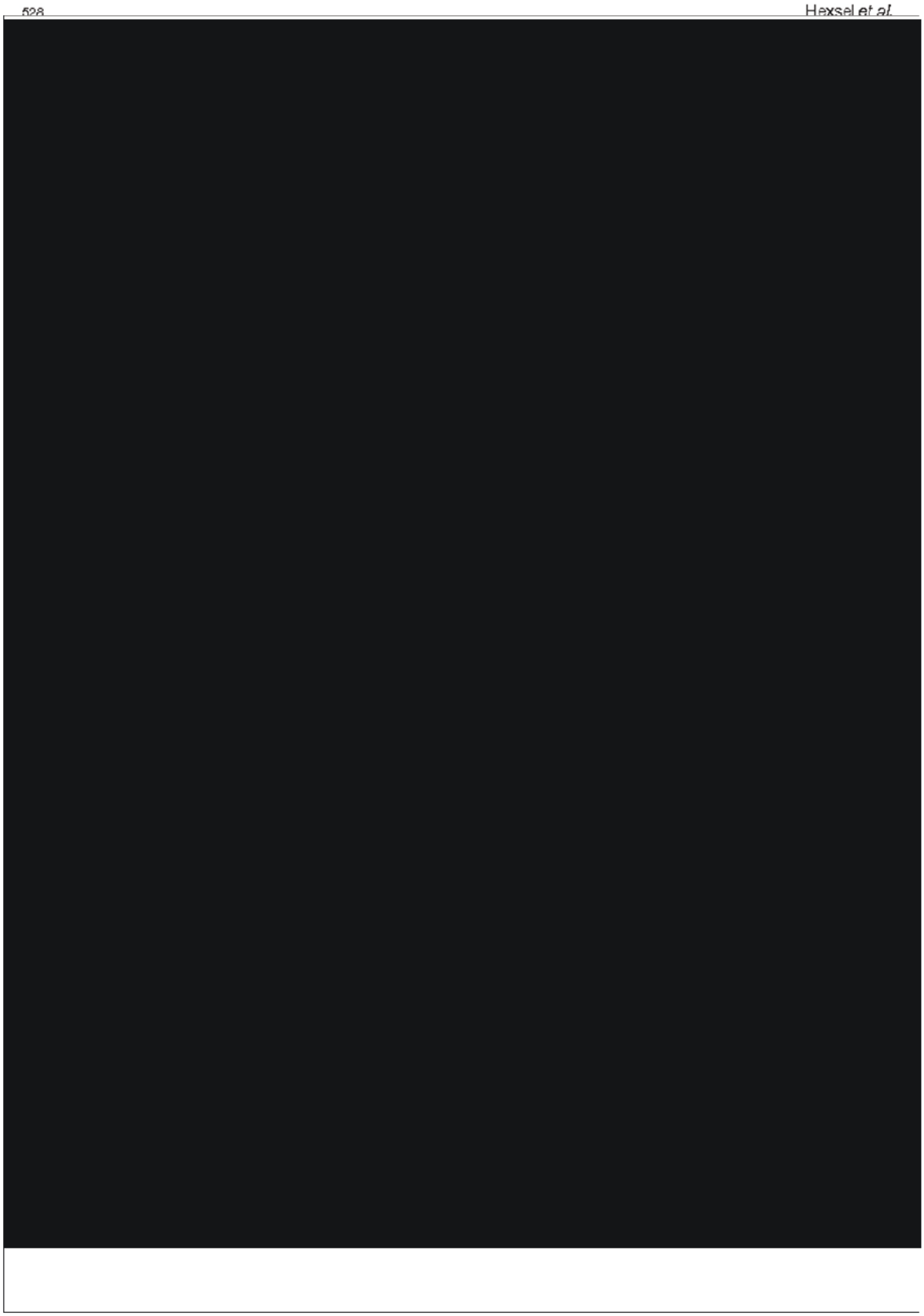
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Hexsel et al.

APPENDIX C. REFERENCE IMAGES FOR HEXSEL SEVERITY RATINGS

[redacted]

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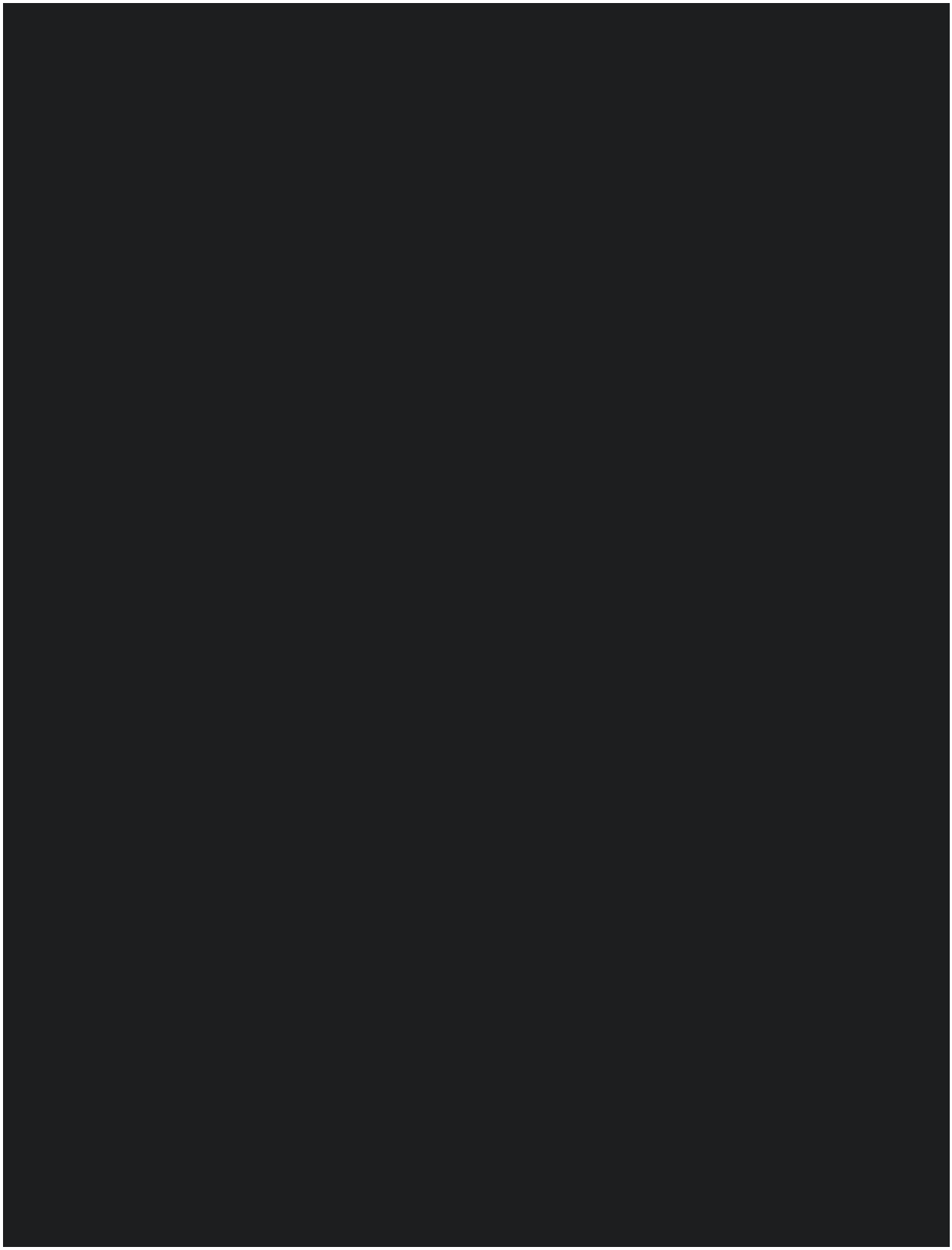
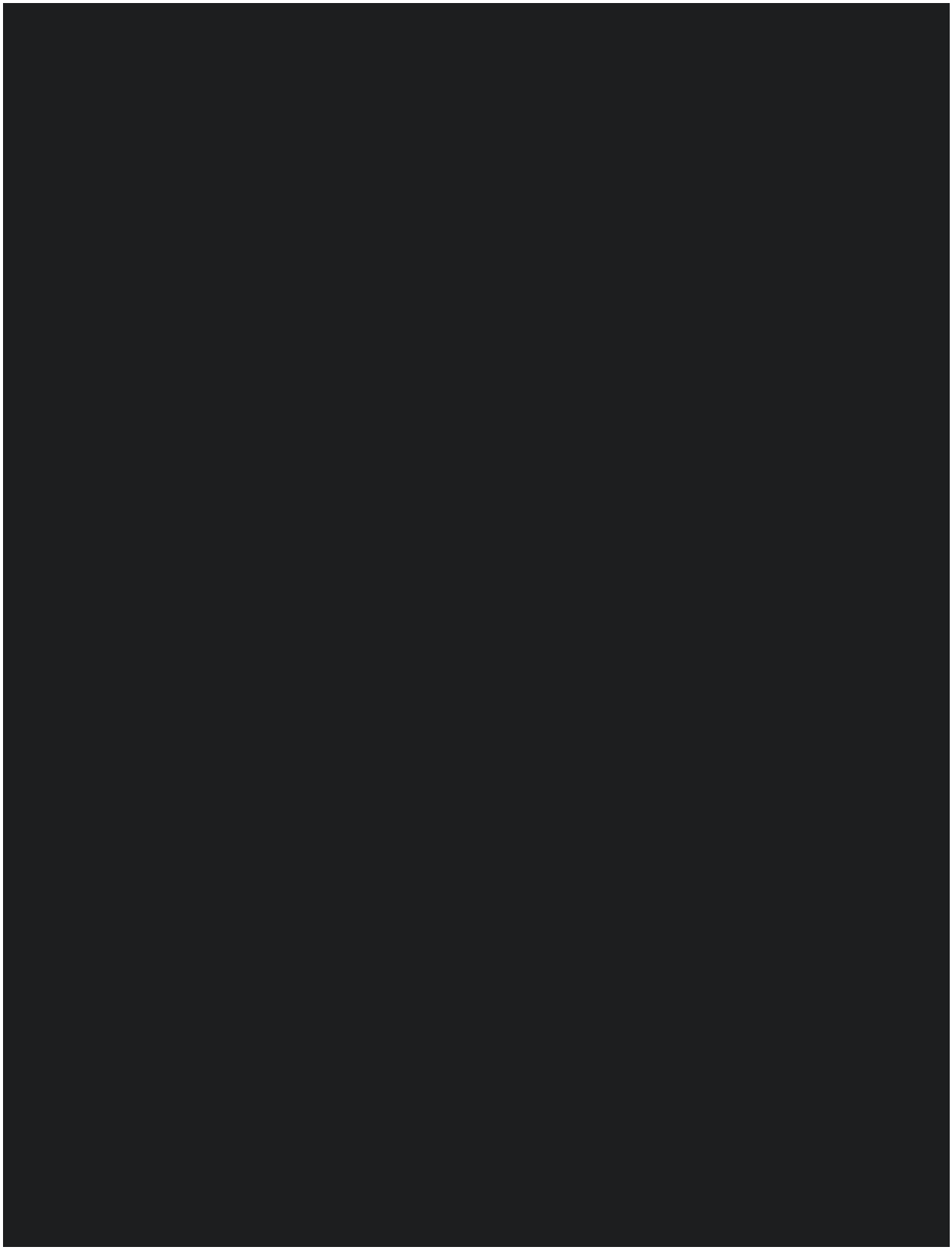
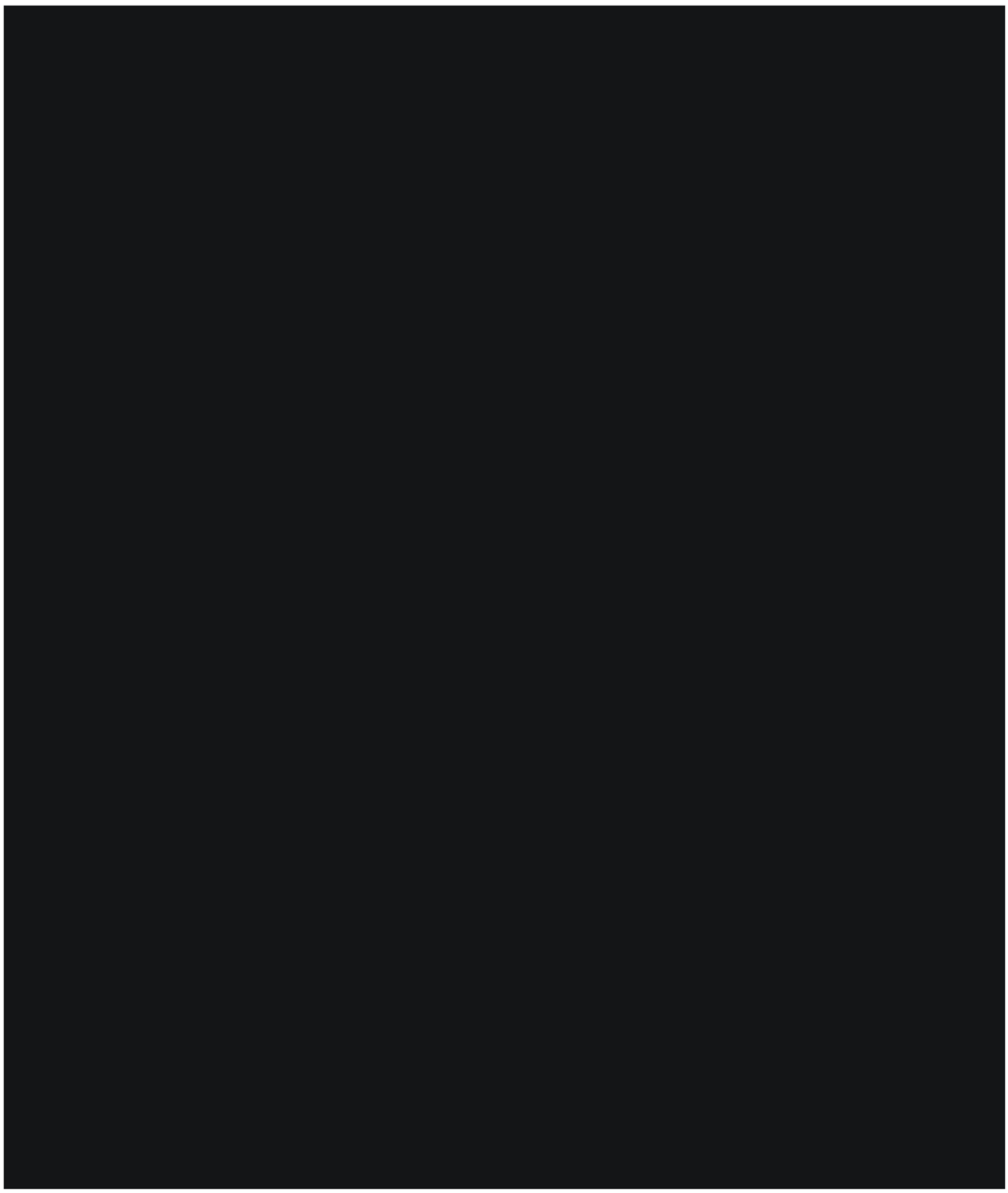
APPENDIX D. PATIENT INSTRUCTIONS FOR USE OF PATIENT-REPORTED PHOTONUMERIC CELLULITE SEVERITY SCALE (PR-PCSS)







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

COLLAGENASE CLOSTRIDIUM HISTOLYTICUM (EN3835)

EN3835-202

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

IND 110077

Amendment 2

Date:

Original Protocol: June 20, 2016

Amendment 1: July 5, 2016

Amendment 2: October 25, 2016

Auxilium Pharmaceuticals, Inc. (Auxilium) was acquired by Endo International plc. in January 2015. The Sponsor of the application remains Auxilium; however, Endo Pharmaceuticals Inc. (Endo) is authorized to act and to communicate on behalf of Auxilium.

Confidentiality Statement

2. SUMMARY OF CHANGES

The EN3835-202 protocol amendment and amended informed consent form (as necessary) have been reviewed and approved by the governing institutional review boards (IRBs) before implementation of the amendment at each study center.

Amendment 1 was incorporated into the protocol on July 5, 2016. The major reason for this amendment is to clarify that the investigators will conduct the assessment.

Section	Original Text	Revised Text
13.1.1.5 Investigator Global Aesthetic Improvement Scale (I-GAIS)	Subjects in the observation-only group will complete the I-GAIS as described below at the final study visit (month 12 or early termination) and a comparison back to the pre-treatment day 1 (Baseline) image of the assigned quadrant of the double-blind study.	Investigators will complete the I-GAIS on subjects in the observation-only group as described below at the final study visit (month 12 or early termination) and a comparison back to the pre-treatment Day 1 (Baseline) image of the assigned quadrant of the double-blind study.

Amendment 2 was incorporated into the protocol on October 25, 2016. The major reasons for this amendment are to improve operational activities and clarifications, and optimize and reduce the number of blood sample collections needed to profile immunogenicity.

Section	Original Text	Revised Text
3 Sponsor Contact Information	[redacted]	[redacted]
3 Sponsor Contact Information	Medical Monitor email [redacted]	Medical Monitor email: [redacted]
3 Sponsor Contact Information	SAE Reporting Pathway: [redacted]	SAE Reporting Pathway: [redacted]
4 Synopsis, Study Period	Estimated date first subject enrolled: Jun-2016 Estimated date last subject completed: May-2017	Estimated date first subject enrolled: Oct-2016 Estimated date last subject completed: Sep-2017

Section	Original Text	Revised Text
4 Synopsis, Objectives, Secondary	To evaluate the durability of response to EN3835 in EFP severity over the 12-month post initial dosing of EN3835 in subjects previously receiving active treatment in study EN3835-201 using the Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS), the Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS), and the Hexsel Cellulite Severity Scale (CSS) To evaluate long-term response to EN3835 in assessments of EFP including subject satisfaction, Investigator Global Aesthetic Improvement Scale (I-GAIS), and Subject Global Aesthetic Improvement Scale (S-GAIS) To evaluate immunogenicity after exposure to EN3835	To assess safety and immunogenicity of re-treating or re-dosing a subject that had previously received treatment with EN3835 To evaluate the durability of response to EN3835 in EFP severity over the 12-month post initial dosing of EN3835 in subjects previously receiving active treatment in study EN3835-201 using the Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS) and the Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS) To evaluate long-term response to EN3835 in assessments of EFP including subject satisfaction, Investigator Global Aesthetic Improvement Scale (I-GAIS), and Subject Global Aesthetic Improvement Scale (S-GAIS) To assess cellulite severity assessments in quadrants treated in this study with EN3835. To evaluate immunogenicity after exposure to EN3835
4 Synopsis, Study Design	Treatments will be administered on days 1, 22, and 43; subjects will be assessed for safety on days 1, 22, 43, and 71 and for cellulite severity assessments on days 1, 43, and 71.	Treatments will be administered on Days 1, 22, and 43; subjects will be assessed for safety on Days 1, 22, 43, and 71 and for cellulite severity assessments at Screening visit and on Days 22, 43, and 71.
4 Synopsis, Diagnosis and inclusion/ exclusion criteria	**Qualification for the Open-Label Treatment Phase of the Study** ***Inclusion criteria for treatment:*** Have participated in and completed the double-blind study EN3835-201 and all day 71 assessments	**Qualification for the Open-Label Treatment Phase of the Study** ***Inclusion criteria for treatment:*** Have participated in and completed the double-blind study EN3835-201
4 Synopsis, Duration of Study	**Follow-up**: For subjects treated with EN3835 in this study, subjects will be observed at treatment visits (Days 1, 22, and 43) and Day 71 after first injection.	**Follow-up**: For subjects treated with EN3835 in this study, subjects will be observed at treatment visits (Days 1, 22, and 43) and Day 71 after first injection. After Day 71, they will be observed every 3 months from their first exposure to EN3835 up to a maximum of 1 year.
5 Schedule of Events	NOTE: Observation visits (Table 2) in the open-label extension study begin after completion of double-blind study (day 71). Treatment sessions (Table 3), if elected, will begin when study drug blind is broken in study EN3835-201 while observation visits continue concurrently.	NOTE: Observation visits (Table 2) in the open-label extension study begin after completion of double-blind study (Day 71). Treatment sessions (Table 3), if elected, will begin after study drug blind is broken in study EN3835-201while observation visits continue concurrently.

Section	Original Text	Revised Text
Table 2 Observation Assessments, Collection of Samples: Anti-AUX-I/anti-AUX-II antibody level	Visit 1: X Visit 2: X Visit 3: X Visit 4: X	Visit 1: Visit 2: Visit 3: Visit 4: X
Table 3 Treatment Session Assessments, Column Heading	Tx Visit 4 End of Treatment/ Early Termination Day 71 (±5 days)[b]	Tx Visit 4 End of Treatment/ Early Termination Day 71 (+5 days)[b]
Table 3 Treatment Session Assessments, Procedures	Screening B[a]: Medical history/EFP history including previous treatments: X[k] Prior/Concomitant Medications/Procedures: X[k] Physical examination: Body weight: X Height: X Collection of samples: Clinical laboratory X Tx Visit 1: Prior/Concomitant Medications/Procedures: X	Screening B[a]: Medical history/EFP history including previous treatments: X[k,m] Prior/Concomitant Medications/Procedures: X[k,m] Physical examination: Body weight: X[m] Height: X[m] Collection of samples: Clinical laboratory: X[m] Tx Visit 1: Prior/Concomitant Medications/Procedures: X[m]
Table 3 Treatment Session Assessments, Collection of Samples: Anti-AUX-I/anti-AUX-II antibody level	Tx Visit 1: X[e] Tx Visit 2: X[e] Tx Visit 3: X[e] Tx Visit 4: X	Tx Visit 1: X[e,m] Tx Visit 2: Tx Visit 3: Tx Visit 4: X
Table 3 Treatment Session Assessments, footnotes	[a] Eligible subjects may choose additional treatment any time after the study drug blind is broken in study EN3835-201. Add	[a] After the study drug blind is broken in study EN3835-201, eligible subjects may elect to receive EN3835 treatments. [m] Do not conduct on subjects eligible and opting-in for a second course of treatment in the current study (EN3835-202) if Screening B visit or Day 1 visit for second treatment course is the same day as Day 71 of the first treatment course in this study or previous study EN3835-201.

Section	Original Text	Revised Text
9.2 Secondary Objectives	To assess safety and immunogenicity of re-treating or re-dosing a subject that had previously received treatment with EN3835 To evaluate the durability of response to EN3835 in EFP severity over the 12-month post initial dosing of EN3835 in subjects previously receiving active-treatment in study EN3835-201 using the PR-PCSS, the CR-PCSS, and the Hexsel CSS To evaluate long-term response to EN3835 in assessments of EFP including subject satisfaction, I-GAIS, and S-GAIS To assess cellulite severity assessments in quadrants treated in this study with EN3835	To assess safety and immunogenicity of re-treating or re-dosing a subject that had previously received treatment with EN3835 To evaluate the durability of response to EN3835 in EFP severity over the 12-month post initial dosing of EN3835 in subjects previously receiving active-treatment in study EN3835-201 using the PR-PCSS and the CR-PCSS To evaluate long-term response to EN3835 in assessments of EFP including subject satisfaction, I-GAIS, and S-GAIS To assess cellulite severity assessments in quadrants treated in this study with EN3835 To evaluate immunogenicity after exposure to EN3835
10.1 Study Design	Following the study drug blind being broken and communicated to centers, treatments of eligible subjects with EN3835 can begin at a visit at the discretion of the subject.	Following the study drug blind being broken and communicated to centers, eligible subjects may elect to receive EN3835 treatment.
11.1 Observation Phase	All subjects who have completed the double-blind study EN3835-201, including all day 71 assessments, and sign informed consent are eligible for enrollment in this open-label extension study and participation in the ongoing safety and cellulite evaluations.	All subjects who have completed the double-blind study EN3835-201 and sign the informed consent are eligible for enrollment in this open-label extension study and participation in the ongoing safety and cellulite evaluations.
11.2.1 Subject Inclusion Criteria for Treatment	Have participated in and completed the double-blind study EN3835-201 and all Day 71 assessments	Have participated in and completed the double-blind study EN3835-201
11.2.2 Subject Exclusion Criteria for Treatment	Add	Presence of any clinically relevant conditions, that in the opinion of the Investigator would interfere with completing the study including, but not limited to, visual problems, hearing problems, cognitive impairment or acute mental illness
12.1.3 Study Entry/ Observational Assessments	A subject who gives written informed consent and who satisfies all eligibility criteria (section 11) may be entered into the observational phase of the study and complete safety and cellulite severity assessments at 3-month intervals as detailed in Table 2.	A subject who gives written informed consent and who satisfies all eligibility criteria (section 11) may be entered into the observational phase of the study and complete safety and cellulite severity assessments at 3-month intervals as detailed in Table 2. The first visit will be determined by the date of enrollment in study EN3835-202 relative to the Schedule of Events for Study EN3835-202 (Table 2). For example, if a subject enrolls after the Day 90 visit window, the first observation visit for that subject would be Day 180.

Section	Original Text	Revised Text
12.1.4 Treatment Assessments (Optional)	If a subject received placebo in the double-blind study, she may be eligible for 2 treatments in the open-label study; if a subject received active drug in the double-blind study, she may be eligible for 1 additional treatment (3 treatment sessions) in the open-label study.	If a subject received placebo in the double-blind study, she may be eligible for 2 treatment courses in the open-label study; if a subject received active drug in the double-blind study, she may be eligible for 1 additional treatment course (3 treatment sessions) in the open-label study.
12.1.4 Treatment Assessments (Optional), Selection of Treatment Quadrant	The Investigator will then assess each of the 4 subject's quadrants live in real-time using the CR-PCSS.	The Investigator will then assess each of the subject's 4 quadrants live in real-time using the CR-PCSS.
12.1.4 Treatment Assessments (Optional), Selection of Treatment Quadrant	A subject who received placebo in the double-blind study may be treated in the same quadrant in the open-label study if the quadrant still meets all 3 criteria OR another qualifying quadrant may be selected for treatment by the Investigator and subject.	A subject who received placebo in the double-blind study may be treated in the same quadrant in the open-label study if the quadrant still meets all 3 criteria OR another qualifying quadrant may be selected for treatment by the subject.
12.1.4 Treatment Assessments (Optional), Selecting and Marking Dimples	The cellulite severity assessments using the PR-PCSS, CR-PCSS, and Hexsel CSS will be completed prior to dimple marking at treatment visits 2, 3, and 4/end of treatment.	The cellulite severity assessments using the PR-PCSS and CR-PCSS will be completed prior to dimple marking at treatment visits 2, 3, and 4/end of treatment.
12.1.4.1 Screening B (Days −14 to −1 Relative to Open-Label Treatment Visit Day 1)	The Investigator will conduct live assessments of subject's cellulite severity of each quadrant using the CR-PCSS (section 13.1.1.4)	The Investigator will conduct independent live assessments of subject's cellulite severity of each quadrant using the CR-PCSS (section 13.1.1.4) after the subject completes her ratings and with no knowledge of the subject's ratings of her quadrants.
12.1.4.1 Screening B (Days −14 to −1 Relative to Open-Label Treatment Visit Day 1)	Collection of samples for: Clinical laboratory testing including Anti-AUX-I and anti-AUX-II antibody testing (section 14.7) Urine pregnancy testing (section 14.7)	Collection of samples for: Clinical laboratory testing (section 14.7) Urine pregnancy testing (section 14.7)
12.1.4.2, Subheading	Treatment Session 1 (Visit 1B)	Treatment Session 1 (Treatment Visit 1)
12.1.4.2 Treatment Session 1 (Treatment Visit 1), Pre-injection	5. Collection of samples for urine pregnancy testing (section 14.7)	Collection of samples for: anti-AUX-I and anti-AUX-II antibody testing (section 14.7.1) urine pregnancy testing (section 14.7)
12.1.4.3, Subheading	Treatment Session 2 (Visit 2/Day 22 ± 3 Days) and Treatment Session 3 (Visit 3/Day 43 ± 3 Days)	Treatment Session 2 (Treatment Visit 2/ Day 22 ± 3 Days) and Treatment Session 3 (Treatment Visit 3/Day 43 ± 3 Days)

Section	Original Text	Revised Text
12.1.4.3 Pre-injection	Investigator live assessment of the severity of cellulite using the CR-PCSS (section 13.1.1.4)	Investigator will conduct an independent live assessment of the severity of cellulite using the CR-PCSS (section 13.1.1.4). The investigator will conduct the assessment of severity only after the subject has completed her rating of her quadrant and without knowledge of the subject's rating of her quadrant.
12.1.4.3	If no injections are given at treatment session 2, subjects will still return for the day 43 visit and the selected quadrant will again be evaluated by the subject (PR-PCSS) and Investigator (CR-PCSS).	If the Investigator rates the selected quadrant as 0, no injections will be given. If no injections are given at treatment session 2, subjects will still return for the Day 43 visit and the selected quadrant will again be evaluated by the subject (PR-PCSS) and Investigator (CR-PCSS).
12.1.4.4 Day 71 (+5 Days) End of Treatment/Early Termination, Subheading	Day 71 (±5 Days) End of Treatment/Early Termination	Day 71 (+5 Days) End of Treatment/Early Termination
12.1.4.4 Day 71 (+5 Days) End of Treatment/Early Termination	Investigator cellulite assessments of selected quadrant using:	Investigator cellulite assessments of selected quadrant independently conducted; ie, with no knowledge of the subject's rating, using:
13.1.1.2 Subject Global Aesthetic Improvement Scale (S-GAIS)	The S-GAIS assessment will be done on day 71 of the treatment course and then at month 12 or the final study visit and compared back to the pre-dosing Screening B image (Baseline for treatment subjects) of the selected quadrant.	For subjects who elected to receive EN3835 treatment, the S-GAIS assessment will be done on Day 71 of the treatment course and then at month 12 or the final study visit and compared back to the pre-dosing Screening B image (Baseline for treatment subjects) of the selected quadrant.
13.1.1.6 Hexsel Cellulite Severity Scale	For subjects in the observation-only group, the Hexsel CSS will be done at month 3 and every 3 months thereafter and at the month 12 or the end of study visit. For subjects who elected to have EN3835 treatments, the Hexsel CSS will be done at 3-month intervals during the observation phase until the study drug blind is broken in study EN3835-201. The Hexsel CSS assessment will be done at Screening B visit and on day 71 of the treatment course and at month 12 or end of study visit. For the subjects electing treatment (re-treatment or re-dosing) with EN3835 the Investigator or qualified designee will use the Hexsel CSS to assess the severity of EFP in all quadrants at Screening B and the selected quadrant on day 71 of the course of treatment.	For subjects in the observation-only group, the Hexsel CSS will be done at the month 12 or the end of study visit. For the subjects electing treatment (re-treatment or re-dosing) with EN3835 the Investigator or qualified designee will independently use the Hexsel CSS to assess the severity of EFP in all quadrants at Screening B visit and the selected quadrant on Day 71 of the course of treatment and at month 12 or end of study visit.

Section	Original Text	Revised Text
14.6.1 Adverse Events of Special Interest	There are no AEs of special interest anticipated in this study. AEs such as bruising, ecchymosis, hematomas, and contusions that occur remote to the site of drug administration will be recorded as an AE or SAE as appropriate (see section 14.1.1, Adverse Events or section 14.1.2, Serious Adverse Events).	[redacted]
14.7 Clinical Laboratory and Immunogenicity Determinations	Urine pregnancy test kits will be supplied by the Sponsor.	DELETED TEXT
14.7.1 Anti-AUX-I and Anti-AUX-II Antibodies	Serum samples will be collected and may be tested for binding and neutralizing anti-AUX-I and anti-AUX-II antibodies at visit 1 through visit 4. Additionally, if a subject consents to treatment in the open-label study, serum samples for antibody testing will be collected before injection at treatment visits 1, 2, 3, and 4 of the open-label treatment period. A subset of subject samples will have neutralizing antibodies tested from day 1 and day 71 visits; additional samples may be analyzed if results or clinical signs warrant testing.	Serum samples will be collected and may be tested for binding and neutralizing anti-AUX-I and anti-AUX-II antibodies at visit 1 and visit 4. Additionally, if a subject consents to treatment in the open-label study, serum samples for antibody testing will be collected before injection at treatment visit 1 and at end of treatment/ early termination visit 4 of the open-label treatment period. A subset of subject samples may have neutralizing antibodies tested from Day 1 and Day 71 visits; additional samples may be analyzed if results or clinical signs warrant testing.
14.8 Vital Signs	These parameters include pulse rate, respiratory rate, systolic and diastolic blood pressure, and body weight.	These parameters include pulse rate, respiratory rate, systolic and diastolic blood pressure, and body temperature.
17.2 Subject Cohorts and Subject Populations	All efficacy and safety analyses will be done within the classified cohort. Durability of treatment effects defined as time period from injection to return to baseline cellulite severity ratings in a EN3835-treated quadrant will be determined for all subjects that were treated with EN3835 in either this study or study EN3835-201.	All efficacy and safety analyses will be done within the classified cohort. Durability of treatment effects defined as the time from onset of change from baseline of PR-PCSS and CR-PCSS in the quadrant treated in study EN3835-201 until the time that the treated quadrant return to baseline cellulite severity ratings of PR-PCSS and CR-PCSS in an EN3835-treated quadrant will be determined for all subjects that were treated with EN3835 in either this study or study EN3835-201.
17.6.1 Prior, Concomitant, and Follow-up Medication	The version used in this study will be stated in the Data Management Plan. Prior medication will be defined as any medication with a start date prior to the day 1 date and are collected at the screening visit and upon admission to the clinic on day −1.	The version used in this study will be stated in the Data Management Plan. Prior medication will be defined as any medication with a start date prior to the Day 1 date.

Section	Original Text	Revised Text
24.4 Use of Investigational Materials	The Investigator is responsible for monitoring subject's use of the study drug to ensure compliance with the protocol. All study supplies shall be returned to Endo Pharmaceuticals Inc. or its designee (this may include empty packaging such as bottles and blister cards). It is the Investigator's responsibility to ensure that subjects return their medication.	The Investigator is responsible for monitoring use of the study drug to ensure compliance with the protocol. All study supplies shall be returned to Endo Pharmaceuticals Inc. or its designee.
18.2 Study Drug Packaging and Labeling	Sterile vials of lyophilized EN3835 (formerly 4500) and sterile diluent will be provided to the Investigator by Endo. Each kit will contain 1 vial each of EN3835 and sterile diluent.	Sterile vials of lyophilized EN3835 and sterile diluent will be provided to the Investigator by Endo. Each kit will contain 2 vials each of EN3835 and sterile diluent.
18.4 Study Drug Preparation	Designated study personnel will visually inspect the study drug vial to determine the integrity and acceptability of the lyophilized drug product for reconstitution.	Designated study personnel will visually inspect the study drug vials to determine the integrity and acceptability of the lyophilized drug product for reconstitution.
24.6 Subject Confidentiality	All subject records submitted to Endo Pharmaceuticals Inc. or its designee will be identified only by initials and code number.	All subject records submitted to Endo Pharmaceuticals Inc. or its designee will be identified only by initials and subject identification number.
24.6 Subject Confidentiality	The Investigator will adhere to all privacy laws to which she is subject.	The Investigator will adhere to all privacy laws to which he/she is subject.

3. SPONSOR CONTACT INFORMATION

Table 1: Sponsor Contact Information

Role in Study	Name	Telephone and Email Address
Clinical Research Scientist	[redacted]	[redacted]
Associate Director, Clinical Operations	[redacted]	[redacted]
Medical Monitor	[redacted]	[redacted]
SAE Reporting Pathway	Not Applicable	[redacted]

A list of other key study personnel and vendors will be provided upon request separately for your reference.

4. SYNOPSIS

Name of Sponsor/Company: Endo Pharmaceuticals Inc.

Name of Investigational Product: EN3835

Name of Active Ingredient: Collagenase clostridium histolyticum

Title of Study: A Phase 2, Open-Label Extension Study of EN3835 in the Treatment of Edematous Fibrosclerotic Panniculopathy

Lead Principal Investigator: To be determined

Study period:	**Phase of development:** Phase 2
Estimated date first subject enrolled: Oct-2016 Estimated date last subject completed: Sep-2017	

Objectives:

Primary:

- The primary objective of this study is to assess long-term safety of EN3835 0.84 mg at scheduled intervals over 1 year (12 months) in all subjects with edematous fibrosclerotic panniculopathy (EFP) who elect to enroll in this open-label trial regardless of their decision to receive treatment (re-treatment or re-dosing) of open-label EN3835 or opt to receive no treatment.

Secondary:

- To evaluate safety and immunogenicity of re-treating or re-dosing a subject that had previously received treatment with EN3835
- To evaluate the durability of response to EN3835 in EFP severity over the 12-month post initial dosing of EN3835 in subjects previously receiving active treatment in study EN3835-201 using the Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS) and the Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS)
- To evaluate long-term response to EN3835 in assessments of EFP including subject satisfaction, Investigator Global Aesthetic Improvement Scale (I-GAIS), and Subject Global Aesthetic Improvement Scale (S-GAIS)
- To assess cellulite severity assessments in quadrants treated in this study with EN3835.
- To evaluate immunogenicity after exposure to EN3835

Study Design: This study is a Phase 2 open-label study for the safety and efficacy of EN3835 in the treatment of EFP. To be eligible, a subject must have participated and completed the previous cellulite study EN3835-201. Subjects will be screened for study eligibility within 14 days prior to enrolling in this study (EN3835-202). Subjects will be assessed for safety and cellulite severity assessments approximately every 3 months for a maximum of 1 year from their first exposure to EN3835. Subjects with at least 1 quadrant with moderate or severe level of cellulite will be eligible for treatment with EN3835 after unblinding of study EN3835-201; a quadrant that was treated with EN3835 in the previous study EN3835-201 will only be eligible for retreatment if the cellulite severity in that quadrant is rated at levels of cellulite severity at baseline in study EN3835-201.

A treatment course will consist of 3 treatment sessions separated by 21 days. Treatment will be allowed in eligible subjects up to a maximum of 2 treatment courses including the treatment course in study EN3835-201 if subject was treated with EN3835. Each treatment session will consist of up to 12 injections (0.07 mg/0.3 mL per injection) of EN3835 for a dose of 0.84 mg and volume of 3.6 mL. Only a quadrant with moderate (rating of 3) or severe (rating 4) level of severity as assessed by the

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subject and investigator using the PR-PCSS and the CR-PCSS, respectively, will be eligible for treatment; if more than 1 eligible quadrant exists, the quadrant selected will be at the discretion of the subject. Treatments will be administered on Days 1, 22, and 43; subjects will be assessed for safety on Days 1, 22, 43, and 71 and for cellulite severity assessments at Screening visit and on Days 22, 43, and 71. After Day 71, they will be observed every 3 months from their first exposure to EN3835 up to a maximum of 1 year. The study will terminate when at least 100 subjects have been assessed at 12 months after the first exposure to EN3835.

Number of subjects (planned): 333

Study center(s): 16 sites in the United States

Diagnosis and inclusion/exclusion criteria:

Qualification for the Open-Label Observation Phase of the Study

Inclusion criteria for observation:

1. Voluntarily sign and date an informed consent agreement
2. Have participated in and completed the double-blind study EN3835-201
3. Be willing to apply sunscreen to any treated quadrant before each exposure to the sun while participating in the study (ie, screening through end of study)

Exclusion criteria for observation:

None

Qualification for the Open-Label Treatment Phase of the Study

Inclusion criteria for treatment:

1. Voluntarily sign and date an informed consent agreement
2. Have participated in and completed the double-blind study EN3835-201
3. Be a female ≥18 years of age
4. At Screening B visit, have at least 1 quadrant with:
   a. a score of 3 or 4 (moderate or severe) as reported by the subject (PR-PCSS), and
   b. a score of 3 or 4 (moderate or severe) as reported by the Investigator (CR-PCSS), and
   c. a Hexsel Cellulite Severity Scale (CSS) score no greater than 13
5. Be willing to apply sunscreen to the selected treatment quadrant before each exposure to the sun while participating in the study (ie, Screening B through end of study)
6. Be judged to be in good health, based upon the results of a medical history, physical examination, and laboratory profile at Screening B
7. Have a negative urine pregnancy test at Screening B and before injection of study drug and be using an 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
8. Be willing and able to cooperate with the requirements of the study
9. Be able to read, complete and understand the patient-reported outcomes rating instruments in English

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***Exclusion criteria for treatment**:*

1. Has used any of the following for the treatment of EFP on the legs or buttock within the timelines identified below or intends to use any of the following at any time during the course of the study:
   - Liposuction on the side of the body selected for treatment during the 12-month period before injection of study drug
   - Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; or surgery (including subcision and/or powered subcision) within the selected treatment quadrant during the 12-month period before injection of study drug
   - Endermologie or similar treatments within the selected treatment quadrant during the 6-month period before injection of study drug
   - Massage therapy within the selected treatment quadrant during the 3-month period before injection of study drug
   - Creams (eg, Celluvera™, TriLastin®) to prevent or mitigate EFP within the selected treatment quadrant during the 2-week period before injection of study drug
2. Is presently nursing a baby or providing breast milk for a baby
3. Intends to become pregnant during the study
4. Has received an investigational drug or treatment within 30 days before injection of study drug
5. Has a known systemic allergy to collagenase or any other excipient of study drug
6. Is currently receiving or plans to receive anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication (except for ≤150 mg aspirin daily) within 7 days before injection of study drug
7. Has a known recent history of stroke, bleeding, or other medical condition, which in the investigator's opinion would make the subject unsuitable for enrollment in this phase of the study
8. Presence of any clinically relevant conditions, that in the opinion of the Investigator would interfere with completing the study including, but not limited to, visual problems, hearing problems, cognitive impairment or acute mental illness

Investigational product, dosage and mode of administration: EN3835, 0.84 mg, subcutaneous. A dose of 0.84 mg of EN3835 will be administered as up to 12 subcutaneous injections (0.3-mL injection administered as three 0.1-mL aliquots per injection, up to 12 injections per treatment session) for a maximum volume of 3.6 mL per treatment session. A treatment course will consist of 3 treatment sessions at 21 days intervals, ie, treatments on Days 1, 22, and 43 of each treatment course.

For the observational periods of this study, subjects will be assessed for safety and cellulite severity assessments at approximately 3-month intervals for a maximum of 1 year following their first exposure to EN3835.

Duration of study: Twelve (12) months from first exposure to EN3835 in study EN3835-201 or study EN3835-202

Screening Phase: Up to 14 days

Observational Phase: Subjects will be assessed at visits that occur approximately every 3 months for a maximum of 1 year after the first exposure to EN3835.

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Follow-up: Subjects will be assessed at visits that occur approximately every 3 months for a maximum of 1 year after the first exposure to EN3835. For subjects treated with EN3835 in this study, subjects will be observed at treatment visits (Days 1, 22, and 43) and Day 71 after first injection. After Day 71, they will be observed every 3 months from their first exposure to EN3835 up to a maximum of 1 year.

Reference therapy, dosage and mode of administration: Not applicable

Criteria for evaluation:

Efficacy:

- PR-PCSS while viewing digital images of the selected quadrant: 5-point scale ranging from 0 (no cellulite) to 4 (severe cellulite) (approximately every 3 months after initial injection [either an injection in previous study EN3835-201 or after an injection in this study]). If treatment is administered in this study, PR-PCSS will be obtained at Screening B (Baseline), Days 22, 43, and 71 after initial treatment within this study.
- Investigator using the CR-PCSS by live assessment: 5-point scale ranging from 0 (no cellulite) to 4 (severe cellulite) (every 3 months after initial injection [either an injection in previous study EN3835-201 or after an injection in this study]). If treatment is administered in this study, CR-PCSS will be obtained at Screening B (Baseline), Days 22, 43, and 71 after initial treatment within this study.
- Investigator rating of cellulite severity using the total score from the Hexsel CSS: scores can range from 0 (no cellulite) to 15 (extremely severe cellulite) (Day 360). If treatment is administered in this study, Hexsel CSS will be obtained in this study at Screening B (Baseline) and Day 71 after initial treatment within this study.
- I-GAIS: 7-point scale ranging from 3 (very much improved) to −3 (very much worse) (Day 71)
- S-GAIS: 7-point scale ranging from 3 (very much improved) to −3 (very much worse) (Day 71)
- Subject satisfaction with cellulite treatment assessment: 5-point scale ranging from 2 (very satisfied) to −2 (very dissatisfied) (Day 71)

Safety:

Safety will be assessed throughout the study through the recording of:

- Adverse events (AEs)
- Vital signs
- Clinical laboratory tests
- Immunogenicity assessment (ie, assessed through the determination of binding and neutralizing anti-AUX-I and anti-AUX-II antibody levels).

In addition, for subjects treated with EN3835 in this study, injection site reactions/local tolerability in treated quadrant (through subject and Investigator reporting) will be assessed.

Statistical methods:

Sample Size Consideration:

The number of subjects (approximately 333) is intended to obtain additional subjects for adequate long-term safety data at the selected dose.

Analysis Populations:

Observational population: The Observational population is defined as all subjects treated with EN3835 in study EN3835-201 who do not receive any treatment in the current study

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Safety population: The Safety population is defined as all enrolled subjects who received at least 1 injection of EN3835 in this study or in study EN38335-201.

Intent-to-Treat (ITT) population: The ITT population is defined as all enrolled subjects in this study.

Modified Intent-to-Treat (mITT) population: The mITT population is defined as ITT subjects who received at least 1 injection of EN3835 in this study with a baseline and 1 post-injection evaluation of both the CR-PCSS and PR-PCSS. All efficacy (cellulite assessments) analyses will be completed on this population.

Per-Protocol population: The Per-Protocol population is defined as those subjects in the Safety population who have no major protocol deviations.

Efficacy Evaluations:

The primary cellulite severity assessment endpoint, the proportion of composite responders with improvement of 2 or better on each scale (CR-PCSS and PR-PCSS) at Day 71, will be summarized as percentages and analyzed using a Cochran-Mantel-Haenszel test that compares the 2 treatment groups and adjusts for Investigator. The ITT population will be evaluated for the primary endpoint with any subjects not having a post-injection evaluation of either CR-PCSS or PR-PCSS classified as a non-responder.

All secondary endpoints, except the Hexsel CSS total score, will be summarized as percentages. The dichotomous secondary endpoints (ie, responders endpoints) will be analyzed using a Cochran-Mantel-Haenszel test adjusted for investigator. Multiple-response endpoints (ie, scales) will be analyzed using the Mann-Whitney test. Change in Hexsel CSS total score will be summarized with descriptive statistics for continuous variable and will be analyzed using analysis of variance (ANOVA).

Safety Analysis:

The following variables are safety endpoints:

- AEs: Mapped to preferred term using the Medical Dictionary for Regulatory Activities (MedDRA)
- Vital signs
- Clinical laboratory tests

AEs will be summarized by proportion of subjects reporting each event. Descriptive statistics will be presented for actual and change from baseline at each visit for vital signs and for each clinical laboratory test parameter.

Immunogenicity: Anti-AUX-I and anti-AUX-II antibody levels will be summarized using descriptive statistics for the actual value at the visit.

5. SCHEDULE OF EVENTS

NOTE: Observation visits (Table 2) in the open-label extension study begin after completion of double-blind study (Day 71). Treatment sessions (Table 3), if elected, will begin after study drug blind is broken in study EN3835-201while observation visits continue concurrently.

Table 2: Observation Assessments

Procedures	Screening A[a] (≥Day 71 Visit of Double-blind Study)	Visit 1 Day 90[b] (±7 days)	Visit 2 Day 180[b] (±7 days)	Visit 3 Day 270[b] (±7 days)	Visit 4 End of Study/ Early Termination Day 360[b] (±7 days)
Informed Consent	X				
Inclusion/Exclusion	X				
Digital photography		X[c]	X[c]	X[c]	X[c]
Body weight		X	X	X	X
Vital signs		X	X	X	X
Collection of samples:					
• Clinical laboratory					X
• Anti-AUX-I/anti-AUX-II antibody level					X
Subject cellulite assessments:					
• Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS)		X[d,e]	X[d,e]	X[d,e]	X[d,e]
• Subject Global Aesthetic Improvement (S-GAIS)					X[d,e]
• Subject satisfaction with cellulite treatment assessment					X[d,e]
Investigator cellulite assessments:					
• Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)		X[e]	X[e]	X[e]	X[e]
• Hexsel Cellulite Severity Scale (CSS)					X[e]
• Investigator Global Aesthetic Improvement (I-GAIS)					X[e]
Injection site reactions/local tolerability in assigned quadrant from EN3835-201 study		X	X	X	X
Adverse events	Monitored Throughout Study				

[a] Informed consent for open-label observation assessments and optional treatment election.
[b] Three (3)-month evaluation periods begin 90 days after Day 1 of the double-blind study (EN3835-201) (ie, within 20 days ±4 days of completion of double-blind study).
[c] Only the treated quadrant(s) is photographed. For subjects participating in observation-only visits, the quadrant treated in the double-blind study (EN3835-201) is photographed; for subjects with open-label treatment (treated with EN3835 in study EN3835-202), the treated quadrant is photographed.
[d] Assessment made via viewing digital image photograph.
[e] Assessment of treated quadrant(s) only.
NOTE: Subject cellulite assessments must be completed before the Investigator cellulite assessments are conducted at each visit.

Table 3: Treatment Session Assessments

Procedures	Screening B[a] (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/ Early Termination Day 71 (+5 days)[b]
Informed Consent	X				
Inclusion/Exclusion	X				
Digital photography	X[c]	X[c,d]	X[c,d]	X[c,d]	X[c]
Medical history/EFP history including previous treatments	X[k,m]				
Prior/Concomitant Medications/Procedures	X[k,m]	X[m]	X	X	X
Physical examination:	X				
• Body weight	X[m]		X[e]	X[e]	X
• Height	X[m]				
Vital signs	X	X[f]	X[f]	X[f]	X
12-lead ECG	X[l]				
Collection of samples:					
• Clinical laboratory	X[m]				X
• Anti-AUX-I/anti-AUX-II antibody level		X[e,m]			X
• Urine pregnancy testing	X	X[e]	X[e]	X[e]	
Subject cellulite assessments:					
• Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS)	X[g,h]		X[e,g,h]	X[e,g,h]	X[g,h]
• Subject Global Aesthetic Improvement (S-GAIS)					X[g,h]
• Subject satisfaction with cellulite treatment assessment					X[g,h]
Investigator cellulite assessments:					
• Selection of dimples to be treated within selected quadrant		X[e]	X[e]	X[e]	
• Marking the dimples to be treated within selected quadrant		X[e]	X[e]	X[e]	
• Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)	X[h]		X[e,h]	X[e,h]	X[h]
• Hexsel Cellulite Severity Scale (CSS)	X[h,i]				X[h]
• Investigator Global Aesthetic Improvement (I-GAIS)					X[h]
Confirm Eligibility	X	X[e]			
Select Quadrant	X[j]				
Study drug administration		X	X	X	
Injection site reactions/local tolerability in selected quadrant		X	X	X	X
Adverse events	Monitored Throughout Study				

[a] After the study drug blind is broken in study EN3835-201, eligible subjects may elect to receive EN3835 treatments.
[b] Upon completion of treatment, subject will be followed at 3-month intervals as in Table 2; if study terminates early, subject will be followed through Visit 4 (Day 71). If subject received placebo in the double-blind study (EN3835-201), she may be eligible for a total of 2 courses of treatment (a total of 6 treatment sessions) in this study.
[c] All 4 quadrants are photographed at screening; at other visits, the selected quadrant only is photographed.
[d] Before and after marking the dimples.
[e] Before injection.
[f] Up to 4 hours before injection; approximately 15 and 30 minutes after injection. Vital signs must be stable before the subject is discharged.
[g] Assessment made via photograph (if treatment session, use photograph taken before marking dimples).
[h] All 4 quadrants are assessed at the Screening B visit; at other visits, the selected quadrant only is assessed.
[i] Initial Hexsel CSS at screening must be ≤13 on selected quadrant (Appendix C).
[j] To qualify for treatment, the selected quadrant must have a score of 3 or 4 (moderate or severe) in both the CR-PCSS and PR-PCSS, and a Hexsel CSS score ≤13; to qualify a quadrant that had been previously treated with EN3835 in study EN3835-201, the quadrant must have CR-PCSS and PR-PCSS scores equal to or greater than study EN3835-201 baseline scores and a Hexsel CSS score ≤13.
[k] Medical history and prior medications will be based on EN3835-201 eCRF; only updates and concomitant medications need to be captured at Screening B visit.
[l] Do not conduct if Screening B visit date is within 12 months of obtaining an ECG during the double-blind study (EN3835-201).
[m] Do not conduct on subjects eligible and opting-in for a second course of treatment in the current study (EN3835-202) if Screening B visit or Day 1 visit for second treatment course is the same day as Day 71 of the first treatment course in this study or previous study EN3835-201.

ECG=Electrocardiogram; eCRF=Electronic case report form; EFP=Edematous fibrosclerotic panniculopathy; Tx=Treatment
NOTE: Subject cellulite assessments must be completed before the Investigator cellulite assessments are conducted at each visit.

6. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

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7. LIST OF ABBREVIATIONS

The following abbreviations and specialist terms are used in this study protocol.

Table 4: Abbreviations and Specialist Terms

Abbreviation	Definition
AE	Adverse event
Assigned quadrant	Assigned quadrant (ie, left or right buttock, or the left or right posterolateral thigh) that was suitable for treatment and was randomly assigned in the double-blind study (EN3835-201). To be suitable for treatment the quadrant must have an Investigator CR-PCSS and subject PR-PCSS score of 3 or 4 and a Hexsel CSS score of no greater than 13 at Screening B visit and at Day 1 visit.
AUX-I	Clostridial class I collagenase
AUX-II	Clostridial class II collagenase
CFR	Code of Federal Regulations
CRF	Case report form
CR-PCSS	Clinician-Reported Photonumeric Cellulite Severity Scale
CSS	Cellulite Severity Scale
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EFP	Edematous fibrosclerotic panniculopathy
FDA	Food and Drug Administration
GCP	Good clinical practice
HREC	Human research ethics committee
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
I-GAIS	Investigator Global Aesthetic Improvement Scale
IND	Investigational new drug
IRB	Institutional review board
ITT	Intent-to-treat
kDa	Kilodalton
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
PCS	Potentially clinically significant
PR-PCSS	Patient-Reported Photonumeric Cellulite Severity Scale
Qualified designee	Qualified by education and training to perform the study procedure (eg, sub-Investigator, nurse)
SAE	Serious adverse event

Table 4: Abbreviations and Specialist Terms (Continued)

Abbreviation	Definition
SAP	Statistical Analysis Plan
Selected quadrant	Quadrant (ie, left or right buttock, or the left or right posterolateral thigh) that is suitable for treatment and is selected by patient and investigator for treatment. To be suitable for treatment the quadrant must have an Investigator CR-PCSS and subject PR-PCSS score of at least 3 or 4 and a Hexsel CSS score of no greater than 13 at Screening B visit.
S-GAIS	Subject Global Aesthetic Improvement Scale
TEAE	Treatment-emergent adverse event; adverse events that occur on or after the first injection of study drug

8. INTRODUCTION

8.1. Edematous Fibrosclerotic Panniculopathy

Edematous fibrosclerotic panniculopathy (EFP), commonly known as cellulite, has been defined as a local metabolic disorder of subcutaneous tissues that results in an alteration of skin topography.(1) The condition manifests as dimpled skin, described as an orange-peel, cottage cheese, or mattress texture, particularly in the gluteal-femoral region.(2,3) EFP is caused by herniation of subcutaneous fat lobules through the dermohypodermal junction. This creates an uneven surface with dimpling.(1) EFP is a medical condition resulting in a potentially cosmetically unacceptable alteration of the skin, and affects an estimated 85% to 98% of postpubertal women.(1,3)

The pathophysiology of EFP is not completely understood, but there are 3 main theories: edema resulting from excessive hydrophilia of the intercellular matrix, alteration of the regional microcirculation, and different anatomical conformation of collagenous subcutaneous tissues in women versus men.(4)

It is known that EFP is different from generalized obesity. In generalized obesity, adipocytes undergo hypertrophy and hyperplasia that are not limited to the pelvis, thighs, and abdomen.(1) In areas of EFP, adipocytes have physiologic and biochemical properties that differ from adipose tissue located elsewhere. Large, metabolically-stable adipocytes characterize EFP-prone areas; thus, the responsiveness to catecholamine-induced lipolysis is less in EFP tissues compared to visceral fat, which has the greatest responsiveness.(1)

Subcutaneous fat lobes are separated from one another by thin, usually rigid strands of collagenous connective tissues, which cross the fatty layers and connect the dermis to the underlying fascia. These septa stabilize the subcutis and divide the fat. In EFP, shortening of the collagen septa due to fibrosis provokes retraction at the insertion points of the trabeculae, causing the depressions that characterize EFP.(2) There are a higher percentage of thinner, perpendicular hypodermal septa in women with EFP than in men.(1) Weight gain makes EFP more noticeable, but it may be present even in thin subjects. Genetics may also play a role since EFP tends to run in families.

8.2. Current Edematous Fibrosclerotic Panniculopathy Treatments

There are therapies that have been utilized in an attempt to treat cellulite. Despite multiple therapeutic modalities, there is little scientific evidence that any of these treatments are beneficial. In fact, much of the evidence is anecdotal, subjective, or based only on patient self-assessment.(5) Some of the historical treatments for EFP have included:

- Weight loss: Weight loss generally decreases the severity of EFP but may only have a variable effect on EFP grades.(6)
- Pharmacological agents (eg, xanthines, retinoids, lactic acid, and herbals): Although there are numerous topical treatments that are available over the counter, there are no well-designed or large-scale studies demonstrating the effectiveness of any of these

therapies.(5) Additionally, ingredients in some of the topical treatments are unknown and may pose an increased risk for adverse effects.(5)

- Massage: Endermologie or lipomassage kneads the skin between rollers. This type of vigorous massage is posited to increase blood flow and reduce excess fluid in EFP prone areas. In a 12-week, randomized, controlled study of 52 women that examined the effectiveness of either endermologie or aminophylline versus a combination of both, there was no statistical difference in the thigh measurement between subjects.(7)
- Liposuction: Liposuction can reshape the body, but it does not typically correct cellulite as it does not interrupt collagen septae in a directed fashion. Additionally, liposuction is not a recommended treatment for cellulite given the potential for poor cosmetic outcome.(5,6)
- Mesotherapy: Mesotherapy involves injecting solutions containing various substances, eg, methylxanthines, to dissolve subcutaneous fat; however, this type of therapy often results in unwanted side effects, including infection, urticarial reactions, and bumpy or uneven skin contours.(6) To date, there are no regulatory approved mesotherapy mixtures for the treatment of EFP.
- Radiofrequency: Radiofrequency systems may temporarily improve the appearance of EFP after a series of treatments; but long-term efficacy has not been demonstrated.(6)
- Subcision: Subcision is an invasive surgical technique that severs the septa holding fat lobules that cause the skin dimpling associated with EFP. In a study conducted by Hexsel and Mazzuco, 232 subjects had subcision for the treatment of EFP.(8) Although 78% of subjects were satisfied after 1 treatment, there were no objective criteria by which to assess improvement, thereby limiting the value of this study. Additionally, side effects reported in this study included pain, bruising for 3 to 6 months, hyperpigmentation for 2 to 10 months, and skin puckering.(5,6) These effects are most likely due to the trauma from shearing the septa with a large gauge needle (eg, 16 or 18 gauge) or other cutting devices.
- Powered subcision: Powered subcision is a surgical technique utilizing a powered needle apparatus to sever the septa holding fat lobules that cause skin dimpling associated with EFP. The Cellfina® powered subcision device was recently approved by Food and Drug Administration (FDA; 2015) for the treatment of cellulite.
- Laser: Intense pulsed light has been investigated for the treatment of cellulite. Triactive® is an FDA-approved low-fluorescence 810-nm light source combined with a 915-nm laser. In a study of 16 female subjects who underwent 12 treatments with the Triactive, 21% had improvement (based on 5 blinded Investigators' analysis of photographs with respect to appearance of cellulite, skin tone, and texture) of their cellulite.(9) The CelluLaze™ system was used to treat cellulite on the thighs of 10 healthy women.(10) In this Investigator-initiated study, subjects received a single treatment with a 1440-nm laser. During the CelluLaze procedure, which is performed under a local tumescent and general anesthetic, the physician inserts a small cannula through the skin and the device technology directs controlled, laser thermal energy to

the treatment zones. The laser is designed to diminish the lumpy pockets of fat by melting the hypodermal fat; release the areas of skin depression through thermal subcision of the septal tissue; and increase the elasticity and thickness of the skin by melting the fat in the dermal invaginations. Subjective physician and subject evaluations indicated improvement in the appearance of cellulite and high patient satisfaction that persisted for a year. For both the Triactive and CelluLaze studies, there were no control groups and significance was not tested.

There remains an unmet medical need for safe and effective nonsurgical therapies to improve the esthetic outcome in women with cellulite. To effectively treat cellulite, a therapeutic approach may require disruption of the dermal septa, which are composed of collagen and cause the skin dimpling which is bothersome to many women.

8.3. EN3835 (Collagenase Clostridium Histolyticum)

Endo Pharmaceuticals Inc. (Endo) is developing EN3835 for the treatment of EFP. Because EN3835 is a proteinase that can hydrolyze the triple-helical region of collagen under physiological conditions, EN3835 has the potential to be effective in lysing subdermal collagen, such as those observed in the dermal septa, which are the underlying cause of the skin dimpling in women with EFP. EN3835 targets the collagenase structural matrix (eg, dermal septa) at the site of injection and does not require systemic exposure to be effective.

EN3835 is a parenteral lyophilized product comprised of 2 collagenases in an approximate 1:1 mass ratio, Collagenase I (AUX-I, Clostridial class I collagenase) and Collagenase II (AUX-II; Clostridial class II collagenase). These collagenases are isolated and purified from the fermentation of *Clostridium histolyticum*. Collagenase AUX-I is a single polypeptide chain containing approximately 1,000 amino acids of known sequence and with a molecular weight of 114 kDa. Collagenase AUX-II is also approximately 1,000 amino acids long and has a molecular weight of 113 kDa. These 2 collagenases are not immunologically cross-reactive and have different specificities, such that together they become synergistic, providing a very broad hydrolyzing reactivity toward collagen. Clostridial collagenases are proteinases that can hydrolyze the triple-helical region of collagen under physiological conditions.

EN3835 is currently approved for: 1) the treatment of adults with Dupuytren's contracture with a palpable cord and, 2) for the treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy.

8.3.1. Studies with EN3835 for the Treatment of Edematous Fibrosclerotic Panniculopathy

The studies summarized in this section are described in more detail in the Investigator's Brochure (IB).

8.3.1.1. Investigator-Initiated Proof-of-Concept Study

In an Investigator-initiated pilot study, 10 female subjects received EN3835 in the treatment of cellulite.(11) A 10×10-cm oval area was outlined on the posterolateral thigh and 0.58 mg EN3835 was injected using a template as 5 concurrent subcutaneous injections of 0.116 mg per injection. Subjects were followed up to 180 days after injection for reduction of the cellulite appearance in the injected area. At 1 month post injection, the area of cellulite (as measured from

photographs) was reduced 89% from baseline. Patient satisfaction score was 1.75 at month 6 (1=completely satisfied, 4=not satisfied). Side effects included the local events of injection area soreness, ecchymosis, and mild edema; these resolved within a mean of 18 days. The results from this study suggest that the collagen septa of EFP may be an appropriate substrate for lysis with injectable collagenase, and that treatment with collagenase appears to be tolerable and possibly effective. However, due to the paucity of the data, no conclusions could be drawn regarding dose, frequency, and injection technique.

8.3.1.2. Endo-Sponsored Phase 1b Dose-Escalation Study AUX-CC-830

A dose-ranging Phase 1b dose escalation study (AUX-CC-830) used a template arrangement of injections as was used in the Investigator-initiated pilot study but injected a matrix of doses, concentrations and injectate volumes to select doses for further development. This Phase 1b study showed efficacy results suggesting that collagenase clostridium histolyticum (CCH) may be effective in the treatment of EFP based on global aesthetic improvement at Day 90 with ratings of "improved" by 43.4% of Investigators and 52.5% of subjects. The majority of subjects (71.7%) were "quite satisfied" or "very satisfied" with treatment on Day 90. Adverse events(AEs) were local injection site events (bruising, pain, erythema, and edema) were mild or moderate and resolved within a period of 3 weeks.

8.3.1.3. Endo-Sponsored Phase 2a Dose-Ranging Study AUX-CC-831

The Phase 2a study (AUX-CC-831) was a double-blind, placebo-controlled, dose-ranging study of 150 women randomized to 0.06, 0.48, or 0.84 mg of CCH; or placebo in a 5:5:5:3 ratio. Each subject could receive up to 3 treatment sessions of study drug separated by approximately 21 days. Efficacy in this study was evaluated based on Investigator Global Aesthetic Improvement Scale (GAIS-I) and Subject Global Aesthetic Improvement Scale (GAIS-S) along with other measures of treatment efficacy. Improvements were observed in cellulite appearance based on the statistically significant changes in the appearance of cellulite based on both the GAIS-I and GAIS-S scores for the high and mid doses compared to placebo ($p<0.05$). The majority of the patients were either satisfied or very satisfied with the results of their cellulite treatment with the mid and high doses compared to placebo ($p<0.05$). Similar to the AEs reported in subjects in the previous study (AUX-CC-830) and subjects who received EN3835 for Dupuytren's contracture and Peyronie's disease, the majority of AEs occurred at the site of injection and resolved before the next scheduled treatment session.

8.3.1.4. Endo-Sponsored Phase 2b Study EN3835-201

Currently there is an ongoing Phase 2b study (EN3835-201) which is a double-blind, placebo-controlled study of 350 adult women randomized to EN3835 0.84 mg or placebo in a 1:1 ratio. Each subject can receive up to 3 treatment sessions of study drug separated by approximately 21 days; last visit is Day 71. Efficacy is being evaluated using a Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS), a Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS), the Hexsel Cellulite Severity Scale (CSS), Investigator Global Aesthetic Improvement Scale (I-GAIS), Subject Global Aesthetic Improvement Scale (S-GAIS), and a subject satisfaction assessment. Subjects that complete study EN3835-201 will be offered the option of participating in study EN3835-202.

8.4. Summary of Nonclinical Studies

Nonclinical studies necessary to support clinical studies have been performed and are summarized in the IB. Nonclinical studies in the following areas were performed: toxicology, reprotoxicity, genotoxicity, and carcinogenicity.

8.5. Summary of Known Risks and Benefits

A summary of safety risks is provided in the IB. The following events have been commonly observed in prior studies: injection site AEs such as bruising, edema, erythema and pain.

There are previously generated potential clinical benefits associated with EN3835 in treating EFP, however, such potential benefits need further clinical evaluation. It is hoped that data from this clinical study will demonstrate a measurable sustained or durable clinical benefit of EN3835 in EFP as well as longer term safety.

8.6. Rationale

This study will allow an evaluation of longer term safety (over 12 months) following EN3835 treatment of subjects with EFP. Additionally, although uncontrolled, an assessment of cellulite assessments (efficacy) of EN3835 in the treatment of quadrants with moderate or severe cellulite will be conducted in subjects treated with placebo or EN3835 in the previous double-blind study (EN3835-201). The safety of re-dosing either in a previously treated quadrant (termed *re-treatment*) or in a naive quadrant (termed *re-dosing*) in subjects that previously received EN3835 treatment in study EN3835-201 will be assessed. Finally, the durability of improvement will be evaluated in enrolled subjects following EN3835 treatment in the double-blind study (EN3835-201) as well as those being treated with EN3835 in this open-label study (EN3835-202).

9. OBJECTIVES

9.1. Primary Objective

The primary objective of this study is to assess long-term safety of EN3835 0.84 mg at scheduled intervals over 1 year (12 months) in all subjects with EFP who elect to enroll in this open-label trial regardless of their decision to receive treatment (re-treatment or re-dosing) of open-label EN3835 or opt to receive no treatment.

9.2. Secondary Objectives

- To assess safety and immunogenicity of re-treating or re-dosing a subject that had previously received treatment with EN3835
- To evaluate the durability of response to EN3835 in EFP severity over the 12-month post initial dosing of EN3835 in subjects previously receiving active-treatment in study EN3835-201 using the PR-PCSS and the CR-PCSS
- To evaluate long-term response to EN3835 in assessments of EFP including subject satisfaction, I-GAIS, and S-GAIS
- To assess cellulite severity assessments in quadrants treated in this study with EN3835
- To evaluate immunogenicity after exposure to EN3835

9.3. Exploratory Objectives

There are no exploratory objectives for this open-label extension study.

10. INVESTIGATIONAL PLAN

10.1. Study Design

This open-label extension study will be performed at multiple centers currently participating in the double-blind, placebo-controlled, parent trial (EN3835-201) in the United States. The open-label extension study will enroll up to 350 subjects. The study is planned to end when at least 100 subjects have 12 months after exposure ie 12 months after first treatment in study EN3835-201 or study EN3835-202. Subjects who completed the entire double-blind study and sign an informed consent will be eligible to enter this open-label extension.

After the Sponsor has broken the EN3835-201 study drug blind, subjects enrolled in the open-label study will have the following options:

- To have no EN3835 treatments in study EN3835-202
- If received EN3835 in study EN3835-201, may elect to have a qualifying quadrant other than the one treated in study EN3835-201 treated with EN3835 (termed *re-dosing*)
- If received EN3835 in study EN3835-201 and the cellulite severity scores of the treated quadrant have returned to or are greater than EN3835-201 baseline scores, may elect to have the previously treated quadrant retreated with EN3835 (termed *re-treatment*)
- If received placebo in study EN3835-201, may elect to have a qualifying quadrant treated with EN3835; also may elect to have a second qualifying quadrant treated with EN3835 after completing the treatment course

Subjects enrolled in study EN3835-202 who elect to receive EN3835 treatment (either re-treatment, re-dosing, or a first treatment) must meet specific inclusion and exclusion criteria for eligibility during re-screening (Screening B) prior to EN3835 dosing.

Following completion of safety and cellulite assessments at Day 71 of the double-blind study (EN3835-201), subjects will be asked if they wish to continue in the open-label extension to the double-blind study (Screening A). At the time of entry into the open-label study, subjects and Investigators will remain blinded to study drug. Until the EN3835-201 study drug blind is broken by the Sponsor, subjects will undergo observation-only visits at 3-month intervals ± 7 days (relative to the initial dose in the double-blind study) where both safety and cellulite severity assessments of the treated quadrant will be made.

Following the study drug blind being broken and communicated to centers, eligible subjects may elect to receive EN3835 treatment. Subjects electing not to receive further EN3835 treatments (observation-only subjects) will continue to be followed for safety and cellulite severity assessments at 3-month intervals through month 12. Up to 14 days prior to initiating treatment injections of EN3835 on open-label treatment visit Day 1, subjects will undergo a screening evaluation (Screening B) to determine if they meet specified inclusion and exclusion criteria and to determine the quadrants, if any, that qualify for treatment.

During Screening B, photographs will be taken of each of the subject's 4 quadrants (left buttock, right buttock, left posterolateral thigh, and right posterolateral thigh). Subjects will again receive instructions for use of the PR-PCSS and will subsequently use the scale to rate the severity of their cellulite in each of the 4 quadrants by comparing digital images of each of their quadrants displayed on standardized computer monitors with the PR-PCSS instrument. This independent self-assessment will take place in a private setting to minimize any potential bias from site personnel. The Investigator will then assess the subject's 4 quadrants live in real-time using the CR-PCSS. The Investigator will rate the 4 quadrants using the Hexsel CSS as described in section 13.1.1.6.(12) Subjects must have at least 1 quadrant that meets the following criteria for inclusion into the treatment phase of the study:

1. PR-PCSS score of 3 or 4, and
2. CR-PCSS score of 3 or 4, and
3. Hexsel CSS score of no greater than 13.

After the independent assessments are completed separately by the subject and the Investigator, the Investigator will review his/her assessments and the subject's assessment to determine which quadrants, if any, are eligible. The eligible quadrant chosen to receive treatment in the open-label study EN3835-202 will be at the discretion of the subject. A quadrant may be chosen for re-treatment if it was the quadrant treated in study EN3835-201 or a new quadrant may be chosen for re-dosing**. NOTE: For subjects who received active drug in the assigned quadrant in the double-blind study, the quadrant must have cellulite severity at (or greater) than the EN3835-201 baseline scores of PR-PCSS and CR-PCSS to qualify for re-treatment.**

Previously placebo-treated subjects will have the option to receive a second course of EN3835 in the same or different qualifying quadrant after at least 28 days following the end of the first treatment course (ie treatment of second quadrant could begin on Day 71 after treating the first quadrant). The selected quadrant can be re-treated or re-dosed.

At each treatment session visit, Investigators will select the dimples within the chosen quadrant to be treated. Selection of dimples to be treated in the quadrant will be at the discretion of the Investigator. The selected EFP dimples in the selected quadrant must be well-defined and evident when the subject is standing in a consistent relaxed pose (without the use of any manipulation such as skin pinching or muscle contraction). The dimples selected to be treated will be circled with a surgical marker and injection site locations should be marked with a dot; if more than 1 injection per dimple is needed, the injection sites should be separated by approximately 2 cm. The selected quadrant will be photographed again after marking dimples. Subjects will be administered a maximum of EN3835 0.84 mg from a total of up to 12 injections. Up to 12 injections will be administered at each treatment session to treat the selected quadrant. Each of the injections will be administered as three 0.1-mL aliquots (total injection volume per injection is 0.3 mL; total injection volume per treatment session is 3.6 mL [12 injections × 0.3 mL], see table below).

Subjects will receive 3 treatment sessions (Day 1, Day 22, and Day 43) unless the chosen quadrant has no further treatable EFP dimples and the Investigator rates the quadrant a score of 0 on the CR-PCSS. The same dimples within a quadrant or different dimples within a quadrant may be treated at each session but injections must all be within the selected quadrant for all 3 sessions. Each treatment session will be separated by approximately 21 days.

Dose per Each Injection[a]	Injection Volume per Each Injection	Maximum Number of Injections per Each Treatment Session	Maximum Dose (mg) per Each Treatment Session	Maximum Injection Volume (mL) per Each Treatment Session	Maximum Cumulative EFP Dose
EN3835 0.07 mg N=333	0.3 mL	12 injections	0.84 mg (12 injections × 0.07 mg)	3.6 mL (12 injections × 0.3 mL)	2.52 mg (3 treatment sessions × 0.84 mg)

[a] Each injection of EN3835 is 0.3 mL administered as three 0.1-mL aliquots.

The complete Schedule of Events is provided in section 5 (Table 2 and Table 3) and summarized in section 12.

10.2. Selection of Doses

Maximum possible doses of EN3835 employed will be the same as that administered in the double-blind, placebo-controlled, parent study (EN3835-201).

10.3. Study Drug Administration

Study drug in the form of sterile vials of lyophilized EN3835 (formerly AA4500) and sterile diluent will be provided by Endo. Study drug administration at each injection site is presented in section 12.1.4.2.

10.4. Discussion of Study Design, Including the Choice of Control Groups

The use of the open-label extension design allows for the following:

- Safety data over a 12-month period will be collected to assist in further defining the safety profile of EN3835 in this population,
- Safety data and immunogenicity after repeat exposure (re-treatment/re-dosing) and monitoring of previously active-treated subjects to EN3835 over a 12-month period,
- Previously placebo-treated subjects to have exposure to EN3835, and
- Durability of the response to EN3835 (cellulite severity assessments) will be assessed.

11. SELECTION AND WITHDRAWAL OF SUBJECTS

11.1. Observation Phase

All subjects who have completed the double-blind study EN3835-201 and sign the informed consent are eligible for enrollment in this open-label extension study and participation in the ongoing safety and cellulite evaluations.

11.1.1. Subject Inclusion Criteria for Observation

To qualify for this open-label observation study a subject must:

1. Voluntarily sign and date an informed consent agreement
2. Have participated in and completed the double-blind study EN3835-201
3. Be willing to apply sunscreen to any treated quadrant before each exposure to the sun while participating in the study (ie, screening through end of study)

11.1.2. Subject Exclusion Criteria for Observation

None

11.2. Treatment

Inclusion and exclusion criteria presented in section 11.2 apply only to those subjects in the open-label study who choose treatment.

At the time that the study drug blind is broken in the double-blind study EN3835-201, qualified subjects enrolled in the open-label study are eligible for treatment. A subject may participate in the observational period of this open-label study regardless of scoring of quadrant; however to receive treatment in this study, a subject must have at least 1 qualifying quadrant.

11.2.1. Subject Inclusion Criteria for Treatment

To qualify for treatment in the study a subject must:

1. Voluntarily sign and date an informed consent agreement
2. Have participated in and completed the double-blind study EN3835-201
3. Be a female ≥18 years of age
4. At Screening B visit, have at least 1 quadrant with:
   a. a score of 3 or 4 (moderate or severe) as reported by the subject (PR-PCSS), and
   b. a score of 3 or 4 (moderate or severe) as reported by the Investigator (CR-PCSS), and
   c. a Hexsel CSS score no greater than 13
5. Be willing to apply sunscreen to the selected treatment quadrant before each exposure to the sun while participating in the study (ie, Screening B through end of study)
6. Be judged to be in good health, based upon the results of a medical history, physical examination, and laboratory profile at Screening B

7. Have a negative urine pregnancy test at Screening B and before injection of study drug and be using an 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.
8. Be willing and able to cooperate with the requirements of the study
9. Be able to read, complete and understand the patient-reported outcomes rating instruments in English

11.2.2. Subject Exclusion Criteria for Treatment

A subject will be **excluded from treatment** in the study (but not from the observation assessments) if she:

1. Has used any of the following for the treatment of EFP on the legs or buttock within the timelines identified below or intends to use any of the following at any time during the course of the study:
   - Liposuction on the side of the body selected for treatment during the 12-month period before injection of study drug
   - Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; or surgery (including subcision and/or powered subcision) within the selected treatment quadrant during the 12-month period before injection of study drug
   - Endermologie or similar treatments within the selected treatment quadrant during the 6-month period before injection of study drug
   - Massage therapy within the selected treatment quadrant during the 3-month period before injection of study drug
   - Creams (eg, Celluvera™, TriLastin®) to prevent or mitigate EFP within the selected treatment quadrant during the 2-week period before injection of study drug
2. Is presently nursing a baby or providing breast milk for a baby
3. Intends to become pregnant during the study
4. Has received an investigational drug or treatment within 30 days before injection of study drug
5. Has a known systemic allergy to collagenase or any other excipient of study drug
6. Is currently receiving or plans to receive anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication (except for ≤150 mg aspirin daily) within 7 days before injection of study drug
7. Has a known recent history of stroke, bleeding, or other medical condition, which in the investigator's opinion would make the subject unsuitable for enrollment in this phase of the study

8. Presence of any clinically relevant conditions, that in the opinion of the Investigator would interfere with completing the study including, but not limited to, visual problems, hearing problems, cognitive impairment or acute mental illness

11.3. Subject Discontinuation Criteria

A premature discontinuation will occur when a subject who signed informed consent ceases participation in the study, regardless of circumstances, prior to the completion of the protocol. Subjects can be prematurely discontinued from the study for one of the following reasons:

- An adverse event (AE)
- A protocol violation (reason must be specified, for example: lack of compliance, use of a prohibited concomitant medication, failure to meet inclusion/exclusion criteria after study entry, etc)
- Withdrawal by subject (reason must be specified)
- The subject was "lost to follow-up"
- Other reasons (reason must be specified, for example: the subject moved, pregnancy, investigator decision, Sponsor decision to terminate trial, etc)

If a subject discontinues from the study, all end-of-study procedures should be conducted as detailed in Schedule of Events. The date a subject discontinues and the reason for discontinuation will be recorded in the source documentation and Electronic Case Report Form (eCRF). If, however, a subject withdraws consent, no end-of-study procedures are required except the collection of AE information. This information should be recorded in the source documentation and the eCRF.

11.3.1. Replacement Procedures

Subjects who discontinue prematurely from the study will not be replaced.

12. PROCEDURES AND TREATMENTS

12.1. Study Visits

The Schedule of Events to be performed at each visit is shown in section 5. Provided below are further details where additional instruction about the assessments that will be performed is deemed to be needed.

12.1.1. Subject Screening

Upon completion of Day 71 assessments in the double-blind study EN3835-201, a subject will be eligible to enter this open-label extension study. Investigators will be expected to maintain a Screening Log of all potential study subjects. This log will include limited information about the potential subject and the date and outcome of the screening process (eg, enrolled into the study, reason for ineligibility, or refused to participate). Investigators will provide information about the study to subjects who appear to meet the criteria for participation in the study.

12.1.2. Screening Assessments

After obtaining informed consent, the full assessment of eligibility will be conducted and prior to study entry, screening assessments will be performed. Details about how the informed consent will be obtained and documented are provided in section 21.3, Subject Information and Consent. The subject may be entered into the observational phase of the study and complete safety and cellulite severity assessments at 3-month intervals as detailed in Table 2. In addition, once the study blind is broken in study EN3835-201, enrolled subjects will be asked if they wish to receive additional open-label treatments. If a subject elects to receive open-label treatment, study assessments will be conducted in accordance with Table 3.

12.1.3. Study Entry/Observational Assessments

A subject who gives written informed consent and who satisfies all eligibility criteria (section 11) may be entered into the observational phase of the study and complete safety and cellulite severity assessments at 3-month intervals as detailed in Table 2. The first visit will be determined by the date of enrollment in study EN3835-202 relative to the Schedule of Events for study EN3835-202 (Table 2). For example, if a subject enrolls after the Day 90 visit window, the first observation visit for that subject would be Day 180. In addition, once the study drug blind is broken in study EN3835-201, enrolled subjects will be asked if they wish to receive additional open-label treatments. If a subject elects to receive open-label treatment, study assessments will be conducted in accordance with Table 3. The subject identification number will be carried over from the double-blind, placebo-controlled study (EN3835-201).

12.1.3.1. Three-Month Assessments

Subjects will return within 20 days (±4 days) of completion of the double-blind study for the first of 4 safety and cellulite severity evaluation visits. Assessments to be completed at these visits are detailed in Table 2. Subjects are to return at 3-month intervals until they have completed 12 months from Day 1 of the double-blind study. At these visits, the quadrant previously treated with EN3835 in the EN3835-201 study or quadrants treated with EN3835 in the open-label study

will be evaluated. If the quadrant treated in study EN3835-201 is retreated in the open-label study, the 3-month assessments will reset to treatment visit 1/Day 1 of the open-label treatment and the study visits will continue as described in Table 3 followed by 3-month assessments as described in Table 2. If a different quadrant is treated in the open-label study, the 3-month assessments of both the quadrant treated in the double-blind study (EN3835-201) and the quadrant treated in the open-label study will continue.

12.1.4. Treatment Assessments (Optional)

After unblinding of treatment assignment in the EN3835-201 study, subjects are eligible for optional treatment in the open-label study, provided they meet the inclusion and exclusion criteria detailed in section 11 and at least 1 quadrant meets the criteria for treatment. A subject may receive a maximum of 2 courses of treatment (6 treatment sessions) overall (total of treatments in double-blind and open-label study). If a subject received placebo in the double-blind study, she may be eligible for 2 treatment courses in the open-label study; if a subject received active drug in the double-blind study, she may be eligible for 1 additional treatment course (3 treatment sessions) in the open-label study.

Selection of Treatment Quadrant

During the Screening B visit, each subject will have photographs taken of the 4 targeted quadrants of the study (eg, their left and right buttocks and left and right posterolateral thighs). Subjects will receive instructions (Appendix D) for using the PR-PCSS and will use the scale to rate the severity of their cellulite in each of the 4 quadrants by comparing each of their digital image photographs with the PR-PCSS instrument. This self-assessment will take place in a private setting to minimize any potential bias from site personnel. The Investigator will then assess each of the subject's 4 quadrants live in real-time using the CR-PCSS. The Investigator will then examine each of the 4 quadrants live to assess the subject using the Hexsel CSS as described in section 13.1.1.6.(12) Subjects must have at least 1 quadrant that meets the following criteria for treatment in the study:

1. PR-PCSS score of 3 or 4, and
2. CR-PCSS score of 3 or 4, and
3. Hexsel CSS score no greater than 13.

After the independent assessments are completed separately by the subject and the Investigator, the Investigator will review his/her assessments and the subject's assessment to determine which quadrants, if any, are eligible. The eligible quadrants (must meet all 3 of the inclusion criteria (PR-PCSS, CR-PCSS, and Hexsel CSS scores), if any, for treatment will be determined by the Investigator after which the quadrant selected will be at the discretion of the subject. For subjects treated with EN3835 in the double-blind study, if the quadrant treated in the double-blind study (EN3835-201) has PR-PCSS and CR-PCSS ratings identical or more severe than the double-blind study (EN3835-201) PR-PCSS and CR-PCSS baseline ratings (Baseline is Day 1 of study EN3835-201), subjects can elect to have that same quadrant re-treated. Subjects who choose re-treatment of the previously treated quadrant will be classified in the re-treatment arm. If another quadrant besides the previously treated quadrant meets all 3 of the inclusion criteria, subjects can choose to be treated in the naive quadrant. Subjects who choose treatment into a naive quadrant will be classified in the re-dosing arm.

Assessments made with the PR-PCSS (from digital image), the CR-PCSS (live assessment), and the Hexsel CSS score during the open-label Screening B visit will be the baseline severity of EFP in the selected quadrant.

A subject who received placebo in the double-blind study may be treated in the same quadrant in the open-label study if the quadrant still meets all 3 criteria OR another qualifying quadrant may be selected for treatment by the subject. Following Day 71 of a treatment course (3 treatment sessions), subjects can choose to receive a second treatment session in either the same quadrant if it still meets qualification criteria or in a different quadrant that meets qualification criteria. For the first treatment course, these subjects will be considered in the treatment arm. For the second treatment course, if the same quadrant is treated, subjects will be in the re-treatment arm; if a different quadrant is treated, subjects will be considered in the re-dosing arm.

If no quadrant meets all 3 criteria, the subject may continue in the observation-only study with safety and cellulite severity evaluations performed at 3-month intervals but may not receive treatment in this study.

Selecting and Marking Dimples

Selection of dimples to be treated in the selected quadrant is at the discretion of the Investigator or qualified designee. Dimples must be well-defined and evident when the subject is standing in a consistent relaxed pose (without the use of any manipulation such as skin pinching or muscle contraction). Each subject will receive 3 treatment sessions of study drug in the selected quadrant. During each treatment session, the treatment quadrant will be photographed before and after dimple marking while the subject is standing in a consistent relaxed pose as described in the Photography Manual. The cellulite severity assessments using the PR-PCSS and CR-PCSS will be completed prior to dimple marking at treatment visits 2, 3, and 4/end of treatment.

12.1.4.1. Screening B (Days −14 to −1 Relative to Open-Label Treatment Visit Day 1)

Subjects meeting the relevant criteria listed in section 11.2 may be eligible for treatment in the open-label study. The following procedures will be performed and documented during the screening period:

1. Evaluate eligibility based on inclusion/exclusion criteria (section 11.2)
2. Subject will have digital photographs taken of the 4 targeted quadrants of the study (left and right buttocks, and left and right posterolateral thighs) (section 13.1)
3. Subjects will get instruction on the use of the PR-PCSS (Appendix D)
4. Subjects will rate each quadrant using the PR-PCSS while viewing their digital images (section 13.1.1.1)
5. The Investigator will conduct independent live assessments of subject's cellulite severity of each quadrant using the CR-PCSS (section 13.1.1.4) after the subject completes her rating and with no knowledge of the subject's ratings of her quadrants.
6. The Investigator will conduct live cellulite evaluation of each quadrant using the Hexsel CSS (section 13.1.1.6).

7. If at least 1 quadrant qualifies based on PR-PCSS, CR-PCSS, and Hexsel CSS ratings, subject may return for treatment on treatment visit 1. If none of the 4 quadrants qualify, the subject may remain in the study and have safety and cellulite severity evaluations performed at 3-month intervals but is not eligible for treatment.
8. Subject will select an eligible quadrant (based on qualifying scores) to be treated at their discretion.
9. Medical history including EFP history. Medical history will be based on EN3835-201 eCRF; only updates to the history need to be captured at Screening B visit.
10. Record prior and concomitant medications/procedures. Prior medications will be based on EN3835-201 eCRF; only updates and concomitant medications need to be captured at Screening B visit (section 12.2).
11. Physical examination including measurement of body weight and height (section 14.10)
12. Vital sign measurements (section 14.8)
13. 12-lead electrocardiogram (ECG), not necessary if the date of the ECG obtained during the double-blind study (EN3835-201) is within 12 months of the date of the Screening B visit (section 14.9)
14. Collection of samples for:
    a. Clinical laboratory testing (section 14.7)
    b. Urine pregnancy testing (section 14.7)
15. Adverse events (section 14)

12.1.4.2. Treatment Session 1 (Treatment Visit 1)

Pre-injection

1. Confirm eligibility criteria (section 11)
2. Take digital photography of selected quadrant before dimple marking (section 13.1)
3. Record concomitant medications/procedures (section 12.2)
4. Vital sign measurements (section 14.8)
5. Collection of samples for:
    a. anti-AUX-I and anti-AUX-II antibody testing (section 14.7.1)
    b. urine pregnancy testing (section 14.7)
6. Select and mark dimples to be treated (section 12.1.4)
7. Take digital photograph of selected quadrant after dimple marking (section 13.1)

Injection

Administration of study drug in the prone position (see below)

Post-injection

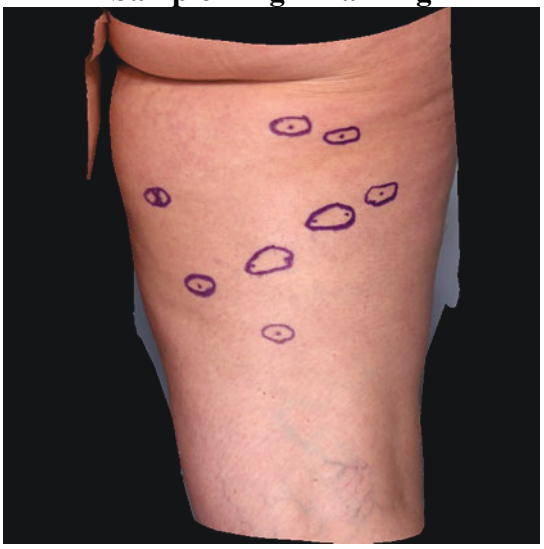
1. Record number of dimples treated and number of injections administered
2. Vital sign measurements (section 14.8)
3. Injection site reactions and local tolerability
4. Adverse events (section 14)

The selected quadrant will be photographed before and after dimple marking while the subject is standing in a consistent relaxed pose as described in the Photography Manual. Before injection at treatment session 1, the Investigator or qualified designee will begin the session by selecting dimples within the chosen quadrant that are well defined, evident when the subject is standing, and suitable for treatment; treatment consists of up to 12 injections per session. Because the goal of treatment is to improve the aesthetic appearance of the entire quadrant, the Investigator will be instructed to select dimples that in his or her opinion would most improve the aesthetic appearance of the entire quadrant. The same dimples within a quadrant or different dimples within a quadrant may be treated at each session but injections must all be within the selected quadrant for all 3 sessions.

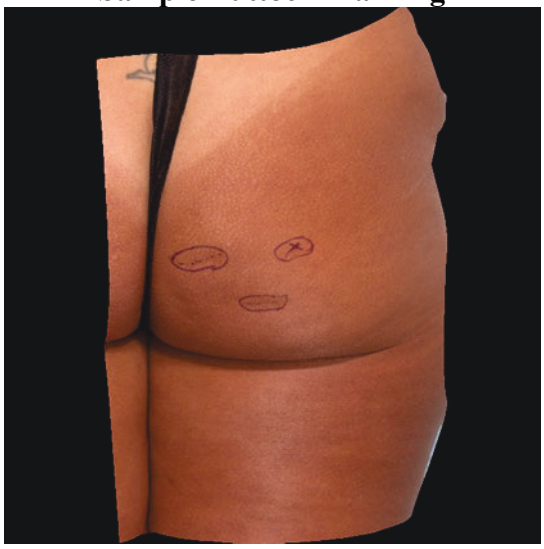
For each dimple selected for treatment, the Investigator or qualified designee will choose injection sites (injection sites within a dimple should be spaced approximately 2 cm apart, if a dimple requires more than 1 injection). Each injection site will be marked with a "dot" using a surgical marker. For round dimples, the "dot" will be placed in the center of the dimple; for elongated dimples, "dots" will be spaced out approximately 2 cm along the longer axis of the dimple. The Investigator or qualified designee will then use a surgical marker to circle each of the dimples selected for treatment. Circles in the selected quadrant should not overlap.

Examples of subject dimple marking:

Sample Thigh Marking



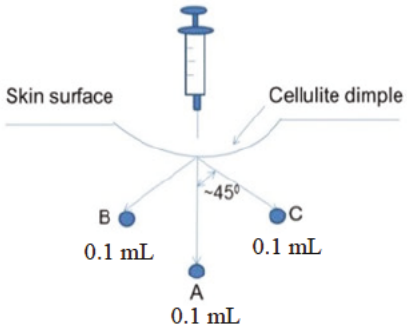
Sample Buttock Marking



Study Drug Administration at Each Injection Site

See section 18.4 for study drug preparation. Study drug will be injected subcutaneously while the subject is in a prone position using a syringe with a 30-gauge ½-inch needle. Each injection site will receive a single skin injection of study drug administered as three 0.1-mL aliquots to Positions A, B and C (for a total injection volume of 0.3 mL) as shown in the following figure. The depth of injection corresponds to the length of the treatment needle (0.5 inches) from the tip of the needle to the hub or base of the needle without downward pressure.

During each treatment session, the Investigator will be supplied with 4 syringes. Each syringe will contain 0.9 mL of study drug (ie, up to 3 injections in each syringe). Up to 12 skin injections of 0.3 mL per injection will be administered within the selected treatment quadrant during each treatment session.



- **Needle Tip Position A**: Position the needle at 90° angle perpendicular to the skin surface at the injection site and inject one 0.1-mL aliquot of study drug by gently pushing on the syringe plunger.
- **Needle Tip Position B**: Withdraw the needle slightly (but not so much as to remove from the injection site) and reposition approximately 45° (**but not more than 45°**) off vertical and above the long axis of the dimple and inject one 0.1-mL aliquot of study drug) by gently pushing on the syringe plunger.
- **Needle Tip Position C**: Withdraw the needle slightly (but not so much as to remove from the injection site) and reposition approximately 45° (**but not more than 45°**) off vertical and below the long axis of the dimple and inject one 0.1-mL aliquot of study drug by gently pushing on the syringe plunger.
- Withdraw needle from the skin completely and move to the next identified injection site. Complete up to a total of three 0.3-mL injections (each administered as three 0.1-mL aliquots) and discard the first syringe appropriately. Use the second, third and fourth syringes to complete dosing in the quadrant (up to three 0.3-mL injections per syringe, each injection administered as three 0.1-mL aliquots). Up to twelve skin injections of 0.3 mL will be administered within the treated quadrant during each treatment session.
- After treatment the subject will remain prone for at least 5 minutes.

The total number of dimples treated and the total number of injections administered will be recorded during treatment sessions 1, 2, and 3.

NOTE: EN3835 is a foreign protein and Investigators must be prepared to address and manage an allergic reaction should it occur. At the time of each injection, a 1:1,000 solution of epinephrine for injection, 50-mg diphenhydramine injection or a suitable equivalent, and oxygen should be available and the Investigator and site staff must be familiar with their use.

Care Procedures After Injection

To evaluate the subject for possible immediate immunological AEs, the subject will remain in direct observation of medical personnel who are skilled in the management of an allergic reaction for 30 minutes after receiving the injection of study drug and until the subject exhibits no sign of an immunological or other clinically significant systemic or local AE. The subject's vital signs should be stable before the subject can leave direct observation (see section 14.8).

The Investigator or qualified designee will then apply a sterile dressing to the injection site with hypoallergenic tape. The subject will be instructed to remove the dressing in the evening.

12.1.4.3. Treatment Session 2 (Treatment Visit 2/Day 22 ± 3 Days) and Treatment Session 3 (Treatment Visit 3/Day 43 ± 3 Days)

Pre-injection

1. Record concomitant medications/procedures (section 12.2)
2. Body weight measurements
3. Vital sign measurements (section 14.8)
4. Collection of samples for urine pregnancy testing (section 14.7)
5. Digital photograph of selected quadrant before dimple marking (section 13.1)
6. Subject assessment of the severity of cellulite using photograph of the selected quadrant via PR-PCSS (section 13.1.1.1). NOTE: Complete the subject (PR-PCSS) assessment before the Investigator (CR-PCSS) assessment and before dimple marking.
7. Investigator will conduct an independent live assessment of the severity of cellulite using the CR-PCSS (section 13.1.1.4). The investigator will conduct the assessment of severity only after the subject has completed her rating of her quadrant and without knowledge of the subject's rating of her quadrant.
8. Selection and marking of dimples to be treated (section 12.1.4)
9. Digital photograph after dimple marking (section 13.1)

Injection

Administration of study drug in the prone position (section 12.1.4.2)

Post-injection

1. Record number of dimples treated and number of injections administered
2. Vital sign measurements (section 14.8)
3. Injection site reactions and local tolerability
4. AEs (section 14)

If the Investigator rates the selected quadrant as 0, no injections will be given. If no injections are given at treatment session 2, subjects will still return for the Day 43 visit and the selected quadrant will again be evaluated by the subject (PR-PCSS) and Investigator (CR-PCSS). If the Investigator rates the selected quadrant greater than 0 on the CR-PCSS, injections at treatment session 3 should be given.

Because the goal of treatment is to improve the aesthetic appearance of the entire quadrant, the Investigator will be instructed to select dimples that in his or her opinion would most improve the aesthetic appearance of the entire quadrant. The same dimples within a quadrant or different dimples within a quadrant may be treated at each session but injections must all be within the selected quadrant for all 3 sessions. Each subject will receive all 3 treatment sessions unless the selected quadrant has no treatable EFP dimples and the Investigator rates the quadrant a score of 0 on the CR-PCSS.

After the dimples are selected, the Investigator or qualified designee will again mark each injection site with a "dot," and circle each dimple (circles should not overlap).

12.1.4.4. Day 71 (+5 Days) End of Treatment/Early Termination

The following procedures will be performed on Day 71:

1. Record concomitant medications/procedures (section 12.2)
2. Measurement of body weight
3. Vital sign measurements (section 14.8)
4. Collection of samples for:
   a. Clinical laboratory testing (section 14.7)
   b. Anti-AUX-I and anti-AUX-II antibody testing (section 14.7.1)
5. Digital photograph of selected quadrant (section 13.1)
6. Subject cellulite assessments of the selected quadrant using the photographic image (NOTE: complete subject cellulite assessments before Investigator cellulite assessments) using:
   a. PR-PCSS assessment (section 13.1.1.1)
   b. S-GAIS (section 13.1.1.2)
   c. Subject satisfaction with cellulite treatment assessment (section 13.1.1.3)
7. Investigator cellulite assessments of selected quadrant independently conducted; ie, with no knowledge of the subject's rating, using:

a. CR-PCSS live assessment of subject (section 13.1.1.4)

b. Hexsel CSS assessment of live subject while subject is standing in a relaxed position (section 13.1.1.6)

c. I-GAIS (section 13.1.1.5)

8. Injection site reactions and local tolerability
9. AEs (section 14)

12.1.4.5. Follow-up Visits

Following the Day 71 visit, the quadrant(s) treated with EN3835 in the open label study will be evaluated every 3 months from the first exposure to EN3835 following the schedule in Table 2. The first follow-up visit will be approximately 20 days after the Day 71 visit (ie approximately Day 90 after treatment session 1). Follow-up visits will continue until the study is terminated when at least 100 subjects have been assessed at 12 months after the first exposure to EN3835.

12.2. Prior and Concomitant Medications and Procedures

All medications (including over-the-counter medications) taken by the subject at screening visit 1 through the end of the study must be recorded.

Additionally, any diagnostic, therapeutic or surgical procedures performed during the study period should be recorded including the date, indication for and description of the procedure.

12.2.1. Prohibited Medications

The following medications are prohibited for those subjects that elect to have treatment with study drug during the treatment 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 the treatment phase of the study. For those subjects in the observational-only phase of study, there are no prohibited medications.

Table 5: Concomitant Medication Restrictions for Subjects During the Treatment Phase of Study

Drug Class	Restrictions
Anticoagulants	Subjects who elect treatment cannot take antiplatelet agents or anticoagulants (except for ≤150 mg aspirin daily) within 7 days before and after the dosing administration.

12.2.2. Prohibited Procedures

The treatments and procedures listed in exclusion criteria are prohibited during the study.

12.3. Treatment Compliance

All subjects who elect to have treatment will receive study drug administered by a clinician at the investigator's site.

Accidental or intentional overdoses should be reported to the Sponsor/designee promptly (see section 14.6.2).

12.4. Blinding and Randomization

This study will be conducted as an open-label investigation; no blinding of assigned treatment will occur.

12.5. End of Study

The end of study is when 100 subjects complete the 1-year safety and cellulite severity evaluations. At the time of study termination, ongoing subjects receiving treatment will be followed through the Day 71 visit. The remaining enrolled subjects (in excess of the first 100 subjects to complete 1 year) will undergo early termination procedures in accord with the Schedule of Events (section 5).

13. ASSESSMENT OF EFFICACY

13.1. Primary Efficacy Measurements

Although measures of efficacious drug effect (ie, durability of improvement) will be made during the observation phase before the study drug blind is broken in the double-blind study (EN3835-201), and thereafter to the end of study, emphasis is on the assessment of safety over 12 months after exposure to EN3835. Cellulite severity assessments will be made at scheduled intervals for both observation-only subjects (not receiving EN3835) as well as subjects who choose re-dosing or re-treatment with EN3835.

Digital Photography: Digital photography will be utilized to assess certain cellulite severity parameters at specific intervals (see Schedule of Events, Table 2) for subjects in the observation-only group as well as those electing to be re-treated or re-dosed with EN3835. At the Screening B visit for subjects electing to receive re-dosing or re-treatment, the Investigator or qualified designee will photograph each quadrant using a Sponsor-supplied standardized digital camera. The subject will be standing for each photography session and will be wearing a standardized photographic garment as described in the Photography Manual. The Investigator or qualified designee will photograph the selected quadrant as follows:

- Screening B (no dimple marking)
- Before and after dimple marking (prior to injections) on Days 1, 22, and 43 of each treatment course
- During the Day 71 visit (end of treatment phase/early termination) of each treatment course

All photographs from this study are the property of Endo and may be utilized for clinical development, scientific communication, marketing, regulatory purposes, and/or legal applications as required/desired by Endo.

13.1.1. Subject and Investigator Cellulite Assessments

As in the double-blind parent study, Investigator cellulite assessments are independent of the subject assessments. Therefore, all subject cellulite assessments must be completed before the Investigator's cellulite assessments are made. After both the subject's and investigator's assessments are completed, the subject's assessments will be revealed and compared to the clinician's assessments to determine eligible quadrants. If more than 1 quadrant is eligible, the subject will select one for treatment.

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

The PR-PCSS will be conducted for the purpose of assessing the severity of cellulite in the buttock or thigh; there are separate scales for buttocks or thighs. The scales are 5-level photonumeric scales developed specifically for patients and used by the subject to assess the severity of their cellulite in the quadrants by viewing digital images of each of their quadrants captured by photography at the visit; the ratings range from 0 (None) to 4 (Severe) with labels and descriptors to aid the subject in the assessments.

All subjects who enter the observation-only phase of the study will have the PR-PCSS evaluation at months 3, 6, 9, and 12.

For subjects electing re-treatment or re-dosing after the study drug blind is broken in study EN3835-201, a Screening B visit (Baseline) within 14 days before dosing Day 1 will occur. Subjects will have digital photographs taken of all 4 quadrants as done in the double-blind trial for qualifying purposes. Subjects will then perform the PR-PCSS for both buttocks (Figure 1) and thighs (Figure 2) and will be reminded of their proper use (Appendix D).

At the beginning of visits on Days 22, 43, and 71; digital photographs of the selected quadrant will be taken. If the buttock is the treated region, subjects will be given the PR-PCSS for the buttock to use to make their evaluation; if the thigh is the treated region, subjects will be given the PR-PCSS for the thigh to make their evaluation.

Figure 1: Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS) for the Buttock

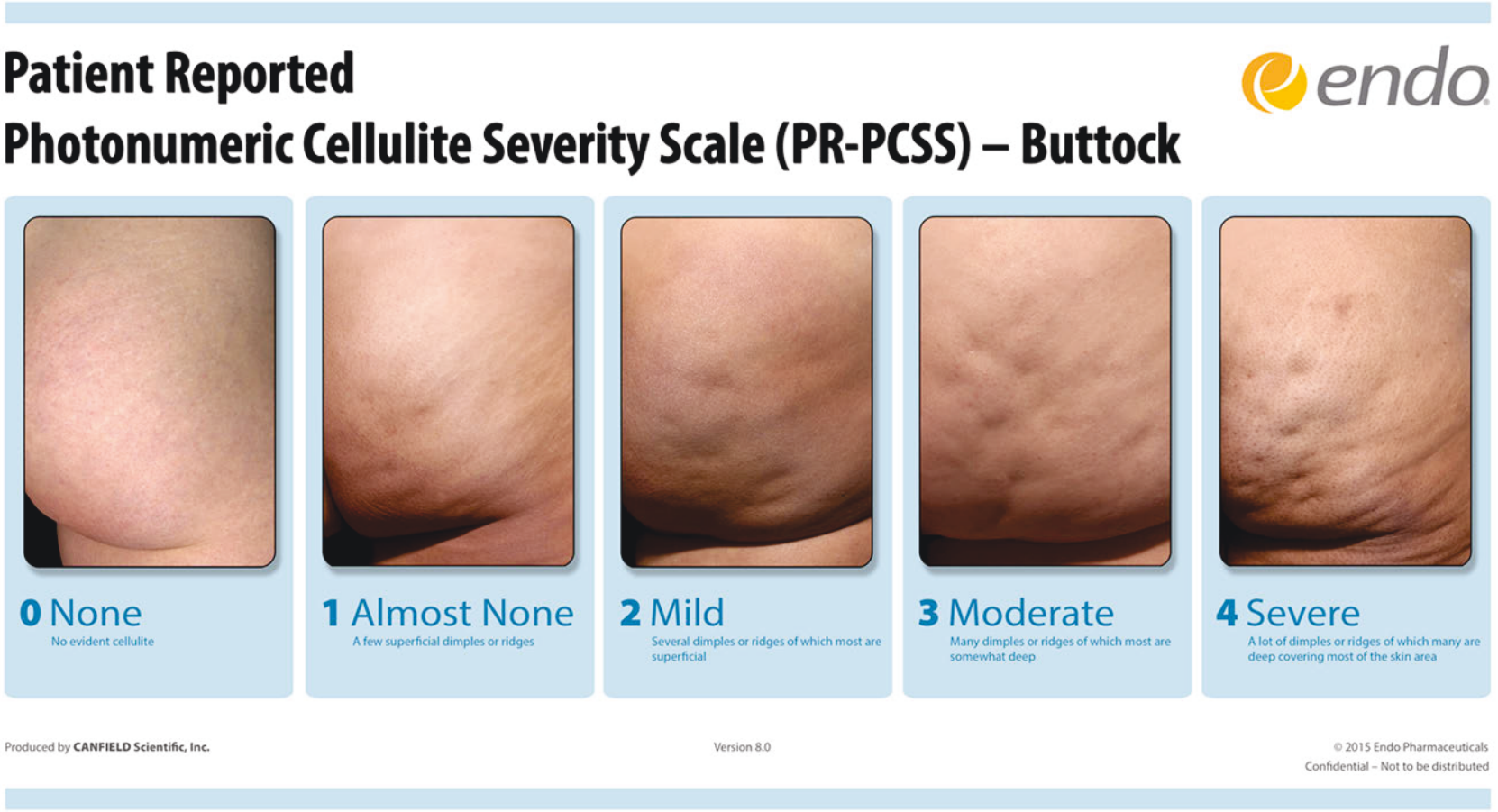


Figure 2: Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS) for the Thigh

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

Subjects in the observation-only group will complete the S-GAIS as described below at the final study visit (month 12 or early termination) using the pre-treatment Day 1 image (Baseline) of the assigned quadrant in the double-blind study for comparison.

For subjects who elected to receive EN3835 treatment, the S-GAIS assessment will be done on Day 71 of the treatment course and then at month 12 or the final study visit and compared back to the pre-dosing Screening B image (Baseline for treatment subjects) of the selected quadrant. All treated subjects will be instructed to answer the following question: *How would you rate the appearance of your treated cellulite after treatment?*

The S-GAIS assessment will occur after the subject has completed the PR-PCSS assessment to avoid introducing potential bias to the static PR-PCSS assessment. Each subject will view the pre-dosing Screening B visit digital image alongside their Day 71 treatment course visit and month 12 or end of study visit digital image of their selected quadrant to aid in the assessment (Table 6). Subjects will circle the rating below that best represents their answer.

Table 6: 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 originally.

13.1.1.3. Subject Satisfaction with Cellulite Treatment Assessment

For observation-only subjects (not receiving EN3835) the subjects will assess their satisfaction with cellulite treatment at the 12 month or end of study visit by being instructed to answer the following question: *Today, how satisfied are you with the results of the cellulite treatment you received on the specific area or areas on your buttocks or thighs that were treated?* Subjects will circle the rating in the below table that best represents their answer.

For subjects who have elected to receive EN3835 either through re-treatment or re-dosing, the subject satisfaction with the cellulite treatment (Table 7) with be done at the treatment course Day 71 and the month 12 visit or end of study visit. Subjects will be instructed to answer the following question: *Today, how satisfied are you with the results of the cellulite treatment you received on the specific area or areas on your buttocks or thighs that were treated?* Subjects will circle the rating below that best represents their answer.

Table 7: Subject Satisfaction with Cellulite Treatment Assessment

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

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

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

Investigators will have been trained on the use of the CR-PCSS. For observation-only subjects, the CR-PCSS will be done at 3, 6, 9, and 12 months or at the end of study visit.

For subjects who elected to receive EN3835 after the study drug blind is broken in study EN3835-201 as a re-treatment or re-dosing, the Investigator, at the Screening B visit (Baseline) will determine severity of cellulite of the 4 quadrants by assessing live subjects using the CR-PCSS for buttock (Figure 3) and thighs (Figure 4) after the subject has completed their self-assessment using the PR-PCSS. The eligible quadrant chosen for injection will be at the discretion of the subject. Before injections on treatment visit Days 22 and 43 and on visit Day 71; Investigators will evaluate the selected quadrant by live assessments. If the buttock is the treated region, the Investigator will use the CR-PCSS for the buttock to make his/her evaluation; if the thigh is the treated region, the Investigator will use the CR-PCSS for the thigh to make his/her evaluation. In each case, the Investigator will make his/her assessment independently and after the subject has conducted their self-assessment using the PR-PCSS.

Figure 3: Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS) for the Buttock

Figure 4: Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS) for the Thigh

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

Investigators will complete the I-GAIS on subjects in the observation-only group as described below at the final study visit (month 12 or early termination) and a comparison back to the pre-treatment Day 1 (Baseline) image of the assigned quadrant of the double-blind study.

On Day 71 of the treatment course and the 12 month or end of study visit, the Investigator will determine the degree of improvement from the Screening B digital image of the selected quadrant by comparing the cellulite in live assessment on Day 71 and at month 12 or study end to the Screening B pre-treatment (Baseline) image of the subject's selected quadrant (Table 8). The I-GAIS assessment will occur after the CR-PCSS assessment (section 13.1.1.4) to avoid introducing potential bias to the static CR-PCSS assessment by the Investigator at the site. The Investigator will circle the rating below that best represents their answer.

Table 8: Investigator Global Aesthetic Improvement Scale (I-GAIS)

Rating	Response Option	Description
+3	Very much improved	Optimal cosmetic result from treatment of the treated dimples
+2	Much improved	Marked improvement in the treated area appearance from before treatment, but not completely optimal
+1	Improved	Obvious improvement in the treated area appearance from before treatment, but additional treatment is indicated
0	No change	The treated area appearance is essentially the same as before treatment
−1	Worse	The treated area appearance is worse than before treatment
−2	Much worse	Marked worsening in appearance from the initial condition
−3	Very much worse	Obvious worsening in appearance from the initial condition

13.1.1.6. Hexsel Cellulite Severity Scale

The Hexsel Cellulite Severity Scale (referred to as the Hexsel CSS) is a photonumeric scale that looks at 5 key morphologic features of cellulite: (A) number of evident depressions, (B) depth of depressions, (C) morphological appearance of skin surface alterations, (D) laxity, flaccidity or sagging of skin, and (E) current classification scale based on medical literature including Nürnberger and Müller.(12,13) Each of these features is evaluated on a 4-point scale from a low of 0 to a high of 3 as described in Table 9 (see Appendix B). The total score is the summation of all 5 features.

For subjects in the observation-only group, the Hexsel CSS will be done at the month 12 or the end of study visit.

For the subjects electing treatment (re-treatment or re-dosing) with EN3835 the Investigator or qualified designee will independently use the Hexsel CSS to assess the severity of EFP in all quadrants at Screening B visit and the selected quadrant on Day 71 of the course of treatment and at month 12 or end of study visit. All cellulite assessments should be made while the subject is in the standing position with relaxed gluteus muscles. However, when evaluating the subject for Category E (classification scale by Nürnberger and Müller) (13) if the subject has no evident depressions, the subject should be asked to contract her gluteus muscles or the pinch test should

be applied (by pinching the skin between the thumb and index finger) so the Investigator or qualified designee can differentiate between scores/grades of zero (0) or I.

Table 9: Hexsel Cellulite Severity Scale

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

Source: Hexsel DM, Dal'Forno T, Hexsel CL. A validated photonumeric cellulite severity scale. *J Eur Acad Dermatol Venereol.* 2009;23(5):523-528.

[a] Subjects should be evaluated in the standing position with relaxed gluteus muscles. However, if the subject has no evident depressions, they should be asked to contract their gluteus muscles or the pinch test should be applied (by pinching the skin between the thumb and index finger) in order to differentiate between grade/stage of zero (0) or I.

14. ASSESSMENT OF SAFETY

14.1. Definitions

14.1.1. Adverse Event

An adverse event (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. AEs will be captured once a subject has signed the informed consent. AEs include:

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

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

All AEs, including both observed or volunteered problems, complaints, signs or symptoms must be recorded on the AE page of the eCRF, regardless of whether associated with the use of 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. The AE should be recorded in standard medical terminology when possible.

14.1.2. Serious Adverse Event

A serious adverse event (SAE) is defined as an AE that:

- Results in death
- Is immediately life-threatening (there is an immediate risk of death from the AE as it occurred; this does not include an AE that had it occurred in a more serious form may have caused death)
- Results in or prolongs an inpatient hospitalization (Note: a hospitalization for elective or pre-planned surgery, procedure, or drug therapy does not constitute an SAE)

- Results in permanent or substantial disability (permanent or substantial disruption of one's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect (in offspring of a subject using the study medication regardless of time to diagnosis)
- Is considered an important medical event

Important medical events are defined as events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the other serious outcomes. Examples of important medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

14.2. Monitoring Adverse Events

At each visit, subjects will be queried regarding any AEs that have occurred since the last visit. Subjects will be asked to volunteer information concerning AEs with a non-leading question such as, "How do you feel?" Study site personnel will then record all pertinent information in the source documents and the eCRF. The study drug compliance record should also be reviewed to detect potential overdoses (intentional/unintentional).

14.3. Relationship to Study Drug

The degree of "relatedness" of the AE to the study medication must be described using the following scale:

- **Not related** indicates that the AE is definitely not related to the study medication.
- **Unlikely related** indicates that there are other, more likely causes and study medication is not suspected as a cause.
- **Possibly related** indicates that a direct cause and effect relationship between study medication and the AE has not been demonstrated, but there is evidence to suggest there is a reasonable possibility that the event was caused by the study medication.
- **Probably related** indicates that there is evidence suggesting a direct cause and effect relationship between the AE and the study medication.

It is the Sponsor's policy to consider "Probably related" and "Possibly related" causality assessments as positive causality. "Not related" and "Unlikely related" causality assessments are considered as negative causality.

Assessments will be recorded on the eCRF and must indicate clearly the relationship being assessed. For example, an AE that appears during a placebo run-in phase would be assessed with respect to the placebo treatment received and/or study procedures conducted during this phase. If the AE continued into an active treatment phase, the relationship would be assessed for the active treatment phase only if the AE worsened.

14.4. Intensity Assessment

The intensity (or severity) of AEs is characterized as mild, moderate, or severe:

- **Mild** AEs are usually transient, requiring no special treatment, and do not interfere with the subject's daily activities.
- **Moderate** AEs introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.
- **Severe** AEs interrupt a subject's usual daily activity and typically require systemic drug therapy or other treatment.

When the intensity category of an AE changes, the greatest intensity during that continuous episode should be recorded.

14.5. Reporting Adverse Events and Serious Adverse Events

14.5.1. Reporting Adverse Events

Throughout the study, AEs will be documented on the source document and on the appropriate page of the eCRF whether or not considered treatment-related. This includes any new signs, symptoms, injury or illness, including increased severity of previously existing signs, symptoms, injury, or illness. Conditions existing prior to screening will be recorded as part of the subject's medical history. The Investigator is responsible for assessing the relationship of AEs to the study medication; relationship will be classified as not related, unlikely related, possibly related, or probably related.

All AEs will be collected by the Investigator from the time of signing the informed consent through 30 days after the last dose of study medication; this includes any AEs that are ongoing at the time of completion/termination of the study. All ongoing AEs must be followed until resolution or for 30 days after the subject's last study visit, whichever comes first.

14.5.2. Reporting Serious Adverse Events

Any SAE, including death resulting from any cause, which occurs to any subject participating in this study must be reported via email or fax by the Investigator using the Endo Clinical Trial Report Form for SAEs within 24 hours of first becoming aware of the SAE. SAEs will be collected by the Investigator from the time of signing the informed consent through 30 days after the last dose of study medication. SAEs that occur within 30 days, following cessation of the study treatment, or within 30 days, following premature discontinuation from the study for any reason, must also be reported within the same timeframe. Any SAE that is felt by the Investigator to be related to the study medication must be reported regardless of the amount of time since the last dose received. Follow-up information collected for any initial report of an SAE must also be reported to the Sponsor within 24 hours of receipt by the Investigator.

All SAEs will be followed until resolution, stabilization of condition, or until follow-up is no longer possible.

In the event discussion is necessary regarding treatment of a subject, call the Medical Monitor (see contact information in section 3).

All SAEs should be sent via the email address, or faxed to the fax number, provided in section 3.

The Sponsor will determine whether the SAE must be reported within 7 or 15 days to regulatory authorities in compliance with local and regional law. If so, the Sponsor (or the Sponsor's representative) will report the event to the appropriate regulatory authorities. The Investigator will report SAEs to the institutional review board (IRB) per their IRB policy.

14.5.2.1. Follow-up Procedures for Serious Adverse Events

To fully understand the nature of any SAE, obtaining follow-up information is important. Whenever possible, relevant medical records such as discharge summaries, medical consultations, and the like should be obtained. In the event of death, regardless of cause, all attempts should be made to obtain the death certificate and any autopsy report. These records should be reviewed in detail, and the Investigator should comment on any event, lab abnormality, or any other finding, noting whether it should be considered a serious or non-serious AE, or whether it should be considered as part of the subject's history. In addition, all events or other findings determined to be SAEs should be identified on the follow-up SAE form and the Investigator should consider whether the event is related or not related to study drug. All events determined to be nonserious should be reported on the eCRF.

14.6. Special Reporting Situations

14.6.1. Adverse Events of Special Interest

[redacted] Events).

14.6.2. Overdose/Misuse/Abuse

Study drug overdose is any accidental or intentional use of study drug in an amount higher than the dose indicated by the protocol for that subject. Study drug compliance (see section 12.3) should be reviewed to detect potential instances of overdose (intentional or accidental).

Any study drug overdose during the study should be noted on the study medication eCRF.

An overdose is not an AE per se, however all AEs associated with an overdose should both be entered on the Adverse Event eCRF and reported using the procedures detailed in section 14.5.2, Reporting of Serious Adverse Events, even if the events do not meet seriousness criteria. If the AE associated with an overdose does not meet seriousness criteria, it must still be reported using the Endo Clinical Trial Report Form for SAEs and in an expedited manner, but should be noted as non-serious on the form and the Adverse Event eCRF.

14.6.3. Pregnancy

Any uncomplicated pregnancy that occurs in a subject during this clinical study will **be reported for tracking purposes only**. All subject pregnancies that are identified during or after this study, where the estimated date of conception is determined to have occurred during study drug therapy or within 30 days of the last dose of study medication need to be reported, followed to conclusion, and the outcome reported, even if the subject is discontinued from the study. The investigator should report all pregnancies within 24 hours using the Initial Pregnancy Report Form, and any pregnancy-associated SAE using the SAE report form, according to the usual timelines and directions for SAE reporting provided in section 14.5.2. Monitoring of the pregnancy should continue until conclusion of the pregnancy; 1 or more Follow-up Pregnancy Report Form(s) detailing progress, and a Two Month Follow-up Pregnancy Report Form detailing the outcome, should be submitted.

Pregnancy itself is not regarded as an AE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not considered AEs. Any SAEs associated with pregnancy (eg, congenital abnormalities/birth defects/spontaneous miscarriages or any other serious events) must additionally be reported as such using the SAE report form. Spontaneous miscarriages should also be reported and handled as SAEs.

Subjects should be instructed to immediately notify the investigator of any pregnancies.

Attempts to obtain the pregnancy follow-up and pregnancy outcome information detailed above are necessary even if a subject discontinues treatment because of pregnancy.

14.6.4. Adverse Events/Serious Adverse Events Experienced by Non-subjects Exposed to Study Medication

Non-subjects are persons who are not enrolled in the study but have been exposed to study medication, including instances of diversion of study medication. All such AEs/SAEs occurring in non-subjects from such exposure will be reported to the Endo Pharmacovigilance and Risk Management (PVRM) Department (when the non-subject agrees) on the departmental form for SAEs regardless of whether the event is serious or not. Instructions for completing the form for events experienced by non-subjects will be provided. SAEs occurring in non-subjects exposed to study medication will be processed within the same SAE reporting timelines as described in section 14.5.2, Serious Adverse Event Reporting. Additionally, the drug accountability source documentation at the site should reflect this occurrence.

14.7. Clinical Laboratory and Immunogenicity Determinations

Clinical laboratory tests will be conducted according to the Schedule of Events (section 5). Clinical laboratory tests will be performed by a designated central laboratory. Each site will be provided with instructions on specimen collection, preparation, packaging and transport. Refer to the central laboratory manual for further information regarding sample collection, handling, and labeling. The results of the tests will be returned to the investigational sites.

Clinical laboratory test data will be reviewed by the investigator, or designee, and additional clinical laboratory tests may be ordered at his/her discretion (eg, if the results of any clinical laboratory test falls outside the reference range or clinical symptoms necessitate additional

testing to ensure safety). Any additional testing will be performed by the designated central laboratory.

The investigator will review all abnormal lab results for clinical significance. Any abnormal clinical laboratory test result meeting the investigator's or Sponsor's criteria for clinical significance (refer to central laboratory manual) will be recorded as an AE or SAE as appropriate (see section 14.1.1, Adverse Events or section 14.1.2, Serious Adverse Events).

Laboratory results will be sent electronically to Endo for data management.

Clinical laboratory parameters that will be measured in this study are listed in Table 10.

Table 10: Clinical Laboratory Parameters

Hematology	Clinical Chemistry	Urinalysis
Hematocrit	Blood urea nitrogen	Specific gravity
Hemoglobin	Creatinine	Ketones
Red blood cell count	Total bilirubin	pH
Red blood cell morphology	Alanine aminotransferase (ALT)	Protein
White blood cell count	Aspartate aminotransferase (AST)	Blood
Neutrophils	Alkaline phosphatase	Glucose
Lymphocytes	Sodium	
Monocytes	Potassium	
Basophils	Calcium	
Eosinophils	Chloride	
Platelets	Phosphate	
	Serum bicarbonate	
	Uric acid	
	Total cholesterol	
	Total protein	
	Glucose	
	Triglycerides	
	Albumin	

Female subjects of childbearing potential must have a negative urine pregnancy test at Screening B and at treatment visits 1, 2, and 3 (section 5) to receive treatment in the study. If necessary, additional urine pregnancy tests can be performed at any time during the study at the discretion of the Investigator.

14.7.1. Anti-AUX-I and Anti-AUX-II Antibodies

Serum samples will be collected and may be tested for binding and neutralizing anti-AUX-I and anti-AUX-II antibodies at visit 1 and visit 4. Additionally, if a subject consents to treatment in the open-label study, serum samples for antibody testing will be collected before injection at treatment visit 1 and at end of treatment/ early termination visit 4 of the open-label treatment period. A subset of subject samples may have neutralizing antibodies tested from Day 1 and Day 71 visits; additional samples may be analyzed if results or clinical signs warrant testing.

The serum samples obtained will be processed, stored and then shipped on dry ice to the designated central clinical laboratory before forwarding to Endo's appointed laboratory for the determination of anti-AUX-I and anti-AUX-II antibodies according to the Laboratory Manual.

14.8. Vital Signs

Vital sign measurements will be documented as described in the Schedule of Events. These parameters include pulse rate, respiratory rate, systolic and diastolic blood pressure, and body temperature. Pulse and blood pressure readings will be taken after the subject has been sitting for 5 minutes. Height should only be recorded at Screening B.

The investigator will review all vital sign values for clinical significance. Any vital sign value meeting the investigator's or Sponsor's criteria for clinical significance will be recorded as an AE or SAE as appropriate (see section 14.1.1, Adverse Events, and section 14.1.2, Serious Adverse Events).

For subjects receiving treatment, vital signs will be assessed at the time points shown in Table 11 after the subject has rested for at least 5 minutes.

Table 11: Vital Signs Measurements on Injection Day

Time Point Relative to Last Injection	Blood Pressure, Respiratory Rate, and Pulse Rate	Body Temperature
Up to 4 hours (before treatment)	X	X
Approximately 15 minutes after	X	
Approximately 30 minutes after	X	X

14.9. Electrocardiogram

Performing a 12-lead electrocardiogram (ECG) is not necessary if Screening B visit date is within 12 months of obtaining an ECG during the double-blind study (EN3835-201).

If the date of Screening B visit is later than 12 months since obtaining the ECG in study EN3835-201, subjects will have a resting 12-lead ECG performed during the Screening B visit. A qualified physician will interpret, sign, and date the ECGs. Electrocardiogram assessments must be "within normal limits" or interpreted as "abnormal, not clinically significant" for the subject to be included in the study.

Any ECG result meeting the investigator's or Sponsor's criteria for clinical significance will be recorded as an AE or SAE as appropriate (see section 14.1.1, Adverse Events and section 14.1.2, Serious Adverse Events).

14.10. Physical Examination

Body weight will be collected as described in the Schedule of Events (section 5). If a subject desires treatment in the open-label study, a complete physical examination will be performed at Screening B. All examinations will be performed by a physician or health professional listed on the Form FDA 1572 and licensed to perform physical examinations.

The investigator will review all physical exam findings for clinical significance. Any physical exam finding meeting the investigator's or Sponsor's criteria for clinical significance will be recorded as an AE or SAE as appropriate (see section 14.1.1, Adverse Events and section 14.1.2, Serious Adverse Events).

14.11. Other Safety Assessments

Not applicable.

15. ASSESSMENT OF PHARMACOKINETICS

Not applicable.

16. ASSESSMENT OF PHARMACODYNAMICS

Not applicable.

17. STATISTICAL CONSIDERATIONS AND METHODS

17.1. Determination of Sample Size

It is estimated that approximately 95% of the 350 subjects randomized in study EN3835-201 will enroll in the current study for a sample size of 333. This sample size should be adequate to determine safety and cellulite assessments of EN3835 for subjects retreated in the same and in different quadrants.

17.2. Subject Cohorts and Subject Populations

Subjects will be classified into 1 of 4 different cohorts depending on where they receive the treatment of EN3835 in relation to where they received treatment in study EN3835-201. The 4 cohorts are:

1. Observational subjects only - subjects who received EN3835 in study EN3835-201 but do not receive any injections in the current study
2. Re-treatment subjects - subjects who received EN3835 in study EN3835-201 and receive EN3835 in the current study in the same quadrant that was treated in the EN3835-201 study. This will only be allowed for subjects who have baseline severity ratings in the current study at or worse than the baseline seen in study EN3835-201 for both the CR-PCSS and PR-PCSS of the quadrant.
3. Re-dosing subjects - subjects who received EN3835 in study EN3835-201 and receive EN3835 in the current study in a quadrant different than the EN3835-treated quadrant in study EN3835-201.
4. Initial treatment subjects - subjects who received placebo in study EN3835-201 and receive EN3835 in the current study.

All efficacy and safety analyses will be done within the classified cohort. Durability of treatment effects defined as the time from onset of change from baseline of PR-PCSS and CR-PCSS in the quadrant treated in study EN3835-201 until the time that the treated quadrant return to baseline cellulite severity ratings of PR-PCSS and CR-PCSS in an EN3835-treated quadrant will be determined for all subjects that were treated with EN3835 in either this study or study EN3835-201.

17.2.1. Observational Population

The Observational population includes all subjects treated with EN3835 in study EN3835-201 who do not receive any treatment in the current study. The durability of a treatment effect and long-term safety analyses for subjects who receive no treatment in the EN3835-201 study will be performed using this population

17.2.2. Safety Population

The Safety population will include all subjects who receive at least 1 dose of EN3835 in the current study or in study EN3835-201. All safety analyses will be performed using this population.

17.2.3. Intent-to-Treat Population

The Intent-to-Treat (ITT) population includes all subjects who enroll in the current study.

17.2.4. Modified Intent-to-Treat Population

The Modified Intent-to-Treat (mITT) population includes all subjects who receive at least 1 dose of EN3835 in the current study (EN3835-202) and have a baseline and at least 1 post-baseline assessment on both the CR-PCSS and PR-PCSS on the quadrant selected for treatment in the current study. All cellulite assessment analyses will be completed on this population.

17.2.5. Per-Protocol Population

The Per-Protocol population includes all subjects in the safety population who have no major protocol deviations. Major protocol deviations excluding subjects from this population will be determined at the protocol deviation assessment meeting prior to the database lock. If more than 10% of the safety population is excluded from the per-protocol population, then all safety and cellulite evaluations will be repeated using the per-protocol population.

17.3. Subject Disposition

The number of subjects included in each study population will be summarized. The number and percentage of subjects completed and discontinued will be presented. Reasons for discontinuation as recorded on the eCRF will be summarized (number and percentage) for all subjects.

17.4. Demographics and Other Baseline Characteristics

Demographic and baseline characteristics, including age, race, and baseline values will be summarized for the Observational population, the Safety population, and the mITT population using descriptive statistics. The descriptive statistics will include frequency tables for all categorical response variables and number, mean, standard deviation, minimum, and maximum for all continuous variables.

17.5. Efficacy Analyses

Cellulite assessments (efficacy) include:

- PR-PCSS: 5-point scale ranging from 0 (no cellulite) to 4 (severe cellulite) (screening visit [Baseline], Days 22, 43, and 71). Also will be done at Day 90, Day 180, Day 270, and Day 360/end of study visits for observational assessments.
- CR-PCSS: 5-point scale ranging from 0 (no cellulite) to 4 (severe cellulite) (screening [Baseline], Days 22, 43, and 71). Also will be done at Day 90, Day 180, Day 270, and Day 360/end of study visits for observational assessments.
- Investigator rating of cellulite severity using the total scores from the Hexsel CSS scale: scores can range from 0 to 15 (screening [Baseline] and Day 71). Also will be done at Day 360/end of study visits for observational assessments.

- I-GAIS: 7-point scale ranging from 3 (very much improved) to −3 (very much worse) (Day 71). Also will be done at Day 360/end of study visit for observational assessments.
- S-GAIS: 7-point scale ranging from 3 (very much improved) to −3 (very much worse) (Day 71). Also will be done at Day 360/end of study visit for observational assessments.
- Subject satisfaction with cellulite treatment assessment: 5-point scale ranging from +2 (very much satisfied) to −2 (very much dissatisfied) (Day 71). Also will be done at Day 360/end of study visit for observational assessments.

All cellulite assessments will be done by treated quadrant. For initial treatment subjects who have 2 quadrants treated, each quadrant will be evaluated separately.

17.5.1. Primary Efficacy Analysis

The primary cellulite severity endpoint is the proportion of composite responders at Day 71 defined as subjects with an improvement in severity from baseline (Screening B visit) of at least 2 levels of severity in the CR-PCSS and an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS.

The primary endpoint, the proportion of composite responders with improvement of 2 or better on each scale (CR-PCSS and PR-PCSS) will be summarized by region treated (buttock or thigh) and overall with percentages.

17.5.2. Secondary Efficacy Analysis

Secondary endpoints for treated quadrants include:

- Proportion of composite responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS. (Day 71)
- Proportion at each level of improvement in the PR-PCSS (Day 71):
  - Proportion of patient responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS
  - Proportion of patient responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS
- Proportion at each level of improvement in the CR-PCSS (Day 71):
  - Proportion of Investigator responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS (Investigator rated)
  - Proportion of Investigator responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS (Investigator rated)

- Proportion of responders at each level of the I-GAIS (Day 71):
  - Proportion of Investigator global responders defined as subjects with a response of 1 (improved) or better in the Investigator GAIS assessment
- Proportion of responders at each level of the S-GAIS (Day 71):
  - Proportion of subject global responders defined as subjects with a response of 1 (improved) or better in the subject GAIS assessment
- Proportion of responders at each level of the subject satisfaction with cellulite treatment (Day 71)
- Change in the Hexsel CSS total score from screening visit to Day 71
- All secondary endpoints, except the Hexsel CSS total score, will be summarized by treated region (buttock or thigh) and overall using percentages. Change in Hexsel CSS total score will be summarized by treated region (buttock or thigh) and overall with descriptive statistics for continuous variables.

Observational endpoints include:

- Proportion of 2-point composite responders as defined by responses in the quadrant treated in study EN3835-201 who either maintained response, lost response but did not return to the baseline of study EN3835-201, or returned to the baseline of study EN3835-201.
- Proportion of 1-point composite responders as defined by responses in the quadrant treated in study EN3835-201 who either maintained response, lost response but did not return to the baseline of study EN3835-201, or returned to the baseline of study EN3835-201.
- Proportion of 2-point CR-PCSS responders as defined by responses in the quadrant treated in study EN3835-201 who either maintained response, lost response but did not return to the baseline of study EN3835-201, or returned to the baseline of study EN3835-201.
- Proportion of 1-point CR-PCSS responders as defined by responses in the quadrant treated in study EN3835-201 who either maintained response, lost response but did not return to the baseline of study EN3835-201, or returned to the baseline of study EN3835-201.
- Proportion of 2-point PR-PCSS responders as defined by responses in the quadrant treated in study EN3835-201 who either maintained response, lost response but did not return to the baseline of study EN3835-201, or returned to the baseline of study EN3835-201.
- Proportion of 1-point PR-PCSS responders as defined by responses in the quadrant treated in study EN3835-201 who either maintained response, lost response but did not return to the baseline of study EN3835-201, or returned to the baseline of study EN3835-201.

- Duration of response as defined by the time from onset of change from baseline of PR-PCSS and CR-PCSS in the quadrant treated in study EN3835-201 until the time that the treated quadrant returned to the baseline PR-PCSS and CR-PCSS ratings from study EN3835-201.
- CR-PCSS change from the study EN3835-201 baseline at Day 71 of study EN3835-201, and Days 90, 180, 270, and 360/end of study of the current study (EN3835-202).
- PR-PCSS change from the study EN3835-201 baseline at Day 71 of study EN3835-201, and Days 90, 180, 270, and 360/end of study of the current study (EN3835-202).
- Hexsel CSS total score changed from the study EN3835-201 baseline at Day 71 of study EN3835-201 and Day 360/end of study of the current study (EN3835-202).
- Proportion of responses at each level of the I-GAIS (Day 360/end of study):
  - Proportion of Investigator global responders defined as subjects with a response of 1 (improved) or better in the Investigator GAIS assessment
  - Change in I-GAIS assessment from Day 71 of study EN3835-201 and Day 360/ end of study of the current study (EN3835-202
- Proportion of responses at each level of the S-GAIS (Day 360/end of study):
  - Proportion of subject global responders defined as subjects with a response of 1 (improved) or better in the subject GAIS assessment
  - Change in S-GAIS assessment from Day 71 of study EN3835-201 and Day 360/ end of study of the current study (EN3835-202)
- Proportion of responses at each level of the subject satisfaction with cellulite treatment (Day 360/end of study)
  - Change in subject satisfaction assessment from Day 71 of study EN3835-201 and Day 360/end of study of the current study (EN3835-202)

For quadrants treated in the current study the following observational endpoints will be analyzed:

- Proportion of 2-point composite responders as defined by the responses in the quadrant treated in this current study (EN3835-202) who either maintained response, lost response but did not return to the study EN3835-202 baseline, or returned to the study EN3835-202 baseline.
- Proportion of 1-point composite responders as defined by the responses in the quadrant treated in the current study who either maintained response, lost response but did not return to the study EN3835-202 baseline, or returned to the study EN3835-202 baseline.
- Proportion of 2-point CR-PCSS responders as defined by the responses in the quadrant treated in this current study who either maintained response, lost response but did not return to the study EN3835-202 baseline, or returned to the study EN3835-202 baseline.

- Proportion of 1-point CR-PCSS responders as defined by the responses in the quadrant treated in the current study who either maintained response, lost response but did not return to the study EN3835-202 baseline, or returned to the study EN3835-202 baseline.
- Proportion of 2-point PR-PCSS responders as defined by the responses in the quadrant treated in the current study who either maintained response, lost response but did not return to the study EN3835-202 baseline, or returned to the study EN3835-202 baseline.
- Proportion of 1-point PR-PCSS responders as defined by the responses in the quadrant treated in the current study who either maintained response, lost response but did not return to the study EN3835-202 baseline, or returned to the study EN3835-202 baseline.
- CR-PCSS change from the study EN3835-202 baseline at Day 71, Day 90, Day 180, Day 270, and Day 360/end of study.
- PR-PCSS change from the study EN3835-202 baseline at Day 71, Day 90, Day 180, Day 270, and Day 360/end of study.
- Duration of response as defined by the time from onset of change from baseline of PR-PCSS and CR-PCSS in the quadrant treated in the current study until the time that the treated quadrant returned to the baseline PR-PCSS and CR-PCSS ratings from study EN3835-202.

17.6. Safety Analyses

The following variables are safety endpoints.

- AEs: Mapped to preferred term using the Medical Dictionary for Regulatory Activities (MedDRA)
- Injection site reactions/local tolerability in selected quadrant (through subject and Investigator reporting)
- Vital signs
- Laboratory testing

AEs will be summarized by treatment group. AE duration will be summarized using descriptive statistics by treatment group.

Descriptive statistics will be presented for each clinical laboratory test for the actual and change from screening at each visit by treatment group and vital signs for the actual and change from Day 1 pre-injection for each injection day at each visit by treatment group.

17.6.1. Prior, Concomitant, and Follow-up Medication

The World Health Organization (WHO) Drug Dictionary will be used to classify prior and concomitant medications by therapeutic class. The version used in this study will be stated in the Data Management Plan. Prior medication will be defined as any medication with a start date prior to the Day 1 date. Concomitant medication is defined as any medication with a start date on

or after the Day 1 date or reported as ongoing. Any medications started after the last dose of study drug will be considered as follow-up medications

Prior and concomitant medication use will be summarized descriptively by the number and percentage of subjects receiving each medication within each therapeutic class. Multiple use of the same medication by a subject will be counted only once.

17.6.2. Study Drug Exposure

For those subjects that elect, are eligible, and do receive treatment, the number of injections will be summarized by counts and percentages. The number of dimples treated will be summarized with counts and percentages.

17.6.3. Measurement of Treatment Compliance

All doses are administered while the subjects are at the investigators' sites. Any dose that was not administered per protocol will recorded as a protocol deviation by the Investigator.

17.6.4. Adverse Events

The MedDRA will be used to code AEs. The version used in this study will be stated in the Data Management Plan.

An AE (classified by preferred term) that started during the treatment period will be considered a TEAE if it was not present prior to the first dose of study drug, or was present prior to the first dose of study drug but increased in intensity during the treatment period. If more than 1 AE is reported prior to the first dose of study drug and coded to the same preferred term, then the AE with the greatest intensity will be used as the benchmark for comparison to the AEs occurring during the treatment period which were also coded to that preferred term. Any AE present prior to the first dose of study drug that increases in intensity during the treatment period will be re-entered with a new start date of the date of increased intensity.

Descriptive statistics (the number and percentage) for subjects reporting TEAEs in each treatment group will be tabulated by system organ class and preferred term; by system organ class, preferred term, and severity; and by system organ class, preferred term, and relationship to study drug. If more than 1 AE is coded to the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to the study drug.

SAEs and AEs leading to premature discontinuation of study drug will be summarized by preferred term and dose received. Listings will be presented for subjects with SAEs, subjects with AEs leading to discontinuation, and subjects who die (if any).

17.6.5. Vital Signs

Descriptive statistics for vital signs (eg, systolic and diastolic blood pressure, pulse rate, and body weight) and their changes from baseline at each visit and at the end of treatment visit will be presented.

Vital sign values are potentially clinically significant (PCS) if they meet both the observed value criteria and the change from baseline criteria. The criteria for PCS vital sign values will be detailed in the Statistical Analysis Plan (SAP). A listing of all AEs for subjects with PCS vital signs will also be provided.

17.6.6. Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values in International System of Units (SI units) and changes from baseline will be presented for each clinical laboratory parameter.

The number and percentage of subjects with PCS post-baseline clinical laboratory values will be tabulated. The criteria for PCS laboratory values will be detailed in the SAP. A listing of all AEs for subjects with PCS laboratory values will also be provided.

17.7. Immunogenicity Analyses

Immunogenicity variables include anti-AUX-I/anti-AUX-II binding antibody results. Binding antibody levels will be determined from samples collected on Days 1, 22, 43, and 71 during the treatment phase and Days 90, 180, 270 and 360 during the observational phase.

Descriptive statistics (percent of positive measurements and average antibody level) will be presented for anti-AUX-I and anti-AUX-II antibody levels at each time point by region treated and overall. Average antibody levels will be summarized on logarithmically transposed titer values.

17.8. Pharmacokinetic Analyses

Not applicable.

17.9. Interim Analysis

Two (2) interim analyses are planned. Following the breaking of the study drug blind in study EN3835-201, all follow-up safety data gathered prior to that time will be analyzed. The second interim analyses will occur following the Day 71 visit for all subjects treated with EN3835 in the current study. A preliminary data lock will be done on all treated quadrants and cellulite assessment and safety analyses will be done. The official database lock will occur after the last Day 360/end of study observational visit and all observational analyses on treated quadrants will be done.

17.10. Statistical Software

Statistical analyses will be performed using Version 9.3 (or higher) of SAS® (SAS Institute, Cary, North Carolina).

18. STUDY DRUG MATERIALS AND MANAGEMENT

18.1. Study Drug Identity

EN3835 is formerly known as AA4500; the 2 product names should be considered synonymous. The investigational product vials will be labeled as EN3835. The components of EN3835 are 0.9 mg of collagenase clostridium histolyticum, [redacted] in a lyophilized cake.

The components of EN3835 sterile diluent for reconstitution are 0.03% (2mM) calcium chloride ($CaCl_2$) in 0.9% (154mM) sodium chloride (NaCl) solution, pH 6.0 to 7.0. Diluent is supplied as a terminally-sterilized liquid at 3.0 mL per vial.

18.2. Study Drug Packaging and Labeling

Sterile vials of lyophilized EN3835 and sterile diluent will be provided to the Investigator by Endo. Each kit will contain 2 vials each of EN3835 and sterile diluent.

18.3. Study Drug Storage

All study drug will be provided by Endo. Study drug must be kept in a refrigerator (2°C-8°C) with locked access.

18.4. Study Drug Preparation

Refer to the Reconstitution Instructions in the Pharmacy Manual for detailed preparation instructions.

Before reconstitution, remove the vials containing the lyophilized study drug powder and the vials containing the sterile diluent from the refrigerator and allow the vials to stand at room temperature for 15 minutes. Designated study personnel will visually inspect the study drug vials to determine the integrity and acceptability of the lyophilized drug product for reconstitution. The written procedures for inspection of the study drug vials will be provided to the site by Endo.

After reconstitution with the sterile diluent, the study drug solution can be kept at room temperature [redacted]. The reconstituted study drug solution should be administered as soon as possible after reconstitution and further dilution. Each vial of study drug powder for reconstitution will be diluted according to the instructions in the Pharmacy Manual. Study personnel will maintain a record of the date and time of reconstitution.

18.5. Study Drug Accountability

Endo or its agent will maintain a master log of kits dispensed to the investigative sites. A drug inventory form must be kept current by the site staff designated to be responsible for reconstitution and must be made available to the clinical monitor, Endo employees, IRB/independent ethics committee (IEC), and regulatory agencies for routine inspection and

accountability during monitoring visits. When instructed by Endo, the Investigator agrees to return all original containers of unused study drug to Endo or its designee.

18.5.1. Study Drug Handling and Disposal

The Investigator is responsible for recording the receipt and use of all drug supplied and for ensuring the supervision of the storage and allocation of these supplies. All unused study drug will be returned, and unit counts will be performed whenever medication is returned. The site must account for all study drug received. The Investigator agrees not to supply study drug to any person except to those subjects enrolled in the study. At the end of the study, all unused drug supplies will be returned to Endo as instructed by the clinical monitor.

19. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

19.1. Source Documents

Source documents include but are not limited to original documents, data and records such as hospital/ medical records (including electronic health records), clinic charts, lab results, subject diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, etc. At a minimum, all data required to be collected by the protocol should have supporting source documentation for entries in the eCRF, unless the protocol specifies that data can be recorded directly on/in the eCRF or other device.

19.2. Study Monitoring

A representative of Endo Pharmaceuticals Inc. will meet with the Investigator and his/her staff prior to the entrance of the first subject to review study procedures and methods of recording findings in the eCRF.

After enrollment of the first subject, an Endo Pharmaceuticals Inc. representative will be assigned to periodically monitor each Investigator site for study progress and to verify that standards of Good Clinical Practice (GCP) were followed. The Investigator is expected to prepare for the monitor visit, ensuring that all source documents, completed eCRFs, signed consent forms, and other study related documents are readily available for review.

19.3. Audits and Inspections

The Investigator shall permit audits and inspections by the Sponsor, its representatives and members of regulatory agencies. The investigator should immediately notify the Sponsor of an upcoming FDA or other regulatory agency inspection.

19.4. Institutional Review Board (IRB)

The Investigator shall permit members of the IRB/IEC to have direct access to source documents.

19.5. Data Recording and Documentation

All data recordings and source documentation (including electronic health records) must be made available to the Sponsor (or designee), FDA and any other regulatory agencies that request access to study records, including source documents, for inspection and copying, in keeping with federal and local regulations.

20. QUALITY CONTROL AND QUALITY ASSURANCE

Steps to assure the accuracy and reliability of data include the selection of qualified principal investigators and appropriate study centers, review of protocol procedures with the principal investigators and associated personnel prior to start of the study, and periodic monitoring visits conducted by the Sponsor or Sponsor representative. Significant and/or repeated non-compliance will be investigated and remedial action instituted when appropriate. Failure to comply with remedial actions may result in investigator site termination and regulatory authority notification.

The Sponsor or its designee will utilize qualified monitors to review and evaluate activities conducted at Investigator Sites.

The data will be entered into the clinical study database and verified for accuracy, following procedures defined by the Sponsor (or designee). Data will be processed and analyzed following procedures defined by the Sponsor (or designee).

The study will be monitored and/or audited at intervals to ensure that the clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the Study Protocol; International Conference on Harmonisation (ICH), E6 consolidated guidelines; and other applicable regulations. The extent, nature, and frequency of monitoring and/or audits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity, and enrollment rate. At the conclusion of a program, a compliance statement will be generated by the Sponsor (or designee) listing all audit activities performed during the clinical study.

21. ETHICS

21.1. Ethics Review

Approval by the IRB/IEC prior to the start of the study will be the responsibility of the Investigator. A copy of approval documentation will be supplied to Endo Pharmaceuticals Inc. along with a roster of IRB members that demonstrates appropriate composition (a Department of Health and Human Services [DHHS] Assurance Number will satisfy this requirement).

The study protocol, the informed consent form, advertisements, materials being provided to subjects and amendments (if any) will be approved to IRB/IECs at each study center in conformance with ICH E6, the Code of Federal Regulations (CFR), Title 21, Part 56 and any other applicable local laws. The Investigator is responsible for supplying the IRB/IEC with a copy of the current IB, Package Insert, or SPC as well as any updates issued during the study. During the course of the study, the Investigator will provide timely and accurate reports to the IRB/IEC on the progress of the study, at intervals not exceeding 1 year (or as appropriate), and will notify the IRB/IEC of SAEs or other significant safety findings, per the policy of the IRB/IEC. At the conclusion of the study, the Investigator will submit a final report or close out report to the IRB/IEC and provide a copy to Endo Pharmaceuticals Inc.

Any amendment to this protocol will be provided to the Investigator in writing by Endo Pharmaceuticals Inc. No protocol amendment may be implemented (with the exceptions noted below) before it has been approved by the IRB and the signature page, signed by the Investigator, has been received by Endo Pharmaceuticals Inc. Where the protocol is amended to eliminate or reduce the risk to the subject, the amendment may be implemented before IRB review and approval. However, the IRB must be informed in writing of such an amendment and approval obtained within reasonable time limits. Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the subject, and must be immediately reported to Endo Pharmaceuticals Inc.

The Investigator will be responsible for supplying updated safety and/or study information to study subjects as it becomes available.

21.2. Ethical Conduct of the Study

This clinical study is designed to comply with the ICH Guidance on General Considerations for Clinical Trials (62 FR 6611, December 17, 1997), Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (62 FR 62922, November 25, 1997), Good Clinical Practice: Consolidated Guidance (62 FR 25692, May 9, 1997) and 21 CFR parts 50, 54, 56, and 312.

The study will be conducted in full compliance with ICH E6, the FDA guidelines for GCP and in accordance with the ethical principles that have their origins in the Declaration of Helsinki defined in 21 CFR, 312.120.

21.3. Subject Information and Consent

Subjects, after having the study explained to them and an opportunity to have their questions answered sufficiently, will give voluntary and written informed consent (in compliance with ICH E6, 4.8 and 21 CFR Parts 50 and 312) before participating in any study-related procedures. The consent shall be written in a language understandable to the subject. Subjects unable to read (illiterate) shall have the consent process performed in the presence of an independent witness who shall also sign the consent. Each subject will read, assent understanding, and sign an instrument of informed consent after having had an opportunity to discuss the study and consent documents with the Investigator before signing, and will be made aware that she may withdraw from the study at any time.

In addition to obtaining informed consent, the Investigator is responsible for obtaining any additional documentation to demonstrate compliance with local privacy laws applicable to activities performed.

The consent process shall be recorded in source documents. Signed copies of the informed consent will be given to the Subject and originals will be placed in the Investigator study files.

A unique Subject identification number will be assigned according to section 12.1.3 at the time that the Subject signs the informed consent form.

22. DATA HANDLING AND RECORDINGKEEPING

22.1. Data Collection

Data collection will involve the use of an EDC system to which only authorized personnel will have access. The system will be secured to prevent unauthorized access to the data or the system. This will include the requirement for a user ID and password to enter or change data. The level of access to the EDC system will be dependent on the person's role in the study.

Study data will be collected from source documents and entered into an eCRF within the EDC system. The Investigator will be responsible for ensuring the eCRFs are completed in a timely manner relative to the subject's visit. In addition to periodic monitoring occurring within the system by a Sponsor monitor, programmatic edit checks will be used to review EDC data for completeness, logic, and adherence to the study protocol. As a result of this monitoring and these checks, queries may be issued electronically to the clinical study sites and closed electronically by the monitor, data management staff or authorized staff at the study site. Additionally, the Investigator will review eCRFs, ensure all missing or corrected data is provided and will sign the eCRF pages with an electronic signature.

An electronic audit trail will be maintained in the EDC system to track all changes made to data entered in the eCRF. Data will be retrievable in such a fashion that all information regarding each individual subject is attributable to that subject. Unless otherwise indicated, all data captured in the eCRF must first be captured in source documents. Data that can be directly recorded in the eCRF will be clearly identified in the section(s) of the protocol that describes the assessment(s).

In addition, any contact with the subject via telephone or other means that provide significant clinical information must be documented in source documents as described above.

22.2. Study Documentation

Upon study completion, the Investigator will be provided with complete electronic copies of the CRF data for his/her files.

23. REPORTING AND PUBLICATION

All data generated in this study are the property of Endo. An integrated clinical and statistical report will be prepared at the completion of the study.

Publication of the results by the Investigator will be subject to mutual agreement between the Investigator and Endo.

24. INVESTIGATOR OBLIGATIONS

24.1. Regulatory Documents

The Investigator is responsible for creating and/or maintaining all study documentation required by 21CFR 50, 54, 56 and 312, ICH, E6 section 8, as well as any other documentation defined in the protocol or the Investigator Agreement. The Investigator must maintain the documentation relating to this study and permit Endo Pharmaceuticals Inc. or a member of a regulatory agency access to such records.

The Investigator must provide the following key documents to Endo Pharmaceuticals Inc. prior to the start of the study:

- A completed and signed Form FDA1572. If during the course of the study any information reported on the Form FDA 1572 changes, a revised Form FDA1572 must be completed and returned to Endo Pharmaceuticals Inc. for submission to the FDA. For studies executed outside the United States, documentation required by the governing regulatory authority may be substituted for the Form FDA 1572.
- A fully executed contract
- The Investigator's Statement page in this protocol signed and dated by the Investigator and any subsequent amendment signature pages
- The IB acknowledgment of receipt page
- Curricula vitae for the Principal Investigator and all Sub-Investigators listed on Form FDA 1572, including a copy of each physician's license (if applicable)
- A copy of the original IRB/IEC approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals or shorter intervals defined by the IRB/IEC. All subsequent modifications must be submitted and approved by the IRB, as described in section 21.1
- A copy of the IRB/IEC-approved informed consent form
- A list of IRB/IEC members or DHHS Assurance Number
- Laboratory certifications and normal ranges (if local labs are required by the protocol)
- A financial disclosure agreement completed and signed by the Investigator and all Sub-Investigators listed on Form FDA 1572. Investigator site staff that submitted an initial financial disclosure are also responsible for informing Endo Pharmaceuticals Inc. of any changes to their initial financial disclosure form 1 year after the completion of the study.

A complete list of required regulatory documents will be supplied by Endo Pharmaceuticals Inc. or its representative.

24.2. Delegation of Responsibilities and Adequate Resources

The Investigator should have adequate time to conduct the study properly and should have an adequate number of qualified staff to assist with the conduct of the study. The Investigator shall delegate tasks only to individuals qualified by education, training and experience to perform the delegated tasks. The Investigator shall have direct oversight of all delegated activities and shall document delegation of responsibilities. The Investigator is responsible for ensuring all delegated staff have been properly trained on the protocol and their assigned study responsibilities.

24.3. Medical Care of Study Subjects

The Investigator and/or a qualified sub-investigator shall be responsible for the subjects' medical care. Any unrelated medical condition discovered during the course of the study should be communicated to the subject so that they may seek appropriate medical care. The Investigator will report all AEs as required by the protocol (section 14.5). The Investigator will inform study subjects of new information regarding the study drug as it becomes available.

24.4. Use of Investigational Materials

The Investigator will acknowledge that the study drug supplies are investigational and as such must be used strictly in accordance with the protocol and only under the supervision of the Principal Investigator or Sub-Investigators listed on Form FDA1572 (or other regulatory document, depending on region). Study drug must be stored in a safe and secure location. At study initiation, a representative from Endo Pharmaceuticals Inc. will inventory the study drug at the site. The Investigator must maintain adequate records documenting the receipt and disposition of all study supplies. Endo Pharmaceuticals Inc. or its representative will supply forms to document total inventory as well as subject specific accountability. The Investigator is responsible for monitoring use of the study drug to ensure compliance with the protocol. All study supplies shall be returned to Endo Pharmaceuticals Inc. or its designee.

24.5. Retention of Records

Federal and local regulations require that the Investigator retain a copy of all regulatory documents and records that support the data for this study (eg, informed consents, laboratory reports, source documents, study drug dispensing records) for whichever of the following is the longest period of time:

- A period of 2 years following the final date of approval by the FDA or other regulatory agency of the study drug for the purposes that were the subject of the investigation; or
- A period of 5 years following the date on which the results of the investigation were submitted to the FDA or other regulatory agency in support of, or as part of, an application for a research or marketing permit for the study drug for the purposes that were the subject of the investigation

Endo will notify Investigators once one of the above 2 timeframes has been satisfied.

If the investigation does not result in the submission of the data in support of, or as part of, an application for a research or marketing permit, records must be retained for a period of 2 years following notification by Endo Pharmaceuticals Inc. that the entire clinical investigation (not merely the Investigator's portion) is completed, terminated, or discontinued or 2 years following withdrawal of the Investigational New Drug application (IND).

If the Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. Endo must be notified in writing of the name and address of the new custodian. Study records should not be destroyed without consultation with Endo Pharmaceuticals Inc.

24.6. Subject Confidentiality

All subject records submitted to Endo Pharmaceuticals Inc. or its designee will be identified only by initials and subject identification number. Subjects' names are not to be transmitted to Endo Pharmaceuticals Inc. The Investigator will keep a Master Subject List on which the identification number and the full name, address, and telephone number of each subject are listed. It is the Investigators' responsibility to inform study subjects that representatives of the Sponsor, FDA, or other regulatory agencies may review all records that support their participation in the study. The Investigator will adhere to all privacy laws to which he/she is subject.

25. TERMINATION OF STUDY

The Sponsor has the right to suspend or terminate the study at any time. The study may be suspended or terminated for any reason.

26. INVESTIGATOR'S AGREEMENT

I agree to conduct the study in accordance with the protocol, and with all applicable government regulations and Good Clinical Practice guidance.

_____ _____/_____/_____

Investigator's Signature Date

_____

Typed Name of Investigator

27. REFERENCES

1. Khan MH, Victor F, Rao B, Sadick NS. Treatment of cellulite: Part I. Pathophysiology. *J Am Acad Dermatol* 2010;62(3):361-370.
2. Hexsel D, de Oliveira Dal'Forno T, Mazzuco R. Definition, clinical aspects, classifications, and diagnostic techniques. In: Goldman MP, Hexsel D, eds. *Cellulite: Pathophysiology and Treatment.* 2nd ed. New York, NY: Informa Healthcare; 2010:13-21.
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13. Nürnberger F, Müller G. So-called cellulite: an invented disease. *J Dermatol Surg Oncol.* 1978;4(3):221-229.

[redacted]

LIST OF APPENDICES

APPENDIX A. DOCUMENTS REQUIRED PRIOR TO INITIATION OF THE STUDY

As a Sponsor of a clinical study, Endo Pharmaceuticals Inc. has an obligation to ensure that the study will be conducted by a qualified Investigator with sufficient resources of time, personnel, and physical facilities to conduct the study and to ensure that the Investigator understands and agrees to comply with the protocol, applicable regulations, policies, and procedures. The following documentation is required:

From the Principal Investigator

1. A signed agreement to perform the study per protocol (the signature page will suffice).
2. A signed Letter of Financial Agreement (including confidentiality statement).
3. Name(s) of the Principal Investigator and of all sub-Investigator(s)
4. All address(es) of the clinical site(s).
5. A current medical license valid where he/she practices and a current curriculum vitae for the Principal Investigator (signed and dated) and all sub-investigators, to contain at least the following elements:
   a. For physicians:
      i. Date of degree in Medicine
      ii. Name of the Institution granting the degree in Medicine.
      iii. Previous clinical postings with dates.
   b. For non-physician allowed by national law or regulations to act as clinical Investigators:
      i. Date and description of most advanced degree.
      ii. Name of the Institution granting the degree in number (i).
      iii. Other accreditation or qualifications relevant to the study.
      iv. Previous postings with dates.
      v. Name and qualification (see 5a above) of the physician or dentist in charge of study subjects.

   Note: If a non-physician is serving as Principal Investigator, then a qualified physician must be assigned as a sub-Investigator for the trial, to be responsible for all trial-related medical decisions.
6. Written notification of Institutional Review Board/Independent Ethics Committee/Human Research Ethics Committee (IRB/IEC/HREC) approval. The minimum requirements are as follows:
   a. Dated letter, including:
      i. The date on which the meeting for the review of the study protocol took place.
      ii. Study protocol/amendment number, and version date

iii. A clear statement of approval of the protocol and the informed consent text with version date, and authorization for the study to proceed.

iv. If the Investigator or any sub-Investigator is a part of the IRB/IEC/HREC Review Board, assurance that the Investigator abstained from voting at the meeting(s) when the study was discussed.

b. A dated list of the members and their occupations.

c. A specimen copy of the Committee-approved informed consent text to be used in the study.

7. Food and Drug Administration (FDA) Form 1572 (for studies submitted under a US Investigational New Drug application [IND]).

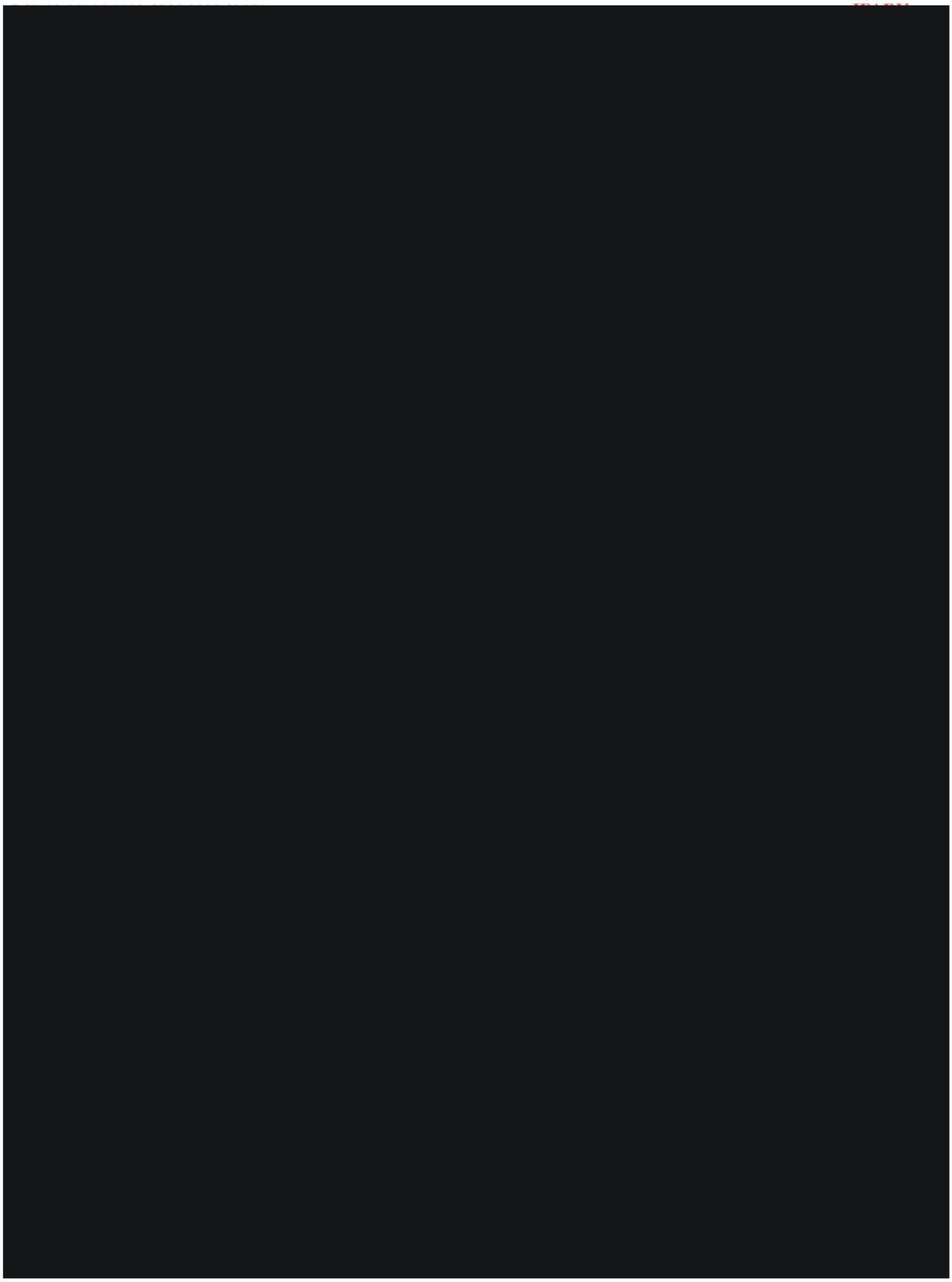
8. Financial Disclosure Certification or Certification of Non-Disclosure (for studies to be submitted for a US New Drug Application/Biologics License Application [NDA/BLA]).

Other

Any other documentation required by national law or regulations to be in the possession of the Sponsor or the Investigator for study participation or study initiation.

[redacted]

APPENDIX B. HEXSEL DM, DAL'FORNO T, HEXSEL CL. A VALIDATED PHOTONUMERIC CELLULITE SEVERITY SCALE. *J EUR ACAD DERMATOL VENEREOL*. 2009;23(5):523-528.



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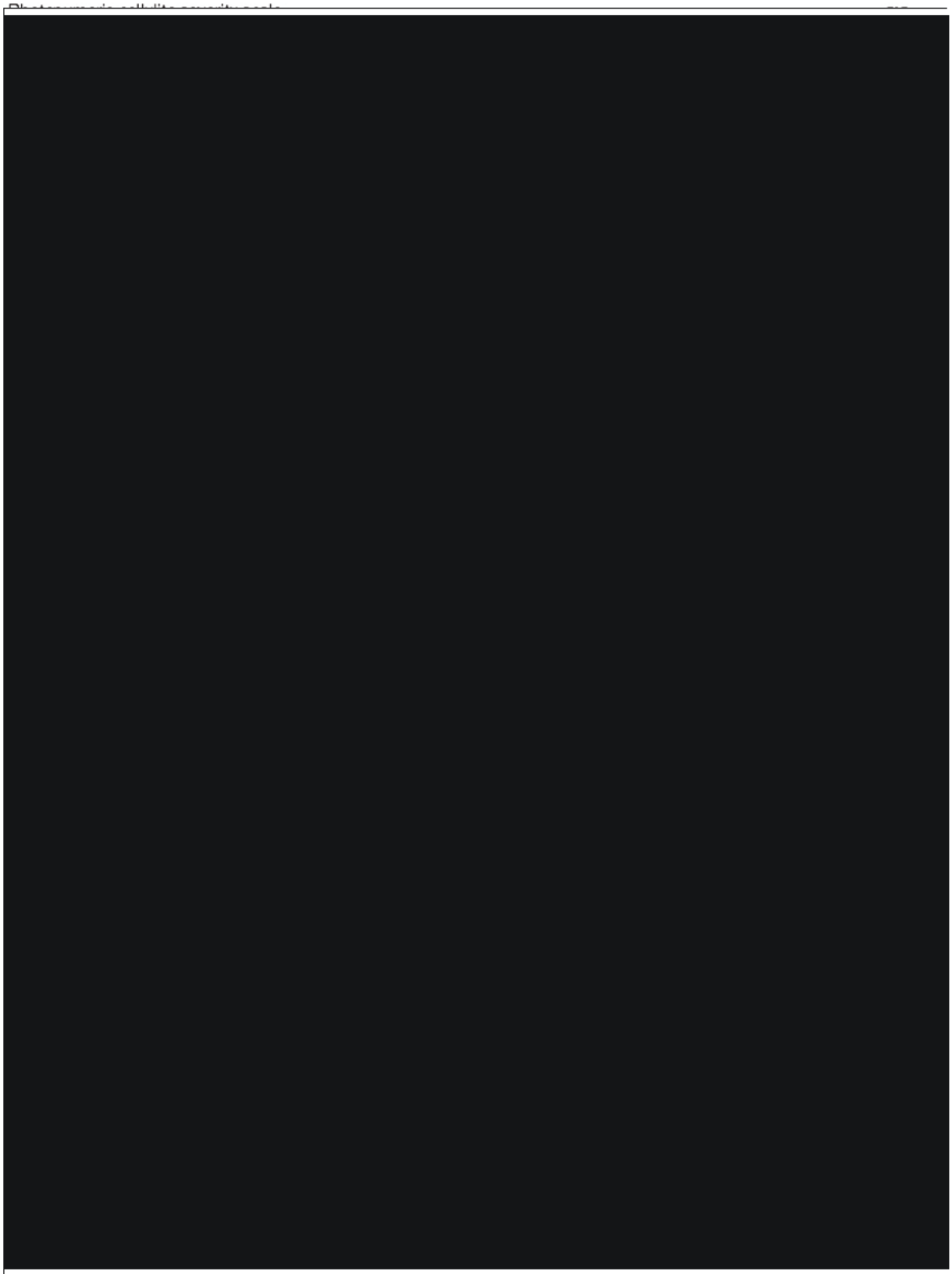
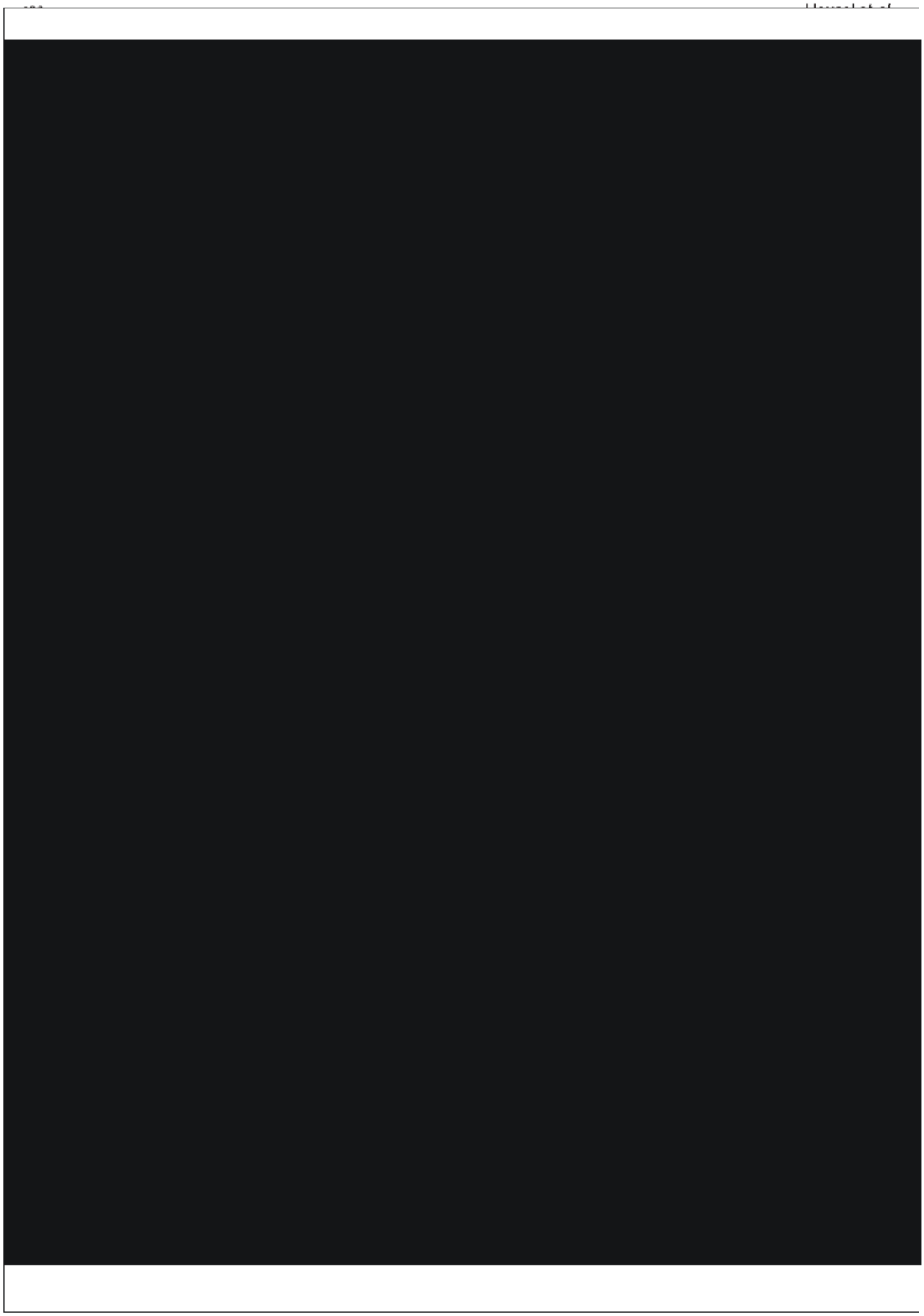
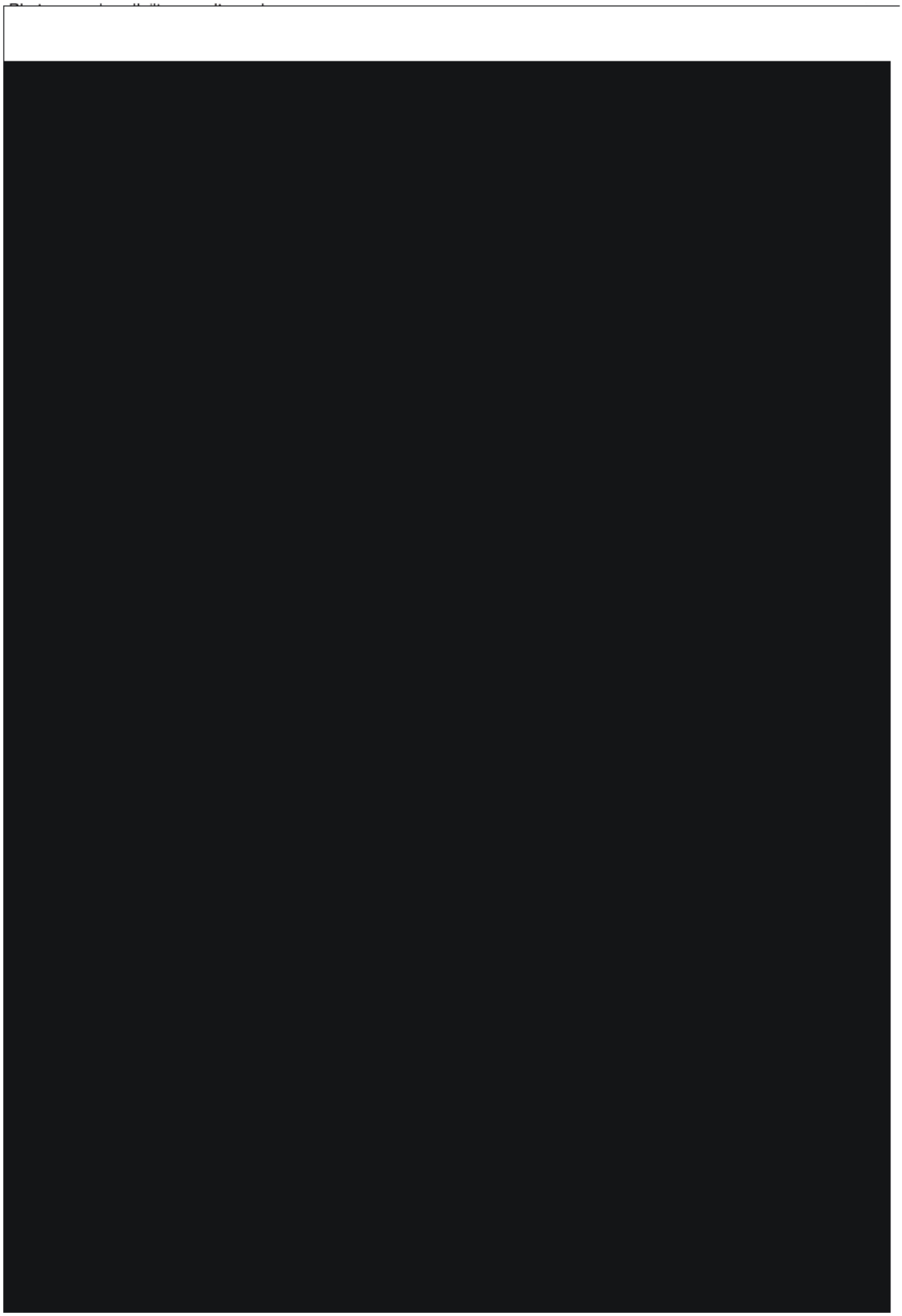
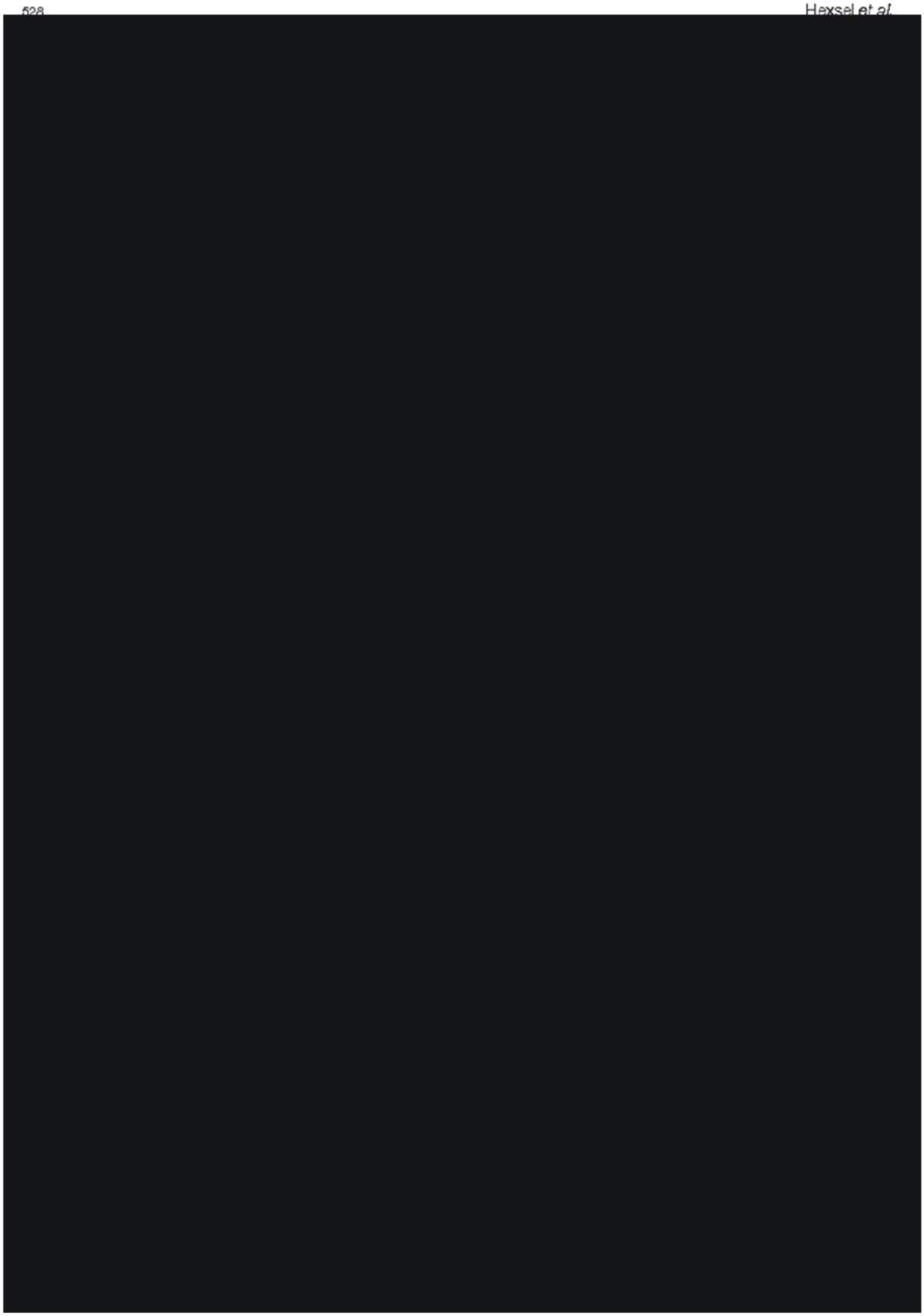
JEADV 2009, 23, 523–528

[redacted]



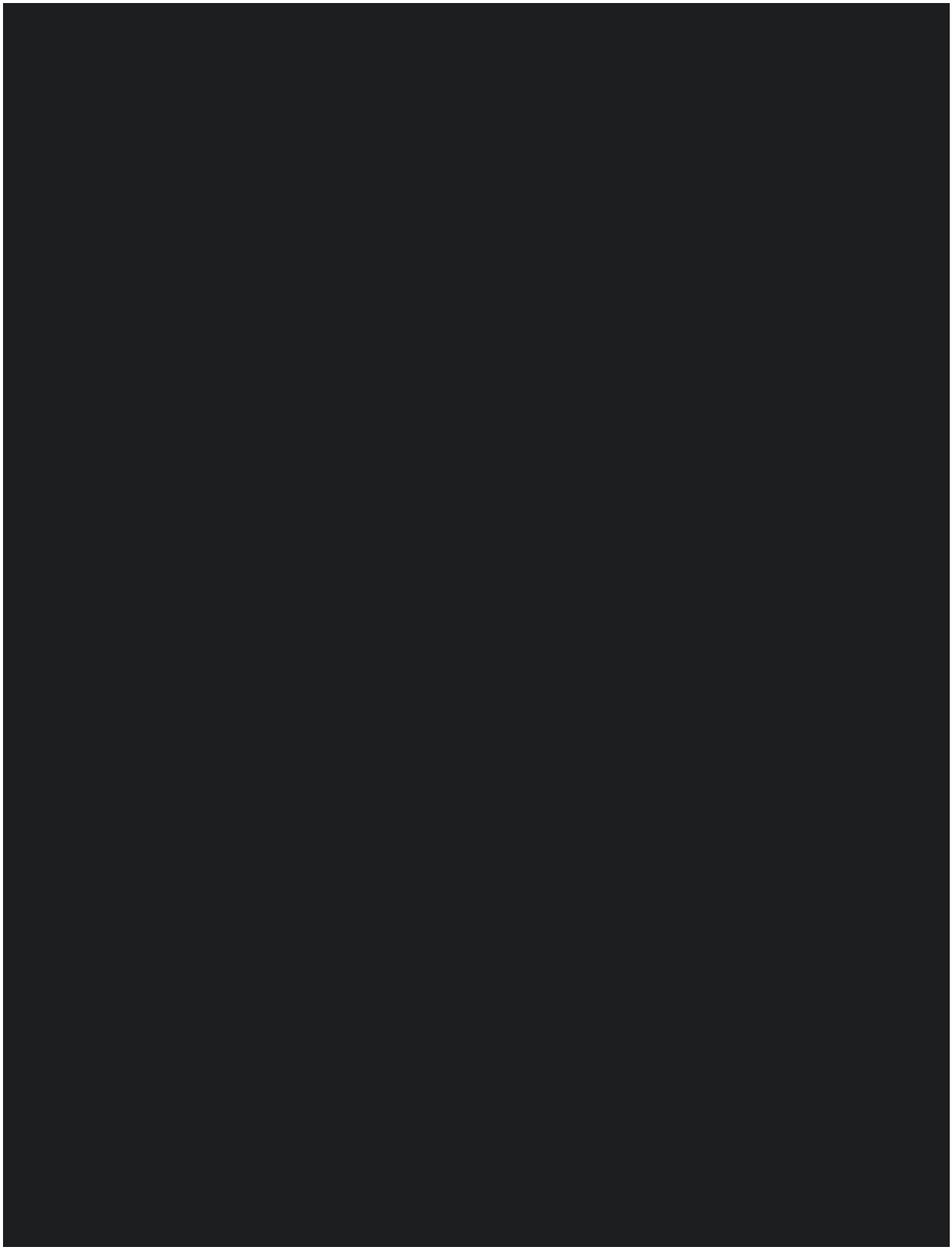


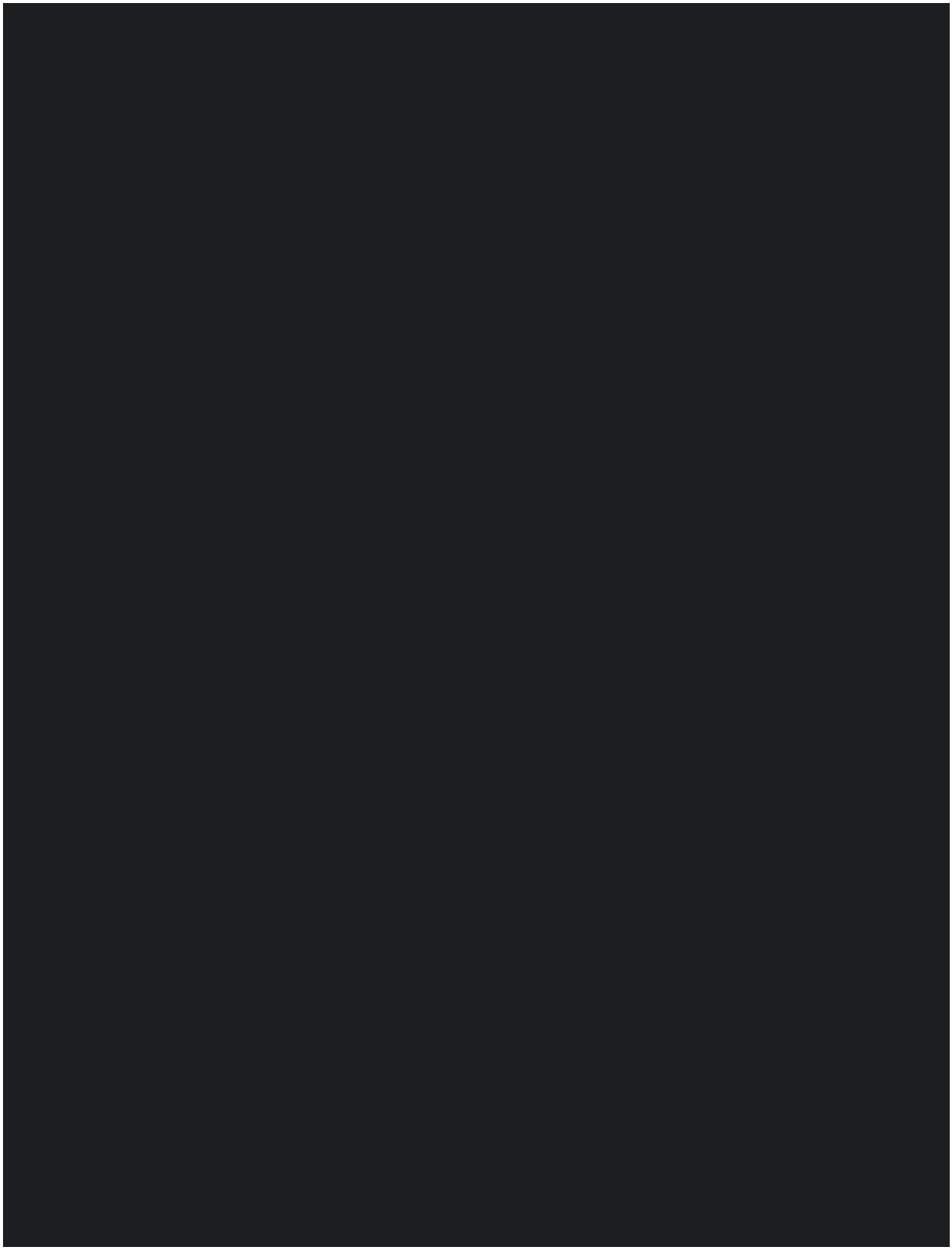


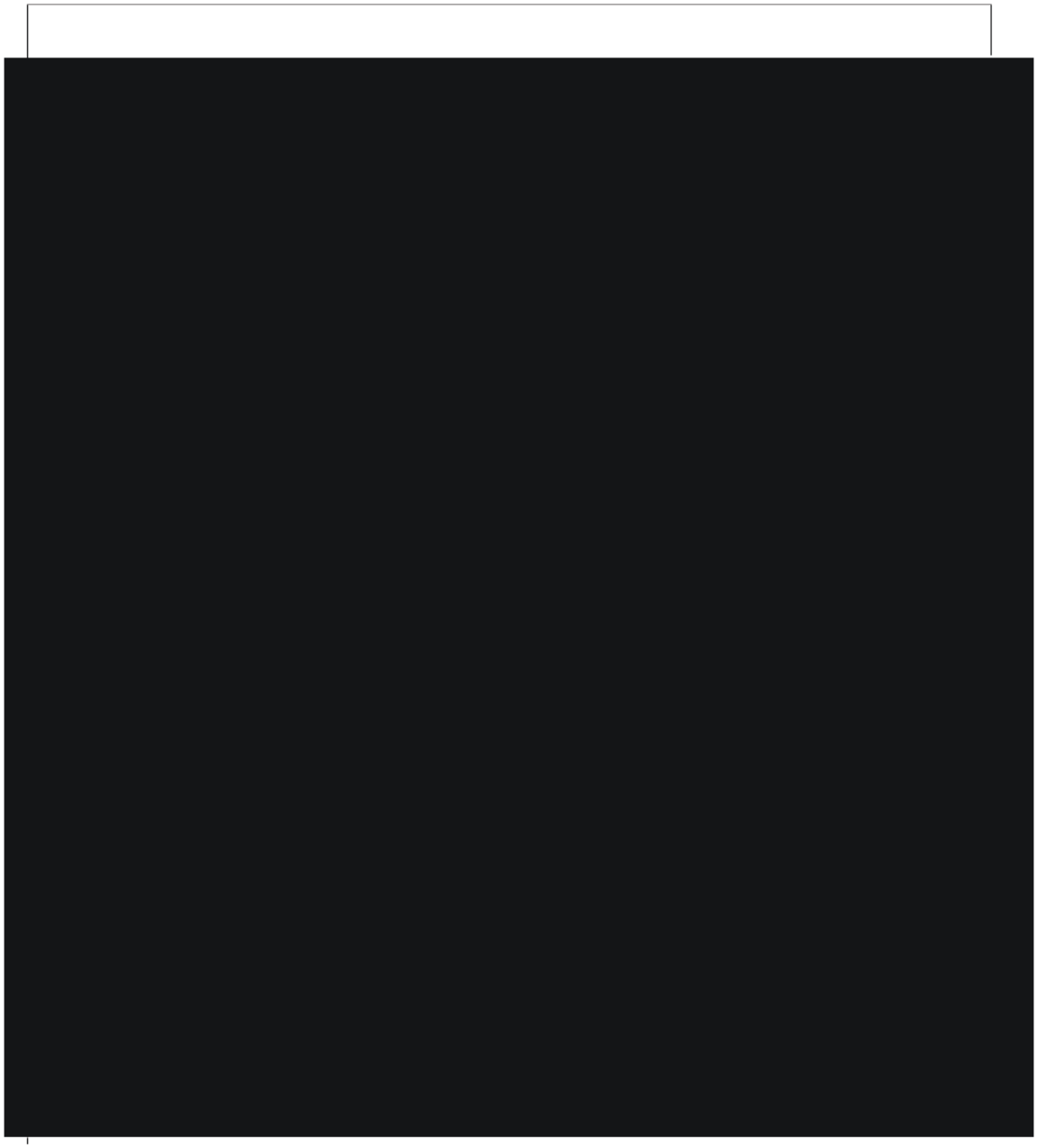


APPENDIX C. REFERENCE IMAGES FOR HEXSEL SEVERITY RATINGS

APPENDIX D. PATIENT INSTRUCTIONS FOR USE OF PATIENT-REPORTED PHOTONUMERIC CELLULITE SEVERITY SCALE (PR-PCSS)







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

COLLAGENASE CLOSTRIDIUM HISTOLYTICUM (EN3835)

EN3835-202

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

IND 110077

Amendment 1

Date:

Original Protocol: June 20, 2016

Amendment 1: July 05, 2016

Auxilium Pharmaceuticals, Inc. (Auxilium) was acquired by Endo International plc. in January 2015. The Sponsor of the application remains Auxilium; however, Endo Pharmaceuticals Inc. is authorized to act and to communicate on behalf of Auxilium.

Confidentiality Statement

2. SUMMARY OF CHANGES

The EN3835-202 protocol amendment and amended informed consent form (as necessary) have been reviewed and approved by the governing IRBs before implementation of the amendment at each study center.

Amendment 1 was incorporated into the protocol on July 5, 2016. The major reason for this amendment is to clarify that the investigators will conduct the assessment.

Section	Original Text	Revised Text
13.1.1.5 Investigator Global Aesthetic Improvement Scale (I-GAIS)	Subjects in the observation-only group will complete the I-GAIS as described below at the final study visit (month 12 or early termination) and a comparison back to the pre-treatment day 1 (Baseline) image of the assigned quadrant of the double-blind study.	Investigators will complete the I-GAIS on subjects in the observation-only group as described below at the final study visit (month 12 or early termination) and a comparison back to the pre-treatment day 1 (Baseline) image of the assigned quadrant of the double-blind study.

3. SPONSOR CONTACT INFORMATION

Table 1: Sponsor Contact Information

Role in Study	Name	Telephone and Email Address
Clinical Research Scientist	[redacted]	[redacted]
Clinical Trial Manager	[redacted]	[redacted]
Medical Monitor	[redacted]	[redacted]
SAE Reporting Pathway	Not Applicable	[redacted]

A list of other key study personnel and vendors will be provided upon request separately for your reference.

4. SYNOPSIS

Name of Sponsor/Company: Endo Pharmaceuticals Inc.

Name of Investigational Product: EN3835

Name of Active Ingredient: Collagenase clostridium histolyticum

Title of Study: A Phase 2, Open-Label Extension Study of EN3835 in the Treatment of Edematous Fibrosclerotic Panniculopathy

Lead Principal Investigator: To be determined

Study period:	**Phase of development:** Phase 2
Estimated date first subject enrolled: Jun-2016 Estimated date last subject completed: May-2017	

Objectives:

Primary:

- The primary objective of this study is to assess long-term safety of EN3835 0.84 mg at scheduled intervals over 1 year (12 months) in all subjects with edematous fibrosclerotic panniculopathy (EFP) who elect to enroll in this open-label trial regardless of their decision to receive treatment (re-treatment or re-dosing) of open-label EN3835 or opt to receive no treatment.

Secondary:

- To evaluate the durability of response to EN3835 in EFP severity over the 12-month post initial dosing of EN3835 in subjects previously receiving active treatment in study EN3835-201 using the Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS), the Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS), and the Hexsel Cellulite Severity Scale (CSS)
- To evaluate long-term response to EN3835 in assessments of EFP including subject satisfaction, Investigator Global Aesthetic Improvement Scale (I-GAIS), and Subject Global Aesthetic Improvement Scale (S-GAIS)
- To evaluate immunogenicity after exposure to EN3835

Study Design: This study is a Phase 2 open-label study for the safety and efficacy of EN3835 in the treatment of EFP. To be eligible, a subject must have participated and completed the previous cellulite study EN3835-201. Subjects will be screened for study eligibility within 14 days prior to enrolling in this study (EN3835-202). Subjects will be assessed for safety and cellulite severity assessments approximately every 3 months for a maximum of 1 year from their first exposure to EN3835. Subjects with at least 1 quadrant with moderate or severe level of cellulite will be eligible for treatment with EN3835 after unblinding of study EN3835-201; a quadrant that was treated with EN3835 in the previous study EN3835-201 will only be eligible for retreatment if the cellulite severity in that quadrant is rated at levels of cellulite severity at baseline in study EN3835-201.

A treatment course will consist of 3 treatment sessions separated by 21 days. Treatment will be allowed in eligible subjects up to a maximum of 2 treatment courses including the treatment course in study EN3835-201 if subject was treated with EN3835. Each treatment session will consist of up to 12 injections (0.07 mg/0.3 mL per injection) of EN3835 for a dose of 0.84 mg and volume of 3.6 mL. Only a quadrant with moderate (rating of 3) or severe (rating 4) level of severity as assessed by the subject and investigator using the PR-PCSS and the CR-PCSS, respectively, will be eligible for

treatment; if more than 1 eligible quadrant exists, the quadrant selected will be at the discretion of the subject. Treatments will be administered on days 1, 22, and 43; subjects will be assessed for safety on days 1, 22, 43, and 71 and for cellulite severity assessments on days 1, 43, and 71. After day 71, they will be observed every 3 months from their first exposure to EN3835 up to a maximum of 1 year. The study will terminate when at least 100 subjects have been assessed at 12 months after the first exposure to EN3835.

Number of subjects (planned): 333

Study center(s): 16 sites in the United States

Diagnosis and inclusion/exclusion criteria:

Qualification for the Open-Label Observation Phase of the Study

Inclusion criteria for observation:

1. Voluntarily sign and date an informed consent agreement
2. Have participated in and completed the double-blind study EN3835-201
3. Be willing to apply sunscreen to any treated quadrant before each exposure to the sun while participating in the study (ie, screening through end of study)

Exclusion criteria for observation:

None

Qualification for the Open-Label Treatment Phase of the Study

Inclusion criteria for treatment:

1. Voluntarily sign and date an informed consent agreement
2. Have participated in and completed the double-blind study EN3835-201 and all day 71 assessments
3. Be a female ≥18 years of age
4. At Screening B visit, have at least 1 quadrant with:
   a. a score of 3 or 4 (moderate or severe) as reported by the subject (PR-PCSS), and
   b. a score of 3 or 4 (moderate or severe) as reported by the Investigator (CR-PCSS), and
   c. a Hexsel CSS score no greater than 13
5. Be willing to apply sunscreen to the selected treatment quadrant before each exposure to the sun while participating in the study (ie, Screening B through end of study)
6. Be judged to be in good health, based upon the results of a medical history, physical examination, and laboratory profile at Screening B
7. Have a negative urine pregnancy test at Screening B and before injection of study drug and be using an 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
8. Be willing and able to cooperate with the requirements of the study
9. Be able to read, complete and understand the patient-reported outcomes rating instruments in English

***Exclusion criteria for treatment**:*

1. Has used any of the following for the treatment of EFP on the legs or buttock within the timelines identified below or intends to use any of the following at any time during the course of the study:
   - Liposuction on the side of the body selected for treatment during the 12-month period before injection of study drug
   - Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; or surgery (including subcision and/or powered subcision) within the selected treatment quadrant during the 12-month period before injection of study drug
   - Endermologie or similar treatments within the selected treatment quadrant during the 6-month period before injection of study drug
   - Massage therapy within the selected treatment quadrant during the 3-month period before injection of study drug
   - Creams (eg, Celluvera™, TriLastin®) to prevent or mitigate EFP within the selected treatment quadrant during the 2-week period before injection of study drug
2. Is presently nursing a baby or providing breast milk for a baby
3. Intends to become pregnant during the study
4. Has received an investigational drug or treatment within 30 days before injection of study drug
5. Has a known systemic allergy to collagenase or any other excipient of study drug
6. Is currently receiving or plans to receive anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication (except for ≤150 mg aspirin daily) within 7 days before injection of study drug
7. Has a known recent history of stroke, bleeding, or other medical condition, which in the investigator's opinion would make the subject unsuitable for enrollment in this phase of the study
8. Presence of any clinically relevant conditions, that in the opinion of the Investigator would interfere with completing the study including, but not limited to, visual problems, hearing problems, cognitive impairment or acute mental illness

Investigational product, dosage and mode of administration: EN3835, 0.84 mg, subcutaneous. A dose of 0.84 mg of EN3835 will be administered as up to 12 subcutaneous injections (0.3-mL injection administered as three 0.1-mL aliquots per injection, up to 12 injections per treatment session) for a maximum volume of 3.6 mL per treatment session. A treatment course will consist of 3 treatment sessions at 21 days intervals, ie, treatments on days 1, 22, and 43 of each treatment course.

For the observational periods of this study, subjects will be assessed for safety and cellulite severity assessments at approximately 3-month intervals for a maximum of 1 year following their first exposure to EN3835.

Duration of study: Twelve (12) months from first exposure to EN3835 in study EN3835-201 or study EN3835-202

Screening Phase: Up to 14 days

Observational Phase: Subjects will be assessed at visits that occur approximately every 3 months for a maximum of 1 year after the first exposure to EN3835.

Follow-up: Subjects will be assessed at visits that occur approximately every 3 months for a maximum of 1 year after the first exposure to EN3835. For subjects treated with EN3835 in this study, subjects will be observed at treatment visits (days 1, 22, and 43) and day 71 after first injection.

Reference therapy, dosage and mode of administration: Not applicable

Criteria for evaluation:

Efficacy:

- PR-PCSS while viewing digital images of the selected quadrant: 5-point scale ranging from 0 (no cellulite) to 4 (severe cellulite) (approximately every 3 months after initial injection [either an injection in previous study EN3835-201 or after an injection in this study]). If treatment is administered in this study, PR-PCSS will be obtained at Screening B (Baseline), days 22, 43, and 71 after initial treatment within this study.
- Investigator using the CR-PCSS by live assessment: 5-point scale ranging from 0 (no cellulite) to 4 (severe cellulite) (every 3 months after initial injection [either an injection in previous study EN3835-201 or after an injection in this study]). If treatment is administered in this study, CR-PCSS will be obtained at Screening B (Baseline), days 22, 43, and 71 after initial treatment within this study.
- Investigator rating of cellulite severity using the total score from the Hexsel CSS: scores can range from 0 (no cellulite) to 15 (extremely severe cellulite) (day 360). If treatment is administered in this study, Hexsel CSS will be obtained in this study at Screening B (Baseline) and day 71 after initial treatment within this study.
- I-GAIS: 7-point scale ranging from 3 (very much improved) to −3 (very much worse) (day 71)
- S-GAIS: 7-point scale ranging from 3 (very much improved) to −3 (very much worse) (day 71)
- Subject satisfaction with cellulite treatment assessment: 5-point scale ranging from 2 (very satisfied) to −2 (very dissatisfied) (day 71)

Safety:

Safety will be assessed throughout the study through the recording of:

- Adverse events (AEs)
- Vital signs
- Clinical laboratory tests
- Immunogenicity assessment (ie, assessed through the determination of binding and neutralizing anti-AUX-I and anti-AUX-II antibody levels).

In addition, for subjects treated with EN3835 in this study, injection site reactions/local tolerability in treated quadrant (through subject and Investigator reporting) will be assessed.

Statistical methods:

Sample Size Consideration:

The number of subjects (approximately 333) is intended to obtain additional subjects for adequate long-term safety data at the selected dose.

Analysis Populations:

Observational population: The Observational population is defined as all subjects treated with EN3835 in study EN3835-201 who do not receive any treatment in the current study

Safety population: The Safety population is defined as all enrolled subjects who received at least 1 injection of EN3835 in this study or in study EN38335-201.

Intent-to-Treat (ITT) population: The ITT population is defined as all enrolled subjects in this study.

Modified Intent-to-Treat (mITT) population: The mITT population is defined as ITT subjects who received at least 1 injection of EN3835 in this study with a baseline and 1 post-injection evaluation of both the CR-PCSS and PR-PCSS. All efficacy (cellulite assessments) analyses will be completed on this population.

Per-Protocol population: The Per-Protocol population is defined as those subjects in the Safety population who have no major protocol deviations.

Efficacy Evaluations:

The primary cellulite severity assessment endpoint, the proportion of composite responders with improvement of 2 or better on each scale (CR-PCSS and PR-PCSS) at day 71, will be summarized as percentages and analyzed using a Cochran-Mantel-Haenszel test that compares the 2 treatment groups and adjusts for Investigator. The ITT population will be evaluated for the primary endpoint with any subjects not having a post-injection evaluation of either CR-PCSS or PR-PCSS classified as a non-responder.

All secondary endpoints, except the Hexsel CSS total score, will be summarized as percentages. The dichotomous secondary endpoints (ie, responders endpoints) will be analyzed using a Cochran-Mantel-Haenszel test adjusted for investigator. Multiple-response endpoints (ie, scales) will be analyzed using the Mann-Whitney test. Change in Hexsel CSS total score will be summarized with descriptive statistics for continuous variable and will be analyzed using analysis of variance (ANOVA).

Safety Analysis:

The following variables are safety endpoints:

- AEs: Mapped to preferred term using the Medical Dictionary for Regulatory Activities (MedDRA)
- Vital signs
- Clinical laboratory tests

AEs will be summarized by proportion of subjects reporting each event. Descriptive statistics will be presented for actual and change from baseline at each visit for vital signs and for each clinical laboratory test parameter.

Immunogenicity: Anti-AUX-I and anti-AUX-II antibody levels will be summarized using descriptive statistics for the actual value at the visit.

5. SCHEDULE OF EVENTS

NOTE: Observation visits (Table 2) in the open-label extension study begin after completion of double-blind study (day 71). Treatment sessions (Table 3), if elected, will begin when study drug blind is broken in study EN3835-201while observation visits continue concurrently.

Table 2: Observation Assessments

Procedures	Screening A[a] (≥Day 71 Visit of Double-blind Study)	Visit 1 Day 90[b] (±7 days)	Visit 2 Day 180[b] (±7 days)	Visit 3 Day 270[b] (±7 days)	Visit 4 End of Study/ Early Termination Day 360[b] (±7 days)
Informed Consent	X				
Inclusion/Exclusion	X				
Digital photography		X[c]	X[c]	X[c]	X[c]
Body weight		X	X	X	X
Vital signs		X	X	X	X
Collection of samples:					
• Clinical laboratory					X
• Anti-AUX-I/anti-AUX-II antibody level		X	X	X	X
Subject cellulite assessments:					
• Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS)		X[d,e]	X[d,e]	X[d,e]	X[d,e]
• Subject Global Aesthetic Improvement (S-GAIS)					X[d,e]
• Subject satisfaction with cellulite treatment assessment					X[d,e]
Investigator cellulite assessments:					
• Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)		X[e]	X[e]	X[e]	X[e]
• Hexsel Cellulite Severity Scale (CSS)					X[e]
• Investigator Global Aesthetic Improvement (I-GAIS)					X[e]
Injection site reactions/local tolerability in assigned quadrant from EN3835-201 study		X	X	X	X
Adverse events	Monitored Throughout Study				

[a] Informed consent for open-label observation assessments and optional treatment election.
[b] Three (3)-month evaluation periods begin 90 days after day 1 of the double-blind study (EN3835-201) (ie, within 20 days ±4 days of completion of double-blind study).
[c] Only the treated quadrant(s) is photographed. For subjects participating in observation-only visits, the quadrant treated in the double-blind study (EN3835-201) is photographed; for subjects with open-label treatment (treated with EN3835 in study EN3835-202), the treated quadrant is photographed.
[d] Assessment made via viewing digital image photograph.
[e] Assessment of treated quadrant(s) only.
NOTE: Subject cellulite assessments must be completed before the Investigator cellulite assessments are conducted at each visit.

Table 3: Treatment Session Assessments

Procedures	Screening B[a] (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/ Early Termination Day 71 (±5 days)[b]
Informed Consent	X				
Inclusion/Exclusion	X				
Digital photography	X[c]	X[c,d]	X[c,d]	X[c,d]	X[c]
Medical history/EFP history including previous treatments	X[k]				
Prior/Concomitant Medications/Procedures	X[k]	X	X	X	X
Physical examination:	X				
• Body weight	X		X[e]	X[e]	X
• Height	X				
Vital signs	X	X[f]	X[f]	X[f]	X
12-lead ECG	X[l]				
Collection of samples:					
• Clinical laboratory	X				X
• Anti-AUX-I/anti-AUX-II antibody level		X[e]	X[e]	X[e]	X
• Urine pregnancy testing	X	X[e]	X[e]	X[e]	
Subject cellulite assessments:					
• Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS)	X[g,h]		X[e,g,h]	X[e,g,h]	X[g,h]
• Subject Global Aesthetic Improvement (S-GAIS)					X[g,h]
• Subject satisfaction with cellulite treatment assessment					X[g,h]
Investigator cellulite assessments:					
• Selection of dimples to be treated within selected quadrant		X[e]	X[e]	X[e]	
• Marking the dimples to be treated within selected quadrant		X[e]	X[e]	X[e]	
• Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)	X[h]		X[e,h]	X[e,h]	X[h]
• Hexsel Cellulite Severity Scale (CSS)	X[h,i]				X[h]
• Investigator Global Aesthetic Improvement (I-GAIS)					X[h]
Confirm Eligibility	X	X[e]			
Select Quadrant	X[j]				
Study drug administration		X	X	X	
Injection site reactions/local tolerability in selected quadrant		X	X	X	X
Adverse events	Monitored Throughout Study				

[a] Eligible subjects may choose additional treatment any time after the study drug blind is broken in study EN3835-201.
[b] Upon completion of treatment, subject will be followed at 3-month intervals as in Table 2; if study terminates early, subject will be followed through Visit 4 (day 71). If subject received placebo in the double-blind study (EN3835-201), she may be eligible for a total of 2 courses of treatment (a total of 6 treatment sessions) in this study.
[c] All 4 quadrants are photographed at screening; at other visits, the selected quadrant only is photographed.
[d] Before and after marking the dimples.
[e] Before injection.
[f] Up to 4 hours before injection; approximately 15 and 30 minutes after injection. Vital signs must be stable before the subject is discharged.
[g] Assessment made via photograph (if treatment session, use photograph taken before marking dimples).
[h] All 4 quadrants are assessed at the Screening B visit; at other visits, the selected quadrant only is assessed.
[i] Initial Hexsel CSS at screening must be ≤13 on selected quadrant (Appendix C).
[j] To qualify for treatment, the selected quadrant must have a score of 3 or 4 (moderate or severe) in both the CR-PCSS and PR-PCSS, and a Hexsel CSS score ≤13; to qualify a quadrant that had been previously treated with EN3835 in study EN3835-201, the quadrant must have CR-PCSS and PR-PCSS scores equal to or greater than study EN38325-201 baseline scores and a Hexsel CSS score ≤13.
[k] Medical history and prior medications will be based on EN3835-201 eCRF; only updates and concomitant medications need to be captured at Screening B visit.
[l] Do not conduct if Screening B visit date is within 12 months of obtaining an ECG during the double-blind study (EN3835-201).

ECG=Electrocardiogram; eCRF=Electronic case report form; EFP=Edematous fibrosclerotic panniculopathy; Tx=Treatment
NOTE: Subject cellulite assessments must be completed before the Investigator cellulite assessments are conducted at each visit.

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7. LIST OF ABBREVIATIONS

The following abbreviations and specialist terms are used in this study protocol.

Table 4: Abbreviations and Specialist Terms

Abbreviation	Definition
AE	Adverse event
Assigned quadrant	Assigned quadrant (ie, left or right buttock, or the left or right posterolateral thigh) that was suitable for treatment and was randomly assigned in the double-blind study (EN3835-201). To be suitable for treatment the quadrant must have an Investigator CR-PCSS and subject PR-PCSS score of 3 or 4 and a Hexsel CSS score of no greater than 13 at Screening B visit and at Day 1 visit.
AUX-I	Clostridial class I collagenase
AUX-II	Clostridial class II collagenase
CFR	Code of Federal Regulations
CRF	Case report form
CR-PCSS	Clinician-Reported Photonumeric Cellulite Severity Scale
CSS	Cellulite Severity Scale
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EFP	Edematous fibrosclerotic panniculopathy
FDA	Food and Drug Administration
GCP	Good clinical practice
HREC	Human research ethics committee
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
I-GAIS	Investigator-Global Aesthetic Improvement Scale
IND	Investigational new drug
IRB	Institutional review board
ITT	Intent-to-treat
kDa	Kilodalton
MedDRA	Medical Dictionary for Regulatory Activities

Table 4: Abbreviations and Specialist Terms (Continued)

Abbreviation	Definition
mITT	Modified intent-to-treat
PCS	Potentially clinically significant
PR-PCSS	Patient-Reported Photonumeric Cellulite Severity Scale
Qualified designee	Qualified by education and training to perform the study procedure (eg, sub-Investigator, nurse)
SAE	Serious adverse event
SAP	Statistical Analysis Plan
Selected quadrant	Quadrant (ie, left or right buttock, or the left or right posterolateral thigh) that is suitable for treatment and is selected by patient and investigator for treatment. To be suitable for treatment the quadrant must have an Investigator CR-PCSS and subject PR-PCSS score of at least 3 or 4 and a Hexsel CSS score of no greater than 13 at Screening B visit.
S-GAIS	Subject – Global Aesthetic Improvement Scale
TEAE	Treatment-emergent adverse event; adverse events that occur on or after the first injection of study drug

8. INTRODUCTION

8.1. Edematous Fibrosclerotic Panniculopathy

Edematous fibrosclerotic panniculopathy (EFP), commonly known as cellulite, has been defined as a local metabolic disorder of subcutaneous tissues that results in an alteration of skin topography.(1) The condition manifests as dimpled skin, described as an orange-peel, cottage cheese, or mattress texture, particularly in the gluteal-femoral region.(2,3) EFP is caused by herniation of subcutaneous fat lobules through the dermohypodermal junction. This creates an uneven surface with dimpling.(1) EFP is a medical condition resulting in a potentially cosmetically unacceptable alteration of the skin, and affects an estimated 85% to 98% of postpubertal women.(1,3)

The pathophysiology of EFP is not completely understood, but there are 3 main theories: edema resulting from excessive hydrophilia of the intercellular matrix, alteration of the regional microcirculation, and different anatomical conformation of collagenous subcutaneous tissues in women versus men.(4)

It is known that EFP is different from generalized obesity. In generalized obesity, adipocytes undergo hypertrophy and hyperplasia that are not limited to the pelvis, thighs, and abdomen.(1) In areas of EFP, adipocytes have physiologic and biochemical properties that differ from adipose tissue located elsewhere. Large, metabolically-stable adipocytes characterize EFP-prone areas; thus, the responsiveness to catecholamine-induced lipolysis is less in EFP tissues compared to visceral fat, which has the greatest responsiveness.(1)

Subcutaneous fat lobes are separated from one another by thin, usually rigid strands of collagenous connective tissues, which cross the fatty layers and connect the dermis to the underlying fascia. These septa stabilize the subcutis and divide the fat. In EFP, shortening of the collagen septa due to fibrosis provokes retraction at the insertion points of the trabeculae, causing the depressions that characterize EFP.(2) There are a higher percentage of thinner, perpendicular hypodermal septa in women with EFP than in men.(1) Weight gain makes EFP more noticeable, but it may be present even in thin subjects. Genetics may also play a role since EFP tends to run in families.

8.2. Current Edematous Fibrosclerotic Panniculopathy Treatments

There are therapies that have been utilized in an attempt to treat cellulite. Despite multiple therapeutic modalities, there is little scientific evidence that any of these treatments are beneficial. In fact, much of the evidence is anecdotal, subjective, or based only on patient self-assessment.(5) Some of the historical treatments for EFP have included:

- Weight loss: Weight loss generally decreases the severity of EFP but may only have a variable effect on EFP grades.(6)
- Pharmacological agents (eg, xanthines, retinoids, lactic acid, and herbals): Although there are numerous topical treatments that are available over the counter, there are no well-designed or large-scale studies demonstrating the effectiveness of any of these

therapies.(5) Additionally, ingredients in some of the topical treatments are unknown and may pose an increased risk for adverse effects.(5)

- Massage: Endermologie or lipomassage kneads the skin between rollers. This type of vigorous massage is posited to increase blood flow and reduce excess fluid in EFP prone areas. In a 12-week, randomized, controlled study of 52 women that examined the effectiveness of either endermologie or aminophylline versus a combination of both, there was no statistical difference in the thigh measurement between subjects.(7)
- Liposuction: Liposuction can reshape the body, but it does not typically correct cellulite as it does not interrupt collagen septae in a directed fashion. Additionally, liposuction is not a recommended treatment for cellulite given the potential for poor cosmetic outcome.(5,6)
- Mesotherapy: Mesotherapy involves injecting solutions containing various substances, eg, methylxanthines, to dissolve subcutaneous fat; however, this type of therapy often results in unwanted side effects, including infection, urticarial reactions, and bumpy or uneven skin contours.(6) To date, there are no regulatory approved mesotherapy mixtures for the treatment of EFP.
- Radiofrequency: Radiofrequency systems may temporarily improve the appearance of EFP after a series of treatments; but long-term efficacy has not been demonstrated.(6)
- Subcision: Subcision is an invasive surgical technique that severs the septa holding fat lobules that cause the skin dimpling associated with EFP. In a study conducted by Hexsel and Mazzuco, 232 subjects had subcision for the treatment of EFP.(8) Although 78% of subjects were satisfied after 1 treatment, there were no objective criteria by which to assess improvement, thereby limiting the value of this study. Additionally, side effects reported in this study included pain, bruising for 3 to 6 months, hyperpigmentation for 2 to 10 months, and skin puckering.(5,6) These effects are most likely due to the trauma from shearing the septa with a large gauge needle (eg, 16 or 18 gauge) or other cutting devices.
- Powered subcision: Powered subcision is a surgical technique utilizing a powered needle apparatus to sever the septa holding fat lobules that cause skin dimpling associated with EFP. The Cellfina® powered subcision device was recently approved by Food and Drug Administration (FDA; 2015) for the treatment of cellulite.
- Laser: Intense pulsed light has been investigated for the treatment of cellulite. Triactive® is an FDA-approved low-fluorescence 810-nm light source combined with a 915-nm laser. In a study of 16 female subjects who underwent 12 treatments with the Triactive, 21% had improvement (based on 5 blinded Investigators' analysis of photographs with respect to appearance of cellulite, skin tone, and texture) of their cellulite.(9) The CelluLaze™ system was used to treat cellulite on the thighs of 10 healthy women.(10) In this Investigator-initiated study, subjects received a single treatment with a 1440-nm laser. During the CelluLaze procedure, which is performed under a local tumescent and general anesthetic, the physician inserts a small cannula through the skin and the device technology directs controlled, laser thermal energy to

the treatment zones. The laser is designed to diminish the lumpy pockets of fat by melting the hypodermal fat; release the areas of skin depression through thermal subcision of the septal tissue; and increase the elasticity and thickness of the skin by melting the fat in the dermal invaginations. Subjective physician and subject evaluations indicated improvement in the appearance of cellulite and high patient satisfaction that persisted for a year. For both the Triactive and CelluLaze studies, there were no control groups and significance was not tested.

There remains an unmet medical need for safe and effective nonsurgical therapies to improve the esthetic outcome in women with cellulite. To effectively treat cellulite, a therapeutic approach may require disruption of the dermal septa, which are composed of collagen and cause the skin dimpling which is bothersome to many women.

8.3. EN3835 (Collagenase Clostridium Histolyticum)

Endo Pharmaceuticals Inc. (Endo) is developing EN3835 for the treatment of EFP. Because EN3835 is a proteinase that can hydrolyze the triple-helical region of collagen under physiological conditions, EN3835 has the potential to be effective in lysing subdermal collagen, such as those observed in the dermal septa, which are the underlying cause of the skin dimpling in women with EFP. EN3835 targets the collagenase structural matrix (eg, dermal septa) at the site of injection and does not require systemic exposure to be effective.

EN3835 is a parenteral lyophilized product comprised of 2 collagenases in an approximate 1:1 mass ratio, Collagenase I (AUX-I, Clostridial class I collagenase) and Collagenase II (AUX-II; Clostridial class II collagenase). These collagenases are isolated and purified from the fermentation of *Clostridium histolyticum*. Collagenase AUX-I is a single polypeptide chain containing approximately 1,000 amino acids of known sequence and with a molecular weight of 114 kDa. Collagenase AUX-II is also approximately 1,000 amino acids long and has a molecular weight of 113 kDa. These 2 collagenases are not immunologically cross-reactive and have different specificities, such that together they become synergistic, providing a very broad hydrolyzing reactivity toward collagen. Clostridial collagenases are proteinases that can hydrolyze the triple-helical region of collagen under physiological conditions.

EN3835 is currently approved for: 1) the treatment of adults with Dupuytren's contracture with a palpable cord and, 2) for the treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy.

8.3.1. Studies with EN3835 for the Treatment of Edematous Fibrosclerotic Panniculopathy

The studies summarized in this section are described in more detail in the Investigator's Brochure (IB).

8.3.1.1. Investigator-Initiated Proof-of-Concept Study

In an Investigator-initiated pilot study, 10 female subjects received EN3835 in the treatment of cellulite.(11) A 10×10-cm oval area was outlined on the posterolateral thigh and 0.58 mg EN3835 was injected using a template as 5 concurrent subcutaneous injections of 0.116 mg per injection. Subjects were followed up to 180 days after injection for reduction of the cellulite appearance in the injected area. At 1 month post injection, the area of cellulite (as measured from

photographs) was reduced 89% from baseline. Patient satisfaction score was 1.75 at month 6 (1=completely satisfied, 4=not satisfied). Side effects included the local events of injection area soreness, ecchymosis, and mild edema; these resolved within a mean of 18 days. The results from this study suggest that the collagen septa of EFP may be an appropriate substrate for lysis with injectable collagenase, and that treatment with collagenase appears to be tolerable and possibly effective. However, due to the paucity of the data, no conclusions could be drawn regarding dose, frequency, and injection technique.

8.3.1.2. Endo-Sponsored Phase 1b Dose-Escalation Study AUX-CC-830

A dose-ranging Phase 1b dose escalation study (AUX-CC-830) used a template arrangement of injections as was used in the Investigator-initiated pilot study but injected a matrix of doses, concentrations and injectate volumes to select doses for further development. This Phase 1b study showed efficacy results suggesting that collagenase clostridium histolyticum (CCH) may be effective in the treatment of EFP based on global aesthetic improvement at day 90 with ratings of "improved" by 43.4% of Investigators and 52.5% of subjects. The majority of subjects (71.7%) were "quite satisfied" or "very satisfied" with treatment on day 90. Adverse events(AEs) were local injection site events (bruising, pain, erythema, and edema) were mild or moderate and resolved within a period of 3 weeks.

8.3.1.3. Endo-Sponsored Phase 2a Dose-Ranging Study AUX-CC-831

The Phase 2a study (AUX-CC-831) was a double-blind, placebo-controlled, dose-ranging study of 150 women randomized to 0.06, 0.48, or 0.84 mg of CCH; or placebo in a 5:5:5:3 ratio. Each subject could receive up to 3 treatment sessions of study drug separated by approximately 21 days. Efficacy in this study was evaluated based on Investigator Global Aesthetic Improvement Scale (GAIS-I) and Subject Global Aesthetic Improvement Scale (GAIS-S) along with other measures of treatment efficacy. Improvements were observed in cellulite appearance based on the statistically significant changes in the appearance of cellulite based on both the GAIS-I and GAIS-S scores for the high and mid doses compared to placebo ($p<0.05$). The majority of the patients were either satisfied or very satisfied with the results of their cellulite treatment with the mid and high doses compared to placebo ($p<0.05$). Similar to the AEs reported in subjects in the previous study (AUX-CC-830) and subjects who received EN3835 for Dupuytren's contracture and Peyronie's disease, the majority of AEs occurred at the site of injection and resolved before the next scheduled treatment session.

8.3.1.4. Endo-Sponsored Phase 2b Study EN3835-201

Currently there is an ongoing Phase 2b study (EN3835-201) which is a double-blind, placebo-controlled study of 350 adult women randomized to EN3835 0.84 mg or placebo in a 1:1 ratio. Each subject can receive up to 3 treatment sessions of study drug separated by approximately 21 days; last visit is day 71. Efficacy is being evaluated using a Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS), a Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS), the Hexsel Cellulite Severity Scale (CSS), GAIS-I, GAIS-S, and a subject satisfaction assessment. Subjects that complete study EN3835-201 will be offered the option of participating in study EN3835-202.

8.4. Summary of Nonclinical Studies

Nonclinical studies necessary to support clinical studies have been performed and are summarized in the IB. Nonclinical studies in the following areas were performed: toxicology, reprotoxicity, genotoxicity, and carcinogenicity.

8.5. Summary of Known Risks and Benefits

A summary of safety risks is provided in the IB. The following events have been commonly observed in prior studies: injection site AEs such as bruising, edema, erythema and pain.

There are previously generated potential clinical benefits associated with EN3835 in treating EFP, however, such potential benefits need further clinical evaluation. It is hoped that data from this clinical study will demonstrate a measurable sustained or durable clinical benefit of EN3835 in EFP as well as longer term safety.

8.6. Rationale

This study will allow an evaluation of longer term safety (over 12 months) following EN3835 treatment of subjects with EFP. Additionally, although uncontrolled, an assessment of cellulite assessments (efficacy) of EN3835 in the treatment of quadrants with moderate or severe cellulite will be conducted in subjects treated with placebo or EN3835 in the previous double-blind study (EN3835-201). The safety of re-dosing either in a previously treated quadrant (termed *re-treatment*) or in a naive quadrant (termed *re-dosing*) in subjects that previously received EN3835 treatment in study EN3835-201 will be assessed. Finally, the durability of improvement will be evaluated in enrolled subjects following EN3835 treatment in the double-blind study (EN3835-201) as well as those being treated with EN3835 in this open-label study (EN3835-202).

9. OBJECTIVES

9.1. Primary Objective

The primary objective of this study is to assess long-term safety of EN3835 0.84 mg at scheduled intervals over 1 year (12 months) in all subjects with EFP who elect to enroll in this open-label trial regardless of their decision to receive treatment (re-treatment or re-dosing) of open-label EN3835 or opt to receive no treatment.

9.2. Secondary Objectives

- To assess safety and immunogenicity of re-treating or re-dosing a subject that had previously received treatment with EN3835
- To evaluate the durability of response to EN3835 in EFP severity over the 12-month post initial dosing of EN3835 in subjects previously receiving active-treatment in study EN3835-201 using the PR-PCSS, the CR-PCSS, and the Hexsel CSS
- To evaluate long-term response to EN3835 in assessments of EFP including subject satisfaction, I-GAIS, and S-GAIS
- To assess cellulite severity assessments in quadrants treated in this study with EN3835

9.3. Exploratory Objectives

There are no exploratory objectives for this open-label extension study.

10. INVESTIGATIONAL PLAN

10.1. Study Design

This open-label extension study will be performed at multiple centers currently participating in the double-blind, placebo-controlled, parent trial (EN3835-201) in the United States. The open-label extension study will enroll up to 350 subjects. The study is planned to end when at least 100 subjects have 12 months after exposure ie 12 months after first treatment in study EN3835-201 or study EN3835-202. Subjects who completed the entire double-blind study and sign an informed consent will be eligible to enter this open-label extension.

After the Sponsor has broken the EN3835-201 study drug blind, subjects enrolled in the open-label study will have the following options:

- To have no EN3835 treatments in study EN3835-202
- If received EN3835 in study EN3835-201, may elect to have a qualifying quadrant other than the one treated in study EN3835-201 treated with EN3835 (termed *re-dosing*)
- If received EN3835 in study EN3835-201 and the cellulite severity scores of the treated quadrant have returned to or are greater than EN3835-201 baseline scores, may elect to have the previously treated quadrant retreated with EN3835 (termed *re-treatment*)
- If received placebo in study EN3835-201, may elect to have a qualifying quadrant treated with EN3835; also may elect to have a second qualifying quadrant treated with EN3835 after completing the treatment course

Subjects enrolled in study EN3835-202 who elect to receive EN3835 treatment (either re-treatment, re-dosing, or a first treatment) must meet specific inclusion and exclusion criteria for eligibility during re-screening (Screening B) prior to EN3835 dosing.

Following completion of safety and cellulite assessments at day 71 of the double-blind study (EN3835-201), subjects will be asked if they wish to continue in the open-label extension to the double-blind study (Screening A). At the time of entry into the open-label study, subjects and Investigators will remain blinded to study drug. Until the EN3835-201 study drug blind is broken by the Sponsor, subjects will undergo observation-only visits at 3-month intervals ± 7 days (relative to the initial dose in the double-blind study) where both safety and cellulite severity assessments of the treated quadrant will be made.

Following the study drug blind being broken and communicated to centers, treatments of eligible subjects with EN3835 can begin at a visit at the discretion of the subject. Subjects electing not to receive further EN3835 treatments (observation-only subjects) will continue to be followed for safety and cellulite severity assessments at 3-month intervals through month 12. Up to 14 days prior to initiating treatment injections of EN3835 on open-label treatment visit day 1, subjects will undergo a screening evaluation (Screening B) to determine if they meet specified inclusion and exclusion criteria and to determine the quadrants, if any, that qualify for treatment.

During Screening B, photographs will be taken of each of the subject's 4 quadrants (left buttocks, right buttocks, left posterolateral thigh, and right posterolateral thigh). Subjects will again receive instructions for use of the PR-PCSS and will subsequently use the scale to rate the severity of their cellulite in each of the 4 quadrants by comparing digital images of each of their quadrants displayed on standardized computer monitors with the PR-PCSS instrument. This independent self-assessment will take place in a private setting to minimize any potential bias from site personnel. The Investigator will then assess the subject's 4 quadrants live in real-time using the CR-PCSS. The Investigator will rate the 4 quadrants using the Hexsel CSS as described in section 13.1.1.6.(12) Subjects must have at least 1 quadrant that meets the following criteria for inclusion into the treatment phase of the study:

1. PR-PCSS score of 3 or 4, and
2. CR-PCSS score of 3 or 4, and
3. Hexsel CSS score of no greater than 13.

After the independent assessments are completed separately by the subject and the Investigator, the Investigator will review his/her assessments and the subject's assessment to determine which quadrants, if any, are eligible. The eligible quadrant chosen to receive treatment in the open-label study EN3835-202 will be at the discretion of the subject. A quadrant may be chosen for re-treatment if it was the quadrant treated in study EN3835-201 or a new quadrant may be chosen for re-dosing**. NOTE: For subjects who received active drug in the assigned quadrant in the double-blind study, the quadrant must have cellulite severity at (or greater) than the EN3835-201 baseline scores of PR-PCSS and CR-PCSS to qualify for re-treatment.**

Previously placebo-treated subjects will have the option to receive a second course of EN3835 in the same or different qualifying quadrant after at least 28 days following end of the first treatment course (ie treatment of second quadrant could begin on day 71 after treating the first quadrant). The selected quadrant can be re-treated or re-dosed.

At each treatment session visit, Investigators will select the dimples within the chosen quadrant to be treated. Selection of dimples to be treated in the quadrant will be at the discretion of the Investigator. The selected EFP dimples in the selected quadrant must be well-defined and evident when the subject is standing in a consistent relaxed pose (without the use of any manipulation such as skin pinching or muscle contraction). The dimples selected to be treated will be circled with a surgical marker and injection site locations should be marked with a dot; if more than 1 injection per dimple is needed, the injection sites should be separated by approximately 2 cm. The selected quadrant will be photographed again after marking dimples. Subjects will be administered a maximum of EN3835 0.84 mg from a total of up to 12 injections. Up to 12 injections will be administered at each treatment session to treat the selected quadrant. Each of the injections will be administered as three 0.1-mL aliquots (total injection volume per injection is 0.3 mL; total injection volume per treatment session is 3.6 mL [12 injections × 0.3 mL], see table below).

Subjects will receive 3 treatment sessions (day 1, day 22, and day 43) unless the chosen quadrant has no further treatable EFP dimples and the Investigator rates the quadrant a score of 0 on the CR-PCSS. The same dimples within a quadrant or different dimples within a quadrant may be

treated at each session but injections must all be within the selected quadrant for all 3 sessions. Each treatment session will be separated by approximately 21 days.

Dose per Each Injection[a]	Injection Volume per Each Injection	Maximum Number of Injections per Each Treatment Session	Maximum Dose (mg) per Each Treatment Session	Maximum Injection Volume (mL) per Each Treatment Session	Maximum Cumulative EFP Dose
EN3835 0.07 mg N=333	0.3 mL	12 injections	0.84 mg (12 injections × 0.07 mg)	3.6 mL (12 injections × 0.3 mL)	2.52 mg (3 treatment sessions × 0.84 mg)

[a] Each injection of EN3835 is 0.3 mL administered as three 0.1-mL aliquots.

The complete Schedule of Events is provided in section 5 (Table 2 and Table 3) and summarized in section 12.

10.2. Selection of Doses

Maximum possible doses of EN3835 employed will be the same as that administered in the double-blind, placebo-controlled, parent study (EN3835-201).

10.3. Study Drug Administration

Study drug in the form of sterile vials of lyophilized EN3835 (formerly AA4500) and sterile diluent will be provided by Endo. Study drug administration at each injection site is presented in section 12.1.4.2.

10.4. Discussion of Study Design, Including the Choice of Control Groups

The use of the open-label extension design allows for the following:

- Safety data over a 12-month period will be collected to assist in further defining the safety profile of EN3835 in this population,
- Safety data and immunogenicity after repeat exposure (re-treatment/re-dosing) and monitoring of previously active-treated subjects to EN3835 over a 12-month period,
- Previously placebo-treated subjects to have exposure to EN3835, and
- Durability of the response to EN3835 (cellulite severity assessments) will be assessed.

11. SELECTION AND WITHDRAWAL OF SUBJECTS

11.1. Observation Phase

All subjects who have completed the double-blind study EN3835-201, including all day 71 assessments, and sign informed consent are eligible for enrollment in this open-label extension study and participation in the ongoing safety and cellulite evaluations.

11.1.1. Subject Inclusion Criteria for Observation

To qualify for this open-label observation study a subject must:

1. Voluntarily sign and date an informed consent agreement
2. Have participated in and completed the double-blind study EN3835-201
3. Be willing to apply sunscreen to any treated quadrant before each exposure to the sun while participating in the study (ie, screening through end of study)

11.1.2. Subject Exclusion Criteria for Observation

None

11.2. Treatment

Inclusion and exclusion criteria presented in section 11.2 apply only to those subjects in the open-label study who choose treatment.

At the time that the study drug blind is broken in the double-blind study EN3835-201, qualified subjects enrolled in the open-label study are eligible for treatment. A subject may participate in the observational period of this open-label study regardless of scoring of quadrant; however to receive treatment in this study, a subject must have at least 1 qualifying quadrant.

11.2.1. Subject Inclusion Criteria for Treatment

To qualify for treatment in the study a subject must:

1. Voluntarily sign and date an informed consent agreement
2. Have participated in and completed the double-blind study EN3835-201
3. Be a female ≥18 years of age
4. At Screening B visit, have at least 1 quadrant with:
   a. a score of 3 or 4 (moderate or severe) as reported by the subject (PR-PCSS), and
   b. a score of 3 or 4 (moderate or severe) as reported by the Investigator (CR-PCSS), and
   c. a Hexsel CSS score no greater than 13
5. Be willing to apply sunscreen to the selected treatment quadrant before each exposure to the sun while participating in the study (ie, Screening B through end of study)
6. Be judged to be in good health, based upon the results of a medical history, physical examination, and laboratory profile at Screening B

7. Have a negative urine pregnancy test at Screening B and before injection of study drug and be using an 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.
8. Be willing and able to cooperate with the requirements of the study
9. Be able to read, complete and understand the patient-reported outcomes rating instruments in English

11.2.2. Subject Exclusion Criteria for Treatment

A subject will be **excluded from treatment** in the study (but not from the observation assessments) if she:

1. Has used any of the following for the treatment of EFP on the legs or buttock within the timelines identified below or intends to use any of the following at any time during the course of the study:
   - Liposuction on the side of the body selected for treatment during the 12-month period before injection of study drug
   - Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; or surgery (including subcision and/or powered subcision) within the selected treatment quadrant during the 12-month period before injection of study drug
   - Endermologie or similar treatments within the selected treatment quadrant during the 6-month period before injection of study drug
   - Massage therapy within the selected treatment quadrant during the 3-month period before injection of study drug
   - Creams (eg, Celluvera™, TriLastin®) to prevent or mitigate EFP within the selected treatment quadrant during the 2-week period before injection of study drug
2. Is presently nursing a baby or providing breast milk for a baby
3. Intends to become pregnant during the study
4. Has received an investigational drug or treatment within 30 days before injection of study drug
5. Has a known systemic allergy to collagenase or any other excipient of study drug
6. Is currently receiving or plans to receive anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication (except for ≤150 mg aspirin daily) within 7 days before injection of study drug
7. Has a known recent history of stroke, bleeding, or other medical condition, which in the investigator's opinion would make the subject unsuitable for enrollment in this phase of the study

11.3. Subject Discontinuation Criteria

A premature discontinuation will occur when a subject who signed informed consent ceases participation in the study, regardless of circumstances, prior to the completion of the protocol. Subjects can be prematurely discontinued from the study for one of the following reasons:

- An adverse event (AE)
- A protocol violation (reason must be specified, for example: lack of compliance, use of a prohibited concomitant medication, failure to meet inclusion/exclusion criteria after study entry, etc)
- Withdrawal by subject (reason must be specified)
- The subject was "lost to follow-up"
- Other reasons (reason must be specified, for example: the subject moved, pregnancy, investigator decision, Sponsor decision to terminate trial, etc)

If a subject discontinues from the study, all end-of-study procedures should be conducted as detailed in Schedule of Events. The date a subject discontinues, the treatment, and the reason for discontinuation will be recorded in the source documentation and Electronic Case Report Form (eCRF). If, however, a subject withdraws consent, no end-of-study procedures are required except the collection of AE information. This information should be recorded in the source documentation and the eCRF.

11.3.1. Replacement Procedures

Subjects who discontinue prematurely from the study will not be replaced.

12. PROCEDURES AND TREATMENTS

12.1. Study Visits

The Schedule of Events to be performed at each visit is shown in section 5. Provided below are further details where additional instruction about the assessments that will be performed is deemed to be needed.

12.1.1. Subject Screening

Upon completion of day 71 assessments in the double-blind study EN3835-201, a subject will be eligible to enter this open-label extension study. Investigators will be expected to maintain a Screening Log of all potential study subjects. This log will include limited information about the potential subject and the date and outcome of the screening process (eg, enrolled into the study, reason for ineligibility, or refused to participate). Investigators will provide information about the study to subjects who appear to meet the criteria for participation in the study.

12.1.2. Screening Assessments

After obtaining informed consent, the full assessment of eligibility will be conducted and prior to study entry, screening assessments will be performed. Details about how the informed consent will be obtained and documented are provided in section 21.3, Subject Information and Consent. The subject may be entered into the observational phase of the study and complete safety and cellulite severity assessments at 3-month intervals as detailed in Table 2. In addition, once the study blind is broken in study EN3835-201, enrolled subjects will be asked if they wish to receive additional open-label treatments. If a subject elects to receive open-label treatment, study assessments will be conducted in accordance with Table 3.

12.1.3. Study Entry/Observational Assessments

A subject who gives written informed consent and who satisfies all eligibility criteria (section 11) may be entered into the observational phase of the study and complete safety and cellulite severity assessments at 3-month intervals as detailed in Table 2. In addition, once the study drug blind is broken in study EN3835-201, enrolled subjects will be asked if they wish to receive additional open-label treatments. If a subject elects to receive open-label treatment, study assessments will be conducted in accordance with Table 3. The subject identification number will be carried over from the double-blind, placebo-controlled study (EN3835-201).

12.1.3.1. Three-Month Assessments

Subjects will return within 20 days (±4 days) of completion of the double-blind study for the first of 4 safety and cellulite severity evaluation visits. Assessments to be completed at these visits are detailed in Table 2. Subjects are to return at 3-month intervals until they have completed 12 months from day 1 of the double-blind study. At these visits, quadrant(s) previously treated with EN3835 in the EN3835-201 study or quadrants treated with EN3835 in the open-label study will be evaluated. If the quadrant treated in study EN3835-201 is retreated in the open-label study, the 3-month assessments will reset to treatment visit 1/day 1 of the open-label treatment and the study visits will continue as described in Table 3 followed by 3-month assessments as

described in Table 2. If a different quadrant is treated in the open-label study, the 3-month assessments of both the quadrant treated in the double-blind study (EN3835-201) and the quadrant treated in the open-label study will continue.

12.1.4. Treatment Assessments (Optional)

At the time of unblinding of treatment assignment in the EN3835-201 study, subjects are eligible for optional treatment in the open-label study, provided they meet the inclusion and exclusion criteria detailed in section 11 and at least 1 quadrant meets the criteria for treatment. A subject may receive a maximum of 2 courses of treatment (6 treatment sessions) overall (total of treatments in double-blind and open-label study). If a subject received placebo in the double-blind study, she may be eligible for 2 treatments in the open-label study; if a subject received active drug in the double-blind study, she may be eligible for 1 additional treatment (3 treatment sessions) in the open-label study.

Selection of Treatment Quadrant

During the Screening B visit, each subject will have photographs taken of the 4 targeted quadrants of the study (eg, their left and right buttocks and left and right posterolateral thighs). Subjects will receive instructions (Appendix D) for using the PR-PCSS and will use the scale to rate the severity of their cellulite in each of the 4 quadrants by comparing each of their digital image photographs with the PR-PCSS instrument. This self-assessment will take place in a private setting to minimize any potential bias from site personnel (the Investigator is blinded to these scores). The Investigator will then assess each of the 4 subject's quadrants live in real-time using the CR-PCSS. The Investigator will then examine each of the 4 quadrants live to assess the subject using the Hexsel CSS as described in section 13.1.1.6.(12) Subjects must have at least 1 quadrant that meets the following criteria for treatment in the study:

1. PR-PCSS score of 3 or 4, and
2. CR-PCSS score of 3 or 4, and
3. Hexsel CSS score no greater than 13.

After the independent assessments are completed separately by the subject and the Investigator, the Investigator will review his/her assessments and the subject's assessment to determine which quadrants, if any, are eligible. The eligible quadrants (must meet all 3 of the inclusion criteria (PR-PCSS, CR-PCSS, and Hexsel CSS scores), if any, for treatment will be determined by the Investigator after which the quadrant selected will be at the discretion of the subject. For subjects treated with EN3835 in the double-blind study, if the quadrant treated in the double-blind study (EN3835-201) has PR-PCSS and CR-PCSS ratings identical or more severe than the double-blind study (EN3835-201) PR-PCSS and CR-PCSS baseline ratings (Baseline is day 1 of study EN3835-201), subjects can elect to have that same quadrant re-treated. Subjects who choose re-treatment of the previously treated quadrant will be classified in the re-treatment arm. If another quadrant besides the previously treated quadrant meets the all 3 of the inclusion criteria, subjects can choose to be treated in the naive quadrant. Subjects who choose treatment into a naive quadrant will be classified in the re-dosing arm.

Assessments made with the PR-PCSS (from digital image), the CR-PCSS (live assessment), and the Hexsel CSS score during the open-label Screening B visit will be the baseline severity of EFP in the selected quadrant.

A subject who received placebo in the double-blind study may be treated in the same quadrant in the open-label study if the quadrant still meets all 3 criteria OR another qualifying quadrant may be selected for treatment by the Investigator and subject. Following day 71 of a treatment course (3 treatment sessions), subjects can choose to receive a second treatment session in either the same quadrant if it still meets qualification criteria or in a different quadrant that meets qualification criteria. For the first treatment session, these subjects will be considered in the treatment arm. For the second treatment session, if the same quadrant is treated, subjects will be in the re-treatment arm; if a different quadrant is treated, subjects will be considered in the re-dosing arm.

If no quadrant meets all 3 criteria, the subject may continue in the observation-only study with safety and cellulite severity evaluations performed at 3-month intervals but may not receive treatment in this study.

Selecting and Marking Dimples

Selection of dimples to be treated in the selected quadrant is at the discretion of the Investigator or qualified designee. Dimples must be well-defined and evident when the subject is standing in a consistent relaxed pose (without the use of any manipulation such as skin pinching or muscle contraction). Each subject will receive 3 treatment sessions of study drug in the selected quadrant. During each treatment session, the treatment quadrant will be photographed before and after dimple marking while the subject is standing in a consistent relaxed pose as described in the Photography Manual. The cellulite severity assessments using the PR-PCSS, CR-PCSS, and Hexsel CSS will be completed prior to dimple marking at treatment visits 2, 3, and 4/end of treatment.

12.1.4.1. Screening B (Days −14 to −1 Relative to Open-Label Treatment Visit Day 1)

Subjects meeting the relevant criteria listed in section 11.2 may be eligible for treatment in the open-label study. The following procedures will be performed and documented during the screening period:

1. Evaluate eligibility based on inclusion/exclusion criteria (section 11.2)
2. Subject will have digital photographs taken of the 4 targeted quadrants of the study (left and right buttocks, and left and right posterolateral thighs) (section 13.1)
3. Subjects will get instruction on the use of the PR-PCSS (Appendix D)
4. Subjects will rate each quadrant using the PR-PCSS while viewing their digital images (section 13.1.1.1)
5. The Investigator will conduct live assessments of subject's cellulite severity of each quadrant using the CR-PCSS (section 13.1.1.4)
6. The Investigator will conduct live cellulite evaluation of each quadrant using the Hexsel CSS (section 13.1.1.6).

7. If at least 1 quadrant qualifies based on PR-PCSS, CR-PCSS, and Hexsel CSS ratings, subject may return for treatment on treatment visit 1. If none of the 4 quadrants qualify, the subject may remain in the study and have safety and cellulite severity evaluations performed at 3-month intervals but is not eligible for treatment.
8. Subject will select an eligible quadrant (based on qualifying scores) to be treated at their discretion.
9. Medical history including EFP history. Medical history will be based on EN3835-201 eCRF; only updates to the history need to be captured at Screening B visit.
10. Record prior and concomitant medications/procedures. Prior medications will be based on EN3835-201 eCRF; only updates and concomitant medications need to be captured at Screening B visit (section 12.2).
11. Physical examination including measurement of body weight and height (section 14.10)
12. Vital sign measurements (section 14.8)
13. 12-lead electrocardiogram (ECG), not necessary if the date of the ECG obtained during the double-blind study (EN3835-201) is within 12 months of the date of the Screening B visit (section 14.9)
14. Collection of samples for:
    a. Clinical laboratory testing including Anti-AUX-I and anti-AUX-II antibody testing (section 14.7)
    b. Urine pregnancy testing (section 14.7)
15. Adverse events (section 14)

12.1.4.2. Treatment Session 1 (Visit 1B)

Pre-injection

1. Confirm eligibility criteria (section 11)
2. Take digital photography of selected quadrant before dimple marking (section 13.1)
3. Record concomitant medications/procedures (section 12.2)
4. Vital sign measurements (section 14.8)
5. Collection of samples for urine pregnancy testing (section 14.7)
6. Select and mark dimples to be treated (section 12.1.4)
7. Take digital photograph of selected quadrant after dimple marking (section 13.1)

Injection

Administration of study drug in the prone position (see below)

Post-injection

1. Record number of dimples treated and number of injections administered

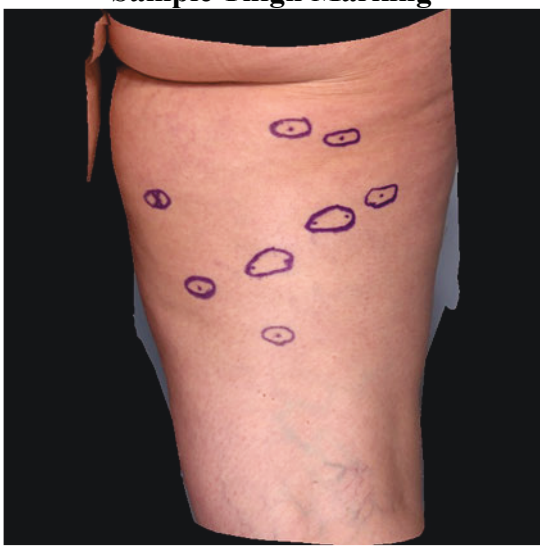
2. Vital sign measurements (section 14.8)
3. Injection site reactions and local tolerability
4. Adverse events (section 14)

The selected quadrant will be photographed before and after dimple marking while the subject is standing in a consistent relaxed pose as described in the Photography Manual. Before injection at treatment session 1, the Investigator or qualified designee will begin the session by selecting dimples within the chosen quadrant that are well defined, evident when the subject is standing, and suitable for treatment; treatment consists of up to 12 injections per session.. Because the goal of treatment is to improve the aesthetic appearance of the entire quadrant, the Investigator will be instructed to select dimples that in his or her opinion would most improve the aesthetic appearance of the entire quadrant. The same dimples within a quadrant or different dimples within a quadrant may be treated at each session but injections must all be within the selected quadrant for all 3 sessions.

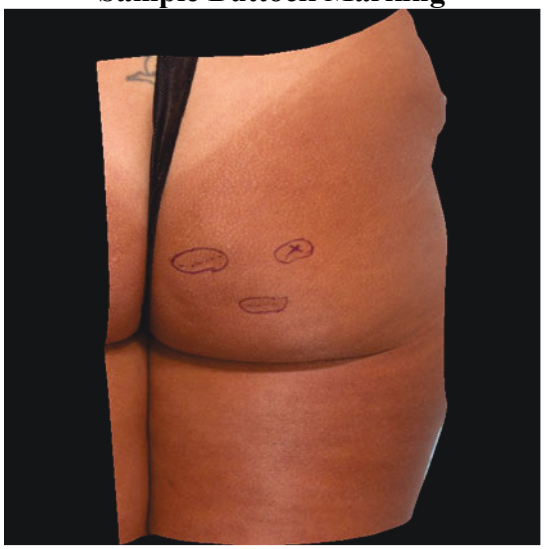
For each dimple selected for treatment, the Investigator or qualified designee will choose injection sites (injection sites within a dimple should be spaced approximately 2 cm apart, if a dimple requires more than 1 injection). Each injection site will be marked with a "dot" using a surgical marker. For round dimples, the "dot" will be placed in the center of the dimple; for elongated dimples, "dots" will be spaced out approximately 2 cm along the longer axis of the dimple. The Investigator or qualified designee will then use a surgical marker to circle each of the dimples selected for treatment. Circles in the selected quadrant should not overlap.

Examples of subject dimple marking:

Sample Thigh Marking



Sample Buttock Marking

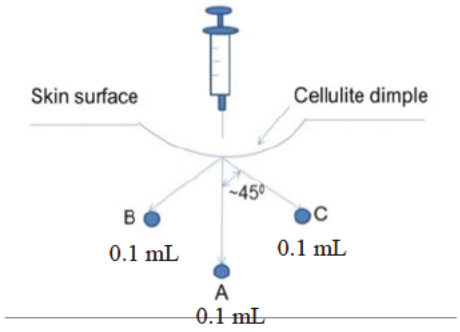


Study Drug Administration at Each Injection Site

See section 18.4 for study drug preparation. Study drug will be injected subcutaneously while the subject is in a prone position using a syringe with a 30-gauge ½-inch needle. Each injection site will receive a single skin injection of study drug administered as three 0.1-mL aliquots to Positions A, B and C (for a total injection volume of 0.3 mL) as shown in the following figure.

The depth of injection corresponds to the length of the treatment needle (0.5 inches) from the tip of the needle to the hub or base of the needle without downward pressure.

During each treatment session, the Investigator will be supplied with 4 syringes. Each syringe will contain 0.9 mL of study drug (ie, up to 3 injections in each syringe). Up to 12 skin injections of 0.3 mL per injection will be administered within the selected treatment quadrant during each treatment session.



- **Needle Tip Position A**: Position the needle at 90° angle perpendicular to the skin surface at the injection site and inject one 0.1-mL aliquot of study drug by gently pushing on the syringe plunger.
- **Needle Tip Position B**: Withdraw the needle slightly (but not so much as to remove from the injection site) and reposition approximately 45° (**but not more than 45°**) off vertical and above the long axis of the dimple and inject one 0.1-mL aliquot of study drug) by gently pushing on the syringe plunger.
- **Needle Tip Position C**: Withdraw the needle slightly (but not so much as to remove from the injection site) and reposition approximately 45° (**but not more than 45°**) off vertical and below the long axis of the dimple and inject one 0.1-mL aliquot of study drug by gently pushing on the syringe plunger.
- Withdraw needle from the skin completely and move to the next identified injection site. Complete up to a total of three 0.3-mL injections (each administered as three 0.1-mL aliquots) and discard the first syringe appropriately. Use the second, third and fourth syringes to complete dosing in the quadrant (up to three 0.3-mL injections per syringe, each injection administered as three 0.1-mL aliquots). Up to twelve skin injections of 0.3 mL will be administered within the treated quadrant during each treatment session.
- After treatment the subject will remain prone for at least 5 minutes.

The total number of dimples treated and the total number of injections administered will be recorded during treatment sessions 1, 2, and 3.

NOTE: EN3835 is a foreign protein and Investigators must be prepared to address and manage an allergic reaction should it occur. At the time of each injection, a 1:1,000 solution of epinephrine for injection, 50-mg diphenhydramine injection or a suitable equivalent, and oxygen should be available and the Investigator and site staff must be familiar with their use.

Care Procedures After Injection

To evaluate the subject for possible immediate immunological AEs, the subject will remain in direct observation of medical personnel who are skilled in the management of an allergic reaction for 30 minutes after receiving the injection of study drug and until the subject exhibits no sign of an immunological or other clinically significant systemic or local AE. The subject's vital signs should be stable before the subject can leave direct observation (see section 14.8).

The Investigator or qualified designee will then apply a sterile dressing to the injection site with hypoallergenic tape. The subject will be instructed to remove the dressing in the evening.

12.1.4.3. Treatment Session 2 (Visit 2/Day 22 ± 3 Days) and Treatment Session 3 (Visit 3/Day 43 ± 3 Days)

Pre-injection

1. Record concomitant medications/procedures (section 12.2)
2. Body weight measurements
3. Vital sign measurements (section 14.8)
4. Collection of samples for urine pregnancy testing (section 14.7)
5. Digital photograph of selected quadrant before dimple marking (section 13.1)
6. Subject assessment of the severity of cellulite using photograph of the selected quadrant via PR-PCSS (section 13.1.1.1). NOTE: Complete the subject (PR-PCSS) assessment before the Investigator (CR-PCSS) assessment and before dimple marking.
7. Investigator live assessment of the severity of cellulite using the CR-PCSS (section 13.1.1.4)
8. Selection and marking of dimples to be treated (section 12.1.4)
9. Digital photograph after dimple marking (section 13.1)

Injection

Administration of study drug in the prone position (section 12.1.4.2)

Post-injection

1. Record number of dimples treated and number of injections administered
2. Vital sign measurements (section 14.8)
3. Injection site reactions and local tolerability
4. AEs (section 14)

If no injections are given at treatment session 2, subjects will still return for the day 43 visit and the selected quadrant will again be evaluated by the subject (PR-PCSS) and Investigator (CR-PCSS). If the Investigator rates the selected quadrant greater than 0 on the CR-PCSS, injections at treatment session 3 should be given.

Because the goal of treatment is to improve the aesthetic appearance of the entire quadrant, the Investigator will be instructed to select dimples that in his or her opinion would most improve the aesthetic appearance of the entire quadrant. The same dimples within a quadrant or different dimples within a quadrant may be treated at each session but injections must all be within the selected quadrant for all 3 sessions. Each subject will receive all 3 treatment sessions unless the selected quadrant has no treatable EFP dimples and the Investigator rates the quadrant a score of 0 on the CR-PCSS.

After the dimples are selected, the Investigator or qualified designee will again mark each injection site with a "dot," and circle each dimple (circles should not overlap).

12.1.4.4. Day 71 (±5 Days) End of Treatment/Early Termination

The following procedures will be performed on Day 71:

1. Record concomitant medications/procedures (section 12.2)
2. Measurement of body weight
3. Vital sign measurements (section 14.8)
4. Collection of samples for:
   a. Clinical laboratory testing (section 14.7)
   b. Anti-AUX-I and anti-AUX-II antibody testing (section 14.7.1)
5. Digital photograph of selected quadrant (section 13.1)
6. Subject cellulite assessments of the selected quadrant using the photographic image (NOTE: complete subject cellulite assessments before Investigator cellulite assessments) using:
   a. PR-PCSS assessment (section 13.1.1.1)
   b. S-GAIS (section 13.1.1.2)
   c. Subject satisfaction with cellulite treatment assessment (section 13.1.1.3)
7. Investigator cellulite assessments of selected quadrant using:
   a. CR-PCSS live assessment of subject (section 13.1.1.4)
   b. Hexsel CSS assessment of live subject while subject is standing in a relaxed position (section 13.1.1.6)
   c. I-GAIS (section 13.1.1.5)
8. Injection site reactions and local tolerability
9. AEs (section 14)

12.1.4.5. Follow-up Visits

Following the day 71 visit, the quadrant(s) treated with EN3835 in the open label study will be evaluated every 3 months from the first exposure to EN3835 following the schedule in Table 2. The first follow-up visit will be approximately 20 days after the day 71 visit (ie approximately day 90 after treatment session 1). Follow-up visits will continue until the study is terminated when at least 100 subjects have been assessed at 12 months after the first exposure to EN3835.

12.2. Prior and Concomitant Medications and Procedures

All medications (including over-the-counter medications) taken by the subject at screening visit 1 through the end of the study must be recorded

Additionally, any diagnostic, therapeutic or surgical procedures performed during the study period should be recorded including the date, indication for and description of the procedure.

12.2.1. Prohibited Medications

The following medications are prohibited for those subjects that elect to have treatment with study drug during the treatment 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 the treatment phase of the study. For those subjects in the observational-only phase of study, there are no prohibited medications:

Table 5: Concomitant Medication Restrictions for Subjects During the Treatment Phase of Study

Drug Class	Restrictions
Anticoagulants	Subjects who elect treatment cannot take antiplatelet agents or anticoagulants (except for ≤150 mg aspirin daily) within 7 days before and after the dosing administration.

12.2.2. Prohibited Procedures

The treatments and procedures listed in exclusion criteria are prohibited during the study.

12.3. Treatment Compliance

All subjects who elect to have treatment will receive study drug administered by a clinician at the investigator's site.

Accidental or intentional overdoses should be reported to the Sponsor/designee promptly (see section 14.6.2).

12.4. Blinding and Randomization

This study will be conducted as an open-label investigation; no blinding of assigned treatment will occur.

12.5. End of Study

The end of study is when 100 subjects complete the 1-year safety and cellulite severity evaluations. At the time of study termination, ongoing subjects receiving treatment will be followed through the day 71 visit. The remaining enrolled subjects (in excess of the first 100 subjects to complete 1 year) will undergo early termination procedures in accord with the Schedule of Events (section 5).

13. ASSESSMENT OF EFFICACY

13.1. Primary Efficacy Measurements

Although measures of efficacious drug effect (ie, durability of improvement) will be made during the observation phase before the study drug blind is broken in the double-blind study (EN3835-201), and thereafter to the end of study, emphasis is on the assessment of safety over 12 months after exposure to EN3835. Cellulite severity assessments will be made at scheduled intervals for both observation-only subjects (not receiving EN3835) as well as subjects who choose re-dosing or re-treatment with EN3835.

Digital Photography: Digital photography will be utilized to assess certain cellulite severity parameters at specific intervals (see Schedule of Events, Table 2) for subjects in the observation-only group as well as those electing to be re-treated or re-dosed with EN3835. At the Screening B visit for subjects electing to receive re-dosing or re-treatment, the Investigator or qualified designee will photograph each quadrant using a Sponsor-supplied standardized digital camera. The subject will be standing for each photography session and will be wearing a standardized photographic garment as described in the Photography Manual. The Investigator or qualified designee will photograph the selected quadrant as follows:

- Screening B (no dimple marking)
- Before and after dimple marking (prior to injections) on days 1, 22, and 43 of each treatment course
- During the day 71 visit (end of treatment phase/early termination) of each treatment course

All photographs from this study are the property of Endo and may be utilized for clinical development, scientific communication, marketing, regulatory purposes, and/or legal applications as required/desired by Endo.

13.1.1. Subject and Investigator Cellulite Assessments

As in the double-blind parent study, Investigator cellulite assessments are independent of the subject assessments. Therefore, all subject cellulite assessments must be completed before the Investigator's cellulite assessments are made. After both the subject's and investigator's assessments are completed, the subject's assessments will be revealed and compared to the clinician's assessments to determine eligible quadrants. If more than 1 quadrant is eligible, the subject will select one for treatment.

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

The PR-PCSS will be conducted for the purpose of assessing the severity of cellulite in the buttock or thigh; there are separate scales for buttocks or thighs. The scales are 5-level photonumeric scales developed specifically for patients and used by the subject to assess the severity of their cellulite in the quadrants by viewing digital images of each of their quadrants captured by photography at the visit; the ratings range from 0 (None) to 4 (Severe) with labels and descriptors to aid the subject in the assessments.

All subjects who enter the observation-only phase of the study will have the PR-PCSS evaluation at months 3, 6, 9, and 12.

For subjects electing re-treatment or re-dosing after the study drug blind is broken in study EN3835-201, a Screening B visit (Baseline) within 14 days before dosing day 1 will occur. Subjects will have digital photographs taken of all 4 quadrants as done in the double-blind trial for qualifying purposes. Subjects will then perform the PR-PCSS for both buttocks (Figure 1) and thighs (Figure 2) and will be reminded of their proper use (Appendix D).

At the beginning of visits on days 22, 43, and 71; digital photographs of the selected quadrant will be taken. If the buttock is the treated region, subjects will be given the PR-PCSS for the buttock to use to make their evaluation; if the thigh is the treated region, subjects will be given the PR-PCSS for the thigh to make their evaluation.

Figure 1: Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS) for the Buttock

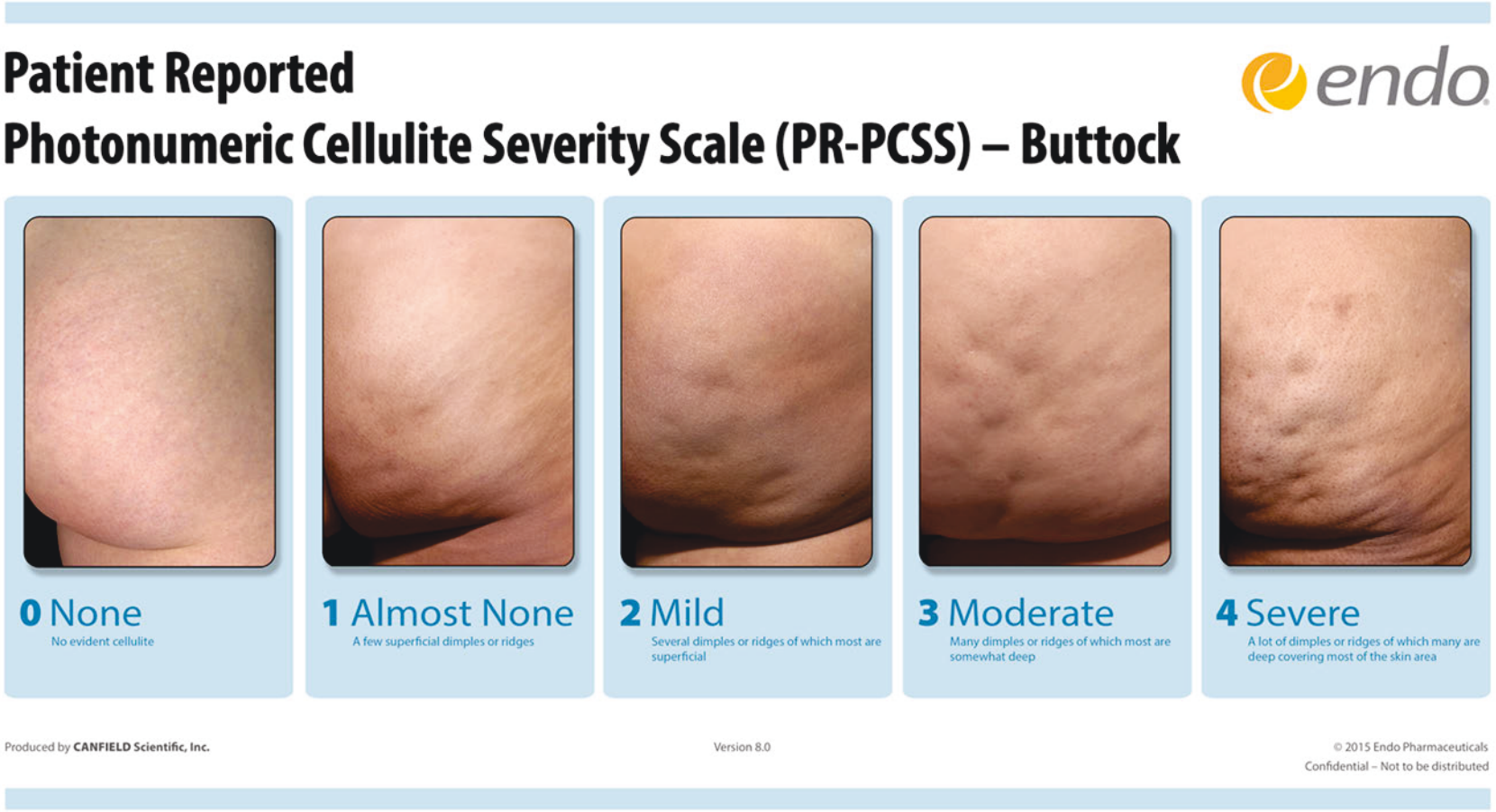


Figure 2: Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS) for the Thigh

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

Subjects in the observation-only group will complete the S-GAIS as described below at the final study visit (month 12 or early termination) using the pre-treatment day 1 image (Baseline) of the assigned quadrant in the double-blind study for comparison.

The S-GAIS assessment will be done on day 71 of the treatment course and then at month 12 or the final study visit and compared back to the pre-dosing Screening B image (Baseline for treatment subjects) of the selected quadrant. All treated subjects will be instructed to answer the following question: *How would you rate the appearance of your treated cellulite after treatment?*

The S-GAIS assessment will occur after the subject has completed the PR-PCSS assessment to avoid introducing potential bias to the static PR-PCSS assessment. Each subject will view the pre-dosing Screening B visit digital image alongside their day 71 treatment course visit and month 12 or end of study visit digital image of their selected quadrant to aid in the assessment (Table 6). Subjects will circle the rating below that best represents their answer.

Table 6: 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 originally.

13.1.1.3. Subject Satisfaction with Cellulite Treatment Assessment

For observation-only subjects (not receiving EN3835) the subjects will assess their satisfaction with cellulite treatment at the 12 month or end of study visit by being instructed to answer the following question: *Today, how satisfied are you with the results of the cellulite treatment you received on the specific area or areas on your buttocks or thighs that were treated?* Subjects will circle the rating in the below table that best represents their answer.

For subjects who have elected to receive EN3835 either through re-treatment or re-dosing, the subject satisfaction with the cellulite treatment (Table 7) with be done at the treatment course day 71 and the month 12 visit or end of study visit. Subjects will be instructed to answer the following question: *Today, how satisfied are you with the results of the cellulite treatment you received on the specific area or areas on your buttocks or thighs that were treated?* Subjects will circle the rating below that best represents their answer.

Table 7: Subject Satisfaction with Cellulite Treatment Assessment

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

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

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

Investigators will have been trained on the use of the CR-PCSS. For observation-only subjects, the CR-PCSS will be done at 3, 6, 9, and 12 months or at the end of study visit.

For subjects who elected to receive EN3835 after the study drug blind is broken in study EN38325-201 as a re-treatment or re-dosing, the Investigator, at the Screening B visit (Baseline) will determine severity of cellulite of the 4 quadrants by assessing live subjects using the CR-PCSS for buttock (Figure 3) and thighs (Figure 4) after the subject has completed their self-assessment using the PR-PCSS. The eligible quadrant chosen for injection will be at the discretion of the subject. Before injections on treatment visit days 22 and 43 and on visit day 71; Investigators will evaluate the selected quadrant by live assessments. If the buttock is the treated region, the Investigator will be use the CR-PCSS for the buttock to make their evaluation; if the thigh is the treated region, the Investigator will use the CR-PCSS for the thigh to make their evaluation. In each case, the Investigator will make his/her assessment independently and after the subject has conducted their self-assessment using the PR-PCSS.

Figure 3: Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS) for the Buttock

Figure 4: Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS) for the Thigh

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

Investigators will complete the I-GAIS on subjects in the observation-only group as described below at the final study visit (month 12 or early termination) and a comparison back to the pre-treatment day 1 (Baseline) image of the assigned quadrant of the double-blind study.

On day 71 of the treatment course and the 12 month or end of study visit, the Investigator will determine the degree of improvement from the Screening B digital image of the selected quadrant by comparing the cellulite in live assessment on day 71 and at month 12 or study end to the Screening B pre-treatment (Baseline) image of the subject's selected quadrant (Table 8). The I-GAIS assessment will occur after the CR-PCSS assessment (section 13.1.1.4) to avoid introducing potential bias to the static CR-PCSS assessment by the Investigator at the site. The Investigator will circle the rating below that best represents their answer.

Table 8: Investigator Global Aesthetic Improvement Scale (I-GAIS)

Rating	Response Option	Description
+3	Very much improved	Optimal cosmetic result from treatment of the treated dimples
+2	Much improved	Marked improvement in the treated area appearance from before treatment, but not completely optimal
+1	Improved	Obvious improvement in the treated area appearance from before treatment, but additional treatment is indicated
0	No change	The treated area appearance is essentially the same as before treatment
−1	Worse	The treated area appearance is worse than before treatment
−2	Much worse	Marked worsening in appearance from the initial condition
−3	Very much worse	Obvious worsening in appearance from the initial condition

13.1.1.6. Hexsel Cellulite Severity Scale

The Hexsel Cellulite Severity Scale (referred to as the Hexsel CSS) is a photonumeric scale that looks at 5 key morphologic features of cellulite: (A) number of evident depressions, (B) depth of depressions, (C) morphological appearance of skin surface alterations, (D) laxity, flaccidity or sagging of skin, and (E) current classification scale based on medical literature including Nürnberger and Müller.(12,13) Each of these features is evaluated on a 4-point scale from a low of 0 to a high of 3 as described in Table 9 (see Appendix B). The total score is the summation of all 5 features.

For subjects in the observation-only group, the Hexsel CSS will be done at month 3 and every 3 months thereafter and at the month 12 or the end of study visit.

For subjects who elected to have EN3835 treatments, the Hexsel CSS will be done at 3-month intervals during the observation phase until the study drug blind is broken in study EN3835-201. The Hexsel CSS assessment will be done at Screening B visit and on day 71 of the treatment course and at month 12 or end of study visit.

For the subjects electing treatment (re-treatment or re-dosing) with EN3835 the Investigator or qualified designee will use the Hexsel CSS to assess the severity of EFP in all quadrants at

Screening B and the selected quadrant on day 71 of the course of treatment. All cellulite assessments should be made while the subject is in the standing position with relaxed gluteus muscles. However, when evaluating the subject for Category E (classification scale by Nürnberger and Müller) (13) if the subject has no evident depressions, the subject should be asked to contract her gluteus muscles or the pinch test should be applied (by pinching the skin between the thumb and index finger) so the Investigator or qualified designee can differentiate between scores/grades of zero (0) or I.

Table 9: Hexsel Cellulite Severity Scale

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

Source: Hexsel DM, Dal'Forno T, Hexsel CL. A validated photonumeric cellulite severity scale. *J Eur Acad Dermatol Venereol.* 2009;23(5):523-528.

[a] Subjects should be evaluated in the standing position with relaxed gluteus muscles. However, if the subject has no evident depressions, they should be asked to contract their gluteus muscles or the pinch test should be applied (by pinching the skin between the thumb and index finger) in order to differentiate between grade/stage of zero (0) or I.

14. ASSESSMENT OF SAFETY

14.1. Definitions

14.1.1. Adverse Event

An adverse event (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. AEs will be captured once a subject has signed the informed consent. AEs include:

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

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

All AEs, including both observed or volunteered problems, complaints, signs or symptoms must be recorded on the AE page of the eCRF, regardless of whether associated with the use of 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. The AE should be recorded in standard medical terminology when possible.

14.1.2. Serious Adverse Event

A serious adverse event (SAE) is defined as an AE that:

- Results in death
- Is immediately life-threatening (there is an immediate risk of death from the AE as it occurred; this does not include an AE that had it occurred in a more serious form may have caused death)
- Results in or prolongs an inpatient hospitalization (Note: a hospitalization for elective or pre-planned surgery, procedure, or drug therapy does not constitute an SAE)

- Results in permanent or substantial disability (permanent or substantial disruption of one's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect (in offspring of a subject using the study medication regardless of time to diagnosis)
- Is considered an important medical event

Important medical events are defined as events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the other serious outcomes. Examples of important medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

14.2. Monitoring Adverse Events

At each visit, subjects will be queried regarding any AEs that have occurred since the last visit. Subjects will be asked to volunteer information concerning AEs with a non-leading question such as, "How do you feel?" Study site personnel will then record all pertinent information in the source documents and the eCRF. The study drug compliance record should also be reviewed to detect potential overdoses (intentional/unintentional).

14.3. Relationship to Study Drug

The degree of "relatedness" of the AE to the study medication must be described using the following scale:

- **Not related** indicates that the AE is definitely not related to the study medication.
- **Unlikely related** indicates that there are other, more likely causes and study medication is not suspected as a cause.
- **Possibly related** indicates that a direct cause and effect relationship between study medication and the AE has not been demonstrated, but there is evidence to suggest there is a reasonable possibility that the event was caused by the study medication.
- **Probably related** indicates that there is evidence suggesting a direct cause and effect relationship between the AE and the study medication.

It is the Sponsor's policy to consider "Probably related" and "Possibly related" causality assessments as positive causality. "Not related" and "Unlikely related" causality assessments are considered as negative causality.

Assessments will be recorded on the eCRF and must indicate clearly the relationship being assessed. For example, an AE that appears during a placebo run-in phase would be assessed with respect to the placebo treatment received and/or study procedures conducted during this phase. If the AE continued into an active treatment phase, the relationship would be assessed for the active treatment phase only if the AE worsened.

14.4. Intensity Assessment

The intensity (or severity) of AEs is characterized as mild, moderate, or severe:

- **Mild** AEs are usually transient, requiring no special treatment, and do not interfere with the subject's daily activities.
- **Moderate** AEs introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.
- **Severe** AEs interrupt a subject's usual daily activity and typically require systemic drug therapy or other treatment.

When the intensity category of an AE changes, the greatest intensity during that continuous episode should be recorded.

14.5. Reporting Adverse Events and Serious Adverse Events

14.5.1. Reporting Adverse Events

Throughout the study, AEs will be documented on the source document and on the appropriate page of the eCRF whether or not considered treatment-related. This includes any new signs, symptoms, injury or illness, including increased severity of previously existing signs, symptoms, injury, or illness. Conditions existing prior to screening will be recorded as part of the subject's medical history. The Investigator is responsible for assessing the relationship of AEs to the study medication; relationship will be classified as not related, unlikely related, possibly related, or probably related.

All AEs will be collected by the Investigator from the time of signing the informed consent through 30 days after the last dose of study medication; this includes any AEs that are ongoing at the time of completion/termination of the study. All ongoing AEs must be followed until resolution or for 30 days after the subject's last study visit, whichever comes first.

14.5.2. Reporting Serious Adverse Events

Any SAE, including death resulting from any cause, which occurs to any subject participating in this study must be reported via email or fax by the Investigator using the Endo Clinical Trial Report Form for SAEs within 24 hours of first becoming aware of the SAE. SAEs will be collected by the Investigator from the time of signing the informed consent through 30 days after the last dose of study medication. SAEs that occur within 30 days, following cessation of the study treatment, or within 30 days, following premature discontinuation from the study for any reason, must also be reported within the same timeframe. Any SAE that is felt by the Investigator to be related to the study medication must be reported regardless of the amount of time since the last dose received. Follow-up information collected for any initial report of an SAE must also be reported to the Sponsor within 24 hours of receipt by the Investigator.

All SAEs will be followed until resolution, stabilization of condition, or until follow-up is no longer possible.

In the event discussion is necessary regarding treatment of a subject, call the Medical Monitor (see contact information in section 3).

All SAEs should be sent via the email address, or faxed to the fax number, provided in section 3.

The Sponsor will determine whether the SAE must be reported within 7 or 15 days to regulatory authorities in compliance with local and regional law. If so, the Sponsor (or the Sponsor's representative) will report the event to the appropriate regulatory authorities. The Investigator will report SAEs to the institutional review board (IRB) per their IRB policy.

14.5.2.1. Follow-up Procedures for Serious Adverse Events

To fully understand the nature of any SAE, obtaining follow-up information is important. Whenever possible, relevant medical records such as discharge summaries, medical consultations, and the like should be obtained. In the event of death, regardless of cause, all attempts should be made to obtain the death certificate and any autopsy report. These records should be reviewed in detail, and the Investigator should comment on any event, lab abnormality, or any other finding, noting whether it should be considered a serious or non-serious AE, or whether it should be considered as part of the subject's history. In addition, all events or other findings determined to be SAEs should be identified on the follow-up SAE form and the Investigator should consider whether the event is related or not related to study drug. All events determined to be nonserious should be reported on the eCRF.

14.6. Special Reporting Situations

14.6.1. Adverse Events of Special Interest

There are no AEs of special interest anticipated in this study. AEs such as bruising, ecchymosis, hematomas, and contusions that occur remote to the site of drug administration will be recorded as an AE or SAE as appropriate (see section 14.1.1, Adverse Events or section 14.1.2, Serious Adverse Events).

14.6.2. Overdose/Misuse/Abuse

Study drug overdose is any accidental or intentional use of study drug in an amount higher than the dose indicated by the protocol for that subject. Study drug compliance (see section 12.3) should be reviewed to detect potential instances of overdose (intentional or accidental).

Any study drug overdose during the study should be noted on the study medication eCRF.

An overdose is not an AE per se, however all AEs associated with an overdose should both be entered on the Adverse Event eCRF and reported using the procedures detailed in section 14.5.2, Reporting of Serious Adverse Events, even if the events do not meet seriousness criteria. If the AE associated with an overdose does not meet seriousness criteria, it must still be reported using the Endo Clinical Trial Report Form for SAEs and in an expedited manner, but should be noted as non-serious on the form and the Adverse Event eCRF.

14.6.3. Pregnancy

Any uncomplicated pregnancy that occurs in a subject during this clinical study will **be reported for tracking purposes only**. All subject pregnancies that are identified during or after this study, where the estimated date of conception is determined to have occurred during study drug therapy or within 30 days of the last dose of study medication need to be reported, followed to conclusion, and the outcome reported, even if the subject is discontinued from the study. The investigator should report all pregnancies within 24 hours using the Initial Pregnancy Report Form, and any pregnancy-associated SAE using the SAE report form, according to the usual timelines and directions for SAE reporting provided in section 14.5.2. Monitoring of the pregnancy should continue until conclusion of the pregnancy; 1 or more Follow-up Pregnancy Report Form(s) detailing progress, and a Two Month Follow-up Pregnancy Report Form detailing the outcome, should be submitted.

Pregnancy itself is not regarded as an AE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not considered AEs. Any SAEs associated with pregnancy (eg, congenital abnormalities/birth defects/spontaneous miscarriages or any other serious events) must additionally be reported as such using the SAE report form. Spontaneous miscarriages should also be reported and handled as SAEs.

Subjects should be instructed to immediately notify the investigator of any pregnancies.

Attempts to obtain the pregnancy follow-up and pregnancy outcome information detailed above are necessary even if a subject discontinues treatment because of pregnancy.

14.6.4. Adverse Events/Serious Adverse Events Experienced by Non-subjects Exposed to Study Medication

Non-subjects are persons who are not enrolled in the study but have been exposed to study medication, including instances of diversion of study medication. All such AEs/SAEs occurring in non-subjects from such exposure will be reported to the Endo Pharmacovigilance and Risk Management (PVRM) Department (when the non-subject agrees) on the departmental form for SAEs regardless of whether the event is serious or not. Instructions for completing the form for events experienced by non-subjects will be provided. SAEs occurring in non-subjects exposed to study medication will be processed within the same SAE reporting timelines as described in section 14.5.2, Serious Adverse Event Reporting. Additionally, the drug accountability source documentation at the site should reflect this occurrence.

14.7. Clinical Laboratory and Immunogenicity Determinations

Clinical laboratory tests will be conducted according to the Schedule of Events (section 5). Clinical laboratory tests will be performed by a designated central laboratory. Each site will be provided with instructions on specimen collection, preparation, packaging and transport. Refer to the central laboratory manual for further information regarding sample collection, handling, and labeling. The results of the tests will be returned to the investigational sites.

Clinical laboratory test data will be reviewed by the investigator, or designee, and additional clinical laboratory tests may be ordered at his/her discretion (eg, if the results of any clinical laboratory test falls outside the reference range or clinical symptoms necessitate additional

testing to ensure safety). Any additional testing will be performed by the designated central laboratory.

The investigator will review all abnormal lab results for clinical significance. Any abnormal clinical laboratory test result meeting the investigator's or Sponsor's criteria for clinical significance (refer to central laboratory manual) will be recorded as an AE or SAE as appropriate (see section 14.1.1, Adverse Events or section 14.1.2, Serious Adverse Events).

Laboratory results will be sent electronically to Endo for data management.

Clinical laboratory parameters that will be measured in this study are listed in Table 10.

Table 10: Clinical Laboratory Parameters

Hematology	Clinical Chemistry	Urinalysis
Hematocrit	Blood urea nitrogen	Specific gravity
Hemoglobin	Creatinine	Ketones
Red blood cell count	Total bilirubin	pH
Red blood cell morphology	Alanine aminotransferase (ALT)	Protein
White blood cell count	Aspartate aminotransferase (AST)	Blood
Neutrophils	Alkaline phosphatase	Glucose
Lymphocytes	Sodium	
Monocytes	Potassium	
Basophils	Calcium	
Eosinophils	Chloride	
Platelets	Phosphate	
	Serum bicarbonate	
	Uric acid	
	Total cholesterol	
	Total protein	
	Glucose	
	Triglycerides	
	Albumin	

Female subjects of childbearing potential must have a negative urine pregnancy test at Screening B and at treatment visits 1, 2, and 3 (section 5) to receive treatment in the study. If necessary, additional urine pregnancy tests can be performed at any time during the study at the discretion of the Investigator. Urine pregnancy test kits will be supplied by the Sponsor.

14.7.1. Anti-AUX-I and Anti-AUX-II Antibodies

Serum samples will be collected and may be tested for binding and neutralizing anti-AUX-I and anti-AUX-II antibodies at visit 1 through visit 4. Additionally, if a subject consents to treatment in the open-label study, serum samples for antibody testing will be collected before injection at treatment visits 1, 2, 3, and 4 of the open-label treatment period. A subset of subject samples will have neutralizing antibodies tested from day 1 and day 71 visits; additional samples may be analyzed if results or clinical signs warrant testing.

The serum samples obtained will be processed, stored and then shipped on dry ice to the designated central clinical laboratory before forwarding to Endo's appointed laboratory for the determination of anti-AUX-I and anti-AUX-II antibodies according to the Laboratory Manual.

14.8. Vital Signs

Vital sign measurements will be documented as described in the Schedule of Events. These parameters include pulse rate, respiratory rate, systolic and diastolic blood pressure, and body weight. Pulse and blood pressure readings will be taken after the subject has been sitting for 5 minutes. Height should only be recorded at Screening B.

The investigator will review all vital sign values for clinical significance. Any vital sign value meeting the investigator's or Sponsor's criteria for clinical significance will be recorded as an AE or SAE as appropriate (see section 14.1.1, Adverse Events, and section 14.1.2, Serious Adverse Events).

For subjects receiving treatment, vital signs will be assessed at the time points shown in Table 11 after the subject has rested for at least 5 minutes.

Table 11: Vital Signs Measurements on Injection Day

Time Point Relative to Last Injection	Blood Pressure, Respiratory Rate, and Pulse Rate	Body Temperature
Up to 4 hours (before treatment)	X	X
Approximately 15 minutes after	X	
Approximately 30 minutes after	X	X

14.9. Electrocardiogram

Performing a 12-lead electrocardiogram (ECG) is not necessary if Screening B visit date is within 12 months of obtaining an ECG during the double-blind study (EN3835-201).

If the date of Screening B visit is later than 12 months since obtaining the ECG in study EN3835-201, subjects will have a resting 12-lead ECG performed during the Screening B visit. A qualified physician will interpret, sign, and date the ECGs. Electrocardiogram assessments must be "within normal limits" or interpreted as "abnormal, not clinically significant" for the subject to be included in the study.

Any ECG result meeting the investigator's or Sponsor's criteria for clinical significance will be recorded as an AE or SAE as appropriate (see section 14.1.1, Adverse Events and section 14.1.2, Serious Adverse Events).

14.10. Physical Examination

Body weight will be collected as described in the Schedule of Events (section 5). If a subject desires treatment in the open-label study, a complete physical examination will be performed at Screening B. All examinations will be performed by a physician or health professional listed on the Form FDA 1572 and licensed to perform physical examinations.

The investigator will review all physical exam findings for clinical significance. Any physical exam finding meeting the investigator's or Sponsor's criteria for clinical significance will be recorded as an AE or SAE as appropriate (see section 14.1.1, Adverse Events and section 14.1.2, Serious Adverse Events).

14.11. Other Safety Assessments

Not applicable.

15. ASSESSMENT OF PHARMACOKINETICS

Not applicable.

16. ASSESSMENT OF PHARMACODYNAMICS

Not applicable.

17. STATISTICAL CONSIDERATIONS AND METHODS

17.1. Determination of Sample Size

It is estimated that approximately 95% of the 350 subjects randomized in study EN3835-201 will enroll in the current study for a sample size of 333. This sample size should be adequate to determine safety and cellulite assessments of EN3835 for subjects retreated in the same and in different quadrants.

17.2. Subject Cohorts and Subject Populations

Subjects will be classified into 1 of 4 different cohorts depending on where they receive the treatment of EN3835 in relation to where they received treatment in study EN3835-201. The 4 cohorts are:

1. Observational subjects only - subjects who received EN3835 in study EN3835-201 but do not receive any injections in the current study
2. Re-treatment subjects - subjects who received EN3835 in study EN3835-201 and receive EN3835 in the current study in the same quadrant that was treated in the EN3835-201 study. This will only be allowed for subjects who have baseline severity ratings in the current study at or worse than the baseline seen in study EN3835-201 for both the CR-PCSS and PR-PCSS of the quadrant.
3. Re-dosing subjects - subjects who received EN3835 in study EN3835-201 and receive EN3835 in the current study in a quadrant different than the EN3835-treated quadrant in study EN3835-201.
4. Initial treatment subjects - subjects who received placebo in study EN3835-201 and receive EN3835 in the current study.

All efficacy and safety analyses will be done within the classified cohort. Durability of treatment effects defined as time period from injection to return to baseline cellulite severity ratings in a EN3835-treated quadrant will be determined for all subjects that were treated with EN3835 in either this study or study EN3835-201.

17.2.1. Observational Population

The Observational population includes all subjects treated with EN3835 in study EN3835-201 who do not receive any treatment in the current study. The durability of a treatment effect and long-term safety analyses for subjects who receive no treatment in the EN3835-201 study will be performed using this population

17.2.2. Safety Population

The Safety population will include all subjects who receive at least 1 dose of EN3835 in the current study or in study EN3835-201. All safety analyses will be performed using this population.

17.2.3. Intent-to-Treat Population

The Intent-to-Treat (ITT) population includes all subjects who enroll in the current study.

17.2.4. Modified Intent-to-Treat Population

The Modified Intent-to-Treat (mITT) population includes all subjects who receive at least 1 dose of EN3835 in the current study (EN3835-202) and have a baseline and at least 1 post-baseline assessment on both the CR-PCSS and PR-PCSS on the quadrant selected for treatment in the current study. All cellulite assessment analyses will be completed on this population.

17.2.5. Per-Protocol Population

The Per-Protocol population includes all subjects in the safety population who have no major protocol deviations. Major protocol deviations excluding subjects from this population will be determined at the protocol deviation assessment meeting prior to the database lock. If more than 10% of the safety population is excluded from the per-protocol population, then all safety and cellulite evaluations will be repeated using the per-protocol population.

17.3. Subject Disposition

The number of subjects included in each study population will be summarized. The number and percentage of subjects completed and discontinued will be presented. Reasons for discontinuation as recorded on the eCRF will be summarized (number and percentage) for all subjects.

17.4. Demographics and Other Baseline Characteristics

Demographic and baseline characteristics, including age, race, and baseline values will be summarized for the Observational population, the Safety population, and the mITT population using descriptive statistics. The descriptive statistics will include frequency tables for all categorical response variables and number, mean, standard deviation, minimum, and maximum for all continuous variables.

17.5. Efficacy Analyses

Cellulite assessments (efficacy) include:

- PR-PCSS: 5-point scale ranging from 0 (no cellulite) to 4 (severe cellulite) (screening visit [Baseline], days 22, 43, and 71). Also will be done at day 90, day 180, day 270, and day 360/end of study visits for observational assessments.
- CR-PCSS: 5-point scale ranging from 0 (no cellulite) to 4 (severe cellulite) (screening [Baseline], days 22, 43, and 71). Also will be done at day 90, day 180, day 270, and day 360/end of study visits for observational assessments.
- Investigator rating of cellulite severity using the total scores from the Hexsel CSS scale: scores can range from 0 to 15 (screening [Baseline] and day 71). Also will be done at day 90, day 180, day 270, and day 360/end of study visits for observational assessments.

- I-GAIS: 7-point scale ranging from 3 (very much improved) to −3 (very much worse) (day 71). Also done at day 360/end of study visit for observational assessments.
- S-GAIS: 7-point scale ranging from 3 (very much improved) to −3 (very much worse) (day 71). Also done at day 360/end of study visit for observational assessments.
- Subject satisfaction with cellulite treatment assessment: 5-point scale ranging from +2 (very much satisfied) to −2 (very much dissatisfied) (day 71). Also done at day 360/end of study visit for observational assessments.

All cellulite assessments will be done by treated quadrant. For initial treatment subjects who have 2 quadrants treated, each quadrant will be evaluated separately.

17.5.1. Primary Efficacy Analysis

The primary cellulite severity endpoint is the proportion of composite responders at day 71 defined as subjects with an improvement in severity from baseline (Screening B visit) of at least 2 levels of severity in the CR-PCSS and an improvement in severity from baseline of at least 2 levels of severity in the PR PCSS.

The primary endpoint, the proportion of composite responders with improvement of 2 or better on each scale (CR-PCSS and PR-PCSS) will be summarized by region treated (buttock or thigh) and overall with percentages.

17.5.2. Secondary Efficacy Analysis

Secondary endpoints for treated quadrants include:

- Proportion of composite responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS. (day 71)
- Proportion at each level of improvement in the PR-PCSS (day 71):
  - Proportion of patient responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS
  - Proportion of patient responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS
- Proportion at each level of improvement in the CR-PCSS (day 71):
  - Proportion of Investigator responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS (Investigator rated)
  - Proportion of Investigator responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS (Investigator rated)

- Proportion of responders at each level of the I-GAIS (day 71):
  - Proportion of Investigator global responders defined as subjects with a response of 1 (improved) or better in the Investigator GAIS assessment
- Proportion of responders at each level of the S-GAIS (day 71):
  - Proportion of subject global responders defined as subjects with a response of 1 (improved) or better in the subject GAIS assessment
- Proportion of responders at each level of the subject satisfaction with cellulite treatment (day 71)
- Change in the Hexsel CSS total score from screening visit to day 71
- All secondary endpoints, except the Hexsel CSS total score, will be summarized by treated region (buttock or thigh) and overall using percentages. Change in Hexsel CSS total score will be summarized by treated region (buttock or thigh) and overall with descriptive statistics for continuous variables.

Observational endpoints include:

- Proportion of 2-point composite responders as defined by responses in the quadrant treated in study EN3835-201 who either maintained response, lost response but did not return to the baseline of study EN3835-201, or returned to the baseline of study EN3835-201.
- Proportion of 1-point composite responders as defined by responses in the quadrant treated in study EN3835-201 who either maintained response, lost response but did not return to the baseline of study EN3835-201, or returned to the baseline of study EN3835-201.
- Proportion of 2-point CR-PCSS responders as defined by responses in the quadrant treated in study EN3835-201 who either maintained response, lost response but did not return to the baseline of study EN3835-201, or returned to the baseline of study EN3835-201.
- Proportion of 1-point CR-PCSS responders as defined by responses in the quadrant treated in study EN3835-201 who either maintained response, lost response but did not return to the baseline of study EN3835-201, or returned to the baseline of study EN3835-201.
- Proportion of 2-point PR-PCSS responders as defined by responses in the quadrant treated in study EN3835-201 who either maintained response, lost response but did not return to the baseline of study EN3835-201, or returned to the baseline of study EN3835-201.
- Proportion of 1-point PR-PCSS responders as defined by responses in the quadrant treated in study EN3835-201 who either maintained response, lost response but did not return to the baseline of study EN3835-201, or returned to the baseline of study EN3835-201.

- Duration of response as defined by the time from onset of change from baseline of PR-PCSS and CR-PCSS in the quadrant treated in study EN3835-201 until the time that the treated quadrant returned to the baseline PR-PCSS and CR-PCSS ratings from study EN3835-201.
- CR-PCSS change from the study EN3835-201 baseline at day 71 of study EN3835-201, and days 90, 180, 270, and 360/end of study of the current study (EN3835-202).
- PR-PCSS change from the study EN3835-201 baseline at day 71 of study EN3835-201, and days 90, 180, 270, and 360/end of study of the current study (EN3835-202).
- Hexsel CSS total score changed from the study EN3835-201 baseline at day 71 of study EN3835-201 and day 360/end of study of the current study (EN3835-202).
- Proportion of responses at each level of the I-GAIS (day 360/end of study):
  - Proportion of Investigator global responders defined as subjects with a response of 1 (improved) or better in the Investigator GAIS assessment
  - Change in I-GAIS assessment from day 71 of study EN3835-201 and day 360/ end of study of the current study (EN3835-202
- Proportion of responses at each level of the S-GAIS (day 360/end of study):
  - Proportion of subject global responders defined as subjects with a response of 1 (improved) or better in the subject GAIS assessment
  - Change in S-GAIS assessment from day 71 of study EN3835-201 and day 360/ end of study of the current study (EN3835-202)
- Proportion of responses at each level of the subject satisfaction with cellulite treatment (day 360/end of study)
  - Change in subject satisfaction assessment from day 71 of study EN3835-201 and day 360/end of study of the current study (EN3835-202)

For quadrants treated in the current study the following observational endpoints will be analyzed:

- Proportion of 2-point composite responders as defined by the responses in the quadrant treated in this current study (EN3835-202) who either maintained response, lost response but did not return to the study EN3835-202 baseline, or returned to the study EN3835-202 baseline.
- Proportion of 1-point composite responders as defined by the responses in the quadrant treated in the current study who either maintained response, lost response but did not return to the study EN3835-202 baseline, or returned to the study EN3835-202 baseline.
- Proportion of 2-point CR-PCSS responders as defined by the responses in the quadrant treated in this current study who either maintained response, lost response but did not return to the study EN3835-202 baseline, or returned to the study EN3835-202 baseline.

- Proportion of 1-point CR-PCSS responders as defined by the responses in the quadrant treated in the current study who either maintained response, lost response but did not return to the study EN3835-202 baseline, or returned to the study EN3835-202 baseline.
- Proportion of 2-point PR-PCSS responders as defined by the responses in the quadrant treated in the current study who either maintained response, lost response but did not return to the study EN3835-202 baseline, or returned to the study EN3835-202 baseline.
- Proportion of 1-point PR-PCSS responders as defined by the responses in the quadrant treated in the current study who either maintained response, lost response but did not return to the study EN3835-202 baseline, or returned to the study EN3835-202 baseline.
- CR-PCSS change from the study EN3835-202 baseline at day 71, day 90, day 180, day 270, and day 360/end of study.
- PR-PCSS change from the study EN3835-202 baseline at day 71, day 90, day 180, day 270, and day 360/end of study.
- Duration of response as defined by the time from onset of change from baseline of PR-PCSS and CR-PCSS in the quadrant treated in the current study until the time that the treated quadrant returned to the baseline PR-PCSS and CR-PCSS ratings from study EN3835-202.

17.6. Safety Analyses

The following variables are safety endpoints.

- AEs: Mapped to preferred term using the Medical Dictionary for Regulatory Activities (MedDRA)
- Injection site reactions/local tolerability in selected quadrant (through subject and Investigator reporting)
- Vital signs
- Laboratory testing

AEs will be summarized by treatment group. AE duration will be summarized using descriptive statistics by treatment group.

Descriptive statistics will be presented for each clinical laboratory test for the actual and change from screening at each visit by treatment group and vital signs for the actual and change from day 1 pre-injection for each injection day at each visit by treatment group.

17.6.1. Prior, Concomitant, and Follow-up Medication

The World Health Organization (WHO) Drug Dictionary will be used to classify prior and concomitant medications by therapeutic class. The version used in this study will be stated in the Data Management Plan. Prior medication will be defined as any medication with a start date prior to the day 1 date and are collected at the screening visit and upon admission to the clinic on

day −1. Concomitant medication is defined as any medication with a start date on or after the day 1 date or reported as ongoing. Any medications started after the last dose of study drug will be considered as follow-up medications

Prior and concomitant medication use will be summarized descriptively by the number and percentage of subjects receiving each medication within each therapeutic class. Multiple use of the same medication by a subject will be counted only once.

17.6.2. Study Drug Exposure

For those subjects that elect, are eligible, and do receive treatment, the number of injections will be summarized by counts and percentages. The number of dimples treated will be summarized with counts and percentages.

17.6.3. Measurement of Treatment Compliance

All doses are administered while the subjects are at the investigators' sites. Any dose that was not administered per protocol will recorded as a protocol deviation by the Investigator.

17.6.4. Adverse Events

The MedDRA will be used to code AEs. The version used in this study will be stated in the Data Management Plan.

An AE (classified by preferred term) that started during the treatment period will be considered a TEAE if it was not present prior to the first dose of study drug, or was present prior to the first dose of study drug but increased in intensity during the treatment period. If more than 1 AE is reported prior to the first dose of study drug and coded to the same preferred term, then the AE with the greatest intensity will be used as the benchmark for comparison to the AEs occurring during the treatment period which were also coded to that preferred term. Any AE present prior to the first dose of study drug that increases in intensity during the treatment period will be re-entered with a new start date of the date of increased intensity.

Descriptive statistics (the number and percentage) for subjects reporting TEAEs in each treatment group will be tabulated by system organ class and preferred term; by system organ class, preferred term, and severity; and by system organ class, preferred term, and relationship to study drug. If more than 1 AE is coded to the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to the study drug.

SAEs and AEs leading to premature discontinuation of study drug will be summarized by preferred term and dose received. Listings will be presented for subjects with SAEs, subjects with AEs leading to discontinuation, and subjects who die (if any).

17.6.5. Vital Signs

Descriptive statistics for vital signs (eg, systolic and diastolic blood pressure, pulse rate, and body weight) and their changes from baseline at each visit and at the end of treatment visit will be presented.

Vital sign values are potentially clinically significant (PCS) if they meet both the observed value criteria and the change from baseline criteria. The criteria for PCS vital sign values will be

detailed in the Statistical Analysis Plan (SAP). A listing of all AEs for subjects with PCS vital signs will also be provided.

17.6.6. Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values in International System of Units (SI units) and changes from baseline will be presented for each clinical laboratory parameter.

The number and percentage of subjects with PCS post-baseline clinical laboratory values will be tabulated. The criteria for PCS laboratory values will be detailed in the SAP. A listing of all AEs for subjects with PCS laboratory values will also be provided.

17.7. Immunogenicity Analyses

Immunogenicity variables include anti-AUX-I/anti-AUX-II binding antibody results. Binding antibody levels will be determined from samples collected on days 1, 22, 43, and 71 during the treatment phase and days 90, 180, 270 and 360 during the observational phase.

Descriptive statistics (percent of positive measurements and average antibody level) will be presented for anti-AUX-I and anti-AUX-II antibody levels at each time point by region treated and overall. Average antibody levels will be summarized on logarithmically transposed titer values.

17.8. Pharmacokinetic Analyses

Not applicable.

17.9. Interim Analysis

Two (2) interim analyses are planned. Following the breaking of the study drug blind in study EN3835-201, all follow-up safety data gathered prior to that time will be analyzed. The second interim analyses will occur following the day 71 visit for all subjects treated with EN3835 in the current study. A preliminary data lock will be done on all treated quadrants and cellulite assessment and safety analyses will be done. The official database lock will occur after the last day 360/end of study observational visit and all observational analyses on treated quadrants will be done.

17.10. Statistical Software

Statistical analyses will be performed using Version 9.3 (or higher) of SAS® (SAS Institute, Cary, North Carolina).

18. STUDY DRUG MATERIALS AND MANAGEMENT

18.1. Study Drug Identity

EN3835 is formerly known as AA4500; the 2 product names should be considered synonymous. The investigational product vials will be labeled as EN3835. The components of EN3835 are 0.9 mg of collagenase clostridium histolyticum, [redacted] in a lyophilized cake.

The components of EN3835 sterile diluent for reconstitution are 0.03% (2mM) calcium chloride ($CaCl_2$) in 0.9% (154mM) sodium chloride (NaCl) solution, pH 6.0 to 7.0. Diluent is supplied as a terminally-sterilized liquid at 3.0 mL per vial.

18.2. Study Drug Packaging and Labeling

Sterile vials of lyophilized EN3835 (formerly AA4500) and sterile diluent will be provided to the Investigator by Endo. Each kit will contain 1 vial each of EN3835 and sterile diluent.

18.3. Study Drug Storage

All study drug will be provided by Endo. Study drug must be kept in a refrigerator (2°C-8°C) with locked access.

18.4. Study Drug Preparation

Refer to the Reconstitution Instructions in the Pharmacy Manual for detailed preparation instructions.

Before reconstitution, remove the vials containing the lyophilized study drug powder and the vials containing the sterile diluent from the refrigerator and allow the vials to stand at room temperature for 15 minutes. Designated study personnel will visually inspect the study drug vial to determine the integrity and acceptability of the lyophilized drug product for reconstitution. The written procedures for inspection of the study drug vials will be provided to the site by Endo.

After reconstitution with the sterile diluent, the study drug solution can be kept at room temperature (20°C to 25°C/68°F to 77°F) [redacted] The reconstituted study drug solution should be administered as soon as possible after reconstitution and further dilution. Each vial of study drug powder for reconstitution will be diluted according to the instructions in the Pharmacy Manual. Study personnel will maintain a record of the date and time of reconstitution.

18.5. Study Drug Accountability

Endo or its agent will maintain a master log of kits dispensed to the investigative sites. A drug inventory form must be kept current by the site staff designated to be responsible for reconstitution and must be made available to the clinical monitor, Endo employees, IRB/independent ethics committee (IEC), and regulatory agencies for routine inspection and

accountability during monitoring visits. When instructed by Endo, the Investigator agrees to return all original containers of unused study drug to Endo or its designee.

18.5.1. Study Drug Handling and Disposal

The Investigator is responsible for recording the receipt and use of all drug supplied and for ensuring the supervision of the storage and allocation of these supplies. All unused study drug will be returned, and unit counts will be performed whenever medication is returned. The site must account for all study drug received. The Investigator agrees not to supply study drug to any person except to those subjects enrolled in the study. At the end of the study, all unused drug supplies will be returned to Endo as instructed by the clinical monitor.

19. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

19.1. Source Documents

Source documents include but are not limited to original documents, data and records such as hospital/ medical records (including electronic health records), clinic charts, lab results, subject diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, etc. At a minimum, all data required to be collected by the protocol should have supporting source documentation for entries in the eCRF, unless the protocol specifies that data can be recorded directly on/in the eCRF or other device.

19.2. Study Monitoring

A representative of Endo Pharmaceuticals Inc. will meet with the Investigator and his/her staff prior to the entrance of the first subject to review study procedures and methods of recording findings in the eCRF.

After enrollment of the first subject, an Endo Pharmaceuticals Inc. representative will be assigned to periodically monitor each Investigator site for study progress and to verify that standards of Good Clinical Practice (GCP) were followed. The Investigator is expected to prepare for the monitor visit, ensuring that all source documents, completed eCRFs, signed consent forms, and other study related documents are readily available for review.

19.3. Audits and Inspections

The Investigator shall permit audits and inspections by the Sponsor, its representatives and members of regulatory agencies. The investigator should immediately notify the Sponsor of an upcoming FDA or other regulatory agency inspection.

19.4. Institutional Review Board (IRB)

The Investigator shall permit members of the IRB/IEC to have direct access to source documents.

19.5. Data Recording and Documentation

All data recordings and source documentation (including electronic health records) must be made available to the Sponsor (or designee), FDA and any other regulatory agencies that request access to study records, including source documents, for inspection and copying, in keeping with federal and local regulations.

20. QUALITY CONTROL AND QUALITY ASSURANCE

Steps to assure the accuracy and reliability of data include the selection of qualified principal investigators and appropriate study centers, review of protocol procedures with the principal investigators and associated personnel prior to start of the study, and periodic monitoring visits conducted by the Sponsor or Sponsor representative. Significant and/or repeated non-compliance will be investigated and remedial action instituted when appropriate. Failure to comply with remedial actions may result in investigator site termination and regulatory authority notification.

The Sponsor or its designee will utilize qualified monitors to review and evaluate activities conducted at Investigator Sites.

The data will be entered into the clinical study database and verified for accuracy, following procedures defined by the Sponsor (or designee). Data will be processed and analyzed following procedures defined by the Sponsor (or designee).

The study will be monitored and/or audited at intervals to ensure that the clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the Study Protocol; International Conference on Harmonisation (ICH), E6 consolidated guidelines; and other applicable regulations. The extent, nature, and frequency of monitoring and/or audits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity, and enrollment rate. At the conclusion of a program, a compliance statement will be generated by the Sponsor (or designee) listing all audit activities performed during the clinical study.

21. ETHICS

21.1. Ethics Review

Approval by the IRB/IEC prior to the start of the study will be the responsibility of the Investigator. A copy of approval documentation will be supplied to Endo Pharmaceuticals Inc. along with a roster of IRB members that demonstrates appropriate composition (a Department of Health and Human Services [DHHS] Assurance Number will satisfy this requirement).

The study protocol, the informed consent form, advertisements, materials being provided to subjects and amendments (if any) will be approved to IRB/IECs at each study center in conformance with ICH E6, the Code of Federal Regulations (CFR), Title 21, Part 56 and any other applicable local laws. The Investigator is responsible for supplying the IRB/IEC with a copy of the current IB, Package Insert, or SPC as well as any updates issued during the study. During the course of the study, the Investigator will provide timely and accurate reports to the IRB/IEC on the progress of the study, at intervals not exceeding 1 year (or as appropriate), and will notify the IRB/IEC of SAEs or other significant safety findings, per the policy of the IRB/IEC. At the conclusion of the study, the Investigator will submit a final report or close out report to the IRB/IEC and provide a copy to Endo Pharmaceuticals Inc.

Any amendment to this protocol will be provided to the Investigator in writing by Endo Pharmaceuticals Inc. No protocol amendment may be implemented (with the exceptions noted below) before it has been approved by the IRB and the signature page, signed by the Investigator, has been received by Endo Pharmaceuticals Inc. Where the protocol is amended to eliminate or reduce the risk to the subject, the amendment may be implemented before IRB review and approval. However, the IRB must be informed in writing of such an amendment and approval obtained within reasonable time limits. Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the subject, and must be immediately reported to Endo Pharmaceuticals Inc.

The Investigator will be responsible for supplying updated safety and/or study information to study subjects as it becomes available.

21.2. Ethical Conduct of the Study

This clinical study is designed to comply with the ICH Guidance on General Considerations for Clinical Trials (62 FR 6611, December 17, 1997), Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (62 FR 62922, November 25, 1997), Good Clinical Practice: Consolidated Guidance (62 FR 25692, May 9, 1997) and 21 CFR parts 50, 54, 56, and 312.

The study will be conducted in full compliance with ICH E6, the FDA guidelines for GCP and in accordance with the ethical principles that have their origins in the Declaration of Helsinki defined in 21 CFR, 312.120.

21.3. Subject Information and Consent

Subjects, after having the study explained to them and an opportunity to have their questions answered sufficiently, will give voluntary and written informed consent (in compliance with ICH E6, 4.8 and 21 CFR Parts 50 and 312) before participating in any study-related procedures. The consent shall be written in a language understandable to the subject. Subjects unable to read (illiterate) shall have the consent process performed in the presence of an independent witness who shall also sign the consent. Each subject will read, assent understanding, and sign an instrument of informed consent after having had an opportunity to discuss the study and consent documents with the Investigator before signing, and will be made aware that she may withdraw from the study at any time.

In addition to obtaining informed consent, the Investigator is responsible for obtaining any additional documentation to demonstrate compliance with local privacy laws applicable to activities performed.

The consent process shall be recorded in source documents. Signed copies of the informed consent will be given to the Subject and originals will be placed in the Investigator study files.

A unique Subject identification number will be assigned according to section 12.1.3 at the time that the Subject signs the informed consent form.

22. DATA HANDLING AND RECORDINGKEEPING

22.1. Data Collection

Data collection will involve the use of an EDC system to which only authorized personnel will have access. The system will be secured to prevent unauthorized access to the data or the system. This will include the requirement for a user ID and password to enter or change data. The level of access to the EDC system will be dependent on the person's role in the study.

Study data will be collected from source documents and entered into an eCRF within the EDC system. The Investigator will be responsible for ensuring the eCRFs are completed in a timely manner relative to the subject's visit. In addition to periodic monitoring occurring within the system by a Sponsor monitor, programmatic edit checks will be used to review EDC data for completeness, logic, and adherence to the study protocol. As a result of this monitoring and these checks, queries may be issued electronically to the clinical study sites and closed electronically by the monitor, data management staff or authorized staff at the study site. Additionally, the Investigator will review eCRFs, ensure all missing or corrected data is provided and will sign the eCRF pages with an electronic signature.

An electronic audit trail will be maintained in the EDC system to track all changes made to data entered in the eCRF. Data will be retrievable in such a fashion that all information regarding each individual subject is attributable to that subject. Unless otherwise indicated, all data captured in the eCRF must first be captured in source documents. Data that can be directly recorded in the eCRF will be clearly identified in the section(s) of the protocol that describes the assessment(s).

In addition, any contact with the subject via telephone or other means that provide significant clinical information must be documented in source documents as described above.

22.2. Study Documentation

Upon study completion, the Investigator will be provided with complete electronic copies of the CRF data for his/her files.

23. REPORTING AND PUBLICATION

All data generated in this study are the property of Endo. An integrated clinical and statistical report will be prepared at the completion of the study.

Publication of the results by the Investigator will be subject to mutual agreement between the Investigator and Endo.

24. INVESTIGATOR OBLIGATIONS

24.1. Regulatory Documents

The Investigator is responsible for creating and/or maintaining all study documentation required by 21CFR 50, 54, 56 and 312, ICH, E6 section 8, as well as any other documentation defined in the protocol or the Investigator Agreement. The Investigator must maintain the documentation relating to this study and permit Endo Pharmaceuticals Inc. or a member of a regulatory agency access to such records.

The Investigator must provide the following key documents to Endo Pharmaceuticals Inc. prior to the start of the study:

- A completed and signed Form FDA1572. If during the course of the study any information reported on the Form FDA 1572 changes, a revised Form FDA1572 must be completed and returned to Endo Pharmaceuticals Inc. for submission to the FDA. For studies executed outside the United States, documentation required by the governing regulatory authority may be substituted for the Form FDA 1572.
- A fully executed contract
- The Investigator's Statement page in this protocol signed and dated by the Investigator and any subsequent amendment signature pages
- The IB acknowledgment of receipt page
- Curricula vitae for the Principal Investigator and all Sub-Investigators listed on Form FDA 1572, including a copy of each physician's license (if applicable)
- A copy of the original IRB/IEC approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals or shorter intervals defined by the IRB/IEC. All subsequent modifications must be submitted and approved by the IRB, as described in section 21.1
- A copy of the IRB/IEC-approved informed consent form
- A list of IRB/IEC members or DHHS Assurance Number
- Laboratory certifications and normal ranges (if local labs are required by the protocol)
- A financial disclosure agreement completed and signed by the Investigator and all Sub-Investigators listed on Form FDA 1572. Investigator site staff that submitted an initial financial disclosure are also responsible for informing Endo Pharmaceuticals Inc. of any changes to their initial financial disclosure form 1 year after the completion of the study.

A complete list of required regulatory documents will be supplied by Endo Pharmaceuticals Inc. or its representative.

24.2. Delegation of Responsibilities and Adequate Resources

The Investigator should have adequate time to conduct the study properly and should have an adequate number of qualified staff to assist with the conduct of the study. The Investigator shall delegate tasks only to individuals qualified by education, training and experience to perform the delegated tasks. The Investigator shall have direct oversight of all delegated activities and shall document delegation of responsibilities. The Investigator is responsible for ensuring all delegated staff have been properly trained on the protocol and their assigned study responsibilities.

24.3. Medical Care of Study Subjects

The Investigator and/or a qualified sub-investigator shall be responsible for the subjects' medical care. Any unrelated medical condition discovered during the course of the study should be communicated to the subject so that they may seek appropriate medical care. The Investigator will report all AEs as required by the protocol (section 14.5). The Investigator will inform study subjects of new information regarding the study drug as it becomes available.

24.4. Use of Investigational Materials

The Investigator will acknowledge that the study drug supplies are investigational and as such must be used strictly in accordance with the protocol and only under the supervision of the Principal Investigator or Sub-Investigators listed on Form FDA1572 (or other regulatory document, depending on region). Study drug must be stored in a safe and secure location. At study initiation, a representative from Endo Pharmaceuticals Inc. will inventory the study drug at the site. The Investigator must maintain adequate records documenting the receipt and disposition of all study supplies. Endo Pharmaceuticals Inc. or its representative will supply forms to document total inventory as well as subject specific accountability. The Investigator is responsible for monitoring subject's use of the study drug to ensure compliance with the protocol. All study supplies shall be returned to Endo Pharmaceuticals Inc. or its designee (this may include empty packaging such as bottles and blister cards). It is the Investigator's responsibility to ensure that subjects return their medication.

24.5. Retention of Records

Federal and local regulations require that the Investigator retain a copy of all regulatory documents and records that support the data for this study (eg, informed consents, laboratory reports, source documents, study drug dispensing records) for whichever of the following is the longest period of time:

- A period of 2 years following the final date of approval by the FDA or other regulatory agency of the study drug for the purposes that were the subject of the investigation; or
- A period of 5 years following the date on which the results of the investigation were submitted to the FDA or other regulatory agency in support of, or as part of, an application for a research or marketing permit for the study drug for the purposes that were the subject of the investigation

Endo will notify Investigators once one of the above 2 timeframes has been satisfied.

If the investigation does not result in the submission of the data in support of, or as part of, an application for a research or marketing permit, records must be retained for a period of 2 years following notification by Endo Pharmaceuticals Inc. that the entire clinical investigation (not merely the Investigator's portion) is completed, terminated, or discontinued or 2 years following withdrawal of the Investigational New Drug application (IND).

If the Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. Endo must be notified in writing of the name and address of the new custodian. Study records should not be destroyed without consultation with Endo Pharmaceuticals Inc.

24.6. Subject Confidentiality

All subject records submitted to Endo Pharmaceuticals Inc. or its designee will be identified only by initials and code number. Subjects' names are not to be transmitted to Endo Pharmaceuticals Inc. The Investigator will keep a Master Subject List on which the identification number and the full name, address, and telephone number of each subject are listed. It is the Investigators' responsibility to inform study subjects that representatives of the Sponsor, FDA, or other regulatory agencies may review all records that support their participation in the study. The Investigator will adhere to all privacy laws to which she is subject.

25. TERMINATION OF STUDY

The Sponsor has the right to suspend or terminate the study at any time. The study may be suspended or terminated for any reason.

26. INVESTIGATOR'S AGREEMENT

I agree to conduct the study in accordance with the protocol, and with all applicable government regulations and Good Clinical Practice guidance.

_____ _____/_____/_____

Investigator's Signature Date

_____

Typed Name of Investigator

27. REFERENCES

1. Khan MH, Victor F, Rao B, Sadick NS. Treatment of cellulite: Part I. Pathophysiology. *J Am Acad Dermatol* 2010;62(3):361-370.
2. Hexsel D, de Oliveira Dal'Forno T, Mazzuco R. Definition, clinical aspects, classifications, and diagnostic techniques. In: Goldman MP, Hexsel D, eds. *Cellulite: Pathophysiology and Treatment.* 2nd ed. New York, NY: Informa Healthcare; 2010:13-21.
3. Rawlings AV. Cellulite and its treatment. *Int J Cosmetic Sci.* 2006;28(3):175-190.
4. Terranova F, Berardesca E, Maibach H. Cellulite: nature and aetiopathogenesis. *Int J Cosmetic Sci.* 2006;28(3):157-167.
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6. Khan MH, Victor F, Rao B, Sadick NS. Treatment of cellulite: Part II. Advances and controversies. *J Am Acad Dermatol* 2010;62(3):373-384.
7. Collis N, Elliot LA, Sharpe C, Sharpe DT. Cellulite treatment: a myth or reality: a prospective randomized, controlled trial of two therapies, endermologie and aminophylline cream. *Plast Reconstr Surg*. 1999;104(4):1110-1114.
8. Hexsel DM, Mazzuco R. Subcision: a treatment for cellulite. *Int J Dermatol.* 2000;39(7):539-544.
9. Boyce S, Pabby A, Chuchaltkaren P, Brazzini B, Goldman MP. Clinical evaluation of a device for the treatment of cellulite: Triactive. *Am J Cosmet Surg*. 2005;22:233-237.
10. DiBernardo BE. Treatment of celllulite using a 1440-nm pulsed laser with one-year follow-up. *Aesthet Surg J.* 2011;31(3):328-341.
11. Dagum AB, Badalamente MA. Collagenase injection in the treatment of cellulite. *Plas Reconst Surg*. 2006;118(suppl 4):53.
12. Hexsel DM, Dal'Forno T, Hexsel CL. A validated photonumeric cellulite severity scale. *J Eur Acad Dermatol Venereol.* 2009;23(5):523-528.
13. Nürnberger F, Müller G. So-called cellulite: an invented disease. *J Dermatol Surg Oncol.* 1978;4(3):221-229.

[redacted]

LIST OF APPENDICES

[redacted]

APPENDIX A. DOCUMENTS REQUIRED PRIOR TO INITIATION OF THE STUDY

As a Sponsor of a clinical study, Endo Pharmaceuticals Inc. has an obligation to ensure that the study will be conducted by a qualified Investigator with sufficient resources of time, personnel, and physical facilities to conduct the study and to ensure that the Investigator understands and agrees to comply with the protocol, applicable regulations, policies, and procedures. The following documentation is required:

From the Principal Investigator

1. A signed agreement to perform the study per protocol (the signature page will suffice).
2. A signed Letter of Financial Agreement (including confidentiality statement).
3. Name(s) of the Principal Investigator and of all sub-Investigator(s)
4. All address(es) of the clinical site(s).
5. A current medical license valid where he/she practices and a current curriculum vitae for the Principal Investigator (signed and dated) and all sub-investigators, to contain at least the following elements:
   a. For physicians:
      i. Date of degree in Medicine
      ii. Name of the Institution granting the degree in Medicine.
      iii. Previous clinical postings with dates.
   b. For non-physician allowed by national law or regulations to act as clinical Investigators:
      i. Date and description of most advanced degree.
      ii. Name of the Institution granting the degree in number (i).
      iii. Other accreditation or qualifications relevant to the study.
      iv. Previous postings with dates.
      v. Name and qualification (see 5a above) of the physician or dentist in charge of study subjects.

   Note: If a non-physician is serving as Principal Investigator, then a qualified physician must be assigned as a sub-Investigator for the trial, to be responsible for all trial-related medical decisions.
6. Written notification of Institutional Review Board/Independent Ethics Committee/Human Research Ethics Committee (IRB/IEC/HREC) approval. The minimum requirements are as follows:
   a. Dated letter, including:
      i. The date on which the meeting for the review of the study protocol took place.
      ii. Study protocol/amendment number, and version date

iii. A clear statement of approval of the protocol and the informed consent text with version date, and authorization for the study to proceed.

iv. If the Investigator or any sub-Investigator is a part of the IRB/IEC/HREC Review Board, assurance that the Investigator abstained from voting at the meeting(s) when the study was discussed.

b. A dated list of the members and their occupations.

c. A specimen copy of the Committee-approved informed consent text to be used in the study.

7. Food and Drug Administration (FDA) Form 1572 (for studies submitted under a US Investigational New Drug application [IND]).

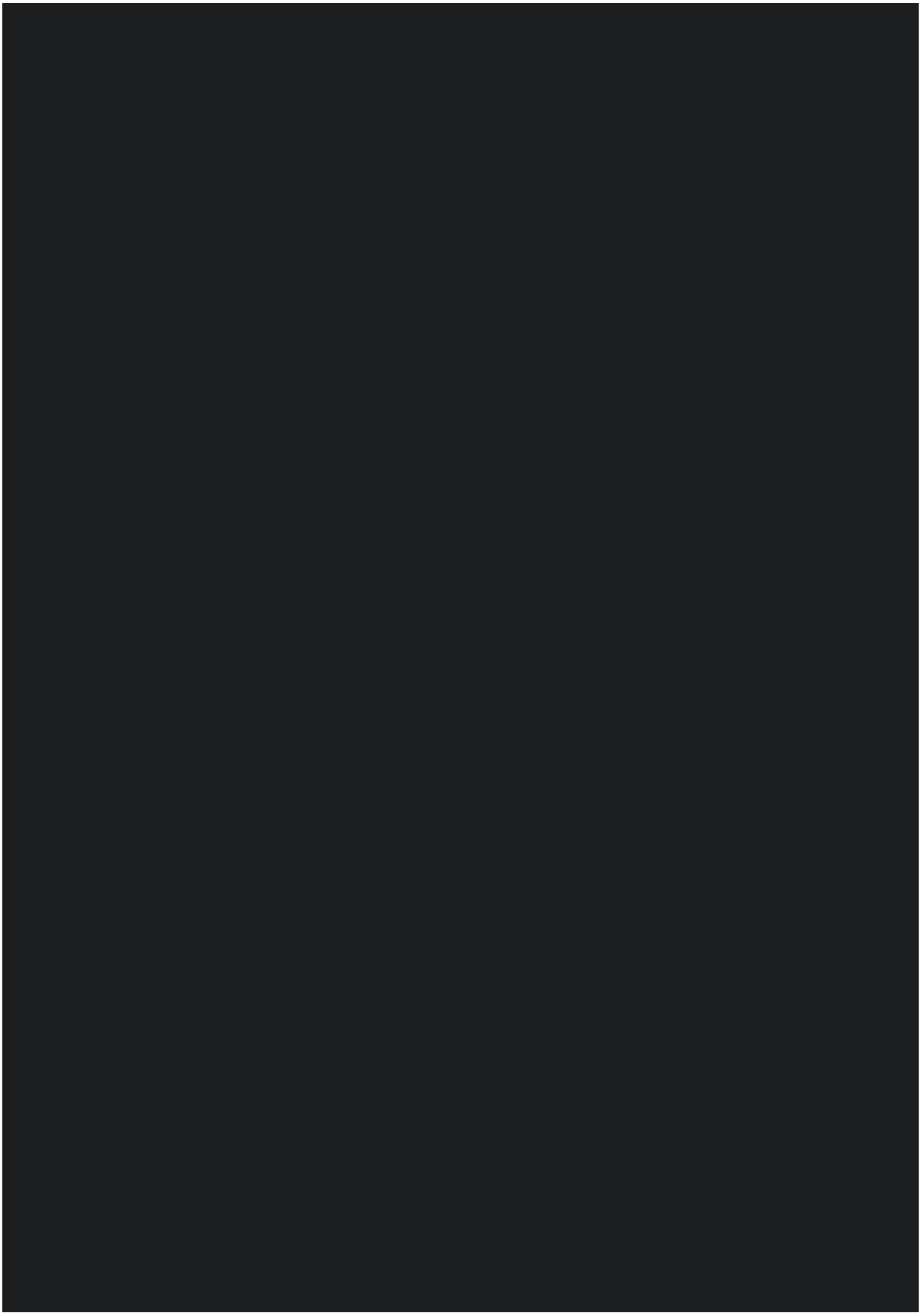
8. Financial Disclosure Certification or Certification of Non-Disclosure (for studies to be submitted for a US New Drug Application/Biologics License Application [NDA/BLA]).

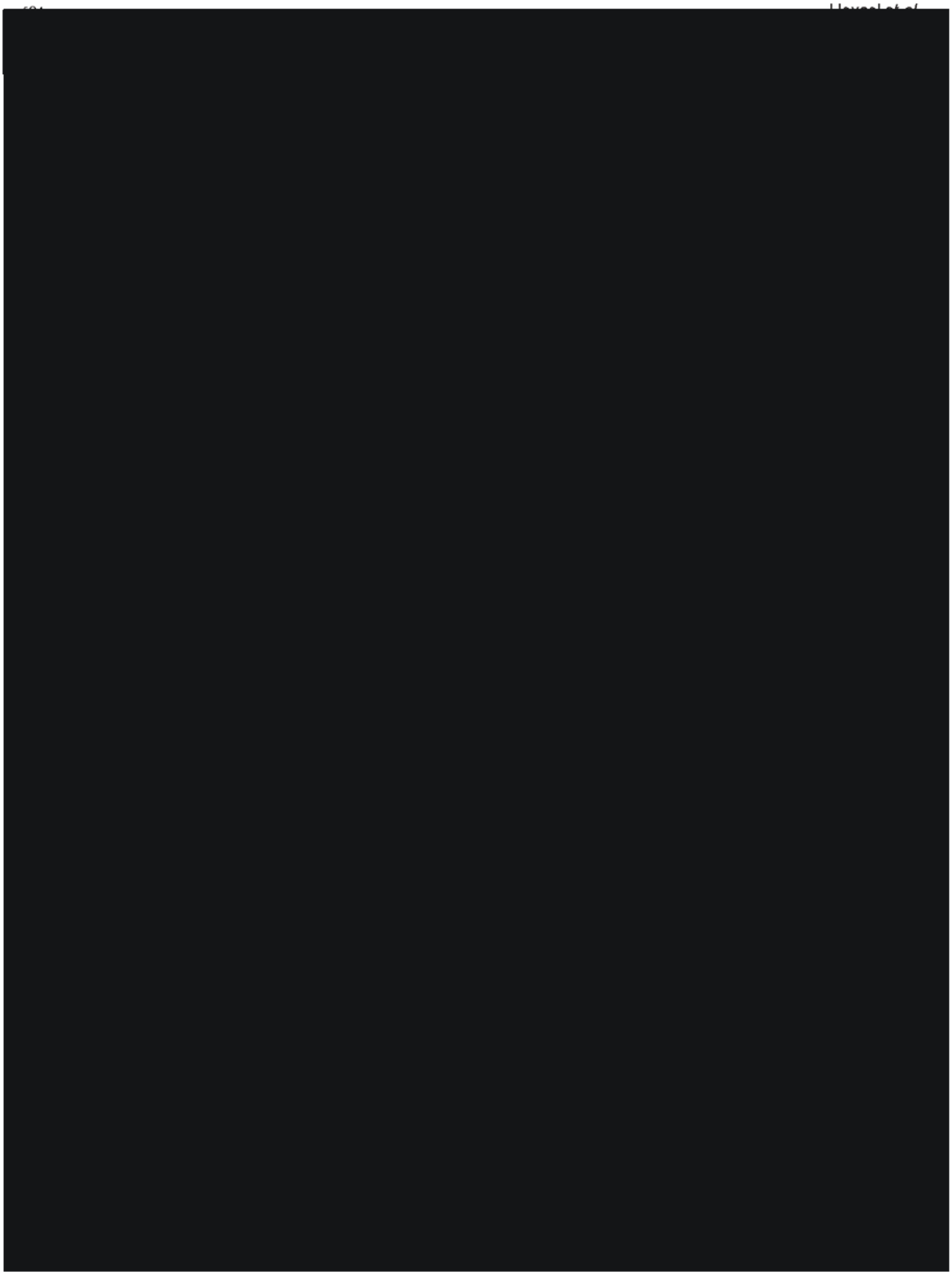
Other

Any other documentation required by national law or regulations to be in the possession of the Sponsor or the Investigator for study participation or study initiation.

[redacted]

APPENDIX B. HEXSEL DM, DAL'FORNO T, HEXSEL CL. A VALIDATED PHOTONUMERIC CELLULITE SEVERITY SCALE. *J EUR ACAD DERMATOL VENEREOL*. 2009;23(5):523-528.





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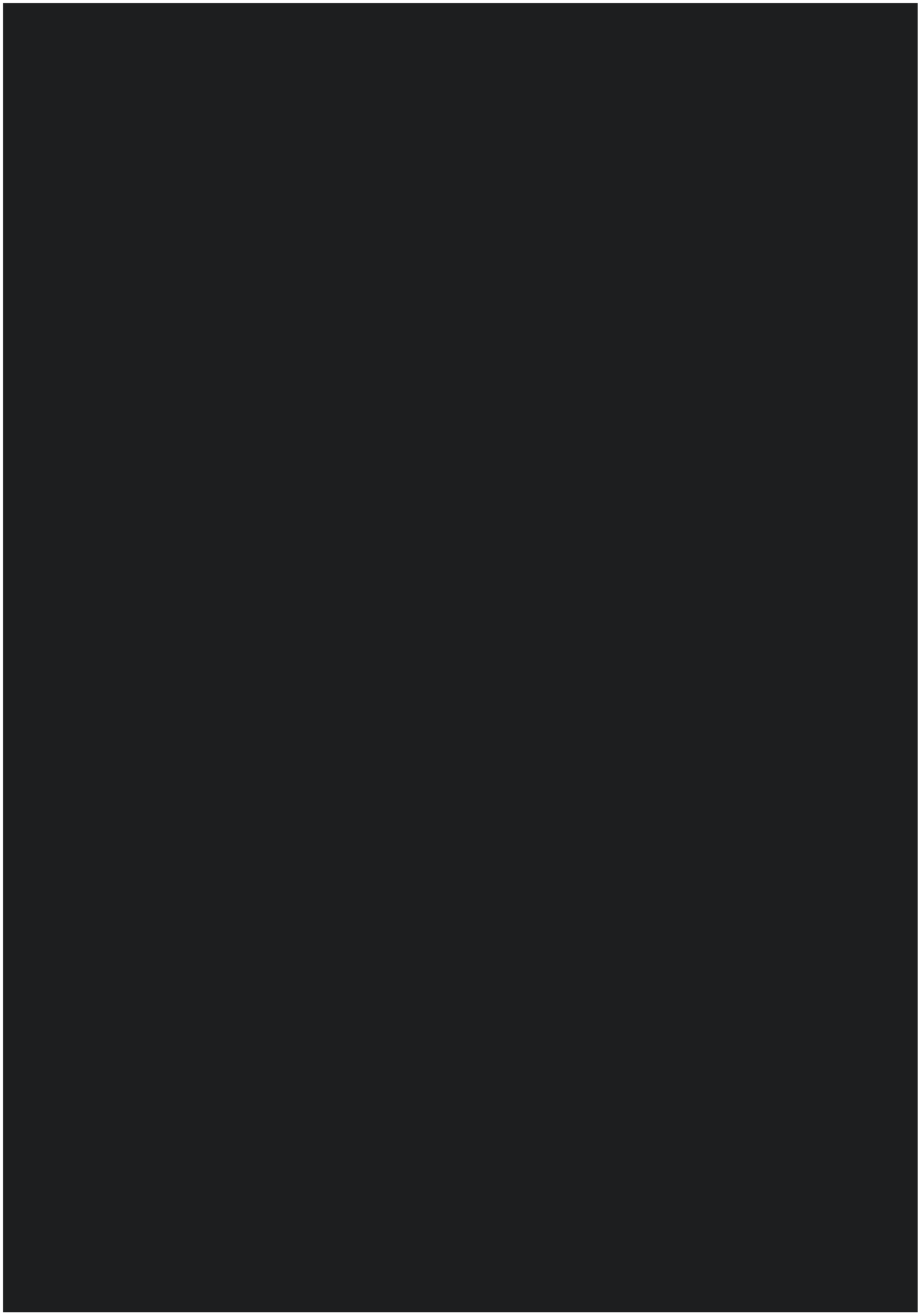
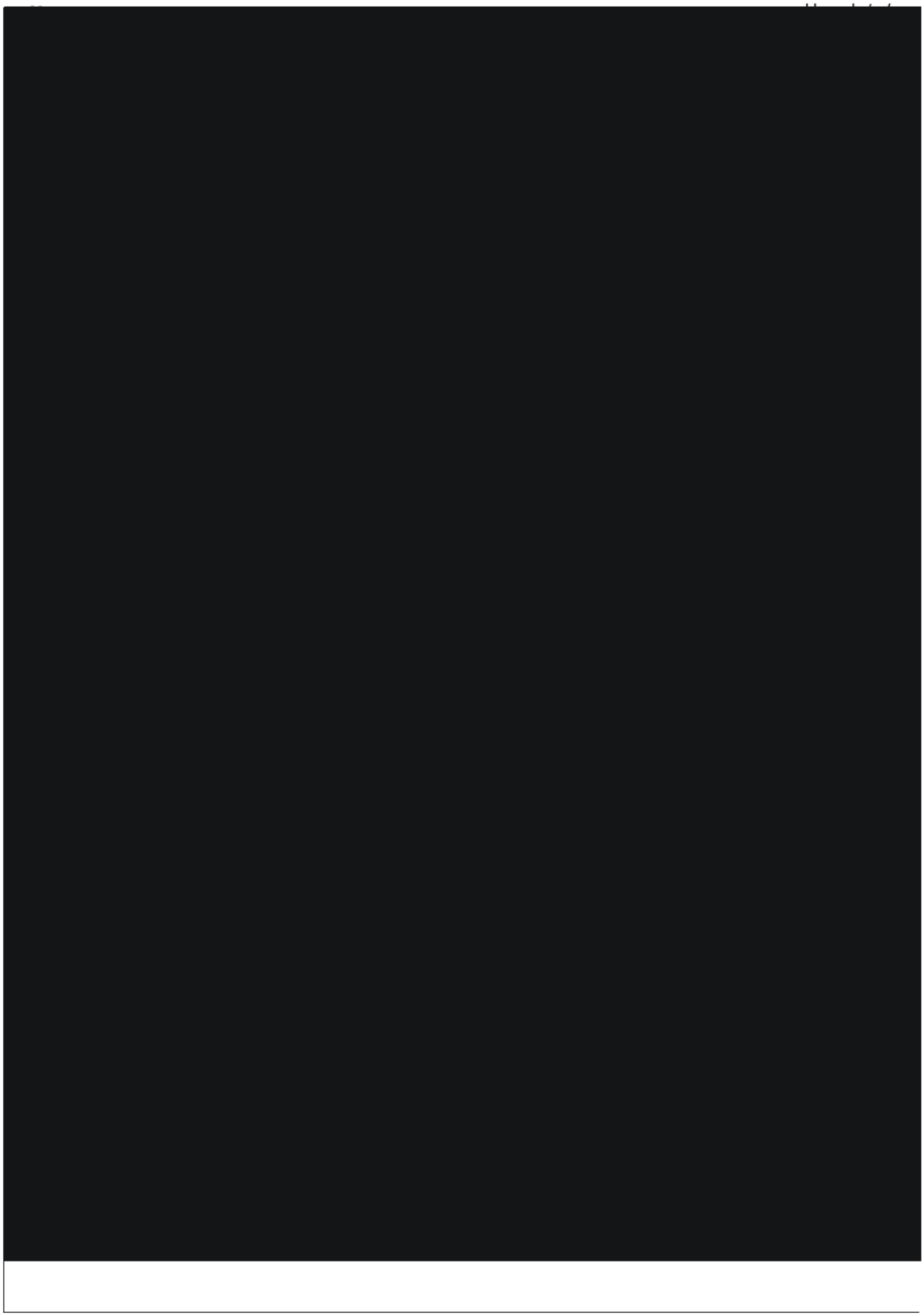
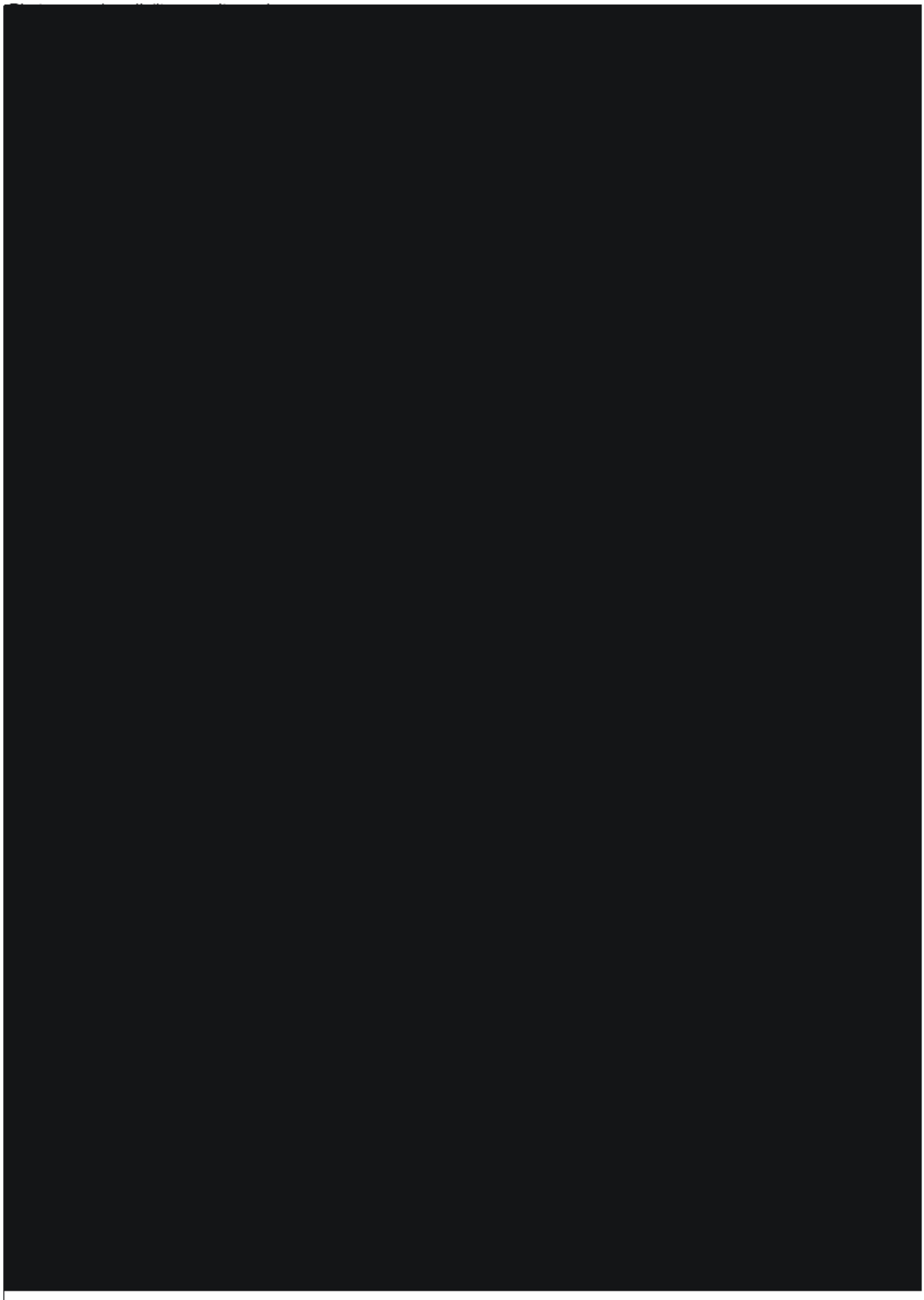
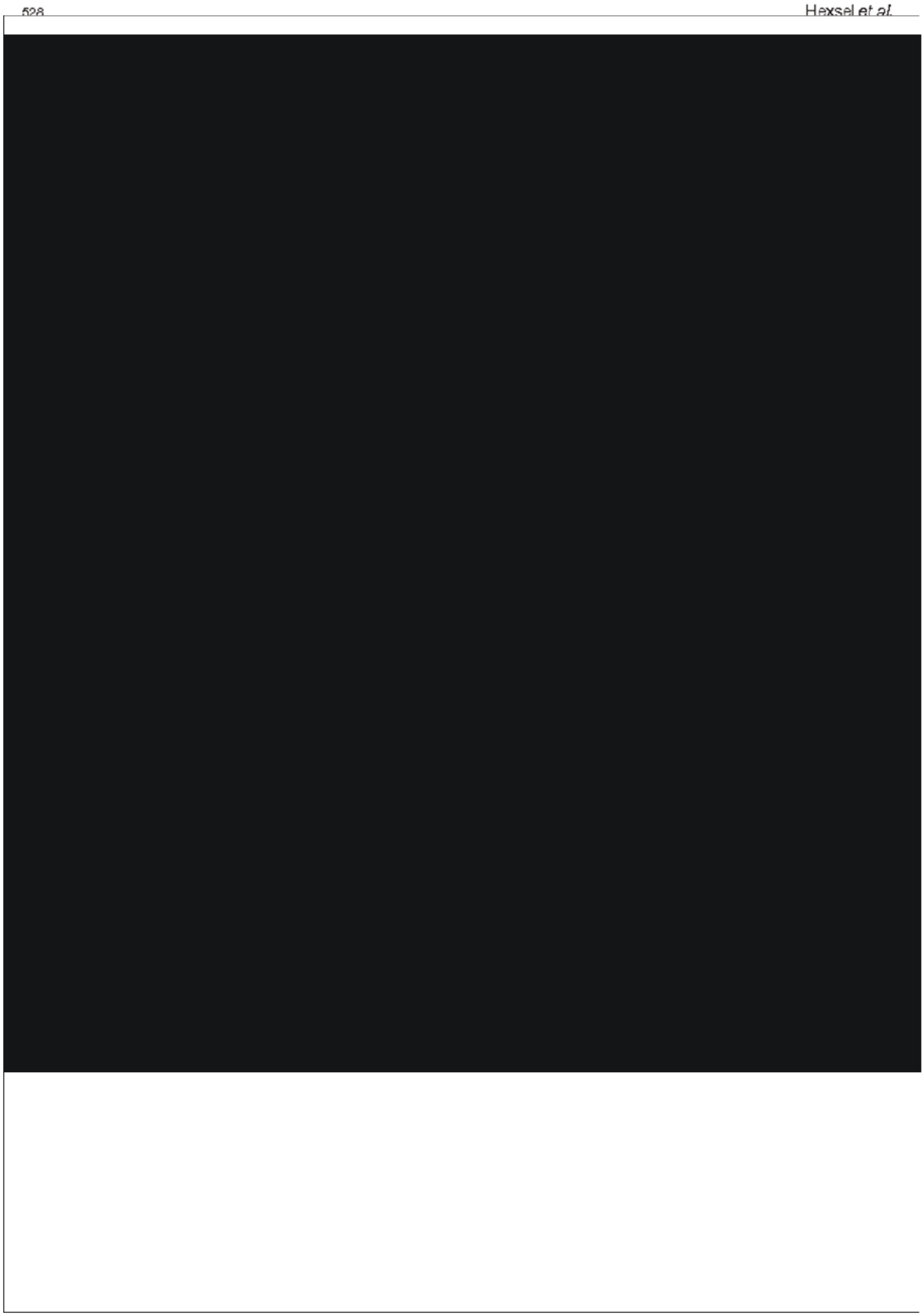


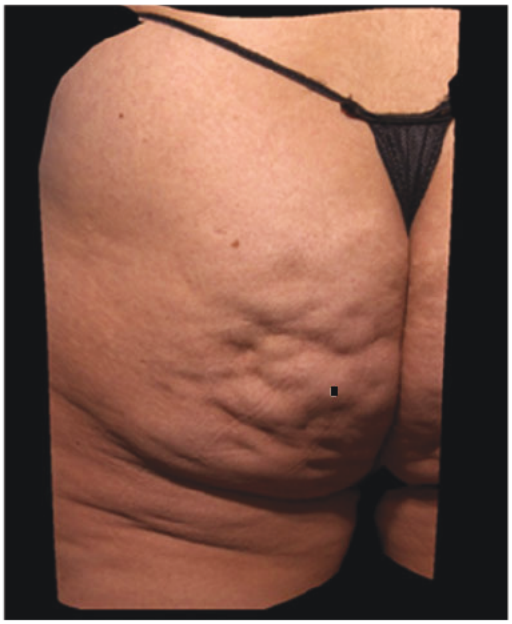





528
Hexsel et al.

APPENDIX C. REFERENCE IMAGES FOR HEXSEL SEVERITY RATINGS

[redacted]



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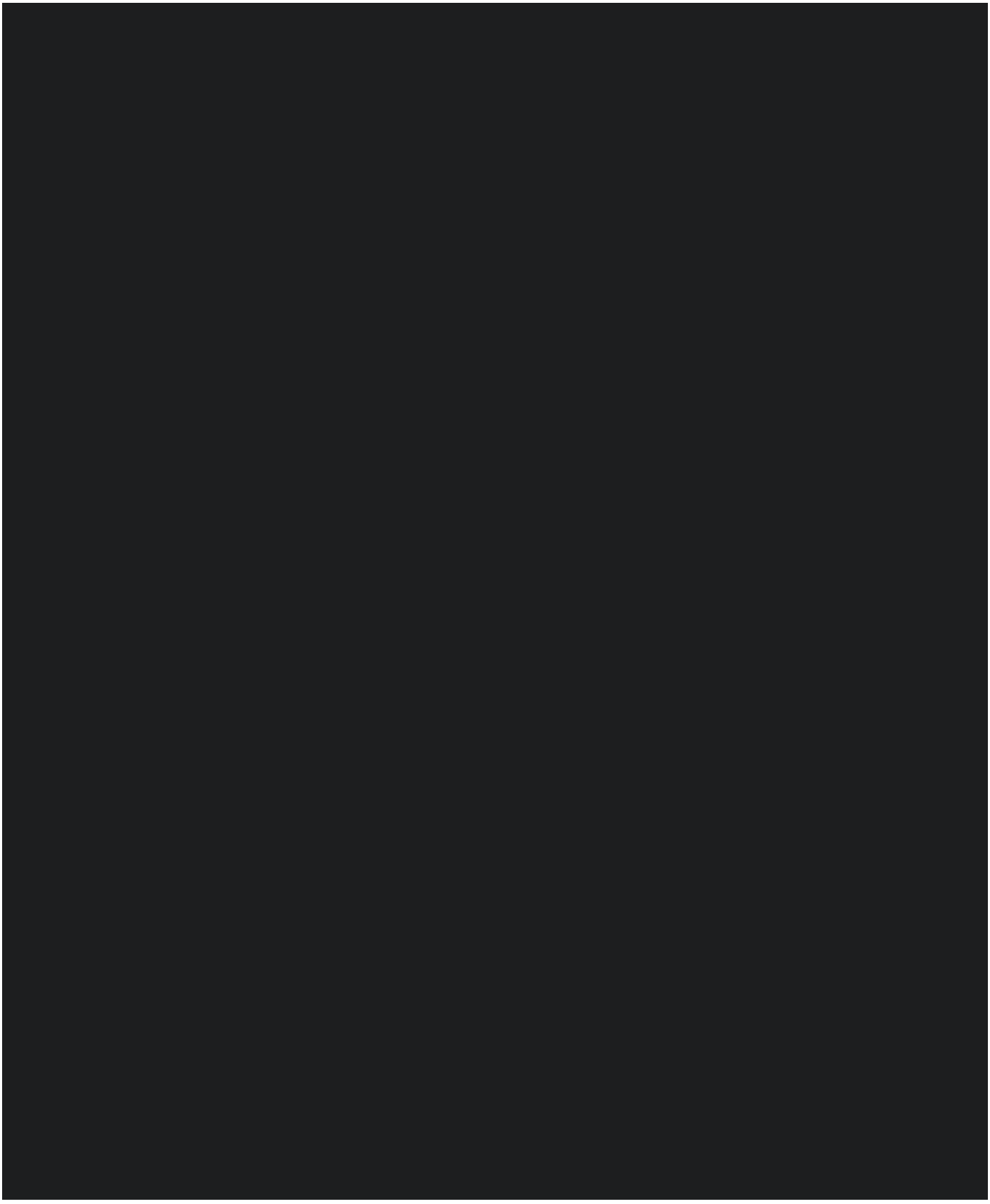
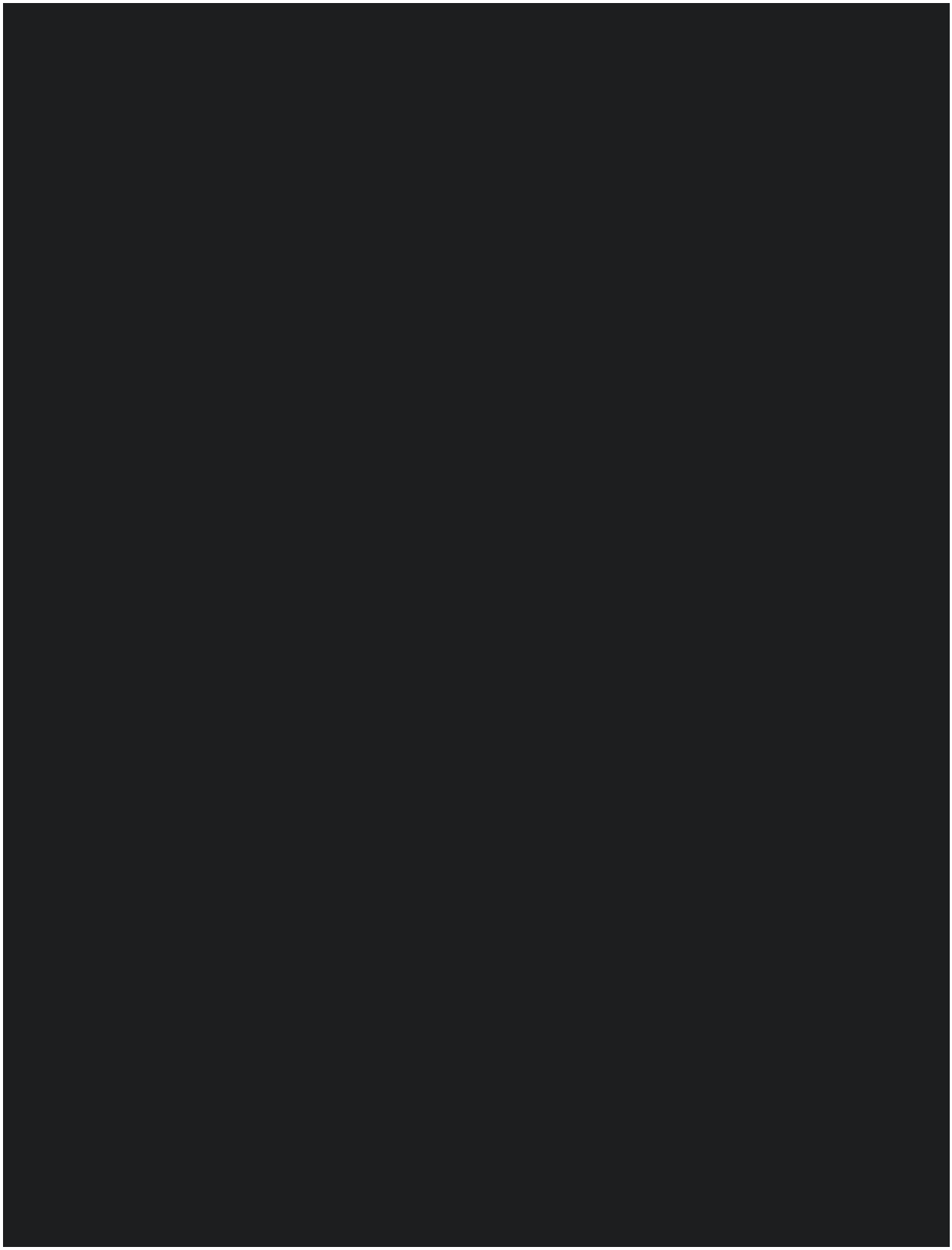
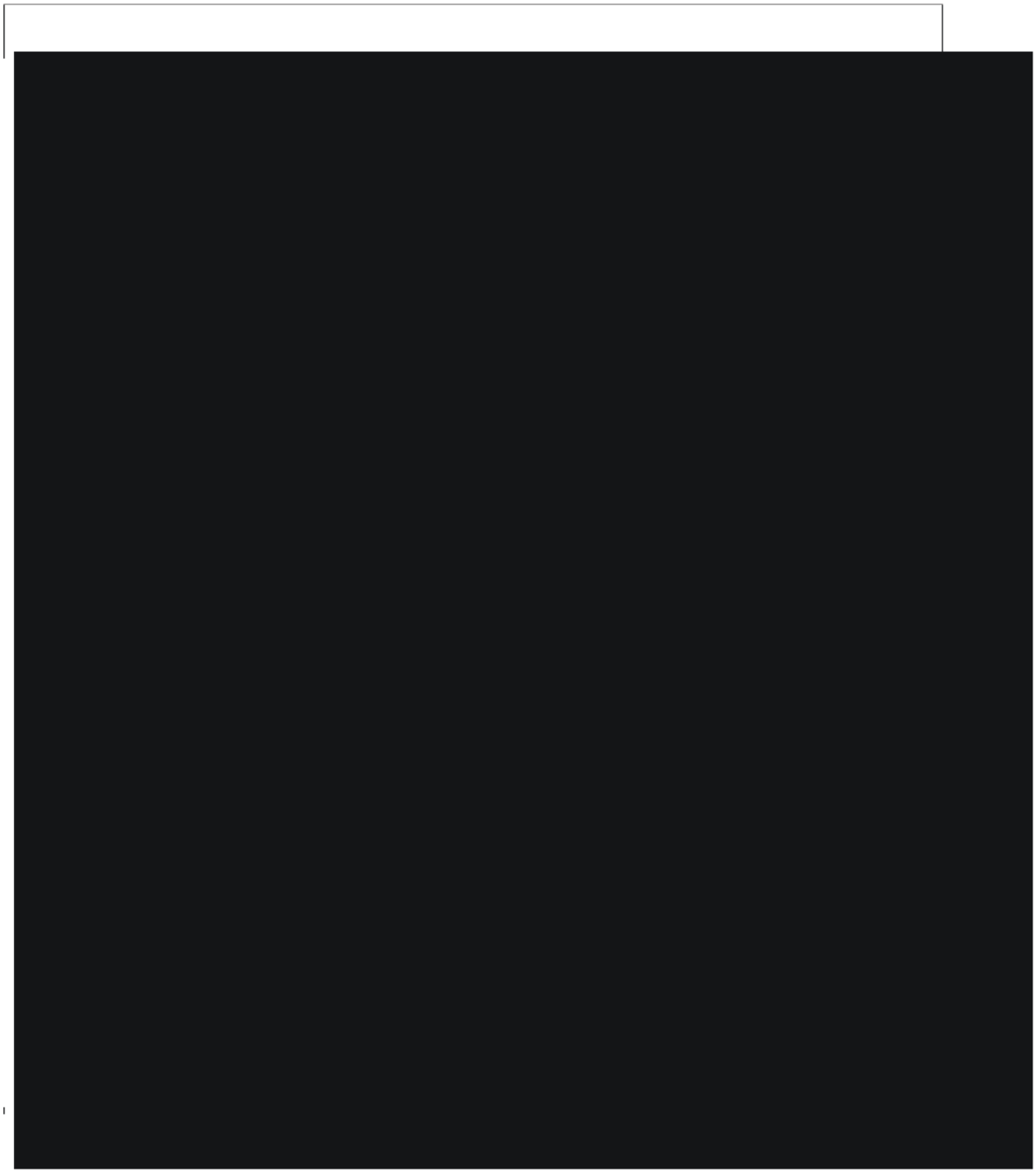
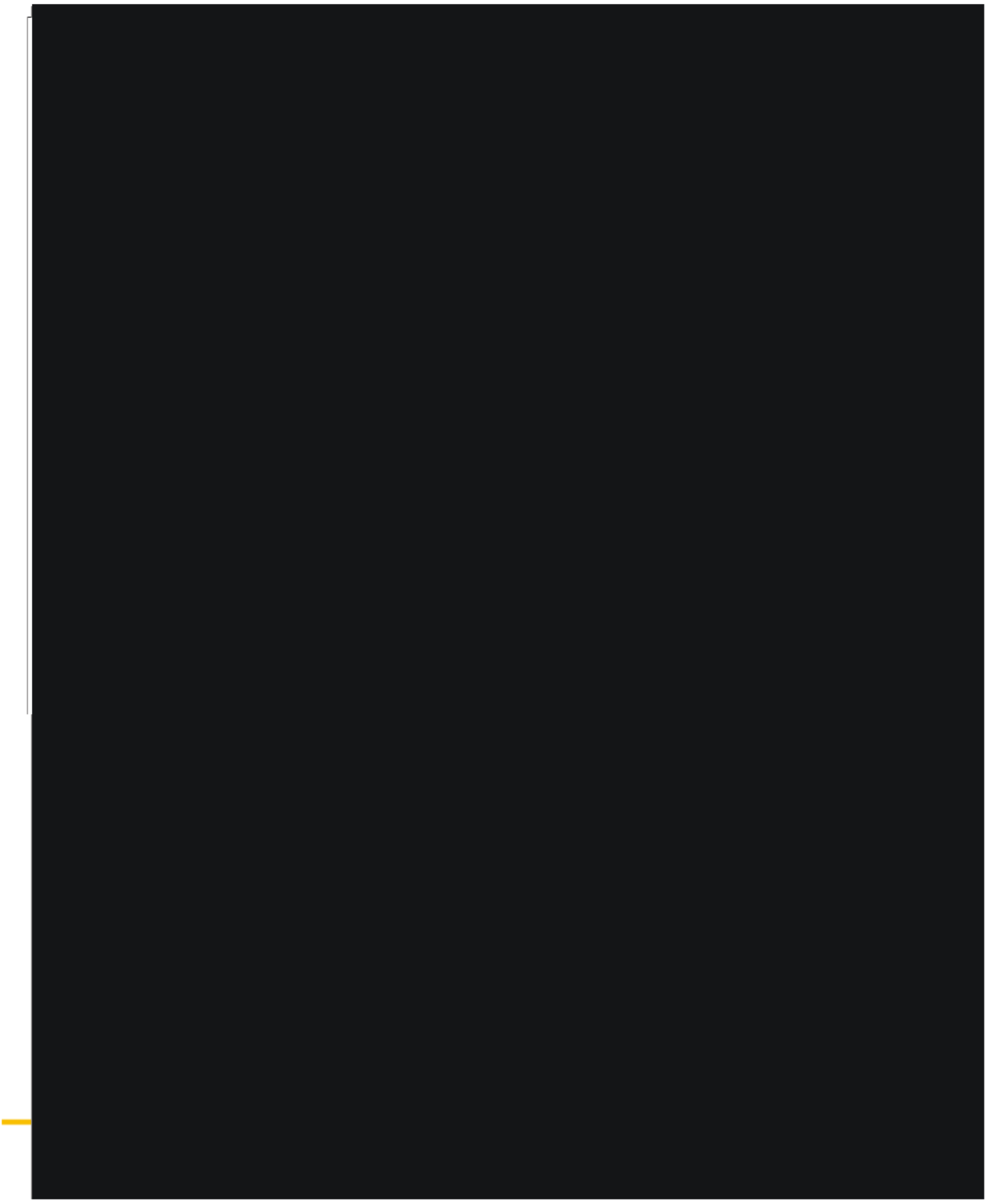
APPENDIX D. PATIENT INSTRUCTIONS FOR USE OF PATIENT-REPORTED PHOTONUMERIC CELLULITE SEVERITY SCALE (PR-PCSS)









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

COLLAGENASE CLOSTRIDIUM HISTOLYTICUM (EN3835)

EN3835-202

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

IND 110077

Date:

June 20, 2016

Auxilium Pharmaceuticals, Inc. (Auxilium) was acquired by Endo International plc. in January 2015. The Sponsor of the application remains Auxilium; however, Endo Pharmaceuticals Inc. is authorized to act and to communicate on behalf of Auxilium.

Confidentiality Statement

2. SUMMARY OF CHANGES

Not applicable

3. SPONSOR CONTACT INFORMATION

Table 1: Sponsor Contact Information

Role in Study	Name	Telephone and Email Address
Clinical Research Scientist	[redacted]	[redacted]
Clinical Trial Manager	[redacted]	[redacted]
Medical Monitor	[redacted] TKL Research Inc	[redacted]
SAE Reporting Pathway	Not Applicable	[redacted]

A list of other key study personnel and vendors will be provided upon request separately for your reference.

4. SYNOPSIS

Name of Sponsor/Company: Endo Pharmaceuticals Inc.	
Name of Investigational Product: EN3835	
Name of Active Ingredient: Collagenase clostridium histolyticum	
Title of Study: A Phase 2, Open-Label Extension Study of EN3835 in the Treatment of Edematous Fibrosclerotic Panniculopathy	
Lead Principal Investigator: To be determined	
Study period: Estimated date first subject enrolled: Jun-2016 Estimated date last subject completed: May-2017	**Phase of development:** Phase 2

Objectives:

Primary:

- The primary objective of this study is to assess long-term safety of EN3835 0.84 mg at scheduled intervals over 1 year (12 months) in all subjects with edematous fibrosclerotic panniculopathy (EFP) who elect to enroll in this open-label trial regardless of their decision to receive treatment (re-treatment or re-dosing) of open-label EN3835 or opt to receive no treatment.

Secondary:

- To evaluate the durability of response to EN3835 in EFP severity over the 12-month post initial dosing of EN3835 in subjects previously receiving active treatment in study EN3835-201 using the Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS), the Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS), and the Hexsel Cellulite Severity Scale (CSS)
- To evaluate long-term response to EN3835 in assessments of EFP including subject satisfaction, Investigator Global Aesthetic Improvement Scale (I-GAIS), and Subject Global Aesthetic Improvement Scale (S-GAIS)
- To evaluate immunogenicity after exposure to EN3835

Study Design: This study is a Phase 2 open-label study for the safety and efficacy of EN3835 in the treatment of EFP. To be eligible, a subject must have participated and completed the previous cellulite study EN3835-201. Subjects will be screened for study eligibility within 14 days prior to enrolling in this study (EN3835-202). Subjects will be assessed for safety and cellulite severity assessments approximately every 3 months for a maximum of 1 year from their first exposure to EN3835. Subjects with at least 1 quadrant with moderate or severe level of cellulite will be eligible for treatment with EN3835 after unblinding of study EN3835-201; a quadrant that was treated with EN3835 in the previous study EN3835-201 will only be eligible for retreatment if the cellulite severity in that quadrant is rated at levels of cellulite severity at baseline in study EN3835-201.

A treatment course will consist of 3 treatment sessions separated by 21 days. Treatment will be allowed in eligible subjects up to a maximum of 2 treatment courses including the treatment course in study EN3835-201 if subject was treated with EN3835. Each treatment session will consist of up to 12 injections (0.07 mg/0.3 mL per injection) of EN3835 for a dose of 0.84 mg and volume of 3.6 mL. Only a quadrant with moderate (rating of 3) or severe (rating 4) level of severity as assessed by the subject and investigator using the PR-PCSS and the CR-PCSS, respectively, will be eligible for

treatment; if more than 1 eligible quadrant exists, the quadrant selected will be at the discretion of the subject. Treatments will be administered on days 1, 22, and 43; subjects will be assessed for safety on days 1, 22, 43, and 71 and for cellulite severity assessments on days 1, 43, and 71. After day 71, they will be observed every 3 months from their first exposure to EN3835 up to a maximum of 1 year. The study will terminate when at least 100 subjects have been assessed at 12 months after the first exposure to EN3835.

Number of subjects (planned): 333

Study center(s): 16 sites in the United States

Diagnosis and inclusion/exclusion criteria:

Qualification for the Open-Label Observation Phase of the Study

Inclusion criteria for observation:

1. Voluntarily sign and date an informed consent agreement
2. Have participated in and completed the double-blind study EN3835-201
3. Be willing to apply sunscreen to any treated quadrant before each exposure to the sun while participating in the study (ie, screening through end of study)

Exclusion criteria for observation:

None

Qualification for the Open-Label Treatment Phase of the Study

Inclusion criteria for treatment:

1. Voluntarily sign and date an informed consent agreement
2. Have participated in and completed the double-blind study EN3835-201 and all day 71 assessments
3. Be a female ≥18 years of age
4. At Screening B visit, have at least 1 quadrant with:
   a. a score of 3 or 4 (moderate or severe) as reported by the subject (PR-PCSS), and
   b. a score of 3 or 4 (moderate or severe) as reported by the Investigator (CR-PCSS), and
   c. a Hexsel CSS score no greater than 13
5. Be willing to apply sunscreen to the selected treatment quadrant before each exposure to the sun while participating in the study (ie, Screening B through end of study)
6. Be judged to be in good health, based upon the results of a medical history, physical examination, and laboratory profile at Screening B
7. Have a negative urine pregnancy test at Screening B and before injection of study drug and be using an 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
8. Be willing and able to cooperate with the requirements of the study
9. Be able to read, complete and understand the patient-reported outcomes rating instruments in English

***Exclusion criteria for treatment**:*

1. Has used any of the following for the treatment of EFP on the legs or buttock within the timelines identified below or intends to use any of the following at any time during the course of the study:
   - Liposuction on the side of the body selected for treatment during the 12-month period before injection of study drug
   - Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; or surgery (including subcision and/or powered subcision) within the selected treatment quadrant during the 12-month period before injection of study drug
   - Endermologie or similar treatments within the selected treatment quadrant during the 6-month period before injection of study drug
   - Massage therapy within the selected treatment quadrant during the 3-month period before injection of study drug
   - Creams (eg, Celluvera™, TriLastin®) to prevent or mitigate EFP within the selected treatment quadrant during the 2-week period before injection of study drug
2. Is presently nursing a baby or providing breast milk for a baby
3. Intends to become pregnant during the study
4. Has received an investigational drug or treatment within 30 days before injection of study drug
5. Has a known systemic allergy to collagenase or any other excipient of study drug
6. Is currently receiving or plans to receive anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication (except for ≤150 mg aspirin daily) within 7 days before injection of study drug
7. Has a known recent history of stroke, bleeding, or other medical condition, which in the investigator's opinion would make the subject unsuitable for enrollment in this phase of the study
8. Presence of any clinically relevant conditions, that in the opinion of the Investigator would interfere with completing the study including, but not limited to, visual problems, hearing problems, cognitive impairment or acute mental illness

Investigational product, dosage and mode of administration: EN3835, 0.84 mg, subcutaneous. A dose of 0.84 mg of EN3835 will be administered as up to 12 subcutaneous injections (0.3-mL injection administered as three 0.1-mL aliquots per injection, up to 12 injections per treatment session) for a maximum volume of 3.6 mL per treatment session. A treatment course will consist of 3 treatment sessions at 21 days intervals, ie, treatments on days 1, 22, and 43 of each treatment course.

For the observational periods of this study, subjects will be assessed for safety and cellulite severity assessments at approximately 3-month intervals for a maximum of 1 year following their first exposure to EN3835.

Duration of study: Twelve (12) months from first exposure to EN3835 in study EN3835-201 or study EN3835-202

Screening Phase: Up to 14 days

Observational Phase: Subjects will be assessed at visits that occur approximately every 3 months for a maximum of 1 year after the first exposure to EN3835.

Follow-up: Subjects will be assessed at visits that occur approximately every 3 months for a maximum of 1 year after the first exposure to EN3835. For subjects treated with EN3835 in this study, subjects will be observed at treatment visits (days 1, 22, and 43) and day 71 after first injection.

Reference therapy, dosage and mode of administration: Not applicable

Criteria for evaluation:

Efficacy:

- PR-PCSS while viewing digital images of the selected quadrant: 5-point scale ranging from 0 (no cellulite) to 4 (severe cellulite) (approximately every 3 months after initial injection [either an injection in previous study EN3835-201 or after an injection in this study]). If treatment is administered in this study, PR-PCSS will be obtained at Screening B (Baseline), days 22, 43, and 71 after initial treatment within this study.
- Investigator using the CR-PCSS by live assessment: 5-point scale ranging from 0 (no cellulite) to 4 (severe cellulite) (every 3 months after initial injection [either an injection in previous study EN3835-201 or after an injection in this study]). If treatment is administered in this study, CR-PCSS will be obtained at Screening B (Baseline), days 22, 43, and 71 after initial treatment within this study.
- Investigator rating of cellulite severity using the total score from the Hexsel CSS: scores can range from 0 (no cellulite) to 15 (extremely severe cellulite) (day 360). If treatment is administered in this study, Hexsel CSS will be obtained in this study at Screening B (Baseline) and day 71 after initial treatment within this study.
- I-GAIS: 7-point scale ranging from 3 (very much improved) to −3 (very much worse) (day 71)
- S-GAIS: 7-point scale ranging from 3 (very much improved) to −3 (very much worse) (day 71)
- Subject satisfaction with cellulite treatment assessment: 5-point scale ranging from 2 (very satisfied) to −2 (very dissatisfied) (day 71)

Safety:

Safety will be assessed throughout the study through the recording of:

- Adverse events (AEs)
- Vital signs
- Clinical laboratory tests
- Immunogenicity assessment (ie, assessed through the determination of binding and neutralizing anti-AUX-I and anti-AUX-II antibody levels).

In addition, for subjects treated with EN3835 in this study, injection site reactions/local tolerability in treated quadrant (through subject and Investigator reporting) will be assessed.

Statistical methods:

Sample Size Consideration:

The number of subjects (approximately 333) is intended to obtain additional subjects for adequate long-term safety data at the selected dose.

Analysis Populations:

Observational population: The Observational population is defined as all subjects treated with EN3835 in study EN3835-201 who do not receive any treatment in the current study

Safety population: The Safety population is defined as all enrolled subjects who received at least 1 injection of EN3835 in this study or in study EN38335-201.

Intent-to-Treat (ITT) population: The ITT population is defined as all enrolled subjects in this study.

[redacted]

Modified Intent-to-Treat (mITT) population: The mITT population is defined as ITT subjects who received at least 1 injection of EN3835 in this study with a baseline and 1 post-injection evaluation of both the CR-PCSS and PR-PCSS. All efficacy (cellulite assessments) analyses will be completed on this population.

Per-Protocol population: The Per-Protocol population is defined as those subjects in the Safety population who have no major protocol deviations.

Efficacy Evaluations:

The primary cellulite severity assessment endpoint, the proportion of composite responders with improvement of 2 or better on each scale (CR-PCSS and PR-PCSS) at day 71, will be summarized as percentages and analyzed using a Cochran-Mantel-Haenszel test that compares the 2 treatment groups and adjusts for Investigator. The ITT population will be evaluated for the primary endpoint with any subjects not having a post-injection evaluation of either CR-PCSS or PR-PCSS classified as a non-responder.

All secondary endpoints, except the Hexsel CSS total score, will be summarized as percentages. The dichotomous secondary endpoints (ie, responders endpoints) will be analyzed using a Cochran-Mantel-Haenszel test adjusted for investigator. Multiple-response endpoints (ie, scales) will be analyzed using the Mann-Whitney test. Change in Hexsel CSS total score will be summarized with descriptive statistics for continuous variable and will be analyzed using analysis of variance (ANOVA).

Safety Analysis:

The following variables are safety endpoints:

- AEs: Mapped to preferred term using the Medical Dictionary for Regulatory Activities (MedDRA)
- Vital signs
- Clinical laboratory tests

AEs will be summarized by proportion of subjects reporting each event. Descriptive statistics will be presented for actual and change from baseline at each visit for vital signs and for each clinical laboratory test parameter.

Immunogenicity: Anti-AUX-I and anti-AUX-II antibody levels will be summarized using descriptive statistics for the actual value at the visit.

5. SCHEDULE OF EVENTS

NOTE: Observation visits (Table 2) in the open-label extension study begin after completion of double-blind study (day 71). Treatment sessions (Table 3), if elected, will begin when study drug blind is broken in study EN3835-201while observation visits continue concurrently.

Table 2: Observation Assessments

Procedures	Screening A[a] (≥Day 71 Visit of Double-blind Study)	Visit 1 Day 90[b] (±7 days)	Visit 2 Day 180[b] (±7 days)	Visit 3 Day 270[b] (±7 days)	Visit 4 End of Study/ Early Termination Day 360[b] (±7 days)
Informed Consent	X				
Inclusion/Exclusion	X				
Digital photography		X[c]	X[c]	X[c]	X[c]
Body weight		X	X	X	X
Vital signs		X	X	X	X
Collection of samples:					
• Clinical laboratory					X
• Anti-AUX-I/anti-AUX-II antibody level		X	X	X	X
Subject cellulite assessments:					
• Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS)		X[d,e]	X[d,e]	X[d,e]	X[d,e]
• Subject Global Aesthetic Improvement (S-GAIS)					X[d,e]
• Subject satisfaction with cellulite treatment assessment					X[d,e]
Investigator cellulite assessments:					
• Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)		X[e]	X[e]	X[e]	X[e]
• Hexsel Cellulite Severity Scale (CSS)					X[e]
• Investigator Global Aesthetic Improvement (I-GAIS)					X[e]
Injection site reactions/local tolerability in assigned quadrant from EN3835-201 study		X	X	X	X
Adverse events	Monitored Throughout Study				

[a] Informed consent for open-label observation assessments and optional treatment election.
[b] Three (3)-month evaluation periods begin 90 days after day 1 of the double-blind study (EN3835-201) (ie, within 20 days ±4 days of completion of double-blind study).
[c] Only the treated quadrant(s) is photographed. For subjects participating in observation-only visits, the quadrant treated in the double-blind study (EN3835-201) is photographed; for subjects with open-label treatment (treated with EN3835 in study EN3835-202), the treated quadrant is photographed.
[d] Assessment made via viewing digital image photograph.
[e] Assessment of treated quadrant(s) only.
NOTE: Subject cellulite assessments must be completed before the Investigator cellulite assessments are conducted at each visit.

Table 3: Treatment Session Assessments

Procedures	Screening B[a] (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/ Early Termination Day 71 (±5 days)[b]
Informed Consent	X				
Inclusion/Exclusion	X				
Digital photography	X[c]	X[c,d]	X[c,d]	X[c,d]	X[c]
Medical history/EFP history including previous treatments	X[k]				
Prior/Concomitant Medications/Procedures	X[k]	X	X	X	X
Physical examination:	X				
• Body weight	X		X[e]	X[e]	X
• Height	X				
Vital signs	X	X[f]	X[f]	X[f]	X
12-lead ECG	X[l]				
Collection of samples:					
• Clinical laboratory	X				X
• Anti-AUX-I/anti-AUX-II antibody level		X[e]	X[e]	X[e]	X
• Urine pregnancy testing	X	X[e]	X[e]	X[e]	
Subject cellulite assessments:					
• Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS)	X[g,h]		X[e,g,h]	X[e,g,h]	X[g,h]
• Subject Global Aesthetic Improvement (S-GAIS)					X[g,h]
• Subject satisfaction with cellulite treatment assessment					X[g,h]
Investigator cellulite assessments:					
• Selection of dimples to be treated within selected quadrant		X[e]	X[e]	X[e]	
• Marking the dimples to be treated within selected quadrant		X[e]	X[e]	X[e]	
• Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)	X[h]		X[e,h]	X[e,h]	X[h]
• Hexsel Cellulite Severity Scale (CSS)	X[h,i]				X[h]
• Investigator Global Aesthetic Improvement (I-GAIS)					X[h]
Confirm Eligibility	X	X[e]			
Select Quadrant	X[j]				
Study drug administration		X	X	X	
Injection site reactions/local tolerability in selected quadrant		X	X	X	X
Adverse events	Monitored Throughout Study				

[a] Eligible subjects may choose additional treatment any time after the study drug blind is broken in study EN3835-201.
[b] Upon completion of treatment, subject will be followed at 3-month intervals as in Table 2; if study terminates early, subject will be followed through Visit 4 (day 71). If subject received placebo in the double-blind study (EN3835-201), she may be eligible for a total of 2 courses of treatment (a total of 6 treatment sessions) in this study.
[c] All 4 quadrants are photographed at screening; at other visits, the selected quadrant only is photographed.
[d] Before and after marking the dimples.
[e] Before injection.
[f] Up to 4 hours before injection; approximately 15 and 30 minutes after injection. Vital signs must be stable before the subject is discharged.
[g] Assessment made via photograph (if treatment session, use photograph taken before marking dimples).
[h] All 4 quadrants are assessed at the Screening B visit; at other visits, the selected quadrant only is assessed.
[i] Initial Hexsel CSS at screening must be ≤13 on selected quadrant (Appendix C).
[j] To qualify for treatment, the selected quadrant must have a score of 3 or 4 (moderate or severe) in both the CR-PCSS and PR-PCSS, and a Hexsel CSS score ≤13; to qualify a quadrant that had been previously treated with EN3835 in study EN3835-201, the quadrant must have CR-PCSS and PR-PCSS scores equal to or greater than study EN38325-201 baseline scores and a Hexsel CSS score ≤13.
[k] Medical history and prior medications will be based on EN3835-201 eCRF; only updates and concomitant medications need to be captured at Screening B visit.
[l] Do not conduct if Screening B visit date is within 12 months of obtaining an ECG during the double-blind study (EN3835-201).

ECG=Electrocardiogram; eCRF=Electronic case report form; EFP=Edematous fibrosclerotic panniculopathy; Tx=Treatment
NOTE: Subject cellulite assessments must be completed before the Investigator cellulite assessments are conducted at each visit.

6. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

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LIST OF TABLES

LIST OF FIGURES

7. LIST OF ABBREVIATIONS

The following abbreviations and specialist terms are used in this study protocol.

Table 4: Abbreviations and Specialist Terms

Abbreviation	Definition
AE	Adverse event
Assigned quadrant	Assigned quadrant (ie, left or right buttock, or the left or right posterolateral thigh) that was suitable for treatment and was randomly assigned in the double-blind study (EN3835-201). To be suitable for treatment the quadrant must have an Investigator CR-PCSS and subject PR-PCSS score of 3 or 4 and a Hexsel CSS score of no greater than 13 at Screening B visit and at Day 1 visit.
AUX-I	Clostridial class I collagenase
AUX-II	Clostridial class II collagenase
CFR	Code of Federal Regulations
CRF	Case report form
CR-PCSS	Clinician-Reported Photonumeric Cellulite Severity Scale
CSS	Cellulite Severity Scale
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EFP	Edematous fibrosclerotic panniculopathy
FDA	Food and Drug Administration
GCP	Good clinical practice
HREC	Human research ethics committee
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
I-GAIS	Investigator-Global Aesthetic Improvement Scale
IND	Investigational new drug
IRB	Institutional review board
ITT	Intent-to-treat
kDa	Kilodalton
MedDRA	Medical Dictionary for Regulatory Activities

Table 4: Abbreviations and Specialist Terms (Continued)

Abbreviation	Definition
mITT	Modified intent-to-treat
PCS	Potentially clinically significant
PR-PCSS	Patient-Reported Photonumeric Cellulite Severity Scale
Qualified designee	Qualified by education and training to perform the study procedure (eg, sub-Investigator, nurse)
SAE	Serious adverse event
SAP	Statistical Analysis Plan
Selected quadrant	Quadrant (ie, left or right buttock, or the left or right posterolateral thigh) that is suitable for treatment and is selected by patient and investigator for treatment. To be suitable for treatment the quadrant must have an Investigator CR-PCSS and subject PR-PCSS score of at least 3 or 4 and a Hexsel CSS score of no greater than 13 at Screening B visit.
S-GAIS	Subject – Global Aesthetic Improvement Scale
TEAE	Treatment-emergent adverse event; adverse events that occur on or after the first injection of study drug

8. INTRODUCTION

8.1. Edematous Fibrosclerotic Panniculopathy

Edematous fibrosclerotic panniculopathy (EFP), commonly known as cellulite, has been defined as a local metabolic disorder of subcutaneous tissues that results in an alteration of skin topography.(1) The condition manifests as dimpled skin, described as an orange-peel, cottage cheese, or mattress texture, particularly in the gluteal-femoral region.(2,3) EFP is caused by herniation of subcutaneous fat lobules through the dermohypodermal junction. This creates an uneven surface with dimpling.(1) EFP is a medical condition resulting in a potentially cosmetically unacceptable alteration of the skin, and affects an estimated 85% to 98% of postpubertal women.(1,3)

The pathophysiology of EFP is not completely understood, but there are 3 main theories: edema resulting from excessive hydrophilia of the intercellular matrix, alteration of the regional microcirculation, and different anatomical conformation of collagenous subcutaneous tissues in women versus men.(4)

It is known that EFP is different from generalized obesity. In generalized obesity, adipocytes undergo hypertrophy and hyperplasia that are not limited to the pelvis, thighs, and abdomen.(1) In areas of EFP, adipocytes have physiologic and biochemical properties that differ from adipose tissue located elsewhere. Large, metabolically-stable adipocytes characterize EFP-prone areas; thus, the responsiveness to catecholamine-induced lipolysis is less in EFP tissues compared to visceral fat, which has the greatest responsiveness.(1)

Subcutaneous fat lobes are separated from one another by thin, usually rigid strands of collagenous connective tissues, which cross the fatty layers and connect the dermis to the underlying fascia. These septa stabilize the subcutis and divide the fat. In EFP, shortening of the collagen septa due to fibrosis provokes retraction at the insertion points of the trabeculae, causing the depressions that characterize EFP.(2) There are a higher percentage of thinner, perpendicular hypodermal septa in women with EFP than in men.(1) Weight gain makes EFP more noticeable, but it may be present even in thin subjects. Genetics may also play a role since EFP tends to run in families.

8.2. Current Edematous Fibrosclerotic Panniculopathy Treatments

There are therapies that have been utilized in an attempt to treat cellulite. Despite multiple therapeutic modalities, there is little scientific evidence that any of these treatments are beneficial. In fact, much of the evidence is anecdotal, subjective, or based only on patient self-assessment.(5) Some of the historical treatments for EFP have included:

- Weight loss: Weight loss generally decreases the severity of EFP but may only have a variable effect on EFP grades.(6)
- Pharmacological agents (eg, xanthines, retinoids, lactic acid, and herbals): Although there are numerous topical treatments that are available over the counter, there are no well-designed or large-scale studies demonstrating the effectiveness of any of these

therapies.(5) Additionally, ingredients in some of the topical treatments are unknown and may pose an increased risk for adverse effects.(5)

- Massage: Endermologie or lipomassage kneads the skin between rollers. This type of vigorous massage is posited to increase blood flow and reduce excess fluid in EFP prone areas. In a 12-week, randomized, controlled study of 52 women that examined the effectiveness of either endermologie or aminophylline versus a combination of both, there was no statistical difference in the thigh measurement between subjects.(7)
- Liposuction: Liposuction can reshape the body, but it does not typically correct cellulite as it does not interrupt collagen septae in a directed fashion. Additionally, liposuction is not a recommended treatment for cellulite given the potential for poor cosmetic outcome.(5,6)
- Mesotherapy: Mesotherapy involves injecting solutions containing various substances, eg, methylxanthines, to dissolve subcutaneous fat; however, this type of therapy often results in unwanted side effects, including infection, urticarial reactions, and bumpy or uneven skin contours.(6) To date, there are no regulatory approved mesotherapy mixtures for the treatment of EFP.
- Radiofrequency: Radiofrequency systems may temporarily improve the appearance of EFP after a series of treatments; but long-term efficacy has not been demonstrated.(6)
- Subcision: Subcision is an invasive surgical technique that severs the septa holding fat lobules that cause the skin dimpling associated with EFP. In a study conducted by Hexsel and Mazzuco, 232 subjects had subcision for the treatment of EFP.(8) Although 78% of subjects were satisfied after 1 treatment, there were no objective criteria by which to assess improvement, thereby limiting the value of this study. Additionally, side effects reported in this study included pain, bruising for 3 to 6 months, hyperpigmentation for 2 to 10 months, and skin puckering.(5,6) These effects are most likely due to the trauma from shearing the septa with a large gauge needle (eg, 16 or 18 gauge) or other cutting devices.
- Powered subcision: Powered subcision is a surgical technique utilizing a powered needle apparatus to sever the septa holding fat lobules that cause skin dimpling associated with EFP. The Cellfina® powered subcision device was recently approved by Food and Drug Administration (FDA; 2015) for the treatment of cellulite.
- Laser: Intense pulsed light has been investigated for the treatment of cellulite. Triactive® is an FDA-approved low-fluorescence 810-nm light source combined with a 915-nm laser. In a study of 16 female subjects who underwent 12 treatments with the Triactive, 21% had improvement (based on 5 blinded Investigators' analysis of photographs with respect to appearance of cellulite, skin tone, and texture) of their cellulite.(9) The CelluLaze™ system was used to treat cellulite on the thighs of 10 healthy women.(10) In this Investigator-initiated study, subjects received a single treatment with a 1440-nm laser. During the CelluLaze procedure, which is performed under a local tumescent and general anesthetic, the physician inserts a small cannula through the skin and the device technology directs controlled, laser thermal energy to

the treatment zones. The laser is designed to diminish the lumpy pockets of fat by melting the hypodermal fat; release the areas of skin depression through thermal subcision of the septal tissue; and increase the elasticity and thickness of the skin by melting the fat in the dermal invaginations. Subjective physician and subject evaluations indicated improvement in the appearance of cellulite and high patient satisfaction that persisted for a year. For both the Triactive and CelluLaze studies, there were no control groups and significance was not tested.

There remains an unmet medical need for safe and effective nonsurgical therapies to improve the esthetic outcome in women with cellulite. To effectively treat cellulite, a therapeutic approach may require disruption of the dermal septa, which are composed of collagen and cause the skin dimpling which is bothersome to many women.

8.3. EN3835 (Collagenase Clostridium Histolyticum)

Endo Pharmaceuticals Inc. (Endo) is developing EN3835 for the treatment of EFP. Because EN3835 is a proteinase that can hydrolyze the triple-helical region of collagen under physiological conditions, EN3835 has the potential to be effective in lysing subdermal collagen, such as those observed in the dermal septa, which are the underlying cause of the skin dimpling in women with EFP. EN3835 targets the collagenase structural matrix (eg, dermal septa) at the site of injection and does not require systemic exposure to be effective.

EN3835 is a parenteral lyophilized product comprised of 2 collagenases in an approximate 1:1 mass ratio, Collagenase I (AUX-I, Clostridial class I collagenase) and Collagenase II (AUX-II; Clostridial class II collagenase). These collagenases are isolated and purified from the fermentation of *Clostridium histolyticum*. Collagenase AUX-I is a single polypeptide chain containing approximately 1,000 amino acids of known sequence and with a molecular weight of 114 kDa. Collagenase AUX-II is also approximately 1,000 amino acids long and has a molecular weight of 113 kDa. These 2 collagenases are not immunologically cross-reactive and have different specificities, such that together they become synergistic, providing a very broad hydrolyzing reactivity toward collagen. Clostridial collagenases are proteinases that can hydrolyze the triple-helical region of collagen under physiological conditions.

EN3835 is currently approved for: 1) the treatment of adults with Dupuytren's contracture with a palpable cord and, 2) for the treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy.

8.3.1. Studies with EN3835 for the Treatment of Edematous Fibrosclerotic Panniculopathy

The studies summarized in this section are described in more detail in the Investigator's Brochure (IB).

8.3.1.1. Investigator-Initiated Proof-of-Concept Study

In an Investigator-initiated pilot study, 10 female subjects received EN3835 in the treatment of cellulite.(11) A 10×10-cm oval area was outlined on the posterolateral thigh and 0.58 mg EN3835 was injected using a template as 5 concurrent subcutaneous injections of 0.116 mg per injection. Subjects were followed up to 180 days after injection for reduction of the cellulite appearance in the injected area. At 1 month post injection, the area of cellulite (as measured from

photographs) was reduced 89% from baseline. Patient satisfaction score was 1.75 at month 6 (1=completely satisfied, 4=not satisfied). Side effects included the local events of injection area soreness, ecchymosis, and mild edema; these resolved within a mean of 18 days. The results from this study suggest that the collagen septa of EFP may be an appropriate substrate for lysis with injectable collagenase, and that treatment with collagenase appears to be tolerable and possibly effective. However, due to the paucity of the data, no conclusions could be drawn regarding dose, frequency, and injection technique.

8.3.1.2. Endo-Sponsored Phase 1b Dose-Escalation Study AUX-CC-830

A dose-ranging Phase 1b dose escalation study (AUX-CC-830) used a template arrangement of injections as was used in the Investigator-initiated pilot study but injected a matrix of doses, concentrations and injectate volumes to select doses for further development. This Phase 1b study showed efficacy results suggesting that collagenase clostridium histolyticum (CCH) may be effective in the treatment of EFP based on global aesthetic improvement at day 90 with ratings of "improved" by 43.4% of Investigators and 52.5% of subjects. The majority of subjects (71.7%) were "quite satisfied" or "very satisfied" with treatment on day 90. Adverse events(AEs) were local injection site events (bruising, pain, erythema, and edema) were mild or moderate and resolved within a period of 3 weeks.

8.3.1.3. Endo-Sponsored Phase 2a Dose-Ranging Study AUX-CC-831

The Phase 2a study (AUX-CC-831) was a double-blind, placebo-controlled, dose-ranging study of 150 women randomized to 0.06, 0.48, or 0.84 mg of CCH; or placebo in a 5:5:5:3 ratio. Each subject could receive up to 3 treatment sessions of study drug separated by approximately 21 days. Efficacy in this study was evaluated based on Investigator Global Aesthetic Improvement Scale (GAIS-I) and Subject Global Aesthetic Improvement Scale (GAIS-S) along with other measures of treatment efficacy. Improvements were observed in cellulite appearance based on the statistically significant changes in the appearance of cellulite based on both the GAIS-I and GAIS-S scores for the high and mid doses compared to placebo ($p<0.05$). The majority of the patients were either satisfied or very satisfied with the results of their cellulite treatment with the mid and high doses compared to placebo ($p<0.05$). Similar to the AEs reported in subjects in the previous study (AUX-CC-830) and subjects who received EN3835 for Dupuytren's contracture and Peyronie's disease, the majority of AEs occurred at the site of injection and resolved before the next scheduled treatment session.

8.3.1.4. Endo-Sponsored Phase 2b Study EN3835-201

Currently there is an ongoing Phase 2b study (EN3835-201) which is a double-blind, placebo-controlled study of 350 adult women randomized to EN3835 0.84 mg or placebo in a 1:1 ratio. Each subject can receive up to 3 treatment sessions of study drug separated by approximately 21 days; last visit is day 71. Efficacy is being evaluated using a Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS), a Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS), the Hexsel Cellulite Severity Scale (CSS), GAIS-I, GAIS-S, and a subject satisfaction assessment. Subjects that complete study EN3835-201 will be offered the option of participating in study EN3835-202.

8.4. Summary of Nonclinical Studies

Nonclinical studies necessary to support clinical studies have been performed and are summarized in the IB. Nonclinical studies in the following areas were performed: toxicology, reprotoxicity, genotoxicity, and carcinogenicity.

8.5. Summary of Known Risks and Benefits

A summary of safety risks is provided in the IB. The following events have been commonly observed in prior studies: injection site AEs such as bruising, edema, erythema and pain.

There are previously generated potential clinical benefits associated with EN3835 in treating EFP, however, such potential benefits need further clinical evaluation. It is hoped that data from this clinical study will demonstrate a measurable sustained or durable clinical benefit of EN3835 in EFP as well as longer term safety.

8.6. Rationale

This study will allow an evaluation of longer term safety (over 12 months) following EN3835 treatment of subjects with EFP. Additionally, although uncontrolled, an assessment of cellulite assessments (efficacy) of EN3835 in the treatment of quadrants with moderate or severe cellulite will be conducted in subjects treated with placebo or EN3835 in the previous double-blind study (EN3835-201). The safety of re-dosing either in a previously treated quadrant (termed *re-treatment*) or in a naive quadrant (termed *re-dosing*) in subjects that previously received EN3835 treatment in study EN3835-201 will be assessed. Finally, the durability of improvement will be evaluated in enrolled subjects following EN3835 treatment in the double-blind study (EN3835-201) as well as those being treated with EN3835 in this open-label study (EN3835-202).

9. OBJECTIVES

9.1. Primary Objective

The primary objective of this study is to assess long-term safety of EN3835 0.84 mg at scheduled intervals over 1 year (12 months) in all subjects with EFP who elect to enroll in this open-label trial regardless of their decision to receive treatment (re-treatment or re-dosing) of open-label EN3835 or opt to receive no treatment.

9.2. Secondary Objectives

- To assess safety and immunogenicity of re-treating or re-dosing a subject that had previously received treatment with EN3835
- To evaluate the durability of response to EN3835 in EFP severity over the 12-month post initial dosing of EN3835 in subjects previously receiving active-treatment in study EN3835-201 using the PR-PCSS, the CR-PCSS, and the Hexsel CSS
- To evaluate long-term response to EN3835 in assessments of EFP including subject satisfaction, I-GAIS, and S-GAIS
- To assess cellulite severity assessments in quadrants treated in this study with EN3835

9.3. Exploratory Objectives

There are no exploratory objectives for this open-label extension study.

10. INVESTIGATIONAL PLAN

10.1. Study Design

This open-label extension study will be performed at multiple centers currently participating in the double-blind, placebo-controlled, parent trial (EN3835-201) in the United States. The open-label extension study will enroll up to 350 subjects. The study is planned to end when at least 100 subjects have 12 months after exposure ie 12 months after first treatment in study EN3835-201 or study EN3835-202. Subjects who completed the entire double-blind study and sign an informed consent will be eligible to enter this open-label extension.

After the Sponsor has broken the EN3835-201 study drug blind, subjects enrolled in the open-label study will have the following options:

- To have no EN3835 treatments in study EN3835-202
- If received EN3835 in study EN3835-201, may elect to have a qualifying quadrant other than the one treated in study EN3835-201 treated with EN3835 (termed *re-dosing*)
- If received EN3835 in study EN3835-201 and the cellulite severity scores of the treated quadrant have returned to or are greater than EN3835-201 baseline scores, may elect to have the previously treated quadrant retreated with EN3835 (termed *re-treatment*)
- If received placebo in study EN3835-201, may elect to have a qualifying quadrant treated with EN3835; also may elect to have a second qualifying quadrant treated with EN3835 after completing the treatment course

Subjects enrolled in study EN3835-202 who elect to receive EN3835 treatment (either re-treatment, re-dosing, or a first treatment) must meet specific inclusion and exclusion criteria for eligibility during re-screening (Screening B) prior to EN3835 dosing.

Following completion of safety and cellulite assessments at day 71 of the double-blind study (EN3835-201), subjects will be asked if they wish to continue in the open-label extension to the double-blind study (Screening A). At the time of entry into the open-label study, subjects and Investigators will remain blinded to study drug. Until the EN3835-201 study drug blind is broken by the Sponsor, subjects will undergo observation-only visits at 3-month intervals ± 7 days (relative to the initial dose in the double-blind study) where both safety and cellulite severity assessments of the treated quadrant will be made.

Following the study drug blind being broken and communicated to centers, treatments of eligible subjects with EN3835 can begin at a visit at the discretion of the subject. Subjects electing not to receive further EN3835 treatments (observation-only subjects) will continue to be followed for safety and cellulite severity assessments at 3-month intervals through month 12. Up to 14 days prior to initiating treatment injections of EN3835 on open-label treatment visit day 1, subjects will undergo a screening evaluation (Screening B) to determine if they meet specified inclusion and exclusion criteria and to determine the quadrants, if any, that qualify for treatment.

During Screening B, photographs will be taken of each of the subject's 4 quadrants (left buttocks, right buttocks, left posterolateral thigh, and right posterolateral thigh). Subjects will again receive instructions for use of the PR-PCSS and will subsequently use the scale to rate the severity of their cellulite in each of the 4 quadrants by comparing digital images of each of their quadrants displayed on standardized computer monitors with the PR-PCSS instrument. This independent self-assessment will take place in a private setting to minimize any potential bias from site personnel. The Investigator will then assess the subject's 4 quadrants live in real-time using the CR-PCSS. The Investigator will rate the 4 quadrants using the Hexsel CSS as described in section 13.1.1.6.(12) Subjects must have at least 1 quadrant that meets the following criteria for inclusion into the treatment phase of the study:

1. PR-PCSS score of 3 or 4, and
2. CR-PCSS score of 3 or 4, and
3. Hexsel CSS score of no greater than 13.

After the independent assessments are completed separately by the subject and the Investigator, the Investigator will review his/her assessments and the subject's assessment to determine which quadrants, if any, are eligible. The eligible quadrant chosen to receive treatment in the open-label study EN3835-202 will be at the discretion of the subject. A quadrant may be chosen for re-treatment if it was the quadrant treated in study EN3835-201 or a new quadrant may be chosen for re-dosing**. NOTE: For subjects who received active drug in the assigned quadrant in the double-blind study, the quadrant must have cellulite severity at (or greater) than the EN3835-201 baseline scores of PR-PCSS and CR-PCSS to qualify for re-treatment.**

Previously placebo-treated subjects will have the option to receive a second course of EN3835 in the same or different qualifying quadrant after at least 28 days following end of the first treatment course (ie treatment of second quadrant could begin on day 71 after treating the first quadrant). The selected quadrant can be re-treated or re-dosed.

At each treatment session visit, Investigators will select the dimples within the chosen quadrant to be treated. Selection of dimples to be treated in the quadrant will be at the discretion of the Investigator. The selected EFP dimples in the selected quadrant must be well-defined and evident when the subject is standing in a consistent relaxed pose (without the use of any manipulation such as skin pinching or muscle contraction). The dimples selected to be treated will be circled with a surgical marker and injection site locations should be marked with a dot; if more than 1 injection per dimple is needed, the injection sites should be separated by approximately 2 cm. The selected quadrant will be photographed again after marking dimples. Subjects will be administered a maximum of EN3835 0.84 mg from a total of up to 12 injections. Up to 12 injections will be administered at each treatment session to treat the selected quadrant. Each of the injections will be administered as three 0.1-mL aliquots (total injection volume per injection is 0.3 mL; total injection volume per treatment session is 3.6 mL [12 injections × 0.3 mL], see table below).

Subjects will receive 3 treatment sessions (day 1, day 22, and day 43) unless the chosen quadrant has no further treatable EFP dimples and the Investigator rates the quadrant a score of 0 on the CR-PCSS. The same dimples within a quadrant or different dimples within a quadrant may be

treated at each session but injections must all be within the selected quadrant for all 3 sessions. Each treatment session will be separated by approximately 21 days.

Dose per Each Injection[a]	Injection Volume per Each Injection	Maximum Number of Injections per Each Treatment Session	Maximum Dose (mg) per Each Treatment Session	Maximum Injection Volume (mL) per Each Treatment Session	Maximum Cumulative EFP Dose
EN3835 0.07 mg N=333	0.3 mL	12 injections	0.84 mg (12 injections × 0.07 mg)	3.6 mL (12 injections × 0.3 mL)	2.52 mg (3 treatment sessions × 0.84 mg)

[a] Each injection of EN3835 is 0.3 mL administered as three 0.1-mL aliquots.

The complete Schedule of Events is provided in section 5 (Table 2 and Table 3) and summarized in section 12.

10.2. Selection of Doses

Maximum possible doses of EN3835 employed will be the same as that administered in the double-blind, placebo-controlled, parent study (EN3835-201).

10.3. Study Drug Administration

Study drug in the form of sterile vials of lyophilized EN3835 (formerly AA4500) and sterile diluent will be provided by Endo. Study drug administration at each injection site is presented in section 12.1.4.2.

10.4. Discussion of Study Design, Including the Choice of Control Groups

The use of the open-label extension design allows for the following:

- Safety data over a 12-month period will be collected to assist in further defining the safety profile of EN3835 in this population,
- Safety data and immunogenicity after repeat exposure (re-treatment/re-dosing) and monitoring of previously active-treated subjects to EN3835 over a 12-month period,
- Previously placebo-treated subjects to have exposure to EN3835, and
- Durability of the response to EN3835 (cellulite severity assessments) will be assessed.

11. SELECTION AND WITHDRAWAL OF SUBJECTS

11.1. Observation Phase

All subjects who have completed the double-blind study EN3835-201, including all day 71 assessments, and sign informed consent are eligible for enrollment in this open-label extension study and participation in the ongoing safety and cellulite evaluations.

11.1.1. Subject Inclusion Criteria for Observation

To qualify for this open-label observation study a subject must:

1. Voluntarily sign and date an informed consent agreement
2. Have participated in and completed the double-blind study EN3835-201
3. Be willing to apply sunscreen to any treated quadrant before each exposure to the sun while participating in the study (ie, screening through end of study)

11.1.2. Subject Exclusion Criteria for Observation

None

11.2. Treatment

Inclusion and exclusion criteria presented in section 11.2 apply only to those subjects in the open-label study who choose treatment.

At the time that the study drug blind is broken in the double-blind study EN3835-201, qualified subjects enrolled in the open-label study are eligible for treatment. A subject may participate in the observational period of this open-label study regardless of scoring of quadrant; however to receive treatment in this study, a subject must have at least 1 qualifying quadrant.

11.2.1. Subject Inclusion Criteria for Treatment

To qualify for treatment in the study a subject must:

1. Voluntarily sign and date an informed consent agreement
2. Have participated in and completed the double-blind study EN3835-201
3. Be a female ≥18 years of age
4. At Screening B visit, have at least 1 quadrant with:
   a. a score of 3 or 4 (moderate or severe) as reported by the subject (PR-PCSS), and
   b. a score of 3 or 4 (moderate or severe) as reported by the Investigator (CR-PCSS), and
   c. a Hexsel CSS score no greater than 13
5. Be willing to apply sunscreen to the selected treatment quadrant before each exposure to the sun while participating in the study (ie, Screening B through end of study)
6. Be judged to be in good health, based upon the results of a medical history, physical examination, and laboratory profile at Screening B

7. Have a negative urine pregnancy test at Screening B and before injection of study drug and be using an 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.
8. Be willing and able to cooperate with the requirements of the study
9. Be able to read, complete and understand the patient-reported outcomes rating instruments in English

11.2.2. Subject Exclusion Criteria for Treatment

A subject will be **excluded from treatment** in the study (but not from the observation assessments) if she:

1. Has used any of the following for the treatment of EFP on the legs or buttock within the timelines identified below or intends to use any of the following at any time during the course of the study:
   - Liposuction on the side of the body selected for treatment during the 12-month period before injection of study drug
   - Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; or surgery (including subcision and/or powered subcision) within the selected treatment quadrant during the 12-month period before injection of study drug
   - Endermologie or similar treatments within the selected treatment quadrant during the 6-month period before injection of study drug
   - Massage therapy within the selected treatment quadrant during the 3-month period before injection of study drug
   - Creams (eg, Celluvera™, TriLastin®) to prevent or mitigate EFP within the selected treatment quadrant during the 2-week period before injection of study drug
2. Is presently nursing a baby or providing breast milk for a baby
3. Intends to become pregnant during the study
4. Has received an investigational drug or treatment within 30 days before injection of study drug
5. Has a known systemic allergy to collagenase or any other excipient of study drug
6. Is currently receiving or plans to receive anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication (except for ≤150 mg aspirin daily) within 7 days before injection of study drug
7. Has a known recent history of stroke, bleeding, or other medical condition, which in the investigator's opinion would make the subject unsuitable for enrollment in this phase of the study

11.3. Subject Discontinuation Criteria

A premature discontinuation will occur when a subject who signed informed consent ceases participation in the study, regardless of circumstances, prior to the completion of the protocol. Subjects can be prematurely discontinued from the study for one of the following reasons:

- An adverse event (AE)
- A protocol violation (reason must be specified, for example: lack of compliance, use of a prohibited concomitant medication, failure to meet inclusion/exclusion criteria after study entry, etc)
- Withdrawal by subject (reason must be specified)
- The subject was "lost to follow-up"
- Other reasons (reason must be specified, for example: the subject moved, pregnancy, investigator decision, Sponsor decision to terminate trial, etc)

If a subject discontinues from the study, all end-of-study procedures should be conducted as detailed in Schedule of Events. The date a subject discontinues, the treatment, and the reason for discontinuation will be recorded in the source documentation and Electronic Case Report Form (eCRF). If, however, a subject withdraws consent, no end-of-study procedures are required except the collection of AE information. This information should be recorded in the source documentation and the eCRF.

11.3.1. Replacement Procedures

Subjects who discontinue prematurely from the study will not be replaced.

12. PROCEDURES AND TREATMENTS

12.1. Study Visits

The Schedule of Events to be performed at each visit is shown in section 5. Provided below are further details where additional instruction about the assessments that will be performed is deemed to be needed.

12.1.1. Subject Screening

Upon completion of day 71 assessments in the double-blind study EN3835-201, a subject will be eligible to enter this open-label extension study. Investigators will be expected to maintain a Screening Log of all potential study subjects. This log will include limited information about the potential subject and the date and outcome of the screening process (eg, enrolled into the study, reason for ineligibility, or refused to participate). Investigators will provide information about the study to subjects who appear to meet the criteria for participation in the study.

12.1.2. Screening Assessments

After obtaining informed consent, the full assessment of eligibility will be conducted and prior to study entry, screening assessments will be performed. Details about how the informed consent will be obtained and documented are provided in section 21.3, Subject Information and Consent. The subject may be entered into the observational phase of the study and complete safety and cellulite severity assessments at 3-month intervals as detailed in Table 2. In addition, once the study blind is broken in study EN3835-201, enrolled subjects will be asked if they wish to receive additional open-label treatments. If a subject elects to receive open-label treatment, study assessments will be conducted in accordance with Table 3.

12.1.3. Study Entry/Observational Assessments

A subject who gives written informed consent and who satisfies all eligibility criteria (section 11) may be entered into the observational phase of the study and complete safety and cellulite severity assessments at 3-month intervals as detailed in Table 2. In addition, once the study drug blind is broken in study EN3835-201, enrolled subjects will be asked if they wish to receive additional open-label treatments. If a subject elects to receive open-label treatment, study assessments will be conducted in accordance with Table 3. The subject identification number will be carried over from the double-blind, placebo-controlled study (EN3835-201).

12.1.3.1. Three-Month Assessments

Subjects will return within 20 days (±4 days) of completion of the double-blind study for the first of 4 safety and cellulite severity evaluation visits. Assessments to be completed at these visits are detailed in Table 2. Subjects are to return at 3-month intervals until they have completed 12 months from day 1 of the double-blind study. At these visits, quadrant(s) previously treated with EN3835 in the EN3835-201 study or quadrants treated with EN3835 in the open-label study will be evaluated. If the quadrant treated in study EN3835-201 is retreated in the open-label study, the 3-month assessments will reset to treatment visit 1/day 1 of the open-label treatment and the study visits will continue as described in Table 3 followed by 3-month assessments as

described in Table 2. If a different quadrant is treated in the open-label study, the 3-month assessments of both the quadrant treated in the double-blind study (EN3835-201) and the quadrant treated in the open-label study will continue.

12.1.4. Treatment Assessments (Optional)

At the time of unblinding of treatment assignment in the EN3835-201 study, subjects are eligible for optional treatment in the open-label study, provided they meet the inclusion and exclusion criteria detailed in section 11 and at least 1 quadrant meets the criteria for treatment. A subject may receive a maximum of 2 courses of treatment (6 treatment sessions) overall (total of treatments in double-blind and open-label study). If a subject received placebo in the double-blind study, she may be eligible for 2 treatments in the open-label study; if a subject received active drug in the double-blind study, she may be eligible for 1 additional treatment (3 treatment sessions) in the open-label study.

Selection of Treatment Quadrant

During the Screening B visit, each subject will have photographs taken of the 4 targeted quadrants of the study (eg, their left and right buttocks and left and right posterolateral thighs). Subjects will receive instructions (Appendix D) for using the PR-PCSS and will use the scale to rate the severity of their cellulite in each of the 4 quadrants by comparing each of their digital image photographs with the PR-PCSS instrument. This self-assessment will take place in a private setting to minimize any potential bias from site personnel (the Investigator is blinded to these scores). The Investigator will then assess each of the 4 subject's quadrants live in real-time using the CR-PCSS. The Investigator will then examine each of the 4 quadrants live to assess the subject using the Hexsel CSS as described in section 13.1.1.6.(12) Subjects must have at least 1 quadrant that meets the following criteria for treatment in the study:

1. PR-PCSS score of 3 or 4, and
2. CR-PCSS score of 3 or 4, and
3. Hexsel CSS score no greater than 13.

After the independent assessments are completed separately by the subject and the Investigator, the Investigator will review his/her assessments and the subject's assessment to determine which quadrants, if any, are eligible. The eligible quadrants (must meet all 3 of the inclusion criteria (PR-PCSS, CR-PCSS, and Hexsel CSS scores), if any, for treatment will be determined by the Investigator after which the quadrant selected will be at the discretion of the subject. For subjects treated with EN3835 in the double-blind study, if the quadrant treated in the double-blind study (EN3835-201) has PR-PCSS and CR-PCSS ratings identical or more severe than the double-blind study (EN3835-201) PR-PCSS and CR-PCSS baseline ratings (Baseline is day 1 of study EN3835-201), subjects can elect to have that same quadrant re-treated. Subjects who choose re-treatment of the previously treated quadrant will be classified in the re-treatment arm. If another quadrant besides the previously treated quadrant meets the all 3 of the inclusion criteria, subjects can choose to be treated in the naive quadrant. Subjects who choose treatment into a naive quadrant will be classified in the re-dosing arm.

Assessments made with the PR-PCSS (from digital image), the CR-PCSS (live assessment), and the Hexsel CSS score during the open-label Screening B visit will be the baseline severity of EFP in the selected quadrant.

A subject who received placebo in the double-blind study may be treated in the same quadrant in the open-label study if the quadrant still meets all 3 criteria OR another qualifying quadrant may be selected for treatment by the Investigator and subject. Following day 71 of a treatment course (3 treatment sessions), subjects can choose to receive a second treatment session in either the same quadrant if it still meets qualification criteria or in a different quadrant that meets qualification criteria. For the first treatment session, these subjects will be considered in the treatment arm. For the second treatment session, if the same quadrant is treated, subjects will be in the re-treatment arm; if a different quadrant is treated, subjects will be considered in the re-dosing arm.

If no quadrant meets all 3 criteria, the subject may continue in the observation-only study with safety and cellulite severity evaluations performed at 3-month intervals but may not receive treatment in this study.

Selecting and Marking Dimples

Selection of dimples to be treated in the selected quadrant is at the discretion of the Investigator or qualified designee. Dimples must be well-defined and evident when the subject is standing in a consistent relaxed pose (without the use of any manipulation such as skin pinching or muscle contraction). Each subject will receive 3 treatment sessions of study drug in the selected quadrant. During each treatment session, the treatment quadrant will be photographed before and after dimple marking while the subject is standing in a consistent relaxed pose as described in the Photography Manual. The cellulite severity assessments using the PR-PCSS, CR-PCSS, and Hexsel CSS will be completed prior to dimple marking at treatment visits 2, 3, and 4/end of treatment.

12.1.4.1. Screening B (Days −14 to −1 Relative to Open-Label Treatment Visit Day 1)

Subjects meeting the relevant criteria listed in section 11.2 may be eligible for treatment in the open-label study. The following procedures will be performed and documented during the screening period:

1. Evaluate eligibility based on inclusion/exclusion criteria (section 11.2)
2. Subject will have digital photographs taken of the 4 targeted quadrants of the study (left and right buttocks, and left and right posterolateral thighs) (section 13.1)
3. Subjects will get instruction on the use of the PR-PCSS (Appendix D)
4. Subjects will rate each quadrant using the PR-PCSS while viewing their digital images (section 13.1.1.1)
5. The Investigator will conduct live assessments of subject's cellulite severity of each quadrant using the CR-PCSS (section 13.1.1.4)
6. The Investigator will conduct live cellulite evaluation of each quadrant using the Hexsel CSS (section 13.1.1.6).

7. If at least 1 quadrant qualifies based on PR-PCSS, CR-PCSS, and Hexsel CSS ratings, subject may return for treatment on treatment visit 1. If none of the 4 quadrants qualify, the subject may remain in the study and have safety and cellulite severity evaluations performed at 3-month intervals but is not eligible for treatment.
8. Subject will select an eligible quadrant (based on qualifying scores) to be treated at their discretion.
9. Medical history including EFP history. Medical history will be based on EN3835-201 eCRF; only updates to the history need to be captured at Screening B visit.
10. Record prior and concomitant medications/procedures. Prior medications will be based on EN3835-201 eCRF; only updates and concomitant medications need to be captured at Screening B visit (section 12.2).
11. Physical examination including measurement of body weight and height (section 14.10)
12. Vital sign measurements (section 14.8)
13. 12-lead electrocardiogram (ECG), not necessary if the date of the ECG obtained during the double-blind study (EN3835-201) is within 12 months of the date of the Screening B visit (section 14.9)
14. Collection of samples for:
    a. Clinical laboratory testing including Anti-AUX-I and anti-AUX-II antibody testing (section 14.7)
    b. Urine pregnancy testing (section 14.7)
15. Adverse events (section 14)

12.1.4.2. Treatment Session 1 (Visit 1B)

Pre-injection

1. Confirm eligibility criteria (section 11)
2. Take digital photography of selected quadrant before dimple marking (section 13.1)
3. Record concomitant medications/procedures (section 12.2)
4. Vital sign measurements (section 14.8)
5. Collection of samples for urine pregnancy testing (section 14.7)
6. Select and mark dimples to be treated (section 12.1.4)
7. Take digital photograph of selected quadrant after dimple marking (section 13.1)

Injection

Administration of study drug in the prone position (see below)

Post-injection

1. Record number of dimples treated and number of injections administered

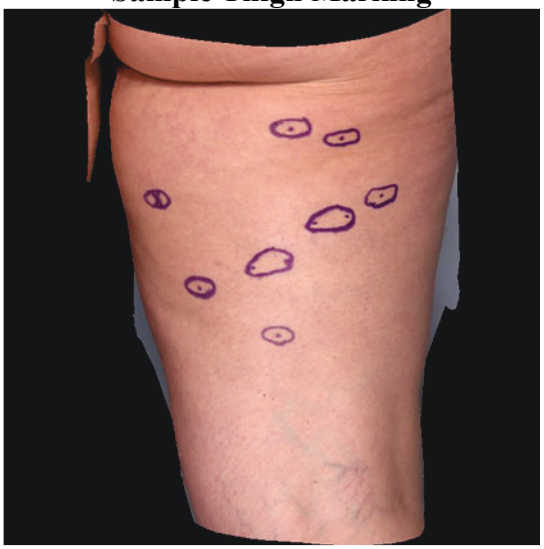
2. Vital sign measurements (section 14.8)
3. Injection site reactions and local tolerability
4. Adverse events (section 14)

The selected quadrant will be photographed before and after dimple marking while the subject is standing in a consistent relaxed pose as described in the Photography Manual. Before injection at treatment session 1, the Investigator or qualified designee will begin the session by selecting dimples within the chosen quadrant that are well defined, evident when the subject is standing, and suitable for treatment; treatment consists of up to 12 injections per session.. Because the goal of treatment is to improve the aesthetic appearance of the entire quadrant, the Investigator will be instructed to select dimples that in his or her opinion would most improve the aesthetic appearance of the entire quadrant. The same dimples within a quadrant or different dimples within a quadrant may be treated at each session but injections must all be within the selected quadrant for all 3 sessions.

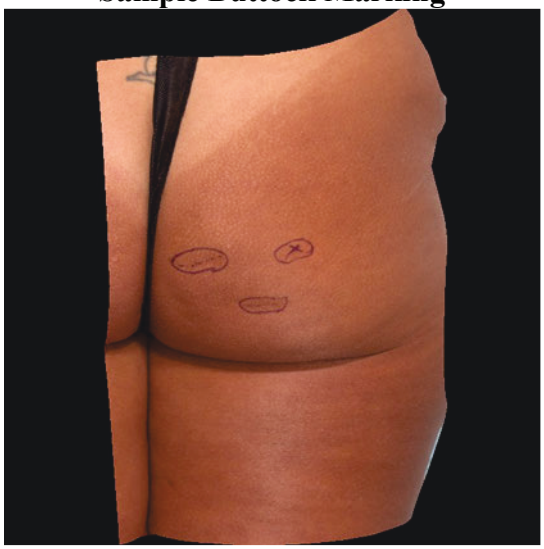
For each dimple selected for treatment, the Investigator or qualified designee will choose injection sites (injection sites within a dimple should be spaced approximately 2 cm apart, if a dimple requires more than 1 injection). Each injection site will be marked with a "dot" using a surgical marker. For round dimples, the "dot" will be placed in the center of the dimple; for elongated dimples, "dots" will be spaced out approximately 2 cm along the longer axis of the dimple. The Investigator or qualified designee will then use a surgical marker to circle each of the dimples selected for treatment. Circles in the selected quadrant should not overlap.

Examples of subject dimple marking:

Sample Thigh Marking



Sample Buttock Marking

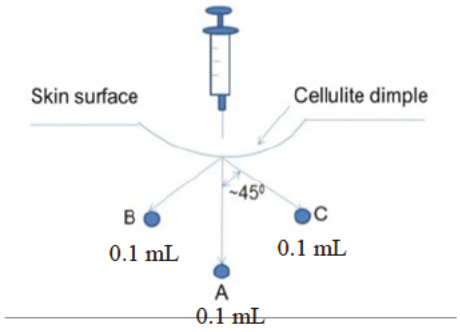


Study Drug Administration at Each Injection Site

See section 18.4 for study drug preparation. Study drug will be injected subcutaneously while the subject is in a prone position using a syringe with a 30-gauge ½-inch needle. Each injection site will receive a single skin injection of study drug administered as three 0.1-mL aliquots to Positions A, B and C (for a total injection volume of 0.3 mL) as shown in the following figure.

The depth of injection corresponds to the length of the treatment needle (0.5 inches) from the tip of the needle to the hub or base of the needle without downward pressure.

During each treatment session, the Investigator will be supplied with 4 syringes. Each syringe will contain 0.9 mL of study drug (ie, up to 3 injections in each syringe). Up to 12 skin injections of 0.3 mL per injection will be administered within the selected treatment quadrant during each treatment session.



- **Needle Tip Position A**: Position the needle at 90° angle perpendicular to the skin surface at the injection site and inject one 0.1-mL aliquot of study drug by gently pushing on the syringe plunger.
- **Needle Tip Position B**: Withdraw the needle slightly (but not so much as to remove from the injection site) and reposition approximately 45° (**but not more than 45°**) off vertical and above the long axis of the dimple and inject one 0.1-mL aliquot of study drug) by gently pushing on the syringe plunger.
- **Needle Tip Position C**: Withdraw the needle slightly (but not so much as to remove from the injection site) and reposition approximately 45° (**but not more than 45°**) off vertical and below the long axis of the dimple and inject one 0.1-mL aliquot of study drug by gently pushing on the syringe plunger.
- Withdraw needle from the skin completely and move to the next identified injection site. Complete up to a total of three 0.3-mL injections (each administered as three 0.1-mL aliquots) and discard the first syringe appropriately. Use the second, third and fourth syringes to complete dosing in the quadrant (up to three 0.3-mL injections per syringe, each injection administered as three 0.1-mL aliquots). Up to twelve skin injections of 0.3 mL will be administered within the treated quadrant during each treatment session.
- After treatment the subject will remain prone for at least 5 minutes.

The total number of dimples treated and the total number of injections administered will be recorded during treatment sessions 1, 2, and 3.

NOTE: EN3835 is a foreign protein and Investigators must be prepared to address and manage an allergic reaction should it occur. At the time of each injection, a 1:1,000 solution of epinephrine for injection, 50-mg diphenhydramine injection or a suitable equivalent, and oxygen should be available and the Investigator and site staff must be familiar with their use.

Care Procedures After Injection

To evaluate the subject for possible immediate immunological AEs, the subject will remain in direct observation of medical personnel who are skilled in the management of an allergic reaction for 30 minutes after receiving the injection of study drug and until the subject exhibits no sign of an immunological or other clinically significant systemic or local AE. The subject's vital signs should be stable before the subject can leave direct observation (see section 14.8).

The Investigator or qualified designee will then apply a sterile dressing to the injection site with hypoallergenic tape. The subject will be instructed to remove the dressing in the evening.

12.1.4.3. Treatment Session 2 (Visit 2/Day 22 ± 3 Days) and Treatment Session 3 (Visit 3/Day 43 ± 3 Days)

Pre-injection

1. Record concomitant medications/procedures (section 12.2)
2. Body weight measurements
3. Vital sign measurements (section 14.8)
4. Collection of samples for urine pregnancy testing (section 14.7)
5. Digital photograph of selected quadrant before dimple marking (section 13.1)
6. Subject assessment of the severity of cellulite using photograph of the selected quadrant via PR-PCSS (section 13.1.1.1). NOTE: Complete the subject (PR-PCSS) assessment before the Investigator (CR-PCSS) assessment and before dimple marking.
7. Investigator live assessment of the severity of cellulite using the CR-PCSS (section 13.1.1.4)
8. Selection and marking of dimples to be treated (section 12.1.4)
9. Digital photograph after dimple marking (section 13.1)

Injection

Administration of study drug in the prone position (section 12.1.4.2)

Post-injection

1. Record number of dimples treated and number of injections administered
2. Vital sign measurements (section 14.8)
3. Injection site reactions and local tolerability
4. AEs (section 14)

If no injections are given at treatment session 2, subjects will still return for the day 43 visit and the selected quadrant will again be evaluated by the subject (PR-PCSS) and Investigator (CR-PCSS). If the Investigator rates the selected quadrant greater than 0 on the CR-PCSS, injections at treatment session 3 should be given.

Because the goal of treatment is to improve the aesthetic appearance of the entire quadrant, the Investigator will be instructed to select dimples that in his or her opinion would most improve the aesthetic appearance of the entire quadrant. The same dimples within a quadrant or different dimples within a quadrant may be treated at each session but injections must all be within the selected quadrant for all 3 sessions. Each subject will receive all 3 treatment sessions unless the selected quadrant has no treatable EFP dimples and the Investigator rates the quadrant a score of 0 on the CR-PCSS.

After the dimples are selected, the Investigator or qualified designee will again mark each injection site with a "dot," and circle each dimple (circles should not overlap).

12.1.4.4. Day 71 (±5 Days) End of Treatment/Early Termination

The following procedures will be performed on Day 71:

1. Record concomitant medications/procedures (section 12.2)
2. Measurement of body weight
3. Vital sign measurements (section 14.8)
4. Collection of samples for:
   a. Clinical laboratory testing (section 14.7)
   b. Anti-AUX-I and anti-AUX-II antibody testing (section 14.7.1)
5. Digital photograph of selected quadrant (section 13.1)
6. Subject cellulite assessments of the selected quadrant using the photographic image (NOTE: complete subject cellulite assessments before Investigator cellulite assessments) using:
   a. PR-PCSS assessment (section 13.1.1.1)
   b. S-GAIS (section 13.1.1.2)
   c. Subject satisfaction with cellulite treatment assessment (section 13.1.1.3)
7. Investigator cellulite assessments of selected quadrant using:
   a. CR-PCSS live assessment of subject (section 13.1.1.4)
   b. Hexsel CSS assessment of live subject while subject is standing in a relaxed position (section 13.1.1.6)
   c. I-GAIS (section 13.1.1.5)
8. Injection site reactions and local tolerability
9. AEs (section 14)

12.1.4.5. Follow-up Visits

Following the day 71 visit, the quadrant(s) treated with EN3835 in the open label study will be evaluated every 3 months from the first exposure to EN3835 following the schedule in Table 2. The first follow-up visit will be approximately20 days after the day 71 visit (ie approximately day 90 after treatment session 1). Follow-up visits will continue until the study is terminated when at least 100 subjects have been assessed at 12 months after the first exposure to EN3835.

12.2. Prior and Concomitant Medications and Procedures

All medications (including over-the-counter medications) taken by the subject at screening visit 1 through the end of the study must be recorded

Additionally, any diagnostic, therapeutic or surgical procedures performed during the study period should be recorded including the date, indication for and description of the procedure.

12.2.1. Prohibited Medications

The following medications are prohibited for those subjects that elect to have treatment with study drug during the treatment 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 the treatment phase of the study. For those subjects in the observational-only phase of study, there are no prohibited medications:

Table 5: Concomitant Medication Restrictions for Subjects During the Treatment Phase of Study

Drug Class	Restrictions
Anticoagulants	Subjects who elect treatment cannot take antiplatelet agents or anticoagulants (except for ≤150 mg aspirin daily) within 7 days before and after the dosing administration.

12.2.2. Prohibited Procedures

The treatments and procedures listed in exclusion criteria are prohibited during the study.

12.3. Treatment Compliance

All subjects who elect to have treatment will receive study drug administered by a clinician at the investigator's site.

Accidental or intentional overdoses should be reported to the Sponsor/designee promptly (see section 14.6.2).

12.4. Blinding and Randomization

This study will be conducted as an open-label investigation; no blinding of assigned treatment will occur.

12.5. End of Study

The end of study is when 100 subjects complete the 1-year safety and cellulite severity evaluations. At the time of study termination, ongoing subjects receiving treatment will be followed through the day 71 visit. The remaining enrolled subjects (in excess of the first 100 subjects to complete 1 year) will undergo early termination procedures in accord with the Schedule of Events (section 5)

13. ASSESSMENT OF EFFICACY

13.1. Primary Efficacy Measurements

Although measures of efficacious drug effect (ie, durability of improvement) will be made during the observation phase before the study drug blind is broken in the double-blind study (EN3835-201), and thereafter to the end of study, emphasis is on the assessment of safety over 12 months after exposure to EN3835. Cellulite severity assessments will be made at scheduled intervals for both observation-only subjects (not receiving EN3835) as well as subjects who choose re-dosing or re-treatment with EN3835.

Digital Photography: Digital photography will be utilized to assess certain cellulite severity parameters at specific intervals (see Schedule of Events, Table 2) for subjects in the observation-only group as well as those electing to be re-treated or re-dosed with EN3835. At the Screening B visit for subjects electing to receive re-dosing or re-treatment, the Investigator or qualified designee will photograph each quadrant using a Sponsor-supplied standardized digital camera. The subject will be standing for each photography session and will be wearing a standardized photographic garment as described in the Photography Manual. The Investigator or qualified designee will photograph the selected quadrant as follows:

- Screening B (no dimple marking)
- Before and after dimple marking (prior to injections) on days 1, 22, and 43 of each treatment course
- During the day 71 visit (end of treatment phase/early termination) of each treatment course

All photographs from this study are the property of Endo and may be utilized for clinical development, scientific communication, marketing, regulatory purposes, and/or legal applications as required/desired by Endo.

13.1.1. Subject and Investigator Cellulite Assessments

As in the double-blind parent study, Investigator cellulite assessments are independent of the subject assessments. Therefore, all subject cellulite assessments must be completed before the Investigator's cellulite assessments are made. After both the subject's and investigator's assessments are completed, the subject's assessments will be revealed and compared to the clinician's assessments to determine eligible quadrants. If more than 1 quadrant is eligible, the subject will select one for treatment.

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

The PR-PCSS will be conducted for the purpose of assessing the severity of cellulite in the buttock or thigh; there are separate scales for buttocks or thighs. The scales are 5-level photonumeric scales developed specifically for patients and used by the subject to assess the severity of their cellulite in the quadrants by viewing digital images of each of their quadrants captured by photography at the visit; the ratings range from 0 (None) to 4 (Severe) with labels and descriptors to aid the subject in the assessments.

All subjects who enter the observation-only phase of the study will have the PR-PCSS evaluation at months 3, 6, 9, and 12.

For subjects electing re-treatment or re-dosing after the study drug blind is broken in study EN3835-201, a Screening B visit (Baseline) within 14 days before dosing day 1 will occur. Subjects will have digital photographs taken of all 4 quadrants as done in the double-blind trial for qualifying purposes. Subjects will then perform the PR-PCSS for both buttocks (Figure 1) and thighs (Figure 2) and will be reminded of their proper use (Appendix D).

At the beginning of visits on days 22, 43, and 71; digital photographs of the selected quadrant will be taken. If the buttock is the treated region, subjects will be given the PR-PCSS for the buttock to use to make their evaluation; if the thigh is the treated region, subjects will be given the PR-PCSS for the thigh to make their evaluation.

Figure 1: Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS) for the Buttock

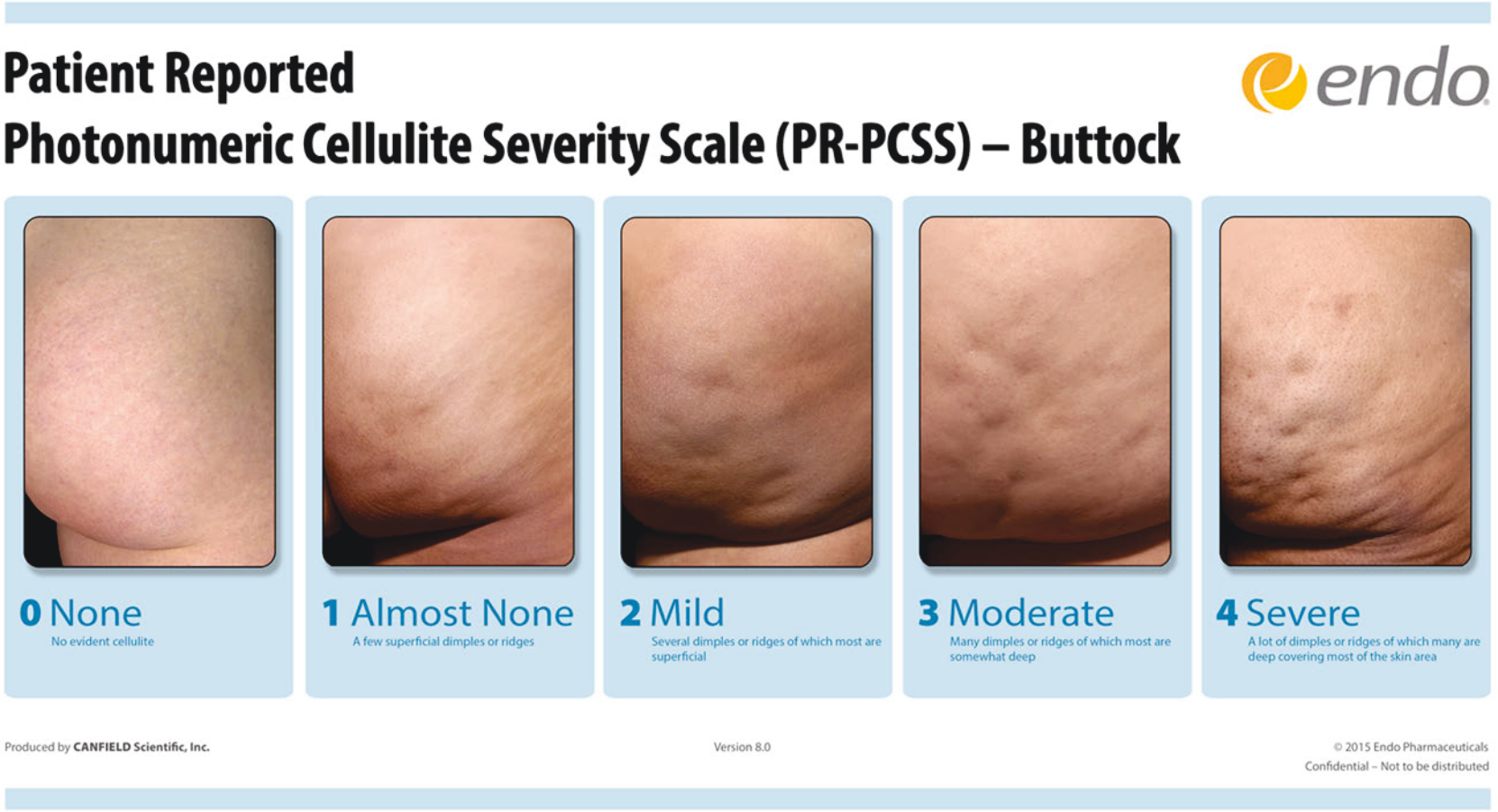


Figure 2: Patient-Reported Photonumeric Cellulite Severity Scale (PR-PCSS) for the Thigh

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

Subjects in the observation-only group will complete the S-GAIS as described below at the final study visit (month 12 or early termination) using the pre-treatment day 1 image (Baseline) of the assigned quadrant in the double-blind study for comparison.

The S-GAIS assessment will be done on day 71 of the treatment course and then at month 12 or the final study visit and compared back to the pre-dosing Screening B image (Baseline for treatment subjects) of the selected quadrant. All treated subjects will be instructed to answer the following question: *How would you rate the appearance of your treated cellulite after treatment?*

The S-GAIS assessment will occur after the subject has completed the PR-PCSS assessment to avoid introducing potential bias to the static PR-PCSS assessment. Each subject will view the pre-dosing Screening B visit digital image alongside their day 71 treatment course visit and month 12 or end of study visit digital image of their selected quadrant to aid in the assessment (Table 6). Subjects will circle the rating below that best represents their answer.

Table 6: 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 originally.

13.1.1.3. Subject Satisfaction with Cellulite Treatment Assessment

For observation-only subjects (not receiving EN3835) the subjects will assess their satisfaction with cellulite treatment at the 12 month or end of study visit by being instructed to answer the following question: *Today, how satisfied are you with the results of the cellulite treatment you received on the specific area or areas on your buttocks or thighs that were treated?* Subjects will circle the rating in the below table that best represents their answer.

For subjects who have elected to receive EN3835 either through re-treatment or re-dosing, the subject satisfaction with the cellulite treatment (Table 7) with be done at the treatment course day 71 and the month 12 visit or end of study visit. Subjects will be instructed to answer the following question: *Today, how satisfied are you with the results of the cellulite treatment you received on the specific area or areas on your buttocks or thighs that were treated?* Subjects will circle the rating below that best represents their answer.

Table 7: Subject Satisfaction with Cellulite Treatment Assessment

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

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

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

Investigators will have been trained on the use of the CR-PCSS. For observation-only subjects, the CR-PCSS will be done at 3, 6, 9, and 12 months or at the end of study visit.

For subjects who elected to receive EN3835 after the study drug blind is broken in study EN38325-201 as a re-treatment or re-dosing, the Investigator, at the Screening B visit (Baseline) will determine severity of cellulite of the 4 quadrants by assessing live subjects using the CR-PCSS for buttock (Figure 3) and thighs (Figure 4) after the subject has completed their self-assessment using the PR-PCSS. The eligible quadrant chosen for injection will be at the discretion of the subject. Before injections on treatment visit days 22 and 43 and on visit day 71; Investigators will evaluate the selected quadrant by live assessments. If the buttock is the treated region, the Investigator will be use the CR-PCSS for the buttock to make their evaluation; if the thigh is the treated region, the Investigator will use the CR-PCSS for the thigh to make their evaluation. In each case, the Investigator will make his/her assessment independently and after the subject has conducted their self-assessment using the PR-PCSS.

Figure 3: Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS) for the Buttock

Figure 4: Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS) for the Thigh

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

Subjects in the observation-only group will complete the I-GAIS as described below at the final study visit (month 12 or early termination) and a comparison back to the pre-treatment day 1 (Baseline) image of the assigned quadrant of the double-blind study.

On day 71 of the treatment course and the 12 month or end of study visit, the Investigator will determine the degree of improvement from the Screening B digital image of the selected quadrant by comparing the cellulite in live assessment on day 71 and at month 12 or study end to the Screening B pre-treatment (Baseline) image of the subject's selected quadrant (Table 8). The I-GAIS assessment will occur after the CR-PCSS assessment (section 13.1.1.4) to avoid introducing potential bias to the static CR-PCSS assessment by the Investigator at the site. The Investigator will circle the rating below that best represents their answer.

Table 8: Investigator Global Aesthetic Improvement Scale (I-GAIS)

Rating	Response Option	Description
+3	Very much improved	Optimal cosmetic result from treatment of the treated dimples
+2	Much improved	Marked improvement in the treated area appearance from before treatment, but not completely optimal
+1	Improved	Obvious improvement in the treated area appearance from before treatment, but additional treatment is indicated
0	No change	The treated area appearance is essentially the same as before treatment
−1	Worse	The treated area appearance is worse than before treatment
−2	Much worse	Marked worsening in appearance from the initial condition
−3	Very much worse	Obvious worsening in appearance from the initial condition

13.1.1.6. Hexsel Cellulite Severity Scale

The Hexsel Cellulite Severity Scale (referred to as the Hexsel CSS) is a photonumeric scale that looks at 5 key morphologic features of cellulite: (A) number of evident depressions, (B) depth of depressions, (C) morphological appearance of skin surface alterations, (D) laxity, flaccidity or sagging of skin, and (E) current classification scale based on medical literature including Nürnberger and Müller.(12,13) Each of these features is evaluated on a 4-point scale from a low of 0 to a high of 3 as described in Table 9 (see Appendix B). The total score is the summation of all 5 features.

For subjects in the observation-only group, the Hexsel CSS will be done at month 3 and every 3 months thereafter and at the month 12 or the end of study visit.

For subjects who elected to have EN3835 treatments, the Hexsel CSS will be done at 3-month intervals during the observation phase until the study drug blind is broken in study EN3835-201. The Hexsel CSS assessment will be done at Screening B visit and on day 71 of the treatment course and at month 12 or end of study visit.

For the subjects electing treatment (re-treatment or re-dosing) with EN3835 the Investigator or qualified designee will use the Hexsel CSS to assess the severity of EFP in all quadrants at

Screening B and the selected quadrant on day 71 of the course of treatment. All cellulite assessments should be made while the subject is in the standing position with relaxed gluteus muscles. However, when evaluating the subject for Category E (classification scale by Nürnberger and Müller) (13) if the subject has no evident depressions, the subject should be asked to contract her gluteus muscles or the pinch test should be applied (by pinching the skin between the thumb and index finger) so the Investigator or qualified designee can differentiate between scores/grades of zero (0) or I.

Table 9: Hexsel Cellulite Severity Scale

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

Source: Hexsel DM, Dal'Forno T, Hexsel CL. A validated photonumeric cellulite severity scale. *J Eur Acad Dermatol Venereol.* 2009;23(5):523-528.

[a] Subjects should be evaluated in the standing position with relaxed gluteus muscles. However, if the subject has no evident depressions, they should be asked to contract their gluteus muscles or the pinch test should be applied (by pinching the skin between the thumb and index finger) in order to differentiate between grade/stage of zero (0) or I.

14. ASSESSMENT OF SAFETY

14.1. Definitions

14.1.1. Adverse Event

An adverse event (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. AEs will be captured once a subject has signed the informed consent. AEs include:

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

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

All AEs, including both observed or volunteered problems, complaints, signs or symptoms must be recorded on the AE page of the eCRF, regardless of whether associated with the use of 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. The AE should be recorded in standard medical terminology when possible.

14.1.2. Serious Adverse Event

A serious adverse event (SAE) is defined as an AE that:

- Results in death
- Is immediately life-threatening (there is an immediate risk of death from the AE as it occurred; this does not include an AE that had it occurred in a more serious form may have caused death)
- Results in or prolongs an inpatient hospitalization (Note: a hospitalization for elective or pre-planned surgery, procedure, or drug therapy does not constitute an SAE)

- Results in permanent or substantial disability (permanent or substantial disruption of one's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect (in offspring of a subject using the study medication regardless of time to diagnosis)
- Is considered an important medical event

Important medical events are defined as events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the other serious outcomes. Examples of important medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

14.2. Monitoring Adverse Events

At each visit, subjects will be queried regarding any AEs that have occurred since the last visit. Subjects will be asked to volunteer information concerning AEs with a non-leading question such as, "How do you feel?" Study site personnel will then record all pertinent information in the source documents and the eCRF. The study drug compliance record should also be reviewed to detect potential overdoses (intentional/unintentional).

14.3. Relationship to Study Drug

The degree of "relatedness" of the AE to the study medication must be described using the following scale:

- **Not related** indicates that the AE is definitely not related to the study medication.
- **Unlikely related** indicates that there are other, more likely causes and study medication is not suspected as a cause.
- **Possibly related** indicates that a direct cause and effect relationship between study medication and the AE has not been demonstrated, but there is evidence to suggest there is a reasonable possibility that the event was caused by the study medication.
- **Probably related** indicates that there is evidence suggesting a direct cause and effect relationship between the AE and the study medication.

It is the Sponsor's policy to consider "Probably related" and "Possibly related" causality assessments as positive causality. "Not related" and "Unlikely related" causality assessments are considered as negative causality.

Assessments will be recorded on the eCRF and must indicate clearly the relationship being assessed. For example, an AE that appears during a placebo run-in phase would be assessed with respect to the placebo treatment received and/or study procedures conducted during this phase. If the AE continued into an active treatment phase, the relationship would be assessed for the active treatment phase only if the AE worsened.

14.4. Intensity Assessment

The intensity (or severity) of AEs is characterized as mild, moderate, or severe:

- **Mild** AEs are usually transient, requiring no special treatment, and do not interfere with the subject's daily activities.
- **Moderate** AEs introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.
- **Severe** AEs interrupt a subject's usual daily activity and typically require systemic drug therapy or other treatment.

When the intensity category of an AE changes, the greatest intensity during that continuous episode should be recorded.

14.5. Reporting Adverse Events and Serious Adverse Events

14.5.1. Reporting Adverse Events

Throughout the study, AEs will be documented on the source document and on the appropriate page of the eCRF whether or not considered treatment-related. This includes any new signs, symptoms, injury or illness, including increased severity of previously existing signs, symptoms, injury, or illness. Conditions existing prior to screening will be recorded as part of the subject's medical history. The Investigator is responsible for assessing the relationship of AEs to the study medication; relationship will be classified as not related, unlikely related, possibly related, or probably related.

All AEs will be collected by the Investigator from the time of signing the informed consent through 30 days after the last dose of study medication; this includes any AEs that are ongoing at the time of completion/termination of the study. All ongoing AEs must be followed until resolution or for 30 days after the subject's last study visit, whichever comes first.

14.5.2. Reporting Serious Adverse Events

Any SAE, including death resulting from any cause, which occurs to any subject participating in this study must be reported via email or fax by the Investigator using the Endo Clinical Trial Report Form for SAEs within 24 hours of first becoming aware of the SAE. SAEs will be collected by the Investigator from the time of signing the informed consent through 30 days after the last dose of study medication. SAEs that occur within 30 days, following cessation of the study treatment, or within 30 days, following premature discontinuation from the study for any reason, must also be reported within the same timeframe. Any SAE that is felt by the Investigator to be related to the study medication must be reported regardless of the amount of time since the last dose received. Follow-up information collected for any initial report of an SAE must also be reported to the Sponsor within 24 hours of receipt by the Investigator.

All SAEs will be followed until resolution, stabilization of condition, or until follow-up is no longer possible.

In the event discussion is necessary regarding treatment of a subject, call the Medical Monitor (see contact information in section 3).

All SAEs should be sent via the email address, or faxed to the fax number, provided in section 3.

The Sponsor will determine whether the SAE must be reported within 7 or 15 days to regulatory authorities in compliance with local and regional law. If so, the Sponsor (or the Sponsor's representative) will report the event to the appropriate regulatory authorities. The Investigator will report SAEs to the institutional review board (IRB) per their IRB policy.

14.5.2.1. Follow-up Procedures for Serious Adverse Events

To fully understand the nature of any SAE, obtaining follow-up information is important. Whenever possible, relevant medical records such as discharge summaries, medical consultations, and the like should be obtained. In the event of death, regardless of cause, all attempts should be made to obtain the death certificate and any autopsy report. These records should be reviewed in detail, and the Investigator should comment on any event, lab abnormality, or any other finding, noting whether it should be considered a serious or non-serious AE, or whether it should be considered as part of the subject's history. In addition, all events or other findings determined to be SAEs should be identified on the follow-up SAE form and the Investigator should consider whether the event is related or not related to study drug. All events determined to be nonserious should be reported on the eCRF.

14.6. Special Reporting Situations

14.6.1. Adverse Events of Special Interest

There are no AEs of special interest anticipated in this study. AEs such as bruising, ecchymosis, hematomas, and contusions that occur remote to the site of drug administration will be recorded as an AE or SAE as appropriate (see section 14.1.1, Adverse Events or section 14.1.2, Serious Adverse Events).

14.6.2. Overdose/Misuse/Abuse

Study drug overdose is any accidental or intentional use of study drug in an amount higher than the dose indicated by the protocol for that subject. Study drug compliance (see section 12.3) should be reviewed to detect potential instances of overdose (intentional or accidental).

Any study drug overdose during the study should be noted on the study medication eCRF.

An overdose is not an AE per se, however all AEs associated with an overdose should both be entered on the Adverse Event eCRF and reported using the procedures detailed in section 14.5.2, Reporting of Serious Adverse Events, even if the events do not meet seriousness criteria. If the AE associated with an overdose does not meet seriousness criteria, it must still be reported using the Endo Clinical Trial Report Form for SAEs and in an expedited manner, but should be noted as non-serious on the form and the Adverse Event eCRF.

14.6.3. Pregnancy

Any uncomplicated pregnancy that occurs in a subject during this clinical study will **be reported for tracking purposes only**. All subject pregnancies that are identified during or after this study, where the estimated date of conception is determined to have occurred during study drug therapy or within 30 days of the last dose of study medication need to be reported, followed to conclusion, and the outcome reported, even if the subject is discontinued from the study. The investigator should report all pregnancies within 24 hours using the Initial Pregnancy Report Form, and any pregnancy-associated SAE using the SAE report form, according to the usual timelines and directions for SAE reporting provided in section 14.5.2. Monitoring of the pregnancy should continue until conclusion of the pregnancy; 1 or more Follow-up Pregnancy Report Form(s) detailing progress, and a Two Month Follow-up Pregnancy Report Form detailing the outcome, should be submitted.

Pregnancy itself is not regarded as an AE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not considered AEs. Any SAEs associated with pregnancy (eg, congenital abnormalities/birth defects/spontaneous miscarriages or any other serious events) must additionally be reported as such using the SAE report form. Spontaneous miscarriages should also be reported and handled as SAEs.

Subjects should be instructed to immediately notify the investigator of any pregnancies.

Attempts to obtain the pregnancy follow-up and pregnancy outcome information detailed above are necessary even if a subject discontinues treatment because of pregnancy.

14.6.4. Adverse Events/Serious Adverse Events Experienced by Non-subjects Exposed to Study Medication

Non-subjects are persons who are not enrolled in the study but have been exposed to study medication, including instances of diversion of study medication. All such AEs/SAEs occurring in non-subjects from such exposure will be reported to the Endo Pharmacovigilance and Risk Management (PVRM) Department (when the non-subject agrees) on the departmental form for SAEs regardless of whether the event is serious or not. Instructions for completing the form for events experienced by non-subjects will be provided. SAEs occurring in non-subjects exposed to study medication will be processed within the same SAE reporting timelines as described in section 14.5.2, Serious Adverse Event Reporting. Additionally, the drug accountability source documentation at the site should reflect this occurrence.

14.7. Clinical Laboratory and Immunogenicity Determinations

Clinical laboratory tests will be conducted according to the Schedule of Events (section 5). Clinical laboratory tests will be performed by a designated central laboratory. Each site will be provided with instructions on specimen collection, preparation, packaging and transport. Refer to the central laboratory manual for further information regarding sample collection, handling, and labeling. The results of the tests will be returned to the investigational sites.

Clinical laboratory test data will be reviewed by the investigator, or designee, and additional clinical laboratory tests may be ordered at his/her discretion (eg, if the results of any clinical laboratory test falls outside the reference range or clinical symptoms necessitate additional

testing to ensure safety). Any additional testing will be performed by the designated central laboratory.

The investigator will review all abnormal lab results for clinical significance. Any abnormal clinical laboratory test result meeting the investigator's or Sponsor's criteria for clinical significance (refer to central laboratory manual) will be recorded as an AE or SAE as appropriate (see section 14.1.1, Adverse Events or section 14.1.2, Serious Adverse Events).

Laboratory results will be sent electronically to Endo for data management.

Clinical laboratory parameters that will be measured in this study are listed in Table 10.

Table 10: Clinical Laboratory Parameters

Hematology	Clinical Chemistry	Urinalysis
Hematocrit	Blood urea nitrogen	Specific gravity
Hemoglobin	Creatinine	Ketones
Red blood cell count	Total bilirubin	pH
Red blood cell morphology	Alanine aminotransferase (ALT)	Protein
White blood cell count	Aspartate aminotransferase (AST)	Blood
Neutrophils	Alkaline phosphatase	Glucose
Lymphocytes	Sodium	
Monocytes	Potassium	
Basophils	Calcium	
Eosinophils	Chloride	
Platelets	Phosphate	
	Serum bicarbonate	
	Uric acid	
	Total cholesterol	
	Total protein	
	Glucose	
	Triglycerides	
	Albumin	

Female subjects of childbearing potential must have a negative urine pregnancy test at Screening B and at treatment visits 1, 2, and 3 (section 5) to receive treatment in the study. If necessary, additional urine pregnancy tests can be performed at any time during the study at the discretion of the Investigator. Urine pregnancy test kits will be supplied by the Sponsor.

14.7.1. Anti-AUX-I and Anti-AUX-II Antibodies

Serum samples will be collected and may be tested for binding and neutralizing anti-AUX-I and anti-AUX-II antibodies at visit 1 through visit 4. Additionally, if a subject consents to treatment in the open-label study, serum samples for antibody testing will be collected before injection at treatment visits 1, 2, 3, and 4 of the open-label treatment period. A subset of subject samples will have neutralizing antibodies tested from day 1 and day 71 visits; additional samples may be analyzed if results or clinical signs warrant testing.

The serum samples obtained will be processed, stored and then shipped on dry ice to the designated central clinical laboratory before forwarding to Endo's appointed laboratory for the determination of anti-AUX-I and anti-AUX-II antibodies according to the Laboratory Manual.

14.8. Vital Signs

Vital sign measurements will be documented as described in the Schedule of Events. These parameters include pulse rate, respiratory rate, systolic and diastolic blood pressure, and body weight. Pulse and blood pressure readings will be taken after the subject has been sitting for 5 minutes. Height should only be recorded at Screening B.

The investigator will review all vital sign values for clinical significance. Any vital sign value meeting the investigator's or Sponsor's criteria for clinical significance will be recorded as an AE or SAE as appropriate (see section 14.1.1, Adverse Events, and section 14.1.2, Serious Adverse Events).

For subjects receiving treatment, vital signs will be assessed at the time points shown in Table 11 after the subject has rested for at least 5 minutes.

Table 11: Vital Signs Measurements on Injection Day

Time Point Relative to Last Injection	Blood Pressure, Respiratory Rate, and Pulse Rate	Body Temperature
Up to 4 hours (before treatment)	X	X
Approximately 15 minutes after	X	
Approximately 30 minutes after	X	X

14.9. Electrocardiogram

Performing a 12-lead electrocardiogram (ECG) is not necessary if Screening B visit date is within 12 months of obtaining an ECG during the double-blind study (EN3835-201).

If the date of Screening B visit is later than 12 months since obtaining the ECG in study EN3835-201, subjects will have a resting 12-lead ECG performed during the Screening B visit. A qualified physician will interpret, sign, and date the ECGs. Electrocardiogram assessments must be "within normal limits" or interpreted as "abnormal, not clinically significant" for the subject to be included in the study.

Any ECG result meeting the investigator's or Sponsor's criteria for clinical significance will be recorded as an AE or SAE as appropriate (see section 14.1.1, Adverse Events and section 14.1.2, Serious Adverse Events).

14.10. Physical Examination

Body weight will be collected as described in the Schedule of Events (section 5). If a subject desires treatment in the open-label study, a complete physical examination will be performed at Screening B. All examinations will be performed by a physician or health professional listed on the Form FDA 1572 and licensed to perform physical examinations.

The investigator will review all physical exam findings for clinical significance. Any physical exam finding meeting the investigator's or Sponsor's criteria for clinical significance will be recorded as an AE or SAE as appropriate (see section 14.1.1, Adverse Events and section 14.1.2, Serious Adverse Events).

14.11. Other Safety Assessments

Not applicable.

15. ASSESSMENT OF PHARMACOKINETICS

Not applicable.

16. ASSESSMENT OF PHARMACODYNAMICS

Not applicable.

17. STATISTICAL CONSIDERATIONS AND METHODS

17.1. Determination of Sample Size

It is estimated that approximately 95% of the 350 subjects randomized in study EN3835-201 will enroll in the current study for a sample size of 333. This sample size should be adequate to determine safety and cellulite assessments of EN3835 for subjects retreated in the same and in different quadrants.

17.2. Subject Cohorts and Subject Populations

Subjects will be classified into 1 of 4 different cohorts depending on where they receive the treatment of EN3835 in relation to where they received treatment in study EN3835-201. The 4 cohorts are:

1. Observational subjects only - subjects who received EN3835 in study EN3835-201 but do not receive any injections in the current study
2. Re-treatment subjects - subjects who received EN3835 in study EN3835-201 and receive EN3835 in the current study in the same quadrant that was treated in the EN3835-201 study. This will only be allowed for subjects who have baseline severity ratings in the current study at or worse than the baseline seen in study EN3835-201 for both the CR-PCSS and PR-PCSS of the quadrant.
3. Re-dosing subjects - subjects who received EN3835 in study EN3835-201 and receive EN3835 in the current study in a quadrant different than the EN3835-treated quadrant in study EN3835-201.
4. Initial treatment subjects - subjects who received placebo in study EN3835-201 and receive EN3835 in the current study.

All efficacy and safety analyses will be done within the classified cohort. Durability of treatment effects defined as time period from injection to return to baseline cellulite severity ratings in a EN3835-treated quadrant will be determined for all subjects that were treated with EN3835 in either this study or study EN3835-201.

17.2.1. Observational Population

The Observational population includes all subjects treated with EN3835 in study EN3835-201 who do not receive any treatment in the current study. The durability of a treatment effect and long-term safety analyses for subjects who receive no treatment in the EN3835-201 study will be performed using this population

17.2.2. Safety Population

The Safety population will include all subjects who receive at least 1 dose of EN3835 in the current study or in study EN3835-201. All safety analyses will be performed using this population.

17.2.3. Intent-to-Treat Population

The Intent-to-Treat (ITT) population includes all subjects who enroll in the current study.

17.2.4. Modified Intent-to-Treat Population

The Modified Intent-to-Treat (mITT) population includes all subjects who receive at least 1 dose of EN3835 in the current study (EN3835-202) and have a baseline and at least 1 post-baseline assessment on both the CR-PCSS and PR-PCSS on the quadrant selected for treatment in the current study. All cellulite assessment analyses will be completed on this population.

17.2.5. Per-Protocol Population

The Per-Protocol population includes all subjects in the safety population who have no major protocol deviations. Major protocol deviations excluding subjects from this population will be determined at the protocol deviation assessment meeting prior to the database lock. If more than 10% of the safety population is excluded from the per-protocol population, then all safety and cellulite evaluations will be repeated using the per-protocol population.

17.3. Subject Disposition

The number of subjects included in each study population will be summarized. The number and percentage of subjects completed and discontinued will be presented. Reasons for discontinuation as recorded on the eCRF will be summarized (number and percentage) for all subjects.

17.4. Demographics and Other Baseline Characteristics

Demographic and baseline characteristics, including age, race, and baseline values will be summarized for the Observational population, the Safety population, and the mITT population using descriptive statistics. The descriptive statistics will include frequency tables for all categorical response variables and number, mean, standard deviation, minimum, and maximum for all continuous variables.

17.5. Efficacy Analyses

Cellulite assessments (efficacy) include:

- PR-PCSS: 5-point scale ranging from 0 (no cellulite) to 4 (severe cellulite) (screening visit [Baseline], days 22, 43, and 71). Also will be done at day 90, day 180, day 270, and day 360/end of study visits for observational assessments.
- CR-PCSS: 5-point scale ranging from 0 (no cellulite) to 4 (severe cellulite) (screening [Baseline], days 22, 43, and 71). Also will be done at day 90, day 180, day 270, and day 360/end of study visits for observational assessments.
- Investigator rating of cellulite severity using the total scores from the Hexsel CSS scale: scores can range from 0 to 15 (screening [Baseline] and day 71). Also will be done at day 90, day 180, day 270, and day 360/end of study visits for observational assessments.

- I-GAIS: 7-point scale ranging from 3 (very much improved) to −3 (very much worse) (day 71). Also done at day 360/end of study visit for observational assessments.
- S-GAIS: 7-point scale ranging from 3 (very much improved) to −3 (very much worse) (day 71). Also done at day 360/end of study visit for observational assessments.
- Subject satisfaction with cellulite treatment assessment: 5-point scale ranging from +2 (very much satisfied) to −2 (very much dissatisfied) (day 71). Also done at day 360/end of study visit for observational assessments.

All cellulite assessments will be done by treated quadrant. For initial treatment subjects who have 2 quadrants treated, each quadrant will be evaluated separately.

17.5.1. Primary Efficacy Analysis

The primary cellulite severity endpoint is the proportion of composite responders at day 71 defined as subjects with an improvement in severity from baseline (Screening B visit) of at least 2 levels of severity in the CR-PCSS and an improvement in severity from baseline of at least 2 levels of severity in the PR PCSS.

The primary endpoint, the proportion of composite responders with improvement of 2 or better on each scale (CR-PCSS and PR-PCSS) will be summarized by region treated (buttock or thigh) and overall with percentages.

17.5.2. Secondary Efficacy Analysis

Secondary endpoints for treated quadrants include:

- Proportion of composite responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS. (day 71)
- Proportion at each level of improvement in the PR-PCSS (day 71):
  - Proportion of patient responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS
  - Proportion of patient responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS
- Proportion at each level of improvement in the CR-PCSS (day 71):
  - Proportion of Investigator responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS (Investigator rated)
  - Proportion of Investigator responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS (Investigator rated)

- Proportion of responders at each level of the I-GAIS (day 71):
  - Proportion of Investigator global responders defined as subjects with a response of 1 (improved) or better in the Investigator GAIS assessment
- Proportion of responders at each level of the S-GAIS (day 71):
  - Proportion of subject global responders defined as subjects with a response of 1 (improved) or better in the subject GAIS assessment
- Proportion of responders at each level of the subject satisfaction with cellulite treatment (day 71)
- Change in the Hexsel CSS total score from screening visit to day 71
- All secondary endpoints, except the Hexsel CSS total score, will be summarized by treated region (buttock or thigh) and overall using percentages. Change in Hexsel CSS total score will be summarized by treated region (buttock or thigh) and overall with descriptive statistics for continuous variables.

Observational endpoints include:

- Proportion of 2-point composite responders as defined by responses in the quadrant treated in study EN3835-201 who either maintained response, lost response but did not return to the baseline of study EN3835-201, or returned to the baseline of study EN3835-201.
- Proportion of 1-point composite responders as defined by responses in the quadrant treated in study EN3835-201 who either maintained response, lost response but did not return to the baseline of study EN3835-201, or returned to the baseline of study EN3835-201.
- Proportion of 2-point CR-PCSS responders as defined by responses in the quadrant treated in study EN3835-201 who either maintained response, lost response but did not return to the baseline of study EN3835-201, or returned to the baseline of study EN3835-201.
- Proportion of 1-point CR-PCSS responders as defined by responses in the quadrant treated in study EN3835-201 who either maintained response, lost response but did not return to the baseline of study EN3835-201, or returned to the baseline of study EN3835-201.
- Proportion of 2-point PR-PCSS responders as defined by responses in the quadrant treated in study EN3835-201 who either maintained response, lost response but did not return to the baseline of study EN3835-201, or returned to the baseline of study EN3835-201.
- Proportion of 1-point PR-PCSS responders as defined by responses in the quadrant treated in study EN3835-201 who either maintained response, lost response but did not return to the baseline of study EN3835-201, or returned to the baseline of study EN3835-201.

- Duration of response as defined by the time from onset of change from baseline of PR-PCSS and CR-PCSS in the quadrant treated in study EN3835-201 until the time that the treated quadrant returned to the baseline PR-PCSS and CR-PCSS ratings from study EN3835-201.
- CR-PCSS change from the study EN3835-201 baseline at day 71 of study EN3835-201, and days 90, 180, 270, and 360/end of study of the current study (EN3835-202).
- PR-PCSS change from the study EN3835-201 baseline at day 71 of study EN3835-201, and days 90, 180, 270, and 360/end of study of the current study (EN3835-202).
- Hexsel CSS total score changed from the study EN3835-201 baseline at day 71 of study EN3835-201 and day 360/end of study of the current study (EN3835-202).
- Proportion of responses at each level of the I-GAIS (day 360/end of study):
  - Proportion of Investigator global responders defined as subjects with a response of 1 (improved) or better in the Investigator GAIS assessment
  - Change in I-GAIS assessment from day 71 of study EN3835-201 and day 360/ end of study of the current study (EN3835-202
- Proportion of responses at each level of the S-GAIS (day 360/end of study):
  - Proportion of subject global responders defined as subjects with a response of 1 (improved) or better in the subject GAIS assessment
  - Change in S-GAIS assessment from day 71 of study EN3835-201 and day 360/ end of study of the current study (EN3835-202)
- Proportion of responses at each level of the subject satisfaction with cellulite treatment (day 360/end of study)
  - Change in subject satisfaction assessment from day 71 of study EN3835-201 and day 360/end of study of the current study (EN3835-202)

For quadrants treated in the current study the following observational endpoints will be analyzed:

- Proportion of 2-point composite responders as defined by the responses in the quadrant treated in this current study (EN3835-202) who either maintained response, lost response but did not return to the study EN3835-202 baseline, or returned to the study EN3835-202 baseline.
- Proportion of 1-point composite responders as defined by the responses in the quadrant treated in the current study who either maintained response, lost response but did not return to the study EN3835-202 baseline, or returned to the study EN3835-202 baseline.
- Proportion of 2-point CR-PCSS responders as defined by the responses in the quadrant treated in this current study who either maintained response, lost response but did not return to the study EN3835-202 baseline, or returned to the study EN3835-202 baseline.

- Proportion of 1-point CR-PCSS responders as defined by the responses in the quadrant treated in the current study who either maintained response, lost response but did not return to the study EN3835-202 baseline, or returned to the study EN3835-202 baseline.
- Proportion of 2-point PR-PCSS responders as defined by the responses in the quadrant treated in the current study who either maintained response, lost response but did not return to the study EN3835-202 baseline, or returned to the study EN3835-202 baseline.
- Proportion of 1-point PR-PCSS responders as defined by the responses in the quadrant treated in the current study who either maintained response, lost response but did not return to the study EN3835-202 baseline, or returned to the study EN3835-202 baseline.
- CR-PCSS change from the study EN3835-202 baseline at day 71, day 90, day 180, day 270, and day 360/end of study.
- PR-PCSS change from the study EN3835-202 baseline at day 71, day 90, day 180, day 270, and day 360/end of study.
- Duration of response as defined by the time from onset of change from baseline of PR-PCSS and CR-PCSS in the quadrant treated in the current study until the time that the treated quadrant returned to the baseline PR-PCSS and CR-PCSS ratings from study EN3835-202.

17.6. Safety Analyses

The following variables are safety endpoints.

- AEs: Mapped to preferred term using the Medical Dictionary for Regulatory Activities (MedDRA)
- Injection site reactions/local tolerability in selected quadrant (through subject and Investigator reporting)
- Vital signs
- Laboratory testing

AEs will be summarized by treatment group. AE duration will be summarized using descriptive statistics by treatment group.

Descriptive statistics will be presented for each clinical laboratory test for the actual and change from screening at each visit by treatment group and vital signs for the actual and change from day 1 pre-injection for each injection day at each visit by treatment group.

17.6.1. Prior, Concomitant, and Follow-up Medication

The World Health Organization (WHO) Drug Dictionary will be used to classify prior and concomitant medications by therapeutic class. The version used in this study will be stated in the Data Management Plan. Prior medication will be defined as any medication with a start date prior to the day 1 date and are collected at the screening visit and upon admission to the clinic on

day −1. Concomitant medication is defined as any medication with a start date on or after the day 1 date or reported as ongoing. Any medications started after the last dose of study drug will be considered as follow-up medications

Prior and concomitant medication use will be summarized descriptively by the number and percentage of subjects receiving each medication within each therapeutic class. Multiple use of the same medication by a subject will be counted only once.

17.6.2. Study Drug Exposure

For those subjects that elect, are eligible, and do receive treatment, the number of injections will be summarized by counts and percentages. The number of dimples treated will be summarized with counts and percentages.

17.6.3. Measurement of Treatment Compliance

All doses are administered while the subjects are at the investigators' sites. Any dose that was not administered per protocol will recorded as a protocol deviation by the Investigator.

17.6.4. Adverse Events

The MedDRA will be used to code AEs. The version used in this study will be stated in the Data Management Plan.

An AE (classified by preferred term) that started during the treatment period will be considered a TEAE if it was not present prior to the first dose of study drug, or was present prior to the first dose of study drug but increased in intensity during the treatment period. If more than 1 AE is reported prior to the first dose of study drug and coded to the same preferred term, then the AE with the greatest intensity will be used as the benchmark for comparison to the AEs occurring during the treatment period which were also coded to that preferred term. Any AE present prior to the first dose of study drug that increases in intensity during the treatment period will be re-entered with a new start date of the date of increased intensity.

Descriptive statistics (the number and percentage) for subjects reporting TEAEs in each treatment group will be tabulated by system organ class and preferred term; by system organ class, preferred term, and severity; and by system organ class, preferred term, and relationship to study drug. If more than 1 AE is coded to the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to the study drug.

SAEs and AEs leading to premature discontinuation of study drug will be summarized by preferred term and dose received. Listings will be presented for subjects with SAEs, subjects with AEs leading to discontinuation, and subjects who die (if any).

17.6.5. Vital Signs

Descriptive statistics for vital signs (eg, systolic and diastolic blood pressure, pulse rate, and body weight) and their changes from baseline at each visit and at the end of treatment visit will be presented.

Vital sign values are potentially clinically significant (PCS) if they meet both the observed value criteria and the change from baseline criteria. The criteria for PCS vital sign values will be

detailed in the Statistical Analysis Plan (SAP). A listing of all AEs for subjects with PCS vital signs will also be provided.

17.6.6. Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values in International System of Units (SI units) and changes from baseline will be presented for each clinical laboratory parameter.

The number and percentage of subjects with PCS post-baseline clinical laboratory values will be tabulated. The criteria for PCS laboratory values will be detailed in the SAP. A listing of all AEs for subjects with PCS laboratory values will also be provided.

17.7. Immunogenicity Analyses

Immunogenicity variables include anti-AUX-I/anti-AUX-II binding antibody results. Binding antibody levels will be determined from samples collected on days 1, 22, 43, and 71 during the treatment phase and days 90, 180, 270 and 360 during the observational phase.

Descriptive statistics (percent of positive measurements and average antibody level) will be presented for anti-AUX-I and anti-AUX-II antibody levels at each time point by region treated and overall. Average antibody levels will be summarized on logarithmically transposed titer values.

17.8. Pharmacokinetic Analyses

Not applicable.

17.9. Interim Analysis

Two (2) interim analyses are planned. Following the breaking of the study drug blind in study EN3835-201, all follow-up safety data gathered prior to that time will be analyzed. The second interim analyses will occur following the day 71 visit for all subjects treated with EN3835 in the current study. A preliminary data lock will be done on all treated quadrants and cellulite assessment and safety analyses will be done. The official database lock will occur after the last day 360/end of study observational visit and all observational analyses on treated quadrants will be done.

17.10. Statistical Software

Statistical analyses will be performed using Version 9.3 (or higher) of SAS® (SAS Institute, Cary, North Carolina).

18. STUDY DRUG MATERIALS AND MANAGEMENT

18.1. Study Drug Identity

EN3835 is formerly known as AA4500; the 2 product names should be considered synonymous. The investigational product vials will be labeled as EN3835. The components of EN3835 are 0.9 mg of collagenase clostridium histolyticum, [redacted] in a lyophilized cake.

The components of EN3835 sterile diluent for reconstitution are 0.03% (2mM) calcium chloride ($CaCl_2$) in 0.9% (154mM) sodium chloride (NaCl) solution, pH 6.0 to 7.0. Diluent is supplied as a terminally-sterilized liquid at 3.0 mL per vial.

18.2. Study Drug Packaging and Labeling

Sterile vials of lyophilized EN3835 (formerly AA4500) and sterile diluent will be provided to the Investigator by Endo. Each kit will contain 1 vial each of EN3835 and sterile diluent.

18.3. Study Drug Storage

All study drug will be provided by Endo. Study drug must be kept in a refrigerator (2°C-8°C) with locked access.

18.4. Study Drug Preparation

Refer to the Reconstitution Instructions in the Pharmacy Manual for detailed preparation instructions.

Before reconstitution, remove the vials containing the lyophilized study drug powder and the vials containing the sterile diluent from the refrigerator and allow the vials to stand at room temperature for 15 minutes. Designated study personnel will visually inspect the study drug vial to determine the integrity and acceptability of the lyophilized drug product for reconstitution. The written procedures for inspection of the study drug vials will be provided to the site by Endo.

After reconstitution with the sterile diluent, the study drug solution can be kept at room temperature [redacted]. The reconstituted study drug solution should be administered as soon as possible after reconstitution and further dilution. Each vial of study drug powder for reconstitution will be diluted according to the instructions in the Pharmacy Manual. Study personnel will maintain a record of the date and time of reconstitution.

18.5. Study Drug Accountability

Endo or its agent will maintain a master log of kits dispensed to the investigative sites. A drug inventory form must be kept current by the site staff designated to be responsible for reconstitution and must be made available to the clinical monitor, Endo employees, IRB/independent ethics committee (IEC), and regulatory agencies for routine inspection and

accountability during monitoring visits. When instructed by Endo, the Investigator agrees to return all original containers of unused study drug to Endo or its designee.

18.5.1. Study Drug Handling and Disposal

The Investigator is responsible for recording the receipt and use of all drug supplied and for ensuring the supervision of the storage and allocation of these supplies. All unused study drug will be returned, and unit counts will be performed whenever medication is returned. The site must account for all study drug received. The Investigator agrees not to supply study drug to any person except to those subjects enrolled in the study. At the end of the study, all unused drug supplies will be returned to Endo as instructed by the clinical monitor.

19. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

19.1. Source Documents

Source documents include but are not limited to original documents, data and records such as hospital/ medical records (including electronic health records), clinic charts, lab results, subject diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, etc. At a minimum, all data required to be collected by the protocol should have supporting source documentation for entries in the eCRF, unless the protocol specifies that data can be recorded directly on/in the eCRF or other device.

19.2. Study Monitoring

A representative of Endo Pharmaceuticals Inc. will meet with the Investigator and his/her staff prior to the entrance of the first subject to review study procedures and methods of recording findings in the eCRF.

After enrollment of the first subject, an Endo Pharmaceuticals Inc. representative will be assigned to periodically monitor each Investigator site for study progress and to verify that standards of Good Clinical Practice (GCP) were followed. The Investigator is expected to prepare for the monitor visit, ensuring that all source documents, completed eCRFs, signed consent forms, and other study related documents are readily available for review.

19.3. Audits and Inspections

The Investigator shall permit audits and inspections by the Sponsor, its representatives and members of regulatory agencies. The investigator should immediately notify the Sponsor of an upcoming FDA or other regulatory agency inspection.

19.4. Institutional Review Board (IRB)

The Investigator shall permit members of the IRB/IEC to have direct access to source documents.

19.5. Data Recording and Documentation

All data recordings and source documentation (including electronic health records) must be made available to the Sponsor (or designee), FDA and any other regulatory agencies that request access to study records, including source documents, for inspection and copying, in keeping with federal and local regulations.

20. QUALITY CONTROL AND QUALITY ASSURANCE

Steps to assure the accuracy and reliability of data include the selection of qualified principal investigators and appropriate study centers, review of protocol procedures with the principal investigators and associated personnel prior to start of the study, and periodic monitoring visits conducted by the Sponsor or Sponsor representative. Significant and/or repeated non-compliance will be investigated and remedial action instituted when appropriate. Failure to comply with remedial actions may result in investigator site termination and regulatory authority notification.

The Sponsor or its designee will utilize qualified monitors to review and evaluate activities conducted at Investigator Sites.

The data will be entered into the clinical study database and verified for accuracy, following procedures defined by the Sponsor (or designee). Data will be processed and analyzed following procedures defined by the Sponsor (or designee).

The study will be monitored and/or audited at intervals to ensure that the clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the Study Protocol; International Conference on Harmonisation (ICH), E6 consolidated guidelines; and other applicable regulations. The extent, nature, and frequency of monitoring and/or audits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity, and enrollment rate. At the conclusion of a program, a compliance statement will be generated by the Sponsor (or designee) listing all audit activities performed during the clinical study.

21. ETHICS

21.1. Ethics Review

Approval by the IRB/IEC prior to the start of the study will be the responsibility of the Investigator. A copy of approval documentation will be supplied to Endo Pharmaceuticals Inc. along with a roster of IRB members that demonstrates appropriate composition (a Department of Health and Human Services [DHHS] Assurance Number will satisfy this requirement).

The study protocol, the informed consent form, advertisements, materials being provided to subjects and amendments (if any) will be approved to IRB/IECs at each study center in conformance with ICH E6, the Code of Federal Regulations (CFR), Title 21, Part 56 and any other applicable local laws. The Investigator is responsible for supplying the IRB/IEC with a copy of the current IB, Package Insert, or SPC as well as any updates issued during the study. During the course of the study, the Investigator will provide timely and accurate reports to the IRB/IEC on the progress of the study, at intervals not exceeding 1 year (or as appropriate), and will notify the IRB/IEC of SAEs or other significant safety findings, per the policy of the IRB/IEC. At the conclusion of the study, the Investigator will submit a final report or close out report to the IRB/IEC and provide a copy to Endo Pharmaceuticals Inc.

Any amendment to this protocol will be provided to the Investigator in writing by Endo Pharmaceuticals Inc. No protocol amendment may be implemented (with the exceptions noted below) before it has been approved by the IRB and the signature page, signed by the Investigator, has been received by Endo Pharmaceuticals Inc. Where the protocol is amended to eliminate or reduce the risk to the subject, the amendment may be implemented before IRB review and approval. However, the IRB must be informed in writing of such an amendment and approval obtained within reasonable time limits. Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the subject, and must be immediately reported to Endo Pharmaceuticals Inc.

The Investigator will be responsible for supplying updated safety and/or study information to study subjects as it becomes available.

21.2. Ethical Conduct of the Study

This clinical study is designed to comply with the ICH Guidance on General Considerations for Clinical Trials (62 FR 6611, December 17, 1997), Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (62 FR 62922, November 25, 1997), Good Clinical Practice: Consolidated Guidance (62 FR 25692, May 9, 1997) and 21 CFR parts 50, 54, 56, and 312.

The study will be conducted in full compliance with ICH E6, the FDA guidelines for GCP and in accordance with the ethical principles that have their origins in the Declaration of Helsinki defined in 21 CFR, 312.120.

21.3. Subject Information and Consent

Subjects, after having the study explained to them and an opportunity to have their questions answered sufficiently, will give voluntary and written informed consent (in compliance with ICH E6, 4.8 and 21 CFR Parts 50 and 312) before participating in any study-related procedures. The consent shall be written in a language understandable to the subject. Subjects unable to read (illiterate) shall have the consent process performed in the presence of an independent witness who shall also sign the consent. Each subject will read, assent understanding, and sign an instrument of informed consent after having had an opportunity to discuss the study and consent documents with the Investigator before signing, and will be made aware that she may withdraw from the study at any time.

In addition to obtaining informed consent, the Investigator is responsible for obtaining any additional documentation to demonstrate compliance with local privacy laws applicable to activities performed.

The consent process shall be recorded in source documents. Signed copies of the informed consent will be given to the Subject and originals will be placed in the Investigator study files.

A unique Subject identification number will be assigned according to section 12.1.3 at the time that the Subject signs the informed consent form.

22. DATA HANDLING AND RECORDINGKEEPING

22.1. Data Collection

Data collection will involve the use of an EDC system to which only authorized personnel will have access. The system will be secured to prevent unauthorized access to the data or the system. This will include the requirement for a user ID and password to enter or change data. The level of access to the EDC system will be dependent on the person's role in the study.

Study data will be collected from source documents and entered into an eCRF within the EDC system. The Investigator will be responsible for ensuring the eCRFs are completed in a timely manner relative to the subject's visit. In addition to periodic monitoring occurring within the system by a Sponsor monitor, programmatic edit checks will be used to review EDC data for completeness, logic, and adherence to the study protocol. As a result of this monitoring and these checks, queries may be issued electronically to the clinical study sites and closed electronically by the monitor, data management staff or authorized staff at the study site. Additionally, the Investigator will review eCRFs, ensure all missing or corrected data is provided and will sign the eCRF pages with an electronic signature.

An electronic audit trail will be maintained in the EDC system to track all changes made to data entered in the eCRF. Data will be retrievable in such a fashion that all information regarding each individual subject is attributable to that subject. Unless otherwise indicated, all data captured in the eCRF must first be captured in source documents. Data that can be directly recorded in the eCRF will be clearly identified in the section(s) of the protocol that describes the assessment(s).

In addition, any contact with the subject via telephone or other means that provide significant clinical information must be documented in source documents as described above.

22.2. Study Documentation

Upon study completion, the Investigator will be provided with complete electronic copies of the CRF data for his/her files.

23. REPORTING AND PUBLICATION

All data generated in this study are the property of Endo. An integrated clinical and statistical report will be prepared at the completion of the study.

Publication of the results by the Investigator will be subject to mutual agreement between the Investigator and Endo.

24. INVESTIGATOR OBLIGATIONS

24.1. Regulatory Documents

The Investigator is responsible for creating and/or maintaining all study documentation required by 21CFR 50, 54, 56 and 312, ICH, E6 section 8, as well as any other documentation defined in the protocol or the Investigator Agreement. The Investigator must maintain the documentation relating to this study and permit Endo Pharmaceuticals Inc. or a member of a regulatory agency access to such records.

The Investigator must provide the following key documents to Endo Pharmaceuticals Inc. prior to the start of the study:

- A completed and signed Form FDA1572. If during the course of the study any information reported on the Form FDA 1572 changes, a revised Form FDA1572 must be completed and returned to Endo Pharmaceuticals Inc. for submission to the FDA. For studies executed outside the United States, documentation required by the governing regulatory authority may be substituted for the Form FDA 1572.
- A fully executed contract
- The Investigator's Statement page in this protocol signed and dated by the Investigator and any subsequent amendment signature pages
- The IB acknowledgment of receipt page
- Curricula vitae for the Principal Investigator and all Sub-Investigators listed on Form FDA 1572, including a copy of each physician's license (if applicable)
- A copy of the original IRB/IEC approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals or shorter intervals defined by the IRB/IEC. All subsequent modifications must be submitted and approved by the IRB, as described in section 21.1
- A copy of the IRB/IEC-approved informed consent form
- A list of IRB/IEC members or DHHS Assurance Number
- Laboratory certifications and normal ranges (if local labs are required by the protocol)
- A financial disclosure agreement completed and signed by the Investigator and all Sub-Investigators listed on Form FDA 1572. Investigator site staff that submitted an initial financial disclosure are also responsible for informing Endo Pharmaceuticals Inc. of any changes to their initial financial disclosure form 1 year after the completion of the study.

A complete list of required regulatory documents will be supplied by Endo Pharmaceuticals Inc. or its representative.

24.2. Delegation of Responsibilities and Adequate Resources

The Investigator should have adequate time to conduct the study properly and should have an adequate number of qualified staff to assist with the conduct of the study. The Investigator shall delegate tasks only to individuals qualified by education, training and experience to perform the delegated tasks. The Investigator shall have direct oversight of all delegated activities and shall document delegation of responsibilities. The Investigator is responsible for ensuring all delegated staff have been properly trained on the protocol and their assigned study responsibilities.

24.3. Medical Care of Study Subjects

The Investigator and/or a qualified sub-investigator shall be responsible for the subjects' medical care. Any unrelated medical condition discovered during the course of the study should be communicated to the subject so that they may seek appropriate medical care. The Investigator will report all AEs as required by the protocol (section 14.5). The Investigator will inform study subjects of new information regarding the study drug as it becomes available.

24.4. Use of Investigational Materials

The Investigator will acknowledge that the study drug supplies are investigational and as such must be used strictly in accordance with the protocol and only under the supervision of the Principal Investigator or Sub-Investigators listed on Form FDA1572 (or other regulatory document, depending on region). Study drug must be stored in a safe and secure location. At study initiation, a representative from Endo Pharmaceuticals Inc. will inventory the study drug at the site. The Investigator must maintain adequate records documenting the receipt and disposition of all study supplies. Endo Pharmaceuticals Inc. or its representative will supply forms to document total inventory as well as subject specific accountability. The Investigator is responsible for monitoring subject's use of the study drug to ensure compliance with the protocol. All study supplies shall be returned to Endo Pharmaceuticals Inc. or its designee (this may include empty packaging such as bottles and blister cards). It is the Investigator's responsibility to ensure that subjects return their medication.

24.5. Retention of Records

Federal and local regulations require that the Investigator retain a copy of all regulatory documents and records that support the data for this study (eg, informed consents, laboratory reports, source documents, study drug dispensing records) for whichever of the following is the longest period of time:

- A period of 2 years following the final date of approval by the FDA or other regulatory agency of the study drug for the purposes that were the subject of the investigation; or
- A period of 5 years following the date on which the results of the investigation were submitted to the FDA or other regulatory agency in support of, or as part of, an application for a research or marketing permit for the study drug for the purposes that were the subject of the investigation

Endo will notify Investigators once one of the above 2 timeframes has been satisfied.

If the investigation does not result in the submission of the data in support of, or as part of, an application for a research or marketing permit, records must be retained for a period of 2 years following notification by Endo Pharmaceuticals Inc. that the entire clinical investigation (not merely the Investigator's portion) is completed, terminated, or discontinued or 2 years following withdrawal of the Investigational New Drug application (IND).

If the Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. Endo must be notified in writing of the name and address of the new custodian. Study records should not be destroyed without consultation with Endo Pharmaceuticals Inc.

24.6. Subject Confidentiality

All subject records submitted to Endo Pharmaceuticals Inc. or its designee will be identified only by initials and code number. Subjects' names are not to be transmitted to Endo Pharmaceuticals Inc. The Investigator will keep a Master Subject List on which the identification number and the full name, address, and telephone number of each subject are listed. It is the Investigators' responsibility to inform study subjects that representatives of the Sponsor, FDA, or other regulatory agencies may review all records that support their participation in the study. The Investigator will adhere to all privacy laws to which she is subject.

25. TERMINATION OF STUDY

The Sponsor has the right to suspend or terminate the study at any time. The study may be suspended or terminated for any reason.

26. INVESTIGATOR'S AGREEMENT

I agree to conduct the study in accordance with the protocol, and with all applicable government regulations and Good Clinical Practice guidance.

_____ _____/_____/_____

Investigator's Signature Date

_____

Typed Name of Investigator

27. REFERENCES

1. Khan MH, Victor F, Rao B, Sadick NS. Treatment of cellulite: Part I. Pathophysiology. *J Am Acad Dermatol* 2010;62(3):361-370.
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[redacted]

LIST OF APPENDICES

APPENDIX A. DOCUMENTS REQUIRED PRIOR TO INITIATION OF THE STUDY

As a Sponsor of a clinical study, Endo Pharmaceuticals Inc. has an obligation to ensure that the study will be conducted by a qualified Investigator with sufficient resources of time, personnel, and physical facilities to conduct the study and to ensure that the Investigator understands and agrees to comply with the protocol, applicable regulations, policies, and procedures. The following documentation is required:

From the Principal Investigator

1. A signed agreement to perform the study per protocol (the signature page will suffice).
2. A signed Letter of Financial Agreement (including confidentiality statement).
3. Name(s) of the Principal Investigator and of all sub-Investigator(s)
4. All address(es) of the clinical site(s).
5. A current medical license valid where he/she practices and a current curriculum vitae for the Principal Investigator (signed and dated) and all sub-investigators, to contain at least the following elements:
   a. For physicians:
      i. Date of degree in Medicine
      ii. Name of the Institution granting the degree in Medicine.
      iii. Previous clinical postings with dates.
   b. For non-physician allowed by national law or regulations to act as clinical Investigators:
      i. Date and description of most advanced degree.
      ii. Name of the Institution granting the degree in number (i).
      iii. Other accreditation or qualifications relevant to the study.
      iv. Previous postings with dates.
      v. Name and qualification (see 5a above) of the physician or dentist in charge of study subjects.

   Note: If a non-physician is serving as Principal Investigator, then a qualified physician must be assigned as a sub-Investigator for the trial, to be responsible for all trial-related medical decisions.
6. Written notification of Institutional Review Board/Independent Ethics Committee/Human Research Ethics Committee (IRB/IEC/HREC) approval. The minimum requirements are as follows:
   a. Dated letter, including:
      i. The date on which the meeting for the review of the study protocol took place.
      ii. Study protocol/amendment number, and version date

iii. A clear statement of approval of the protocol and the informed consent text with version date, and authorization for the study to proceed.

iv. If the Investigator or any sub-Investigator is a part of the IRB/IEC/HREC Review Board, assurance that the Investigator abstained from voting at the meeting(s) when the study was discussed.

b. A dated list of the members and their occupations.

c. A specimen copy of the Committee-approved informed consent text to be used in the study.

7. Food and Drug Administration (FDA) Form 1572 (for studies submitted under a US Investigational New Drug application [IND]).

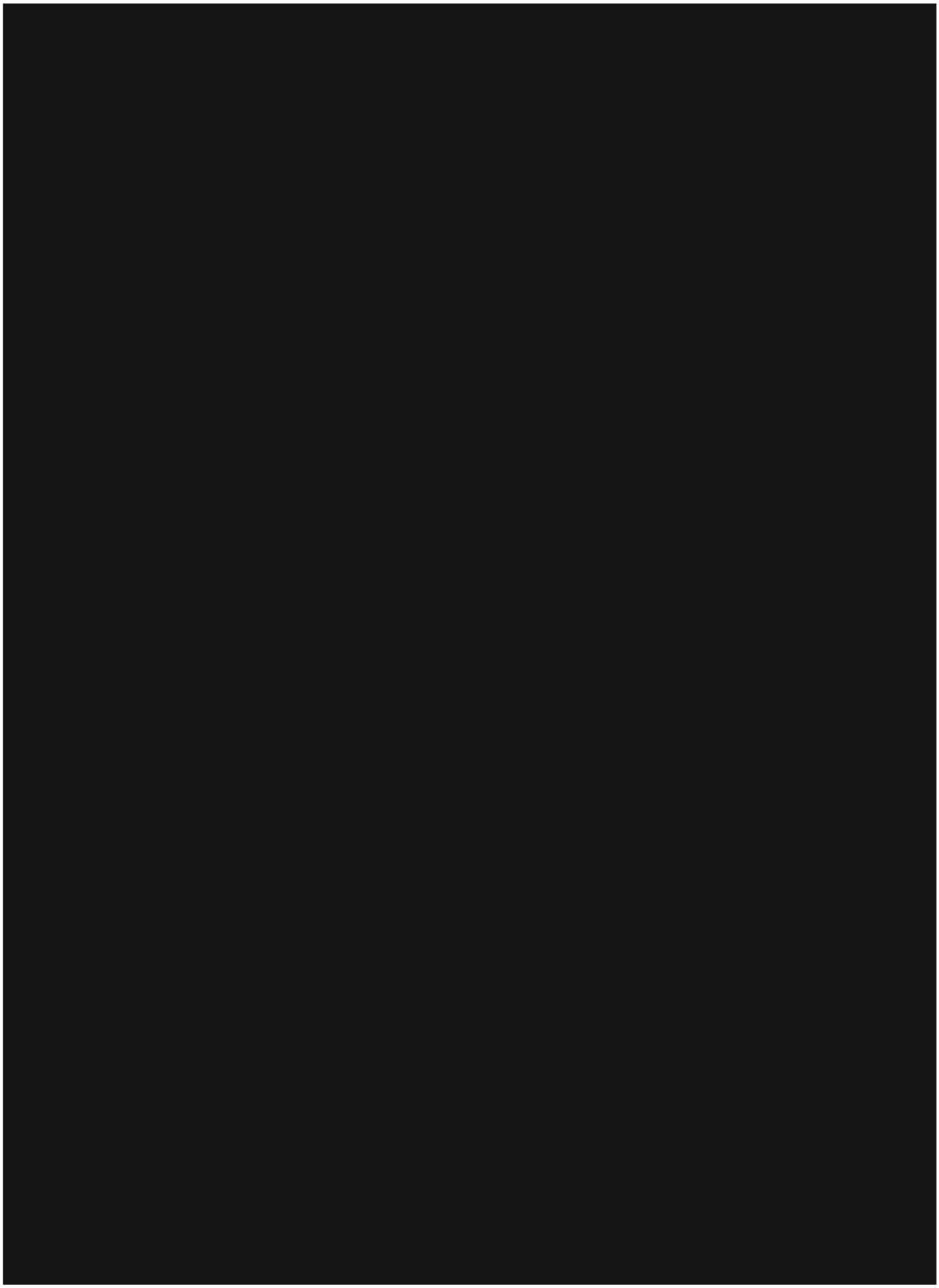
8. Financial Disclosure Certification or Certification of Non-Disclosure (for studies to be submitted for a US New Drug Application/Biologics License Application [NDA/BLA]).

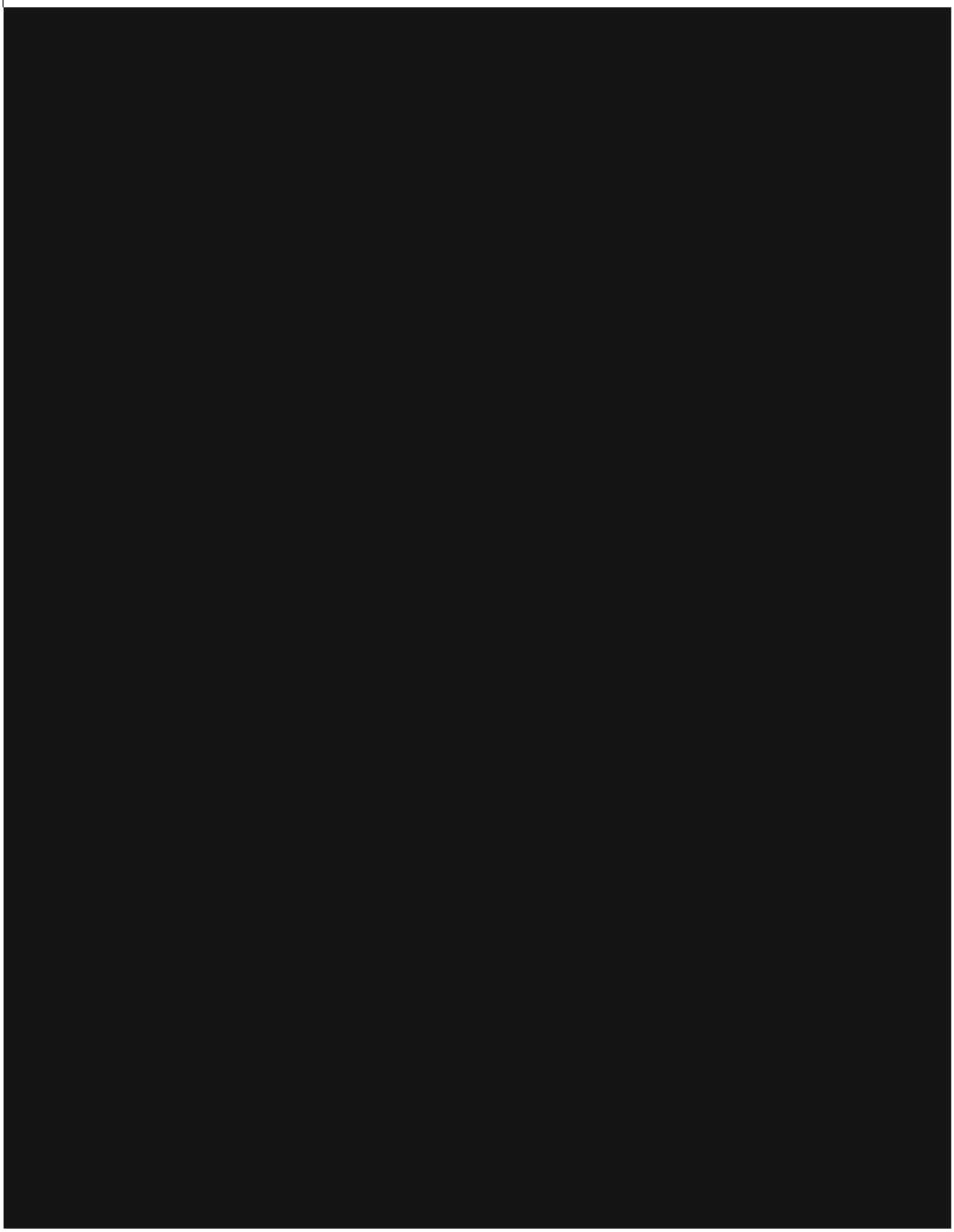
Other

Any other documentation required by national law or regulations to be in the possession of the Sponsor or the Investigator for study participation or study initiation.

[redacted]

APPENDIX B. HEXSEL DM, DAL'FORNO T, HEXSEL CL. A VALIDATED PHOTONUMERIC CELLULITE SEVERITY SCALE. *J EUR ACAD DERMATOL VENEREOL*. 2009;23(5):523-528.





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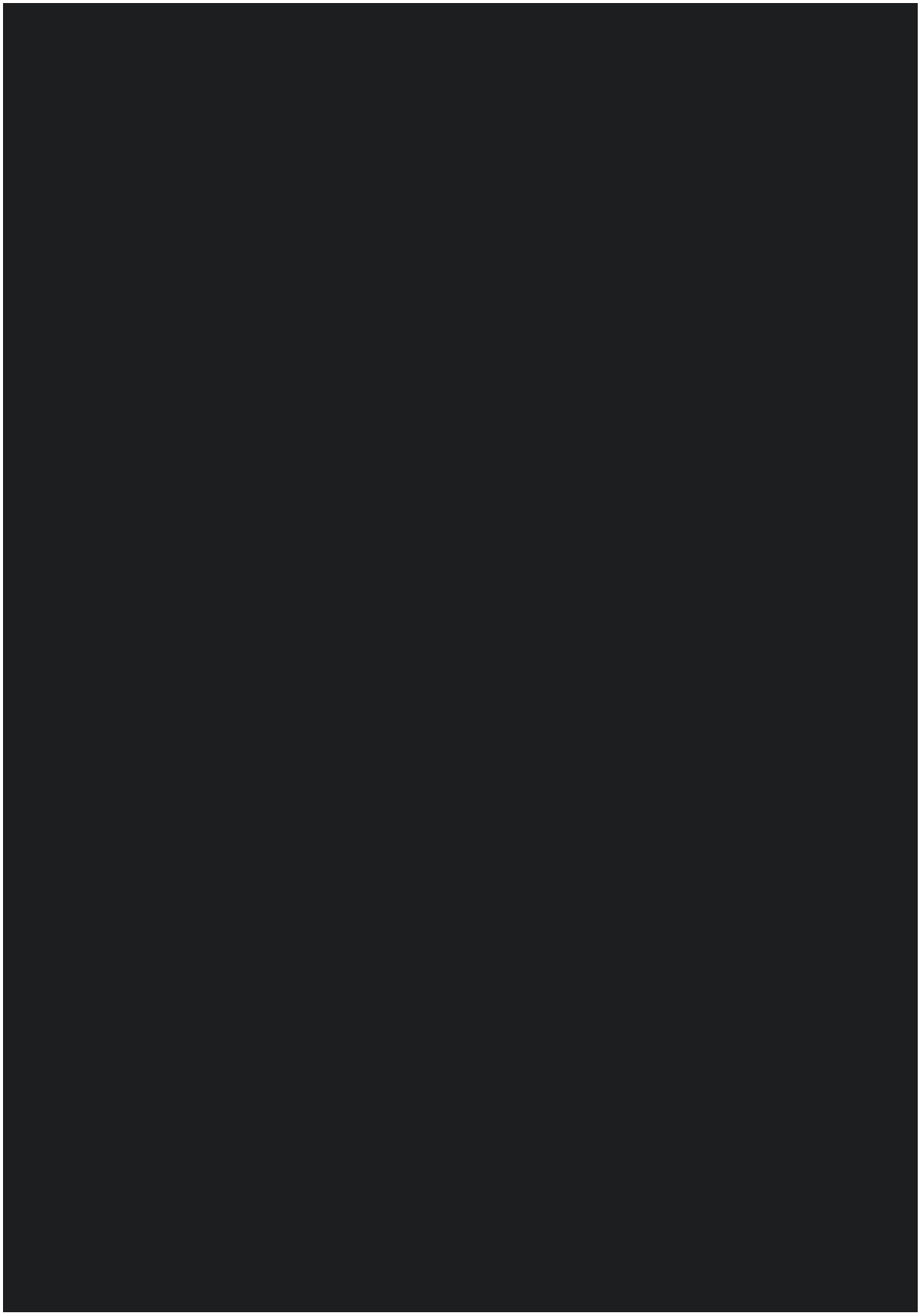

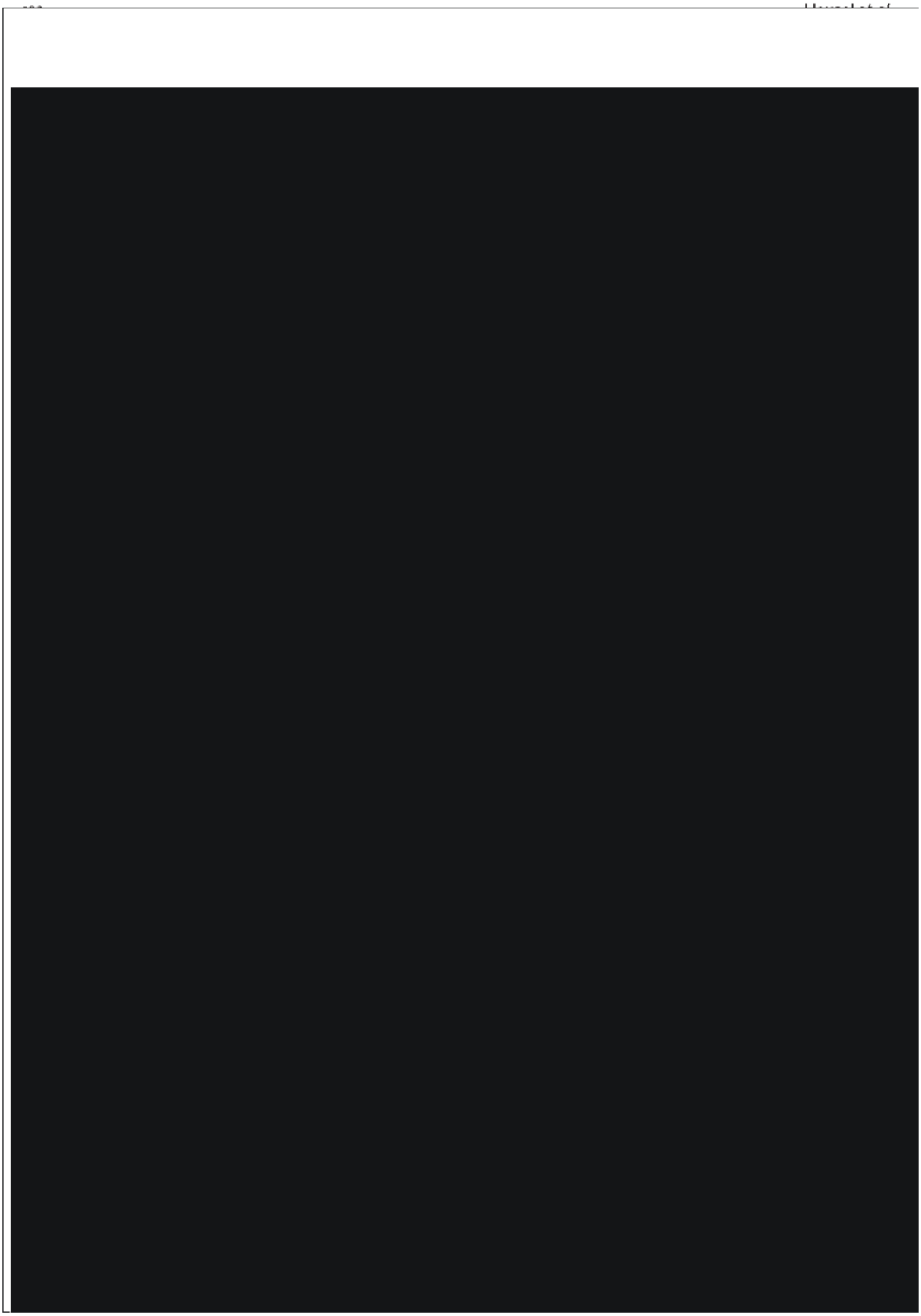

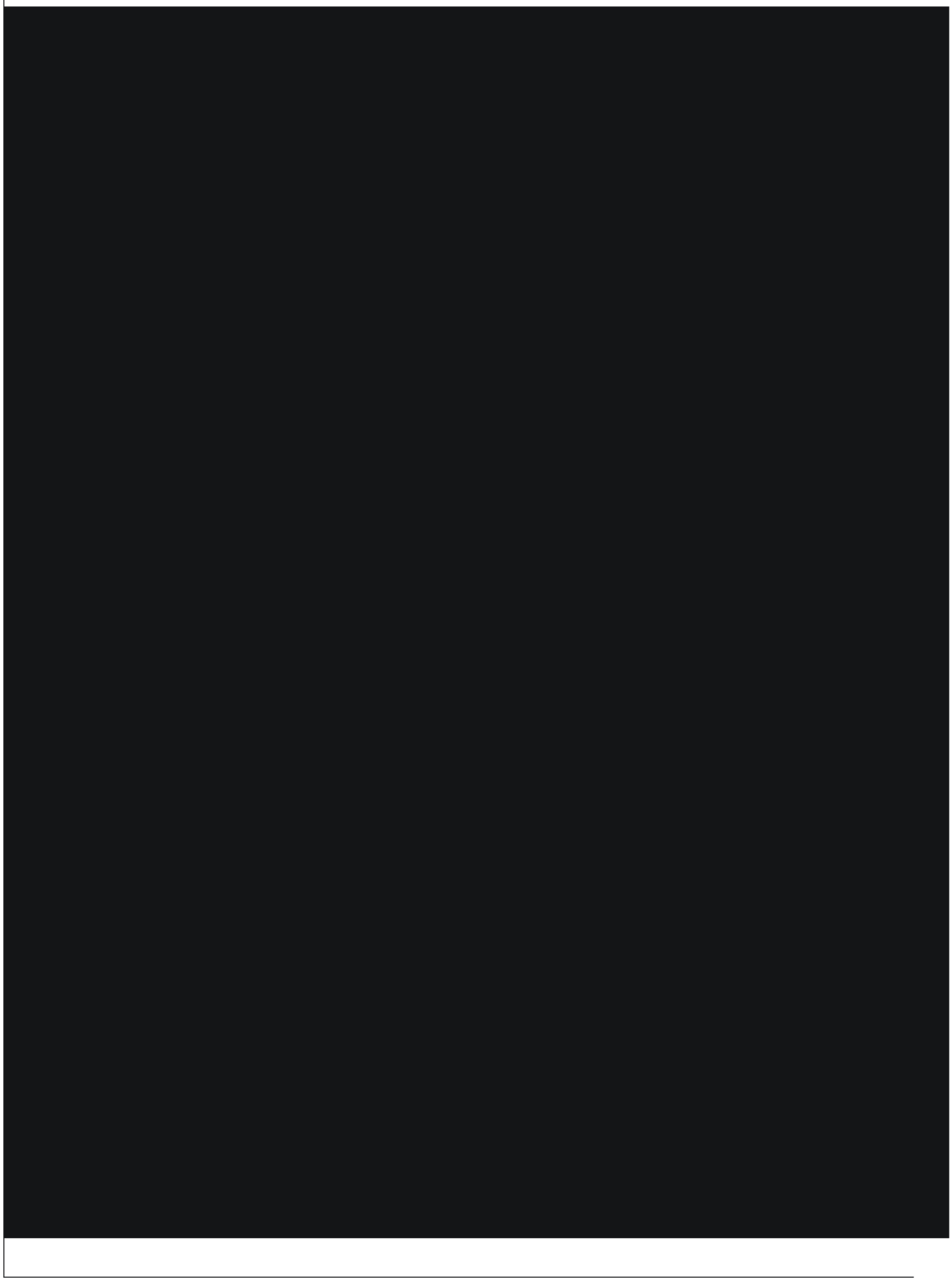

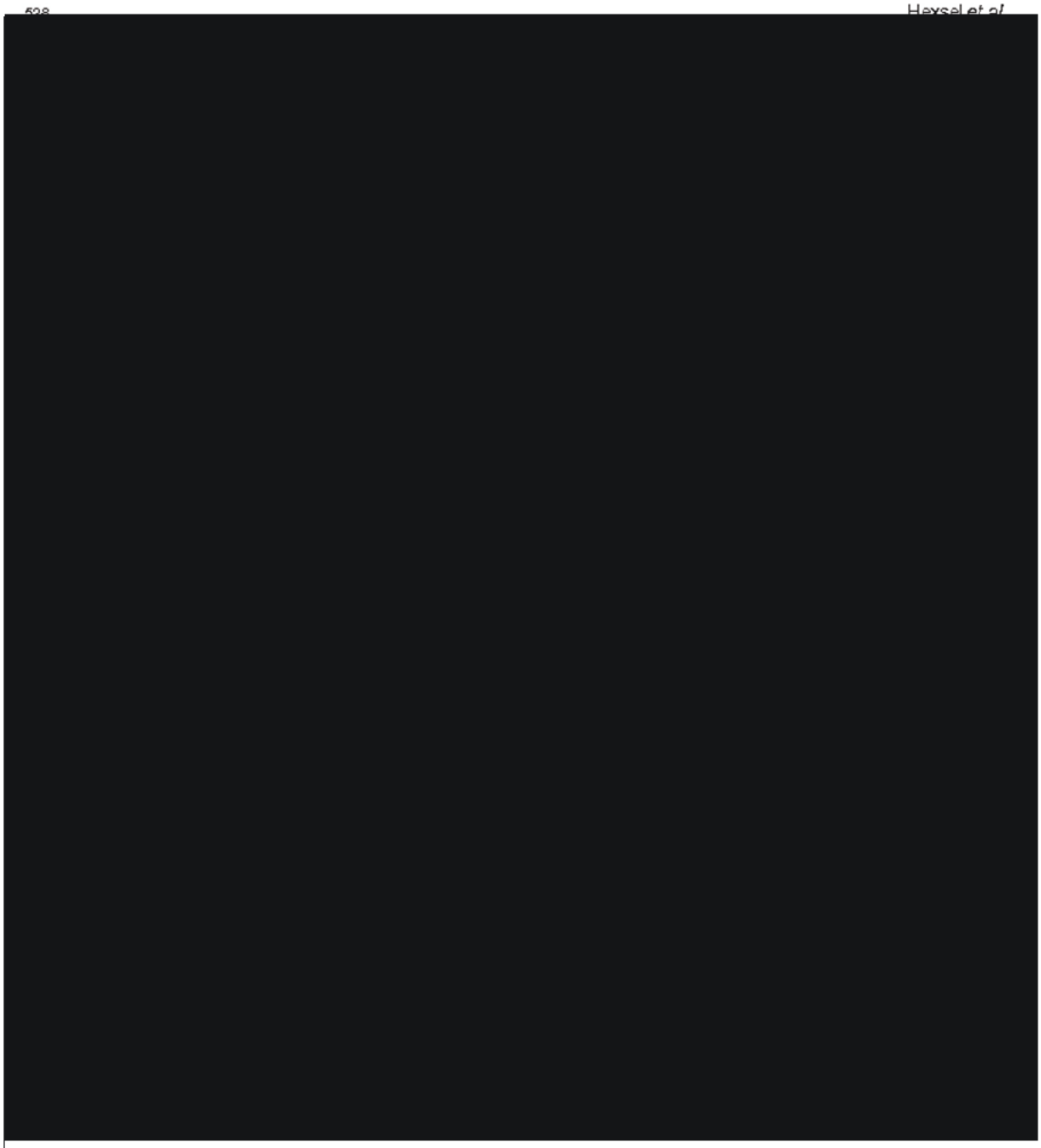

APPENDIX C. REFERENCE IMAGES FOR HEXSEL SEVERITY RATINGS

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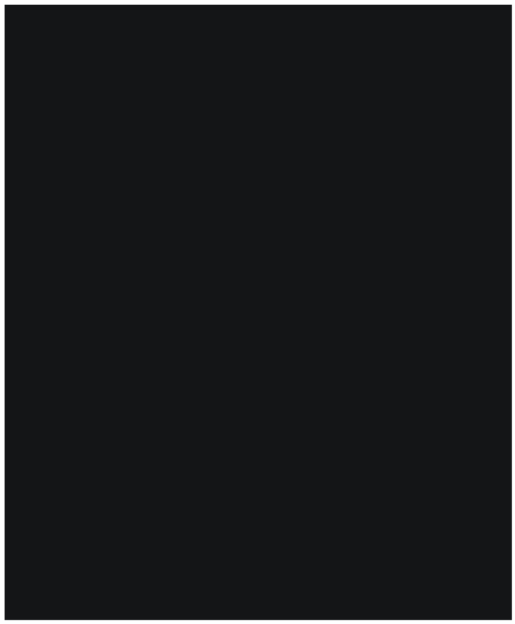

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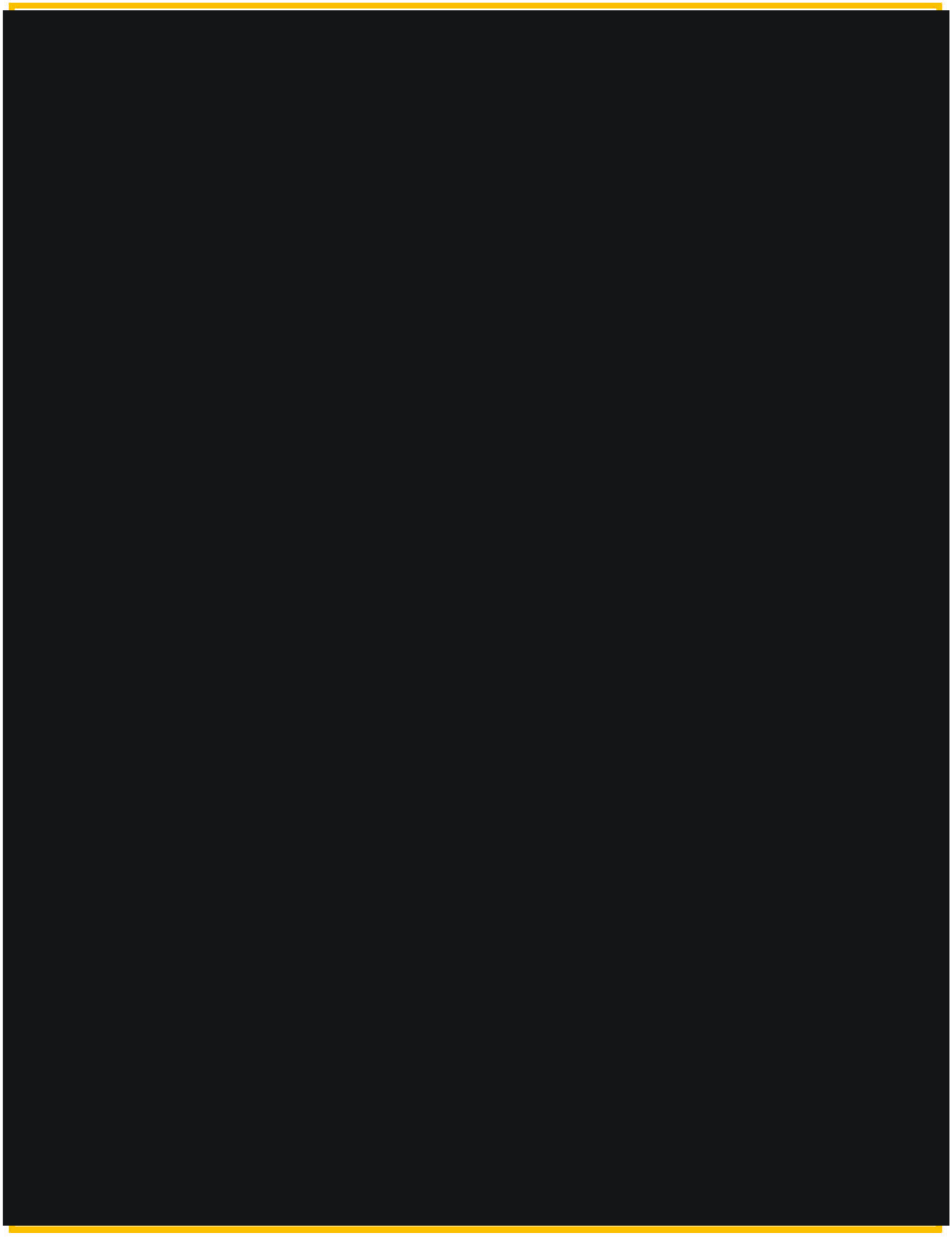
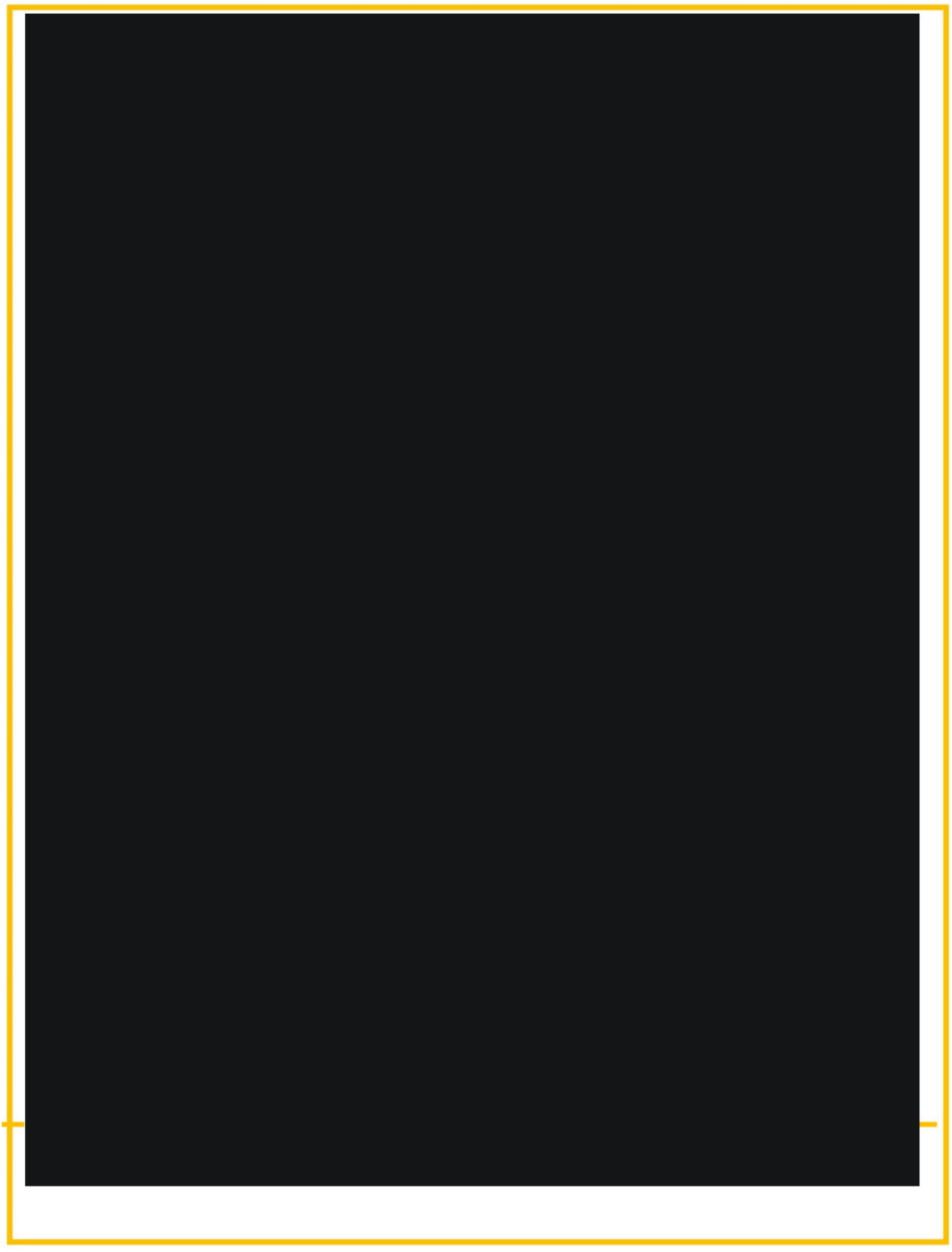
APPENDIX D. PATIENT INSTRUCTIONS FOR USE OF PATIENT-REPORTED PHOTONUMERIC CELLULITE SEVERITY SCALE (PR-PCSS)





STATISTICAL ANALYSIS PLAN
MODULE 1

STUDY EN3835-202

A Phase 2, Open-label Extension Study of EN3835 in the Treatment of Edematous Fibrosclerotic Panniculopathy

Version 1.0

August 1, 2018

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

Confidentiality Statement

[redacted]

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

Table 1: Abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse Events of Special Interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUX-I	Clostridial Class I Collagenase
AUX-II	Clostridial Class II Collagenase
BMI	Body mass index
bpm	Beats per minute
brpm	Breaths per minute
BUN	Blood urea mitrogen
CR-PCSS	Clinician Reported Photonumeric Cellulite Severity Scale
CSS	Cellulite Severity Scale
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EFP	Edematous fibrosclerotic panniculopathy
EN3835	Collagenase clostridium histolyticum
EOS	End of Study
EOT/ET	End of Treatment/Early Termination
GAIS	Global Aesthetic Improvement Scale
I-GAIS	Investigator Global Aesthetic Improvement Scale
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MH	Medical history
mL	Milliliter
mmHg	Millimeters of mercury
mmol	Millimoles
PCI	Potentially clinically importance/important
PR-PCSS	Patient Reported Photonumeric Cellulite Severity Scale

Table 1: Abbreviations (Continued)

Abbreviation	Definition
SAE	Serious adverse event
SAP	Statistical Analysis Plan
S-GAIS	Subject Global Aesthetic Improvement Scale
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
µmol	Micromoles
WHO	World Health Organization

0. REVISION HISTORY

1. STUDY DESIGN

1.1. Description of Study Design

This clinical study is a multicenter, open-label extension study. Subjects who completed the entire double-blind, placebo-controlled, parent trial (EN3835-201) and sign an informed consent form will be eligible to participate in this study.

After the Sponsor has broken the EN3835-201 study drug blind, subjects enrolled in the open-label study will have the following options:

- To have no EN3835 treatments in study EN3835-202
- If received EN3835 in study EN3835-201, may elect to have a qualifying quadrant other than the one treated with EN3835 in study EN3835-201 (termed *re-dosing*)
- If received EN3835 in study EN3835-201 and the cellulite severity scores of the treated quadrant have returned to or are higher than EN3835-201 baseline scores, may elect to have the previously treated quadrant retreated with EN3835 (termed *re-treatment*)
- If received placebo in study EN3835-201, may elect to have a qualifying quadrant treated with EN3835; also may elect to have a second qualifying quadrant treated with EN3835 after completing the treatment course

Following completion of safety and cellulite assessments at Day 71 of the double-blind study (EN3835-201), subjects will be asked if they wish to continue in the open-label extension to the double-blind study (Screening A). Subjects enrolled in study EN3835-202 who elect to receive EN3835 treatment (either re-treatment, re-dosing, or a first treatment) must meet specific inclusion and exclusion criteria for eligibility during re-screening (Screening B) prior to EN3835 dosing.

Previously placebo-treated subjects will have the option to receive a second course of EN3835 in the same or different qualifying quadrant after at least 28 days following the end of the first treatment course (eg, the Screening B visit of second quadrant could be performed on Day 71 after treating the first quadrant). The selected quadrant can be re-treatment or re-dosing.

At each treatment course, subjects will receive 3 treatment sessions (Day 1, Day 22, and Day 43) unless the chosen quadrant has no further treatable edematous fibrosclerotic panniculopathy (EFP) dimples and the Investigator rates the quadrant a score of 0 on the Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS). The same dimples within a quadrant or different dimples within a quadrant may be treated at each session but injections must all be within the selected quadrant for all 3 sessions. Each treatment session will be separated by approximately 21 days. Day 71 visit (end of treatment/early termination [EOT/ET]) will be performed for each subject. After Day 71, the subjects will be observed every 3 months from their first exposure to EN3835 up to a maximum of 1 year in each treated quadrant (including

both open-label and double-blind treated quadrants, if different quadrants were treated across both studies). Durability beyond Day 360 will be assessed in subjects who received active treatment in EN3835-201 and showed a composite improvement of at least 1 level on both the CR-PCSS and the Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS). In these subjects, the original quadrant treated in EN3835-201 will be assessed until the end of the current study, in addition to any treated quadrants occurring in the current study. Assessments of durability beyond Day 360 may also include subjects who opted not to receive additional treatments in EN3835-202.

1.2. Schedule of Study Assessments

Table 2 lists the schedule of observation assessments, Table 3 lists the schedule of treatment session assessments, Table 4 lists the schedule of long-term durability assessments.

The schedule of observation assessments is applicable for both observation only and treated subjects in current study. For example, if subjects received treatments (ie, re-treatment, re-dosing, or a first treatment) in current study may be scheduled for observation assessments up to maximum of 1 year for each treated quadrant.

NOTE: Observation visits (Table 2) in the open-label extension study begin after completion of double-blind study (Day 71). Treatment sessions (Table 3), if elected, will begin after study drug blind is broken in study EN3835-201while observation visits continue concurrently. Durability visits (Table 4) are for the subjects who received active treatment in EN3835-201 and scored an improvement of at least 1 level on both the CR-PCSS and the PR-PCSS at the same visit on or before Day 71 in the double-blind study EN3835-201.

Table 2: Schedule of Observation Assessments

Procedures	Screening A[a] (≥Day 71 Visit of Double-blind Study)	Visit 1 Day 90[b] (±7 days)	Visit 2 Day 180[b] (±7 days)	Visit 3 Day 270[b] (±7 days)	Visit 4 End of Study/ Early Termination Day 360[b,f] (±7 days)
Informed Consent	X				
Inclusion/Exclusion	X				
Digital photography		X[c]	X[c]	X[c]	X[c]
Prior/Concomitant Medications/Procedures	X	X	X	X	X
Body weight		X	X	X	X
Vital signs		X	X	X	X
Collection of samples:					
• Clinical laboratory					X
• Anti-AUX-I/anti-AUX-II antibody level					X
Subject cellulite assessments:					
• Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS)		X[d,e]	X[d,e]	X[d,e]	X[d,e]
• Subject Global Aesthetic Improvement (S-GAIS)					X[d,e]
• Subject satisfaction with cellulite treatment assessment					X[d,e]
Investigator cellulite assessments:					
• Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)		X[e]	X[e]	X[e]	X[e]
• Hexsel Cellulite Severity Scale (CSS)					X[e]
• Investigator Global Aesthetic Improvement (I-GAIS)					X[e]
Injection site reactions/local tolerability in assigned quadrant from EN3835-201 study		X	X	X	X
Adverse events	Monitored Throughout Study				

[a] Informed consent for open-label observation assessments and optional treatment election.
[b] Four (4) visits at 3-month periods begin 90 days after Day 1 of the double-blind study (EN3835-201) (ie, within 20 days ± 4 days of completion of double-blind study).
[c] Only the treated quadrant(s) is photographed. For subjects participating in observation-only visits, the quadrant treated in the double-blind study (EN3835-201) is photographed; for subjects with open-label treatment (treated with EN3835 in study EN3835-202), the treated quadrant is photographed.
[d] Assessment made via viewing digital image photograph.
[e] Assessment of treated quadrant(s) only.
[f] For subjects treated with active EN3835 in the double-blind study and having a different quadrant treated in the open-label study, refer to Table 4 for continued assessments of the double-blind treated quadrant for durability beyond Day 360. NOTE: Subject cellulite assessments must be completed before the Investigator cellulite assessments are conducted at each visit.

NOTE: Subject cellulite assessments must be completed before the Investigator cellulite assessments are conducted at each visit.

Table 3: Treatment Session Assessments

Procedures	Screening B[a] (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/ Early Termination Day 71 (+5 days)[b]
Inclusion/Exclusion	X				
Digital photography	X[c]	X[c,d]	X[c,d]	X[c,d]	X[c]
Medical history/EFP history including previous treatments	X[k,m]				
Prior/Concomitant Medications/Procedures	X[k,m]	X[m]	X	X	X
Physical examination:	X				
• Body weight	X[m]		X[e]	X[e]	X
• Height	X[m]				
Vital signs	X	X[f]	X[f]	X[f]	X
12-lead ECG	X[l]				
Collection of samples:					
• Clinical laboratory	X[m]				X
• Anti-AUX-I/anti-AUX-II antibody level		X[e,m]			X
• Urine pregnancy testing	X	X[e]	X[e]	X[e]	
Subject cellulite assessments:					
• Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS)	X[g,h]		X[e,g,h]	X[e,g,h]	X[g,h]
• Subject Global Aesthetic Improvement (S-GAIS)					X[g,h]
• Subject satisfaction with cellulite treatment assessment					X[g,h]
Investigator cellulite assessments:					
• Selection of dimples to be treated within selected quadrant		X[e]	X[e]	X[e]	
• Marking the dimples to be treated within selected quadrant		X[e]	X[e]	X[e]	
• Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)	X[h]		X[e,h]	X[e,h]	X[h]
• Hexsel Cellulite Severity Scale (CSS)	X[h,i]				X[h]
• Investigator Global Aesthetic Improvement (I-GAIS)					X[h]
Confirm Eligibility	X	X[e]			
Select Quadrant	X[j]				
Study drug administration		X	X	X	
Injection site reactions/local tolerability in selected quadrant		X	X	X	X
Adverse events	Monitored Throughout Study				

[a] After the study drug blind is broken in study EN3835-201, eligible subjects may elect to receive EN3835 treatments.
[b] Upon completion of treatment, subject will be followed at 3-month intervals as in Table 2; if study terminates early, subject will be followed through Visit 4 (Day 71). If subject received placebo in the double-blind study (EN3835-201), she may be eligible for a total of 2 courses of treatment (a total of 6 treatment sessions) in this study.
[c] All 4 quadrants are photographed at screening; at other visits, the selected quadrant only is photographed.
[d] Before and after marking the dimples.
[e] Before injection.
[f] Up to 4 hours before injection; approximately 15 and 30 minutes after injection. Vital signs must be stable before the subject is discharged.
[g] Assessment made via photograph (if treatment session, use photograph taken before marking dimples).
[h] All 4 quadrants are assessed at the Screening B visit; at other visits, the selected quadrant only is assessed.
[i] Initial Hexsel CSS at screening must be ≤13 on selected quadrant.
[j] To qualify for treatment, the selected quadrant must have a score of 3 or 4 (moderate or severe) in both the CR-PCSS and PR-PCSS, and a Hexsel CSS score ≤13; to qualify a quadrant that had been previously treated with EN3835 in study EN3835-201, the quadrant must have CR-PCSS and PR-PCSS scores equal to or greater than study EN3835-201 baseline scores and a Hexsel CSS score ≤13.
[k] Medical history and prior medications will be based on EN3835-201 eCRF; only updates and concomitant medications need to be captured at Screening B visit.
[l] Do not conduct if Screening B visit date is within 12 months of obtaining an ECG during the double-blind study (EN3835-201).
[m] Do not conduct on subjects eligible and opting-in for a second course of treatment in the current study (EN3835-202) if Screening B visit or Day 1 visit for second treatment course is the same day as Day 71 of the first treatment course in this study or previous study EN3835-201.

ECG=Electrocardiogram; eCRF=Electronic case report form; EFP=Edematous fibrosclerotic panniculopathy; Tx=Treatment
NOTE: Subject cellulite assessments must be completed before the Investigator cellulite assessments are conducted at each visit.

Table 4: Assessments for Durability (Beyond Day 360)

Procedures	Long-term Durability Visit 1 Day 450[a] (±30 days)	Long-term Durability Visit 2 Day 540[a] (±30 days)	Long-term Durability Visit 3 Day 630[a] (±30 days)	End of Long-term Durability Study Day 720[a] or EOS/ET (±30 days)
Informed Consent	X			
Inclusion/Exclusion	X			
Digital photography	X	X	X	X
Medical history/EFP history including previous treatments	X[b]			
Prior/Concomitant Medications/Procedures	X[b]	X	X	X
Subject cellulite assessments:				
• Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS)	X[c d]	X[c d]	X[c d]	X[c d]
Investigator cellulite assessments:				
• Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)	X[d]	X[d]	X[d]	X[d]
• Hexsel Cellulite Severity Scale (CSS)	X[d]	X[d]	X[d]	X[d]
Adverse events	Monitored Throughout Study			

[a] Days listed reflect time from Day 1 visit in the double-blind study (EN3835-201).
[b] Only updates to medical history, prior medications, and concomitant medications need to be captured at this visit.
[c] Assessment made via photograph.
[d] Only the quadrant treated with active EN3835 in study EN3835-201 is assessed for subjects participating in durability assessments beyond Day 360.
EFP=Edematous fibrosclerotic panniculopathy; EOS=End of study; ET=Early termination

1.3. Study Objectives

1.3.1. Primary Objective

The primary objective of this study is to assess long-term safety of EN3835 0.84 mg at scheduled intervals over 1 year (12 months) or more in all subjects with EFP who elect to enroll in this open-label trial regardless of their decision to receive treatment (re-treatment or re-dosing) of open-label EN3835 or opt to receive no treatment.

1.3.2. Secondary Objectives

The secondary objectives of this study are:

- To evaluate safety and immunogenicity of re-treating or re-dosing a subject that had previously received treatment with EN3835
- To evaluate the durability of response to EN3835 in EFP severity over the 12-month post initial dosing of EN3835 in subjects previously receiving active treatment in study EN3835-201 using the PR-PCSS and the CR-PCSS
- To evaluate the durability of response to EN3835 in EFP severity beyond 12-month post initial dosing of EN3835 in subjects previously receiving active treatment in study EN3835-201 using the PR-PCSS and the CR-PCSS
- To evaluate long-term response to EN3835 in assessments of EFP including subject satisfaction, Investigator Global Aesthetic Improvement Scale (I-GAIS), and Subject Global Aesthetic Improvement Scale (S-GAIS)
- To assess cellulite severity assessments in quadrants treated in this study with EN3835
- To evaluate immunogenicity after exposure to EN3835

1.4. Study Medication

Subjects will be administered a maximum of EN3835 0.84 mg from a total of up to 12 injections. Up to 12 injections will be administered at each treatment session to treat the selected quadrant. Each of the injections will be administered as three 0.1-mL aliquots (total injection volume per injection is 0.3 mL; total injection volume per treatment session is 3.6 mL [12 injections × 0.3 mL], see Table 5 below).

Subjects will receive 3 treatment sessions (Day 1, Day 22, and Day 43) separated at least 21 days unless the chosen quadrant has no further treatable EFP dimples and the Investigator rates the quadrant a score of 0 on the CR-PCSS.

Table 5: EN3835 Administration

Dose per Each Injection[a]	Injection Volume per Each Injection	Maximum Number of Injections per Each Treatment Session	Maximum Dose (mg) per Each Treatment Session	Maximum Injection Volume (mL) per Each Treatment Session	Maximum Cumulative EFP Dose
EN3835 0.07 mg	0.3 mL	12 injections	0.84 mg (12 injections × 0.07 mg)	3.6 mL (12 injections × 0.3 mL)	2.52 mg (3 treatment sessions × 0.84 mg)

[a] Each injection of EN3835 is 0.3 mL administered as three 0.1-mL aliquots.

The complete Schedule of Events is provided in Section 1.2 (Table 2, Table 3 and Table 4).

1.5. Randomization and Unblinding

This study will be conducted as an open-label investigation; no randomization and blinding of assigned treatment will occur.

1.6. Interim Analysis

No interim analysis is planned for this study.

1.7. Sample Size Justification

Approximately 350 subjects that completed the EN3835-201 study will enroll in the current study. This sample size should be adequate to determine long term safety and cellulite assessments of EN3835.

2. ANALYSIS POPULATIONS AND PHASES

The following populations will be considered in the statistical analysis of the study:

- Observation Population: The Observation population includes all subjects rolled over from study EN3835-201. The cellulite assessment evaluations and safety analyses on data collected during observation phase will be performed using this population.
- Safety Population: The Safety population will include all subjects who receive at least 1 dose of EN3835 in the current study. All safety analyses for the treatment phase will be performed using this population. For by region summaries, safety population is considered within each treatment course.
- Effectiveness Population: The Effectiveness population includes all safety subjects who have a baseline and at least 1 post-baseline assessment on both the CR-PCSS and PR-PCSS on the quadrant selected for treatment in the current study. All analysis of effectiveness for the treatment phase will be based on this population. For by region summaries, effectiveness population is considered within each treatment course.
- Durability Population: This population is defined as all active responders who have both CR-PCSS and PR-PCSS at 180 days or above. The active responders are subjects treated with EN3835 with improvements of at least 1 level on each

scale (CR-PCSS and PR-PCSS) at Day 71 visit compared to the baseline. Analysis of durability of treatment effect will be performed using this population.

- Durability Population for Double-blind Treated Subjects: This population is defined as all subjects in the durability population who showed an improvement of at least 1 level on each scale (CR-PCSS and PR-PCSS) at Day 71 visit compared to the baseline for the quadrant treated with EN3835 in double-blind study EN3835-201.
- Durability Population for Open-label Treated Subjects: This population is defined as all subjects in the durability population who showed an improvement of at least 1 level on each scale (CR-PCSS and PR-PCSS) at Day 71 visit compared to the baseline for the quadrant treated with EN3835 in the open-label study EN3835-202 study, who did not have the same quadrant treated with EN3835 in double-blind study EN3835-201. For by region summaries, this population is considered within each treatment course.

The following 2 phases will be summarized in the statistical analysis of the study:

- Observation phase: Observation phase is defined as the time period from Screening A to the first treatment date of the same quadrant in study EN3835-202 or the end of study EN3835-202 if there is no treatment received for the same quadrant in study EN3835-202. Observation phase is defined within each treated quadrant, unless the summary is for subject level only and cannot be differentiated by the treated quadrant, ie, disposition, adverse event (AE). For subject level summaries, observation phase is defined as the time period from Screening A to the first treatment date in study EN3835-202 or the end of study EN3835-202 if there is no treatment received in study EN3835-202.
- Treatment phase: Treatment phase is defined as the time period from the first treatment date of certain quadrant in study EN3835-202 to the end of study EN3835-202. Treatment phase is defined within each treated quadrant, unless the summary is for subject level only and cannot be differentiated by the treated quadrant, ie, disposition, AE. For subject level summaries, treatment phase is defined as the time period from the first treatment date to the end of study EN3835-202.

3. STATISTICAL METHODS AND CONSIDERATIONS

3.1. Descriptive Statistics

All analysis results will be presented in summary table using appropriate descriptive statistics, unless otherwise stated. The statistics include the number (count) and percentage for all categorical variables. The denominator will be based on the number of subjects in each column group in the summary table, unless otherwise stated. All continuous variables will be summarized with observed count, mean, standard deviation, median, minimum, and maximum value.

3.2. Baseline Considerations

The baselines for all cellulite assessments, including CR-PCSS, PR-PCSS, and Hexsel CSS will be the observed values at visit Day 1 before subjects receive EN3835 treatment. If the values at Day 1 are missing, the values at Screening will be used for those assessments. For observation phase before EN3835 treatment in current study, the baselines will be the values at Day 1 for study EN3835-201. The reference values will be the observed scores at Day 71 in study EN3835-201 for those assessments. For the potentially clinically importance (PCI) calculation for vital sign values, the baseline refers to the latest vital sign assessment values before the first treatment in study EN3835-202.

All baselines for safety measures, ie, vital signs, clinical laboratory parameters, will use the latest values before subjects receive the first treatment in study EN3835-202.

3.3. Protocol Deviation Subjects Handling

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

3.4. Reporting Precision

Summary statistics will be presented to the following degree of precision, unless otherwise specified:

Statistics	**Degree of Precision**
Mean, Geometric Mean, Median, Quartiles, Confidence Limit Boundaries	One (1) decimal place more than the raw data
Standard Deviation, Standard Error	Two (2) decimal places more than the raw data
Minimum, Maximum	The same as the raw data
Percentage	One (1) decimal place. A percentage of 100% will be reported as 100.0. Percentages of zero will be reported as 0.0.

Up to 3 decimal places will be presented. Fractional numeric values will be presented with a zero to the left of the decimal point (for example, 0.12 – 0.30).

4. SUBJECT DISPOSITION

The number of subjects included in each study population will be summarized. The number and percentage of subjects completed and discontinued will be presented by observation and treatment phase. Reasons for discontinuation as recorded on the eCRF will be summarized (number and percentage) and listed for all subjects.

5. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic and baseline characteristics, including age, age group, race, and some other baseline values will be summarized for the Safety population and the Effectiveness population using appropriate descriptive statistics. Demographic and baseline characteristics will also be listed.

6. EFFECTIVENESS ANALYSES

6.1. Cellulite assessments

- PR-PCSS: 5-level ratings ranging from 0 (none) to 4 (severe). It will be assessed at Screening B, Days 22, Day 43, Day 71 and observational visits Day 90, Day 180, Day 270, Day 360 and Long-term Durability Visits, ie, Day 450, Day 540, Day 630, and Day 720.
- CR-PCSS: 5-level ratings ranging from 0 (none) to 4 (severe). It will be assessed at Screening B, Days 22, Day 43, Day 71 and observational visits Day 90, Day 180, Day 270, Day 360 and Long-term Durability Visits, ie, Day 450, Day 540, Day 630, and Day 720.
- Investigator rating of cellulite severity using the total scores from the Hexsel CSS scale: scores can range from 0 to 15. It will be assessed at Screening B, Day 71, Day 360 and Long-term Durability Visits.
- I-GAIS: 7-level ratings ranging from 3 (very much improved) to −3 (very much worse). This will be assessed at Day 71 and Day 360.
- S-GAIS: 7-level ratings ranging from 3 (very much improved) to −3 (very much worse). This will be assessed at Day 71 and Day 360.
- Subject satisfaction with cellulite treatment assessment: 5-level ratings ranging from +2 (very much satisfied) to −2 (very much dissatisfied). This will be assessed at Day 71 and Day 360.

All cellulite assessments will be done by treated quadrant and overall. For initial treatment subjects who have 2 quadrants treated, each quadrant will be evaluated separately. In the observation phase, those assessments will be also done corresponding to the treated quadrant.

6.2. Effectiveness Analysis

6.2.1. Composite Endpoints

The composite endpoints for cellulite severity are the proportions of composite responders defined as subjects with an improvement in severity from baseline of at least 2 (or 1) levels of severity in the CR-PCSS and an improvement in severity from baseline of at least 2 (or 1) levels of severity in the PR-PCSS.

These endpoints will be summarized by treated quadrant and overall (buttocks and thighs) and by study day using appropriate descriptive statistics.

6.2.2. Other Cellulite Assessment Endpoints

Other endpoints for treated quadrants in study EN3835-202 include:

- Change from baseline for PR-PCSS
- Proportion at each level of improvement in the PR-PCSS:
  - Proportion of patient responders defined as subjects with an improvement in severity from baseline of at least 2 levels on the PR-PCSS
  - Proportion of patient responders defined as subjects with an improvement in severity from baseline of at least 1 level on the PR-PCSS
- Change from baseline for CR-PCSS
- Proportion at each level of improvement in the CR-PCSS:
  - Proportion of Investigator responders defined as subjects with an improvement in severity from baseline of at least 2 levels on the CR-PCSS (Investigator rated)
  - Proportion of Investigator responders defined as subjects with an improvement in severity from baseline of at least 1 level on the CR-PCSS (Investigator rated)
- Proportion of responders at each level of the I-GAIS:
  - Proportion of subjects at each level of the I-GAIS ranging from 3 (very much improved) to −3 (very much worse). It will be assessed at Day 71 and Day 360.
- Proportion of responders at each level of the S-GAIS:
  - Proportion of subjects at each level of the S-GAIS ranging from 3 (very much improved) to −3 (very much worse). It will be assessed at Day 71 and Day 360.
- Proportion of responders at each level of the subject satisfaction with cellulite treatment
- Change in the Hexsel CSS total score from screening visit

All endpoints will be summarized by treated region (buttock or thigh) and overall and by study day using appropriate descriptive statistics, unless specified otherwise (eg, by treatment course).

6.2.3. Observation Endpoints

Observational endpoints for treated quadrant in study EN3835-201 include:

- Change from baseline for PR-PCSS
- Proportions of composite responders defined as subjects with an improvement in severity from baseline of at least 2 (or 1) levels of severity in the CR-PCSS and an improvement in severity from baseline of at least 2 (or 1) levels of severity in the PR-PCSS

- Proportion at each level of improvement in the PR-PCSS:
  - Proportion of patient responders defined as subjects with an improvement in severity from baseline of at least 2 levels on the PR-PCSS
  - Proportion of patient responders defined as subjects with an improvement in severity from baseline of at least 1 level on the PR-PCSS
- Change from baseline for CR-PCSS
- Proportion at each level of improvement in the CR-PCSS:
  - Proportion of Investigator responders defined as subjects with an improvement in severity from baseline of at least 2 levels on the CR-PCSS (Investigator rated)
  - Proportion of Investigator responders defined as subjects with an improvement in severity from baseline of at least 1 level on the CR-PCSS (Investigator rated)
- Proportion of responders at each level of the subject satisfaction at Day 360
- Hexsel CSS total score changed from the study EN3835-201 baseline at Day 71 of study EN3835-201 and Day 360 or Day 360 Beyond long-term durability visits.

These endpoints will be summarized by treatment groups assigned in study EN3835-201 and treated region (buttock or thigh) and overall and by study day using appropriate descriptive statistics.

6.3. Durability of Treatment Effect

The durability of treatment effect will be accessed based on the longitudinal responses of cellulites assessments of CR-PCSS and PR-PCSS. The number and percentage of responders at each level (ie, 1 level or 2 levels improvements) for CR-PCSS, PR-PCSS and their combinations (ie, composite score, 1 level or 2 levels improvements for both scores) associated with treated quadrants will be summarized by study day. The treatment failure is defined as active responders whose CR-PCSS and PR-PCSS return to the baseline or worse in an EN3835-treated quadrant during a certain follow-up period. The number and percentage will be summarized by study day, ie, Day 180, Day 360, Day 540, and Day 720.

Since there are 2 groups of responders, one group was subjects who were treated with EN3835 in the double-blind EN3835-201 study and followed up in the current EN3835-202 study up to 2 years. The durability analysis described above for this group will be based on the durability population in double-blind treated subjects. The other group will be subjects who will be treated with EN3835 and then followed up to 1 year in the current EN3835-202 study. The durability analysis for this group will be based on the durability population in open-label treated subjects.

7. SAFETY ANALYSES

The following variables are safety endpoints.

- AEs

- Injection site reactions/local tolerability in selected quadrant (through subject and Investigator reporting)
- Study drug exposure and compliance
- Prior and concomitant medications
- Vital signs
- Laboratory testing
- Immunogenicity data

7.1. Prior, Concomitant, and Follow-up Medications

The World Health Organization (WHO) Drug Dictionary (Version 10MAR2016) will be used to classify prior and concomitant medications by therapeutic class. Prior medication will be defined as any medication with a start date prior to the first treatment start date in study EN3835-202. Concomitant medication is defined as any medication with a start date on or after the first treatment start date in study EN3835-202 and on or before the last dose date. If the medication starts before the first treatment start date in study EN3835-202 and stops on or after the first treatment start date in study EN3835-202, it will be considered as both prior and concomitant medication. If a medication has partial or missing start date and cannot be determined if it is a prior medication based on the start date, it will be considered as a prior medication. If a medication has partial or missing end date and cannot be determined if it is a concomitant medication based on start and end date, it will be considered as a concomitant medication. Any medications started after the last dose date of study drug will be considered as follow-up medications.

Prior, concomitant, and follow-up medication use will be summarized descriptively by the number and percentage of subjects receiving each medication within each therapeutic class. Multiple use of the same medication by a subject will be counted only once. Tables will be sorted by class and preferred term in decreasing frequency of the number of subjects.

7.2. Study Drug Exposure

For those subjects that elect, are eligible, and do receive treatment in study EN3835-202, the number of injections in each treatment session and the reason for the treatment session not done will be summarized by treatment region and overall using appropriate descriptive statistics. If a subject receives more than 1 treatment course in study EN3835-202, each treatment course will be summarized independently.

7.3. Treatment Administration and Compliance

All doses are administered while the subjects are at the investigational site. Any dose that was not administered per protocol will be recorded as a protocol deviation by the Investigator. The number and percentage of subjects treated in each quadrant will be presented in the summary table. The number of injections, number of dimples treated as well as average number of injections per dimple will be tabulated for each treatment session by treatment course and by treatment region. The number of subjects that received 12 injections for all treatment sessions as

well as the number of subjects that didn't receive 12 injections for all treatment sessions will be tabulated by treatment region. Subjects with protocol deviation will be listed. In addition, subjects who did not receive 3 treatment sessions and subjects who didn't receive 12 injections at a treatment session will also be listed separately.

7.4. Adverse Events

Treatment-emergent adverse events (TEAEs) is defined as any AE with onset date on or after the treatment start date in each treatment course in study EN3835-202. TEAEs are defined within each treatment course in study EN3835-202. AEs with missing or partial onset date and cannot be determined in which treatment course it occurred with its onset and end dates will be considered as TEAEs in treatment course 1. AEs with missing or partial onset date and cannot be determined in which treatment session it occurred with its onset and end dates will be considered as earliest treatment course and earliest treatment session possible.

Treatment-related adverse events are TEAEs with a relationship to study medication of possible, probable, or missing.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 19.0.

Overall AE summaries for observation phase as well as overall TEAE summaries for treatment phase will be tabulated. Descriptive statistics (the number and percentage) for subjects reporting AEs, TEAEs, and Adverse Events of Special Interest (AESI) will be tabulated by system organ class (SOC) and preferred term (PT); by SOC, PT, and severity; and by SOC, PT, severity and relationship to study drug. TEAE will also be summarized by SOC, PT, and treatment course. The duration of treatment related AE descriptive statistics will be summarized within each PT under each SOC. The TEAE tables will be sorted by SOC and PT in decreasing frequency of the number of subjects in the overall column.

If there are more than 1 AE coded to the same SOC or PT for the same subject under a certain column in the summary table, the subject will be counted only once for that SOC or PT under that column. If there are more than 1 AE coded to the same PT for the same subject, the subject will be counted only once for that PT using the most severe and most related occurrence for the summarization by severity and by relationship to the study drug. If there are more than 1 AE coded to the same PT, the longest AE will be used for that PT for the duration descriptive statistics.

Serious adverse events (SAEs) and AEs leading to premature discontinuation of study drug will be summarized. Listings will be presented for subjects with AEs, SAEs, AESI, AEs leading to discontinuation, and subjects who die (if any).

7.5. Vital Signs

Descriptive statistics for vital signs (body weight, body mass index [BMI], systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature) and their changes from baseline at each visit and at the end of treatment visit will be presented.

Vital sign values are potentially clinically important (PCI) if they meet both the observed value criteria and the change from baseline criteria. The criteria for PCI vital sign values are detailed

in Appendix A. The baseline in PCI rules refers to the latest vital sign assessment values before the first treatment in study EN3835-202.

A listing of all subjects with PCI vital signs will also be provided.

7.6. Clinical Laboratory Parameters

Table 6 lists all testing parameters for clinical laboratory in this study.

Descriptive statistics for clinical laboratory values in International System of Units (SI) and changes from baseline will be presented for each clinical laboratory parameter.

Table 6: Clinical Laboratory Parameters

Hematology	Clinical Chemistry	Urinalysis
Hematocrit Hemoglobin Red blood cell count Red blood cell morphology White blood cell count Neutrophils Lymphocytes Monocytes Basophils Eosinophils Platelets	Blood urea nitrogen Creatinine Total bilirubin Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Alkaline phosphatase Sodium Potassium Calcium Chloride Phosphate Serum bicarbonate Uric acid Total cholesterol Total protein Glucose Triglycerides Albumin	Specific gravity Ketones pH Protein Blood Glucose

The number and percentage of subjects with PCI post-baseline clinical laboratory values will be tabulated. The criteria for PCI laboratory values are detailed in Appendix A. A listing of all subjects with PCI laboratory values will also be provided.

7.7. Immunogenicity Analyses

Immunogenicity variables include anti-AUX-I/anti-AUX-II binding antibody results. Binding antibody levels will be determined from samples collected on Day 1 Day 71 and Day 360.

Descriptive statistics (percent of positive measurements and average antibody level) will be presented for anti-AUX-I and anti-AUX-II antibody levels at each time point by region treated, treatment course and overall. Average antibody levels will be summarized on logarithmically transposed titer values.

In addition, a subset of these immunogenicity samples will be analyzed for neutralizing antibodies by calculating the frequency count of the positive samples and the negative samples and the percentage of samples in each category.

8. HANDLING OF MISSING DATA

8.1. Handling Missing Data on Efficacy Variable

Subjects may have missing data on observational visits at Day 90, Day 180, Day 270, Day 360, and some long-term durability visits, Day 450, Day 540, Day 630 and Day 720. The backward imputation method will be utilized for the values of CR-PCSS and PR-PCSS. For instance, if a subject missed Day 90, Day 180 visits, but he/she has values at Day 270. Then the values at Day 270 will be imputed for the values at Day 180, and Day 90 visits.

No imputation will be applied to other cellulite assessments

8.2. Handling Partial or Missing Dates on AE, CM, and MH

Partial or complete missing date for AEs, concomitant medication (CM), and medical history (MH) will not be imputed. TEAE and prior and concomitant medication will be determined by using available date information. If available date information cannot determine, refer to section 7.1 for prior and concomitant medication, section 7.4 for TEAE.

9. CHANGES TO PLANNED ANALYSES

The EN3835-202 protocol [Section 17.2] defines the 4 different cohorts and states all efficacy and safety analyses will be done within the classified cohort. In this statistical analysis plan, the efficacy and safety analyses are summarized by different phases (observation phase, treatment phase, long-term durability visits) and populations (observation population, safety population, effectiveness population, and durability population) instead.

The EN3835-202 protocol [Section 17.2.1] defines the observational population as including all subjects rolled over from the EN3835-201 study who do not receive any treatment in the current study. This population is renamed to “Observation Population” for this document, as described in section 2. It is defined as: The observation population includes all subjects rolled over from the EN3835-201 study. The cellulite assessment evaluations and safety analyses for the data collected from Screening A to Day 360 will be based on this population. This change will allow the data observed during observation phase to be summarized under this new population.

APPENDIX A. PCI CRITERIA

Laboratory Values

Test	Low	High
Platelets (10^9/L)	≤100	≥650
Hemoglobin (g/L)	≤100	≥190
Hematocrit	≤0.3	≥0.6
ALT	---	≥3 × ULN
AST	---	≥3 × ULN
Creatinine (µmol/L)	---	≥300
BUN (mmol/L)	---	≥12

Vital Signs

Test	Low	High
Systolic Blood Pressure	≤90 mmHg and decrease ≥20 mmHg from baseline	≥180 mmHg and increase ≥20 mmHg from baseline
Diastolic Blood Pressure	≤50 mmHg and decrease ≥15 mmHg from baseline	≥105 mmHg and increase ≥15 mmHg from baseline
Pulse Rate	≤50 bpm and decrease ≥15 bpm from baseline	≥120 bpm and increase ≥15 bpm from baseline
Respiratory Rate	≤8 brpm and decrease ≥7 brpm from baseline	≥25 brpm and increase ≥7 brpm from baseline
Temperature	---	≥38.3°C and increase ≥1.1°C from baseline