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

EN3835

EN3835-303

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF EN3835 IN THE TREATMENT OF EDEMATOUS FIBROSCLEROTIC PANNICULOPATHY

IND 110077

NCT ID: NCT03446781

Amendment 3

Date:

Original Protocol: September 27, 2017

Amendment 1: December 19, 2017

Amendment 2: January 18, 2018

Amendment 3: June 5, 2018

Auxilium Pharmaceuticals, Inc. (Auxilium) was acquired by Endo International plc. in January 2015. The sponsor of the application remains as Auxilium Pharmaceuticals, LLC, 1400 Atwater Drive, Malvern, PA; however, Endo Pharmaceuticals Inc. is authorized to act and to communicate on behalf of Auxilium.

Confidentiality Statement

2. SUMMARY OF CHANGES

EN3835-303 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 3 was incorporated into the protocol on June 5, 2018. The major reasons for this amendment are clarification of the use of one of the cellulite assessments, additional subject and investigator training requirements, and clarification of the Per Protocol population exclusions.

Section	Original Text	Revised Text
3 Sponsor Contact Information	[redacted]	[redacted]
4 Synopsis, Statistical Methods, Analysis Populations	Per-Protocol population: The Per-Protocol population is defined as those mITT subjects who do not have any major deviations.	Per-Protocol (PP) population: The PP population is defined as the mITT subjects without any of the following: - Placebo randomized subject who receives EN3835 treatment. - EN3835 randomized subject who receives placebo treatment only throughout study. - Any subject who uses protocol-prohibited medications. - Subject missing PR-PCSS and/or CR-PCSS assessment at Day 71. - Subject with a buttock not receiving all three treatment sessions without medical reasons (e.g., adverse events or CR-PCSS. rated as zero (0)). - Subject who did not meet all inclusion and exclusion criteria.
13.1.2 Subject and Investigator Assessments	Added text	At each visit prior to the subject assessments being completed, subjects will watch an ePRO and scale tutorial video and instructions. The site will document subject review of the training (video and instructions) in source documentation.
13.1.2.4 Subject Satisfaction with Cellulite Treatment Assessment	At the Day 71 visit, subjects will be instructed to answer a question related to their treated buttocks.	At the Day 71 visit, subjects will be instructed to answer a question related to their treated buttocks while viewing digital images of their buttocks.
13.1.2.7 Investigator Global Aesthetic Improvement Scale (I-GAIS)	Added text	Investigators will be trained by Endo or their designee on the use of the I-GAIS prior to assessing any subjects. At each visit, the Investigator may review the training and use material for the I-GAIS.

Section	Original Text	Revised Text
17.2.4 Per-Protocol (PP) Population	The PP population is defined as the mITT subjects without any of the following : • Placebo-assigned subject receives EN3835 treatment • EN3835-assigned subject receives placebo treatment only throughout study • Any subject receives protocol-prohibited medications • Subject lacking PR-PCSS and/or CR-PCSS assessment at Day 71 • Any major protocol deviation that is deemed as impact subject efficacy	The PP population is defined as the mITT subjects without any of the following : • Placebo randomized subject who receives EN3835 treatment. • EN3835 randomized subject who receives placebo treatment only throughout study. • Any subject who uses protocol-prohibited medications. • Subject missing PR-PCSS and/or CR-PCSS assessment at Day 71. • Subject with a buttock not receiving all three treatment sessions without medical reasons (e.g., adverse events or CR-PCSS rated as zero (0)). • Subject who did not meet all inclusion and exclusion criteria.

Amendment 2 was incorporated into the protocol on January 18, 2018. The major reasons for this amendment are revising the primary efficacy variable from at least one buttock to a randomly selected target buttock, revising key secondary endpoints, and adding an additional efficacy assessment.

Section	Original Text	Revised Text
4 Synopsis, Study Period	Estimated date first subject enrolled: Feb-2018 Estimated date last subject completed: Sep-2018	Estimated date first subject enrolled: Feb-2018 Estimated date last subject completed: Oct-2018
4 Synopsis, Study Design	Added text	Of the two assigned eligible buttocks, one buttock will be randomly selected as the target buttock for the primary efficacy endpoint. The other (remaining) buttock will be considered the non-target buttock. Subjects, investigators, site personnel, and Endo personnel will be blinded to the identification of the target and the non-target buttocks.
	At Day 1, the subject will complete a Patient Reported Cellulite Impact Scale (PR-CIS) assessment.	At Day 1, the subject will complete a Patient Reported Cellulite Impact Scale (PR-CIS) assessment and a Subject Self-Rating Scale (SSRS) assessment.
4 Synopsis, Diagnosis and Inclusion/Exclusion Criteria, Exclusion Criteria	13. Was a subject in a previous cellulite clinical trial of collagenase clostridium histolyticum (CCH): AUX-CC-830, AUX-CC-831, EN3835-102, EN3835-104, EN3835-201, and/or EN3835-202	13 Was a subject in a previous cellulite clinical trial of collagenase clostridium histolyticum (CCH): AUX-CC-830, AUX-CC-831, EN3835-102, EN3835-104, EN3835-201, EN3835-202, and/or EN3835-205

Section	Original Text	Revised Text
4 Synopsis, Criteria for Evaluation, Efficacy	• Subject using PR-PCSS while viewing digital image of the left buttock: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the left buttock • Subject using PR-PCSS while viewing digital image of the right buttock: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the right buttock • Investigator using the CR-PCSS by live assessment: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the left buttock • Investigator using the CR-PCSS by live assessment: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the right buttock • Investigator Global Aesthetic Improvement Scale (I-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the left buttock • Investigator Global Aesthetic Improvement Scale (I-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the right buttock • Subject Global Aesthetic Improvement Scale (S-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the left buttock • Subject Global Aesthetic Improvement Scale (S-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the right buttock • Patient Reported Cellulite Impact Scale (PR-CIS): 6 questions with responses to each question consisting of a numerical rating scale (NRS) ranging from 0 (Not at all) to 10 (Extremely) • Subject satisfaction with cellulite treatment assessment: 5-level scale ranging from 2 (very satisfied) to −2 (very dissatisfied) (Day 71) for both left and right buttocks	• Subject using PR-PCSS while viewing digital image of the target buttock: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the target buttock • Subject using PR-PCSS while viewing digital image of the non-target buttock: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the non-target buttock • Investigator using the CR-PCSS by live assessment: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the target buttock • Investigator using the CR-PCSS by live assessment: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the non-target buttock • Investigator Global Aesthetic Improvement Scale (I-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the target buttock • Investigator Global Aesthetic Improvement Scale (I-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the non-target buttock • Subject Global Aesthetic Improvement Scale (S-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the target buttock • Subject Global Aesthetic Improvement Scale (S-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the non-target buttock • Patient Reported Cellulite Impact Scale (PR-CIS): 6 questions with responses to each question consisting of a numerical rating scale (NRS) ranging from 0 (Not at all) to 10 (Extremely) • Subject Self-Rating Scale (SSRS): 7-level scale ranging from 0 (extremely dissatisfied) to 6 (extremely satisfied) (Day 1 (Baseline) and Day 71)

Section	Original Text	Revised Text
		• Subject satisfaction with cellulite treatment assessment: 5-level scale ranging from 2 (very satisfied) to −2 (very dissatisfied) (Day 71) for both left and right buttocks
4 Synopsis, Criteria for Evaluation, Safety	• Adverse events (AEs) (including those of special interest (AESI); which are adverse events such as bruising, ecchymosis, hematomas, and contusions that occur remote to the site of drug administration, or any hypersensitivity reactions, including anaphylaxis)	• Adverse events (AEs) (including those of special interest (AESI); which are AEs such as bruising, ecchymosis, hematomas, and contusions that occur remote to the site of drug administration, or any hypersensitivity reactions, including anaphylaxis; and local AEs associated with the injection site, including bruising, pain, nodules/mass, ulceration, erythema, pruritus, swelling, and/or induration)
4 Synopsis, Statistical Methods	The primary endpoint is the proportion of 2-level composite responders at Day 71 defined as subjects with at least one of two treated buttocks with: • an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator, and • an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS as assessed by the subject while viewing the digital image of the same buttock. A subject will be considered a responder if these criteria are met in either the left buttock or right buttock or both buttocks in that subject.	The primary endpoint is the proportion of 2-level composite responders at Day 71 defined as subjects with: • an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator of the target buttock, and • an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS as assessed by the subject while viewing the digital image of the target buttock. A subject will be considered a responder if these criteria are met in the randomized target buttock of that subject.
4 Synopsis, Statistical Methods, Sample Size Consideration	The sample size calculation was based on the following assumptions: [redacted] (Odds ratio≥4.4) of the right treated buttocks; 3) treatment effect of at least 12% of composite responders with an improvement of at least 2 levels on both the PR-PCSS and the CR-PCSS for at least one treated buttock; 4) Fisher exact test; 5) type I error of 0.05; 6) a power of at least 90%; and 7) dropout rate of approximately 10%.	The sample size calculation was based on the following assumptions: [redacted] 2) Fisher exact test; 3) type I error of 0.05; 4) power of at least 90%; and 5) dropout rate of approximately 10%.
	This sample size will also provide >90% power with type 1 error of 0.025 to detect 1-level responder rate difference for buttocks using the PR-PCSS of 72% in the EN3835 group and 48% in the placebo group as well as 1-level responder rate difference using the S-GAIS of 75% in the EN3835 group and 39% in the placebo group, which were estimated from the EN3835-201 study.	This sample size will also provide >90% power with type 1 error of 0.05 to detect the treatment difference for all the key secondary endpoints based on previous study results.

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4 Synopsis, Statistical Methods, Analyses, Analyses of Primary Endpoint	The primary endpoint is the proportion of 2-level composite responders at Day 71 defined as subjects with at least one of two treated buttocks with: • an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator, and • an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS as assessed by the subject while viewing the digital image of the same buttock. A subject will be considered a responder if these criteria are met in the left buttock or right buttock or both buttocks in that subject.	The primary endpoint is the proportion of 2-level composite responders at Day 71 defined as subjects with: • an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator of the target buttock, and • an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS as assessed by the subject while viewing the digital image of the target buttock. A subject will be considered a responder if these criteria are met in the randomized target buttock of that subject.
4 Synopsis, Statistical Methods, Analyses, Analyses of Key Secondary Endpoints	There will be 4 key secondary endpoints grouped as two families of 2 endpoints per family analyzed in a hierarchical order. • Family #1 – two endpoints: − Proportion of 1-level PR-PCSS responders defined as subjects with ≥1-level improvement in PR-PCSS severity rating of left buttock at Day 71 compared to Day 1 − Proportion of 1-level PR-PCSS responders defined as subjects with ≥1-level improvement in PR-PCSS severity rating of right buttock at Day 71 compared to Day 1 • Family #2 – two endpoints: − Proportion of 1-level S-GAIS responders defined as subjects with ≥1-level improvement (improved, much improved or very much improved) in the S-GAIS assessment of left buttock at Day 71 − Proportion of 1-level S-GAIS responders defined as subjects with ≥1-level improvement (improved, much improved or very much improved) in the S-GAIS assessment of right buttock at Day 71	There will be 8 key secondary endpoints grouped as three families of 2-4 endpoints per family analyzed in hierarchical order. • Family #1 – four endpoints: − Proportion of 1-level PR-PCSS responders defined as subjects with ≥1-level improvement in PR-PCSS severity rating of the target buttock at Day 71 compared to Day 1 − Proportion of 2-level PR-PCSS responders defined as subjects with ≥2-level improvement in PR-PCSS severity rating of the target buttock at Day 71 compared to Day 1 − Proportion of 1-level composite responders of the target buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of the target buttock) at Day 71 compared to Day 1 − Proportion of 2-level composite responders of the non-target buttock at Day 71 compared to Day 1 • Family #2 – two endpoints: − Proportion of 1-level SSRS responders defined as subjects who were at least slightly satisfied at Day 71 (SSRS rating ≥ 4) − Change from baseline (Day1) of the PR-CIS at Day 71

Section	Original Text	Revised Text
		• Family #3 – two endpoints: − Proportion of 1-level S-GAIS responders defined as subjects with ≥1-level improvement (improved, much improved or very much improved) in the S-GAIS assessment of the target buttock at Day 71 − Proportion of 2-level S-GAIS responders defined as subjects with ≥2-level improvement (much improved or very much improved) in the S-GAIS assessment of the target buttock at Day 71
	The family #1 key secondary efficacy analyses will be performed only if the primary efficacy analysis is significant at a significance level of $p \leq 0.05$ (gatekeeping strategy). Similarly, family #2 key secondary efficacy analyses will be performed only if at least one of the key secondary efficacy endpoints of family #1 is significant at a significance level of $p \leq 0.025$ (parallel gatekeeping strategy)	The family #1 key secondary efficacy analyses will be performed only if the primary efficacy analysis is significant at a significance level of $p \leq 0.05$ (gatekeeping strategy). Similarly, family #2 key secondary efficacy analyses will be performed only if at least one of the key secondary efficacy endpoints of family #1 is significant at a significance level of $p \leq 0.0125$ and family #3 key secondary efficacy analyses will be performed only if at least one of the key secondary efficacy endpoints of family #2 is significant (parallel gatekeeping strategy).
4 Synopsis, Statistical Methods, Analysis, Supportive Endpoints	• Proportion of 2-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS) of the left buttock (Days 22, 43, and 71) • Proportion of 2-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS) of the right buttock (Days 22, 43, and 71) • Proportion of 1-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS) of the left buttock (Days 22, 43, and 71) • Proportion of 1-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS) of the right buttock (Days 22, 43, and 71) • Proportion of 2-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject.	• Proportion of 2-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS) of the target buttock (Days 22, 43, and 71) • Proportion of 2-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS) of the non-target buttock (Days 22, 43, and 71) • Proportion of 1-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS) of the target buttock (Days 22, 43, and 71) • Proportion of 1-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS) of the non-target buttock (Days 22, 43, and 71) • Proportion of 2-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject.

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	• Proportion of 1-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject. • Proportion of 2-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks. • Proportion of 1-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks. • Proportion of 2-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS) of the left buttock (Days 22, 43, and 71) • Proportion of 2-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS) of the right buttock (Days 22, 43, and 71) • Proportion of 1-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS) of the left buttock (Days 22, 43, and 71) • Proportion of 1-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS) of the right buttock (Days 22, 43, and 71) • Proportion of 2-level CR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject • Proportion of 1-level CR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject	• Proportion of 1-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject. • Proportion of 2-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks. • Proportion of 1-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks. • Proportion of 2-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS) of the target buttock (Days 22, 43, and 71) • Proportion of 2-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS) of the non-target buttock (Days 22, 43, and 71) • Proportion of 1-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS) of the target buttock (Days 22, 43, and 71) • Proportion of 1-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS) of the non-target buttock (Days 22, 43, and 71) • Proportion of 2-level CR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject • Proportion of 1-level CR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject

Section	Original Text	Revised Text
	• Proportion of 2-level CR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks • Proportion of 1-level CR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks • Proportion of 1-level composite responders of the left buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the left buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same left buttock) (Days 22, 43, and 71) • Proportion of 1-level composite responders of the right buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the right buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same right buttock) (Days 22, 43, and 71) • Proportion of 1-level composite responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject. • Proportion of 1-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks. • Proportion of 2-level composite responders of the left buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the left buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same left buttock) (Days 22, 43, and 71)	• Proportion of 2-level CR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks • Proportion of 1-level CR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks • Proportion of 1-level composite responders of the target buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same target buttock) (Days 22, 43, and 71) • Proportion of 1-level composite responders of the non-target buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the non-target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same non-target buttock) (Days 22, 43, and 71) • Proportion of 1-level composite responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject. • Proportion of 1-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks.

Section	Original Text	Revised Text
	• Proportion of 2-level composite responders of the right buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the right buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same right buttock) (Days 22, 43, and 71) • Proportion of 2-level composite responders of at least one of two buttocks (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject. • Proportion of 2-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks. • Proportion of subjects at each level of the S-GAIS of the left buttock (Days 22, 43, and 71) • Proportion of subjects at each level of the S-GAIS of the right buttock (Days 22, 43, and 71) • Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S- GAIS of the left buttock (Days 22, 43, and 71) • Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S- GAIS of the right buttock (Days 22, 43, and 71) • Proportion 1-level S-GAIS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject. • Proportion of 1-level S-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks. • Proportion of subjects at each level of the I-GAIS of the left buttock (Days 22, 43, and 71) • Proportion of subjects at each level of the I-GAIS of the right buttock (Days 22, 43, and 71)	• Proportion of 2-level composite responders of the target buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same target buttock) (Days 22, 43, and 71) • Proportion of 2-level composite responders of the non-target buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the non-target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same non-target buttock) (Days 22, 43, and 71) • Proportion of 2-level composite responders of at least one of two buttocks (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject. • Proportion of 2-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks. • Proportion of subjects at each level of the S-GAIS of the target buttock (Days 22, 43, and 71) • Proportion of subjects at each level of the S-GAIS of the non-target buttock (Days 22, 43, and 71) • Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S-GAIS of the target buttock (Days 22, 43, and 71) • Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S-GAIS of the non-target buttock (Days 22, 43, and 71) • Proportion 1-level S-GAIS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject.

[redacted]

Section	Original Text	Revised Text
	• Proportion of 1-level I-GAIS responders (defined as subjects with a response of at least 1 (improved) in the Investigator GAIS assessment) of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject. • Proportion of 1-level I-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks. • Change from baseline (Day 1) of the PR-CIS total score at Day 71 • Change from baseline (Day 1) of the abbreviated PR-CIS score at Day 71 • Proportion of subjects with a change from baseline (Day1) of the PR-CIS ≥12 at Day 71 • Proportion of subjects with a change from baseline (Day 1) of the abbreviated PR-CIS ≥10 at Day 71 • Proportion of subjects at each level of the subject satisfaction with cellulite treatment (Day 71) • Proportion of satisfied responders (defined as subjects with a response of at least 1 (ie, 1 Satisfied or 2-Very Satisfied) in the subject satisfaction with cellulite treatment assessment (Day 71)	• Proportion of 1-level S-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks. • Proportion of subjects at each level of the I-GAIS of the target buttock (Days 22, 43, and 71) • Proportion of subjects at each level of the I-GAIS of the non-target buttock (Days 22, 43, and 71) • Proportion of 1-level I-GAIS responders defined as subjects with a response of at least 1 (improved) in the I-GAIS of the target buttock (Days 22, 43, and 71) • Proportion of 1-level I-GAIS responders defined as subjects with a response of at least 1 (improved) in the I-GAIS of the non-target buttock (Days 22, 43, and 71) • Proportion of 1-level I-GAIS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject. • Proportion of 1-level I-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks. • Change from baseline (Day 1) of the PR-CIS score at Day 71 • Change from baseline (Day 1) of the abbreviated PR-CIS score at Day 71 • Proportion of subjects with a change from baseline (Day1) of the PR-CIS ≥12 at Day 71 • Proportion of subjects with a change from baseline (Day 1) of the abbreviated PR-CIS ≥10 at Day 71 • Proportion of subjects at each level of the subject self-rating scale (SSRS) (Day 1 (Baseline) and Day 71 • Proportion of 1-level SSRS responders defined as subjects who were at least slightly satisfied at Day 71 (SSRS rating ≥ 4) • Proportion of subjects at each level of the subject satisfaction with cellulite treatment assessment (Day 71)

Section	Original Text	Revised Text
		• Proportion of satisfied responders (defined as subjects with a response of at least 1 (ie, 1 Satisfied or 2-Very Satisfied) in the subject satisfaction with cellulite treatment assessment (Day 71)
5 Schedule of Events	Added table row	• Subject Self-Rating Scale (SSRS) Day 1 Treatment Visit 1: X[c] Day 71 (+ 5d)/End of Study/Early Termination: X
7 List of Abbreviations, Table 2: Abbreviations and Special Terms	Added table rows	SSRS: Subject Self-Rating Scale MI: Multiple imputation
11.2 Subject Exclusion Criteria	13. Was a subject in a previous cellulite clinical trial of CCH: AUX-CC-830, AUX-CC-831, EN3835-102, EN3835-104, EN3835-201, and/or EN3835-202	13. Was a subject in a previous cellulite clinical trial of CCH: AUX-CC-830, AUX-CC-831, EN3835-102, EN3835-104, EN3835-201, EN3835-202, and/or EN3835-205
12.4.1 Treatment Visit 1: Pre-Injection	Added text	6. Subjects will complete the SSRS assessment (section 13.1.2.5); the Investigator is blinded to these ratings
	Added text	9. Upon confirmation of two buttocks eligible for treatment (eligible criteria being each buttock have PR-PCSS and CR-PCSS scores of 3 or 4), the IWRS system will randomly assign one buttock as the target buttock in the background. Subjects, investigators, site personnel and Endo personnel will be blinded to target buttock assignment.
	8. Randomization of subjects with two buttocks eligible for treatment (eligible criteria being each buttock have PR-PCSS and CR-PCSS scores of 3 or 4) to treatment (section 12.10); obtain kit numbers of study treatment	10. Randomization of subjects with two buttocks eligible for treatment (eligible criteria being each buttock have PR-PCSS and CR-PCSS scores of 3 or 4) to treatment (section 12.10); obtain kit numbers of study treatment. Subjects, investigators, site personnel, and Endo personnel will be blinded to treatment assignment.
12.6 Day 71 (+5 days) / End of Study / Early Termination	6. Subject Cellulite Assessment of each of the two buttocks using the photographic image before marking dimples and injection sites (NOTE: complete subject cellulite assessments before Investigator cellulite assessments) using: a. Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) assessment (section 13.1.2.1) b. Subject Global Aesthetic Improvement Scale (S-GAIS) (section 13.1.2.2)	6. Subject Cellulite Assessment of each of the two buttocks using the photographic image before marking dimples and injection sites (NOTE: complete subject cellulite assessments before Investigator cellulite assessments) using: a. Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) assessment (section 13.1.2.1) b. Subject Global Aesthetic Improvement Scale (S-GAIS) (section 13.1.2.2)

Section	Original Text	Revised Text
	c. Patient Reported Cellulite Impact Scale (PR-CIS) assessment (section 13.1.2.3); note this assessment is of both left and right buttocks rather than each individual buttock d. Subject Satisfaction with Cellulite Treatment Assessment (section 13.1.2.4); note this assessment is of both left and right buttocks rather than each individual buttock	c. Patient Reported Cellulite Impact Scale (PR-CIS assessment (section 13.1.2.3); note this assessment is of both left and right buttocks rather than each individual buttock d. Subject Satisfaction with Cellulite Treatment Assessment (section 13.1.2.4); note this assessment is of both left and right buttocks rather than each individual buttock e. Subject Self-Rating Scale assessment (section 13.1.2.5); note this assessment is of both left and right buttocks rather than each individual buttock
12.10 Blinding and Randomization	On Day 1, if each of the buttocks again meet the criteria (3 or 4 on the PR-PCSS and CR-PCSS), the subject will be randomized to a treatment group.	On Day 1, if each of the buttocks (ie, both buttocks) again meet the criteria (3 or 4 on the PR-PCSS and CR-PCSS), one buttock will be randomly assigned by the IWRS as the target buttock for the primary efficacy endpoint. Subjects, investigators, site personnel and Endo personnel will be blinded to the identification of the target buttock. On Day 1, if each of the buttocks (ie, both buttocks) again meet the criteria (3 or 4 on the PR-PCSS and CR-PCSS), the subject will be randomized to a treatment group.
13.1.2.5 Subject Self-Rating Scale (SSRS)	Added section	13.1.2.5. Subject Self-Rating Scale (SSRS) The SSRS is a measure that assesses subject satisfaction with appearance in association with cellulite on the buttocks using whole numbers on a 7-level scale that ranges from 0 (extremely dissatisfied) to 6 (extremely satisfied). The patient will be asked to respond to the question related to the satisfaction with appearance of the cellulite on their buttocks on the appropriate visit day (note Day 71 question is different than Day 1 question). No photographs or reference to previous ratings or evaluations will be used. Subjects will be given a list of responses and they will provide a rating from those below that best represents their answer (Table 7); the list of responses is the same for Day 1 and for Day 71. On Day 1 (Baseline), subjects will be instructed to answer: *Considering your appearance in association with your cellulite on your buttocks, how satisfied do you feel with your appearance at the present time?*

<table>
<tr><th>Section</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td></td><td></td><td>On Day 71, subjects will be instructed to answer: Considering your appearance in association with your cellulite on your buttocks, how satisfied do you feel with your appearance at the present time whether or not in your judgment it is due entirely to treatment with EN3835?

This variable will 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 7: Subject Self-Rating Scale (SSRS)
<table>
<tr><th>Rating</th><th>Response Option</th></tr>
<tr><td>6</td><td>Extremely satisfied</td></tr>
<tr><td>5</td><td>Satisfied</td></tr>
<tr><td>4</td><td>Slightly satisfied</td></tr>
<tr><td>3</td><td>Neither satisfied nor dissatisfied</td></tr>
<tr><td>2</td><td>Slightly dissatisfied</td></tr>
<tr><td>1</td><td>Dissatisfied</td></tr>
<tr><td>0</td><td>Extremely dissatisfied</td></tr>
</table></td></tr>
<tr><td>14.6.1 Adverse Events of Special Interest</td><td>Adverse events such as bruising, ecchymosis, hematomas, and contusions that occur remote to the site of drug administration, or any hypersensitivity reactions, including anaphylaxis, will be recorded as an AE or SAE as appropriate (see section 14.1.1, Adverse Events or section 14.1.2, Serious Adverse Events).</td><td>Adverse events such as bruising, ecchymosis, hematomas, and contusions that occur remote to the site of drug administration, or any hypersensitivity reactions, including anaphylaxis, will be recorded and evaluated for seriousness and severity (see section 14.1.1, Adverse Events or section 14.1.2, Serious Adverse Events).

In addition, local AEs associated with the injection site, including bruising, pain, nodules/mass, ulceration, erythema, pruritus, swelling, and/or induration, will be recorded and evaluated for seriousness and severity (see as appropriate, section 14.1.1, Adverse Events or section 14.1.2, Serious Adverse Events)</td></tr>
<tr><td>17.1 Determination of Sample Size</td><td>The primary variable is the proportion of 2-level composite responders at Day 71 defined as subjects with at least one of two treated buttocks with:
an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator, and
an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS as assessed by the subject while viewing the digital image of the same buttock.</td><td>The primary variable is the proportion of 2-leve composite responders at Day 71 defined as subjects with:
an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator of the target buttock, and
an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS as assessed by the subject while viewing the digital image of the target buttock.</td></tr>
</table>

<table>
<tr><th>Section</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td></td><td>A subject will be considered a responder if these criteria are met in either the left buttock or right buttock or both buttocks in that subject. In other words, a subject will be considered a responder if she has an improvement of at least 2 levels on the PR-PCSS and an improvement of at least 2 levels on the CR-PCSS on that same buttock; that buttock could be the left buttock or right buttock or both buttocks.

The sample size calculation was based on the following assumptions: [redacted] 3) treatment effect of at least 12% of composite responders with an improvement of at least 2 levels on both the PR-PCSS and the CR-PCSS for at least one treated buttock; 4) Fisher exact test; 5) type I error of 0.05; 6) an power of at least 90%; and 7) dropout rate of approximate 10%.

This sample size will also provide >90% power with type 1 error of 0.025 to detect 1-level responder rate difference for buttocks using the PR-PCSS of 72% in the EN3835 group and 48% in the placebo group as well as 1-level responder rate difference using the S-GAIS of 75% in the EN3835 group and 39% in the placebo group, which were estimated from the EN3835-201 study.</td><td>A subject will be considered a responder if these criteria are met in the randomized target buttock of that subject

The sample size calculation was based on the following [redacted] 2) Fisher exact test; 3) type I error of 0.05; 4) power of at least 90%; and 5) dropout rate of approximate 10%.

This sample size will also provide >90% power with type 1 error of 0.05 to detect the treatment difference for all the key secondary endpoints based on previous study results.

Table 12: Previous Results as Basis for Sample Size
<table>
<tr><th>Efficacy Endpoint</th><th>EN3835</th><th>Placebo</th><th>Power</th></tr>
<tr><td>1-level PR-PCSS responders of target buttock</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>2-level PR-PCSS responders of target buttock</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>1-level composite responders of target buttock</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>2-level composite responders of non-target buttock</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Proportion of subjects with SSRS rating ≥ 4</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Change in PR-CIS Score, Mean (SD)</td><td>[redacted]</td><td colspan="2">[redacted]</td></tr>
<tr><td>1-level S-GAIS responders of target buttock</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>2-level S-GAIS responders of target buttock</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
[a] Rates are estimated based on the reported results from the pooled pivotal studies of a drug approved for an aesthetic indication.</td></tr>
</table>

Section	Original Text	Revised Text
17.2.3 Modified Intent-to-Treat (mITT) Population	The mITT population is defined as all intent-to-treat subjects with a baseline and at least 1 post-injection evaluation of both the Investigator CR-PCSS and subject PR-PCSS for both left and right buttocks..	The mITT population is defined as all intent-to-treat subjects with a baseline and at least 1 post-injection evaluation of both the Investigator CR-PCSS and subject PR-PCSS for both the target and non-target buttocks.
17.2.4 Per-Protocol (PP) Population	The per-protocol population is defined as the mITT subjects without any major protocol deviation that will impact the subject's efficacy and safety.	The per-protocol population is defined as the mITT subjects without any of the following: • Placebo-assigned subject receives EN3835 treatment • EN3835-assigned subject receives placebo treatment only throughout the study • Any subject receives protocol-prohibited medications • Subject lacking PR-PCSS and/or CR-PCSS assessment at Day 71 • Any major protocol deviation that is deemed as impacting subject efficacy
17.5 Efficacy Analysis	Changes in the PR-PCSS ratings and CR-PCSS ratings from baselines, S-GAIS scores, and I-GAIS scores will be analyzed using the Wilcoxon rank sum test.	Changes in the PR-PCSS ratings and CR-PCSS ratings from baselines, S-GAIS scores, I-GAIS scores, and SSRS scores will be analyzed using the Wilcoxon rank sum test. Changes in PR-CIS from baselines will be analyzed using an analysis of covariance (ANCOVA) adjusted for baseline values.
	Similarly family #2 key secondary efficacy analyses will be performed only if at least one of the key secondary efficacy endpoints of family #1 is significant ($p \leq 0.025$; parallel gatekeeping strategy	Similarly family #2 key secondary efficacy analyses will be performed only if at least one of the key secondary efficacy endpoints of family #1 is significant ($p \leq 0.0125$; parallel gatekeeping strategy) and family #3 key secondary efficacy analyses will be performed only if at least one of the key secondary efficacy endpoints of family #2 is significant (parallel gatekeeping strategy).
	Changes in the PR-PCSS ratings and CR-PCSS ratings from baselines, S-GAIS scores, and I-GAIS scores will be analyzed using the Wilcoxon rank sum test.	Changes in the PR-PCSS ratings and CR-PCSS ratings from baselines, S-GAIS scores, I-GAIS scores, and SSRS scores will be analyzed using the Wilcoxon rank sum test.
17.5.1 Primary Efficacy Variable	The primary efficacy variable is the proportion of 2-level composite responders at Day 71 defined as subjects with at least one of two treated buttocks with: • an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator, and • an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS by the subject while viewing the digital image of the same buttock.	The primary efficacy variable is the proportion of 2-level composite responders at Day 71 defined as subjects with: • an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator of the target buttock, and • an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS by the subject while viewing the digital image of the target buttock.

Section	Original Text	Revised Text
	A subject will be considered a responder if these criteria are met in either the left buttock or right buttock or both buttocks in that subject. In other words, a subject will be considered a responder if she has an improvement of at least 2 levels on the PR-PCSS and an improvement of at least 2 levels on the CR-PCSS on that same buttock; that buttock could be the left buttock or right buttock or both buttocks.	A subject will be considered a responder if these criteria are met in the randomized target buttock of that subject.
17.5.2.1 Key Secondary Variables	There will be 4 key secondary endpoints grouped in two families of 2 endpoints per family analyzed in a hierarchical order. • Family #1 – two endpoints: − Proportion of 1-level PR-PCSS responders defined as subjects with ≥1-level improvement in PR-PCSS severity rating of left buttock at Day 71 compared to Day 1 − Proportion of 1-level PR-PCSS responders defined as subjects with ≥1-level improvement in PR-PCSS severity rating of right buttock at Day 71 compared to Day 1 • Family #2 – two endpoints: − Proportion of 1-level S-GAIS responders defined as subjects with ≥1-level improvement (improved, much improved or very much improved) in the S- GAIS assessment of left buttock at Day 71 − Proportion of 1-level S-GAIS responders defined as subjects with ≥1-level improvement (improved, much improved or very much improved) in the S-GAIS assessment of right buttock at Day 71	There will be 8 key secondary endpoints grouped in three families of 2-4 endpoints per family analyzed in hierarchical order. • Family #1 – four endpoints: − Proportion of 1-level PR-PCSS responders defined as subjects with ≥1-level improvement in PR-PCSS severity rating of target buttock at Day 71 compared to Day 1 − Proportion of 2-level PR-PCSS responders defined as subjects with ≥2-level improvement in PR-PCSS severity rating of target buttock at Day 71 compared to Day 1 − Proportion of 1-level composite responders of target buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of the target buttock) at Day 71 compared to Day 1 − Proportion of 2-level composite responders of non-target buttock at Day 71 compared to Day 1 • Family #2 – two endpoints: − Proportion of 1-level SSRS responders defined as subjects who were at least slightly satisfied at Day 71 (SSRS rating ≥ 4) − Proportion of subjects with a change from baseline (Day1) of the PR-CIS ≥12 at Day 71 • Family #3 – two endpoints: − Proportion of 1-level S-GAIS responders defined as subjects with ≥1-level improvement (improved, much improved or very much improved) in the S-GAIS assessment of the target buttock at Day 71

Section	Original Text	Revised Text
		− Proportion of 2-level S-GAIS responders defined as subjects with ≥2-level improvement (much improved or very much improved) in the S-GAIS assessment of the target buttock at Day 71
	Added text	Sensitivity analyses for the key secondary endpoints will include: • ITT subjects with missing data handled by multiple imputation (MI) approach • ITT subjects with missing data handled by an LOCF approach • mITT subjects with missing data handled by an LOCF approach • Observed data only (no missing data handling) • Per-protocol (PP) subjects with missing data handled by an LOCF approach if 10% or more subjects are excluded in the PP population from mITT population
17.5.3.1 Supportive Variables	• Proportion of 2-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS of the left buttock (Days 22, 43, and 71) • Proportion of 2-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS of the right buttock (Days 22, 43, and 71) • Proportion of 1-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS of left buttock (Days 22, 43, and 71) • Proportion of 1-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS of right buttock (Days 22, 43, and 71) • Proportion of 2-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject. • Proportion of 1-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject.	• Proportion of 2-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS of the target buttock (Days 22, 43, and 71) • Proportion of 2-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS of the non-target buttock (Days 22, 43, and 71) • Proportion of 1-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS of the target buttock (Days 22, 43, and 71) • Proportion of 1-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS of the non-target buttock (Days 22, 43, and 71) • Proportion of 2-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject. • Proportion of 1-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject.

Section	Original Text	Revised Text
	• Proportion of 2-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks. • Proportion of 1-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks. • Proportion of 2-level CR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the left buttock (Days 22, 43, and 71) • Proportion of 2-level CR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the right buttock (Days 22, 43, and 71) • Proportion of 1-level CR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the left buttock (Days 22, 43, and 71) • Proportion of 1-level CR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the right buttock (Days 22, 43, and 71) • Proportion of 2-level CR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject. • Proportion of 1-level CR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject. • Proportion of 2-level CR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks.	• Proportion of 2-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks. • Proportion of 1-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks. • Proportion of 2-level CR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the target buttock (Days 22, 43, and 71) • Proportion of 2-level CR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the non-target buttock (Days 22, 43, and 71) • Proportion of 1-level CR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the target buttock (Days 22, 43, and 71) • Proportion of 1-level CR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the non-target buttock (Days 22, 43, and 71) • Proportion of 2-level CR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject. • Proportion of 1-level CR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject. • Proportion of 2-level CR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks.

[redacted]

Section	Original Text	Revised Text
	• Proportion of 1-level CR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks. • Proportion of 1-level composite responders of the left buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the left buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same left buttock) (Days 22, 43, and 71) • Proportion of 1-level composite responders of the right buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the right buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same right buttock) (Days 22, 43, and 71) • Proportion of 1-level composite responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject. • Proportion of 1-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks. • Proportion of 2-level composite responders of the left buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the left buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same left buttock) (Days 22, 43, and 71)	• Proportion of 1-level CR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks. • Proportion of 1-level composite responders of the target buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same target buttock) (Days 22, 43, and 71) • Proportion of 1-level composite responders of the non-target buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the non-target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same non-target buttock) (Days 22, 43, and 71) • Proportion of 1-level composite responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject. • Proportion of 1-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks. • Proportion of 2-level composite responders of the target buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same target buttock) (Days 22, 43, and 71)

Section	Original Text	Revised Text
	• Proportion of 2-level composite responders of the right buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the right buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same right buttock) (Days 22, 43, and 71) • Proportion of 2-level composite responders of at least one of two buttocks (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject. • Proportion of 2-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks. • Proportion of subjects at each level of the S-GAIS of the left buttock (Days 22, 43, and 71) • Proportion of subjects at each level of the S-GAIS of the right buttock (Days 22, 43, and 71) • Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S- GAIS of the left buttock (Days 22, 43, and 71) • Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S- GAIS of the right buttock (Days 22, 43, and 71) • Proportion 1-level S-GAIS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject. • Proportion of 1-level S-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks. • Proportion of subjects at each level of the I-GAIS of the left buttock (Days 22, 43, and 71)	• Proportion of 2-level composite responders of the non-target buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the non-target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same non-target buttock) (Days 22, 43, and 71) • Proportion of 2-level composite responders of at least one of two buttocks (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject. • Proportion of 2-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks. • Proportion of subjects at each level of the S-GAIS of the target buttock (Days 22, 43, and 71) • Proportion of subjects at each level of the S-GAIS of the non-target buttock (Days 22, 43, and 71) • Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S-GAIS of the target buttock (Days 22, 43, and 71) • Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S-GAIS of the non-target buttock (Days 22, 43, and 71) • Proportion 1-level S-GAIS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject. • Proportion of 1-level S-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target right buttocks. • Proportion of subjects at each level of the I-GAIS of the target buttock (Days 22, 43, and 71)

Section	Original Text	Revised Text
	• Proportion of subjects at each level of the I-GAIS of the right buttock (Days 22, 43, and 71) • Proportion of 1-level I-GAIS responders (defined as subjects with a response of at least 1 (improved) in the Investigator GAIS assessment) of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject. • Proportion of 1-level I-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks. • Change from baseline (Day 1) of the PR-CIS total score at Day 71 • Change from baseline (Day 1) of the abbreviated PR-CIS score at Day 71 • Proportion of subjects with a change from baseline (Day 1) of the PR-CIS ≥ 12 at Day 71 • Proportion of subjects with a change from baseline (Day 1) of the abbreviated PR-CIS ≥ 10 at Day 71 • Proportion of subjects at each level of the subject satisfaction with cellulite treatment (Day 71) • Proportion of satisfied responders (defined as subjects with a response of at least 1 (ie, 1 Satisfied or 2 Very Satisfied) in the subject satisfaction with cellulite treatment assessment (Day 71)	• Proportion of subjects at each level of the I-GAIS of the non-target buttock (Days 22, 43, and 71) • Proportion of 1-level I-GAIS responders defined as subjects with a response of at least 1 (improved) in the I-GAIS of the target buttock (Days 22, 43, and 71) • Proportion of 1-level I-GAIS responders defined as subjects with a response of at least 1 (improved) in the I-GAIS of the non-target buttock (Days 22, 43, and 71) • Proportion of 1-level I-GAIS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject. • Proportion of 1-level I-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks. • Change from baseline (Day 1) of the PR-CIS total score at Day 71 • Change from baseline (Day 1) of the abbreviated PR-CIS score at Day 71 • Proportion of subjects with a change from baseline (Day 1) of the PR-CIS ≥ 12 at Day 71 • Proportion of subjects with a change from baseline (Day 1) of the abbreviated PR-CIS ≥ 10 at Day 71 • Proportion of subjects at each level of the SSRS (Day 1 (Baseline) and Day 71) • Proportion of 1-level SSRS responders defined as subjects who were at least slightly satisfied at Day 71 (SSRS rating ≥ 4) • Proportion of subjects at each level of the subject satisfaction with cellulite treatment assessment (Day 71) • Proportion of satisfied responders (defined as subjects with a response of at least 1 (ie, 1 Satisfied or 2 Very Satisfied) in the subject satisfaction with cellulite treatment assessment (Day 71)

Section	Original Text	Revised Text
17.6.9 Other Safety Measurements	Not applicable.	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 treatment group. Average antibody levels will be summarized on logarithmically transposed titer values. In addition, by-treatment percentages of neutralizing anti-AUX-I and anti-AUX-II antibodies in a subset of subjects' samples [redacted]) will be summarized at Day 71.
18.2 Study Drug Packaging and Labeling	Each kit will contain one vial of EN3835 or placebo and sufficient sterile diluent to perform reconstitution of the one product vial.	Each kit will contain one vial of EN3835 or placebo and one vial of sterile diluent.
19.1 Source Documents	This study allows for direct data entry (DDE) for selected data points as outlined below: • PR-PCSS • CR-PCSS • S-GAIS • I-GAIS • PR-CIS • Subject Satisfaction with Cellulite Treatment Assessment	This study allows for direct data entry (DDE) for selected data points as outlined below: • PR-PCSS • CR-PCSS • S-GAIS • I-GAIS • PR-CIS • Subject Satisfaction with Cellulite Treatment Assessment • SSRS
27 References	11. Investigational Brochure: Collagenase Clostridium Histolyticum for Injection (AA4500/EN3835), Version 8.0. Endo Pharmaceuticals Inc.; July 2017.	11. Investigational Brochure: Collagenase Clostridium Histolyticum for Injection (AA4500/EN3835), Version 8.0. Endo Pharmaceuticals Inc.; July 2017.

Amendment 1 was incorporated into the protocol on December 19, 2017. The major reasons for this amendment were to add an additional efficacy assessment and to revise inclusion and exclusion criteria.

Section	Original Text	Revised Text
3 Sponsor Contact Information	C[redacted]	[redacted]
4 Synopsis, Study Period	Estimated date first subject enrolled: Jan-2018	Estimated date first subject enrolled: Feb-2018

Section	Original Text	Revised Text
4 Synopsis, Study Design	Subjects with 2 treatment areas (bilateral buttocks) (also referred to as quadrants) with moderate or severe levels of cellulite as independently assessed by the subject using the Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) and by the Investigator using the Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) and a Hexsel Cellulite Severity Scale no greater than 13 will be eligible.	Subjects with 2 treatment areas (bilateral buttocks) (also referred to as quadrants) with moderate or severe levels of cellulite as independently assessed by the subject using the Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) and by the Investigator using the Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) will be eligible.
	Add text	At Day 1, the subject will complete a Patient Reported Cellulite Impact Scale (PR-CIS) assessment.
4 Synopsis, Diagnosis and Inclusion/ Exclusion Criteria, Inclusion Criteria	3. At Screening visit, have 2 bilateral buttocks with each buttock having: 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	3. At Screening visit, have 2 bilateral buttocks with each buttock having: 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)
	4. At Day 1 visit, have 2 bilateral buttocks with each buttock having: 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	4. At Day 1visit, have 2 bilateral buttocks with each buttock having: 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)
4 Synopsis, Diagnosis and Inclusion/ Exclusion Criteria, Exclusion Criteria	2. Has any of the following local conditions in the areas to be treated: a. History of lower extremity thrombosis or post-thrombosis syndrome b. Vascular disorder (eg, varicose veins, telangiectasia) in area to be treated c. Inflammation or active infection d. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer e. Has a tattoo and/or a mole located within 2 cm of the site of injection	2. Has any of the following local conditions in the areas to be treated: a. History of lower extremity thrombosis or post-thrombosis syndrome b. Vascular disorder (eg, varicose veins, telangiectasia) in area to be treated c. Inflammation or active infection d. Severe skin laxity, flaccidity, and/or sagging e. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer f. Has a tattoo and/or a mole located within 2 cm of the site of injection
4 Synopsis, Criteria for Evaluation, Efficacy	Added text	• Patient Reported Cellulite Impact Scale: 6 questions with responses to each question consisting of a numerical rating scale (NRS) ranging from 0 (Not at all) to 10 (Extremely)

Section	Original Text	Revised Text
4 Synopsis, Statistical Methods, Analysis, Supportive Endpoints	Added text	• Change from baseline (Day 1) of the PR-CIS total score at Day 71 • Change from baseline (Day 1) of the abbreviated PR-CIS score at Day 71 • Proportion of subjects with a change from baseline (Day1) of the PR-CIS ≥12 at Day 71 • Proportion of subjects with a change from baseline (Day 1) of the abbreviated PR-CIS ≥10 at Day 71
5 Schedule of Events, Physical examination	Day -14 to -1 Screening: X Day 71 (+ 5d)/End of Study/Early Termination: X	Day -14 to -1 Screening: X
5 Schedule of Events, Subject cellulite assessments, Patient Reported Cellulite Impact Scale (PR-CIS)	Added table row	• Patient Reported Cellulite Impact Scale (PR-CIS) Day 1 Treatment Visit 1: X[c,g] Day 71 (+ 5d)/End of Study/Early Termination: X[g]
5 Schedule of Events, Investigator cellulite assessments, Hexsel Cellulite Severity Scale (CSS)	• Hexsel Cellulite Severity Scale (CSS) Day -14 to -1 Screening: X[b,i] Day 1 Treatment Visit 1: X[c,b,i]	Deleted table row
5 Schedule of Events, Table footnotes	[i] Initial Hexsel CSS at Screening must be ≤13 on each of 2 bilateral buttocks and the buttocks must again be ≤13 at Day 1 visit	Deleted text
	[j] Before randomization, each of the subject's buttocks must have ratings of 3 or 4 (moderate or severe) in both the CR-PCSS and PR-PCSS, and Hexsel CSS score ≤13.	[i] Before randomization, each of the subject's buttocks must have ratings of 3 or 4 (moderate or severe) in both the CR-PCSS and PR-PCSS.
7. List of Abbreviations, Table 2: Abbreviations and Special Terms	CSS: Cellulite severity scale	Deleted table row
	Added table row	PR-CIS: Patient Reported Cellulite Impact Scale
11.1 Subject Inclusion Criteria	3. At Screening visit, have 2 bilateral buttocks with each buttock having: 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	3. At Screening visit, have 2 bilateral buttocks with each buttock having: 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)

Section	Original Text	Revised Text
	4. At Day 1 visit, have 2 bilateral buttocks with each buttock having: 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	4. At Day 1 visit, have 2 bilateral buttocks with each buttock having: 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)
11.2 Subject Exclusion Criteria	2. Has any of the following local conditions in the areas to be treated: a. History of lower extremity thrombosis or post-thrombosis syndrome b. Vascular disorder (eg, varicose veins, telangiectasia) in area to be treated c. Inflammation or active infection d. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer e. Has a tattoo and/or a mole located within 2 cm of the site of injection	2. Has any of the following local conditions in the areas to be treated: a. History of lower extremity thrombosis or post-thrombosis syndrome b. Vascular disorder (eg, varicose veins, telangiectasia) in area to be treated c. Inflammation or active infection d. Severe skin laxity, flaccidity, and/or sagging e. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer f. Has a tattoo and/or a mole located within 2 cm of the site of injection
12.1.2.2 Screening Period (Day -14 to Day -1)	5. Prior to Investigator CR-PCSS or Hexsel CSS assessment, subjects will rate each of their two buttocks using the PR-PCSS while viewing their digital images (section 13.1.2.1); the Investigator is blinded to these scores	5. Prior to Investigator CR-PCSS assessment, subjects will rate each of their two buttocks using the PR-PCSS while viewing their digital images (section 13.1.2.1); the Investigator is blinded to these ratings
	6. After the subject has completed the PR-PCSS ratings, the Investigator will conduct live assessments of subject's cellulite severity of each of the two buttocks using the CR-PCSS (section 13.1.2.4); the subject is blinded to these ratings 7. After the Investigator has completed the CR-PCSS ratings, the Investigator will conduct live evaluation of each of the two buttocks using the Hexsel CSS; the subject is blinded to these ratings. The ratings from the PR-PCSS, CR-PCSS, and Hexsel CSS (section 13.1.2.6) will be used to assess initial eligibility of the buttocks for study entry	6. After the subject has completed the PR-PCSS ratings, the Investigator will conduct live assessments of subject's cellulite severity of each of the two buttocks using the CR-PCSS (section 13.1.2.5); the subject is blinded to these ratings. The ratings from the PR-PCSS and CR-PCSS will be used to assess initial eligibility of the buttocks for study entry
12.2 Selecting and Marking Dimples during Treatment Visits	The cellulite severity assessments using the PR-PCSS, CR-PCSS, and Hexsel CSS (note that the Hexsel CSS assessment is performed at Screening visit and Day 1 visit only) will be completed prior to marking dimples and injection sites.	The cellulite severity assessments using the PR-PCSS and CR-PCSS, will be completed prior to marking dimples and injection sites.

Section	Original Text	Revised Text
12.4.1 Treatment Visit 1: Pre-Injection	4. Subjects will rate each of their buttocks using the PR-PCSS (section 13.1.2.1); the Investigator is blinded to these scores	4. Subjects will rate each of their buttocks using the PR-PCSS (section 13.1.2.1); the Investigator is blinded to these ratings
	Added text	5. Subjects will complete the Patient Reported Cellulite Impact Scale assessment (PR-CIS; section 13.1.2.3): the Investigator is blinded to this rating
	5. The Investigator will conduct live assessments of subject's cellulite severity of each of the buttocks using the CR-PCSS (section 13.1.2.4); the subject is blinded to these ratings 6. The Investigator will conduct live cellulite evaluation of each of the buttocks using the Hexsel CSS. The ratings from the PR-PCSS, CR-PCSS and Hexsel CSS (section 13.1.2.6) will be used to assess eligibility for randomization	6. The Investigator will conduct live assessments of subject's cellulite severity of each of the buttocks using the CR-PCSS (section 13.1.2.5); the subject is blinded to these ratings. The ratings from the PR-PCSS and CR-PCSS will be used to assess eligibility for randomization
	7. Subjects with PR-PCSS or CR-PCSS ratings in either of the buttocks <3 or a Hexsel CSS total score in either of the buttocks greater than 13 (section 13.1.2.6) will be excluded from participation	7. Subjects with PR-PCSS or CR-PCSS ratings in either of the buttocks <3 will be excluded from participation
	8. Randomization of subjects with two buttocks eligible for treatment (eligible criteria being each buttock have PR-PCSS and CR-PCSS scores of 3 or 4 and a Hexsel CSS total score not greater than 13) to treatment (section 12.10); obtain kit numbers of study treatment	8. Randomization of subjects with two buttocks eligible for treatment (eligible criteria being each buttock have PR-PCSS and CR-PCSS scores of 3 or 4) to treatment (section 12.10); obtain kit numbers of study treatment
12.6 Day 71 (+5 days)/End of Study/Early Termination	6. Subject Cellulite Assessment of each of the two buttocks using the photographic image before marking dimples and injection sites (NOTE: complete subject cellulite assessments before Investigator cellulite assessments) using: a. Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) assessment (section 13.1.2.1) b. Subject Global Aesthetic Improvement Scale (S-GAIS) (section 13.1.2.2) c. Subject Satisfaction with Cellulite Treatment Assessment (section 13.1.2.3); note this assessment is of both left and right buttocks rather than each individual buttock	6. Subject Cellulite Assessment of each of the two buttocks using the photographic image before marking dimples and injection sites (NOTE: complete subject cellulite assessments before Investigator cellulite assessments) using: a. Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) assessment (section 13.1.2.1) b. Subject Global Aesthetic Improvement Scale (S-GAIS) (section 13.1.2.2) c. Patient Reported Cellulite Impact Scale (PR-CIS assessment (section 13.1.2.3); note this assessment is of both left and right buttocks rather than each individual buttock d. Subject Satisfaction with Cellulite Treatment Assessment (section 13.1.2.4); note this assessment is of both left and right buttocks rather than each individual buttock

Section	Original Text	Revised Text
12.10 Blinding and Random-ization	On Day 1, if each of the buttocks again meet the criteria (3 or 4 on the PR-PCSS and CR-PCSS and no greater than 13 on Hexsel CSS) the subject will be randomized to a treatment group.	On Day 1, if each of the buttocks again meet the criteria (3 or 4 on the PR-PCSS and CR-PCSS) the subject will be randomized to a treatment group.
13.1.2.3 Patient Reported Cellulite Impact Scale (PR-CIS)	Added section	13.1.2.3. Patient Reported Cellulite Impact Scale (PR-CIS) At the Day 1 visit and Day 71 visit, subjects will be instructed to answer 6 questions related to the areas selected for treatment on their buttocks on the Patient Reported Cellulite Impact Scale (Appendix D) while viewing digital images of their buttocks. The PR-CIS assesses the visual and emotional impact of cellulite (happy, bothered, self-conscious, embarrassed, looking older or looking overweight or out of shape) using a 6-question survey, with each question rated on a numerical rating scale from 0 (not at all) to 10 (extremely). This variable will 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.
13.1.2.4 Subject Satisfaction	Added text	This variable will 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.
13.1.2.6 Hexsel Cellulite Severity Scale	13.1.2.6. 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 8. The total score is the summation of all 5 features (Appendix D).	Deleted section and table

Section	Original Text	Revised Text
	The Investigator or qualified designee will independently use the Hexsel CSS to assess the severity of EFP in each of the two buttocks at the Screening visit and each of the two buttocks on Day 1 (Note: In this study, the Hexsel CSS is used exclusively for assessment of subject eligibility; it is not used as an efficacy assessment). 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 will 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]	
17.5 Efficacy Analyses	All supportive endpoints will be summarized as percentages.	All supportive endpoints will be summarized as subject counts and percentages for categorical data or n, mean, SD, median, minimum, and maximum for continuous data.
	Added text	Changes in PR-CIS from baselines will be analyzed using an analysis of covariance (ANCOVA) adjusted for baseline values
17.5.3.1 Supportive Variables	Added text	• Change from baseline (Day 1) of PR-CIS total score at Day 71 • Change from baseline (Day 1) of abbreviated PR-CIS score at Day 71 • Proportion of subjects with a change from baseline (Day 1) of PR-CIS ≥ 12 at Day 71 • Proportion of subjects with a change from baseline (Day 1) of abbreviated PR-CIS ≥ 10 at Day 71
19.1 Source Documents	This study allows for direct data entry (DDE) for selected data points as outlined below: • PR-PCSS • CR-PCSS • Hexsel CSS • S-GAIS • I-GAIS • Subject Satisfaction with Cellulite Treatment Assessment	This study allows for direct data entry (DDE) for selected data points as outlined below: • PR-PCSS • CR-PCSS • S-GAIS • I-GAIS • PR-CIS • Subject Satisfaction with Cellulite Treatment Assessment

Section	Original Text	Revised Text
27 References	12. Hexsel DM, Dal'Forno T, Hexsel CL. A validated photonumeric cellulite severity scale. *J Eur Acad Dermatol Venereol*. 2009;23(5):523-8. 13. Nürnberger F, Müller G. So-called cellulite: an invented disease. *J Dermatol Surg Oncol*. 1978;4(3):221-9.	Deleted text
APPENDIX D	APPENDIX D. HEXSEL DM, DAL'FORNO T, HEXSEL CL. A VALIDATED PHOTONUMERIC CELLULITE SEVERITY SCALE. *J EUR ACAD DERMATOL VENEREOL*. 2009;23(5):523-8 [Article]	APPENDIX D. PATIENT REPORTED CELLULITE IMPACT SCALE (PR-CIS) Please select the rating that best represents your answer on a scale of 0 to 10 with 0 representing "Not at all" and 10 representing "Extremely" while viewing digital images of your buttocks. Please answer each question. 1. Thinking about the areas selected for treatment, how happy are you with the appearance of your cellulite? [Scale] 2. Thinking about the areas selected for treatment, how bothered are you by the appearance of your cellulite? [Scale] 3. Thinking about the areas selected for treatment, how self-conscious are you about the appearance of your cellulite? [Scale] 4. Thinking about the areas selected for treatment, how embarrassed are you about the appearance of your cellulite? [Scale] 5. Thinking about the areas selected for treatment, how much older do you look because of your cellulite? [Scale] 6. Thinking about the areas selected for treatment, how overweight or out of shape do you look because of your cellulite? [Scale]
APPENDIX E. REFERENCE IMAGES FOR HEXSEL SEVERITY RATINGS	APPENDIX E. REFERENCE IMAGES FOR HEXSEL SEVERITY RATINGS The 2 images below are representative of a Hexsel score of 13, the maximum severity level to be included in the study. Subjects with cellulite severity that exceeds a Hexsel score of 13 should be excluded. [Image 1] [Image 2] The image below represents a Hexsel score >13, and depicts excessive skin laxity in the buttock and posterolateral thigh. Subjects with a Hexsel score >13 should be excluded from the study. [Image 3]	Deleted appendix and images

3. SPONSOR CONTACT INFORMATION

Table 1: Sponsor Contact Information

Role in Study	Name	Telephone and Email Address
Clinical Development Lead	[redacted]	Office: [redacted] Cell: [redacted] Email: [redacted]
Clinical Operations Lead	[redacted]	Office: [redacted] Email: [redacted]
Medical Monitor	[redacted]	Office: [redacted] Cell: [redacted] Email: [redacted]
SAE Reporting Pathway	Not Applicable	FAX: [redacted] Email: [redacted]

A list of other key study personnel and vendors will be provided 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 3, Randomized, Double-Blind, Placebo-Controlled Study of EN3835 in the Treatment of Edematous Fibrosclerotic Panniculopathy	
Lead Principal Investigator:	
Study Period: Estimated date first subject enrolled: Feb-2018 Estimated date last subject completed: Oct-2018	**Phase of Development**: 3
Objectives: To assess the efficacy and safety of EN3835 in the treatment of edematous fibrosclerotic panniculopathy (EFP), commonly known as cellulite, in adult women	
Study Design: This study is a Phase 3 randomized, double-blind, placebo-controlled study of the efficacy and safety of EN3835 in the treatment of EFP in adult women. Subjects will be screened for study eligibility within 14 days prior to enrolling in this study. Subjects with 2 treatment areas (bilateral buttocks) (also referred to as quadrants) with moderate or severe levels of cellulite as independently assessed by the subject using the Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) and by the Investigator using the Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) will be eligible. The eligibility of the buttocks will be confirmed on Day 1. Once the eligibility of the buttocks is confirmed, subjects will be randomly assigned to a treatment group (EN3835 0.84 mg per buttock or placebo) in a 1:1 ratio within an investigational site. Each subject will receive a treatment course which consists of up to 3 treatment visits (sessions), separated by 21 days (ie, Days 1, 22, and 43). Each treatment visit will consist of 12 injections (0.3 mL per injection of EN3835 0.07 mg/injection or placebo; 0.84 mg in 3.6 mL per buttock) in each of the two buttocks for a total volume of 7.2 mL (1.68 mg). Selection of dimples to be treated in the buttocks will be at the discretion of the Investigator. End of study will occur at study day 71. Of the two assigned eligible buttocks, one buttock will be randomly selected as the target buttock for the primary efficacy endpoint. The other (remaining) buttock will be considered the non-target buttock. Subjects, investigators, site personnel, and Endo personnel will be blinded to the identification of the target and non-target buttocks. At each treatment visit, each of the buttocks will be photographed before and after marking dimples and injection sites while the subject is in a consistent, standardized relaxed standing pose. The subject will assess the digital photographic image (pre-marking) of each of the buttocks using the PR-PCSS to determine the severity of EFP in each of the buttocks. In addition, the subject will evaluate each of the buttocks using a Subject Global Aesthetic Improvement Scale (S-GAIS). Subsequently, the Investigator will conduct live assessments of each buttock using the CR-PCSS. At Day 1, the subject will complete a Patient Reported Cellulite Impact Scale (PR-CIS) assessment and a Subject Self-Rating Scale (SSRS) assessment. The subject assessments will always be completed prior to and independently of the Investigator assessments at each treatment visit. In addition, the Investigator will assess each of the buttocks using an Investigator Global Aesthetic Improvement Scale (I-GAIS). All of the assessments must be done before the dimple marking.	

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At Day 71 (End of Study/Early Termination), photographs of each of the buttocks will be taken and evaluated by subject using the PR-PCSS. The Investigator will conduct live assessments of each of the buttocks using the CR-PCSS. Global assessment evaluations will be completed by both the subject and the Investigator.

Number of Subjects (Planned): 420

Study Center(s): Approximately 25 sites in United States

Diagnosis and Inclusion/Exclusion Criteria:

Inclusion Criteria:

1. Voluntarily sign and date an informed consent agreement
2. Be a female ≥18 years of age
3. At Screening visit, have 2 bilateral buttocks with each buttock having:
   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)
4. At Day 1 visit, have 2 bilateral buttocks with each buttock having:
   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)
5. Be willing to apply sunscreen to the buttocks before each exposure to the sun while participating in the study (ie, Screening 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
7. Have a negative serum pregnancy test at Screening and a negative urine pregnancy test before injection of study drug and be using a stable and effective contraception method (eg, abstinence, intrauterine device [IUD], hormonal [estrogen/progestin] contraceptives, or double barrier method) for at least 1 menstrual cycle prior to study enrollment and for the duration of the study; or be menopausal defined as 12 months of amenorrhea in the absence of other biological or physiological causes, as determined by the Investigator; or post-menopausal for at least 1 year; or be surgically sterile
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:

A subject will be excluded from study participation if she:

1. Has any of the following systemic conditions:
   a. Coagulation disorder
   b. Evidence or history of malignancy (other than excised basal-cell carcinoma) unless there has been no recurrence in at least 5 years
   c. History of keloidal scarring or abnormal wound healing

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d. Concurrent diseases or conditions that might interfere with the conduct of the study, confound the interpretation of the study results, or endanger the subject's well-being. Any questions about concurrent diseases should be discussed with the Medical Monitor
e. Evidence of clinically significant abnormalities on physical examination, vital signs, electrocardiogram (ECG), or clinical laboratory values

2. Has any of the following local conditions in the areas to be treated:
   a. History of lower extremity thrombosis or post-thrombosis syndrome
   b. Vascular disorder (eg, varicose veins, telangiectasia) in area to be treated
   c. Inflammation or active infection
   d. Severe skin laxity, flaccidity, and/or sagging
   e. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer
   f. Has a tattoo and/or a mole located within 2 cm of the site of injection
3. Requires the following concomitant medications before or during participation in the trial:
   a. Anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication (except for ≤150 mg aspirin daily) within 7 days before injection of study drug
4. Has used any of the following for the treatment of EFP on a buttock within the timelines identified below or intends to use any of the following at any time during the course of the study:
   a. Liposuction in a buttock during the 12-month period before injection of study drug
   b. Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; buttock implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision) within a buttock during the 12-month period before injection of study drug
   c. Any investigational treatment for EFP on a buttock during the 12-month period before injection of study drug
   d. Endermologie™ or similar treatments within a buttock during the 6-month period before injection of study drug
   e. Massage therapy within a buttock during the 3-month period before injection of study drug
   f. Creams (eg, Celluvera™, TriLastin®) and/or home therapies to prevent or mitigate EFP within a buttock during the 2-week period before injection of study drug
5. Is presently nursing or providing breast milk
6. Intends to become pregnant during the study
7. Intends to initiate an intensive sport or exercise program during the study
8. Intends to initiate a weight reduction program during the study
9. Intends to use tanning spray or tanning booths during the study
10. Has received an investigational drug or treatment within 30 days before injection of study drug
11. Has a known systemic allergy to collagenase or any other excipient of study drug
12. Has received any collagenase treatments at any time prior to treatment

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13. Was a subject in a previous cellulite clinical trial of collagenase clostridium histolyticum (CCH): AUX-CC-830, AUX-CC-831, EN3835-102, EN3835-104, EN3835-201, EN3835-202, and/or EN3835-205
14. Any other condition(s) that, in the Investigator's opinion, might indicate the subject to be unsuitable for the study

Investigational Product, Dosage and Mode of Administration: EN3835, 1.68 mg, subcutaneous. A dose of 0.84 mg of EN3835 per buttock will be administered as 12 subcutaneous injections (0.3-mL injection administered as three 0.1-mL aliquots per injection) in each of two buttocks for a total dose of 1.68 mg and a total volume of 7.2 mL (3.6 mL per buttock). Total number of injections will be 24 injections per treatment visit into the two buttocks. There will be 3 treatment visits at 21 days intervals, ie, treatments on Days 1, 22, and 43 will be administered.

Duration of Study: Approximately 84 days (includes screening phase)

Screening Phase: Up to 14 days

Criteria for Evaluation:

Efficacy:

- Subject using PR-PCSS while viewing digital image of the target buttock: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the target buttock
- Subject using PR-PCSS while viewing digital image of the non-target buttock: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the non-target buttock
- Investigator using the CR-PCSS by live assessment: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the target buttock
- Investigator using the CR-PCSS by live assessment: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the non-target buttock
- Investigator Global Aesthetic Improvement Scale (I-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the target buttock
- Investigator Global Aesthetic Improvement Scale (I-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the non-target buttock
- Subject Global Aesthetic Improvement Scale (S-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the target buttock
- Subject Global Aesthetic Improvement Scale (S-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the non-target buttock
- Patient Reported Cellulite Impact Scale (PR-CIS): 6 questions with responses to each question consisting of a numerical rating scale (NRS) ranging from 0 (Not at all) to 10 (Extremely

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- Subject Self-Rating Scale (SSRS): 7-level scale ranging from 0 (extremely dissatisfied) to 6 (extremely satisfied) (Day 1 (Baseline) and Day 71)
- Subject satisfaction with cellulite treatment assessment: 5-level scale ranging from 2 (very satisfied) to −2 (very dissatisfied) (Day 71) for both the target and non-target buttocks

Safety:

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

- Adverse events (AEs) (including those of special interest (AESI); which are AEs such as bruising, ecchymosis, hematomas, and contusions that occur remote to the site of drug administration, or any hypersensitivity reactions, including anaphylaxis; and local AEs associated with the injection site, including bruising, pain, nodules/mass, ulceration, erythema, pruritus, swelling, and/or induration)
- 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 study drug in this study, injection site reactions/local tolerability in the treated buttocks (through subject and Investigator reporting) will be assessed.

Statistical Methods:

The primary endpoint is the proportion of 2-level composite responders at Day 71 defined as subjects with:

- an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator of the target buttock, and
- an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS as assessed by the subject while viewing the digital image of the target buttock.

A subject will be considered a responder if these criteria are met in the randomized target buttock of that subject.

Sample Size Consideration: The results of a prior Phase 2b study of this drug (Study EN3835-201) demonstrated the overall rate for treated buttocks of composite responders with an improvement of at least 2 levels on both the PR-PCSS and the CR-PCSS was 14.9% in the EN3835 treatment group versus 1.1% in the Placebo group. Given this result, the study is planned to randomize 420 subjects with a 1:1 ratio into either the EN3835 arm (0.84 mg/buttock, 1.68 mg total dose) or placebo arm.

The sample size calculation was based on the following assumptions: [redacted] 2) Fisher exact test; 3) type I error of 0.05; 4) power of at least 90%; and 5) dropout rate of approximately 10%.

This sample size will also provide >90% power with type 1 error of 0.05 to detect the treatment difference for all the key secondary endpoints based on previous study results.

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Analysis Populations:

- The intent-to-treat (ITT) population: The ITT population is defined as all randomized subjects who have received at least 1 injection of study medication.
- Modified intent-to-treat (mITT) population: The mITT population is defined as all intent-to-treat subjects with a baseline and 1 post-injection evaluation of both the CR-PCSS and PR-PCSS for each buttock.
- Safety population: The Safety population is defined as all subjects who have received at least 1 injection of study medication.
- Per-Protocol (PP) population: The PP population is defined as the mITT subjects without any of the following:
  - Placebo randomized subject who receives EN3835 treatment.
  - EN3835 randomized subject who receives placebo treatment only throughout study.
  - Any subject who uses protocol-prohibited medications.
  - Subject missing PR-PCSS and/or CR-PCSS assessment at Day 71.
  - Subject with a buttock not receiving all three treatment sessions without medical reasons (e.g., adverse events or CR-PCSS rated as zero (0)).
  - Subject who did not meet all inclusion and exclusion criteria.

Analyses:

Analyses of Primary Endpoint:

The primary endpoint is the proportion of 2-level composite responders at Day 71 defined as subjects with:

- an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator of the target buttock, and
- an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS as assessed by the subject while viewing the digital image of the target buttock.

A subject will be considered a responder if these criteria are met in the randomized target buttock of that subject.

The primary endpoint will be summarized as percentages and analyzed using a Cochran-Mantel-Haenszel test that compares the 2 treatment groups and adjusts for Investigator at a level of significance of 0.05. The ITT population will be evaluated for the primary endpoint with any subject not having an evaluation of CR-PCSS and/or PR-PCSS at Day 71 classified as a non-responder.

Sensitivity analyses for the primary endpoint will include:

- ITT subjects with missing data handled by multiple imputation (MI) approach
- ITT subjects with missing data handled by a last observation carried forward (LOCF) approach
- mITT subjects with missing data handled by an LOCF approach
- Observed data only (no missing data imputed)
- Per-protocol (PP) subjects with missing data handled by an LOCF approach if 10% or more subjects are excluded in the PP population from mITT population.

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Analyses of Key Secondary Endpoints:

There will be 8 key secondary endpoints grouped as three families of 2 to 4 endpoints per family analyzed in hierarchical order.

- Family #1 – four endpoints:
  - Proportion of 1-level PR-PCSS responders defined as subjects with ≥1-level improvement in PR-PCSS severity rating of the target buttock at Day 71 compared to Day 1
  - Proportion of 2-level PR-PCSS responders defined as subjects with ≥2-level improvement in PR-PCSS severity rating of target buttock at Day 71 compared to Day 1
  - Proportion of 1-level composite responders of target buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of the target buttock) at Day 71 compared to Day 1
  - Proportion of 2-level composite responders of the non-target buttock at Day 71 compared to Day 1
- Family #2 – two endpoints:
  - Proportion of 1-level SSRS responders defined as subjects who were at least slightly satisfied at Day 71 (SSRS rating ≥ 4)
  - Change from baseline (Day 1) of the PR-CIS total score at Day 71
- Family #3 – two endpoints:
  - Proportion of 1-level S-GAIS responders defined as subjects with ≥1-level improvement (improved, much improved or very much improved) in the S-GAIS assessment of the target buttock at Day 71
  - Proportion of 2-level S-GAIS responders defined as subjects with ≥2-level improvement (much improved or very much improved) in the S-GAIS assessment of the target buttock at Day 71

The key secondary efficacy analyses will be analyzed in the same manner as the primary endpoint based on the ITT population. The family #1 key secondary efficacy analyses will be performed only if the primary efficacy analysis is significant at a significance level of $p \leq 0.05$ (gatekeeping strategy). Similarly, family #2 key secondary efficacy analyses will be performed only if at least one of the key secondary efficacy endpoints of family #1 is significant at a significance level of $p \leq 0.0125$ and family #3 key secondary efficacy analyses will be performed only if at least one of the key secondary efficacy endpoints of family #2 is significant (parallel gatekeeping strategy). Within a family of key secondary efficacy endpoints, the Bonferroni method will be performed to relocate unused alpha for testing each endpoint to assure an overall error rate of $p \leq 0.05$. The details of the testing procedures will be provided in the statistical analysis plan for the study.

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Supportive Endpoints: The supportive variables will evaluate assessments at various study time points and using various populations. • Proportion of 2-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS) of the target buttock (Days 22, 43, and 71) • Proportion of 2-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS) of the non-target buttock (Days 22, 43, and 71) • Proportion of 1-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS) of the target buttock (Days 22, 43, and 71) • Proportion of 1-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS) of the non-target buttock (Days 22, 43, and 71) • Proportion of 2-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject. • Proportion of 1-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject. • Proportion of 2-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks. • Proportion of 1-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks. • Proportion of 2-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS) of the target buttock (Days 22, 43, and 71) • Proportion of 2-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS) of the non-target buttock (Days 22, 43, and 71) • Proportion of 1-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS) of the target buttock (Days 22, 43, and 71) • Proportion of 1-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS) of the non-target buttock (Days 22, 43, and 71

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• Proportion of 2-level CR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject • Proportion of 1-level CR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject • Proportion of 2-level CR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks • Proportion of 1-level CR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks • Proportion of 1-level composite responders of the target buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same target buttock) (Days 22, 43, and 71) • Proportion of 1-level composite responders of the non-target buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the non-target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same non-target buttock) (Days 22, 43, and 71) • Proportion of 1-level composite responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject. • Proportion of 1-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks. • Proportion of 2-level composite responders of the target buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same target buttock) (Days 22, 43, and 71) • Proportion of 2-level composite responders of the non-target buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the non-target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same non-target buttock) (Days 22, 43, and 71) • Proportion of 2-level composite responders of at least one of two buttocks (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject.

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• Proportion of 2-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks. • Proportion of subjects at each level of the S-GAIS of the target buttock (Days 22, 43, and 71) • Proportion of subjects at each level of the S-GAIS of the non-target buttock (Days 22, 43, and 71) • Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S-GAIS of the target buttock (Days 22, 43, and 71) • Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S-GAIS of the non-target buttock (Days 22, 43, and 71) • Proportion 1-level S-GAIS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject. • Proportion of 1-level S-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks. • Proportion of subjects at each level of the I-GAIS of the target buttock (Days 22, 43, and 71) • Proportion of subjects at each level of the I-GAIS of the non-target buttock (Days 22, 43, and 71) • Proportion of 1-level I-GAIS responders defined as subjects with a response of at least 1 (improved) in the I-GAIS of the target buttock (Days 22, 43, and 71) • Proportion of I-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the I-GAIS of the non-target buttock (Days 22, 43, and 71) • Proportion of 1-level I-GAIS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject. • Proportion of 1-level I-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks. • Change from baseline (Day 1) of the PR-CIS score at Day 71 • Change from baseline (Day 1) of the abbreviated PR-CIS score at Day 71 • Proportion of subjects with a change from baseline (Day1) of the PR-CIS ≥12 at Day 71 • Proportion of subjects with a change from baseline (Day 1) of the abbreviated PR-CIS ≥10 at Day 71 • Proportion of subjects at each level of the subject self-rating scale (SSRS) (Day 1 (Baseline) and Day 71

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- Proportion of 1-level SSRS responders defined as subjects who were at least slightly satisfied at Day 71 (SSRS rating ≥ 4)
- Proportion of subjects at each level of the subject satisfaction with cellulite treatment assessment (Day 71)
- Proportion of satisfied responders (defined as subjects with a response of at least 1 (ie, 1-Satisfied or 2-Very Satisfied) in the subject satisfaction with cellulite treatment assessment (Day 71)

All supportive endpoints will be summarized as percentages. The dichotomous secondary endpoints (ie, responder endpoints) will be analyzed using a Cochran-Mantel-Haenszel test adjusted for Investigator. Changes in the PR-PCSS ratings and CR-PCSS ratings from baselines, S-GAIS scores, and I-GAIS scores will be analyzed using the Mann-Whitney test.

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. The Fisher exact test will be used to compare EN3835 to placebo. Descriptive statistics will be presented for actual and change from baseline at each visit for vital signs and for each clinical laboratory test parameter. The comparison between treatment groups will be based on the change from baseline for clinical laboratory tests and vital signs using an analysis of variance (ANOVA) with a factor of drug (EN3835 or placebo).

Immunogenicity: Anti-AUX-I and anti-AUX-II antibody levels will be summarized using descriptive statistics for the actual value at the visit. Samples from Day 1, Day 22, Day 43, and Day 71 visits will be analyzed for anti-AUX-I and anti-AUX-II antibodies and a subset of Day 1 and Day 71 samples will be analyzed for neutralizing antibodies.

5. SCHEDULE OF EVENTS

Procedures	Day -14 to -1 Screening	Day 1 Treatment Visit 1	Day 22 (± 3 d) Treatment Visit 2	Day 43 (± 3 d) Treatment Visit 3	Day 71 (+ 5 d) / End of Study / Early Termination	Unscheduled Clinic Visit[a]
Informed consent	X					
Inclusion/exclusion	X					
Digital photography	X	X[b]	X[b]	X[b]	X	X
Medical history/EFP history including previous treatments	X					
Prior/concomitant medications/procedures	X	X	X	X	X	X
Physical examination:	X					
• Body weight	X		X[c]	X[c]	X	X
• Height	X					
• Fitzpatrick skin type	X					
Vital signs	X	X[d]	X[d]	X[d]	X	X
12-lead ECG	X					
Collection of samples:						
• Clinical laboratory	X				X	X
• Anti-AUX-I/anti-AUX-II antibody level		X[c]	X[c]	X[c]	X	
• Pregnancy testing	X[e]	X[c,e]	X[c,e]	X[c,e]	X[e]	X
Subject cellulite assessments[f]:						
• Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS)	X[g,h]	X[c,g,h]	X[c,g,h]	X[c,g,h]	X[g,h]	
• Subject Global Aesthetic Improvement (S-GAIS)			X[c,g,h]	X[c,g,h]	X[g,h]	
• Patient Reported Cellulite Impact Scale (PR-CIS)		X[c,g]			X[g]	
• Subject Satisfaction With Cellulite Treatment Assessment					X[g]	
• Subject Self-Rating Scale (SSRS)		X[c]			X	

Procedures	Day -14 to -1 Screening	Day 1 Treatment Visit 1	Day 22 (± 3 d) Treatment Visit 2	Day 43 (± 3 d) Treatment Visit 3	Day 71 (+ 5 d) / End of Study / Early Termination	Unscheduled Clinic Visit[a]
Investigator cellulite assessments:						
• Selection of dimples to be treated within the two buttocks		X[c]	X[c]	X[c]		
• Marking the dimples and injection sites to be treated within the buttocks		X[c]	X[c]	X[c]		
• Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)	X	X[c,h]	X[c,h]	X[c,h]	X[h]	
• Investigator Global Aesthetic Improvement (I-GAIS)			X[c,h]	X[c,h]	X[c,h]	
Confirm eligibility		X[c]				
Randomize to treatment		X[c,i]				
Study drug administration		X	X	X		
Injection site reactions/local tolerability in the buttocks		X	X	X	X	X
Adverse events	Monitored Throughout Study					

[a] During unscheduled visits, the Investigator or designee may perform any study procedure that they deem clinically necessary (eg, vital signs, clinical lab assessments, and pregnancy test).
[b] Before and after marking the dimples and injection sites.
[c] Before injection.
[d] Up to 4 hours before injection; approximately 15 and 30 minutes after injection. Vital signs must be stable before the subject is discharged.
[e] Serum pregnancy test on Screening visit and Day 71/EOS visit; urine pregnancy test on Day 1, Day 22, and Day 43 visits.
[f] Subject assessments should be completed independently and prior to Investigator assessments at each visit.
[g] Assessment made via photographs (if treatment visit, use photographs taken before marking dimples and injection sites).
[h] Assessment of each of the 2 buttocks independently.
[i] Before randomization, each of the subject's buttocks must have ratings of 3 or 4 (moderate or severe) in both the CR-PCSS and PR-PCSS.
NOTE: Subject cellulite assessments must be completed before the Investigator cellulite assessments are conducted at each visit.
d=Days; ECG=Electrocardiogram; EFP=Edematous fibrosclerotic panniculopathy; EOS=End of study

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7. LIST OF ABBREVIATIONS

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

Table 2: Abbreviations and Special Terms

Abbreviation	Definition
AE	Adverse event
AUX-I	Clostridial class I collagenase
AUX-II	Clostridial class II collagenase
BMI	Body mass index
CR-PCSS	Clinician Reported Photonumeric Cellulite Severity Scale
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EFP	Edematous fibrosclerotic panniculopathy
ePRO	Electronic patient reported outcome
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HREC	Human Research Ethics Committee
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
I-GAIS	Investigator-Global Aesthetic Improvement Scale
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive web response system
LOCF	Last observation carried forward
MI	Multiple imputation
mITT	Modified intent-to-treat
PR-CIS	Patient Reported Cellulite Impact Scale
PR-PCSS	Patient Reported Photonumeric Cellulite Severity Scale
Quadrant	A quadrant is a treatment area
Qualified designee	Qualified by education and training to perform the study procedure (eg, sub-Investigator, nurse).
SAE	Serious adverse event
S-GAIS	Subject – Global Aesthetic Improvement Scale
SSRS	Subject Self-Rating Scale
TEAE	Treatment-emergent adverse event. Adverse events that occur on or after the first injection of study drug.

8. INTRODUCTION

8.1. Background

8.1.1. 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 a contour abnormality of the skin.(1) The condition manifests as dimpled skin, particularly in the gluteal-femoral region.(2,3) EFP is caused by herniation of subcutaneous fat lobules through the dermohypodermal junction and/or shortening of the collagen septa that cross the hypodermal layer and connects the dermis to the underlying fascia. This creates an uneven surface with dimpling.(1,2) 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.

8.1.2. Current EFP Treatments

There are therapies that have been utilized in an attempt to treat cellulite; however, there are no approved pharmacologic treatments. 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,(6) topical agents,(5) massage,(7) liposuction,(5,6) mesotherapy,(6) radiofrequency,(6) subcision and powered subcision,(8) and laser therapies;(9,10) some of these treatments may pose an increased risk for adverse effects.(5)

There remains an unmet medical need for safe and effective therapies to improve the aesthetic 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 that is bothersome to many women.

8.1.3. 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 (brand name is XIAFLEX®) 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° at the start of therapy.

A recent Phase 2b, randomized, double-blind, placebo-controlled study (EN3835-201) of 375 women randomized to treatment of one treatment area (quadrant) (quadrant was defined in study EN3835-201 as a left buttock, a right buttock, a left posterolateral thigh or a right posterolateral thigh) of cellulite with EN3835 0.84 mg or placebo in a 1:1 ratio assessed the effectiveness and safety of EN3835. Efficacy in this study was evaluated based on cellulite assessments using Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS), Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS), Investigator Global Aesthetic Improvement Scale (GAIS-I), Subject Global Aesthetic Improvement Scale (GAIS-S), and Subject Satisfaction with Cellulite Treatment.

Results from the Phase 2b study demonstrated that treatment (3 visits approximately 21 days apart) improved the cellulite severity of the treatment area as assessed by the primary endpoint of 2-level composite responder analyses, the proportion of responders based on an improvement of ≥2 levels in the appearance of cellulite in both the patient PR-PCSS and the clinician CR-PCSS of buttocks and thighs was statistically significantly greater in subjects who received EN3835 0.84 mg (10.6%; $p<0.001$) compared to subjects who received placebo (1.6%); 1-level (or greater) responders in the PR-PCSS of EN3835-treated subjects (72.3%) was significantly

greater than 1-level responders in the placebo group (51.6%) ($p<0.001$); statistically significant ($p\leq0.001$) improvement in the appearance of cellulite based on the subject S-GAIS were observed in EN3835 0.84-mg group (73.1%) compared to the placebo group (44.0%); and 62.9% of subjects in the EN3835 0.84 mg group were satisfied or very satisfied with the results of their cellulite treatment compared with only 35.9% of subjects in the placebo group ($p<0.001$). In subjects treated in buttocks (n=187), the proportion of 2-level composite responders was statistically significantly greater in subjects who received EN3835 0.84 mg (14.9%; $p<0.001$) compared to subjects who received placebo (1.1%); 1-level (or greater) responders in the PR-PCSS of EN3835-treated subjects (72.7%) was significantly greater than 1-level responders in the placebo group (47.8%) ($p<0.001$).

The study also demonstrated EN3835 to be well tolerated with no serious adverse events (SAEs) related to EN3835. Safety results from a total of 4 studies (1 pilot, 2 Phase 1, and 2 Phase 2 studies) in which 435 adult females received subcutaneous injections of EN3835 indicate that the majority of treatment-emergent adverse events (TEAEs) are transient, non-serious, mild or moderate in intensity, and related to the local administration of EN3835. The immunogenicity profile after 3 treatment visits of EN3835 indicate that greater than 90% of EN3835-treated subjects were seropositive for AUX-I and/or AUX-II antibodies; this profile of EN3835 is similar to that observed in the Dupuytren's contracture and Peyronie's disease programs.

A Phase 1, open-label safety and pharmacokinetic study of a single dose of EN3835 0.84 mg in 11 female subjects with EFP showed that there was no quantifiable levels of AUX-I or AUX-II at any time point after subcutaneous injection of EN3835 0.84 mg into one quadrant. A second Phase 1, open-label safety and pharmacokinetic study of a single dose of EN3835 0.84 mg per treatment area in two treatment areas (buttock-buttock, thigh-thigh, or buttock-thigh) concurrently (total dose of 1.68 mg) showed that there was no quantifiable levels of AUX-I or AUX-II at any time point post-dose attributable to the injection of EN3835 1.68 mg.

The results from these studies suggest that subcutaneous injections of EN3835 in the area of cellulite may be a well-tolerated and effective medical treatment for adults with EFP.

8.2. Summary of Nonclinical Studies

Non-clinical studies necessary to support clinical studies have been performed and are summarized in the Investigator Brochure (IB).(11) Non-clinical studies in the following areas were performed: toxicology, reprotoxicity, genotoxicity, and hypersensitivity.

8.3. Summary of Known Risks and Benefits

A summary of safety risks is provided in the IB.(11) The following events have been commonly observed: local injection site reactions (injection site bruising, injection site swelling, injection site pain) for the various approved indications as well as those being investigated. In the phase 2b study of EN3835 in women with EFP, the following treatment related adverse events ≥2% of 189 EN3835-treated women were reported: injection site bruising (75.1%), injection site pain (59.3%), injection site nodule (14.3%), injection site pruritus (11.1%), injection site swelling (7.4%), injection site induration (5.8%), injection site mass (5.3%), injection site discolouration (3.2%), and injection site erythema (2.1%). These events are similar to events reported in the clinical trials of EN3835 for the approved indications. Postmarketing safety data are consistent with safety data reported in clinical trials.

Although a thorough benefit of EN3835 has not been fully evaluated in the treatment of EFP, the efficacy results from the Phase 2b study and previous EFP studies warranted further development.

8.4. Rationale

The results from the Phase 2b EFP study (EN3835-201) further suggested that EN3835 0.84 mg per treatment area (quadrant) is an effective treatment of EFP based on improvement in the severity of cellulite as determined by the Investigator and the subject. There were no safety concerns following 0.84 mg per treatment area in the treatment of EFP (section 8.1.3). Safety findings from the Phase 2b EFP study are similar to that observed in previous clinical studies with EN3835 in the treatment of EFP and XIAFLEX in the treatment of Dupuytren's contracture and Peyronie's disease, in that that the majority of AEs occurred at the site of injection and resolved before the next scheduled treatment. The immunogenicity profile of EN3835 in the Phase 2b EFP study is similar in previous studies and programs.

Based on the efficacy and safety findings from the Phase 2a and 2b EFP studies, the EN3835 0.84-mg dose per treatment area in two treatment areas (buttocks) warranted further investigation in this study.

Treating two buttocks at each treatment visit will potentially provide a symmetrical-like improvement in appearance. Support for evaluation of the treatment of two buttocks concurrently is based on: 1) the safety findings from the previous EFP studies are local to the injection site, 2) the pharmacological activity of EN3835 is local and does not require systemic exposure, and 3) no significant quantifiable systemic concentration has been attributable to injection of two buttocks concurrently.

The integration of dose and use justification supports this study of evaluation of EN3835 0.84 mg per treatment area in two treatment areas (buttocks) concurrently.

9. OBJECTIVES

9.1. Primary Objective

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

9.2. Secondary Objectives

There are no secondary objectives of this study.

9.3. Exploratory Objectives

There are no exploratory objectives of this study.

10. INVESTIGATIONAL PLAN

10.1. Study Design

This study will be performed at approximately 25 study centers located in the United States. This clinical study will be conducted as a multicenter, randomized, double-blind, placebo-controlled study comparing EN3835 to placebo in adult women with EFP. The study will consist of 71 days of double-blind treatment. Subjects meeting the entry criteria for this study will be randomized to EN3835 treatment or placebo treatment in a 1:1 ratio within an investigational site.

The complete Schedule of Events is provided in section 5.

Figure 1: Study Design

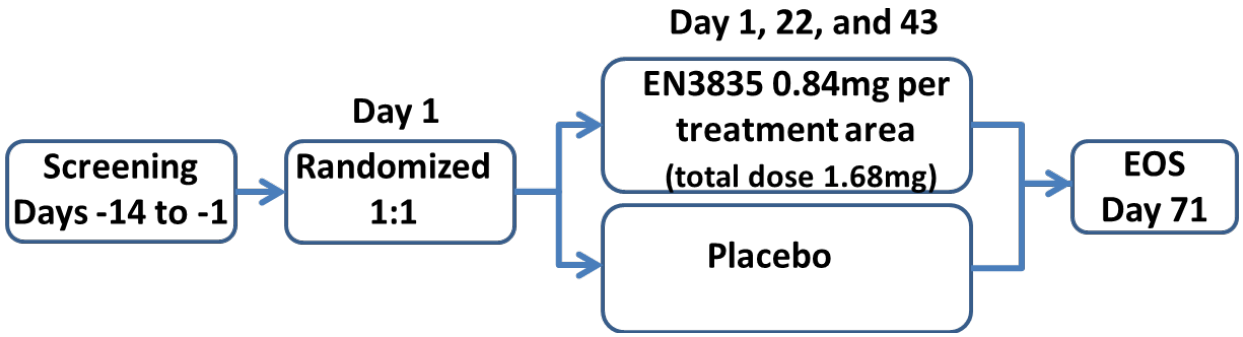


Table 3: Study Treatment Groups

Dose per Each Injection[a] / Number of Subjects	Injection Volume per Each Injection	Number of Injections at Each Treatment Visit	Dose (mg) at Each Treatment Visit	Injection Volume (mL) per Each Treatment Visit	Cumulative EFP Dose
EN3835 0.07 mg / N=210	0.3 mL	12 per buttock × 2 buttocks = 24 injections	0.84 mg per buttock × 2 buttocks = 1.68 mg (12 injections per buttock × 0.07 mg/injection × 2 buttocks)	3.6 mL per buttock × 2 buttocks = 7.2 mL (24 injections × 0.3 mL)	5.04 mg (3 treatment visits × 0.84 mg per buttock × 2 buttocks)
Placebo / N=210	0.3 mL	12 per buttock × 2 buttocks = 24 injections	-	3.6 mL per buttock × 2 buttocks = 7.2 mL (24 injections × 0.3 mL)	-

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

10.2. Selection of Doses

The dose of EN3835 chosen for this study was based on the results from earlier studies.

The data from the Phase 2a EFP dose-ranging study (AUX-CC-831) suggest that EN3835 0.84 mg is most effective in the treatment of EFP based on improvement in the severity of

cellulite as determined by both the Investigator and the subject, although the EN3835 0.48-mg group did show improvement in some of the efficacy parameters.

- There were no safety concerns following administration of up to 3 treatment visits of EN3835 0.84 mg in the treatment of EFP (AUX-CC-831 CSR). The safety profile of EN3835 0.84 mg in the treatment of EFP was similar to that observed in the EN3835 0.06-mg group and the EN3835 0.48-mg group. No notable differences were observed across the 3 treatment groups.
- Safety findings from the Phase 2a EFP dose-ranging study are similar to that observed in previous clinical studies with XIAFLEX in the treatment of Dupuytren's contracture and Peyronie's disease, in that the majority of AEs occurred at the site of injection and resolved before the next scheduled treatment.
- The immunogenicity profile of EN3835 in the Phase 2a EFP dose-ranging study is similar to that observed in the Dupuytren's contracture and Peyronie's disease programs.
- Based on the efficacy and safety findings from the Phase 2a EFP dose-ranging study, the EN3835 0.84-mg dose was carried forward to the Phase 2b study.

The results from the Phase 2b EFP study (EN3835-201) further suggested that EN3835 0.84 mg is an effective treatment of EFP based on improvement in the severity of cellulite as determined by the Investigator and the subject. There were no safety concerns following EN3835 0.84 mg in the treatment of EFP (section 8.4). Safety findings from the Phase 2b EFP study are similar to that observed in previous clinical studies with XIAFLEX in the treatment of Dupuytren's contracture and Peyronie's disease, in that that the majority of AEs occurred at the site of injection and resolved before the next scheduled treatment. The immunogenicity profile of EN3835 in the Phase 2b EFP study is similar to that observed in the Dupuytren's contracture and Peyronie's disease programs.

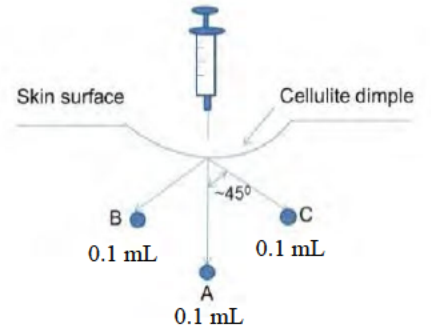
Based on the efficacy and safety findings from the Phase 2a and 2b EFP studies, the EN3835 0.84-mg dose per treatment area was carried forward to this study. The findings from previous studies that the majority of adverse events after EN3835 treatment are local to the injection site and that there is no quantifiable systemic exposure observed after concurrent treatment of two buttocks (total dose of 1.68 mg) supports the proposed study to evaluate EN3835 treatment of two buttocks.

10.3. Study Drug Administration

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 visit, 8 syringes (4 syringes per buttock) will be prepared for dosing. Each syringe will contain 0.9 mL of study drug (ie, 3 injections in each syringe). Twelve (12) skin injections of 0.3 mL per injection will be administered within each of the two buttocks during each treatment visit.

Figure 2: Study Drug Administration at Each Injection Site



- **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 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 each buttock (three 0.3-mL injections per syringe, each injection administered as three 0.1-mL aliquots). Twelve (12) skin injections of 0.3 mL will be administered within each of the two treated buttocks during each treatment visit.
- The plane containing injection deposition points A, B, and C should be perpendicular to the skin and perpendicular to the long axis of a dimple if the dimple is an elongated trough-like dimple.
- 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 Visits 1, 2, and 3.

NOTE: EN3835 is a foreign protein and Investigators should 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 must be available with the Investigator and site staff must be familiar with their use.

10.4. 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 injections 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 14.9).

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

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

The design of this study was based on the primary objective to evaluate the efficacy and safety of EN3835 0.84 mg per buttock in the concurrent treatment (total dose of 1.68 mg) of 2 bilateral buttocks with EFP in adult women compared with placebo treatment. The study design, a multi-center, double-blind, placebo-controlled study is in accordance with regulatory guidelines of adequate and well-controlled clinical studies (Food and Drug Administration [FDA] Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, 1998.; ICH E8 and E10).

11. SELECTION AND WITHDRAWAL OF SUBJECTS

11.1. Subject Inclusion Criteria

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

1. Voluntarily sign and date an informed consent agreement
2. Be a female ≥18 years of age
3. At Screening visit, have 2 bilateral buttocks with each buttock having:
   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)
4. At Day 1 visit, have 2 bilateral buttocks with each buttock having:
   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)
5. Be willing to apply sunscreen to the buttocks before each exposure to the sun while participating in the study (ie, Screening 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
7. Have a negative serum pregnancy test at Screening and a negative urine pregnancy test before injection of study drug and be using a stable and effective contraception method (eg, abstinence, intrauterine device [IUD], hormonal [estrogen/progestin] contraceptives, or double barrier method) for at least 1 menstrual cycle prior to study enrollment and for the duration of the study; or be menopausal defined as 12 months of amenorrhea in the absence of other biological or physiological causes, as determined by the Investigator; or post-menopausal for at least 1 year; or be surgically sterile
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. Subject Exclusion Criteria

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

1. Has any of the following systemic conditions:
   a. Coagulation disorder
   b. Evidence or history of malignancy (other than excised basal-cell carcinoma) unless there has been no recurrence in at least 5 years
   c. History of keloidal scarring or abnormal wound healing
   d. Concurrent diseases or conditions that might interfere with the conduct of the study, confound the interpretation of the study results, or endanger the subject's well-being.

Any questions about concurrent diseases should be discussed with the Medical Monitor

e. Evidence of clinically significant abnormalities on physical examination, vital signs, electrocardiogram (ECG), or clinical laboratory values

2. Has any of the following local conditions in the areas to be treated:
   a. History of lower extremity thrombosis or post-thrombosis syndrome
   b. Vascular disorder (eg, varicose veins, telangiectasia) in area to be treated
   c. Inflammation or active infection
   d. Severe skin laxity, flaccidity, and/or sagging
   e. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer
   f. Has a tattoo and/or a mole located within 2 cm of the site of injection
3. Requires the following concomitant medications before or during participation in the trial:
   a. Anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication (except for ≤150 mg aspirin daily) within 7 days before injection of study drug
4. Has used any of the following for the treatment of EFP on a buttock within the timelines identified below or intends to use any of the following at any time during the course of the study:
   a. Liposuction in a buttock during the 12-month period before injection of study drug
   b. Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; buttock implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision) within a buttock during the 12-month period before injection of study drug
   c. Any investigational treatment for EFP on a buttock during the 12-month period before the injection of study drug
   d. Endermologie or similar treatments within a buttock during the 6-month period before injection of study drug
   e. Massage therapy within a buttock during the 3-month period before injection of study drug
   f. Creams (eg, Celluvera™, TriLastin®) and/or home therapies to prevent or mitigate EFP within a buttock during the 2-week period before injection of study drug
5. Is presently nursing or providing breast milk
6. Intends to become pregnant during the study
7. Intends to initiate an intensive sport or exercise program during the study
8. Intends to initiate a weight reduction program during the study
9. Intends to use tanning spray or tanning booths during the study

10. Has received an investigational drug or treatment within 30 days before injection of study drug
11. Has a known systemic allergy to collagenase or any other excipient of study drug
12. Has received any collagenase treatments at any time prior to treatment
13. Was a subject in a previous cellulite clinical trial of CCH: AUX-CC-830, AUX-CC-831, EN3835-102, EN3835-104, EN3835-201, EN3835-202, and/or EN3835-205
14. Any other condition(s) that, in the Investigator's opinion, might indicate the subject to be unsuitable for 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
- Lack of efficacy
- 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 including safety and efficacy assessments should be conducted as detailed in the Schedule of Events (section 5). 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 and assessments are required (but are encouraged to reduce missing information) except the collection of adverse event (AE) information. This information should be recorded in the source documentation and the eCRF.

11.3.1. Replacement Procedures

Subjects who discontinue from the study will not be replaced.

12. TREATMENT OF SUBJECTS

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. Informed Consent

Signed and dated informed consent will be obtained from each subject before any study procedures are undertaken, or before any changes to the subject's medication regimen are made. Details about how the informed consent will be obtained and documented are provided in section 21.3, Subject Information and Consent.

12.1.2. Subject Screening

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. The screening log will be captured directly by the electronic data capture (EDC) system.

12.1.2.1. Medical History

During the screening period, the Investigator or qualified designee will obtain a medical history from each subject that includes relevant diagnoses and/or procedures/therapies with onset/resolutions dates. Medical histories should also include history of EFP (start date and family history), and history of tobacco and alcohol use (never, current, former).

12.1.2.2. Screening Period (Day -14 to Day -1)

Subjects meeting the relevant eligibility criteria listed in section 11 may be enrolled in the study after the nature and purpose of the protocol have been explained and written informed consent to participate has been voluntarily provided by the subject or their legally authorized representative.

The subject identification number will consist of 8 digits. The first 4 digits represent the study site number followed by a 4-digit subject number.

The following procedures will be performed and documented during the screening period:

1. Obtain written informed consent (section 12.1.1)
2. Evaluate eligibility based on inclusion/exclusion criteria (section 11.1 and section 11.2)
3. Subject will have digital photographs taken of her two buttocks (section 13.1.1)
4. Subjects will get instruction on the use of the PR-PCSS (section 13.1.2.1)

5. Prior to Investigator CR-PCSS assessment, subjects will rate each of their two buttocks using the PR-PCSS while viewing their digital images (section 13.1.2.1); the Investigator is blinded to these ratings
6. After the subject has completed the PR-PCSS ratings, the Investigator will conduct live assessments of subject's cellulite severity of each of the two buttocks using the CR-PCSS (section 13.1.2.6); the subject is blinded to these ratings. The ratings from the PR-PCSS and CR-PCSS will be used to assess initial eligibility of the buttocks for study entry
7. Medical history including EFP history (section 12.1.2.1)
8. Record prior and concomitant medications/procedures (section 12.8)
9. Physical examination including measurement of body weight, height, Fitzpatrick skin type (section 14.11)
10. Vital sign measurements (section 14.9)
11. 12-lead ECG (section 14.10)
12. Collection of samples for:
    a. Clinical laboratory testing (section 14.7)
    b. Serum pregnancy testing (section 14.7)
13. Adverse events (section 14)

12.2. Selecting and Marking Dimples during Treatment Visits

Selection of dimples to be treated in the two buttocks is at the discretion of the Investigator. Dimples must be well-defined and evident when the subject is standing in a consistent, standardized relaxed pose (without the use of any manipulation such as skin pinching or muscle contraction). Each subject will receive 3 treatment visits of study drug according to randomization unless the buttock is dimple-free (score of 0 on CR-PCSS as reported by the Investigator) at Treatment Visit 2 and/or Treatment Visit 3 (a dimple -free buttock at Treatment Visit 1 is precluded by the eligibility criteria); a dimple-free buttock at Treatment Visit 2 and/or Treatment Visit 3 does not preclude treatment of the contralateral buttock unless it is dimple-free also. During each treatment visit, each of the buttocks will be photographed before and after marking dimples and injection sites while the subject is standing in a consistent, standardized relaxed pose as described in the Photography Manual. The cellulite severity assessments using the PR-PCSS and CR-PCSS will be completed prior to marking dimples and injection sites.

The Investigator or qualified designee will select dimples within each buttock that are well-defined, evident when the subject is standing, and suitable for treatment; treatment consists of 12 injections per buttock (24 injections total in two buttocks) per treatment visit. Because the goal of treatment is to improve the aesthetic appearance of each entire buttock, the Investigator will be instructed to select dimples that in his or her opinion would most improve the aesthetic appearance of each entire buttock. The same dimples within a buttock or different dimples within a buttock may be treated at each treatment visit but injections must all be within the buttocks (12 injections per buttock) for all 3 visits. Each buttock will receive all 3 treatment visits unless the buttock has no treatable EFP dimples and the Investigator rates the buttock a score of 0 on the CR-PCSS. If no injections in a particular buttock (right or left) are given at Treatment

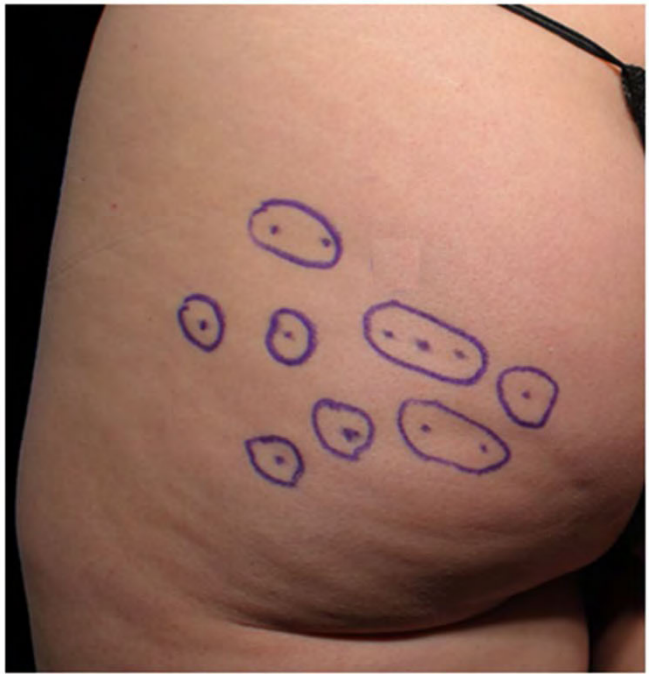
Visit 2, subjects will still be assessed for treatment in the contralateral buttock at Treatment Visit 2, and will return for the Day 43 visit and each of the buttocks will again be evaluated by the subject (PR-PCSS) and Investigator (CR-PCSS). If the Investigator rates either or both of the buttocks greater than 0 on the CR-PCSS, injections at Treatment Visit 3 should be given.

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; locating at least one injection site at the nadir, if present, of the dimple). 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 buttock should not overlap.

Each of the buttocks will be photographed before and after marking dimples and injection sites while the subject is standing in a consistent, standardized relaxed pose as described in the Photography Manual.

Examples of subject dimple and injection site markings are shown as follows:

Sample Buttock Marking



12.3. Digital Photography during Treatment Visits 1, 2, and 3

During each treatment visit, each of the two buttocks will be photographed before and after marking dimples and injections sites while the subject is standing in a consistent, standardized relaxed pose as described in section 13.1.1.

12.4. Treatment Visit 1 (Day 1)

12.4.1. Treatment Visit 1: Pre-Injection

1. Confirm eligibility criteria
2. Take digital photography of each of the buttocks before marking dimples and injection sites (section 13.1.1)
3. Subjects will get instruction on the use of the PR-PCSS (Patient Instructions for Use of PR-PCSS)
4. Subjects will rate each of their buttocks using the PR-PCSS (section 13.1.2.1); the Investigator is blinded to these ratings
5. Subjects will complete the Patient Reported Cellulite Impact Scale assessment (PR-CIS; section 13.1.2.3): the Investigator is blinded to this rating
6. Subjects will complete the Subject Self-Rating Scale (SSRS) assessment (section 13.1.2.5); the Investigator is blinded to these ratings
7. The Investigator will conduct live assessments of subject's cellulite severity of each of the buttocks using the CR-PCSS (section 13.1.2.6); the subject is blinded to these ratings. The ratings from the PR-PCSS and CR-PCSS will be used to assess eligibility for randomization
8. Subjects with PR-PCSS or CR-PCSS ratings in either of the buttocks <3 will be excluded from participation
9. Upon confirmation of two buttocks eligible for treatment (eligible criteria being each buttock have PR-PCSS and CR-PCSS scores of 3 or 4), the IWRS system will randomly assign one buttock as the target buttock in the background. Subjects, investigators, site personnel and Endo personnel will be blinded to target buttock assignment.
10. Randomization of subjects with two buttocks eligible for treatment (eligible criteria being each buttock have PR-PCSS and CR-PCSS scores of 3 or 4) to treatment (section 12.10); obtain kit numbers of study treatment. Subjects, investigators, site personnel, and Endo personnel will be blinded to treatment assignment.
11. Record concomitant medications/procedures (section 12.8)
12. Vital sign measurements (section 14.9)
13. Collection of samples for:
    a. Anti-AUX-I and anti-AUX-II antibody testing (section 14.8)
    b. Urine pregnancy testing (section 14.7)
14. Select and mark dimples to be treated in each of the buttocks (section 12.2)
15. Take digital photograph of each of the buttocks after marking dimples and injection sites (section 13.1.1)

12.4.2. Treatment Visit 1: Injection and Post-injection

1. Administration of study drug in the prone position (section 10.3)
2. Record number of dimples treated and number of injections administered in each of the two buttocks
3. Vital sign measurements (section 14.9)
4. Injection site reactions and local tolerability
5. Adverse events (section 14)

12.5. Treatment Visit 2 (Day 22 [±3 days]) and Treatment Visit 3 (Day 43 [±3 days])

12.5.1. Treatment Visits 2 and 3: Pre-injection

1. Record concomitant medications/procedures (section 12.8)
2. Body weight measurements
3. Vital sign measurements (section 14.9)
4. Collection of samples for:
   a. Anti-AUX-I and anti-AUX-II antibody testing (section 14.8)
   b. Urine pregnancy testing (section 14.7)
5. Digital photographs of each of the two buttocks before marking dimples and injection sites (section 13.1.1)
6. Subject Cellulite Assessments of each of the buttocks using the photographic image of each buttock before marking dimples and injection sites (NOTE: complete subject cellulite assessments before Investigator cellulite assessments) in the following sequential order using:
   a. Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) assessment (section 13.1.2.1); complete this prior to conducting S-GAIS
   b. Subject Global Aesthetic Improvement Scale (S-GAIS) (section 13.1.2.2)
7. Investigator Cellulite Assessments live of each of the buttocks in the following sequential order prior to marking dimples and injection sites using:
   a. Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) live assessment of subject (section 13.1.2.6)
   b. Investigator Global Aesthetic Improvement Scale (I-GAIS) (section 13.1.2.7)
8. Select and mark dimples to be treated in each buttock (section 12.2)
9. Digital photographs of each buttock after marking dimples and injection sites (section 13.1.1)
10. For eligible buttock(s), obtain kit number(s) of study treatment

12.5.2. Treatment Visits 2 and 3: Injection and Post-injection

1. Administration of study drug in the prone position (section 10.3)
2. Record number of dimples treated and number of injections administered in each buttock
3. Vital sign measurements (section 14.9)
4. Injection site reactions and local tolerability
5. Adverse events (section 14)

12.6. Day 71 (+5 days) / End of Study / Early Termination

The following procedures will be performed on Day 71:

1. Record concomitant medications/procedures (section 12.8)
2. Measurement of body weight
3. Vital sign measurements (section 14.9)
4. Collection of samples for:
   a. Clinical laboratory testing (section 14.7)
   b. Serum pregnancy test (section 14.7)
   c. Anti-AUX-I and anti-AUX-II antibody testing (section 14.8)
5. Digital photographs of each of the buttocks
6. Subject Cellulite Assessment of each of the two buttocks using the photographic image before marking dimples and injection sites (NOTE: complete subject cellulite assessments before Investigator cellulite assessments) using:
   a. Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) assessment (section 13.1.2.1)
   b. Subject Global Aesthetic Improvement Scale (S-GAIS) (section 13.1.2.2)
   c. Patient Reported Cellulite Impact Scale (PR-CIS) assessment (section 13.1.2.3); note this assessment is of both left and right buttocks rather than each individual buttock
   d. Subject Satisfaction with Cellulite Treatment Assessment (section 13.1.2.4); note this assessment is of both left and right buttocks rather than each individual buttock
   e. Subject Self-Rating Scale (SSRS) assessment (section 13.1.2.5); note this assessment is of both left and right buttocks rather than each individual buttock
7. Investigator Cellulite Assessments of each of the buttocks live using:
   a. Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) live assessment of subject (section 13.1.2.6)
   b. Investigator Global Aesthetic Improvement Scale (I-GAIS) (section 13.1.2.7)
8. Injection site reactions and local tolerability
9. Adverse events (section 14)

12.7. Unscheduled Visits

If any subject needs to return to the site prior to her next scheduled visit, site staff should follow the Unscheduled Visit procedures outlined in section 5. Site staff may conduct additional study procedures if required.

12.8. Prior and Concomitant Medications and Procedures

All prior medications taken within 90 days before randomization will be recorded. All medications (including over-the-counter medications) taken by the subject on Day 1 through the end of the study must be recorded. Any prior treatments (medications or procedures) for EFP through the end of the study must be recorded on the appropriate eCRF page.

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.

12.8.1. Prohibited Medications or Procedures

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

Procedures listed in exclusion criterion #4 (section 11.2, Exclusion Criterion #4) are prohibited for randomized subjects during the study.

Table 4: Concomitant Medication Restrictions for Subjects during the Treatment Phase of Study

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

12.9. Treatment Compliance

Randomized subjects will receive study drug administered by an Investigator at the Investigator's site.

Accidental or intentional overdoses should be reported to the Sponsor/designee promptly (see section 14.6.2.1, Overdose).

12.10. Blinding and Randomization

On Day 1, if each of the buttocks (ie, both buttocks) again meet the criteria (3 or 4 on the PR-PCSS and CR-PCSS), one buttock will be randomly assigned by the IWRS as the target buttock for the primary efficacy endpoint. Subjects, investigators, site personnel, and Endo personnel will be blinded to the identification of the target buttock.

On Day 1, if each of the buttocks (ie, both buttocks) again meet the criteria (3 or 4 on the PR-PCSS and CR-PCSS), the subject will be randomized to a treatment group. The interactive web response system (IWRS) will randomly assign each subject to a treatment group (EN3835 0.84 mg per buttock × two buttocks or placebo) in a 1:1 ratio within an investigational site. The treatment group will remain blinded to the Investigator, subjects, all site personnel, and the sponsor. The IWRS will assign the subject study drug kit numbers associated with the randomized treatment. At Day 22 and 43 visits, the IWRS will again assign the subject study drug kit numbers associated with the randomized treatment assigned at Day 1.

All precautions will be taken to ensure that the blinding of EN3835 and placebo is maintained throughout the study period. Unblinding will not be permitted by the study site unless it is deemed necessary for treatment of a medical emergency. Before breaking the blind, the Investigator should make every attempt to contact the Medical Monitor to discuss the necessity of breaking the blind. The study site will have the ability to immediately determine treatment identification in the event of an emergency by using the unblinding function within the IWRS, however, the Medical Monitor must be notified immediately. The Investigator will be required to make a full written explanation of the reason for unblinding the subject and the date. In the event that a subject is unblinded prior to contacting the Medical Monitor, the Investigator must provide this information in writing to the Medical Monitor as soon as possible. Breaking the blind at the investigative site will immediately disqualify the subject from further participation in the study. In addition, the event(s) leading to emergency unblinding must be reported as an SAE according to instructions in section 14.5.2, Reporting Serious Adverse Events.

In addition, it may be necessary for the Investigator or qualified designee to unblind a subject as a result of a clinically significant finding noted during safety review by the Investigator, Safety Monitor, Medical Monitor and/or qualified designee that might jeopardize subject safety.

13. ASSESSMENT OF EFFICACY

13.1. Efficacy Measurements

13.1.1. Digital Photography

Although digital photographs are not direct efficacy measurements, digital photography will be utilized in the assessment of certain efficacy measurements ie to assess certain cellulite severity parameters at specific intervals (see section 5, Schedule of Events). At the Screening visit, the Investigator or qualified designee will photograph each buttock using a Sponsor-supplied standardized digital camera in a standardized manner. 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 each of the two buttocks while the subject is standing in a consistent, standardized relaxed standing pose, ie, standing position with relaxed gluteus muscles, at the following time points:

- Screening (no markings of dimples or injection site) - each of the two buttocks
- Before and after marking dimples and injection sites (prior to injections) on Days 1, 22, and 43 - each of the two buttocks
- During the Day 71 visit (end of study/early termination) (no dimple or injection site markings) - each of the two buttocks

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.

13.1.2. Subject and Investigator Cellulite Assessments

Investigator cellulite assessments are independent of the subject assessments. Therefore, all subject cellulite assessments must be completed before the Investigator's cellulite assessments are initiated. At each visit prior to the subject assessments being completed, subjects will watch an ePRO and scale tutorial video and instructions. The site will document subject review of the training (video and instructions) in source documentation. The subject assessments will be done using a subject-assigned password protected electronic patient reported outcome (ePRO) system and the Investigator and study site personnel will not have access to the subject's assessments or password; the clinician assessment will be recorded in an investigator-assigned password protected system and the subject will not have access to the Investigator's assessments or password. Subject assessments will be done alone with no study site personnel in the room. Investigators will be instructed not to verbalize their ratings while in the presence of the subject.

13.1.2.1. 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. The scale is a 5-level photonumeric scale developed specifically for patients and used by the subject to assess the severity of their cellulite in the buttocks by viewing digital images of each of their buttocks 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.

At Screening and at the beginning of their visits on Day 1, Day 22, Day 43, and Day 71, subjects will have digital photographs taken of each of their two buttocks. Subjects will be given instructions in the proper use (Patient Instructions for Use of PR-PCSS) of the PR-PCSS and then perform the PR-PCSS for each of the buttocks (Appendix B). While viewing the digital images of each of their buttocks on a standardized computer monitor and using PR-PCSS for buttock, subjects will be instructed to answer the following question for each buttock: *Today, how would you rate the severity of your cellulite in the area displayed using the PR-PCSS?* The subject will be given the following explanations*: Please try to match the severity of your cellulite, as seen in this digital image, with one of the cellulite levels on the PR-PCSS. Please look at the image of your cellulite and the pictures, labels, and descriptions on the PR-PCSS carefully before selecting your answer. If you feel that your cellulite level is between 2 of the levels, please select the level that is closest to your image. If you feel that your cellulite is exactly halfway between two PR-PCSS levels of cellulite severity, please select the more severe response.*

The subject will enter their rating electronically into an ePRO system; the Investigator and other site personnel will be blinded to the rating entered by the subject. This variable will 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.

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

Subjects will complete the S-GAIS for each of the buttocks as described below at the Day 22, Day 43, and Day 71 study visits using the pre-treatment Day 1 digital image (Baseline) of each of the buttocks for comparison.

All treated subjects will be instructed to answer the following question for each buttock:

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. The subject will view each of their pre-treatment Day 1 digital images alongside their Day 22, Day 43 or Day 71/End of study visit digital images of each of their buttocks to aid in the assessment (Table 5). Subjects will provide a rating from those below that best represents their answer for each treated buttock.

This variable will 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 5: Subject Global Aesthetic Improvement Scale (S-GAIS)

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

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

At the Day 1 visit and the Day 71 visit, subjects will be instructed to answer 6 questions related to the areas selected for treatment on their buttocks on the PR-CIS (Appendix D) while viewing digital images of their buttocks. The PR-CIS assesses the visual and emotional impact of cellulite (happy, bothered, self-conscience, embarrassed, looking older, or looking overweight or out of shape) using a 6-question survey, with each question rated on a numerical rating scale from 0 (not at all) to 10 (extremely).

This variable will 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.

13.1.2.4. Subject Satisfaction with Cellulite Treatment Assessment

At the Day 71 visit, subjects will be instructed to answer a question related to their treated buttocks while viewing digital images of their buttocks. Subjects will be given a list of responses and they will provide a rating from those below that best represents their answer (Table 6).

Today, how satisfied are you with the results of the cellulite treatment you received on the specific area or areas on your buttocks that were treated?

This variable will 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 6: Subject Satisfaction with Cellulite Treatment Assessment - Buttocks

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

13.1.2.5. Subject Self-Rating Scale (SSRS)

The SSRS is a measure that assesses subject satisfaction with appearance in association with cellulite on the buttocks using whole numbers on a 7-level scale that ranges from 0 (extremely dissatisfied to 6 (extremely satisfied). The patient will be asked to respond to the question related to the satisfaction with appearance of the cellulite on their buttocks on the appropriate visit day (note Day 71 question is different than Day 1 question). No photographs or reference to previous ratings or evaluations will be used. Subjects will be given a list of responses and they will provide a rating from those below that best represents their answer (Table 7); the list of responses is the same for Day 1 and for Day 71.

On Day 1 (Baseline), subjects will be instructed to answer: *Considering your appearance in association with your cellulite on your buttocks, how satisfied do you feel with your appearance at the present time?*

On Day 71, subjects will be instructed to answer: *Considering your appearance in association with your cellulite on your buttocks, how satisfied do you feel with your appearance at the present time whether or not in your judgment it is due entirely to treatment with EN3835?*

This variable will 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 7: Subject Self-Rating Scale (SSRS)

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

13.1.2.6. 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. The scale is a 5-level photonumeric scale developed specifically for clinicians and used by the Investigator to assess the severity of the subject's cellulite in each buttock by live assessments; the ratings range from 0 (None) to 4 (Severe) with labels and descriptors to aid the Investigator in the assessments.

Investigators will be trained and qualified on the use of the CR-PCSS prior to assessing any subjects.

At the Screening visit, the Investigator will determine severity of cellulite of each of the two buttocks via live assessment of the subject using the CR-PCSS for buttock (Appendix C) after the subject has completed her self-assessment using the PR-PCSS. Before injections on treatment visits Day 1, Day 22, and Day 43, and on visit Day 71; Investigators will evaluate each of the two buttocks by live assessments using the CR-PCSS for the buttock to make his/her

evaluation. At each visit, the Investigator will make his/her assessment independently and after the subject has conducted her self-assessment using the PR-PCSS.

This variable will 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.

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

Investigators will be trained by Endo or their designee on the use of the I-GAIS prior to assessing any subjects. At each visit, the Investigator may review the training and use material for the I-GAIS. On the Day 22, Day 43, and Day 71 study visits, the Investigator will determine the degree of improvement of each buttock by comparing the cellulite from the Day 1 pre-treatment (Baseline) digital image of each buttock to the cellulite seen in a live assessment (Table 8). The I-GAIS assessment will occur after the CR-PCSS assessment (section 13.1.2.6) to avoid introducing potential bias to the static CR-PCSS assessment by the Investigator. For each buttock, the Investigator will provide the rating from those below that best represents his/her answer.

This variable will 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

14. ASSESSMENT OF SAFETY

14.1. Definitions

14.1.1. Adverse Events

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. Adverse events 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 Events

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 malignancy, 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 28 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 28 days after the last dose of study medication. SAEs that occur within 28 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 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.

14.6. Special Reporting Situations

14.6.1. Adverse Events of Special Interest

Adverse events such as bruising, ecchymosis, hematomas, and contusions that occur remote to the site of drug administration, or any hypersensitivity reactions, including anaphylaxis, will be recorded and evaluated for seriousness and severity (see section 14.1.1, Adverse Events or section 14.1.2, Serious Adverse Events).

In addition, local AEs associated with the injection site, including bruising, pain, nodules/mass, ulceration, erythema, pruritus, swelling, and/or induration, will be recorded and evaluated for seriousness and severity (see as appropriate, section 14.1.1, Adverse Events or section 14.1.2, Serious Adverse Events)

14.6.2. Overdose/Misuse/Abuse

14.6.2.1. Overdose

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 12.9) 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

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

Any 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 28 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.

A subject who becomes pregnant must be withdrawn from the study. 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. AEs/SAEs 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 PVRM Department (when the non-subject agrees) on the departmental form for serious adverse experiences 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, Reporting Serious Adverse Events. Additionally, the drug accountability source documentation at the site should reflect this occurrence.

14.7. Clinical Laboratory 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 or qualified designee must acknowledge the review of laboratory results.

The Investigator will review all abnormal lab results for potentially clinically important. Any abnormal clinical laboratory test result meeting the Investigator's criteria for potentially clinically important (refer to central laboratory manual) 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).

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

Clinical laboratory parameters that will be measured in this study are listed in Table 9.

Table 9: Clinical Laboratory Tests

Hematology	Biochemistry	Urinalysis
Hemoglobin	Glucose	Glucose
Hematocrit	Sodium	Protein
Red blood cell	Potassium	Specific gravity
White blood cell (WBC)	Calcium	pH
Platelets	Chloride	Ketones
WBC Differential	CO_2	Bilirubin
	Inorganic phosphate	Urobilinogen
	Blood urea nitrogen	Nitrite
	Creatinine	Blood*
	Creatinine clearance (estimated)	Leukocytes*
	Aspartate transaminase (AST)	
	Alanine transaminase (ALT)	
	Gamma-glutamyl transferase (GGT)	
	Total bilirubin (TBL) (direct bilirubin reflex if elevated)	
	Albumin	
	Alkaline phosphatase (ALP)	
	Uric acid	

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

For women of childbearing potential, a serum pregnancy test will be performed at Screening and Day 71/End of Study/Early Termination, and urine pregnancy tests will be performed at Day 1, Day 22, and Day 43 (refer to section 5). Female subjects of childbearing potential must have a negative pregnancy test at the Screening Visit and at Day 1 (Baseline), Day 22, and Day 43 to be randomized and/or 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.

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

Serum samples will be collected and will be tested for binding anti-AUX-I and anti-AUX-II antibody testing before injection on Days 1, 22, and 43, and at the Day 71 visit. A subset [redacted] of subject samples will be tested for neutralizing antibodies from Day 1 and Day 71 visits; additional samples will be retained.

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.

14.9. Vital Signs

Vital sign measurements will be documented as described in the Schedule of Events (section 5). 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.

The Investigator will review all vital sign values for clinical significance prior to discharge. 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 10 after the subject has rested for at least 5 minutes.

Table 10: 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

14.10. Electrocardiogram

A 12-lead ECG recording will be conducted at the Screening Visit. The subject should be in a supine position for at least 5 minutes before the recording is conducted. Lead position will be that of a standard 12-lead ECG; no additional or special lead placements will be necessary.

A qualified physician will interpret, sign, and date the ECGs. ECG findings will be documented as normal; abnormal, clinically significant; or abnormal, not clinically significant. The Investigator or qualified designee must sign and date the ECG, thereby acknowledging review of ECG results. 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).

14.11. Physical Examination

A complete physical examination will be performed at the Screening Visit. All examinations will be performed by a physician or health professional listed on the Form FDA 1572 and licensed to perform physical examinations. Height and body weight will be measured and recorded at screening.

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).

At screening, the Investigator will also assess the subject's skin type using the Fitzpatrick scale (Table 11). Only the Fitzpatrick Scale shown below may be used during the study.

Table 11: Fitzpatrick Scale

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

Follow-up body weight will be measured before injection on Day 22 and Day 43 and at the Day 71 visit.

14.12. 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

The primary variable is the proportion of 2-level composite responders at Day 71 defined as subjects with:

- an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator of the target buttock, and
- an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS as assessed by the subject while viewing the digital image of the target buttock.

A subject will be considered a responder if these criteria are met in the randomized target buttock of that subject.

The results of a prior Phase 2b study of this drug (Study EN3835-201) demonstrated the overall rate for treated buttocks of composite responders with an improvement of at least 2 levels on both the PR-PCSS and the CR-PCSS was 14.9% in the EN3835 treatment group versus 1.1% in the Placebo group. Given this result, the study is planned to randomize 420 subjects with a 1:1 ratio into either the EN3835 arm (0.84 mg/buttock, 1.68 mg total dose) or placebo arm.

The sample size calculation was based on the following assumptions: 1 [redacted] 2) Fisher exact test; 3) type I error of 0.05; 4) power of at least 90%; and 5) dropout rate of approximate 10%.

This sample size will also provide >90% power with type 1 error of 0.05 to detect the treatment difference for all the key secondary endpoints based on the following results, majority of which were estimated from previous EN3835 study results.

Table 12: Previous Results as Basis for Sample Size

Efficacy Endpoint	EN3835	Placebo	Power
1-level PR-PCSS responders of target buttock	[redacted]	[redacted]	[redacted]
2-level PR-PCSS responders of target buttock	[redacted]	[redacted]	[redacted]
1-level composite responders of target buttock	[redacted]	[redacted]	[redacted]
2-level composite responders of non-target buttock	[redacted]	[redacted]	[redacted]
Proportion of subjects with SSRS rating ≥ 4	[redacted]	[redacted]	[redacted]
Change in PR-CIS Score, Mean (SD)	[redacted]	[redacted]	[redacted]
1-level S-GAIS responders of target buttock	[redacted]	[redacted]	[redacted]
2-level S-GAIS responders of target buttock	[redacted]	[redacted]	[redacted]

[a] Rates are estimated based on the reported results from the pooled pivotal studies of a drug approved for an aesthetic indication.

17.2. Subject Populations

Four (4) populations are considered in the statistical analysis of the study: safety, intent-to-treat (ITT), modified ITT (mITT), and per-protocol (PP).

17.2.1. Safety Population

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

17.2.2. Intent-to-Treat (ITT) Population

The ITT population is defined as all randomized subjects who have received at least one injection of study medication. All demographic and baseline characteristic summaries will be based on this population. The primary and key secondary efficacy parameters will be summarized based on this population.

17.2.3. Modified Intent-to-Treat (mITT) Population

The mITT population is defined as all intent-to-treat subjects with a baseline and at least 1 post-injection evaluation of both the Investigator CR-PCSS and subject PR-PCSS for both the target and non-target buttocks. All secondary and supportive efficacy evaluations will be based on the mITT population.

17.2.4. Per-Protocol (PP) Population

The PP population is defined as the mITT subjects without any of the following :

- Placebo randomized subject who receives EN3835 treatment.
- EN3835 randomized subject who receives placebo treatment only throughout study.
- Any subject who uses protocol-prohibited medications.
- Subject missing PR-PCSS and/or CR-PCSS assessment at Day 71.
- Subject with a buttock not receiving all three treatment sessions without medical reasons (e.g., adverse events or CR-PCSS rated as zero (0)).
- Subject who did not meet all inclusion and exclusion criteria.

This population may be used in the efficacy sensitivity analysis.

17.3. Subject Disposition

The number of subjects included in each study population will be summarized by treatment group. Subjects excluded from the safety and efficacy (eg, ITT) populations will be listed by treatment group.

The number and percentage of subjects completed and prematurely discontinued during the treatment period will be presented for each treatment group and pooled across treatment groups. Screen failures (ie, screened but not randomized subjects) and the associated failure reasons will be tabulated overall. Reasons for premature discontinuation from the treatment period as recorded on the termination page of the eCRF will be summarized (number and percentage) by

treatment group for all randomized subjects. Percentage of premature discontinuations will be compared between treatment groups.

17.4. Demographics and Other Baseline Characteristics

The summarization of demographic variables (eg, age, sex, race, weight, height, and body mass index [BMI]), medical and surgical history, and other baseline characteristics relevant to the indication studied in the study will be described.

Demographic characteristics, including sex, age, age group, race, height, and weight, will be summarized by treatment group, for the ITT population, using descriptive statistics. All screening characteristics and medical information will also be summarized by treatment group using descriptive statistics. The descriptive summaries will include frequency tables for all categorical response variables and n, mean, standard deviation (SD), median, minimum, and maximum for all continuous variables.

17.5. Efficacy Analyses

All efficacy endpoints including supportive efficacy analysis will be summarized as percentages. The dichotomous secondary endpoints (ie, responder endpoints) will be analyzed using a Cochran-Mantel-Haenszel test adjusted for Investigator. Changes in the PR-PCSS ratings and CR-PCSS ratings from baselines, S-GAIS scores, I-GAIS scores, and SSRS scores will be analyzed using the Wilcoxon rank sum test. Changes in PR-CIS from baselines will be analyzed using an analysis of covariance (ANCOVA) adjusted for baseline values. All the tests are two-sided.

The primary endpoint will be summarized as percentages and analyzed using a Cochran-Mantel-Haenszel test that compares the 2 treatment groups and adjusts for Investigator at a level of significance of 0.05 based on the ITT population. Any subject who does not have an evaluation of CR-PCSS and/or PR-PCSS at Day 71 will be classified as a non-responder.

The key secondary efficacy analyses will be analyzed in the same manner as the primary endpoint based on the ITT population. Any subject who does not have an evaluation at Day 71 will be classified as a non-responder for the analyses. The family #1 key secondary efficacy analyses will be performed only if the primary efficacy analysis is significant ($p \leq 0.05$; gatekeeping strategy). Similarly family #2 key secondary efficacy analyses will be performed only if at least one of the key secondary efficacy endpoints of family #1 is significant ($p \leq 0.0125$; parallel gatekeeping strategy) and family #3 key secondary efficacy analyses will be performed only if at least one of the key secondary efficacy endpoints of family #2 is significant (parallel gatekeeping strategy). Within a family of key secondary efficacy endpoints, the Bonferroni method will be performed to relocate unused alpha for testing each endpoint to assure an overall error rate of $p \leq 0.05$. The details of the testing procedures will be provided in the statistical analysis plan for the study.

All supportive endpoints will be summarized as subject counts and percentages for categorical data or n, mean, SD, median, minimum, and maximum for continuous data. All the supportive analyses will be performed based on all observed data (ie, missing data not imputed) in the mITT population at all visits without multiplicity adjustment. This analysis will also be performed at Day 71 with missing data at Day 71 imputed by a last observation carried forward (LOCF)

approach if subjects have at least one post-dose assessment. The dichotomous secondary endpoints (ie, responder endpoints) will be analyzed using a Cochran-Mantel-Haenszel test adjusted for Investigator. Changes in the PR-PCSS ratings and CR-PCSS ratings from baselines, S-GAIS scores, I-GAIS scores, and SSRS scores will be analyzed using the Wilcoxon rank sum test. Changes in PR-CIS from baselines will be analyzed using an analysis of covariance (ANCOVA) adjusted for baseline values.

17.5.1. Primary Efficacy Variable

The primary efficacy variable is the proportion of 2-level composite responders at Day 71 defined as subjects with:

- an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator of the target buttock, and
- an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS by the subject while viewing the digital image of the target buttock.

A subject will be considered a responder if these criteria are met in the randomized target buttock of that subject.

Sensitivity analyses for the primary endpoint will include:

- ITT subjects with missing data handled by multiple imputation (MI) approach
- ITT subjects with missing data handled by an LOCF approach
- mITT subjects with missing data handled by an LOCF approach
- Observed data only (no missing data handling)
- Per-protocol (PP) subjects with missing data handled by an LOCF approach if 10% or more subjects are excluded in the PP population from mITT population

17.5.2. Secondary Efficacy Variables

17.5.2.1. Key Secondary Variables

There will be 8 key secondary endpoints grouped in three families of 2 to 4 endpoints per family analyzed in hierarchical order.

- Family #1 – four endpoints:
  - Proportion of 1-level PR-PCSS responders defined as subjects with ≥1-level improvement in PR-PCSS severity rating of the target buttock at Day 71 compared to Day 1
  - Proportion of 2-level PR-PCSS responders defined as subjects with ≥2-level improvement in PR-PCSS severity rating of the target buttock at Day 71 compared to Day 1
  - Proportion of 1-level composite responders of the target buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the target buttock assessed live by the Investigator

and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of the target buttock) at Day 71 compared to Day 1

- Proportion of 2-level composite responders of the non-target buttock at Day 71 compared to Day 1

- Family #2 – two endpoints:
  - Proportion of 1-level SSRS responders defined as subjects who were at least slightly satisfied at Day 71 (SSRS rating ≥ 4)
  - Change from baseline (Day 1) of the PR-CIS total score at Day 71
- Family #3 – two endpoints:
  - Proportion of 1-level S-GAIS responders defined as subjects with ≥1-level improvement (improved, much improved or very much improved) in the S-GAIS assessment of the target buttock at Day 71
  - Proportion of 2-level S-GAIS responders defined as subjects with ≥2-level improvement (much improved or very much improved) in the S-GAIS assessment of the target buttock at Day 71

Sensitivity analyses for the key secondary endpoints will include:

- ITT subjects with missing data handled by MI approach
- ITT subjects with missing data handled by an LOCF approach
- mITT subjects with missing data handled by an LOCF approach
- Observed data only (no missing data handling)
- Per-protocol (PP) subjects with missing data handled by an LOCF approach if 10% or more subjects are excluded in the PP population from mITT population

17.5.3. Supportive Efficacy Variables

17.5.3.1. Supportive Variables

The supportive variables will evaluate assessments at various study time points and using various populations.

- Proportion of 2-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS of the target buttock (Days 22, 43, and 71)
- Proportion of 2-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS of the non-target buttock (Days 22, 43, and 71)
- Proportion of 1-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS of the target buttock (Days 22, 43, and 71)

- Proportion of 1-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS of the non-target buttock (Days 22, 43, and 71)
- Proportion of 2-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject.
- Proportion of 1-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject.
- Proportion of 2-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks.
- Proportion of 1-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks.
- Proportion of 2-level CR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the target buttock (Days 22, 43, and 71)
- Proportion of 2-level CR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the non-target buttock (Days 22, 43, and 71)
- Proportion of 1-level CR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the target buttock (Days 22, 43, and 71)
- Proportion of 1-level CR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the non-target buttock (Days 22, 43, and 71)
- Proportion of 2-level CR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject.
- Proportion of 1-level CR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject.
- Proportion of 2-level CR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks.
- Proportion of 1-level CR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks.

- Proportion of 1-level composite responders of the target buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same target buttock) (Days 22, 43, and 71)
- Proportion of 1-level composite responders of the non-target buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the non-target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same non-target buttock) (Days 22, 43, and 71)
- Proportion of 1-level composite responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject.
- Proportion of 1-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks.
- Proportion of 2-level composite responders of the target buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same target buttock) (Days 22, 43, and 71)
- Proportion of 2-level composite responders of the non-target buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the non-target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same non-target buttock) (Days 22, 43, and 71)
- Proportion of 2-level composite responders of at least one of two buttocks (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject.
- Proportion of 2-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks.
- Proportion of subjects at each level of the S-GAIS of the target buttock (Days 22, 43, and 71)
- Proportion of subjects at each level of the S-GAIS of the non-target buttock (Days 22, 43, and 71)
- Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S-GAIS of the target buttock (Days 22, 43, and 71)
- Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S-GAIS of the non-target buttock (Days 22, 43, and 71)

- Proportion 1-level S-GAIS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject.
- Proportion of 1-level S-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target right buttocks.
- Proportion of subjects at each level of the I-GAIS of the target buttock (Days 22, 43, and 71)
- Proportion of subjects at each level of the I-GAIS of the non-target buttock (Days 22, 43, and 71)
- Proportion of 1-level I-GAIS responders defined as subjects with a response of at least 1 (improved) in the I-GAIS of the target buttock (Days 22, 43, and 71).
- Proportion of 1-level I-GAIS responders defined as subjects with a response of at least 1 (improved) in the I-GAIS of the non-target buttock (Days 22, 43, and 71).
- Proportion of 1-level I-GAIS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject.
- Proportion of 1-level I-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks.
- Change from baseline (Day 1) of the PR-CIS total score at Day 71
- Change from baseline (Day 1) of the abbreviated PR-CIS score at Day 71
- Proportion of subjects with a change from baseline (Day 1) of the PR-CIS $\geq$ 12 at Day 71
- Proportion of subjects with a change from baseline (Day 1) of the abbreviated PR-CIS $\geq$ 10 at Day 71
- Proportion of subjects at each level of the SSRS (Day 1 (Baseline) and Day 71)
- Proportion of 1-level SSRS responders defined as subjects who were at least slightly satisfied at Day 71 (SSRS rating $\geq$ 4)
- Proportion of subjects at each level of the subject satisfaction with cellulite treatment assessment (Day 71)
- Proportion of satisfied responders (defined as subjects with a response of at least 1 (ie, 1-Satisfied or 2-Very Satisfied) in the subject satisfaction with cellulite treatment assessment (Day 71)

17.6. Safety Analyses

Safety variables include adverse events, laboratory parameters, vital signs, ECG parameters, and physical examinations. For each safety parameter, the last assessment made prior to the first dose of study drug will be used as the baseline for all analyses of that safety parameter.

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. Prior medication will be defined as any medication taken prior to the first dose of study drug. Concomitant medication is defined as any medication taken on or after the date of first dose of study drug.

Prior and concomitant medication use will be summarized descriptively by the number and percentage of subjects for each preferred term (generic name from WHO dictionary) by treatment. Multiple use of the same medication by a subject will be counted only once.

17.6.2. Study Drug Exposure

The following information regarding treatment will be summarized per each treated buttock by treatment group:

- Total number of treatment visits
- Number of subjects who had treatment session done or treatment session not done at each treatment visit
- For subjects who had the treatment session done, the number of subjects who got all 24 injections at the treatment visit or who received less than 24 injections
- Number of injections given at each treatment visit
- Number of dimples treated at each treatment visit
- Average number of injections per dimple at each treatment visit

Subjects who did not receive all 3 treatment visits and who did not receive 24 injections at a treatment visit will be listed.

17.6.3. Measurement of Treatment Compliance

Not applicable (the study drug is administered at the site by the study investigator).

17.6.4. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code AEs.

An AE (classified by preferred term) that started on or after the date of the first dose of the study drug 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.

The by-frequency summaries will also include incidence of the SAEs and non-SAEs by preferred term that at least 2% of the subjects in one treatment group. Duration of AEs will be tabulated by treatment group.

The Fisher exact test will be used to compare EN3835 to placebo.

Listings will be presented for subjects with SAEs, subjects with AEs leading to discontinuation of study or study drug, 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 study will be presented by treatment group.

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 will be detailed in the Statistical Analysis Plan (SAP). The PCI percentages will be calculated relative to the number of subjects with baseline and at least one post-baseline assessment. A supportive listing of subject values will be provided including the subject ID, study center, treatment group, baseline and post-baseline values.

The change from baseline for vital signs parameters are compared between EN3835 and placebo using an analysis of variance (ANOVA) with a factor of drug (EN3835 or placebo) while the Fisher exact test will be used for the incidence of PCI values.

17.6.6. Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values in International System of Units (SI units) and changes from baseline at Day 71 will be presented by treatment group for each clinical laboratory parameter.

The number and percentage of subjects with potentially clinically important (PCI) post-baseline clinical laboratory values will be tabulated by treatment group. The criteria for PCI laboratory values will be detailed in the Statistical Analysis Plan (SAP). The PCI percentages will be calculated relative to the number of subjects with at least one post-baseline assessment. A supportive listing of subjects with post-baseline PCI values will be provided, including the subject ID, study center, treatment group, baseline and post-baseline values.

The change from baseline for clinical laboratory parameters are compared between EN3835 and placebo using an ANOVA with a factor of drug (EN3835 or placebo) while the Fisher exact test will be used for the incidence of PCI values.

17.6.7. Electrocardiogram

Not applicable (ECG is done only at screening for the subject's enrollment eligibility).

17.6.8. Physical Examination

Body weight and BMI at Day 22, Day 43, and Day 71 as well as their change from baseline (Day 1) at those time points will be presented by treatment group.

17.6.9. Other Safety Measurements

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 treatment group. Average antibody levels will be summarized on logarithmically transposed titer values. In addition, by-treatment percentages of neutralizing anti-AUX-I and anti-AUX-II antibodies in a subset of subjects' samples [redacted] ill be summarized at Day 71.

17.7. Pharmacokinetic Analyses

Not applicable.

17.8. Pharmacodynamic Analyses

Not applicable.

17.9. Other Data (eg, Health Economics/QOL, Pharmacogenetic, etc.)

Not applicable.

17.10. Interim Analysis

No interim analysis is planned for this study.

17.11. Statistical Software

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

18. STUDY DRUG MATERIALS AND MANAGEMENT

18.1. Study Drug Identity

EN3835 is manufactured and supplied by Endo.

EN3835 is a sterile lyophilized powder consisting of 0.92 mg of collagenase clostridium histolyticum, 18.9 mg sucrose, 1.1 mg Tris, 37.7 mg mannitol, hydrochloric acid QS to pH 8.5, in a 5-mL vial.

Placebo for injection is a sterile lyophilized powder consisting of 18.9 mg sucrose, 1.1 mg Tris, 37.7 mg mannitol, hydrochloric acid QS to pH 8.5, in a 5-mL vial.

EN3835 sterile diluent for reconstitution is 0.6% sodium chloride and 0.03% calcium chloride dehydrate in water for injection filled into 5-mL vials.

18.2. Study Drug Packaging and Labeling

Each vial of study drug and diluent will minimally be labeled with contents, Sponsor identification, storage, administration/use, and appropriate cautions statements. Each kit will contain one vial of EN3835 or placebo and one vial of sterile diluent. Kits containing EN3835 or placebo will be indistinguishable and only identifiable by their unique kit number.

18.3. Study Drug Storage

All study drug will be provided by Endo. Study drug must be stored in an appropriate, secure area. Study drug must be kept in a temperature-monitored refrigerator (2°C-8°C) with locked access until used or returned to Endo.

18.4. Study Drug Preparation

Refer to the Reconstitution Instructions for detailed preparation instructions.

For each dose session, the IWRS will dispense 2 kits, 1 kit for each buttock to be treated. Four (4) 0.9-mL syringes will be prepared from each vial of EN3835 or placebo, 4 syringes/kit, for a total of 8 syringes (4 syringes for each buttock).

Used drug vials should be returned to the kit carton and stored in a secure location until reconciled and returned by the Clinical Research Associate (CRA). Dispose of used diluent vials, needles, and syringes per local regulations.

The reconstituted study drug solution should be administered as soon as possible after reconstitution. The study drug solution can be kept at room temperature [redacted] Remove drug/prepared syringes from the refrigerator and allow it to stand at room temperature for 15 minutes prior to injection of study drug.

18.5. Study Drug Accountability

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/IEC, and regulatory agencies for routine inspection and accountability during monitoring visits. When instructed by Endo, the Investigator agrees to return all original used or unused study drug kits to Endo's return vendor.

18.5.1. Study Drug Handling and Disposal

The Investigator agrees not to supply study drug to any person except to those subjects enrolled in the study. The Investigator is responsible for recording the receipt and use of all drugs supplied and for ensuring the supervision of the storage and allocation of these supplies. All used and 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 and its use. At the end of the study, all used and unused drug supplies will be returned to Endo’s return vendor.

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:

- PR-PCSS
- CR-PCSS
- S-GAIS
- I-GAIS
- PR-CIS
- Subject Satisfaction with Cellulite Treatment Assessment
- SSRS

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/assent, the Investigator is responsible for obtaining any additional documentation to demonstrate compliance with local privacy laws applicable to activities performed.

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

A unique Subject identification number will be assigned according to section 12.1.2.2 at the time that the Subject signs the informed consent form.

22. DATA HANDLING AND RECORDKEEPING

22.1. Data Collection

Endo will provide an electronic data capture (EDC) system for this study. 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).

Data entries will be corrected by changing the entry in the EDC system. Any changes or corrections to eCRF data will be electronically tracked and will include the reason for correction, who made the correction and the date/time stamp when the correction was made within the audit trail of the EDC system.

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 case report form (CRF) data for his/her files.

23. REPORTING AND PUBLICATION

All data generated in this study are the property of Endo Pharmaceuticals Inc. 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 Pharmaceuticals Inc.

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 FDA 1572. If during the course of the study any information reported on the Form FDA 1572 changes, a revised Form FDA 1572 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 FDA 1572 (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.

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 Pharmaceuticals Inc. 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)/Clinical Trial Authorization (CTA) or request for marketing approval (New Drew Application [NDA]/Marketing Authorization Application [MAA]).

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 Pharmaceuticals Inc. 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 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.

[redacted]

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 STATEMENT

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):361-70.
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):175-90.
4. Terranova F, Berardesca E, Maibach H. Cellulite: nature and aetiopathogenesis. *Int J Cosmetic Sci.* 2006;28(3):157-67.
5. Avram MM. Cellulite: a review of its physiology and treatment. *J Cosmet Laser Ther.* 2004;6(4):181-5.
6. Khan MH, Victor F, Rao B, Sadick NS. Treatment of cellulite: Part II. Advances and controversies. *J Am Acad Dermatol* 2010;62(3):373-84.
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):1110-4.
8. Hexsel DM, Mazzuco R. Subcision: a treatment for cellulite. *Int J Dermatol.* 2000;39(7):539-44.
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;22:233-7.
10. DiBernardo BE. Treatment of cellulite using a 1440-nm pulsed laser with one-year follow-up. *Aesthet Surg J.* 2011;31(3):328-41.
11. Investigational Brochure: Collagenase Clostridium Histolyticum for Injection (AA4500/EN3835), Version 8.0. Endo Pharmaceuticals Inc.; July 2017.

[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]).

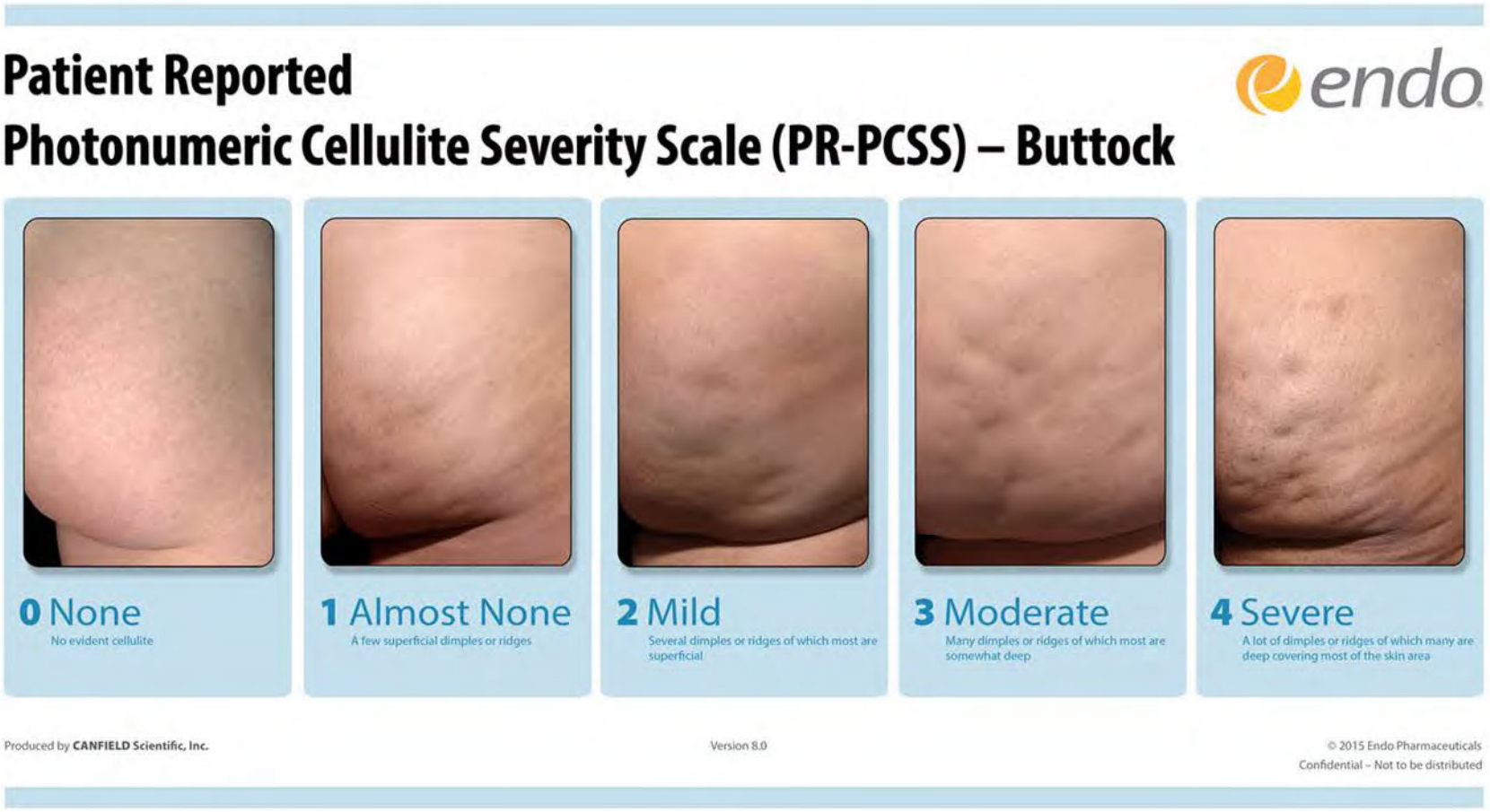
8. Financial Disclosure Certification or Certification of Non-Disclosure (for studies to be submitted for a US New Drug Application/Biologics License Application [NDA/BLA]).

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. PATIENT-REPORTED PHOTONUMERIC CELLULITE SEVERITY SCALE (PR-PCSS) FOR THE BUTTOCK



APPENDIX C. CLINICIAN-REPORTED PHOTONUMERIC CELLULITE SEVERITY SCALE (CR-PCSS) FOR THE BUTTOCK

APPENDIX D. PATIENT REPORTED CELLULITE IMPACT SCALE (PR-CIS)

Please select the rating that best represents your answer on a scale of 0 to 10 with 0 representing "Not at all" and 10 representing "Extremely" while viewing digital images of your buttocks. Please answer each question.

1. Thinking about the areas selected for treatment, how happy are you with the appearance of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

2. Thinking about the areas selected for treatment, how bothered are you by the appearance of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

3. Thinking about the areas selected for treatment, how self-conscious are you about the appearance of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

4. Thinking about the areas selected for treatment, how embarrassed are you about the appearance of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

5. Thinking about the areas selected for treatment, how much older do you look because of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

6. Thinking about the areas selected for treatment, how overweight or out of shape do you look because of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

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

EN3835

EN3835-303

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF EN3835 IN THE TREATMENT OF EDEMATOUS FIBROSCLEROTIC PANNICULOPATHY

IND 110077

Amendment 2

Date:

Original Protocol: September 27, 2017

Amendment 1: December 19, 2017

Amendment 2: January 18, 2018

Auxilium Pharmaceuticals, Inc. (Auxilium) was acquired by Endo International plc. in January 2015. The sponsor of the application remains as Auxilium Pharmaceuticals, LLC, 1400 Atwater Drive, Malvern, PA; however, Endo Pharmaceuticals Inc. is authorized to act and to communicate on behalf of Auxilium.

Confidentiality Statement

2. SUMMARY OF CHANGES

EN3835-303 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 2 was incorporated into the protocol on January 18, 2018. The major reasons for this amendment are revising the primary efficacy variable from at least one buttock to a randomly selected target buttock, revising key secondary endpoints, and adding an additional efficacy assessment.

Section	Original Text	Revised Text
4 Synopsis, Study Period	Estimated date first subject enrolled: Feb-2018 Estimated date last subject completed: Sep-2018	Estimated date first subject enrolled: Feb-2018 Estimated date last subject completed: Oct-2018
4 Synopsis, Study Design	Added text	Of the two assigned eligible buttocks, one buttock will be randomly selected as the target buttock for the primary efficacy endpoint. The other (remaining) buttock will be considered the non-target buttock. Subjects, investigators, site personnel, and Endo personnel will be blinded to the identification of the target and the non-target buttocks.
	At Day 1, the subject will complete a Patient Reported Cellulite Impact Scale (PR-CIS) assessment.	At Day 1, the subject will complete a Patient Reported Cellulite Impact Scale (PR-CIS) assessment and a Subject Self-Rating Scale (SSRS) assessment.
4 Synopsis, Diagnosis and Inclusion/Exclusion Criteria, Exclusion Criteria	13. Was a subject in a previous cellulite clinical trial of collagenase clostridium histolyticum (CCH): AUX-CC-830, AUX-CC-831, EN3835-102, EN3835-104, EN3835-201, and/or EN3835-202	13. Was a subject in a previous cellulite clinical trial of collagenase clostridium histolyticum (CCH): AUX-CC-830, AUX-CC-831, EN3835-102, EN3835-104, EN3835-201, EN3835-202, and/or EN3835-205
4 Synopsis, Criteria for Evaluation, Efficacy	• Subject using PR-PCSS while viewing digital image of the left buttock: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the left buttock • Subject using PR-PCSS while viewing digital image of the right buttock: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the right buttock • Investigator using the CR-PCSS by live assessment: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the left buttock	• Subject using PR-PCSS while viewing digital image of the target buttock: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the target buttock • Subject using PR-PCSS while viewing digital image of the non-target buttock: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the non-target buttock • Investigator using the CR-PCSS by live assessment: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the target buttock

Section	Original Text	Revised Text
	• Investigator using the CR-PCSS by live assessment: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the right buttock • Investigator Global Aesthetic Improvement Scale (I-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the left buttock • Investigator Global Aesthetic Improvement Scale (I-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the right buttock • Subject Global Aesthetic Improvement Scale (S-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the left buttock • Subject Global Aesthetic Improvement Scale (S-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the right buttock • Patient Reported Cellulite Impact Scale (PR-CIS): 6 questions with responses to each question consisting of a numerical rating scale (NRS) ranging from 0 (Not at all) to 10 (Extremely) • Subject satisfaction with cellulite treatment assessment: 5-level scale ranging from 2 (very satisfied) to −2 (very dissatisfied) (Day 71) for both left and right buttocks	• Investigator using the CR-PCSS by live assessment: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the non-target buttock • Investigator Global Aesthetic Improvement Scale (I-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the target buttock • Investigator Global Aesthetic Improvement Scale (I-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the non-target buttock • Subject Global Aesthetic Improvement Scale (S-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the target buttock • Subject Global Aesthetic Improvement Scale (S-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the non-target buttock • Patient Reported Cellulite Impact Scale (PR-CIS): 6 questions with responses to each question consisting of a numerical rating scale (NRS) ranging from 0 (Not at all) to 10 (Extremely) • Subject Self-Rating Scale (SSRS): 7-level scale ranging from 0 (extremely dissatisfied) to 6 (extremely satisfied) (Day 1 (Baseline) and Day 71) • Subject satisfaction with cellulite treatment assessment: 5-level scale ranging from 2 (very satisfied) to −2 (very dissatisfied) (Day 71) for both left and right buttocks
4 Synopsis, Criteria for Evaluation, Safety	• Adverse events (AEs) (including those of special interest (AESI); which are adverse events such as bruising, ecchymosis, hematomas, and contusions that occur remote to the site of drug administration, or any hypersensitivity reactions, including anaphylaxis)	• Adverse events (AEs) (including those of special interest (AESI); which are AEs such as bruising, ecchymosis, hematomas, and contusions that occur remote to the site of drug administration, or any hypersensitivity reactions, including anaphylaxis; and local AEs associated with the injection site, including bruising, pain, nodules/mass, ulceration, erythema, pruritus, swelling, and/or induration)

Section	Original Text	Revised Text
4 Synopsis, Statistical Methods	The primary endpoint is the proportion of 2-level composite responders at Day 71 defined as subjects with at least one of two treated buttocks with: • an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator, and • an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS as assessed by the subject while viewing the digital image of the same buttock. A subject will be considered a responder if these criteria are met in either the left buttock or right buttock or both buttocks in that subject.	The primary endpoint is the proportion of 2-level composite responders at Day 71 defined as subjects with: • an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator of the target buttock, and • an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS as assessed by the subject while viewing the digital image of the target buttock. A subject will be considered a responder if these criteria are met in the randomized target buttock of that subject.
4 Synopsis, Statistical Methods, Sample Size Consideration	The sample size calculation was based on the following assumptions: [redacted]) treatment effect of at least 12% of composite responders with an improvement of at least 2 levels on both the PR-PCSS and the CR-PCSS for at least one treated buttock; 4) Fisher exact test; 5) type I error of 0.05; 6) a power of at least 90%; and 7) dropout rate of approximately 10%.	The sample size calculation was based on the following assumptions: [redacted] 2) Fisher exact test; 3) type I error of 0.05; 4) power of at least 90%; and 5) dropout rate of approximately 10%.
	This sample size will also provide >90% power with type 1 error of 0.025 to detect 1-level responder rate difference for buttocks using the PR-PCSS of 72% in the EN3835 group and 48% in the placebo group as well as 1-level responder rate difference using the S-GAIS of 75% in the EN3835 group and 39% in the placebo group, which were estimated from the EN3835-201 study.	This sample size will also provide >90% power with type 1 error of 0.05 to detect the treatment difference for all the key secondary endpoints based on previous study results.

Section	Original Text	Revised Text
4 Synopsis, Statistical Methods, Analyses, Analyses of Primary Endpoint	The primary endpoint is the proportion of 2-level composite responders at Day 71 defined as subjects with at least one of two treated buttocks with: • an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator, and • an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS as assessed by the subject while viewing the digital image of the same buttock. A subject will be considered a responder if these criteria are met in the left buttock or right buttock or both buttocks in that subject.	The primary endpoint is the proportion of 2-level composite responders at Day 71 defined as subjects with: • an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator of the target buttock, and • an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS as assessed by the subject while viewing the digital image of the target buttock. A subject will be considered a responder if these criteria are met in the randomized target buttock of that subject.
4 Synopsis, Statistical Methods, Analyses, Analyses of Key Secondary Endpoints	There will be 4 key secondary endpoints grouped as two families of 2 endpoints per family analyzed in a hierarchical order. • Family #1 – two endpoints: – Proportion of 1-level PR-PCSS responders defined as subjects with ≥1-level improvement in PR-PCSS severity rating of left buttock at Day 71 compared to Day 1 – Proportion of 1-level PR-PCSS responders defined as subjects with ≥1-level improvement in PR-PCSS severity rating of right buttock at Day 71 compared to Day 1 • Family #2 – two endpoints: – Proportion of 1-level S-GAIS responders defined as subjects with ≥1-level improvement (improved, much improved or very much improved) in the S-GAIS assessment of left buttock at Day 71 – Proportion of 1-level S-GAIS responders defined as subjects with ≥1-level improvement (improved, much improved or very much improved) in the S-GAIS assessment of right buttock at Day 71	There will be 8 key secondary endpoints grouped as three families of 2-4 endpoints per family analyzed in hierarchical order. • Family #1 – four endpoints: – Proportion of 1-level PR-PCSS responders defined as subjects with ≥1-level improvement in PR-PCSS severity rating of the target buttock at Day 71 compared to Day 1 – Proportion of 2-level PR-PCSS responders defined as subjects with ≥2-level improvement in PR-PCSS severity rating of the target buttock at Day 71 compared to Day 1 – Proportion of 1-level composite responders of the target buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of the target buttock) at Day 71 compared to Day 1 – Proportion of 2-level composite responders of the non-target buttock at Day 71 compared to Day 1 • Family #2 – two endpoints: – Proportion of 1-level SSRS responders defined as subjects who were at least slightly satisfied at Day 71 (SSRS rating ≥ 4) – Change from baseline (Day1) of the PR-CIS at Day 71

Section	Original Text	Revised Text
		• Family #3 – two endpoints: – Proportion of 1-level S-GAIS responders defined as subjects with ≥1-level improvement (improved, much improved or very much improved) in the S-GAIS assessment of the target buttock at Day 71 – Proportion of 2-level S-GAIS responders defined as subjects with ≥2-level improvement (much improved or very much improved) in the S-GAIS assessment of the target buttock at Day 71
	The family #1 key secondary efficacy analyses will be performed only if the primary efficacy analysis is significant at a significance level of $p \leq 0.05$ (gatekeeping strategy). Similarly, family #2 key secondary efficacy analyses will be performed only if at least one of the key secondary efficacy endpoints of family #1 is significant at a significance level of $p \leq 0.025$ (parallel gatekeeping strategy)	The family #1 key secondary efficacy analyses will be performed only if the primary efficacy analysis is significant at a significance level of $p \leq 0.05$ (gatekeeping strategy). Similarly, family #2 key secondary efficacy analyses will be performed only if at least one of the key secondary efficacy endpoints of family #1 is significant at a significance level of $p \leq 0.0125$ and family #3 key secondary efficacy analyses will be performed only if at least one of the key secondary efficacy endpoints of family #2 is significant (parallel gatekeeping strategy).
4 Synopsis, Statistical Methods, Analysis, Supportive Endpoints	• Proportion of 2-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS) of the left buttock (Days 22, 43, and 71) • Proportion of 2-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS) of the right buttock (Days 22, 43, and 71) • Proportion of 1-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS) of the left buttock (Days 22, 43, and 71) • Proportion of 1-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS) of the right buttock (Days 22, 43, and 71) • Proportion of 2-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject.	• Proportion of 2-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS) of the target buttock (Days 22, 43, and 71) • Proportion of 2-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS) of the non-target buttock (Days 22, 43, and 71) • Proportion of 1-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS) of the target buttock (Days 22, 43, and 71) • Proportion of 1-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS) of the non-target buttock (Days 22, 43, and 71) • Proportion of 2-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject.

Section	Original Text	Revised Text
	• Proportion of 1-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject. • Proportion of 2-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks. • Proportion of 1-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks. • Proportion of 2-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS) of the left buttock (Days 22, 43, and 71) • Proportion of 2-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS) of the right buttock (Days 22, 43, and 71) • Proportion of 1-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS) of the left buttock (Days 22, 43, and 71) • Proportion of 1-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS) of the right buttock (Days 22, 43, and 71) • Proportion of 2-level CR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject • Proportion of 1-level CR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject	• Proportion of 1-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject. • Proportion of 2-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks. • Proportion of 1-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks. • Proportion of 2-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS) of the target buttock (Days 22, 43, and 71) • Proportion of 2-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS) of the non-target buttock (Days 22, 43, and 71) • Proportion of 1-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS) of the target buttock (Days 22, 43, and 71) • Proportion of 1-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS) of the non-target buttock (Days 22, 43, and 71) • Proportion of 2-level CR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject • Proportion of 1-level CR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject

Section	Original Text	Revised Text
	• Proportion of 2-level CR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks • Proportion of 1-level CR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks • Proportion of 1-level composite responders of the left buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the left buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same left buttock) (Days 22, 43, and 71) • Proportion of 1-level composite responders of the right buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the right buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same right buttock) (Days 22, 43, and 71) • Proportion of 1-level composite responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject. • Proportion of 1-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks. • Proportion of 2-level composite responders of the left buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the left buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same left buttock) (Days 22, 43, and 71)	• Proportion of 2-level CR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks • Proportion of 1-level CR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks • Proportion of 1-level composite responders of the target buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same target buttock) (Days 22, 43, and 71) • Proportion of 1-level composite responders of the non-target buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the non-target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same non-target buttock) (Days 22, 43, and 71) • Proportion of 1-level composite responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject. • Proportion of 1-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks. • Proportion of 2-level composite responders of the target buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same target buttock) (Days 22, 43, and 71)

Section	Original Text	Revised Text
	• Proportion of 2-level composite responders of the right buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the right buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same right buttock) (Days 22, 43, and 71) • Proportion of 2-level composite responders of at least one of two buttocks (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject. • Proportion of 2-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks. • Proportion of subjects at each level of the S-GAIS of the left buttock (Days 22, 43, and 71) • Proportion of subjects at each level of the S-GAIS of the right buttock (Days 22, 43, and 71) • Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S- GAIS of the left buttock (Days 22, 43, and 71) • Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S- GAIS of the right buttock (Days 22, 43, and 71) • Proportion 1-level S-GAIS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject. • Proportion of 1-level S-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks. • Proportion of subjects at each level of the I-GAIS of the left buttock (Days 22, 43, and 71)	• Proportion of 2-level composite responders of the non-target buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the non-target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same non-target buttock) (Days 22, 43, and 71) • Proportion of 2-level composite responders of at least one of two buttocks (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject. • Proportion of 2-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks. • Proportion of subjects at each level of the S-GAIS of the target buttock (Days 22, 43, and 71) • Proportion of subjects at each level of the S-GAIS of the non-target buttock (Days 22, 43, and 71) • Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S-GAIS of the target buttock (Days 22, 43, and 71) • Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S-GAIS of the non-target buttock (Days 22, 43, and 71) • Proportion 1-level S-GAIS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject. • Proportion of 1-level S-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks. • Proportion of subjects at each level of the I-GAIS of the target buttock (Days 22, 43, and 71)

Section	Original Text	Revised Text
	• Proportion of subjects at each level of the I-GAIS of the right buttock (Days 22, 43, and 71) • Proportion of 1-level I-GAIS responders (defined as subjects with a response of at least 1 (improved) in the Investigator GAIS assessment) of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject. • Proportion of 1-level I-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks. • Change from baseline (Day 1) of the PR-CIS total score at Day 71 • Change from baseline (Day 1) of the abbreviated PR-CIS score at Day 71 • Proportion of subjects with a change from baseline (Day1) of the PR-CIS ≥12 at Day 71 • Proportion of subjects with a change from baseline (Day 1) of the abbreviated PR-CIS ≥10 at Day 71 • Proportion of subjects at each level of the subject satisfaction with cellulite treatment (Day 71) • Proportion of satisfied responders (defined as subjects with a response of at least 1 (ie, 1 Satisfied or 2-Very Satisfied) in the subject satisfaction with cellulite treatment assessment (Day 71)	• Proportion of subjects at each level of the I-GAIS of the non-target buttock (Days 22, 43, and 71) • Proportion of 1-level I-GAIS responders defined as subjects with a response of at least 1 (improved) in the I-GAIS of the target buttock (Days 22, 43, and 71) • Proportion of 1-level I-GAIS responders defined as subjects with a response of at least 1 (improved) in the I-GAIS of the non-target buttock (Days 22, 43, and 71) • Proportion of 1-level I-GAIS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject. • Proportion of 1-level I-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks. • Change from baseline (Day 1) of the PR-CIS score at Day 71 • Change from baseline (Day 1) of the abbreviated PR-CIS score at Day 71 • Proportion of subjects with a change from baseline (Day1) of the PR-CIS ≥12 at Day 71 • Proportion of subjects with a change from baseline (Day 1) of the abbreviated PR-CIS ≥10 at Day 71 • Proportion of subjects at each level of the subject self-rating scale (SSRS) (Day 1 (Baseline) and Day 71 • Proportion of 1-level SSRS responders defined as subjects who were at least slightly satisfied at Day 71 (SSRS rating ≥ 4) • Proportion of subjects at each level of the subject satisfaction with cellulite treatment assessment (Day 71) • Proportion of satisfied responders (defined as subjects with a response of at least 1 (ie, 1 Satisfied or 2-Very Satisfied) in the subject satisfaction with cellulite treatment assessment (Day 71)

Section	Original Text	Revised Text
5 Schedule of Events	Added table row	• Subject Self-Rating Scale (SSRS) Day 1 Treatment Visit 1: X[c] Day 71 (+ 5d)/End of Study/Early Termination: X
7 List of Abbreviations, Table 2: Abbreviations and Special Terms	Added table rows	SSRS: Subject Self-Rating Scale MI: Multiple imputation
11.2 Subject Exclusion Criteria	13. Was a subject in a previous cellulite clinical trial of CCH: AUX-CC-830, AUX-CC-831, EN3835-102, EN3835-104, EN3835-201, and/or EN3835-202	13. Was a subject in a previous cellulite clinical trial of CCH: AUX-CC-830, AUX-CC-831, EN3835-102, EN3835-104, EN3835-201, EN3835-202, and/or EN3835-205
12.4.1 Treatment Visit 1: Pre-Injection	Added text	6. Subjects will complete the SSRS assessment (section 13.1.2.5); the Investigator is blinded to these ratings
	Added text	9. Upon confirmation of two buttocks eligible for treatment (eligible criteria being each buttock have PR-PCSS and CR-PCSS scores of 3 or 4), the IWRS system will randomly assign one buttock as the target buttock in the background. Subjects, investigators, site personnel and Endo personnel will be blinded to target buttock assignment.
	8. Randomization of subjects with two buttocks eligible for treatment (eligible criteria being each buttock have PR-PCSS and CR-PCSS scores of 3 or 4) to treatment (section 12.10); obtain kit numbers of study treatment	10. Randomization of subjects with two buttocks eligible for treatment (eligible criteria being each buttock have PR-PCSS and CR-PCSS scores of 3 or 4) to treatment (section 12.10); obtain kit numbers of study treatment. Subjects, investigators, site personnel, and Endo personnel will be blinded to treatment assignment.

Section	Original Text	Revised Text
12.6 Day 71 (+5 days) / End of Study / Early Termination	6. Subject Cellulite Assessment of each of the two buttocks using the photographic image before marking dimples and injection sites (NOTE: complete subject cellulite assessments before Investigator cellulite assessments) using: a. Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) assessment (section 13.1.2.1) b. Subject Global Aesthetic Improvement Scale (S-GAIS) (section 13.1.2.2) c. Patient Reported Cellulite Impact Scale (PR-CIS) assessment (section 13.1.2.3); note this assessment is of both left and right buttocks rather than each individual buttock d. Subject Satisfaction with Cellulite Treatment Assessment (section 13.1.2.4); note this assessment is of both left and right buttocks rather than each individual buttock	6. Subject Cellulite Assessment of each of the two buttocks using the photographic image before marking dimples and injection sites (NOTE: complete subject cellulite assessments before Investigator cellulite assessments) using: a. Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) assessment (section 13.1.2.1) b. Subject Global Aesthetic Improvement Scale (S-GAIS) (section 13.1.2.2) c. Patient Reported Cellulite Impact Scale (PR-CIS assessment (section 13.1.2.3); note this assessment is of both left and right buttocks rather than each individual buttock d. Subject Satisfaction with Cellulite Treatment Assessment (section 13.1.2.4); note this assessment is of both left and right buttocks rather than each individual buttock e. Subject Self-Rating Scale assessment (section 13.1.2.5); note this assessment is of both left and right buttocks rather than each individual buttock
12.10 Blinding and Randomization	On Day 1, if each of the buttocks again meet the criteria (3 or 4 on the PR-PCSS and CR-PCSS), the subject will be randomized to a treatment group.	On Day 1, if each of the buttocks (ie, both buttocks) again meet the criteria (3 or 4 on the PR-PCSS and CR-PCSS), one buttock will be randomly assigned by the IWRS as the target buttock for the primary efficacy endpoint. Subjects, investigators, site personnel and Endo personnel will be blinded to the identification of the target buttock. On Day 1, if each of the buttocks (ie, both buttocks) again meet the criteria (3 or 4 on the PR-PCSS and CR-PCSS), the subject will be randomized to a treatment group.

<table>
<tr><th>Section</th><th>Original Text</th><th>Revised Text</th></tr>
<tr><td>13.1.2.5 Subject Self-Rating Scale (SSRS)</td><td>Added section</td><td>13.1.2.5. Subject Self-Rating Scale (SSRS)
The SSRS is a measure that assesses subject satisfaction with appearance in association with cellulite on the buttocks using whole numbers on a 7-level scale that ranges from 0 (extremely dissatisfied) to 6 (extremely satisfied). The patient will be asked to respond to the question related to the satisfaction with appearance of the cellulite on their buttocks on the appropriate visit day (note Day 71 question is different than Day 1 question). No photographs or reference to previous ratings or evaluations will be used. Subjects will be given a list of responses and they will provide a rating from those below that best represents their answer (Table 7); the list of responses is the same for Day 1 and for Day 71.
On Day 1 (Baseline), subjects will be instructed to answer: Considering your appearance in association with your cellulite on your buttocks, how satisfied do you feel with your appearance at the present time?
On Day 71, subjects will be instructed to answer: Considering your appearance in association with your cellulite on your buttocks, how satisfied do you feel with your appearance at the present time whether or not in your judgment it is due entirely to treatment with EN3835?
This variable will 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 7: Subject Self-Rating Scale (SSRS)
<table>
<tr><th>Rating</th><th>Response Option</th></tr>
<tr><td>6</td><td>Extremely satisfied</td></tr>
<tr><td>5</td><td>Satisfied</td></tr>
<tr><td>4</td><td>Slightly satisfied</td></tr>
<tr><td>3</td><td>Neither satisfied nor dissatisfied</td></tr>
<tr><td>2</td><td>Slightly dissatisfied</td></tr>
<tr><td>1</td><td>Dissatisfied</td></tr>
<tr><td>0</td><td>Extremely dissatisfied</td></tr>
</table>
</td></tr>
</table>

Section	Original Text	Revised Text
14.6.1 Adverse Events of Special Interest	Adverse events such as bruising, ecchymosis, hematomas, and contusions that occur remote to the site of drug administration, or any hypersensitivity reactions, including anaphylaxis, will be recorded as an AE or SAE as appropriate (see section 14.1.1, Adverse Events or section 14.1.2, Serious Adverse Events).	Adverse events such as bruising, ecchymosis, hematomas, and contusions that occur remote to the site of drug administration, or any hypersensitivity reactions, including anaphylaxis, will be recorded and evaluated for seriousness and severity (see section 14.1.1, Adverse Events or section 14.1.2, Serious Adverse Events). In addition, local AEs associated with the injection site, including bruising, pain, nodules/mass, ulceration, erythema, pruritus, swelling, and/or induration, will be recorded and evaluated for seriousness and severity (see as appropriate, section 14.1.1, Adverse Events or section 14.1.2, Serious Adverse Events)
17.1 Determination of Sample Size	The primary variable is the proportion of 2-level composite responders at Day 71 defined as subjects with at least one of two treated buttocks with: • an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator, and • an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS as assessed by the subject while viewing the digital image of the same buttock. A subject will be considered a responder if these criteria are met in either the left buttock or right buttock or both buttocks in that subject. In other words, a subject will be considered a responder if she has an improvement of at least 2 levels on the PR-PCSS and an improvement of at least 2 levels on the CR-PCSS on that same buttock; that buttock could be the left buttock or right buttock or both buttocks.	The primary variable is the proportion of 2-level composite responders at Day 71 defined as subjects with: • an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator of the target buttock, and • an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS as assessed by the subject while viewing the digital image of the target buttock. A subject will be considered a responder if these criteria are met in the randomized target buttock of that subject

<table>
<tr><th>Section</th><th>Original Text</th><th>Revised Text</th></tr>
<tr>
<td></td>
<td>The sample size calculation was based on the following assumptions [redacted] 3) treatment effect of at least 12% of composite responders with an improvement of at least 2 levels on both the PR-PCSS and the CR-PCSS for at least one treated buttock; 4) Fisher exact test; 5) type I error of 0.05; 6) an power of at least 90%; and 7) dropout rate of approximate 10%.

This sample size will also provide >90% power with type 1 error of 0.025 to detect 1-level responder rate difference for buttocks using the PR-PCSS of 72% in the EN3835 group and 48% in the placebo group as well as 1-level responder rate difference using the S-GAIS of 75% in the EN3835 group and 39% in the placebo group, which were estimated from the EN3835-201 study.</td>
<td>The sample size calculation was based on the following assumptions: [redacted] 2) Fisher exact test; 3) type I error of 0.05; 4) power of at least 90%; and 5) dropout rate of approximate 10%.

This sample size will also provide >90% power with type 1 error of 0.05 to detect the treatment difference for all the key secondary endpoints based on previous study results.

Table 12: Previous Results as Basis for Sample Size
<table>
<tr><th>Efficacy Endpoint</th><th>EN3835</th><th>Placebo</th><th>Power</th></tr>
<tr><td>1-level PR-PCSS responders of target buttock</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>2-level PR-PCSS responders of target buttock</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>1-level composite responders of target buttock</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>2-level composite responders of non-target buttock</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Proportion of subjects with SSRS rating ≥ 4</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Change in PR-CIS Score, Mean (SD)</td><td>[redacted]</td><td colspan="2">[redacted]</td></tr>
<tr><td>1-level S-GAIS responders of target buttock</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>2-level S-GAIS responders of target buttock</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
[a] Rates are estimated based on the reported results from the pooled pivotal studies of a drug approved for an aesthetic indication.</td>
</tr>
</table>

Section	Original Text	Revised Text
17.2.3 Modified Intent-to-Treat (mITT) Population	The mITT population is defined as all intent-to-treat subjects with a baseline and at least 1 post-injection evaluation of both the Investigator CR-PCSS and subject PR-PCSS for both left and right buttocks..	The mITT population is defined as all intent-to-treat subjects with a baseline and at least 1 post-injection evaluation of both the Investigator CR-PCSS and subject PR-PCSS for both the target and non-target buttocks.
17.2.4 Per-Protocol (PP) Population	The per-protocol population is defined as the mITT subjects without any major protocol deviation that will impact the subject's efficacy and safety.	The per-protocol population is defined as the mITT subjects without any of the following: • Placebo-assigned subject receives EN3835 treatment • EN3835-assigned subject receives placebo treatment only throughout the study • Any subject receives protocol-prohibited medications • Subject lacking PR-PCSS and/or CR-PCSS assessment at Day 71 • Any major protocol deviation that is deemed as impacting subject efficacy
17.5 Efficacy Analysis	Changes in the PR-PCSS ratings and CR-PCSS ratings from baselines, S-GAIS scores, and I-GAIS scores will be analyzed using the Wilcoxon rank sum test.	Changes in the PR-PCSS ratings and CR-PCSS ratings from baselines, S-GAIS scores, I-GAIS scores, and SSRS scores will be analyzed using the Wilcoxon rank sum test. Changes in PR-CIS from baselines will be analyzed using an analysis of covariance (ANCOVA) adjusted for baseline values.
	Similarly family #2 key secondary efficacy analyses will be performed only if at least one of the key secondary efficacy endpoints of family #1 is significant ($p \leq 0.025$; parallel gatekeeping strategy	Similarly family #2 key secondary efficacy analyses will be performed only if at least one of the key secondary efficacy endpoints of family #1 is significant ($p \leq 0.0125$; parallel gatekeeping strategy) and family #3 key secondary efficacy analyses will be performed only if at least one of the key secondary efficacy endpoints of family #2 is significant (parallel gatekeeping strategy).
	Changes in the PR-PCSS ratings and CR-PCSS ratings from baselines, S-GAIS scores, and I-GAIS scores will be analyzed using the Wilcoxon rank sum test.	Changes in the PR-PCSS ratings and CR-PCSS ratings from baselines, S-GAIS scores, I-GAIS scores, and SSRS scores will be analyzed using the Wilcoxon rank sum test.

Section	Original Text	Revised Text
17.5.1 Primary Efficacy Variable	The primary efficacy variable is the proportion of 2-level composite responders at Day 71 defined as subjects with at least one of two treated buttocks with: • an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator, and • an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS by the subject while viewing the digital image of the same buttock. A subject will be considered a responder if these criteria are met in either the left buttock or right buttock or both buttocks in that subject. In other words, a subject will be considered a responder if she has an improvement of at least 2 levels on the PR-PCSS and an improvement of at least 2 levels on the CR-PCSS on that same buttock; that buttock could be the left buttock or right buttock or both buttocks.	The primary efficacy variable is the proportion of 2-level composite responders at Day 71 defined as subjects with: • an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator of the target buttock, and • an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS by the subject while viewing the digital image of the target buttock. A subject will be considered a responder if these criteria are met in the randomized target buttock of that subject.
17.5.2.1 Key Secondary Variables	There will be 4 key secondary endpoints grouped in two families of 2 endpoints per family analyzed in a hierarchical order. • Family #1 – two endpoints: – Proportion of 1-level PR-PCSS responders defined as subjects with ≥1-level improvement in PR-PCSS severity rating of left buttock at Day 71 compared to Day 1 – Proportion of 1-level PR-PCSS responders defined as subjects with ≥1-level improvement in PR-PCSS severity rating of right buttock at Day 71 compared to Day 1	There will be 8 key secondary endpoints grouped in three families of 2-4 endpoints per family analyzed in hierarchical order. • Family #1 – four endpoints: – Proportion of 1-level PR-PCSS responders defined as subjects with ≥1-level improvement in PR-PCSS severity rating of target buttock at Day 71 compared to Day 1 – Proportion of 2-level PR-PCSS responders defined as subjects with ≥2-level improvement in PR-PCSS severity rating of target buttock at Day 71 compared to Day 1 – Proportion of 1-level composite responders of target buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of the target buttock) at Day 71 compared to Day 1 – Proportion of 2-level composite responders of non-target buttock at Day 71 compared to Day 1

Section	Original Text	Revised Text
	• Family #2 – two endpoints: − Proportion of 1-level S-GAIS responders defined as subjects with ≥1-level improvement (improved, much improved or very much improved) in the S- GAIS assessment of left buttock at Day 71 − Proportion of 1-level S-GAIS responders defined as subjects with ≥1-level improvement (improved, much improved or very much improved) in the S-GAIS assessment of right buttock at Day 71	• Family #2 – two endpoints: − Proportion of 1-level SSRS responders defined as subjects who were at least slightly satisfied at Day 71 (SSRS rating ≥ 4) − Proportion of subjects with a change from baseline (Day1) of the PR-CIS ≥12 at Day 71 • Family #3 – two endpoints: − Proportion of 1-level S-GAIS responders defined as subjects with ≥1-level improvement (improved, much improved or very much improved) in the S-GAIS assessment of the target buttock at Day 71 − Proportion of 2-level S-GAIS responders defined as subjects with ≥2-level improvement (much improved or very much improved) in the S-GAIS assessment of the target buttock at Day 71
	Added text	Sensitivity analyses for the key secondary endpoints will include: • ITT subjects with missing data handled by multiple imputation (MI) approach • ITT subjects with missing data handled by an LOCF approach • mITT subjects with missing data handled by an LOCF approach • Observed data only (no missing data handling) • Per-protocol (PP) subjects with missing data handled by an LOCF approach if 10% or more subjects are excluded in the PP population from mITT population

Section	Original Text	Revised Text
17.5.3.1 Supportive Variables	• Proportion of 2-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS of the left buttock (Days 22, 43, and 71) • Proportion of 2-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS of the right buttock (Days 22, 43, and 71) • Proportion of 1-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS of left buttock (Days 22, 43, and 71) • Proportion of 1-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS of right buttock (Days 22, 43, and 71) • Proportion of 2-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject. • Proportion of 1-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject. • Proportion of 2-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks. • Proportion of 1-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks.	• Proportion of 2-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS of the target buttock (Days 22, 43, and 71) • Proportion of 2-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS of the non-target buttock (Days 22, 43, and 71) • Proportion of 1-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS of the target buttock (Days 22, 43, and 71) • Proportion of 1-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS of the non-target buttock (Days 22, 43, and 71) • Proportion of 2-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject. • Proportion of 1-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject. • Proportion of 2-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks. • Proportion of 1-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks.

Section	Original Text	Revised Text
	• Proportion of 1-level composite responders of the left buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the left buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same left buttock) (Days 22, 43, and 71)	• Proportion of 1-level composite responders of the target buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same target buttock) (Days 22, 43, and 71)
	• Proportion of 1-level composite responders of the right buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the right buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same right buttock) (Days 22, 43, and 71)	• Proportion of 1-level composite responders of the non-target buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the non-target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same non-target buttock) (Days 22, 43, and 71)
	• Proportion of 1-level composite responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject.	• Proportion of 1-level composite responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject.
	• Proportion of 1-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks.	• Proportion of 1-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks.
	• Proportion of 2-level composite responders of the left buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the left buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same left buttock) (Days 22, 43, and 71)	• Proportion of 2-level composite responders of the target buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same target buttock) (Days 22, 43, and 71)
	• Proportion of 2-level composite responders of the right buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the right buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same right buttock) (Days 22, 43, and 71)	• Proportion of 2-level composite responders of the non-target buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the non-target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same non-target buttock) (Days 22, 43, and 71)

Section	Original Text	Revised Text
	• Proportion of 2-level composite responders of at least one of two buttocks (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject. • Proportion of 2-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks. • Proportion of subjects at each level of the S-GAIS of the left buttock (Days 22, 43, and 71) • Proportion of subjects at each level of the S-GAIS of the right buttock (Days 22, 43, and 71) • Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S- GAIS of the left buttock (Days 22, 43, and 71) • Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S- GAIS of the right buttock (Days 22, 43, and 71) • Proportion 1-level S-GAIS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject. • Proportion of 1-level S-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks. • Proportion of subjects at each level of the I-GAIS of the left buttock (Days 22, 43, and 71) • Proportion of subjects at each level of the I-GAIS of the right buttock (Days 22, 43, and 71)	• Proportion of 2-level composite responders of at least one of two buttocks (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject. • Proportion of 2-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks. • Proportion of subjects at each level of the S-GAIS of the target buttock (Days 22, 43, and 71) • Proportion of subjects at each level of the S-GAIS of the non-target buttock (Days 22, 43, and 71) • Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S-GAIS of the target buttock (Days 22, 43, and 71) • Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S-GAIS of the non-target buttock (Days 22, 43, and 71) • Proportion 1-level S-GAIS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject. • Proportion of 1-level S-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target right buttocks. • Proportion of subjects at each level of the I-GAIS of the target buttock (Days 22, 43, and 71) • Proportion of subjects at each level of the I-GAIS of the non-target buttock (Days 22, 43, and 71)

Section	Original Text	Revised Text
	• Proportion of 1-level I-GAIS responders (defined as subjects with a response of at least 1 (improved) in the Investigator GAIS assessment) of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject. • Proportion of 1-level I-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks. • Change from baseline (Day 1) of the PR-CIS total score at Day 71 • Change from baseline (Day 1) of the abbreviated PR-CIS score at Day 71 • Proportion of subjects with a change from baseline (Day 1) of the PR-CIS ≥ 12 at Day 71 • Proportion of subjects with a change from baseline (Day 1) of the abbreviated PR-CIS ≥ 10 at Day 71 • Proportion of subjects at each level of the subject satisfaction with cellulite treatment (Day 71) • Proportion of satisfied responders (defined as subjects with a response of at least 1 (ie, 1 Satisfied or 2 Very Satisfied) in the subject satisfaction with cellulite treatment assessment (Day 71)	• Proportion of 1-level I-GAIS responders defined as subjects with a response of at least 1 (improved) in the I-GAIS of the target buttock (Days 22, 43, and 71) • Proportion of 1-level I-GAIS responders defined as subjects with a response of at least 1 (improved) in the I-GAIS of the non-target buttock (Days 22, 43, and 71) • Proportion of 1-level I-GAIS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject. • Proportion of 1-level I-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks. • Change from baseline (Day 1) of the PR-CIS total score at Day 71 • Change from baseline (Day 1) of the abbreviated PR-CIS score at Day 71 • Proportion of subjects with a change from baseline (Day 1) of the PR-CIS ≥ 12 at Day 71 • Proportion of subjects with a change from baseline (Day 1) of the abbreviated PR-CIS ≥ 10 at Day 71 • Proportion of subjects at each level of the SSRS (Day 1 (Baseline) and Day 71) • Proportion of 1-level SSRS responders defined as subjects who were at least slightly satisfied at Day 71 (SSRS rating ≥ 4) • Proportion of subjects at each level of the subject satisfaction with cellulite treatment assessment (Day 71) • Proportion of satisfied responders (defined as subjects with a response of at least 1 (ie, 1 Satisfied or 2 Very Satisfied) in the subject satisfaction with cellulite treatment assessment (Day 71)

Section	Original Text	Revised Text
17.6.9 Other Safety Measurements	Not applicable.	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 treatment group. Average antibody levels will be summarized on logarithmically transposed titer values. In addition, by-treatment percentages of neutralizing anti-AUX-I and anti-AUX-II antibodies in a subset of subjects' samples [redacted]) will be summarized at Day 71.
18.2 Study Drug Packaging and Labeling	Each kit will contain one vial of EN3835 or placebo and sufficient sterile diluent to perform reconstitution of the one product vial.	Each kit will contain one vial of EN3835 or placebo and one vial of sterile diluent.
19.1 Source Documents	This study allows for direct data entry (DDE) for selected data points as outlined below: • PR-PCSS • CR-PCSS • S-GAIS • I-GAIS • PR-CIS • Subject Satisfaction with Cellulite Treatment Assessment	This study allows for direct data entry (DDE) for selected data points as outlined below: • PR-PCSS • CR-PCSS • S-GAIS • I-GAIS • PR-CIS • Subject Satisfaction with Cellulite Treatment Assessment • SSRS
27 References	11. Investigational Brochure: Collagenase Clostridium Histolyticum for Injection (AA4500/EN3835), Version 8.0. Endo Pharmaceuticals Inc.; July 2017.	11. Investigational Brochure: Collagenase Clostridium Histolyticum for Injection (AA4500/EN3835), Version 8.0. Endo Pharmaceuticals Inc.; July 2017.

Amendment 1 was incorporated into the protocol on December 19, 2017. The major reasons for this amendment were to add an additional efficacy assessment and to revise inclusion and exclusion criteria.

Section	Original Text	Revised Text
3 Sponsor Contact Information	[redacted]	[redacted]
4 Synopsis, Study Period	Estimated date first subject enrolled: Jan-2018	Estimated date first subject enrolled: Feb-2018
4 Synopsis, Study Design	Subjects with 2 treatment areas (bilateral buttocks) (also referred to as quadrants) with moderate or severe levels of cellulite as independently assessed by the subject using the Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) and by the Investigator using the Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) and a Hexsel Cellulite Severity Scale no greater than 13 will be eligible.	Subjects with 2 treatment areas (bilateral buttocks) (also referred to as quadrants) with moderate or severe levels of cellulite as independently assessed by the subject using the Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) and by the Investigator using the Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) will be eligible.
	Add text	At Day 1, the subject will complete a Patient Reported Cellulite Impact Scale (PR-CIS) assessment.
4 Synopsis, Diagnosis and Inclusion/ Exclusion Criteria, Inclusion Criteria	3. At Screening visit, have 2 bilateral buttocks with each buttock having: 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	3. At Screening visit, have 2 bilateral buttocks with each buttock having: 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)
	4. At Day 1 visit, have 2 bilateral buttocks with each buttock having: 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	4. At Day 1visit, have 2 bilateral buttocks with each buttock having: 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)

Section	Original Text	Revised Text
4 Synopsis, Diagnosis and Inclusion/ Exclusion Criteria, Exclusion Criteria	2. Has any of the following local conditions in the areas to be treated: a. History of lower extremity thrombosis or post-thrombosis syndrome b. Vascular disorder (eg, varicose veins, telangiectasia) in area to be treated c. Inflammation or active infection d. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer e. Has a tattoo and/or a mole located within 2 cm of the site of injection	2. Has any of the following local conditions in the areas to be treated: a. History of lower extremity thrombosis or post-thrombosis syndrome b. Vascular disorder (eg, varicose veins, telangiectasia) in area to be treated c. Inflammation or active infection d. Severe skin laxity, flaccidity, and/or sagging e. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer f. Has a tattoo and/or a mole located within 2 cm of the site of injection
4 Synopsis, Criteria for Evaluation, Efficacy	Added text	• Patient Reported Cellulite Impact Scale: 6 questions with responses to each question consisting of a numerical rating scale (NRS) ranging from 0 (Not at all) to 10 (Extremely)
4 Synopsis, Statistical Methods, Analysis, Supportive Endpoints	Added text	• Change from baseline (Day 1) of the PR-CIS total score at Day 71 • Change from baseline (Day 1) of the abbreviated PR-CIS score at Day 71 • Proportion of subjects with a change from baseline (Day1) of the PR-CIS ≥12 at Day 71 • Proportion of subjects with a change from baseline (Day 1) of the abbreviated PR-CIS ≥10 at Day 71
5 Schedule of Events, Physical examination	Day -14 to -1 Screening: X Day 71 (+ 5d)/End of Study/Early Termination: X	Day -14 to -1 Screening: X
5 Schedule of Events, Subject cellulite assessments, Patient Reported Cellulite Impact Scale (PR-CIS)	Added table row	• Patient Reported Cellulite Impact Scale (PR-CIS) Day 1 Treatment Visit 1: $X^{c,g}$ Day 71 (+ 5d)/End of Study/Early Termination: X^{g}
5 Schedule of Events, Investigator cellulite assessments, Hexsel Cellulite Severity Scale (CSS)	• Hexsel Cellulite Severity Scale (CSS) Day -14 to -1 Screening: $X^{b,i}$ Day 1 Treatment Visit 1: $X^{c,b,i}$	Deleted table row

Section	Original Text	Revised Text
5 Schedule of Events, Table footnotes	[i] Initial Hexsel CSS at Screening must be ≤13 on each of 2 bilateral buttocks and the buttocks must again be ≤13 at Day 1 visit	Deleted text
	[j] Before randomization, each of the subject's buttocks must have ratings of 3 or 4 (moderate or severe) in both the CR-PCSS and PR-PCSS, and Hexsel CSS score ≤13.	[i] Before randomization, each of the subject's buttocks must have ratings of 3 or 4 (moderate or severe) in both the CR-PCSS and PR-PCSS.
7. List of Abbreviations, Table 2: Abbreviations and Special Terms	CSS: Cellulite severity scale	Deleted table row
	Added table row	PR-CIS: Patient Reported Cellulite Impact Scale
11.1 Subject Inclusion Criteria	3. At Screening visit, have 2 bilateral buttocks with each buttock having: 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	3. At Screening visit, have 2 bilateral buttocks with each buttock having: 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)
	4. At Day 1 visit, have 2 bilateral buttocks with each buttock having: 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	4. At Day 1 visit, have 2 bilateral buttocks with each buttock having: 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)
11.2 Subject Exclusion Criteria	2. Has any of the following local conditions in the areas to be treated: a. History of lower extremity thrombosis or post-thrombosis syndrome b. Vascular disorder (eg, varicose veins, telangiectasia) in area to be treated c. Inflammation or active infection d. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer e. Has a tattoo and/or a mole located within 2 cm of the site of injection	2. Has any of the following local conditions in the areas to be treated: a. History of lower extremity thrombosis or post-thrombosis syndrome b. Vascular disorder (eg, varicose veins, telangiectasia) in area to be treated c. Inflammation or active infection d. Severe skin laxity, flaccidity, and/or sagging e. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer f. Has a tattoo and/or a mole located within 2 cm of the site of injection

Section	Original Text	Revised Text
12.1.2.2 Screening Period (Day -14 to Day -1)	5. Prior to Investigator CR-PCSS or Hexsel CSS assessment, subjects will rate each of their two buttocks using the PR-PCSS while viewing their digital images (section 13.1.2.1); the Investigator is blinded to these scores	5. Prior to Investigator CR-PCSS assessment, subjects will rate each of their two buttocks using the PR-PCSS while viewing their digital images (section 13.1.2.1); the Investigator is blinded to these ratings
	6. After the subject has completed the PR-PCSS ratings, the Investigator will conduct live assessments of subject's cellulite severity of each of the two buttocks using the CR-PCSS (section 13.1.2.4); the subject is blinded to these ratings 7. After the Investigator has completed the CR-PCSS ratings, the Investigator will conduct live evaluation of each of the two buttocks using the Hexsel CSS; the subject is blinded to these ratings. The ratings from the PR-PCSS, CR-PCSS, and Hexsel CSS (section 13.1.2.6) will be used to assess initial eligibility of the buttocks for study entry	6. After the subject has completed the PR-PCSS ratings, the Investigator will conduct live assessments of subject's cellulite severity of each of the two buttocks using the CR-PCSS (section 13.1.2.5); the subject is blinded to these ratings. The ratings from the PR-PCSS and CR-PCSS will be used to assess initial eligibility of the buttocks for study entry
12.2 Selecting and Marking Dimples during Treatment Visits	The cellulite severity assessments using the PR-PCSS, CR-PCSS, and Hexsel CSS (note that the Hexsel CSS assessment is performed at Screening visit and Day 1 visit only) will be completed prior to marking dimples and injection sites.	The cellulite severity assessments using the PR-PCSS and CR-PCSS, will be completed prior to marking dimples and injection sites.
12.4.1 Treatment Visit 1: Pre-Injection	4. Subjects will rate each of their buttocks using the PR-PCSS (section 13.1.2.1); the Investigator is blinded to these scores	4. Subjects will rate each of their buttocks using the PR-PCSS (section 13.1.2.1); the Investigator is blinded to these ratings
	Added text	5. Subjects will complete the Patient Reported Cellulite Impact Scale assessment (PR-CIS; section 13.1.2.3): the Investigator is blinded to this rating
	5. The Investigator will conduct live assessments of subject's cellulite severity of each of the buttocks using the CR-PCSS (section 13.1.2.4); the subject is blinded to these ratings 6. The Investigator will conduct live cellulite evaluation of each of the buttocks using the Hexsel CSS. The ratings from the PR-PCSS, CR-PCSS and Hexsel CSS (section 13.1.2.6) will be used to assess eligibility for randomization	6. The Investigator will conduct live assessments of subject's cellulite severity of each of the buttocks using the CR-PCSS (section 13.1.2.5); the subject is blinded to these ratings. The ratings from the PR-PCSS and CR-PCSS will be used to assess eligibility for randomization

Section	Original Text	Revised Text
	7. Subjects with PR-PCSS or CR-PCSS ratings in either of the buttocks <3 or a Hexsel CSS total score in either of the buttocks greater than 13 (section 13.1.2.6) will be excluded from participation	7. Subjects with PR-PCSS or CR-PCSS ratings in either of the buttocks <3 will be excluded from participation
	8. Randomization of subjects with two buttocks eligible for treatment (eligible criteria being each buttock have PR-PCSS and CR-PCSS scores of 3 or 4 and a Hexsel CSS total score not greater than 13) to treatment (section 12.10); obtain kit numbers of study treatment	8. Randomization of subjects with two buttocks eligible for treatment (eligible criteria being each buttock have PR-PCSS and CR-PCSS scores of 3 or 4) to treatment (section 12.10); obtain kit numbers of study treatment
12.6 Day 71 (+5 days)/End of Study/Early Termination	6. Subject Cellulite Assessment of each of the two buttocks using the photographic image before marking dimples and injection sites (NOTE: complete subject cellulite assessments before Investigator cellulite assessments) using: a. Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) assessment (section 13.1.2.1) b. Subject Global Aesthetic Improvement Scale (S-GAIS) (section 13.1.2.2) c. Subject Satisfaction with Cellulite Treatment Assessment (section 13.1.2.3); note this assessment is of both left and right buttocks rather than each individual buttock	6. Subject Cellulite Assessment of each of the two buttocks using the photographic image before marking dimples and injection sites (NOTE: complete subject cellulite assessments before Investigator cellulite assessments) using: a. Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) assessment (section 13.1.2.1) b. Subject Global Aesthetic Improvement Scale (S-GAIS) (section 13.1.2.2) c. Patient Reported Cellulite Impact Scale (PR-CIS assessment (section 13.1.2.3); note this assessment is of both left and right buttocks rather than each individual buttock d. Subject Satisfaction with Cellulite Treatment Assessment (section 13.1.2.4); note this assessment is of both left and right buttocks rather than each individual buttock
12.10 Blinding and Randomization	On Day 1, if each of the buttocks again meet the criteria (3 or 4 on the PR-PCSS and CR-PCSS and no greater than 13 on Hexsel CSS) the subject will be randomized to a treatment group.	On Day 1, if each of the buttocks again meet the criteria (3 or 4 on the PR-PCSS and CR-PCSS) the subject will be randomized to a treatment group.

Section	Original Text	Revised Text
13.1.2.3 Patient Reported Cellulite Impact Scale (PR-CIS)	Added section	13.1.2.3. Patient Reported Cellulite Impact Scale (PR-CIS) At the Day 1 visit and Day 71 visit, subjects will be instructed to answer 6 questions related to the areas selected for treatment on their buttocks on the Patient Reported Cellulite Impact Scale (Appendix D) while viewing digital images of their buttocks. The PR-CIS assesses the visual and emotional impact of cellulite (happy, bothered, self-conscious, embarrassed, looking older or looking overweight or out of shape) using a 6-question survey, with each question rated on a numerical rating scale from 0 (not at all) to 10 (extremely). This variable will 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.
13.1.2.4 Subject Satisfaction	Added text	This variable will 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
13.1.2.6 Hexsel Cellulite Severity Scale	13.1.2.6. 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 8. The total score is the summation of all 5 features (Appendix D). The Investigator or qualified designee will independently use the Hexsel CSS to assess the severity of EFP in each of the two buttocks at the Screening visit and each of the two buttocks on Day 1 (Note: In this study, the Hexsel CSS is used exclusively for assessment of subject eligibility; it is not used as an efficacy assessment). 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 will 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]	Deleted section and table
17.5 Efficacy Analyses	All supportive endpoints will be summarized as percentages.	All supportive endpoints will be summarized as subject counts and percentages for categorical data or n, mean, SD, median, minimum, and maximum for continuous data.
	Added text	Changes in PR-CIS from baselines will be analyzed using an analysis of covariance (ANCOVA) adjusted for baseline values

Section	Original Text	Revised Text
17.5.3.1 Supportive Variables	Added text	• Change from baseline (Day 1) of PR-CIS total score at Day 71 • Change from baseline (Day 1) of abbreviated PR-CIS score at Day 71 • Proportion of subjects with a change from baseline (Day 1) of PR-CIS ≥ 12 at Day 71 • Proportion of subjects with a change from baseline (Day 1) of abbreviated PR-CIS ≥ 10 at Day 71
19.1 Source Documents	This study allows for direct data entry (DDE) for selected data points as outlined below: • PR-PCSS • CR-PCSS • Hexsel CSS • S-GAIS • I-GAIS • Subject Satisfaction with Cellulite Treatment Assessment	This study allows for direct data entry (DDE) for selected data points as outlined below: • PR-PCSS • CR-PCSS • S-GAIS • I-GAIS • PR-CIS • Subject Satisfaction with Cellulite Treatment Assessment
27 References	12. Hexsel DM, Dal'Forno T, Hexsel CL. A validated photonumeric cellulite severity scale. *J Eur Acad Dermatol Venereol*. 2009;23(5):523-8. 13. Nürnberger F, Müller G. So-called cellulite: an invented disease. *J Dermatol Surg Oncol*. 1978;4(3):221-9.	Deleted text

Section	Original Text	Revised Text
APPENDIX D	APPENDIX D. HEXSEL DM, DAL'FORNO T, HEXSEL CL. A VALIDATED PHOTONUMERIC CELLULITE SEVERITY SCALE. *J EUR ACAD DERMATOL VENEREOL*. 2009;23(5):523-8 [Article]	APPENDIX D. PATIENT REPORTED CELLULITE IMPACT SCALE (PR-CIS) Please select the rating that best represents your answer on a scale of 0 to 10 with 0 representing "Not at all" and 10 representing "Extremely" while viewing digital images of your buttocks. Please answer each question. 1. Thinking about the areas selected for treatment, how happy are you with the appearance of your cellulite? [Scale] 2. Thinking about the areas selected for treatment, how bothered are you by the appearance of your cellulite? [Scale] 3. Thinking about the areas selected for treatment, how self-conscious are you about the appearance of your cellulite? [Scale] 4. Thinking about the areas selected for treatment, how embarrassed are you about the appearance of your cellulite? [Scale] 5. Thinking about the areas selected for treatment, how much older do you look because of your cellulite? [Scale] 6. Thinking about the areas selected for treatment, how overweight or out of shape do you look because of your cellulite? [Scale]
APPENDIX E. REFERENCE IMAGES FOR HEXSEL SEVERITY RATINGS	APPENDIX E. REFERENCE IMAGES FOR HEXSEL SEVERITY RATINGS The 2 images below are representative of a Hexsel score of 13, the maximum severity level to be included in the study. Subjects with cellulite severity that exceeds a Hexsel score of 13 should be excluded. [Image 1] [Image 2] The image below represents a Hexsel score >13, and depicts excessive skin laxity in the buttock and posterolateral thigh. Subjects with a Hexsel score >13 should be excluded from the study. [Image 3]	Deleted appendix and images

3. SPONSOR CONTACT INFORMATION

Table 1: Sponsor Contact Information

Role in Study	Name	Telephone and Email Address
Clinical Development Lead	[redacted]	[redacted]
Clinical Operations Lead	[redacted]	[redacted]
Medical Monitor	[redacted]	[redacted]
SAE Reporting Pathway	Not Applicable	[redacted]

A list of other key study personnel and vendors will be provided 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 3, Randomized, Double-Blind, Placebo-Controlled Study of EN3835 in the Treatment of Edematous Fibrosclerotic Panniculopathy	
Lead Principal Investigator:	
Study Period: Estimated date first subject enrolled: Feb-2018 Estimated date last subject completed: Oct-2018	**Phase of Development**: 3
Objectives: To assess the efficacy and safety of EN3835 in the treatment of edematous fibrosclerotic panniculopathy (EFP), commonly known as cellulite, in adult women	
Study Design: This study is a Phase 3 randomized, double-blind, placebo-controlled study of the efficacy and safety of EN3835 in the treatment of EFP in adult women. Subjects will be screened for study eligibility within 14 days prior to enrolling in this study. Subjects with 2 treatment areas (bilateral buttocks) (also referred to as quadrants) with moderate or severe levels of cellulite as independently assessed by the subject using the Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) and by the Investigator using the Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) will be eligible. The eligibility of the buttocks will be confirmed on Day 1. Once the eligibility of the buttocks is confirmed, subjects will be randomly assigned to a treatment group (EN3835 0.84 mg per buttock or placebo) in a 1:1 ratio within an investigational site. Each subject will receive a treatment course which consists of up to 3 treatment visits (sessions), separated by 21 days (ie, Days 1, 22, and 43). Each treatment visit will consist of 12 injections (0.3 mL per injection of EN3835 0.07 mg/injection or placebo; 0.84 mg in 3.6 mL per buttock) in each of the two buttocks for a total volume of 7.2 mL (1.68 mg). Selection of dimples to be treated in the buttocks will be at the discretion of the Investigator. End of study will occur at study day 71. Of the two assigned eligible buttocks, one buttock will be randomly selected as the target buttock for the primary efficacy endpoint. The other (remaining) buttock will be considered the non-target buttock. Subjects, investigators, site personnel, and Endo personnel will be blinded to the identification of the target and non-target buttocks. At each treatment visit, each of the buttocks will be photographed before and after marking dimples and injection sites while the subject is in a consistent, standardized relaxed standing pose. The subject will assess the digital photographic image (pre-marking) of each of the buttocks using the PR-PCSS to determine the severity of EFP in each of the buttocks. In addition, the subject will evaluate each of the buttocks using a Subject Global Aesthetic Improvement Scale (S-GAIS). Subsequently, the Investigator will conduct live assessments of each buttock using the CR-PCSS. At Day 1, the subject will complete a Patient Reported Cellulite Impact Scale (PR-CIS) assessment and a Subject Self-Rating Scale (SSRS) assessment. The subject assessments will always be completed prior to and independently of the Investigator assessments at each treatment visit. In addition, the Investigator will assess each of the buttocks using an Investigator Global Aesthetic Improvement Scale (I-GAIS). All of the assessments must be done before the dimple marking. At Day 71 (End of Study/Early Termination), photographs of each of the buttocks will be taken and evaluated by subject using the PR-PCSS. The Investigator will conduct live assessments of each of the	

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buttocks using the CR-PCSS. Global assessment evaluations will be completed by both the subject and the Investigator.

Number of Subjects (Planned): 420

Study Center(s): Approximately 25 sites in United States

Diagnosis and Inclusion/Exclusion Criteria:

Inclusion Criteria:

1. Voluntarily sign and date an informed consent agreement
2. Be a female ≥18 years of age
3. At Screening visit, have 2 bilateral buttocks with each buttock having:
   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)
4. At Day 1 visit, have 2 bilateral buttocks with each buttock having:
   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)
5. Be willing to apply sunscreen to the buttocks before each exposure to the sun while participating in the study (ie, Screening 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
7. Have a negative serum pregnancy test at Screening and a negative urine pregnancy test before injection of study drug and be using a stable and effective contraception method (eg, abstinence, intrauterine device [IUD], hormonal [estrogen/progestin] contraceptives, or double barrier method) for at least 1 menstrual cycle prior to study enrollment and for the duration of the study; or be menopausal defined as 12 months of amenorrhea in the absence of other biological or physiological causes, as determined by the Investigator; or post-menopausal for at least 1 year; or be surgically sterile
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:

A subject will be excluded from study participation if she:

1. Has any of the following systemic conditions:
   a. Coagulation disorder
   b. Evidence or history of malignancy (other than excised basal-cell carcinoma) unless there has been no recurrence in at least 5 years
   c. History of keloidal scarring or abnormal wound healing
   d. Concurrent diseases or conditions that might interfere with the conduct of the study, confound the interpretation of the study results, or endanger the subject's well-being. Any questions about concurrent diseases should be discussed with the Medical Monitor

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e. Evidence of clinically significant abnormalities on physical examination, vital signs, electrocardiogram (ECG), or clinical laboratory values

2. Has any of the following local conditions in the areas to be treated:
   a. History of lower extremity thrombosis or post-thrombosis syndrome
   b. Vascular disorder (eg, varicose veins, telangiectasia) in area to be treated
   c. Inflammation or active infection
   d. Severe skin laxity, flaccidity, and/or sagging
   e. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer
   f. Has a tattoo and/or a mole located within 2 cm of the site of injection
3. Requires the following concomitant medications before or during participation in the trial:
   a. Anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication (except for ≤150 mg aspirin daily) within 7 days before injection of study drug
4. Has used any of the following for the treatment of EFP on a buttock within the timelines identified below or intends to use any of the following at any time during the course of the study:
   a. Liposuction in a buttock during the 12-month period before injection of study drug
   b. Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; buttock implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision) within a buttock during the 12-month period before injection of study drug
   c. Any investigational treatment for EFP on a buttock during the 12-month period before injection of study drug
   d. Endermologie™ or similar treatments within a buttock during the 6-month period before injection of study drug
   e. Massage therapy within a buttock during the 3-month period before injection of study drug
   f. Creams (eg, Celluvera™, TriLastin®) and/or home therapies to prevent or mitigate EFP within a buttock during the 2-week period before injection of study drug
5. Is presently nursing or providing breast milk
6. Intends to become pregnant during the study
7. Intends to initiate an intensive sport or exercise program during the study
8. Intends to initiate a weight reduction program during the study
9. Intends to use tanning spray or tanning booths during the study
10. Has received an investigational drug or treatment within 30 days before injection of study drug
11. Has a known systemic allergy to collagenase or any other excipient of study drug
12. Has received any collagenase treatments at any time prior to treatment
13. Was a subject in a previous cellulite clinical trial of collagenase clostridium histolyticum (CCH): AUX-CC-830, AUX-CC-831, EN3835-102, EN3835-104, EN3835-201, EN3835-202, and/or EN3835-205
14. Any other condition(s) that, in the Investigator's opinion, might indicate the subject to be unsuitable for the study

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Investigational Product, Dosage and Mode of Administration: EN3835, 1.68 mg, subcutaneous. A dose of 0.84 mg of EN3835 per buttock will be administered as 12 subcutaneous injections (0.3-mL injection administered as three 0.1-mL aliquots per injection) in each of two buttocks for a total dose of 1.68 mg and a total volume of 7.2 mL (3.6 mL per buttock). Total number of injections will be 24 injections per treatment visit into the two buttocks. There will be 3 treatment visits at 21 days intervals, ie, treatments on Days 1, 22, and 43 will be administered.

Duration of Study: Approximately 84 days (includes screening phase)

Screening Phase: Up to 14 days

Criteria for Evaluation:

Efficacy:

- Subject using PR-PCSS while viewing digital image of the target buttock: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the target buttock
- Subject using PR-PCSS while viewing digital image of the non-target buttock: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the non-target buttock
- Investigator using the CR-PCSS by live assessment: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the target buttock
- Investigator using the CR-PCSS by live assessment: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the non-target buttock
- Investigator Global Aesthetic Improvement Scale (I-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the target buttock
- Investigator Global Aesthetic Improvement Scale (I-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the non-target buttock
- Subject Global Aesthetic Improvement Scale (S-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the target buttock
- Subject Global Aesthetic Improvement Scale (S-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the non-target buttock
- Patient Reported Cellulite Impact Scale (PR-CIS): 6 questions with responses to each question consisting of a numerical rating scale (NRS) ranging from 0 (Not at all) to 10 (Extremely)
- Subject Self-Rating Scale (SSRS): 7-level scale ranging from 0 (extremely dissatisfied) to 6 (extremely satisfied) (Day 1 (Baseline) and Day 71)
- Subject satisfaction with cellulite treatment assessment: 5-level scale ranging from 2 (very satisfied) to −2 (very dissatisfied) (Day 71) for both the target and non-target buttocks

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Safety:

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

- Adverse events (AEs) (including those of special interest (AESI); which are AEs such as bruising, ecchymosis, hematomas, and contusions that occur remote to the site of drug administration, or any hypersensitivity reactions, including anaphylaxis; and local AEs associated with the injection site, including bruising, pain, nodules/mass, ulceration, erythema, pruritus, swelling, and/or induration)
- 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 study drug in this study, injection site reactions/local tolerability in the treated buttocks (through subject and Investigator reporting) will be assessed.

Statistical Methods:

The primary endpoint is the proportion of 2-level composite responders at Day 71 defined as subjects with:

- an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator of the target buttock, and
- an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS as assessed by the subject while viewing the digital image of the target buttock.

A subject will be considered a responder if these criteria are met in the randomized target buttock of that subject.

Sample Size Consideration: The results of a prior Phase 2b study of this drug (Study EN3835-201) demonstrated the overall rate for treated buttocks of composite responders with an improvement of at least 2 levels on both the PR-PCSS and the CR-PCSS was 14.9% in the EN3835 treatment group versus 1.1% in the Placebo group. Given this result, the study is planned to randomize 420 subjects with a 1:1 ratio into either the EN3835 arm (0.84 mg/buttock, 1.68 mg total dose) or placebo arm.

The sample size calculation was based on the following assumptions: [redacted] 2) Fisher exact test; 3) type I error of 0.05; 4) power of at least 90%; and 5) dropout rate of approximately 10%.

This sample size will also provide >90% power with type 1 error of 0.05 to detect the treatment difference for all the key secondary endpoints based on previous study results.

Analysis Populations:

- The intent-to-treat (ITT) population: The ITT population is defined as all randomized subjects who have received at least 1 injection of study medication.
- Modified intent-to-treat (mITT) population: The mITT population is defined as all intent-to-treat subjects with a baseline and 1 post-injection evaluation of both the CR-PCSS and PR-PCSS for each buttock.

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- Safety population: The Safety population is defined as all subjects who have received at least 1 injection of study medication.
- Per-Protocol population: The Per-Protocol population is defined as those mITT subjects who do not have any major protocol deviations.

Analyses:

Analyses of Primary Endpoint:

The primary endpoint is the proportion of 2-level composite responders at Day 71 defined as subjects with:

- an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator of the target buttock, and
- an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS as assessed by the subject while viewing the digital image of the target buttock.

A subject will be considered a responder if these criteria are met in the randomized target buttock of that subject.

The primary endpoint will be summarized as percentages and analyzed using a Cochran-Mantel-Haenszel test that compares the 2 treatment groups and adjusts for Investigator at a level of significance of 0.05. The ITT population will be evaluated for the primary endpoint with any subject not having an evaluation of CR-PCSS and/or PR-PCSS at Day 71 classified as a non-responder.

Sensitivity analyses for the primary endpoint will include:

- ITT subjects with missing data handled by multiple imputation (MI) approach
- ITT subjects with missing data handled by a last observation carried forward (LOCF) approach
- mITT subjects with missing data handled by an LOCF approach
- Observed data only (no missing data imputed)
- Per-protocol (PP) subjects with missing data handled by an LOCF approach if 10% or more subjects are excluded in the PP population from mITT population.

Analyses of Key Secondary Endpoints:

There will be 8 key secondary endpoints grouped as three families of 2 to 4 endpoints per family analyzed in hierarchical order.

- Family #1 – four endpoints:
  - Proportion of 1-level PR-PCSS responders defined as subjects with ≥1-level improvement in PR-PCSS severity rating of the target buttock at Day 71 compared to Day 1
  - Proportion of 2-level PR-PCSS responders defined as subjects with ≥2-level improvement in PR-PCSS severity rating of target buttock at Day 71 compared to Day 1

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- Proportion of 1-level composite responders of target buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of the target buttock) at Day 71 compared to Day 1
- Proportion of 2-level composite responders of the non-target buttock at Day 71 compared to Day 1

- Family #2 – two endpoints:
  - Proportion of 1-level SSRS responders defined as subjects who were at least slightly satisfied at Day 71 (SSRS rating ≥ 4)
  - Change from baseline (Day 1) of the PR-CIS total score at Day 71
- Family #3 – two endpoints:
  - Proportion of 1-level S-GAIS responders defined as subjects with ≥1-level improvement (improved, much improved or very much improved) in the S-GAIS assessment of the target buttock at Day 71
  - Proportion of 2-level S-GAIS responders defined as subjects with ≥2-level improvement (much improved or very much improved) in the S-GAIS assessment of the target buttock at Day 71

The key secondary efficacy analyses will be analyzed in the same manner as the primary endpoint based on the ITT population. The family #1 key secondary efficacy analyses will be performed only if the primary efficacy analysis is significant at a significance level of $p \leq 0.05$ (gatekeeping strategy). Similarly, family #2 key secondary efficacy analyses will be performed only if at least one of the key secondary efficacy endpoints of family #1 is significant at a significance level of $p \leq 0.0125$ and family #3 key secondary efficacy analyses will be performed only if at least one of the key secondary efficacy endpoints of family #2 is significant (parallel gatekeeping strategy). Within a family of key secondary efficacy endpoints, the Bonferroni method will be performed to relocate unused alpha for testing each endpoint to assure an overall error rate of $p \leq 0.05$. The details of the testing procedures will be provided in the statistical analysis plan for the study.

Supportive Endpoints:

The supportive variables will evaluate assessments at various study time points and using various populations.

- Proportion of 2-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS) of the target buttock (Days 22, 43, and 71)
- Proportion of 2-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS) of the non-target buttock (Days 22, 43, and 71)
- Proportion of 1-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS) of the target buttock (Days 22, 43, and 71)

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• Proportion of 1-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS) of the non-target buttock (Days 22, 43, and 71) • Proportion of 2-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject. • Proportion of 1-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject. • Proportion of 2-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks. • Proportion of 1-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks. • Proportion of 2-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS) of the target buttock (Days 22, 43, and 71) • Proportion of 2-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS) of the non-target buttock (Days 22, 43, and 71) • Proportion of 1-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS) of the target buttock (Days 22, 43, and 71) • Proportion of 1-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS) of the non-target buttock (Days 22, 43, and 71) • Proportion of 2-level CR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject • Proportion of 1-level CR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject • Proportion of 2-level CR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks • Proportion of 1-level CR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks

[redacted]

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- Proportion of 1-level composite responders of the target buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same target buttock) (Days 22, 43, and 71)
- Proportion of 1-level composite responders of the non-target buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the non-target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same non-target buttock) (Days 22, 43, and 71)
- Proportion of 1-level composite responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject.
- Proportion of 1-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks.
- Proportion of 2-level composite responders of the target buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same target buttock) (Days 22, 43, and 71)
- Proportion of 2-level composite responders of the non-target buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the non-target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same non-target buttock) (Days 22, 43, and 71)
- Proportion of 2-level composite responders of at least one of two buttocks (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject.
- Proportion of 2-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks.
- Proportion of subjects at each level of the S-GAIS of the target buttock (Days 22, 43, and 71)
- Proportion of subjects at each level of the S-GAIS of the non-target buttock (Days 22, 43, and 71)
- Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S-GAIS of the target buttock (Days 22, 43, and 71)
- Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S-GAIS of the non-target buttock (Days 22, 43, and 71)

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- Proportion 1-level S-GAIS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject.
- Proportion of 1-level S-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks.
- Proportion of subjects at each level of the I-GAIS of the target buttock (Days 22, 43, and 71)
- Proportion of subjects at each level of the I-GAIS of the non-target buttock (Days 22, 43, and 71)
- Proportion of 1-level I-GAIS responders defined as subjects with a response of at least 1 (improved) in the I-GAIS of the target buttock (Days 22, 43, and 71)
- Proportion of I-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the I-GAIS of the non-target buttock (Days 22, 43, and 71)
- Proportion of 1-level I-GAIS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject.
- Proportion of 1-level I-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks.
- Change from baseline (Day 1) of the PR-CIS score at Day 71
- Change from baseline (Day 1) of the abbreviated PR-CIS score at Day 71
- Proportion of subjects with a change from baseline (Day1) of the PR-CIS ≥12 at Day 71
- Proportion of subjects with a change from baseline (Day 1) of the abbreviated PR-CIS ≥10 at Day 71
- Proportion of subjects at each level of the subject self-rating scale (SSRS) (Day 1 (Baseline) and Day 71
- Proportion of 1-level SSRS responders defined as subjects who were at least slightly satisfied at Day 71 (SSRS rating ≥ 4)
- Proportion of subjects at each level of the subject satisfaction with cellulite treatment assessment (Day 71)
- Proportion of satisfied responders (defined as subjects with a response of at least 1 (ie, 1-Satisfied or 2-Very Satisfied) in the subject satisfaction with cellulite treatment assessment (Day 71)

All supportive endpoints will be summarized as percentages. The dichotomous secondary endpoints (ie, responder endpoints) will be analyzed using a Cochran-Mantel-Haenszel test adjusted for Investigator. Changes in the PR-PCSS ratings and CR-PCSS ratings from baselines, S-GAIS scores, and I-GAIS scores will be analyzed using the Mann-Whitney test.

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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. The Fisher exact test will be used to compare EN3835 to placebo. Descriptive statistics will be presented for actual and change from baseline at each visit for vital signs and for each clinical laboratory test parameter. The comparison between treatment groups will be based on the change from baseline for clinical laboratory tests and vital signs using an analysis of variance (ANOVA) with a factor of drug (EN3835 or placebo). Immunogenicity: Anti-AUX-I and anti-AUX-II antibody levels will be summarized using descriptive statistics for the actual value at the visit. Samples from Day 1, Day 22, Day 43, and Day 71 visits will be analyzed for anti-AUX-I and anti-AUX-II antibodies and a subset of Day 1 and Day 71 samples will be analyzed for neutralizing antibodies.

5. SCHEDULE OF EVENTS

Procedures	Day -14 to -1 Screening	Day 1 Treatment Visit 1	Day 22 (± 3 d) Treatment Visit 2	Day 43 (± 3 d) Treatment Visit 3	Day 71 (+ 5 d) / End of Study / Early Termination	Unscheduled Clinic Visit[a]
Informed consent	X					
Inclusion/exclusion	X					
Digital photography	X	X[b]	X[b]	X[b]	X	X
Medical history/EFP history including previous treatments	X					
Prior/concomitant medications/procedures	X	X	X	X	X	X
Physical examination:	X					
• Body weight	X		X[c]	X[c]	X	X
• Height	X					
• Fitzpatrick skin type	X					
Vital signs	X	X[d]	X[d]	X[d]	X	X
12-lead ECG	X					
Collection of samples:						
• Clinical laboratory	X				X	X
• Anti-AUX-I/anti-AUX-II antibody level		X[c]	X[c]	X[c]	X	
• Pregnancy testing	X[e]	X[c,e]	X[c,e]	X[c,e]	X[e]	X
Subject cellulite assessments[f]:						
• Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS)	X[g,h]	X[c,g,h]	X[c,g,h]	X[c,g,h]	X[g,h]	
• Subject Global Aesthetic Improvement (S-GAIS)			X[c,g,h]	X[c,g,h]	X[g,h]	
• Patient Reported Cellulite Impact Scale (PR-CIS)		X[c,g]			X[g]	
• Subject Satisfaction With Cellulite Treatment Assessment					X[g]	
• Subject Self-Rating Scale (SSRS)		X[c]			X	

Procedures	Day -14 to -1 Screening	Day 1 Treatment Visit 1	Day 22 (± 3 d) Treatment Visit 2	Day 43 (± 3 d) Treatment Visit 3	Day 71 (+ 5 d) / End of Study / Early Termination	Unscheduled Clinic Visit[a]
Investigator cellulite assessments:						
• Selection of dimples to be treated within the two buttocks		X[c]	X[c]	X[c]		
• Marking the dimples and injection sites to be treated within the buttocks		X[c]	X[c]	X[c]		
• Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)	X	X[c,h]	X[c,h]	X[c,h]	X[h]	
• Investigator Global Aesthetic Improvement (I-GAIS)			X[c,h]	X[c,h]	X[c,h]	
Confirm eligibility		X[c]				
Randomize to treatment		X[c,i]				
Study drug administration		X	X	X		
Injection site reactions/local tolerability in the buttocks		X	X	X	X	X
Adverse events	Monitored Throughout Study					

[a] During unscheduled visits, the Investigator or designee may perform any study procedure that they deem clinically necessary (eg, vital signs, clinical lab assessments, and pregnancy test).
[b] Before and after marking the dimples and injection sites.
[c] Before injection.
[d] Up to 4 hours before injection; approximately 15 and 30 minutes after injection. Vital signs must be stable before the subject is discharged.
[e] Serum pregnancy test on Screening visit and Day 71/EOS visit; urine pregnancy test on Day 1, Day 22, and Day 43 visits.
[f] Subject assessments should be completed independently and prior to Investigator assessments at each visit.
[g] Assessment made via photographs (if treatment visit, use photographs taken before marking dimples and injection sites).
[h] Assessment of each of the 2 buttocks independently.
[i] Before randomization, each of the subject's buttocks must have ratings of 3 or 4 (moderate or severe) in both the CR-PCSS and PR-PCSS.
NOTE: Subject cellulite assessments must be completed before the Investigator cellulite assessments are conducted at each visit.
d=Days; ECG=Electrocardiogram; EFP=Edematous fibrosclerotic panniculopathy; EOS=End of study

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7. LIST OF ABBREVIATIONS

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

Table 2: Abbreviations and Special Terms

Abbreviation	Definition
AE	Adverse event
AUX-I	Clostridial class I collagenase
AUX-II	Clostridial class II collagenase
BMI	Body mass index
CR-PCSS	Clinician Reported Photonumeric Cellulite Severity Scale
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EFP	Edematous fibrosclerotic panniculopathy
ePRO	Electronic patient reported outcome
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HREC	Human Research Ethics Committee
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
I-GAIS	Investigator-Global Aesthetic Improvement Scale
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive web response system
LOCF	Last observation carried forward
MI	Multiple imputation
mITT	Modified intent-to-treat
PR-CIS	Patient Reported Cellulite Impact Scale
PR-PCSS	Patient Reported Photonumeric Cellulite Severity Scale
Quadrant	A quadrant is a treatment area
Qualified designee	Qualified by education and training to perform the study procedure (eg, sub-Investigator, nurse).
SAE	Serious adverse event
S-GAIS	Subject – Global Aesthetic Improvement Scale
SSRS	Subject Self-Rating Scale
TEAE	Treatment-emergent adverse event. Adverse events that occur on or after the first injection of study drug.

8. INTRODUCTION

8.1. Background

8.1.1. 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 a contour abnormality of the skin.(1) The condition manifests as dimpled skin, particularly in the gluteal-femoral region.(2,3) EFP is caused by herniation of subcutaneous fat lobules through the dermohypodermal junction and/or shortening of the collagen septa that cross the hypodermal layer and connects the dermis to the underlying fascia. This creates an uneven surface with dimpling.(1,2) 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.

8.1.2. Current EFP Treatments

There are therapies that have been utilized in an attempt to treat cellulite; however, there are no approved pharmacologic treatments. 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,(6) topical agents,(5) massage,(7) liposuction,(5,6) mesotherapy,(6) radiofrequency,(6) subcision and powered subcision,(8) and laser therapies;(9,10) some of these treatments may pose an increased risk for adverse effects.(5)

There remains an unmet medical need for safe and effective therapies to improve the aesthetic 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 that is bothersome to many women.

8.1.3. 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 (brand name is XIAFLEX®) 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° at the start of therapy.

A recent Phase 2b, randomized, double-blind, placebo-controlled study (EN3835-201) of 375 women randomized to treatment of one treatment area (quadrant) (quadrant was defined in study EN3835-201 as a left buttock, a right buttock, a left posterolateral thigh or a right posterolateral thigh) of cellulite with EN3835 0.84 mg or placebo in a 1:1 ratio assessed the effectiveness and safety of EN3835. Efficacy in this study was evaluated based on cellulite assessments using Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS), Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS), Investigator Global Aesthetic Improvement Scale (GAIS-I), Subject Global Aesthetic Improvement Scale (GAIS-S), and Subject Satisfaction with Cellulite Treatment.

Results from the Phase 2b study demonstrated that treatment (3 visits approximately 21 days apart) improved the cellulite severity of the treatment area as assessed by the primary endpoint of 2-level composite responder analyses, the proportion of responders based on an improvement of ≥2 levels in the appearance of cellulite in both the patient PR-PCSS and the clinician CR-PCSS of buttocks and thighs was statistically significantly greater in subjects who received EN3835 0.84 mg (10.6%; $p<0.001$) compared to subjects who received placebo (1.6%); 1-level (or greater) responders in the PR-PCSS of EN3835-treated subjects (72.3%) was significantly

greater than 1-level responders in the placebo group (51.6%) ($p<0.001$); statistically significant ($p\leq0.001$) improvement in the appearance of cellulite based on the subject S-GAIS were observed in EN3835 0.84-mg group (73.1%) compared to the placebo group (44.0%); and 62.9% of subjects in the EN3835 0.84 mg group were satisfied or very satisfied with the results of their cellulite treatment compared with only 35.9% of subjects in the placebo group ($p<0.001$). In subjects treated in buttocks (n=187), the proportion of 2-level composite responders was statistically significantly greater in subjects who received EN3835 0.84 mg (14.9%; $p<0.001$) compared to subjects who received placebo (1.1%); 1-level (or greater) responders in the PR-PCSS of EN3835-treated subjects (72.7%) was significantly greater than 1-level responders in the placebo group (47.8%) ($p<0.001$).

The study also demonstrated EN3835 to be well tolerated with no serious adverse events (SAEs) related to EN3835. Safety results from a total of 4 studies (1 pilot, 2 Phase 1, and 2 Phase 2 studies) in which 435 adult females received subcutaneous injections of EN3835 indicate that the majority of treatment-emergent adverse events (TEAEs) are transient, non-serious, mild or moderate in intensity, and related to the local administration of EN3835. The immunogenicity profile after 3 treatment visits of EN3835 indicate that greater than 90% of EN3835-treated subjects were seropositive for AUX-I and/or AUX-II antibodies; this profile of EN3835 is similar to that observed in the Dupuytren's contracture and Peyronie's disease programs.

A Phase 1, open-label safety and pharmacokinetic study of a single dose of EN3835 0.84 mg in 11 female subjects with EFP showed that there was no quantifiable levels of AUX-I or AUX-II at any time point after subcutaneous injection of EN3835 0.84 mg into one quadrant. A second Phase 1, open-label safety and pharmacokinetic study of a single dose of EN3835 0.84 mg per treatment area in two treatment areas (buttock-buttock, thigh-thigh, or buttock-thigh) concurrently (total dose of 1.68 mg) showed that there was no quantifiable levels of AUX-I or AUX-II at any time point post-dose attributable to the injection of EN3835 1.68 mg.

The results from these studies suggest that subcutaneous injections of EN3835 in the area of cellulite may be a well-tolerated and effective medical treatment for adults with EFP.

8.2. Summary of Nonclinical Studies

Non-clinical studies necessary to support clinical studies have been performed and are summarized in the Investigator Brochure (IB).(11) Non-clinical studies in the following areas were performed: toxicology, reprotoxicity, genotoxicity, and hypersensitivity.

8.3. Summary of Known Risks and Benefits

A summary of safety risks is provided in the IB.(11) The following events have been commonly observed: local injection site reactions (injection site bruising, injection site swelling, injection site pain) for the various approved indications as well as those being investigated. In the phase 2b study of EN3835 in women with EFP, the following treatment related adverse events ≥2% of 189 EN3835-treated women were reported: injection site bruising (75.1%), injection site pain (59.3%), injection site nodule (14.3%), injection site pruritus (11.1%), injection site swelling (7.4%), injection site induration (5.8%), injection site mass (5.3%), injection site discolouration (3.2%), and injection site erythema (2.1%). These events are similar to events reported in the clinical trials of EN3835 for the approved indications. Postmarketing safety data are consistent with safety data reported in clinical trials.

Although a thorough benefit of EN3835 has not been fully evaluated in the treatment of EFP, the efficacy results from the Phase 2b study and previous EFP studies warranted further development.

8.4. Rationale

The results from the Phase 2b EFP study (EN3835-201) further suggested that EN3835 0.84 mg per treatment area (quadrant) is an effective treatment of EFP based on improvement in the severity of cellulite as determined by the Investigator and the subject. There were no safety concerns following 0.84 mg per treatment area in the treatment of EFP (section 8.1.3). Safety findings from the Phase 2b EFP study are similar to that observed in previous clinical studies with EN3835 in the treatment of EFP and XIAFLEX in the treatment of Dupuytren's contracture and Peyronie's disease, in that that the majority of AEs occurred at the site of injection and resolved before the next scheduled treatment. The immunogenicity profile of EN3835 in the Phase 2b EFP study is similar in previous studies and programs.

Based on the efficacy and safety findings from the Phase 2a and 2b EFP studies, the EN3835 0.84-mg dose per treatment area in two treatment areas (buttocks) warranted further investigation in this study.

Treating two buttocks at each treatment visit will potentially provide a symmetrical-like improvement in appearance. Support for evaluation of the treatment of two buttocks concurrently is based on: 1) the safety findings from the previous EFP studies are local to the injection site, 2) the pharmacological activity of EN3835 is local and does not require systemic exposure, and 3) no significant quantifiable systemic concentration has been attributable to injection of two buttocks concurrently.

The integration of dose and use justification supports this study of evaluation of EN3835 0.84 mg per treatment area in two treatment areas (buttocks) concurrently.

9. OBJECTIVES

9.1. Primary Objective

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

9.2. Secondary Objectives

There are no secondary objectives of this study.

9.3. Exploratory Objectives

There are no exploratory objectives of this study.

10. INVESTIGATIONAL PLAN

10.1. Study Design

This study will be performed at approximately 25 study centers located in the United States. This clinical study will be conducted as a multicenter, randomized, double-blind, placebo-controlled study comparing EN3835 to placebo in adult women with EFP. The study will consist of 71 days of double-blind treatment. Subjects meeting the entry criteria for this study will be randomized to EN3835 treatment or placebo treatment in a 1:1 ratio within an investigational site.

The complete Schedule of Events is provided in section 5.

Figure 1: Study Design

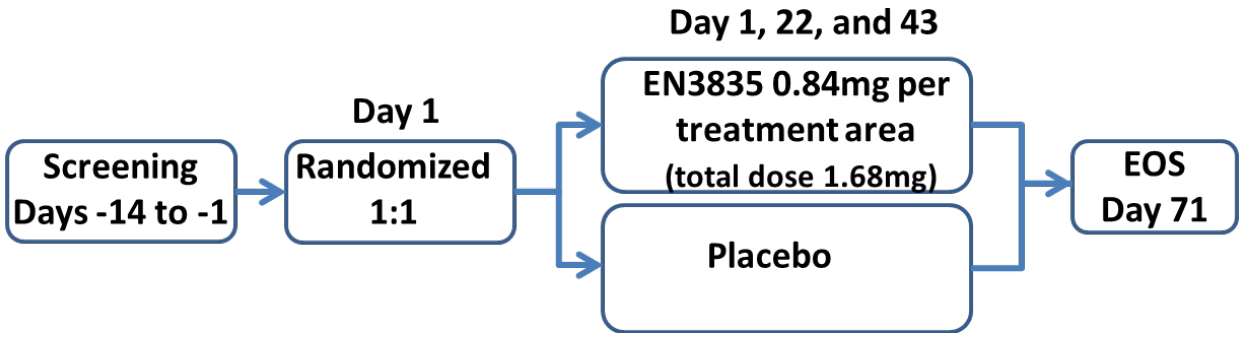


Table 3: Study Treatment Groups

Dose per Each Injection[a] / Number of Subjects	Injection Volume per Each Injection	Number of Injections at Each Treatment Visit	Dose (mg) at Each Treatment Visit	Injection Volume (mL) per Each Treatment Visit	Cumulative EFP Dose
EN3835 0.07 mg / N=210	0.3 mL	12 per buttock × 2 buttocks = 24 injections	0.84 mg per buttock × 2 buttocks = 1.68 mg (12 injections per buttock × 0.07 mg/injection × 2 buttocks)	3.6 mL per buttock × 2 buttocks = 7.2 mL (24 injections × 0.3 mL)	5.04 mg (3 treatment visits × 0.84 mg per buttock × 2 buttocks)
Placebo / N=210	0.3 mL	12 per buttock × 2 buttocks = 24 injections	-	3.6 mL per buttock × 2 buttocks = 7.2 mL (24 injections × 0.3 mL)	-

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

10.2. Selection of Doses

The dose of EN3835 chosen for this study was based on the results from earlier studies.

The data from the Phase 2a EFP dose-ranging study (AUX-CC-831) suggest that EN3835 0.84 mg is most effective in the treatment of EFP based on improvement in the severity of

cellulite as determined by both the Investigator and the subject, although the EN3835 0.48-mg group did show improvement in some of the efficacy parameters.

- There were no safety concerns following administration of up to 3 treatment visits of EN3835 0.84 mg in the treatment of EFP (AUX-CC-831 CSR). The safety profile of EN3835 0.84 mg in the treatment of EFP was similar to that observed in the EN3835 0.06-mg group and the EN3835 0.48-mg group. No notable differences were observed across the 3 treatment groups.
- Safety findings from the Phase 2a EFP dose-ranging study are similar to that observed in previous clinical studies with XIAFLEX in the treatment of Dupuytren's contracture and Peyronie's disease, in that the majority of AEs occurred at the site of injection and resolved before the next scheduled treatment.
- The immunogenicity profile of EN3835 in the Phase 2a EFP dose-ranging study is similar to that observed in the Dupuytren's contracture and Peyronie's disease programs.
- Based on the efficacy and safety findings from the Phase 2a EFP dose-ranging study, the EN3835 0.84-mg dose was carried forward to the Phase 2b study.

The results from the Phase 2b EFP study (EN3835-201) further suggested that EN3835 0.84 mg is an effective treatment of EFP based on improvement in the severity of cellulite as determined by the Investigator and the subject. There were no safety concerns following EN3835 0.84 mg in the treatment of EFP (section 8.4). Safety findings from the Phase 2b EFP study are similar to that observed in previous clinical studies with XIAFLEX in the treatment of Dupuytren's contracture and Peyronie's disease, in that that the majority of AEs occurred at the site of injection and resolved before the next scheduled treatment. The immunogenicity profile of EN3835 in the Phase 2b EFP study is similar to that observed in the Dupuytren's contracture and Peyronie's disease programs.

Based on the efficacy and safety findings from the Phase 2a and 2b EFP studies, the EN3835 0.84-mg dose per treatment area was carried forward to this study. The findings from previous studies that the majority of adverse events after EN3835 treatment are local to the injection site and that there is no quantifiable systemic exposure observed after concurrent treatment of two buttocks (total dose of 1.68 mg) supports the proposed study to evaluate EN3835 treatment of two buttocks.

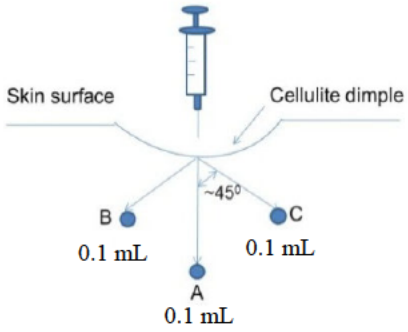
10.3. Study Drug Administration

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 visit, 8 syringes (4 syringes per buttock) will be prepared for dosing. Each syringe will contain 0.9 mL of study drug (ie, 3 injections in each syringe). Twelve (12) skin

injections of 0.3 mL per injection will be administered within each of the two buttocks during each treatment visit.

Figure 2: Study Drug Administration at Each Injection Site



- **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 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 each buttock (three 0.3-mL injections per syringe, each injection administered as three 0.1-mL aliquots). Twelve (12) skin injections of 0.3 mL will be administered within each of the two treated buttocks during each treatment visit.
- The plane containing injection deposition points A, B, and C should be perpendicular to the skin and perpendicular to the long axis of a dimple if the dimple is an elongated trough-like dimple.
- 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 Visits 1, 2, and 3.

NOTE: EN3835 is a foreign protein and Investigators should 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 must be available with the Investigator and site staff must be familiar with their use.

10.4. 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 injections 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 14.9).

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

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

The design of this study was based on the primary objective to evaluate the efficacy and safety of EN3835 0.84 mg per buttock in the concurrent treatment (total dose of 1.68 mg) of 2 bilateral buttocks with EFP in adult women compared with placebo treatment. The study design, a multi-center, double-blind, placebo-controlled study is in accordance with regulatory guidelines of adequate and well-controlled clinical studies (Food and Drug Administration [FDA] Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, 1998.; ICH E8 and E10).

11. SELECTION AND WITHDRAWAL OF SUBJECTS

11.1. Subject Inclusion Criteria

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

1. Voluntarily sign and date an informed consent agreement
2. Be a female ≥18 years of age
3. At Screening visit, have 2 bilateral buttocks with each buttock having:
   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)
4. At Day 1 visit, have 2 bilateral buttocks with each buttock having:
   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)
5. Be willing to apply sunscreen to the buttocks before each exposure to the sun while participating in the study (ie, Screening 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
7. Have a negative serum pregnancy test at Screening and a negative urine pregnancy test before injection of study drug and be using a stable and effective contraception method (eg, abstinence, intrauterine device [IUD], hormonal [estrogen/progestin] contraceptives, or double barrier method) for at least 1 menstrual cycle prior to study enrollment and for the duration of the study; or be menopausal defined as 12 months of amenorrhea in the absence of other biological or physiological causes, as determined by the Investigator; or post-menopausal for at least 1 year; or be surgically sterile
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. Subject Exclusion Criteria

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

1. Has any of the following systemic conditions:
   a. Coagulation disorder
   b. Evidence or history of malignancy (other than excised basal-cell carcinoma) unless there has been no recurrence in at least 5 years
   c. History of keloidal scarring or abnormal wound healing
   d. Concurrent diseases or conditions that might interfere with the conduct of the study, confound the interpretation of the study results, or endanger the subject's well-being.

Any questions about concurrent diseases should be discussed with the Medical Monitor

e. Evidence of clinically significant abnormalities on physical examination, vital signs, electrocardiogram (ECG), or clinical laboratory values

2. Has any of the following local conditions in the areas to be treated:
   a. History of lower extremity thrombosis or post-thrombosis syndrome
   b. Vascular disorder (eg, varicose veins, telangiectasia) in area to be treated
   c. Inflammation or active infection
   d. Severe skin laxity, flaccidity, and/or sagging
   e. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer
   f. Has a tattoo and/or a mole located within 2 cm of the site of injection
3. Requires the following concomitant medications before or during participation in the trial:
   a. Anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication (except for ≤150 mg aspirin daily) within 7 days before injection of study drug
4. Has used any of the following for the treatment of EFP on a buttock within the timelines identified below or intends to use any of the following at any time during the course of the study:
   a. Liposuction in a buttock during the 12-month period before injection of study drug
   b. Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; buttock implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision) within a buttock during the 12-month period before injection of study drug
   c. Any investigational treatment for EFP on a buttock during the 12-month period before the injection of study drug
   d. Endermologie or similar treatments within a buttock during the 6-month period before injection of study drug
   e. Massage therapy within a buttock during the 3-month period before injection of study drug
   f. Creams (eg, Celluvera™, TriLastin®) and/or home therapies to prevent or mitigate EFP within a buttock during the 2-week period before injection of study drug
5. Is presently nursing or providing breast milk
6. Intends to become pregnant during the study
7. Intends to initiate an intensive sport or exercise program during the study
8. Intends to initiate a weight reduction program during the study
9. Intends to use tanning spray or tanning booths during the study

10. Has received an investigational drug or treatment within 30 days before injection of study drug
11. Has a known systemic allergy to collagenase or any other excipient of study drug
12. Has received any collagenase treatments at any time prior to treatment
13. Was a subject in a previous cellulite clinical trial of CCH: AUX-CC-830, AUX-CC-831, EN3835-102, EN3835-104, EN3835-201, EN3835-202, and/or EN3835-205
14. Any other condition(s) that, in the Investigator's opinion, might indicate the subject to be unsuitable for 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
- Lack of efficacy
- 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 including safety and efficacy assessments should be conducted as detailed in the Schedule of Events (section 5). 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 and assessments are required (but are encouraged to reduce missing information) except the collection of adverse event (AE) information. This information should be recorded in the source documentation and the eCRF.

11.3.1. Replacement Procedures

Subjects who discontinue from the study will not be replaced.

12. TREATMENT OF SUBJECTS

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. Informed Consent

Signed and dated informed consent will be obtained from each subject before any study procedures are undertaken, or before any changes to the subject's medication regimen are made. Details about how the informed consent will be obtained and documented are provided in section 21.3, Subject Information and Consent.

12.1.2. Subject Screening

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. The screening log will be captured directly by the electronic data capture (EDC) system.

12.1.2.1. Medical History

During the screening period, the Investigator or qualified designee will obtain a medical history from each subject that includes relevant diagnoses and/or procedures/therapies with onset/resolutions dates. Medical histories should also include history of EFP (start date and family history), and history of tobacco and alcohol use (never, current, former).

12.1.2.2. Screening Period (Day -14 to Day -1)

Subjects meeting the relevant eligibility criteria listed in section 11 may be enrolled in the study after the nature and purpose of the protocol have been explained and written informed consent to participate has been voluntarily provided by the subject or their legally authorized representative.

The subject identification number will consist of 8 digits. The first 4 digits represent the study site number followed by a 4-digit subject number.

The following procedures will be performed and documented during the screening period:

1. Obtain written informed consent (section 12.1.1)
2. Evaluate eligibility based on inclusion/exclusion criteria (section 11.1 and section 11.2)
3. Subject will have digital photographs taken of her two buttocks (section 13.1.1)
4. Subjects will get instruction on the use of the PR-PCSS (section 13.1.2.1)

5. Prior to Investigator CR-PCSS assessment, subjects will rate each of their two buttocks using the PR-PCSS while viewing their digital images (section 13.1.2.1); the Investigator is blinded to these ratings
6. After the subject has completed the PR-PCSS ratings, the Investigator will conduct live assessments of subject's cellulite severity of each of the two buttocks using the CR-PCSS (section 13.1.2.6); the subject is blinded to these ratings. The ratings from the PR-PCSS and CR-PCSS will be used to assess initial eligibility of the buttocks for study entry
7. Medical history including EFP history (section 12.1.2.1)
8. Record prior and concomitant medications/procedures (section 12.8)
9. Physical examination including measurement of body weight, height, Fitzpatrick skin type (section 14.11)
10. Vital sign measurements (section 14.9)
11. 12-lead ECG (section 14.10)
12. Collection of samples for:
    a. Clinical laboratory testing (section 14.7)
    b. Serum pregnancy testing (section 14.7)
13. Adverse events (section 14)

12.2. Selecting and Marking Dimples during Treatment Visits

Selection of dimples to be treated in the two buttocks is at the discretion of the Investigator. Dimples must be well-defined and evident when the subject is standing in a consistent, standardized relaxed pose (without the use of any manipulation such as skin pinching or muscle contraction). Each subject will receive 3 treatment visits of study drug according to randomization unless the buttock is dimple-free (score of 0 on CR-PCSS as reported by the Investigator) at Treatment Visit 2 and/or Treatment Visit 3 (a dimple -free buttock at Treatment Visit 1 is precluded by the eligibility criteria); a dimple-free buttock at Treatment Visit 2 and/or Treatment Visit 3 does not preclude treatment of the contralateral buttock unless it is dimple-free also. During each treatment visit, each of the buttocks will be photographed before and after marking dimples and injection sites while the subject is standing in a consistent, standardized relaxed pose as described in the Photography Manual. The cellulite severity assessments using the PR-PCSS and CR-PCSS will be completed prior to marking dimples and injection sites.

The Investigator or qualified designee will select dimples within each buttock that are well-defined, evident when the subject is standing, and suitable for treatment; treatment consists of 12 injections per buttock (24 injections total in two buttocks) per treatment visit. Because the goal of treatment is to improve the aesthetic appearance of each entire buttock, the Investigator will be instructed to select dimples that in his or her opinion would most improve the aesthetic appearance of each entire buttock. The same dimples within a buttock or different dimples within a buttock may be treated at each treatment visit but injections must all be within the buttocks (12 injections per buttock) for all 3 visits. Each buttock will receive all 3 treatment visits unless the buttock has no treatable EFP dimples and the Investigator rates the buttock a score of 0 on the CR-PCSS. If no injections in a particular buttock (right or left) are given at Treatment

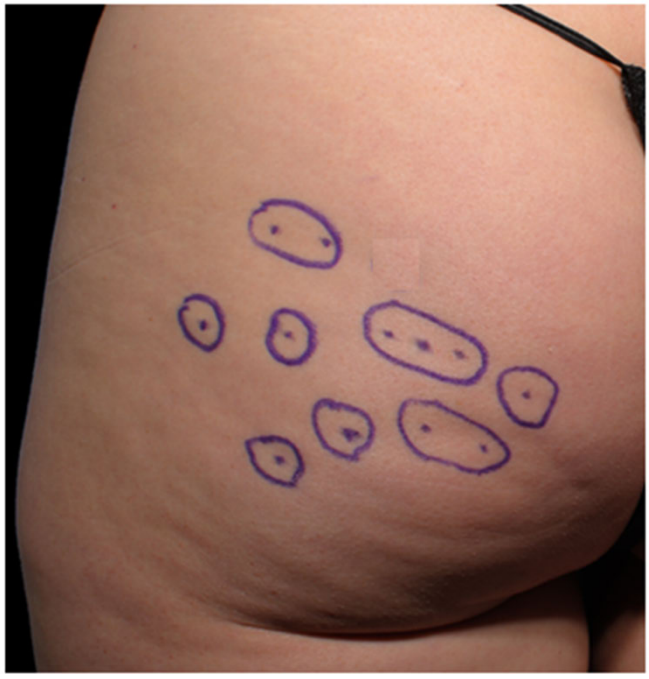
Visit 2, subjects will still be assessed for treatment in the contralateral buttock at Treatment Visit 2, and will return for the Day 43 visit and each of the buttocks will again be evaluated by the subject (PR-PCSS) and Investigator (CR-PCSS). If the Investigator rates either or both of the buttocks greater than 0 on the CR-PCSS, injections at Treatment Visit 3 should be given.

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; locating at least one injection site at the nadir, if present, of the dimple). 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 buttock should not overlap.

Each of the buttocks will be photographed before and after marking dimples and injection sites while the subject is standing in a consistent, standardized relaxed pose as described in the Photography Manual.

Examples of subject dimple and injection site markings are shown as follows:

Sample Buttock Marking



12.3. Digital Photography during Treatment Visits 1, 2, and 3

During each treatment visit, each of the two buttocks will be photographed before and after marking dimples and injections sites while the subject is standing in a consistent, standardized relaxed pose as described in section 13.1.1.

12.4. Treatment Visit 1 (Day 1)

12.4.1. Treatment Visit 1: Pre-Injection

1. Confirm eligibility criteria
2. Take digital photography of each of the buttocks before marking dimples and injection sites (section 13.1.1)
3. Subjects will get instruction on the use of the PR-PCSS (Patient Instructions for Use of PR-PCSS)
4. Subjects will rate each of their buttocks using the PR-PCSS (section 13.1.2.1); the Investigator is blinded to these ratings
5. Subjects will complete the Patient Reported Cellulite Impact Scale assessment (PR-CIS; section 13.1.2.3): the Investigator is blinded to this rating
6. Subjects will complete the Subject Self-Rating Scale (SSRS) assessment (section 13.1.2.5); the Investigator is blinded to these ratings
7. The Investigator will conduct live assessments of subject's cellulite severity of each of the buttocks using the CR-PCSS (section 13.1.2.6); the subject is blinded to these ratings. The ratings from the PR-PCSS and CR-PCSS will be used to assess eligibility for randomization
8. Subjects with PR-PCSS or CR-PCSS ratings in either of the buttocks <3 will be excluded from participation
9. Upon confirmation of two buttocks eligible for treatment (eligible criteria being each buttock have PR-PCSS and CR-PCSS scores of 3 or 4), the IWRS system will randomly assign one buttock as the target buttock in the background. Subjects, investigators, site personnel and Endo personnel will be blinded to target buttock assignment.
10. Randomization of subjects with two buttocks eligible for treatment (eligible criteria being each buttock have PR-PCSS and CR-PCSS scores of 3 or 4) to treatment (section 12.10); obtain kit numbers of study treatment. Subjects, investigators, site personnel, and Endo personnel will be blinded to treatment assignment.
11. Record concomitant medications/procedures (section 12.8)
12. Vital sign measurements (section 14.9)
13. Collection of samples for:
    a. Anti-AUX-I and anti-AUX-II antibody testing (section 14.8)
    b. Urine pregnancy testing (section 14.7)
14. Select and mark dimples to be treated in each of the buttocks (section 12.2)
15. Take digital photograph of each of the buttocks after marking dimples and injection sites (section 13.1.1)

12.4.2. Treatment Visit 1: Injection and Post-injection

1. Administration of study drug in the prone position (section 10.3)
2. Record number of dimples treated and number of injections administered in each of the two buttocks
3. Vital sign measurements (section 14.9)
4. Injection site reactions and local tolerability
5. Adverse events (section 14)

12.5. Treatment Visit 2 (Day 22 [±3 days]) and Treatment Visit 3 (Day 43 [±3 days])

12.5.1. Treatment Visits 2 and 3: Pre-injection

1. Record concomitant medications/procedures (section 12.8)
2. Body weight measurements
3. Vital sign measurements (section 14.9)
4. Collection of samples for:
   a. Anti-AUX-I and anti-AUX-II antibody testing (section 14.8)
   b. Urine pregnancy testing (section 14.7)
5. Digital photographs of each of the two buttocks before marking dimples and injection sites (section 13.1.1)
6. Subject Cellulite Assessments of each of the buttocks using the photographic image of each buttock before marking dimples and injection sites (NOTE: complete subject cellulite assessments before Investigator cellulite assessments) in the following sequential order using:
   a. Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) assessment (section 13.1.2.1); complete this prior to conducting S-GAIS
   b. Subject Global Aesthetic Improvement Scale (S-GAIS) (section 13.1.2.2)
7. Investigator Cellulite Assessments live of each of the buttocks in the following sequential order prior to marking dimples and injection sites using:
   a. Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) live assessment of subject (section 13.1.2.6)
   b. Investigator Global Aesthetic Improvement Scale (I-GAIS) (section 13.1.2.7)
8. Select and mark dimples to be treated in each buttock (section 12.2)
9. Digital photographs of each buttock after marking dimples and injection sites (section 13.1.1)
10. For eligible buttock(s), obtain kit number(s) of study treatment

12.5.2. Treatment Visits 2 and 3: Injection and Post-injection

1. Administration of study drug in the prone position (section 10.3)
2. Record number of dimples treated and number of injections administered in each buttock
3. Vital sign measurements (section 14.9)
4. Injection site reactions and local tolerability
5. Adverse events (section 14)

12.6. Day 71 (+5 days) / End of Study / Early Termination

The following procedures will be performed on Day 71:

1. Record concomitant medications/procedures (section 12.8)
2. Measurement of body weight
3. Vital sign measurements (section 14.9)
4. Collection of samples for:
   a. Clinical laboratory testing (section 14.7)
   b. Serum pregnancy test (section 14.7)
   c. Anti-AUX-I and anti-AUX-II antibody testing (section 14.8)
5. Digital photographs of each of the buttocks
6. Subject Cellulite Assessment of each of the two buttocks using the photographic image before marking dimples and injection sites (NOTE: complete subject cellulite assessments before Investigator cellulite assessments) using:
   a. Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) assessment (section 13.1.2.1)
   b. Subject Global Aesthetic Improvement Scale (S-GAIS) (section 13.1.2.2)
   c. Patient Reported Cellulite Impact Scale (PR-CIS) assessment (section 13.1.2.3); note this assessment is of both left and right buttocks rather than each individual buttock
   d. Subject Satisfaction with Cellulite Treatment Assessment (section 13.1.2.4); note this assessment is of both left and right buttocks rather than each individual buttock
   e. Subject Self-Rating Scale (SSRS) assessment (section 13.1.2.5); note this assessment is of both left and right buttocks rather than each individual buttock
7. Investigator Cellulite Assessments of each of the buttocks live using:
   a. Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) live assessment of subject (section 13.1.2.6)
   b. Investigator Global Aesthetic Improvement Scale (I-GAIS) (section 13.1.2.7)
8. Injection site reactions and local tolerability
9. Adverse events (section 14)

12.7. Unscheduled Visits

If any subject needs to return to the site prior to her next scheduled visit, site staff should follow the Unscheduled Visit procedures outlined in section 5. Site staff may conduct additional study procedures if required.

12.8. Prior and Concomitant Medications and Procedures

All prior medications taken within 90 days before randomization will be recorded. All medications (including over-the-counter medications) taken by the subject on Day 1 through the end of the study must be recorded. Any prior treatments (medications or procedures) for EFP through the end of the study must be recorded on the appropriate eCRF page.

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.

12.8.1. Prohibited Medications or Procedures

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

Procedures listed in exclusion criterion #4 (section 11.2, Exclusion Criterion #4) are prohibited for randomized subjects during the study.

Table 4: Concomitant Medication Restrictions for Subjects during the Treatment Phase of Study

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

12.9. Treatment Compliance

Randomized subjects will receive study drug administered by an Investigator at the Investigator's site.

Accidental or intentional overdoses should be reported to the Sponsor/designee promptly (see section 14.6.2.1, Overdose).

12.10. Blinding and Randomization

On Day 1, if each of the buttocks (ie, both buttocks) again meet the criteria (3 or 4 on the PR-PCSS and CR-PCSS), one buttock will be randomly assigned by the IWRS as the target buttock for the primary efficacy endpoint. Subjects, investigators, site personnel, and Endo personnel will be blinded to the identification of the target buttock.

On Day 1, if each of the buttocks (ie, both buttocks) again meet the criteria (3 or 4 on the PR-PCSS and CR-PCSS), the subject will be randomized to a treatment group. The interactive

web response system (IWRS) will randomly assign each subject to a treatment group (EN3835 0.84 mg per buttock × two buttocks or placebo) in a 1:1 ratio within an investigational site. The treatment group will remain blinded to the Investigator, subjects, all site personnel, and the sponsor. The IWRS will assign the subject study drug kit numbers associated with the randomized treatment. At Day 22 and 43 visits, the IWRS will again assign the subject study drug kit numbers associated with the randomized treatment assigned at Day 1.

All precautions will be taken to ensure that the blinding of EN3835 and placebo is maintained throughout the study period. Unblinding will not be permitted by the study site unless it is deemed necessary for treatment of a medical emergency. Before breaking the blind, the Investigator should make every attempt to contact the Medical Monitor to discuss the necessity of breaking the blind. The study site will have the ability to immediately determine treatment identification in the event of an emergency by using the unblinding function within the IWRS, however, the Medical Monitor must be notified immediately. The Investigator will be required to make a full written explanation of the reason for unblinding the subject and the date. In the event that a subject is unblinded prior to contacting the Medical Monitor, the Investigator must provide this information in writing to the Medical Monitor as soon as possible. Breaking the blind at the investigative site will immediately disqualify the subject from further participation in the study. In addition, the event(s) leading to emergency unblinding must be reported as an SAE according to instructions in section 14.5.2, Reporting Serious Adverse Events.

In addition, it may be necessary for the Investigator or qualified designee to unblind a subject as a result of a clinically significant finding noted during safety review by the Investigator, Safety Monitor, Medical Monitor and/or qualified designee that might jeopardize subject safety.

13. ASSESSMENT OF EFFICACY

13.1. Efficacy Measurements

13.1.1. Digital Photography

Although digital photographs are not direct efficacy measurements, digital photography will be utilized in the assessment of certain efficacy measurements ie to assess certain cellulite severity parameters at specific intervals (see section 5, Schedule of Events). At the Screening visit, the Investigator or qualified designee will photograph each buttock using a Sponsor-supplied standardized digital camera in a standardized manner. 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 each of the two buttocks while the subject is standing in a consistent, standardized relaxed standing pose, ie, standing position with relaxed gluteus muscles, at the following time points:

- Screening (no markings of dimples or injection site) - each of the two buttocks
- Before and after marking dimples and injection sites (prior to injections) on Days 1, 22, and 43 - each of the two buttocks
- During the Day 71 visit (end of study/early termination) (no dimple or injection site markings) - each of the two buttocks

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.

13.1.2. Subject and Investigator Cellulite Assessments

Investigator cellulite assessments are independent of the subject assessments. Therefore, all subject cellulite assessments must be completed before the Investigator's cellulite assessments are initiated. The subject assessments will be done using a subject-assigned password protected electronic patient reported outcome (ePRO) system and the Investigator and study site personnel will not have access to the subject's assessments or password; the clinician assessment will be recorded in an investigator-assigned password protected system and the subject will not have access to the Investigator's assessments or password. Subject assessments will be done alone with no study site personnel in the room. Investigators will be instructed not to verbalize their ratings while in the presence of the subject.

13.1.2.1. 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. The scale is a 5-level photonumeric scale developed specifically for patients and used by the subject to assess the severity of their cellulite in the buttocks by viewing digital images of each of their buttocks 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.

At Screening and at the beginning of their visits on Day 1, Day 22, Day 43, and Day 71, subjects will have digital photographs taken of each of their two buttocks. Subjects will be given instructions in the proper use (Patient Instructions for Use of PR-PCSS) of the PR-PCSS and then perform the PR-PCSS for each of the buttocks (Appendix B). While viewing the digital images of each of their buttocks on a standardized computer monitor and using PR-PCSS for buttock, subjects will be instructed to answer the following question for each buttock: *Today, how would you rate the severity of your cellulite in the area displayed using the PR-PCSS?* The subject will be given the following explanations*: Please try to match the severity of your cellulite, as seen in this digital image, with one of the cellulite levels on the PR-PCSS. Please look at the image of your cellulite and the pictures, labels, and descriptions on the PR-PCSS carefully before selecting your answer. If you feel that your cellulite level is between 2 of the levels, please select the level that is closest to your image. If you feel that your cellulite is exactly halfway between two PR-PCSS levels of cellulite severity, please select the more severe response.*

The subject will enter their rating electronically into an ePRO system; the Investigator and other site personnel will be blinded to the rating entered by the subject. This variable will 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.

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

Subjects will complete the S-GAIS for each of the buttocks as described below at the Day 22, Day 43, and Day 71 study visits using the pre-treatment Day 1 digital image (Baseline) of each of the buttocks for comparison.

All treated subjects will be instructed to answer the following question for each buttock:

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. The subject will view each of their pre-treatment Day 1 digital images alongside their Day 22, Day 43 or Day 71/End of study visit digital images of each of their buttocks to aid in the assessment (Table 5). Subjects will provide a rating from those below that best represents their answer for each treated buttock.

This variable will 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 5: Subject Global Aesthetic Improvement Scale (S-GAIS)

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

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

At the Day 1 visit and the Day 71 visit, subjects will be instructed to answer 6 questions related to the areas selected for treatment on their buttocks on the PR-CIS (Appendix D) while viewing digital images of their buttocks. The PR-CIS assesses the visual and emotional impact of cellulite (happy, bothered, self-conscience, embarrassed, looking older, or looking overweight or out of shape) using a 6-question survey, with each question rated on a numerical rating scale from 0 (not at all) to 10 (extremely).

This variable will 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.

13.1.2.4. Subject Satisfaction with Cellulite Treatment Assessment

At the Day 71 visit, subjects will be instructed to answer a question related to their treated buttocks. Subjects will be given a list of responses and they will provide a rating from those below that best represents their answer (Table 6).

Today, how satisfied are you with the results of the cellulite treatment you received on the specific area or areas on your buttocks that were treated?

This variable will 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 6: Subject Satisfaction with Cellulite Treatment Assessment - Buttocks

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

13.1.2.5. Subject Self-Rating Scale (SSRS)

The SSRS is a measure that assesses subject satisfaction with appearance in association with cellulite on the buttocks using whole numbers on a 7-level scale that ranges from 0 (extremely dissatisfied to 6 (extremely satisfied). The patient will be asked to respond to the question related to the satisfaction with appearance of the cellulite on their buttocks on the appropriate visit day (note Day 71 question is different than Day 1 question). No photographs or reference to previous ratings or evaluations will be used. Subjects will be given a list of responses and they will provide a rating from those below that best represents their answer (Table 7); the list of responses is the same for Day 1 and for Day 71.

On Day 1 (Baseline), subjects will be instructed to answer: *Considering your appearance in association with your cellulite on your buttocks, how satisfied do you feel with your appearance at the present time?*

On Day 71, subjects will be instructed to answer: *Considering your appearance in association with your cellulite on your buttocks, how satisfied do you feel with your appearance at the present time whether or not in your judgment it is due entirely to treatment with EN3835?*

This variable will 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 7: Subject Self-Rating Scale (SSRS)

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

13.1.2.6. 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. The scale is a 5-level photonumeric scale developed specifically for clinicians and used by the Investigator to assess the severity of the subject's cellulite in each buttock by live assessments; the ratings range from 0 (None) to 4 (Severe) with labels and descriptors to aid the Investigator in the assessments.

Investigators will be trained and qualified on the use of the CR-PCSS prior to assessing any subjects.

At the Screening visit, the Investigator will determine severity of cellulite of each of the two buttocks via live assessment of the subject using the CR-PCSS for buttock (Appendix C) after the subject has completed her self-assessment using the PR-PCSS. Before injections on treatment visits Day 1, Day 22, and Day 43, and on visit Day 71; Investigators will evaluate each of the two buttocks by live assessments using the CR-PCSS for the buttock to make his/her

evaluation. At each visit, the Investigator will make his/her assessment independently and after the subject has conducted her self-assessment using the PR-PCSS.

This variable will 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.

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

On the Day 22, Day 43, and Day 71 study visits, the Investigator will determine the degree of improvement of each buttock by comparing the cellulite from the Day 1 pre-treatment (Baseline) digital image of each buttock to the cellulite seen in a live assessment (Table 8). The I-GAIS assessment will occur after the CR-PCSS assessment (section 13.1.2.6) to avoid introducing potential bias to the static CR-PCSS assessment by the Investigator. For each buttock, the Investigator will provide the rating from those below that best represents his/her answer.

This variable will 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

14. ASSESSMENT OF SAFETY

14.1. Definitions

14.1.1. Adverse Events

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. Adverse events 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 Events

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 malignancy, 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 28 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 28 days after the last dose of study medication. SAEs that occur within 28 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 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.

14.6. Special Reporting Situations

14.6.1. Adverse Events of Special Interest

Adverse events such as bruising, ecchymosis, hematomas, and contusions that occur remote to the site of drug administration, or any hypersensitivity reactions, including anaphylaxis, will be recorded and evaluated for seriousness and severity (see section 14.1.1, Adverse Events or section 14.1.2, Serious Adverse Events).

In addition, local AEs associated with the injection site, including bruising, pain, nodules/mass, ulceration, erythema, pruritus, swelling, and/or induration, will be recorded and evaluated for seriousness and severity (see as appropriate, section 14.1.1, Adverse Events or section 14.1.2, Serious Adverse Events)

14.6.2. Overdose/Misuse/Abuse

14.6.2.1. Overdose

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 12.9) 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

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

Any 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 28 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.

A subject who becomes pregnant must be withdrawn from the study. 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. AEs/SAEs 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 PVRM Department (when the non-subject agrees) on the departmental form for serious adverse experiences 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, Reporting Serious Adverse Events. Additionally, the drug accountability source documentation at the site should reflect this occurrence.

14.7. Clinical Laboratory 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 or qualified designee must acknowledge the review of laboratory results.

The Investigator will review all abnormal lab results for potentially clinically important. Any abnormal clinical laboratory test result meeting the Investigator's criteria for potentially clinically important (refer to central laboratory manual) 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).

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

Clinical laboratory parameters that will be measured in this study are listed in Table 9.

Table 9: Clinical Laboratory Tests

Hematology	Biochemistry	Urinalysis
Hemoglobin	Glucose	Glucose
Hematocrit	Sodium	Protein
Red blood cell	Potassium	Specific gravity
White blood cell (WBC)	Calcium	pH
Platelets	Chloride	Ketones
WBC Differential	CO_2	Bilirubin
	Inorganic phosphate	Urobilinogen
	Blood urea nitrogen	Nitrite
	Creatinine	Blood*
	Creatinine clearance (estimated)	Leukocytes*
	Aspartate transaminase (AST)	
	Alanine transaminase (ALT)	
	Gamma-glutamyl transferase (GGT)	
	Total bilirubin (TBL) (direct bilirubin reflex if elevated)	
	Albumin	
	Alkaline phosphatase (ALP)	
	Uric acid	

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

For women of childbearing potential, a serum pregnancy test will be performed at Screening and Day 71/End of Study/Early Termination, and urine pregnancy tests will be performed at Day 1, Day 22, and Day 43 (refer to section 5). Female subjects of childbearing potential must have a negative pregnancy test at the Screening Visit and at Day 1 (Baseline), Day 22, and Day 43 to be randomized and/or 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.

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

Serum samples will be collected and will be tested for binding anti-AUX-I and anti-AUX-II antibody testing before injection on Days 1, 22, and 43, and at the Day 71 visit. A subset [redacted] of subject samples will be tested for neutralizing antibodies from Day 1 and Day 71 visits; additional samples will be retained.

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.

14.9. Vital Signs

Vital sign measurements will be documented as described in the Schedule of Events (section 5). 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.

The Investigator will review all vital sign values for clinical significance prior to discharge. 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 10 after the subject has rested for at least 5 minutes.

Table 10: 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

14.10. Electrocardiogram

A 12-lead ECG recording will be conducted at the Screening Visit. The subject should be in a supine position for at least 5 minutes before the recording is conducted. Lead position will be that of a standard 12-lead ECG; no additional or special lead placements will be necessary.

A qualified physician will interpret, sign, and date the ECGs. ECG findings will be documented as normal; abnormal, clinically significant; or abnormal, not clinically significant. The Investigator or qualified designee must sign and date the ECG, thereby acknowledging review of ECG results. 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).

14.11. Physical Examination

A complete physical examination will be performed at the Screening Visit. All examinations will be performed by a physician or health professional listed on the Form FDA 1572 and licensed to perform physical examinations. Height and body weight will be measured and recorded at screening.

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).

At screening, the Investigator will also assess the subject's skin type using the Fitzpatrick scale (Table 11). Only the Fitzpatrick Scale shown below may be used during the study.

Table 11: Fitzpatrick Scale

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

Follow-up body weight will be measured before injection on Day 22 and Day 43 and at the Day 71 visit.

14.12. 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

The primary variable is the proportion of 2-level composite responders at Day 71 defined as subjects with:

- an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator of the target buttock, and
- an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS as assessed by the subject while viewing the digital image of the target buttock.

A subject will be considered a responder if these criteria are met in the randomized target buttock of that subject.

The results of a prior Phase 2b study of this drug (Study EN3835-201) demonstrated the overall rate for treated buttocks of composite responders with an improvement of at least 2 levels on both the PR-PCSS and the CR-PCSS was 14.9% in the EN3835 treatment group versus 1.1% in the Placebo group. Given this result, the study is planned to randomize 420 subjects with a 1:1 ratio into either the EN3835 arm (0.84 mg/buttock, 1.68 mg total dose) or placebo arm.

The sample size calculation was based on the following assumptions: [redacted]) Fisher exact test; 3) type I error of 0.05; 4) power of at least 90%; and 5) dropout rate of approximate 10%.

This sample size will also provide >90% power with type 1 error of 0.05 to detect the treatment difference for all the key secondary endpoints based on the following results, majority of which were estimated from previous EN3835 study results.

Table 12: Previous Results as Basis for Sample Size

Efficacy Endpoint	EN3835	Placebo	Power
1-level PR-PCSS responders of target buttock	[redacted]	[redacted]	[redacted]
2-level PR-PCSS responders of target buttock	[redacted]	[redacted]	[redacted]
1-level composite responders of target buttock	[redacted]	[redacted]	[redacted]
2-level composite responders of non-target buttock	[redacted]	[redacted]	[redacted]
Proportion of subjects with SSRS rating ≥ 4	[redacted]	[redacted]	[redacted]
Change in PR-CIS Score, Mean (SD)	[redacted]	[redacted]	[redacted]
1-level S-GAIS responders of target buttock	[redacted]	[redacted]	[redacted]
2-level S-GAIS responders of target buttock	[redacted]	[redacted]	[redacted]

[a] Rates are estimated based on the reported results from the pooled pivotal studies of a drug approved for an aesthetic indication.

17.2. Subject Populations

Four (4) populations are considered in the statistical analysis of the study: safety, intent-to-treat (ITT), modified ITT (mITT), and per-protocol (PP).

17.2.1. Safety Population

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

17.2.2. Intent-to-Treat (ITT) Population

The ITT population is defined as all randomized subjects who have received at least one injection of study medication. All demographic and baseline characteristic summaries will be based on this population. The primary and key secondary efficacy parameters will be summarized based on this population.

17.2.3. Modified Intent-to-Treat (mITT) Population

The mITT population is defined as all intent-to-treat subjects with a baseline and at least 1 post-injection evaluation of both the Investigator CR-PCSS and subject PR-PCSS for both the target and non-target buttocks. All secondary and supportive efficacy evaluations will be based on the mITT population.

17.2.4. Per-Protocol (PP) Population

The per-protocol population is defined as the mITT subjects without any of the following :

- Placebo-assigned subject receives EN3835 treatment
- EN3835-assigned subject receives placebo treatment only throughout study
- Any subject receives protocol-prohibited medications
- Subject lacking PR-PCSS and/or CR-PCSS assessment at Day 71
- Any major protocol deviation that is deemed as impact subject efficacy

This population may be used in the efficacy sensitivity analysis.

17.3. Subject Disposition

The number of subjects included in each study population will be summarized by treatment group. Subjects excluded from the safety and efficacy (eg, ITT) populations will be listed by treatment group.

The number and percentage of subjects completed and prematurely discontinued during the treatment period will be presented for each treatment group and pooled across treatment groups. Screen failures (ie, screened but not randomized subjects) and the associated failure reasons will be tabulated overall. Reasons for premature discontinuation from the treatment period as recorded on the termination page of the eCRF will be summarized (number and percentage) by treatment group for all randomized subjects. Percentage of premature discontinuations will be compared between treatment groups.

17.4. Demographics and Other Baseline Characteristics

The summarization of demographic variables (eg, age, sex, race, weight, height, and body mass index [BMI]), medical and surgical history, and other baseline characteristics relevant to the indication studied in the study will be described.

Demographic characteristics, including sex, age, age group, race, height, and weight, will be summarized by treatment group, for the ITT population, using descriptive statistics. All screening characteristics and medical information will also be summarized by treatment group using descriptive statistics. The descriptive summaries will include frequency tables for all categorical response variables and n, mean, standard deviation (SD), median, minimum, and maximum for all continuous variables.

17.5. Efficacy Analyses

All efficacy endpoints including supportive efficacy analysis will be summarized as percentages. The dichotomous secondary endpoints (ie, responder endpoints) will be analyzed using a Cochran-Mantel-Haenszel test adjusted for Investigator. Changes in the PR-PCSS ratings and CR-PCSS ratings from baselines, S-GAIS scores, I-GAIS scores, and SSRS scores will be analyzed using the Wilcoxon rank sum test. Changes in PR-CIS from baselines will be analyzed using an analysis of covariance (ANCOVA) adjusted for baseline values. All the tests are two-sided.

The primary endpoint will be summarized as percentages and analyzed using a Cochran-Mantel-Haenszel test that compares the 2 treatment groups and adjusts for Investigator at a level of significance of 0.05 based on the ITT population. Any subject who does not have an evaluation of CR-PCSS and/or PR-PCSS at Day 71 will be classified as a non-responder.

The key secondary efficacy analyses will be analyzed in the same manner as the primary endpoint based on the ITT population. Any subject who does not have an evaluation at Day 71 will be classified as a non-responder for the analyses. The family #1 key secondary efficacy analyses will be performed only if the primary efficacy analysis is significant ($p \leq 0.05$; gatekeeping strategy). Similarly family #2 key secondary efficacy analyses will be performed only if at least one of the key secondary efficacy endpoints of family #1 is significant ($p \leq 0.0125$; parallel gatekeeping strategy) and family #3 key secondary efficacy analyses will be performed only if at least one of the key secondary efficacy endpoints of family #2 is significant (parallel gatekeeping strategy). Within a family of key secondary efficacy endpoints, the Bonferroni method will be performed to relocate unused alpha for testing each endpoint to assure an overall error rate of $p \leq 0.05$. The details of the testing procedures will be provided in the statistical analysis plan for the study.

All supportive endpoints will be summarized as subject counts and percentages for categorical data or n, mean, SD, median, minimum, and maximum for continuous data. All the supportive analyses will be performed based on all observed data (ie, missing data not imputed) in the mITT population at all visits without multiplicity adjustment. This analysis will also be performed at Day 71 with missing data at Day 71 imputed by a last observation carried forward (LOCF) approach if subjects have at least one post-dose assessment. The dichotomous secondary endpoints (ie, responder endpoints) will be analyzed using a Cochran-Mantel-Haenszel test adjusted for Investigator. Changes in the PR-PCSS ratings and CR-PCSS ratings from baselines,

S-GAIS scores, I-GAIS scores, and SSRS scores will be analyzed using the Wilcoxon rank sum test. Changes in PR-CIS from baselines will be analyzed using an analysis of covariance (ANCOVA) adjusted for baseline values.

17.5.1. Primary Efficacy Variable

The primary efficacy variable is the proportion of 2-level composite responders at Day 71 defined as subjects with:

- an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator of the target buttock, and
- an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS by the subject while viewing the digital image of the target buttock.

A subject will be considered a responder if these criteria are met in the randomized target buttock of that subject.

Sensitivity analyses for the primary endpoint will include:

- ITT subjects with missing data handled by multiple imputation (MI) approach
- ITT subjects with missing data handled by an LOCF approach
- mITT subjects with missing data handled by an LOCF approach
- Observed data only (no missing data handling)
- Per-protocol (PP) subjects with missing data handled by an LOCF approach if 10% or more subjects are excluded in the PP population from mITT population

17.5.2. Secondary Efficacy Variables

17.5.2.1. Key Secondary Variables

There will be 8 key secondary endpoints grouped in three families of 2 to 4 endpoints per family analyzed in hierarchical order.

- Family #1 – four endpoints:
  - Proportion of 1-level PR-PCSS responders defined as subjects with ≥1-level improvement in PR-PCSS severity rating of the target buttock at Day 71 compared to Day 1
  - Proportion of 2-level PR-PCSS responders defined as subjects with ≥2-level improvement in PR-PCSS severity rating of the target buttock at Day 71 compared to Day 1
  - Proportion of 1-level composite responders of the target buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of the target buttock) at Day 71 compared to Day 1

  - Proportion of 2-level composite responders of the non-target buttock at Day 71 compared to Day 1

- Family #2 – two endpoints:
  - Proportion of 1-level SSRS responders defined as subjects who were at least slightly satisfied at Day 71 (SSRS rating ≥ 4)
  - Change from baseline (Day 1) of the PR-CIS total score at Day 71
- Family #3 – two endpoints:
  - Proportion of 1-level S-GAIS responders defined as subjects with ≥1-level improvement (improved, much improved or very much improved) in the S-GAIS assessment of the target buttock at Day 71
  - Proportion of 2-level S-GAIS responders defined as subjects with ≥2-level improvement (much improved or very much improved) in the S-GAIS assessment of the target buttock at Day 71

Sensitivity analyses for the key secondary endpoints will include:

- ITT subjects with missing data handled by MI approach
- ITT subjects with missing data handled by an LOCF approach
- mITT subjects with missing data handled by an LOCF approach
- Observed data only (no missing data handling)
- Per-protocol (PP) subjects with missing data handled by an LOCF approach if 10% or more subjects are excluded in the PP population from mITT population

17.5.3. Supportive Efficacy Variables

17.5.3.1. Supportive Variables

The supportive variables will evaluate assessments at various study time points and using various populations.

- Proportion of 2-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS of the target buttock (Days 22, 43, and 71)
- Proportion of 2-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS of the non-target buttock (Days 22, 43, and 71)
- Proportion of 1-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS of the target buttock (Days 22, 43, and 71)
- Proportion of 1-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS of the non-target buttock (Days 22, 43, and 71)

- Proportion of 2-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject.
- Proportion of 1-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject.
- Proportion of 2-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks.
- Proportion of 1-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks.
- Proportion of 2-level CR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the target buttock (Days 22, 43, and 71)
- Proportion of 2-level CR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the non-target buttock (Days 22, 43, and 71)
- Proportion of 1-level CR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the target buttock (Days 22, 43, and 71)
- Proportion of 1-level CR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the non-target buttock (Days 22, 43, and 71)
- Proportion of 2-level CR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject.
- Proportion of 1-level CR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject.
- Proportion of 2-level CR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks.
- Proportion of 1-level CR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks.
- Proportion of 1-level composite responders of the target buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the target buttock assessed live by the Investigator and an improvement

of severity from baseline of at least 1 level of severity in the PR-PCSS of that same target buttock) (Days 22, 43, and 71)

- Proportion of 1-level composite responders of the non-target buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the non-target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same non-target buttock) (Days 22, 43, and 71)
- Proportion of 1-level composite responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject.
- Proportion of 1-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks.
- Proportion of 2-level composite responders of the target buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same target buttock) (Days 22, 43, and 71)
- Proportion of 2-level composite responders of the non-target buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the non-target buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same non-target buttock) (Days 22, 43, and 71)
- Proportion of 2-level composite responders of at least one of two buttocks (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject.
- Proportion of 2-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks.
- Proportion of subjects at each level of the S-GAIS of the target buttock (Days 22, 43, and 71)
- Proportion of subjects at each level of the S-GAIS of the non-target buttock (Days 22, 43, and 71)
- Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S-GAIS of the target buttock (Days 22, 43, and 71)
- Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S-GAIS of the non-target buttock (Days 22, 43, and 71)
- Proportion 1-level S-GAIS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject.

- Proportion of 1-level S-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target right buttocks.
- Proportion of subjects at each level of the I-GAIS of the target buttock (Days 22, 43, and 71)
- Proportion of subjects at each level of the I-GAIS of the non-target buttock (Days 22, 43, and 71)
- Proportion of 1-level I-GAIS responders defined as subjects with a response of at least 1 (improved) in the I-GAIS of the target buttock (Days 22, 43, and 71).
- Proportion of 1-level I-GAIS responders defined as subjects with a response of at least 1 (improved) in the I-GAIS of the non-target buttock (Days 22, 43, and 71).
- Proportion of 1-level I-GAIS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the target buttock or non-target buttock or both buttocks in that subject.
- Proportion of 1-level I-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both the target and non-target buttocks.
- Change from baseline (Day 1) of the PR-CIS total score at Day 71
- Change from baseline (Day 1) of the abbreviated PR-CIS score at Day 71
- Proportion of subjects with a change from baseline (Day 1) of the PR-CIS ≥ 12 at Day 71
- Proportion of subjects with a change from baseline (Day 1) of the abbreviated PR-CIS ≥ 10 at Day 71
- Proportion of subjects at each level of the SSRS (Day 1 (Baseline) and Day 71)
- Proportion of 1-level SSRS responders defined as subjects who were at least slightly satisfied at Day 71 (SSRS rating ≥ 4)
- Proportion of subjects at each level of the subject satisfaction with cellulite treatment assessment (Day 71)
- Proportion of satisfied responders (defined as subjects with a response of at least 1 (ie, 1-Satisfied or 2-Very Satisfied) in the subject satisfaction with cellulite treatment assessment (Day 71)

17.6. Safety Analyses

Safety variables include adverse events, laboratory parameters, vital signs, ECG parameters, and physical examinations. For each safety parameter, the last assessment made prior to the first dose of study drug will be used as the baseline for all analyses of that safety parameter.

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. Prior medication will be defined as any medication taken prior to the first dose of study drug. Concomitant medication is defined as any medication taken on or after the date of first dose of study drug.

Prior and concomitant medication use will be summarized descriptively by the number and percentage of subjects for each preferred term (generic name from WHO dictionary) by treatment. Multiple use of the same medication by a subject will be counted only once.

17.6.2. Study Drug Exposure

The following information regarding treatment will be summarized per each treated buttock by treatment group:

- Total number of treatment visits
- Number of subjects who had treatment session done or treatment session not done at each treatment visit
- For subjects who had the treatment session done, the number of subjects who got all 24 injections at the treatment visit or who received less than 24 injections
- Number of injections given at each treatment visit
- Number of dimples treated at each treatment visit
- Average number of injections per dimple at each treatment visit

Subjects who did not receive all 3 treatment visits and who did not receive 24 injections at a treatment visit will be listed.

17.6.3. Measurement of Treatment Compliance

Not applicable (the study drug is administered at the site by the study investigator).

17.6.4. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code AEs.

An AE (classified by preferred term) that started on or after the date of the first dose of the study drug 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.

The by-frequency summaries will also include incidence of the SAEs and non-SAEs by preferred term that at least 2% of the subjects in one treatment group. Duration of AEs will be tabulated by treatment group.

The Fisher exact test will be used to compare EN3835 to placebo.

Listings will be presented for subjects with SAEs, subjects with AEs leading to discontinuation of study or study drug, 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 study will be presented by treatment group.

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 will be detailed in the Statistical Analysis Plan (SAP). The PCI percentages will be calculated relative to the number of subjects with baseline and at least one post-baseline assessment. A supportive listing of subject values will be provided including the subject ID, study center, treatment group, baseline and post-baseline values.

The change from baseline for vital signs parameters are compared between EN3835 and placebo using an analysis of variance (ANOVA) with a factor of drug (EN3835 or placebo) while the Fisher exact test will be used for the incidence of PCI values.

17.6.6. Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values in International System of Units (SI units) and changes from baseline at Day 71 will be presented by treatment group for each clinical laboratory parameter.

The number and percentage of subjects with potentially clinically important (PCI) post-baseline clinical laboratory values will be tabulated by treatment group. The criteria for PCI laboratory values will be detailed in the Statistical Analysis Plan (SAP). The PCI percentages will be calculated relative to the number of subjects with at least one post-baseline assessment. A supportive listing of subjects with post-baseline PCI values will be provided, including the subject ID, study center, treatment group, baseline and post-baseline values.

The change from baseline for clinical laboratory parameters are compared between EN3835 and placebo using an ANOVA with a factor of drug (EN3835 or placebo) while the Fisher exact test will be used for the incidence of PCI values.

17.6.7. Electrocardiogram

Not applicable (ECG is done only at screening for the subject's enrollment eligibility).

17.6.8. Physical Examination

Body weight and BMI at Day 22, Day 43, and Day 71 as well as their change from baseline (Day 1) at those time points will be presented by treatment group.

17.6.9. Other Safety Measurements

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 treatment group. Average antibody levels will be summarized on logarithmically transposed titer values. In addition, by-treatment percentages of neutralizing anti-AUX-I and anti-AUX-II antibodies in a subset of subjects' samples [redacted] will be summarized at Day 71.

17.7. Pharmacokinetic Analyses

Not applicable.

17.8. Pharmacodynamic Analyses

Not applicable.

17.9. Other Data (eg, Health Economics/QOL, Pharmacogenetic, etc)

Not applicable.

17.10. Interim Analysis

No interim analysis is planned for this study.

17.11. Statistical Software

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

18. STUDY DRUG MATERIALS AND MANAGEMENT

18.1. Study Drug Identity

EN3835 is manufactured and supplied by Endo.

EN3835 is a sterile lyophilized powder consisting of 0.92 mg of collagenase clostridium histolyticum, 18.9 mg sucrose, 1.1 mg Tris, 37.7 mg mannitol, hydrochloric acid QS to pH 8.5, in a 5-mL vial.

Placebo for injection is a sterile lyophilized powder consisting of 18.9 mg sucrose, 1.1 mg Tris, 37.7 mg mannitol, hydrochloric acid QS to pH 8.5, in a 5-mL vial.

EN3835 sterile diluent for reconstitution is 0.6% sodium chloride and 0.03% calcium chloride dehydrate in water for injection filled into 5-mL vials.

18.2. Study Drug Packaging and Labeling

Each vial of study drug and diluent will minimally be labeled with contents, Sponsor identification, storage, administration/use, and appropriate cautions statements. Each kit will contain one vial of EN3835 or placebo and one vial of sterile diluent. Kits containing EN3835 or placebo will be indistinguishable and only identifiable by their unique kit number.

18.3. Study Drug Storage

All study drug will be provided by Endo. Study drug must be stored in an appropriate, secure area. Study drug must be kept in a temperature-monitored refrigerator (2°C-8°C) with locked access until used or returned to Endo.

18.4. Study Drug Preparation

Refer to the Reconstitution Instructions for detailed preparation instructions.

For each dose session, the IWRS will dispense 2 kits, 1 kit for each buttock to be treated. Four (4) 0.9-mL syringes will be prepared from each vial of EN3835 or placebo, 4 syringes/kit, for a total of 8 syringes (4 syringes for each buttock).

Used drug vials should be returned to the kit carton and stored in a secure location until reconciled and returned by the Clinical Research Associate (CRA). Dispose of used diluent vials, needles, and syringes per local regulations.

The reconstituted study drug solution should be administered as soon as possible after reconstitution. The study drug solution can be kept at room temperature [redacted] emove drug/prepared syringes from the refrigerator and allow it to stand at room temperature for 15 minutes prior to injection of study drug.

18.5. Study Drug Accountability

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/IEC, and regulatory agencies for routine inspection and accountability during monitoring visits. When instructed by Endo, the Investigator agrees to return all original used or unused study drug kits to Endo's return vendor.

18.5.1. Study Drug Handling and Disposal

The Investigator agrees not to supply study drug to any person except to those subjects enrolled in the study. The Investigator is responsible for recording the receipt and use of all drugs supplied and for ensuring the supervision of the storage and allocation of these supplies. All used and 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 and its use. At the end of the study, all used and unused drug supplies will be returned to Endo’s return vendor.

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:

- PR-PCSS
- CR-PCSS
- S-GAIS
- I-GAIS
- PR-CIS
- Subject Satisfaction with Cellulite Treatment Assessment
- SSRS

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/assent, the Investigator is responsible for obtaining any additional documentation to demonstrate compliance with local privacy laws applicable to activities performed.

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

A unique Subject identification number will be assigned according to section 12.1.2.2 at the time that the Subject signs the informed consent form.

22. DATA HANDLING AND RECORDKEEPING

22.1. Data Collection

Endo will provide an electronic data capture (EDC) system for this study. 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).

Data entries will be corrected by changing the entry in the EDC system. Any changes or corrections to eCRF data will be electronically tracked and will include the reason for correction, who made the correction and the date/time stamp when the correction was made within the audit trail of the EDC system.

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 case report form (CRF) data for his/her files.

23. REPORTING AND PUBLICATION

All data generated in this study are the property of Endo Pharmaceuticals Inc. 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 Pharmaceuticals Inc.

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 FDA 1572. If during the course of the study any information reported on the Form FDA 1572 changes, a revised Form FDA 1572 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 FDA 1572 (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.

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 Pharmaceuticals Inc. 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)/Clinical Trial Authorization (CTA) or request for marketing approval (New Drew Application [NDA]/Marketing Authorization Application [MAA]).

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 Pharmaceuticals Inc. 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 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 STATEMENT

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

[redacted]

27. REFERENCES

1. Khan MH, Victor F, Rao B, Sadick NS. Treatment of cellulite: Part I. Pathophysiology. *J Am Acad Dermatol* 2010;62(3):361-70.
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):175-90.
4. Terranova F, Berardesca E, Maibach H. Cellulite: nature and aetiopathogenesis. *Int J Cosmetic Sci.* 2006;28(3):157-67.
5. Avram MM. Cellulite: a review of its physiology and treatment. *J Cosmet Laser Ther.* 2004;6(4):181-5.
6. Khan MH, Victor F, Rao B, Sadick NS. Treatment of cellulite: Part II. Advances and controversies. *J Am Acad Dermatol* 2010;62(3):373-84.
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):1110-4.
8. Hexsel DM, Mazzuco R. Subcision: a treatment for cellulite. *Int J Dermatol.* 2000;39(7):539-44.
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;22:233-7.
10. DiBernardo BE. Treatment of cellulite using a 1440-nm pulsed laser with one-year follow-up. *Aesthet Surg J.* 2011;31(3):328-41.
11. Investigational Brochure: Collagenase Clostridium Histolyticum for Injection (AA4500/EN3835), Version 8.0. Endo Pharmaceuticals Inc.; July 2017.

[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]).

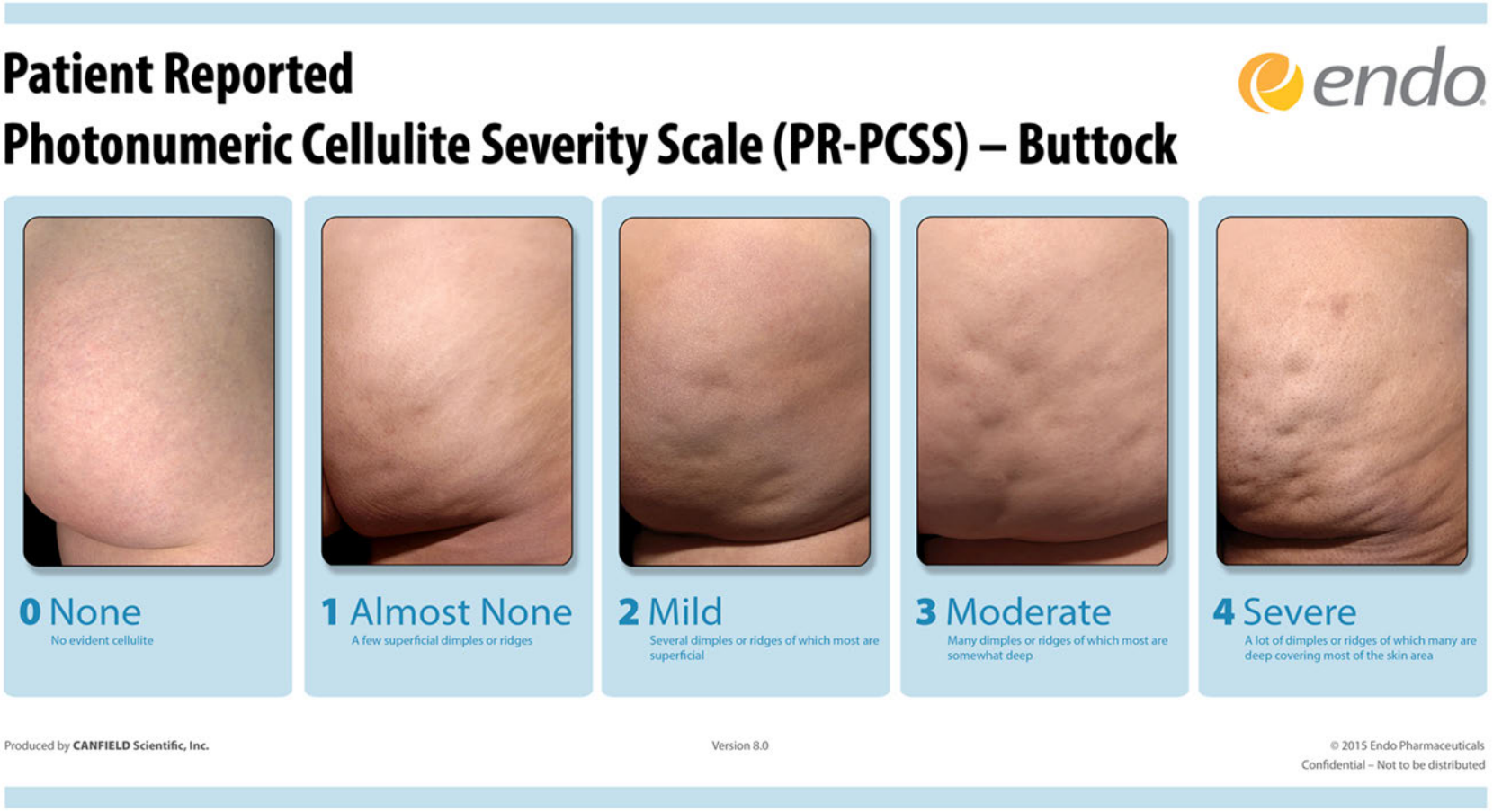
8. Financial Disclosure Certification or Certification of Non-Disclosure (for studies to be submitted for a US New Drug Application/Biologics License Application [NDA/BLA]).

Other

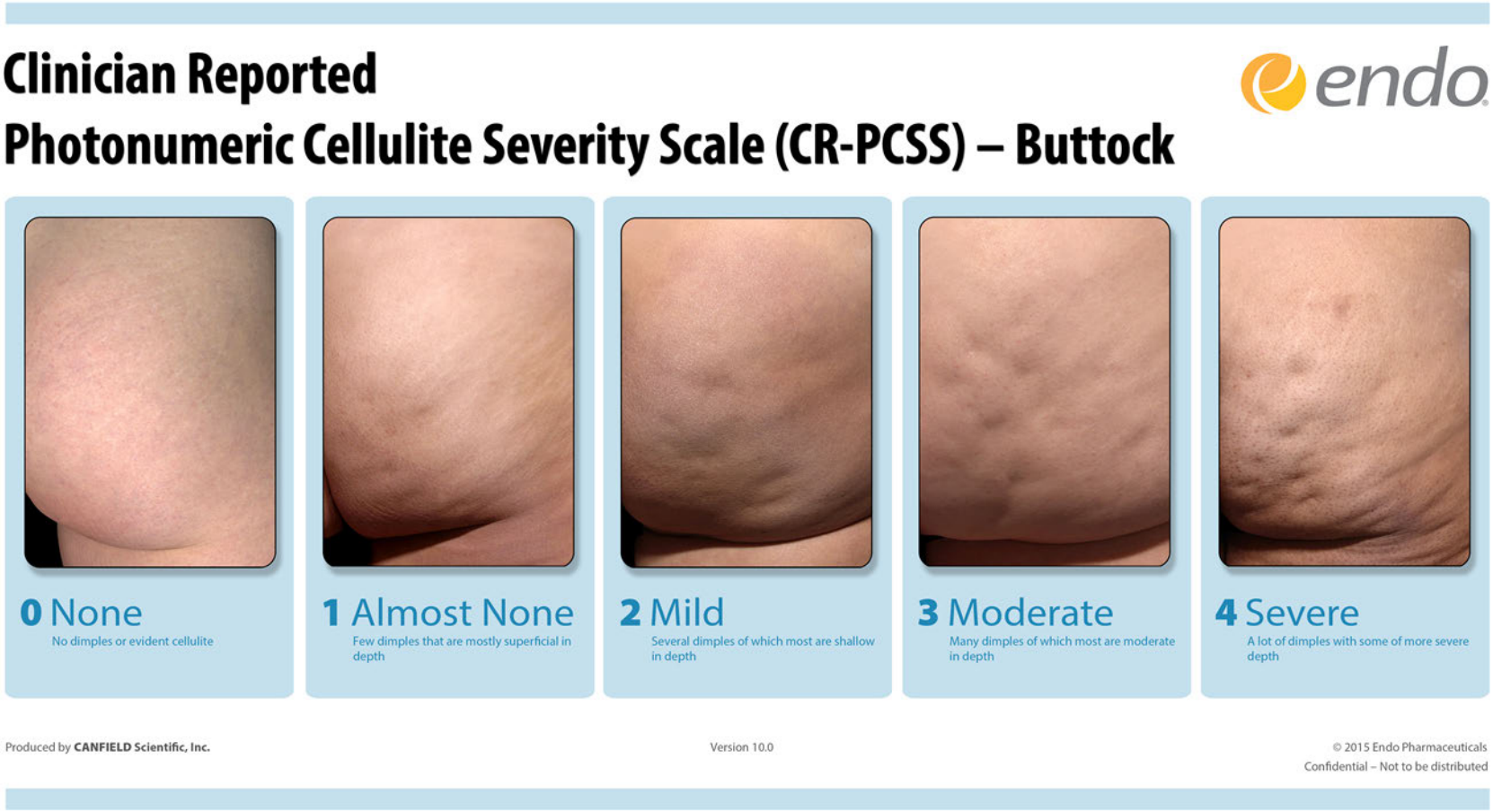
Any other documentation required by national law or regulations to be in the possession of the sponsor or the Investigator for study participation or study initiation.

[redacted]

APPENDIX B. PATIENT-REPORTED PHOTONUMERIC CELLULITE SEVERITY SCALE (PR-PCSS) FOR THE BUTTOCK



APPENDIX C. CLINICIAN-REPORTED PHOTONUMERIC CELLULITE SEVERITY SCALE (CR-PCSS) FOR THE BUTTOCK



APPENDIX D. PATIENT REPORTED CELLULITE IMPACT SCALE (PR-CIS)

Please select the rating that best represents your answer on a scale of 0 to 10 with 0 representing "Not at all" and 10 representing "Extremely" while viewing digital images of your buttocks. Please answer each question.

1. Thinking about the areas selected for treatment, how happy are you with the appearance of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

2. Thinking about the areas selected for treatment, how bothered are you by the appearance of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

3. Thinking about the areas selected for treatment, how self-conscious are you about the appearance of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

4. Thinking about the areas selected for treatment, how embarrassed are you about the appearance of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

5. Thinking about the areas selected for treatment, how much older do you look because of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

6. Thinking about the areas selected for treatment, how overweight or out of shape do you look because of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

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

EN3835

EN3835-303

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF EN3835 IN THE TREATMENT OF EDEMATOUS FIBROSCLEROTIC PANNICULOPATHY

IND 110077

Amendment 1

Date:

Original Protocol: September 27, 2017

Amendment 1: December 19, 2017

Auxilium Pharmaceuticals, Inc. (Auxilium) was acquired by Endo International plc. in January 2015. The sponsor of the application remains as Auxilium Pharmaceuticals, LLC, 1400 Atwater Drive, Malvern, PA; however, Endo Pharmaceuticals Inc. is authorized to act and to communicate on behalf of Auxilium.

2. SUMMARY OF CHANGES

EN3835-303 protocol amendment and amended informed consent forms (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 December 19, 2017. The major reasons for this amendment are adding an additional efficacy assessment and revising inclusion and exclusion criteria.

Section	Original Text	Revised Text
3., Sponsor Contact Information	[redacted]	[redacted]
4., Synopsis, Study Period	Estimated date first subject enrolled: Jan-2018	Estimated date first subject enrolled: Feb-2018
4., Study Design	Subjects with 2 treatment areas (bilateral buttocks) (also referred to as quadrants) with moderate or severe levels of cellulite as independently assessed by the subject using the Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) and by the Investigator using the Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) and a Hexsel Cellulite Severity Scale no greater than 13 will be eligible.	Subjects with 2 treatment areas (bilateral buttocks) (also referred to as quadrants) with moderate or severe levels of cellulite as independently assessed by the subject using the Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) and by the Investigator using the Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) will be eligible.
	Add text	At Day 1, the subject will complete a Patient Reported Cellulite Impact Scale (PR-CIS) assessment.
4., Synopsis, Diagnosis and Inclusion/ Exclusion Criteria, Inclusion Criteria	3. At Screening visit, have 2 bilateral buttocks with each buttock having: 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	3. At Screening visit, have 2 bilateral buttocks with each buttock having: 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)
	4. At Day 1 visit, have 2 bilateral buttocks with each buttock having: 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	4. At Day 1visit, have 2 bilateral buttocks with each buttock having: 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)

Section	Original Text	Revised Text
4., Synopsis, Diagnosis and Inclusion/ Exclusion Criteria, Exclusion Criteria	2. Has any of the following local conditions in the areas to be treated: a. History of lower extremity thrombosis or post-thrombosis syndrome b. Vascular disorder (eg, varicose veins, telangiectasia) in area to be treated c. Inflammation or active infection d. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer e. Has a tattoo and/or a mole located within 2 cm of the site of injection	2. Has any of the following local conditions in the areas to be treated: a. History of lower extremity thrombosis or post-thrombosis syndrome b. Vascular disorder (eg, varicose veins, telangiectasia) in area to be treated c. Inflammation or active infection d. Severe skin laxity, flaccidity, and/or sagging e. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer f. Has a tattoo and/or a mole located within 2 cm of the site of injection
4., Synopsis, Criteria for Evaluation, Efficacy	Added text	• Patient Reported Cellulite Impact Scale: 6 questions with responses to each question consisting of a numerical rating scale (NRS) ranging from 0 (Not at all) to 10 (Extremely)
4., Synopsis, Statistical Methods, Analysis, Supportive Endpoints	Added text	• Change from baseline (Day 1) of the PR-CIS total score at Day 71 • Change from baseline (Day 1) of the abbreviated PR-CIS score at Day 71 • Proportion of subjects with a change from baseline (Day1) of the PR-CIS ≥12 at Day 71 • Proportion of subjects with a change from baseline (Day 1) of the abbreviated PR-CIS ≥10 at Day 71
5., Schedule of Events, Physical examination	Day -14 to -1 Screening: X Day 71 (+ 5d)/End of Study/Early Termination: X	Day -14 to -1 Screening: X
5., Schedule of Events, Subject cellulite assessments, Patient Reported Cellulite Impact Scale (PR-CIS)	Added table row	• Patient Reported Cellulite Impact Scale (PR-CIS) Day 1 Treatment Visit 1: X[c,g] Day 71 (+ 5d)/End of Study/Early Termination: X[g]
5., Schedule of Events, Investigator cellulite assessments, Hexsel Cellulite Severity Scale (CSS)	• Hexsel Cellulite Severity Scale (CSS) Day -14 to -1 Screening: X[b,i] Day 1 Treatment Visit 1: X[c,b,i]	Deleted table row

Section	Original Text	Revised Text
5., Schedule of Events, Table footnotes	[i] Initial Hexsel CSS at Screening must be ≤13 on each of 2 bilateral buttocks and the buttocks must again be ≤13 at Day 1 visit	Deleted text
	[j] Before randomization, each of the subject's buttocks must have ratings of 3 or 4 (moderate or severe) in both the CR-PCSS and PR-PCSS, and Hexsel CSS score ≤13.	[i] Before randomization, each of the subject's buttocks must have ratings of 3 or 4 (moderate or severe) in both the CR-PCSS and PR-PCSS.
7., List of Abbreviations, Table 2: Abbreviations and Special Terms	CSS: Cellulite severity scale	Deleted table row
	Added table row	PR-CIS: Patient Reported Cellulite Impact Scale
11.1., Subject Inclusion Criteria	3. At Screening visit, have 2 bilateral buttocks with each buttock having: 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	3. At Screening visit, have 2 bilateral buttocks with each buttock having: 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)
	4. At Day 1 visit, have 2 bilateral buttocks with each buttock having: 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	4. At Day 1 visit, have 2 bilateral buttocks with each buttock having: 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)
11.2., Subject Exclusion Criteria	2. Has any of the following local conditions in the areas to be treated: a. History of lower extremity thrombosis or post-thrombosis syndrome b. Vascular disorder (eg, varicose veins, telangiectasia) in area to be treated c. Inflammation or active infection d. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer e. Has a tattoo and/or a mole located within 2 cm of the site of injection	2. Has any of the following local conditions in the areas to be treated: a. History of lower extremity thrombosis or post-thrombosis syndrome b. Vascular disorder (eg, varicose veins, telangiectasia) in area to be treated c. Inflammation or active infection d. Severe skin laxity, flaccidity, and/or sagging e. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer f. Has a tattoo and/or a mole located within 2 cm of the site of injection

Section	Original Text	Revised Text
12.1.2.2., Screening Period (Day -14 to Day -1)	5. Prior to Investigator CR-PCSS or Hexsel CSS assessment, subjects will rate each of their two buttocks using the PR-PCSS while viewing their digital images (section 13.1.2.1); the Investigator is blinded to these scores	5. Prior to Investigator CR-PCSS assessment, subjects will rate each of their two buttocks using the PR-PCSS while viewing their digital images (section 13.1.2.1); the Investigator is blinded to these ratings
	6. After the subject has completed the PR-PCSS ratings, the Investigator will conduct live assessments of subject's cellulite severity of each of the two buttocks using the CR-PCSS (section 13.1.2.4); the subject is blinded to these ratings 7. After the Investigator has completed the CR-PCSS ratings, the Investigator will conduct live evaluation of each of the two buttocks using the Hexsel CSS; the subject is blinded to these ratings. The ratings from the PR-PCSS, CR-PCSS, and Hexsel CSS (section 13.1.2.6) will be used to assess initial eligibility of the buttocks for study entry	6. After the subject has completed the PR-PCSS ratings, the Investigator will conduct live assessments of subject's cellulite severity of each of the two buttocks using the CR-PCSS (section 13.1.2.5); the subject is blinded to these ratings. The ratings from the PR-PCSS and CR-PCSS will be used to assess initial eligibility of the buttocks for study entry
12.2., Selecting and Marking Dimples during Treatment Visits	The cellulite severity assessments using the PR-PCSS, CR-PCSS, and Hexsel CSS (note that the Hexsel CSS assessment is performed at Screening visit and Day 1 visit only) will be completed prior to marking dimples and injection sites.	The cellulite severity assessments using the PR-PCSS and CR-PCSS will be completed prior to marking dimples and injection sites.
12.4.1., Treatment Visit 1: Pre-Injection	4. Subjects will rate each of their buttocks using the PR-PCSS (section 13.1.2.1); the Investigator is blinded to these scores	4. Subjects will rate each of their buttocks using the PR-PCSS (section 13.1.2.1); the Investigator is blinded to these ratings
	Added text	5. Subjects will complete the Patient Reported Cellulite Impact Scale assessment (PR-CIS; section 13.1.2.3): the Investigator is blinded to this rating
	5. The Investigator will conduct live assessments of subject's cellulite severity of each of the buttocks using the CR-PCSS (section 13.1.2.4); the subject is blinded to these ratings 6. The Investigator will conduct live cellulite evaluation of each of the buttocks using the Hexsel CSS. The ratings from the PR-PCSS, CR-PCSS and Hexsel CSS (section 13.1.2.6) will be used to assess eligibility for randomization	6. The Investigator will conduct live assessments of subject's cellulite severity of each of the buttocks using the CR-PCSS (section 13.1.2.5); the subject is blinded to these ratings. The ratings from the PR-PCSS and CR-PCSS will be used to assess eligibility for randomization

Section	Original Text	Revised Text
	7. Subjects with PR-PCSS or CR-PCSS ratings in either of the buttocks <3 or a Hexsel CSS total score in either of the buttocks greater than 13 (section 13.1.2.6) will be excluded from participation	7. Subjects with PR-PCSS or CR-PCSS ratings in either of the buttocks <3 will be excluded from participation
	8. Randomization of subjects with two buttocks eligible for treatment (eligible criteria being each buttock have PR-PCSS and CR-PCSS scores of 3 or 4 and a Hexsel CSS total score not greater than 13) to treatment (section 12.10); obtain kit numbers of study treatment	8. Randomization of subjects with two buttocks eligible for treatment (eligible criteria being each buttock have PR-PCSS and CR-PCSS scores of 3 or 4) to treatment (section 12.10); obtain kit numbers of study treatment
12.6., Day 71 (+5 days)/End of Study/Early Termination	6. Subject Cellulite Assessment of each of the two buttocks using the photographic image before marking dimples and injection sites (NOTE: complete subject cellulite assessments before Investigator cellulite assessments) using: a. Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) assessment (section 13.1.2.1) b. Subject Global Aesthetic Improvement Scale (S-GAIS) (section 13.1.2.2) c. Subject Satisfaction with Cellulite Treatment Assessment (section 13.1.2.3); note this assessment is of both left and right buttocks rather than each individual buttock	6. Subject Cellulite Assessment of each of the two buttocks using the photographic image before marking dimples and injection sites (NOTE: complete subject cellulite assessments before Investigator cellulite assessments) using: a. Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) assessment (section 13.1.2.1) b. Subject Global Aesthetic Improvement Scale (S-GAIS) (section 13.1.2.2) c. Patient Reported Cellulite Impact Scale (PR-CIS assessment (section 13.1.2.3); note this assessment is of both left and right buttocks rather than each individual buttock d. Subject Satisfaction with Cellulite Treatment Assessment (section 13.1.2.4); note this assessment is of both left and right buttocks rather than each individual buttock
12.10., Blinding and Randomization	On Day 1, if each of the buttocks again meet the criteria (3 or 4 on the PR-PCSS and CR-PCSS and no greater than 13 on Hexsel CSS) the subject will be randomized to a treatment group.	On Day 1, if each of the buttocks again meet the criteria (3 or 4 on the PR-PCSS and CR-PCSS) the subject will be randomized to a treatment group.

Section	Original Text	Revised Text
13.1.2.3, Patient Reported Cellulite Impact Scale (PR-CIS)	Added section	13.1.2.3. Patient Reported Cellulite Impact Scale (PR-CIS) At the Day 1 visit and Day 71 visit, subjects will be instructed to answer 6 questions related to the areas selected for treatment on their buttocks on the Patient Reported Cellulite Impact Scale (Appendix D) while viewing digital images of their buttocks. The PR-CIS assesses the visual and emotional impact of cellulite (happy, bothered, self-conscious, embarrassed, looking older or looking overweight or out of shape) using a 6-question survey, with each question rated on a numerical rating scale from 0 (not at all) to 10 (extremely). This variable will 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.
13.1.2.4, Subject Satisfaction	Added text	This variable will 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.
13.1.2.6, Hexsel Cellulite Severity Scale	13.1.2.6. 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 8. The total score is the summation of all 5 features (Appendix D).	Deleted section and table

Section	Original Text	Revised Text
	The Investigator or qualified designee will independently use the Hexsel CSS to assess the severity of EFP in each of the two buttocks at the Screening visit and each of the two buttocks on Day 1 (Note: In this study, the Hexsel CSS is used exclusively for assessment of subject eligibility; it is not used as an efficacy assessment). 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 will 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]	
17.5, Efficacy Analyses	All supportive endpoints will be summarized as percentages.	All supportive endpoints will be summarized as subject counts and percentages for categorical data or n, mean, SD, median, minimum, and maximum for continuous data.
	Added text	Changes in PR-CIS from baselines will be analyzed using an analysis of covariance (ANCOVA) adjusted for baseline values
17.5.3.1, Supportive Variables	Added text	• Change from baseline (Day 1) of PR-CIS total score at Day 71 • Change from baseline (Day 1) of abbreviated PR-CIS score at Day 71 • Proportion of subjects with a change from baseline (Day 1) of PR-CIS ≥ 12 at Day 71 • Proportion of subjects with a change from baseline (Day 1) of abbreviated PR-CIS ≥ 10 at Day 71

Section	Original Text	Revised Text
19.1, Source Documents	This study allows for direct data entry (DDE) for selected data points as outlined below: • PR-PCSS • CR-PCSS • Hexsel CSS • S-GAIS • I-GAIS • Subject Satisfaction with Cellulite Treatment Assessment	This study allows for direct data entry (DDE) for selected data points as outlined below: • PR-PCSS • CR-PCSS • S-GAIS • I-GAIS • PR-CIS • Subject Satisfaction with Cellulite Treatment Assessment
27, References	12. Hexsel DM, Dal'Forno T, Hexsel CL. A validated photonumeric cellulite severity scale. *J Eur Acad Dermatol Venereol*. 2009;23(5):523-8. 13. Nürnberger F, Müller G. So-called cellulite: an invented disease. *J Dermatol Surg Oncol*. 1978;4(3):221-9.	Deleted text
Appendix D	APPENDIX D. HEXSEL DM, DAL'FORNO T, HEXSEL CL. A VALIDATED PHOTONUMERIC CELLULITE SEVERITY SCALE. *J EUR ACAD DERMATOL VENEREOL*. 2009;23(5):523-8 [Article]	APPENDIX D. PATIENT REPORTED CELLULITE IMPACT SCALE (PR-CIS) Please select the rating that best represents your answer on a scale of 0 to 10 with 0 representing "Not at all" and 10 representing "Extremely" while viewing digital images of your buttocks. Please answer each question. 1. Thinking about the areas selected for treatment, how happy are you with the appearance of your cellulite? [Scale] 2. Thinking about the areas selected for treatment, how bothered are you by the appearance of your cellulite? [Scale] 3. Thinking about the areas selected for treatment, how self-conscious are you about the appearance of your cellulite? [Scale] 4. Thinking about the areas selected for treatment, how embarrassed are you about the appearance of your cellulite? [Scale] 5. Thinking about the areas selected for treatment, how much older do you look because of your cellulite? [Scale] 6. Thinking about the areas selected for treatment, how overweight or out of shape do you look because of your cellulite? [Scale]

Section	Original Text	Revised Text
APPENDIX E. REFERENCE IMAGES FOR HEXSEL SEVERITY RATINGS	APPENDIX E. REFERENCE IMAGES FOR HEXSEL SEVERITY RATINGS The 2 images below are representative of a Hexsel score of 13, the maximum severity level to be included in the study. Subjects with cellulite severity that exceeds a Hexsel score of 13 should be excluded. [Image 1] [Image 2] The image below represents a Hexsel score >13, and depicts excessive skin laxity in the buttock and posterolateral thigh. Subjects with a Hexsel score >13 should be excluded from the study. [Image 3]	Deleted appendix and images

3. SPONSOR CONTACT INFORMATION

Table 1: Sponsor Contact Information

Role in Study	Name	Telephone and Email Address
Clinical Development Lead	[redacted]	[redacted]
Clinical Operations Lead	[redacted]	[redacted]
Medical Monitor	[redacted]	[redacted]
SAE Reporting Pathway	Not Applicable	[redacted]

A list of other key study personnel and vendors will be provided 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 3, Randomized, Double-Blind, Placebo-Controlled Study of EN3835 in the Treatment of Edematous Fibrosclerotic Panniculopathy	
Lead Principal Investigator:	
Study Period: Estimated date first subject enrolled: Feb-2018 Estimated date last subject completed: Sep-2018	**Phase of Development**: 3
Objectives: To assess the efficacy and safety of EN3835 in the treatment of edematous fibrosclerotic panniculopathy (EFP), commonly known as cellulite, in adult women	
Study Design: This study is a Phase 3 randomized, double-blind, placebo-controlled study of the efficacy and safety of EN3835 in the treatment of EFP in adult women. Subjects will be screened for study eligibility within 14 days prior to enrolling in this study. Subjects with 2 treatment areas (bilateral buttocks) (also referred to as quadrants) with moderate or severe levels of cellulite as independently assessed by the subject using the Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) and by the Investigator using the Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) will be eligible. The eligibility of the buttocks will be confirmed on Day 1. Once the eligibility of the buttocks is confirmed, subjects will be randomly assigned to a treatment group (EN3835 0.84 mg per buttock or placebo) in a 1:1 ratio within an investigational site. Each subject will receive a treatment course which consists of up to 3 treatment visits (sessions), separated by 21 days (ie, Days 1, 22, and 43). Each treatment visit will consist of 12 injections (0.3 mL per injection of EN3835 0.07 mg/injection or placebo; 0.84 mg in 3.6 mL per buttock) in each of the two buttocks for a total volume of 7.2 mL (1.68 mg). Selection of dimples to be treated in the buttocks will be at the discretion of the Investigator. End of study will occur at study day 71. At each treatment visit, each of the buttocks will be photographed before and after marking dimples and injection sites while the subject is in a consistent, standardized relaxed standing pose. The subject will assess the digital photographic image (pre-marking) of each of the buttocks using the PR-PCSS to determine the severity of EFP in each of the buttocks. In addition, the subject will evaluate each of the buttocks using a Subject Global Aesthetic Improvement Scale (S-GAIS). Subsequently, the Investigator will conduct live assessments of each buttock using the CR-PCSS. At Day 1, the subject will complete a Patient Reported Cellulite Impact Scale (PR-CIS) assessment. The subject assessments will always be completed prior to and independently of the Investigator assessments at each treatment visit. In addition, the Investigator will assess each of the buttocks using an Investigator Global Aesthetic Improvement Scale (I-GAIS). All of the assessments must be done before the dimple marking. At Day 71 (End of Study/Early Termination), photographs of each of the buttocks will be taken and evaluated by subject using the PR-PCSS. The Investigator will conduct live assessments of each of the buttocks using the CR-PCSS. Global assessment evaluations will be completed by both the subject and the Investigator.	
Number of Subjects (Planned): 420	

Name of Sponsor/Company: Endo Pharmaceuticals Inc.

Name of Investigational Product: EN3835

Name of Active Ingredient: Collagenase clostridium histolyticum

Study Center(s): Approximately 25 sites in United States

Diagnosis and Inclusion/Exclusion Criteria:

Inclusion Criteria:

1. Voluntarily sign and date an informed consent agreement
2. Be a female ≥18 years of age
3. At Screening visit, have 2 bilateral buttocks with each buttock having:
   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)
4. At Day 1 visit, have 2 bilateral buttocks with each buttock having:
   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)
5. Be willing to apply sunscreen to the buttocks before each exposure to the sun while participating in the study (ie, Screening 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
7. Have a negative serum pregnancy test at Screening and a negative urine pregnancy test before injection of study drug and be using a stable and effective contraception method (eg, abstinence, intrauterine device [IUD], hormonal [estrogen/progestin] contraceptives, or double barrier method) for at least 1 menstrual cycle prior to study enrollment and for the duration of the study; or be menopausal defined as 12 months of amenorrhea in the absence of other biological or physiological causes, as determined by the Investigator; or post-menopausal for at least 1 year; or be surgically sterile
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:

A subject will be excluded from study participation if she:

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

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

b. Vascular disorder (eg, varicose veins, telangiectasia) in area to be treated
c. Inflammation or active infection
d. Severe skin laxity, flaccidity, and/or sagging
e. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer
f. Has a tattoo and/or a mole located within 2 cm of the site of injection

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

Name of Sponsor/Company: Endo Pharmaceuticals Inc.

Name of Investigational Product: EN3835

Name of Active Ingredient: Collagenase clostridium histolyticum

Investigational Product, Dosage and Mode of Administration: EN3835, 1.68 mg, subcutaneous. A dose of 0.84 mg of EN3835 per buttock will be administered as 12 subcutaneous injections (0.3-mL injection administered as three 0.1-mL aliquots per injection) in each of two buttocks for a total dose of 1.68 mg and a total volume of 7.2 mL (3.6 mL per buttock). Total number of injections will be 24 injections per treatment visit into the two buttocks. There will be 3 treatment visits at 21 days intervals, ie, treatments on Days 1, 22, and 43 will be administered.

Duration of Study: Approximately 84 days (includes screening phase)

Screening Phase: Up to 14 days

Criteria for Evaluation:

Efficacy:

- Subject using PR-PCSS while viewing digital image of the left buttock: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the left buttock
- Subject using PR-PCSS while viewing digital image of the right buttock: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the right buttock
- Investigator using the CR-PCSS by live assessment: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the left buttock
- Investigator using the CR-PCSS by live assessment: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the right buttock
- Investigator Global Aesthetic Improvement Scale (I-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the left buttock
- Investigator Global Aesthetic Improvement Scale (I-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the right buttock
- Subject Global Aesthetic Improvement Scale (S-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the left buttock
- Subject Global Aesthetic Improvement Scale (S-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the right buttock
- Patient Reported Cellulite Impact Scale: 6 questions with responses to each question consisting of a numerical rating scale (NRS) ranging from 0 (Not at all) to 10 (Extremely)
- Subject satisfaction with cellulite treatment assessment: 5-level scale ranging from 2 (very satisfied) to −2 (very dissatisfied) (Day 71) for both left and right buttocks

Safety:

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

- Adverse events (AEs) (including those of special interest (AESI); which are adverse events such as bruising, ecchymosis, hematomas, and contusions that occur remote to the site of drug administration, or any hypersensitivity reactions, including anaphylaxis)

[redacted]

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- 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 study drug in this study, injection site reactions/local tolerability in the treated buttocks (through subject and Investigator reporting) will be assessed.

Statistical Methods:

The primary endpoint is the proportion of 2-level composite responders at Day 71 defined as subjects with at least one of two treated buttocks with:

- an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator, and
- an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS as assessed by the subject while viewing the digital image of the same buttock.

A subject will be considered a responder if these criteria are met in either the left buttock or right buttock or both buttocks in that subject.

Sample Size Consideration: The results of a prior Phase 2b study of this drug (Study EN3835-201) demonstrated the overall rate for treated buttocks of composite responders with an improvement of at least 2 levels on both the PR-PCSS and the CR-PCSS was 14.9% in the EN3835 treatment group versus 1.1% in the Placebo group. Given this result, the study is planned to randomize 420 subjects with a 1:1 ratio into either the EN3835 arm (0.84 mg/buttock, 1.68 mg total dose) or placebo arm.

The sample size calculation was based on the following assumptions: [redacted] 3) treatment effect of at least 12% of composite responders with an improvement of at least 2 levels on both the PR-PCSS and the CR-PCSS for at least one treated buttock; 4) Fisher exact test; 5) type I error of 0.05; 6) a power of at least 90%; and 7) dropout rate of approximately 10%.

This sample size will also provide >90% power with type 1 error of 0.025 to detect 1-level responder rate difference for buttocks using the PR-PCSS of 72% in the EN3835 group and 48% in the placebo group as well as 1-level responder rate difference using the S-GAIS of 75% in the EN3835 group and 39% in the placebo group, which were estimated from the EN3835-201 study.

Analysis Populations:

- The intent-to-treat (ITT) population: The ITT population is defined as all randomized subjects who have received at least 1 injection of study medication.
- Modified intent-to-treat (mITT) population: The mITT population is defined as all intent-to-treat subjects with a baseline and 1 post-injection evaluation of both the CR-PCSS and PR-PCSS for each buttock.
- Safety population: The Safety population is defined as all subjects who have received at least 1 injection of study medication.
- Per-Protocol population: The Per-Protocol population is defined as those mITT subjects who do not have any major protocol deviations.

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Analyses:

Analyses of Primary Endpoint:

The primary endpoint is the proportion of 2-level composite responders at Day 71 defined as subjects with at least one of two treated buttocks with:

- an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator, and
- an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS as assessed by the subject while viewing the digital image of the same buttock.

A subject will be considered a responder if these criteria are met in the left buttock or right buttock or both buttocks in that subject.

The primary endpoint will be summarized as percentages and analyzed using a Cochran-Mantel-Haenszel test that compares the 2 treatment groups and adjusts for Investigator at a level of significance of 0.05. The ITT population will be evaluated for the primary endpoint with any subject not having an evaluation of CR-PCSS and/or PR-PCSS at Day 71 classified as a non-responder.

Sensitivity analyses for the primary endpoint will include:

- ITT subjects with missing data handled by multiple imputation (MI) approach
- ITT subjects with missing data handled by a last observation carried forward (LOCF) approach
- mITT subjects with missing data handled by an LOCF approach
- Observed data only (no missing data imputed)
- Per-protocol (PP) subjects with missing data handled by an LOCF approach if 10% or more subjects are excluded in the PP population from mITT population.

Analyses of Key Secondary Endpoints:

There will be 4 key secondary endpoints grouped as two families of 2 endpoints per family analyzed in a hierarchical order.

- Family #1 – two endpoints:
  - Proportion of 1-level PR-PCSS responders defined as subjects with ≥1-level improvement in PR-PCSS severity rating of left buttock at Day 71 compared to Day 1
  - Proportion of 1-level PR-PCSS responders defined as subjects with ≥1-level improvement in PR-PCSS severity rating of right buttock at Day 71 compared to Day 1
- Family #2 – two endpoints:
  - Proportion of 1-level S-GAIS responders defined as subjects with ≥1-level improvement (improved, much improved or very much improved) in the S-GAIS assessment of left buttock at Day 71
  - Proportion of 1-level S-GAIS responders defined as subjects with ≥1-level improvement (improved, much improved or very much improved) in the S-GAIS assessment of right buttock at Day 71

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The key secondary efficacy analyses will be analyzed in the same manner as the primary endpoint based on the ITT population. The family #1 key secondary efficacy analyses will be performed only if the primary efficacy analysis is significant at a significance level of $p \leq 0.05$ (gatekeeping strategy). Similarly, family #2 key secondary efficacy analyses will be performed only if at least one of the key secondary efficacy endpoints of family #1 is significant at a significance level of $p \leq 0.025$ (parallel gatekeeping strategy). Within a family of key secondary efficacy endpoints, Bonferroni method will be performed to relocate unused alpha for testing each endpoint to assure an overall error rate of $p \leq 0.05$. The details of the testing procedures will be provided in the statistical analysis plan for the study.

Supportive Endpoints:

The supportive variables will evaluate assessments at various study time points and using various populations.

- Proportion of 2-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS) of the left buttock (Days 22, 43, and 71)
- Proportion of 2-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS) of the right buttock (Days 22, 43, and 71)
- Proportion of 1-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS) of the left buttock (Days 22, 43, and 71)
- Proportion of 1-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS) of the right buttock (Days 22, 43, and 71)
- Proportion of 2-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject.
- Proportion of 1-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject.
- Proportion of 2-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks.
- Proportion of 1-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks.
- Proportion of 2-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS) of the left buttock (Days 22, 43, and 71)
- Proportion of 2-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS) of the right buttock (Days 22, 43, and 71)

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• Proportion of 1-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS) of the left buttock (Days 22, 43, and 71) • Proportion of 1-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS) of the right buttock (Days 22, 43, and 71) • Proportion of 2-level CR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject • Proportion of 1-level CR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject • Proportion of 2-level CR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks • Proportion of 1-level CR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks • Proportion of 1-level composite responders of the left buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the left buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same left buttock) (Days 22, 43, and 71) • Proportion of 1-level composite responders of the right buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the right buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same right buttock) (Days 22, 43, and 71) • Proportion of 1-level composite responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject. • Proportion of 1-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks. • Proportion of 2-level composite responders of the left buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the left buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same left buttock) (Days 22, 43, and 71)

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- Proportion of 2-level composite responders of the right buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the right buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same right buttock) (Days 22, 43, and 71)
- Proportion of 2-level composite responders of at least one of two buttocks (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject.
- Proportion of 2-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks.
- Proportion of subjects at each level of the S-GAIS of the left buttock (Days 22, 43, and 71)
- Proportion of subjects at each level of the S-GAIS of the right buttock (Days 22, 43, and 71)
- Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S- GAIS of the left buttock (Days 22, 43, and 71)
- Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S- GAIS of the right buttock (Days 22, 43, and 71)
- Proportion 1-level S-GAIS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject.
- Proportion of 1-level S-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks.
- Proportion of subjects at each level of the I-GAIS of the left buttock (Days 22, 43, and 71)
- Proportion of subjects at each level of the I-GAIS of the right buttock (Days 22, 43, and 71)
- Proportion of 1-level I-GAIS responders (defined as subjects with a response of at least 1 (improved) in the Investigator GAIS assessment) of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject.
- Proportion of 1-level I-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks.
- Change from baseline (Day 1) of the PR-CIS total score at Day 71
- Change from baseline (Day 1) of the abbreviated PR-CIS score at Day 71
- Proportion of subjects with a change from baseline (Day1) of the PR-CIS ≥12 at Day 71
- Proportion of subjects with a change from baseline (Day 1) of the abbreviated PR-CIS ≥10 at Day 71
- Proportion of subjects at each level of the subject satisfaction with cellulite treatment (Day 71)

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- Proportion of satisfied responders (defined as subjects with a response of at least 1 (ie, 1-Satisfied or 2-Very Satisfied) in the subject satisfaction with cellulite treatment assessment (Day 71)

All supportive endpoints will be summarized as percentages. The dichotomous secondary endpoints (ie, responder endpoints) will be analyzed using a Cochran-Mantel-Haenszel test adjusted for Investigator. Changes in the PR-PCSS ratings and CR-PCSS ratings from baselines, S-GAIS scores, and I-GAIS scores will be analyzed using the Mann-Whitney test.

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. Fisher exact test will be used to compare EN3835 to placebo. Descriptive statistics will be presented for actual and change from baseline at each visit for vital signs and for each clinical laboratory test parameter. The comparison between treatment groups will be based on the change from baseline for clinical laboratory tests and vital signs using an analysis of variance (ANOVA) with a factor of drug (EN3835 or placebo).

Immunogenicity: Anti-AUX-I and anti-AUX-II antibody levels will be summarized using descriptive statistics for the actual value at the visit. Samples from Day 1, Day 22, Day 43, and Day 71 visits will be analyzed for anti-AUX-I and anti-AUX-II antibodies and a subset of Day 1 and Day 71 samples will be analyzed for neutralizing antibodies.

5. SCHEDULE OF EVENTS

Procedures	Day -14 to -1 Screening	Day 1 Treatment Visit 1	Day 22 (± 3 d) Treatment Visit 2	Day 43 (± 3 d) Treatment Visit 3	Day 71 (+ 5 d) / End of Study / Early Termination	Unscheduled Clinic Visit[a]
Informed consent	X					
Inclusion/exclusion	X					
Digital photography	X	X[b]	X[b]	X[b]	X	X
Medical history/EFP history including previous treatments	X					
Prior/concomitant medications/procedures	X	X	X	X	X	X
Physical examination:	X					
• Body weight	X		X[c]	X[c]	X	X
• Height	X					
• Fitzpatrick skin type	X					
Vital signs	X	X[d]	X[d]	X[d]	X	X
12-lead ECG	X					
Collection of samples:						
• Clinical laboratory	X				X	X
• Anti-AUX-I/anti-AUX-II antibody level		X[c]	X[c]	X[c]	X	
• Pregnancy testing	X[e]	X[c,e]	X[c,e]	X[c,e]	X[e]	X
Subject cellulite assessments[f]:						
• Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS)	X[g,h]	X[c,g,h]	X[c,g,h]	X[c,g,h]	X[g,h]	
• Subject Global Aesthetic Improvement (S-GAIS)			X[c,g,h]	X[c,g,h]	X[g,h]	
• Patient Reported Cellulite Impact Scale (PR-CIS)		X[c,g]			X[g]	
• Subject Satisfaction With Cellulite Treatment Assessment					X[g]	
Investigator cellulite assessments:						
• Selection of dimples to be treated within the two buttocks		X[c]	X[c]	X[c]		
• Marking the dimples and injection sites to be treated within the buttocks		X[c]	X[c]	X[c]		
• Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)	X	X[c,h]	X[c,h]	X[c,h]	X[h]	
• Investigator Global Aesthetic Improvement (I-GAIS)			X[c,h]	X[c,h]	X[c,h]	

Procedures	Day -14 to -1 Screening	Day 1 Treatment Visit 1	Day 22 (± 3 d) Treatment Visit 2	Day 43 (± 3 d) Treatment Visit 3	Day 71 (+ 5 d) / End of Study / Early Termination	Unscheduled Clinic Visit[a]
Confirm eligibility		X[c]				
Randomize to treatment		X[c,i]				
Study drug administration		X	X	X		
Injection site reactions/local tolerability in the buttocks		X	X	X	X	X
Adverse events	Monitored Throughout Study					

[a] During unscheduled visits, the Investigator or designee may perform any study procedure that they deem clinically necessary (eg, vital signs, clinical lab assessments, and pregnancy test).
[b] Before and after marking the dimples and injection sites.
[c] Before injection.
[d] Up to 4 hours before injection; approximately 15 and 30 minutes after injection. Vital signs must be stable before the subject is discharged.
[e] Serum pregnancy test on Screening visit and Day 71/EOS visit; urine pregnancy test on Day 1, Day 22, and Day 43 visits.
[f] Subject assessments should be completed independently and prior to Investigator assessments at each visit.
[g] Assessment made via photographs (if treatment visit, use photographs taken before marking dimples and injection sites).
[h] Assessment of each of the 2 buttocks independently.
[i] Before randomization, each of the subject's buttocks must have ratings of 3 or 4 (moderate or severe) in both the CR-PCSS and PR-PCSS.
NOTE: Subject cellulite assessments must be completed before the Investigator cellulite assessments are conducted at each visit.
d=Days; ECG=Electrocardiogram; EFP=Edematous fibrosclerotic panniculopathy; EOS=End of study

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

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7. LIST OF ABBREVIATIONS

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

Table 2: Abbreviations and Special Terms

Abbreviation	Definition
AE	Adverse event
AUX-I	Clostridial class I collagenase
AUX-II	Clostridial class II collagenase
BMI	Body mass index
CR-PCSS	Clinician Reported Photonumeric Cellulite Severity Scale
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EFP	Edematous fibrosclerotic panniculopathy
ePRO	Electronic patient reported outcome
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HREC	Human Research Ethics Committee
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
I-GAIS	Investigator-Global Aesthetic Improvement Scale
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive web response system
LOCF	Last observation carried forward
mITT	Modified intent-to-treat
PR-CIS	Patient Reported Cellulite Impact Scale
PR-PCSS	Patient Reported Photonumeric Cellulite Severity Scale
Quadrant	A quadrant is a treatment area
Qualified designee	Qualified by education and training to perform the study procedure (eg, sub-Investigator, nurse).
SAE	Serious adverse event
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. Background

8.1.1. 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 a contour abnormality of the skin.(1) The condition manifests as dimpled skin, particularly in the gluteal-femoral region.(2,3) EFP is caused by herniation of subcutaneous fat lobules through the dermohypodermal junction and/or shortening of the collagen septa that cross the hypodermal layer and connects the dermis to the underlying fascia. This creates an uneven surface with dimpling.(1,2) 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.

8.1.2. Current EFP Treatments

There are therapies that have been utilized in an attempt to treat cellulite; however, there are no approved pharmacologic treatments. 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,(6) topical agents,(5) massage,(7) liposuction,(5,6) mesotherapy,(6) radiofrequency,(6) subcision and powered subcision,(8) and laser therapies;(9,10) some of these treatments may pose an increased risk for adverse effects.(5)

There remains an unmet medical need for safe and effective therapies to improve the aesthetic 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 that is bothersome to many women.

8.1.3. 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 (brand name is XIAFLEX®) 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° at the start of therapy.

A recent Phase 2b, randomized, double-blind, placebo-controlled study (EN3835-201) of 375 women randomized to treatment of one treatment area (quadrant) (quadrant was defined in study EN3835-201 as a left buttock, a right buttock, a left posterolateral thigh or a right posterolateral thigh) of cellulite with EN3835 0.84 mg or placebo in a 1:1 ratio assessed the effectiveness and safety of EN3835. Efficacy in this study was evaluated based on cellulite assessments using Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS), Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS), Investigator Global Aesthetic Improvement Scale (GAIS-I), Subject Global Aesthetic Improvement Scale (GAIS-S), and Subject Satisfaction with Cellulite Treatment.

Results from the Phase 2b study demonstrated that treatment (3 visits approximately 21 days apart) improved the cellulite severity of the treatment area as assessed by the primary endpoint of 2-level composite responder analyses, the proportion of responders based on an improvement of ≥2 levels in the appearance of cellulite in both the patient PR-PCSS and the clinician CR-PCSS of buttocks and thighs was statistically significantly greater in subjects who received EN3835 0.84 mg (10.6%; $p<0.001$) compared to subjects who received placebo (1.6%); 1-level (or greater) responders in the PR-PCSS of EN3835-treated subjects (72.3%) was significantly

greater than 1-level responders in the placebo group (51.6%) ($p<0.001$); statistically significant ($p\leq0.001$) improvement in the appearance of cellulite based on the subject S-GAIS were observed in EN3835 0.84-mg group (73.1%) compared to the placebo group (44.0%); and 62.9% of subjects in the EN3835 0.84 mg group were satisfied or very satisfied with the results of their cellulite treatment compared with only 35.9% of subjects in the placebo group ($p<0.001$). In subjects treated in buttocks (n=187), the proportion of 2-level composite responders was statistically significantly greater in subjects who received EN3835 0.84 mg (14.9%; $p<0.001$) compared to subjects who received placebo (1.1%); 1-level (or greater) responders in the PR-PCSS of EN3835-treated subjects (72.7%) was significantly greater than 1-level responders in the placebo group (47.8%) ($p<0.001$).

The study also demonstrated EN3835 to be well tolerated with no serious adverse events (SAEs) related to EN3835. Safety results from a total of 4 studies (1 pilot, 2 Phase 1, and 2 Phase 2 studies) in which 435 adult females received subcutaneous injections of EN3835 indicate that the majority of treatment-emergent adverse events (TEAEs) are transient, non-serious, mild or moderate in intensity, and related to the local administration of EN3835. The immunogenicity profile after 3 treatment visits of EN3835 indicate that greater than 90% of EN3835-treated subjects were seropositive for AUX-I and/or AUX-II antibodies; this profile of EN3835 is similar to that observed in the Dupuytren's contracture and Peyronie's disease programs.

A Phase 1, open-label safety and pharmacokinetic study of a single dose of EN3835 0.84 mg in 11 female subjects with EFP showed that there was no quantifiable levels of AUX-I or AUX-II at any time point after subcutaneous injection of EN3835 0.84 mg into one quadrant. A second Phase 1, open-label safety and pharmacokinetic study of a single dose of EN3835 0.84 mg per treatment area in two treatment areas (buttock-buttock, thigh-thigh, or buttock-thigh) concurrently (total dose of 1.68 mg) showed that there was no quantifiable levels of AUX-I or AUX-II at any time point post-dose attributable to the injection of EN3835 1.68 mg.

The results from these studies suggest that subcutaneous injections of EN3835 in the area of cellulite may be a well-tolerated and effective medical treatment for adults with EFP.

8.2. Summary of Nonclinical Studies

Non-clinical studies necessary to support clinical studies have been performed and are summarized in the Investigator Brochure (IB).(11) Non-clinical studies in the following areas were performed: toxicology, reprotoxicity, genotoxicity, and hypersensitivity.

8.3. Summary of Known Risks and Benefits

A summary of safety risks is provided in the IB.(11) The following events have been commonly observed: local injection site reactions (injection site bruising, injection site swelling, injection site pain) for the various approved indications as well as those being investigated. In the phase 2b study of EN3835 in women with EFP, the following treatment related adverse events ≥2% of 189 EN3835-treated women were reported: injection site bruising (75.1%), injection site pain (59.3%), injection site nodule (14.3%), injection site pruritus (11.1%), injection site swelling (7.4%), injection site induration (5.8%), injection site mass (5.3%), injection site discolouration (3.2%), and injection site erythema (2.1%). These events are similar to events reported in the clinical trials of EN3835 for the approved indications. Postmarketing safety data are consistent with safety data reported in clinical trials.

Although a thorough benefit of EN3835 has not been fully evaluated in the treatment of EFP, the efficacy results from the Phase 2b study and previous EFP studies warranted further development.

8.4. Rationale

The results from the Phase 2b EFP study (EN3835-201) further suggested that EN3835 0.84 mg per treatment area (quadrant) is an effective treatment of EFP based on improvement in the severity of cellulite as determined by the Investigator and the subject. There were no safety concerns following 0.84 mg per treatment area in the treatment of EFP (section 8.1.3). Safety findings from the Phase 2b EFP study are similar to that observed in previous clinical studies with EN3835 in the treatment of EFP and XIAFLEX in the treatment of Dupuytren's contracture and Peyronie's disease, in that that the majority of AEs occurred at the site of injection and resolved before the next scheduled treatment. The immunogenicity profile of EN3835 in the Phase 2b EFP study is similar in previous studies and programs.

Based on the efficacy and safety findings from the Phase 2a and 2b EFP studies, the EN3835 0.84-mg dose per treatment area in two treatment areas (buttocks) warranted further investigation in this study.

Treating two buttocks at each treatment visit will potentially provide a symmetrical-like improvement in appearance. Support for evaluation of the treatment of two buttocks concurrently is based on: 1) the safety findings from the previous EFP studies are local to the injection site, 2) the pharmacological activity of EN3835 is local and does not require systemic exposure, and 3) no significant quantifiable systemic concentration has been attributable to injection of two buttocks concurrently.

The integration of dose and use justification supports this study of evaluation of EN3835 0.84 mg per treatment area in two treatment areas (buttocks) concurrently.

9. OBJECTIVES

9.1. Primary Objective

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

9.2. Secondary Objectives

There are no secondary objectives of this study.

9.3. Exploratory Objectives

There are no exploratory objectives of this study.

10. INVESTIGATIONAL PLAN

10.1. Study Design

This study will be performed at approximately 25 study centers located in the United States. This clinical study will be conducted as a multicenter, randomized, double-blind, placebo-controlled study comparing EN3835 to placebo in adult women with EFP. The study will consist of 71 days of double-blind treatment. Subjects meeting the entry criteria for this study will be randomized to EN3835 treatment or placebo treatment in a 1:1 ratio within an investigational site.

The complete Schedule of Events is provided in section 5.

Figure 1: Study Design

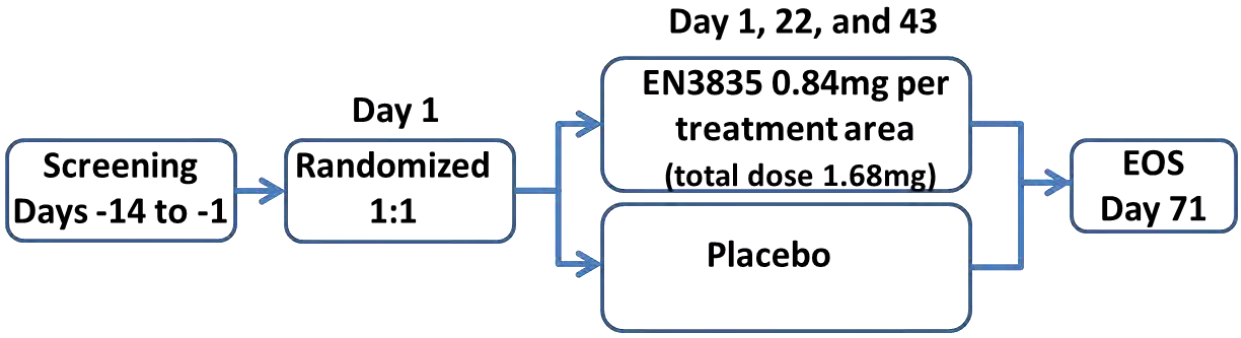


Table 3: Study Treatment Groups

Dose per Each Injection[a] / Number of Subjects	Injection Volume per Each Injection	Number of Injections at Each Treatment Visit	Dose (mg) at Each Treatment Visit	Injection Volume (mL) per Each Treatment Visit	Cumulative EFP Dose
EN3835 0.07 mg / N=210	0.3 mL	12 per buttock × 2 buttocks = 24 injections	0.84 mg per buttock × 2 buttocks = 1.68 mg (12 injections per buttock × 0.07 mg/injection × 2 buttocks)	3.6 mL per buttock × 2 buttocks = 7.2 mL (24 injections × 0.3 mL)	5.04 mg (3 treatment visits × 0.84 mg per buttock × 2 buttocks)
Placebo / N=210	0.3 mL	12 per buttock × 2 buttocks = 24 injections	-	3.6 mL per buttock × 2 buttocks = 7.2 mL (24 injections × 0.3 mL)	-

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

10.2. Selection of Doses

The dose of EN3835 chosen for this study was based on the results from earlier studies.

The data from the Phase 2a EFP dose-ranging study (AUX-CC-831) suggest that EN3835 0.84 mg is most effective in the treatment of EFP based on improvement in the severity of cellulite as determined by both the Investigator and the subject, although the EN3835 0.48-mg group did show improvement in some of the efficacy parameters.

- There were no safety concerns following administration of up to 3 treatment visits of EN3835 0.84 mg in the treatment of EFP (AUX-CC-831 CSR). The safety profile of EN3835 0.84 mg in the treatment of EFP was similar to that observed in the EN3835 0.06-mg group and the EN3835 0.48-mg group. No notable differences were observed across the 3 treatment groups.
- Safety findings from the Phase 2a EFP dose-ranging study are similar to that observed in previous clinical studies with XIAFLEX in the treatment of Dupuytren's contracture and Peyronie's disease, in that the majority of AEs occurred at the site of injection and resolved before the next scheduled treatment.
- The immunogenicity profile of EN3835 in the Phase 2a EFP dose-ranging study is similar to that observed in the Dupuytren's contracture and Peyronie's disease programs.
- Based on the efficacy and safety findings from the Phase 2a EFP dose-ranging study, the EN3835 0.84-mg dose was carried forward to the Phase 2b study.

The results from the Phase 2b EFP study (EN3835-201) further suggested that EN3835 0.84 mg is an effective treatment of EFP based on improvement in the severity of cellulite as determined by the Investigator and the subject. There were no safety concerns following EN3835 0.84 mg in the treatment of EFP (section 8.4). Safety findings from the Phase 2b EFP study are similar to that observed in previous clinical studies with XIAFLEX in the treatment of Dupuytren's contracture and Peyronie's disease, in that that the majority of AEs occurred at the site of injection and resolved before the next scheduled treatment. The immunogenicity profile of EN3835 in the Phase 2b EFP study is similar to that observed in the Dupuytren's contracture and Peyronie's disease programs.

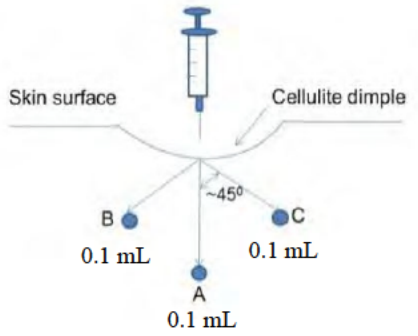
Based on the efficacy and safety findings from the Phase 2a and 2b EFP studies, the EN3835 0.84-mg dose per treatment area was carried forward to this study. The findings from previous studies that the majority of adverse events after EN3835 treatment are local to the injection site and that there is no quantifiable systemic exposure observed after concurrent treatment of two buttocks (total dose of 1.68 mg) supports the proposed study to evaluate EN3835 treatment of two buttocks.

10.3. Study Drug Administration

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 visit, 8 syringes (4 syringes per buttock) will be prepared for dosing. Each syringe will contain 0.9 mL of study drug (ie, 3 injections in each syringe). Twelve (12) skin injections of 0.3 mL per injection will be administered within each of the two buttocks during each treatment visit.

Figure 2: Study Drug Administration at Each Injection Site



- **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 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 each buttock (three 0.3-mL injections per syringe, each injection administered as three 0.1-mL aliquots). Twelve (12) skin injections of 0.3 mL will be administered within each of the two treated buttocks during each treatment visit.
- The plane containing injection deposition points A, B, and C should be perpendicular to the skin and perpendicular to the long axis of a dimple if the dimple is an elongated trough-like dimple.
- 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 Visits 1, 2, and 3.

NOTE: EN3835 is a foreign protein and Investigators should 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 must be available with the Investigator and site staff must be familiar with their use.

10.4. 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 injections 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 14.9).

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

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

The design of this study was based on the primary objective to evaluate the efficacy and safety of EN3835 0.84 mg per buttock in the concurrent treatment (total dose of 1.68 mg) of 2 bilateral buttocks with EFP in adult women compared with placebo treatment. The study design, a multi-center, double-blind, placebo-controlled study is in accordance with regulatory guidelines of adequate and well-controlled clinical studies (Food and Drug Administration [FDA] Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, 1998.; ICH E8 and E10).

11. SELECTION AND WITHDRAWAL OF SUBJECTS

11.1. Subject Inclusion Criteria

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

1. Voluntarily sign and date an informed consent agreement
2. Be a female ≥18 years of age
3. At Screening visit, have 2 bilateral buttocks with each buttock having:
   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)
4. At Day 1 visit, have 2 bilateral buttocks with each buttock having:
   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)
5. Be willing to apply sunscreen to the buttocks before each exposure to the sun while participating in the study (ie, Screening 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
7. Have a negative serum pregnancy test at Screening and a negative urine pregnancy test before injection of study drug and be using a stable and effective contraception method (eg, abstinence, intrauterine device [IUD], hormonal [estrogen/progestin] contraceptives, or double barrier method) for at least 1 menstrual cycle prior to study enrollment and for the duration of the study; or be menopausal defined as 12 months of amenorrhea in the absence of other biological or physiological causes, as determined by the Investigator; or post-menopausal for at least 1 year; or be surgically sterile
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. Subject Exclusion Criteria

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

1. Has any of the following systemic conditions:
   a. Coagulation disorder
   b. Evidence or history of malignancy (other than excised basal-cell carcinoma) unless there has been no recurrence in at least 5 years
   c. History of keloidal scarring or abnormal wound healing

   d. Concurrent diseases or conditions that might interfere with the conduct of the study, confound the interpretation of the study results, or endanger the subject's well-being. Any questions about concurrent diseases should be discussed with the Medical Monitor
   e. Evidence of clinically significant abnormalities on physical examination, vital signs, electrocardiogram (ECG), or clinical laboratory values

2. Has any of the following local conditions in the areas to be treated:
   a. History of lower extremity thrombosis or post-thrombosis syndrome
   b. Vascular disorder (eg, varicose veins, telangiectasia) in area to be treated
   c. Inflammation or active infection
   d. Severe skin laxity, flaccidity, and/or sagging
   e. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer
   f. Has a tattoo and/or a mole located within 2 cm of the site of injection
3. Requires the following concomitant medications before or during participation in the trial:
   a. Anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication (except for ≤150 mg aspirin daily) within 7 days before injection of study drug
4. Has used any of the following for the treatment of EFP on a buttock within the timelines identified below or intends to use any of the following at any time during the course of the study:
   a. Liposuction in a buttock during the 12-month period before injection of study drug
   b. Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; buttock implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision) within a buttock during the 12-month period before injection of study drug
   c. Any investigational treatment for EFP on a buttock during the 12-month period before the injection of study drug
   d. Endermologie or similar treatments within a buttock during the 6-month period before injection of study drug
   e. Massage therapy within a buttock during the 3-month period before injection of study drug
   f. Creams (eg, Celluvera™, TriLastin®) and/or home therapies to prevent or mitigate EFP within a buttock during the 2-week period before injection of study drug
5. Is presently nursing or providing breast milk
6. Intends to become pregnant during the study
7. Intends to initiate an intensive sport or exercise program during the study
8. Intends to initiate a weight reduction program during the study
9. Intends to use tanning spray or tanning booths during the study

10. Has received an investigational drug or treatment within 30 days before injection of study drug
11. Has a known systemic allergy to collagenase or any other excipient of study drug
12. Has received any collagenase treatments at any time prior to treatment
13. Was a subject in a previous cellulite clinical trial of CCH: AUX-CC-830, AUX-CC-831, EN3835-102, EN3835-104, EN3835-201, and/or EN3835-202
14. Any other condition(s) that, in the Investigator's opinion, might indicate the subject to be unsuitable for the study

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
- Lack of efficacy
- 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 including safety and efficacy assessments should be conducted as detailed in the Schedule of Events (section 5). 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 and assessments are required (but are encouraged to reduce missing information) except the collection of adverse event (AE) information. This information should be recorded in the source documentation and the eCRF.

11.3.1. Replacement Procedures

Subjects who discontinue from the study will not be replaced.

12. TREATMENT OF SUBJECTS

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. Informed Consent

Signed and dated informed consent will be obtained from each subject before any study procedures are undertaken, or before any changes to the subject's medication regimen are made. Details about how the informed consent will be obtained and documented are provided in section 21.3, Subject Information and Consent.

12.1.2. Subject Screening

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. The screening log will be captured directly by the electronic data capture (EDC) system.

12.1.2.1. Medical History

During the screening period, the Investigator or qualified designee will obtain a medical history from each subject that includes relevant diagnoses and/or procedures/therapies with onset/resolutions dates. Medical histories should also include history of EFP (start date and family history), and history of tobacco and alcohol use (never, current, former).

12.1.2.2. Screening Period (Day -14 to Day -1)

Subjects meeting the relevant eligibility criteria listed in section 11 may be enrolled in the study after the nature and purpose of the protocol have been explained and written informed consent to participate has been voluntarily provided by the subject or their legally authorized representative.

The subject identification number will consist of 8 digits. The first 4 digits represent the study site number followed by a 4-digit subject number.

The following procedures will be performed and documented during the screening period:

1. Obtain written informed consent (section 12.1.1)
2. Evaluate eligibility based on inclusion/exclusion criteria (section 11.1 and section 11.2)
3. Subject will have digital photographs taken of her two buttocks (section 13.1.1)
4. Subjects will get instruction on the use of the PR-PCSS (section 13.1.2.1)

5. Prior to Investigator CR-PCSS assessment, subjects will rate each of their two buttocks using the PR-PCSS while viewing their digital images (section 13.1.2.1); the Investigator is blinded to these scores
6. After the subject has completed the PR-PCSS ratings, the Investigator will conduct live assessments of subject's cellulite severity of each of the two buttocks using the CR-PCSS (section 13.1.2.5); the subject is blinded to these ratings. The ratings from the PR-PCSS and CR-PCSS will be used to assess initial eligibility of the buttocks for study entry.
7. Medical history including EFP history (section 12.1.2.1)
8. Record prior and concomitant medications/procedures (section 12.8)
9. Physical examination including measurement of body weight, height, Fitzpatrick skin type (section 14.11)
10. Vital sign measurements (section 14.9)
11. 12-lead ECG (section 14.10)
12. Collection of samples for:
    a. Clinical laboratory testing (section 14.7)
    b. Serum pregnancy testing (section 14.7)
13. Adverse events (section 14)

12.2. Selecting and Marking Dimples during Treatment Visits

Selection of dimples to be treated in the two buttocks is at the discretion of the Investigator. Dimples must be well-defined and evident when the subject is standing in a consistent, standardized relaxed pose (without the use of any manipulation such as skin pinching or muscle contraction). Each subject will receive 3 treatment visits of study drug according to randomization unless the buttock is dimple-free (score of 0 on CR-PCSS as reported by the Investigator) at Treatment Visit 2 and/or Treatment Visit 3 (a dimple -free buttock at Treatment Visit 1 is precluded by the eligibility criteria); a dimple-free buttock at Treatment Visit 2 and/or Treatment Visit 3 does not preclude treatment of the contralateral buttock unless it is dimple-free also. During each treatment visit, each of the buttocks will be photographed before and after marking dimples and injection sites while the subject is standing in a consistent, standardized relaxed pose as described in the Photography Manual. The cellulite severity assessments using the PR-PCSS and CR-PCSS will be completed prior to marking dimples and injection sites.

The Investigator or qualified designee will select dimples within each buttock that are well-defined, evident when the subject is standing, and suitable for treatment; treatment consists of 12 injections per buttock (24 injections total in two buttocks) per treatment visit. Because the goal of treatment is to improve the aesthetic appearance of each entire buttock, the Investigator will be instructed to select dimples that in his or her opinion would most improve the aesthetic appearance of each entire buttock. The same dimples within a buttock or different dimples within a buttock may be treated at each treatment visit but injections must all be within the buttocks (12 injections per buttock) for all 3 visits. Each buttock will receive all 3 treatment visits unless the buttock has no treatable EFP dimples and the Investigator rates the buttock a score of 0 on the CR-PCSS. If no injections in a particular buttock (right or left) are given at Treatment Visit

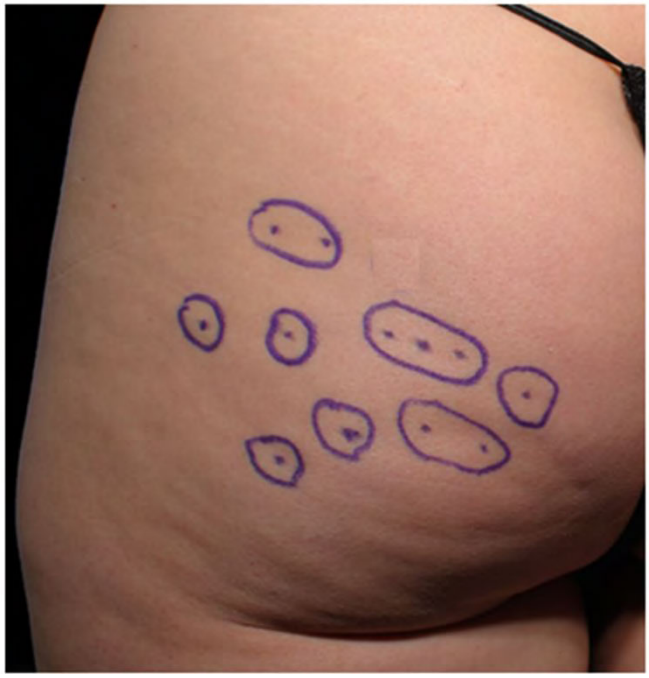
2, subjects will still be assessed for treatment in the contralateral buttock at Treatment Visit 2, and will return for the Day 43 visit and each of the buttocks will again be evaluated by the subject (PR-PCSS) and Investigator (CR-PCSS). If the Investigator rates either or both of the buttocks greater than 0 on the CR-PCSS, injections at Treatment Visit 3 should be given.

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; locating at least one injection site at the nadir, if present, of the dimple). 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 buttock should not overlap.

Each of the buttocks will be photographed before and after marking dimples and injection sites while the subject is standing in a consistent, standardized relaxed pose as described in the Photography Manual.

Examples of subject dimple and injection site markings are shown as follows:

Sample Buttock Marking



12.3. Digital Photography during Treatment Visits 1, 2, and 3

During each treatment visit, each of the two buttocks will be photographed before and after marking dimples and injections sites while the subject is standing in a consistent, standardized relaxed pose as described in section 13.1.1.

12.4. Treatment Visit 1 (Day 1)

12.4.1. Treatment Visit 1: Pre-Injection

1. Confirm eligibility criteria
2. Take digital photography of each of the buttocks before marking dimples and injection sites (section 13.1.1)
3. Subjects will get instruction on the use of the PR-PCSS (Patient Instructions for Use of PR-PCSS)
4. Subjects will rate each of their buttocks using the PR-PCSS (section 13.1.2.1); the Investigator is blinded to these ratings
5. Subjects will complete the Patient Reported Cellulite Impact Scale assessment (PR-CIS; section 13.1.2.3): the Investigator is blinded to this rating
6. The Investigator will conduct live assessments of subject's cellulite severity of each of the buttocks using the CR-PCSS (section 13.1.2.5); the subject is blinded to these ratings. The ratings from the PR PCSS and CR-PCSS will be used to assess eligibility for randomization
7. Subjects with PR-PCSS or CR-PCSS ratings in either of the buttocks <3 will be excluded from participation
8. Randomization of subjects with two buttocks eligible for treatment (eligible criteria being each buttock have PR-PCSS and CR-PCSS scores of 3 or 4) to treatment (section 12.10); obtain kit numbers of study treatment
9. Record concomitant medications/procedures (section 12.8)
10. Vital sign measurements (section 14.9)
11. Collection of samples for:
    a. Anti-AUX-I and anti-AUX-II antibody testing (section 14.8)
    b. Urine pregnancy testing (section 14.7)
12. Select and mark dimples to be treated in each of the buttocks (section 12.2)
13. Take digital photograph of each of the buttocks after marking dimples and injection sites (section 13.1.1)

12.4.2. Treatment Visit 1: Injection and Post-injection

1. Administration of study drug in the prone position (section 10.3)
2. Record number of dimples treated and number of injections administered in each of the two buttocks
3. Vital sign measurements (section 14.9)
4. Injection site reactions and local tolerability
5. Adverse events (section 14)

12.5. Treatment Visit 2 (Day 22 [±3 days]) and Treatment Visit 3 (Day 43 [±3 days])

12.5.1. Treatment Visits 2 and 3: Pre-injection

1. Record concomitant medications/procedures (section 12.8)
2. Body weight measurements
3. Vital sign measurements (section 14.9)
4. Collection of samples for:
   a. Anti-AUX-I and anti-AUX-II antibody testing (section 14.8)
   b. Urine pregnancy testing (section 14.7)
5. Digital photographs of each of the two buttocks before marking dimples and injection sites (section 13.1.1)
6. Subject Cellulite Assessments of each of the buttocks using the photographic image of each buttock before marking dimples and injection sites (NOTE: complete subject cellulite assessments before Investigator cellulite assessments) in the following sequential order using:
   a. Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) assessment (section 13.1.2.1); complete this prior to conducting S-GAIS
   b. Subject Global Aesthetic Improvement Scale (S-GAIS) (section 13.1.2.2)
7. Investigator Cellulite Assessments live of each of the buttocks in the following sequential order prior to marking dimples and injection sites using:
   a. Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) live assessment of subject (section 13.1.2.5)
   b. Investigator Global Aesthetic Improvement Scale (I-GAIS) (section 13.1.2.6)
8. Select and mark dimples to be treated in each buttock (section 12.2)
9. Digital photographs of each buttock after marking dimples and injection sites (section 13.1.1)
10. For eligible buttock(s), obtain kit number(s) of study treatment

12.5.2. Treatment Visits 2 and 3: Injection and Post-injection

1. Administration of study drug in the prone position (section 10.3)
2. Record number of dimples treated and number of injections administered in each buttock
3. Vital sign measurements (section 14.9)
4. Injection site reactions and local tolerability
5. Adverse events (section 14)

12.6. Day 71 (+5 days) End of Study / Early Termination

The following procedures will be performed on Day 71:

1. Record concomitant medications/procedures (section 12.8)
2. Measurement of body weight
3. Vital sign measurements (section 14.9)
4. Collection of samples for:
   a. Clinical laboratory testing (section 14.7)
   b. Serum pregnancy test (section 14.7)
   c. Anti-AUX-I and anti-AUX-II antibody testing (section 14.8)
5. Digital photographs of each of the buttocks
6. Subject Cellulite Assessment of each of the two buttocks using the photographic image before marking dimples and injection sites (NOTE: complete subject cellulite assessments before Investigator cellulite assessments) using:
   a. Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) assessment (section 13.1.2.1)
   b. Subject Global Aesthetic Improvement Scale (S-GAIS) (section 13.1.2.2)
   c. Patient Reported Cellulite Impact Scale (PR-CIS) assessment (section 13.1.2.3); note this assessment is of both left and right buttocks rather than each individual buttock
   d. Subject Satisfaction with Cellulite Treatment Assessment (section 13.1.2.4); note this assessment is of both left and right buttocks rather than each individual buttock
7. Investigator Cellulite Assessments of each of the buttocks live using:
   a. Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) live assessment of subject (section 13.1.2.5)
   b. Investigator Global Aesthetic Improvement Scale (I-GAIS) (section 13.1.2.6)
8. Injection site reactions and local tolerability
9. Adverse events (section 14)

12.7. Unscheduled Visits

If any subject needs to return to the site prior to her next scheduled visit, site staff should follow the Unscheduled Visit procedures outlined in section 5. Site staff may conduct additional study procedures if required.

12.8. Prior and Concomitant Medications and Procedures

All prior medications taken within 90 days before randomization will be recorded. All medications (including over-the-counter medications) taken by the subject on Day 1 through the end of the study must be recorded. Any prior treatments (medications or procedures) for EFP through the end of the study must be recorded on the appropriate eCRF page.

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.

12.8.1. Prohibited Medications or Procedures

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

Procedures listed in exclusion criterion #4 (section 11.2, Exclusion Criterion #4) are prohibited for randomized subjects during the study.

Table 4: Concomitant Medication Restrictions for Subjects during the Treatment Phase of Study

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

12.9. Treatment Compliance

Randomized subjects will receive study drug administered by an Investigator at the Investigator's site.

Accidental or intentional overdoses should be reported to the Sponsor/designee promptly (see section 14.6.2.1, Overdose).

12.10. Blinding and Randomization

On Day 1, if each of the buttocks again meet the criteria (3 or 4 on the PR-PCSS and CR-PCSS) the subject will be randomized to a treatment group. The interactive web response system (IWRS) will randomly assign each subject to a treatment group (EN3835 0.84 mg per buttock × two buttocks or placebo) in a 1:1 ratio within an investigational site. The treatment group will remain blinded to the Investigator, subjects, all site personnel, and the sponsor. The IWRS will assign the subject study drug kit numbers associated with the randomized treatment. At Day 22 and 43 visits, the IWRS will again assign the subject study drug kit numbers associated with the randomized treatment assigned at Day 1.

All precautions will be taken to ensure that the blinding of EN3835 and placebo is maintained throughout the study period. Unblinding will not be permitted by the study site unless it is deemed necessary for treatment of a medical emergency. Before breaking the blind, the Investigator should make every attempt to contact the Medical Monitor to discuss the necessity of breaking the blind. The study site will have the ability to immediately determine treatment identification in the event of an emergency by using the unblinding function within the IWRS, however, the Medical Monitor must be notified immediately. The Investigator will be required to make a full written explanation of the reason for unblinding the subject and the date. In the event that a subject is unblinded prior to contacting the Medical Monitor, the Investigator must provide

this information in writing to the Medical Monitor as soon as possible. Breaking the blind at the investigative site will immediately disqualify the subject from further participation in the study. In addition, the event(s) leading to emergency unblinding must be reported as an SAE according to instructions in section 14.5.2, Reporting Serious Adverse Events.

In addition, it may be necessary for the Investigator or qualified designee to unblind a subject as a result of a clinically significant finding noted during safety review by the Investigator, Safety Monitor, Medical Monitor and/or qualified designee that might jeopardize subject safety.

13. ASSESSMENT OF EFFICACY

13.1. Efficacy Measurements

13.1.1. Digital Photography

Although digital photographs are not direct efficacy measurements, digital photography will be utilized in the assessment of certain efficacy measurements ie to assess certain cellulite severity parameters at specific intervals (see section 5, Schedule of Events). At the Screening visit, the Investigator or qualified designee will photograph each buttock using a Sponsor-supplied standardized digital camera in a standardized manner. 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 each of the two buttocks while the subject is standing in a consistent, standardized relaxed standing pose, ie, standing position with relaxed gluteus muscles, at the following time points:

- Screening (no markings of dimples or injection site) - each of the two buttocks
- Before and after marking dimples and injection sites (prior to injections) on Days 1, 22, and 43 - each of the two buttocks
- During the Day 71 visit (end of study/early termination) (no dimple or injection site markings) - each of the two buttocks

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.

13.1.2. Subject and Investigator Cellulite Assessments

Investigator cellulite assessments are independent of the subject assessments. Therefore, all subject cellulite assessments must be completed before the Investigator's cellulite assessments are initiated. The subject assessments will be done using a subject-assigned password protected electronic patient reported outcome (ePRO) system and the Investigator and study site personnel will not have access to the subject's assessments or password; the clinician assessment will be recorded in an investigator-assigned password protected system and the subject will not have access to the Investigator's assessments or password. Subject assessments will be done alone with no study site personnel in the room. Investigators will be instructed not to verbalize their ratings while in the presence of the subject.

13.1.2.1. 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. The scale is a 5-level photonumeric scale developed specifically for patients and used by the subject to assess the severity of their cellulite in the buttocks by viewing digital images of each of their buttocks 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.

At Screening and at the beginning of their visits on Day 1, Day 22, Day 43, and Day 71, subjects will have digital photographs taken of each of their two buttocks. Subjects will be given instructions in the proper use (Patient Instructions for Use of PR-PCSS) of the PR-PCSS and then perform the PR-PCSS for each of the buttocks (Appendix B). While viewing the digital images of each of their buttocks on a standardized computer monitor and using PR-PCSS for buttock, subjects will be instructed to answer the following question for each buttock: *Today, how would you rate the severity of your cellulite in the area displayed using the PR-PCSS?* The subject will be given the following explanations*: Please try to match the severity of your cellulite, as seen in this digital image, with one of the cellulite levels on the PR-PCSS. Please look at the image of your cellulite and the pictures, labels, and descriptions on the PR-PCSS carefully before selecting your answer. If you feel that your cellulite level is between 2 of the levels, please select the level that is closest to your image. If you feel that your cellulite is exactly halfway between two PR-PCSS levels of cellulite severity, please select the more severe response.*

The subject will enter their rating electronically into an ePRO system; the Investigator and other site personnel will be blinded to the rating entered by the subject. This variable will 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.

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

Subjects will complete the S-GAIS for each of the buttocks as described below at the Day 22, Day 43, and Day 71 study visits using the pre-treatment Day 1 digital image (Baseline) of each of the buttocks for comparison.

All treated subjects will be instructed to answer the following question for each buttock:

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. The subject will view each of their pre-treatment Day 1 digital images alongside their Day 22, Day 43 or Day 71/End of study visit digital images of each of their buttocks to aid in the assessment (Table 5). Subjects will provide a rating from those below that best represents their answer for each treated buttock.

This variable will 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 5: Subject Global Aesthetic Improvement Scale (S-GAIS)

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

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

At the Day 1 visit and the Day 71 visit, subjects will be instructed to answer 6 questions related to the areas selected for treatment on their buttocks on the PR-CIS (Appendix D) while viewing digital images of their buttocks. The PR-CIS assesses the visual and emotional impact of cellulite (happy, bothered, self-conscience, embarrassed, looking older, or looking overweight or out of shape) using a 6-question survey, with each question rated on a numerical rating scale from 0 (not at all) to 10 (extremely).

This variable will 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.

13.1.2.4. Subject Satisfaction with Cellulite Treatment Assessment

At the Day 71 visit, subjects will be instructed to answer a question related to their treated buttocks. Subjects will be given a list of responses and they will provide a rating from those below that best represents their answer (Table 6).

Today, how satisfied are you with the results of the cellulite treatment you received on the specific area or areas on your buttocks that were treated?

This variable will 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 6: Subject Satisfaction with Cellulite Treatment Assessment - Buttocks

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

13.1.2.5. 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. The scale is a 5-level photonumeric scale developed specifically for clinicians and used by the Investigator to assess the severity of the subject's cellulite in each buttock by live assessments; the ratings range from 0 (None) to 4 (Severe) with labels and descriptors to aid the Investigator in the assessments.

Investigators will be trained and qualified on the use of the CR-PCSS prior to assessing any subjects.

At the Screening visit, the Investigator will determine severity of cellulite of each of the two buttocks via live assessment of the subject using the CR-PCSS for buttock (Appendix C) after the subject has completed her self-assessment using the PR-PCSS. Before injections on treatment visits Day 1, Day 22, and Day 43, and on visit Day 71; Investigators will evaluate each of the two buttocks by live assessments using the CR-PCSS for the buttock to make his/her evaluation. At each visit, the Investigator will make his/her assessment independently and after the subject has conducted her self-assessment using the PR-PCSS.

This variable will 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.

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

On the Day 22, Day 43, and Day 71 study visits, the Investigator will determine the degree of improvement of each buttock by comparing the cellulite from the Day 1 pre-treatment (Baseline) digital image of each buttock to the cellulite seen in a live assessment (Table 7). The I-GAIS assessment will occur after the CR-PCSS assessment (section 13.1.2.5) to avoid introducing potential bias to the static CR-PCSS assessment by the Investigator. For each buttock, the Investigator will provide the rating from those below that best represents his/her answer.

This variable will 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 7: 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

14. ASSESSMENT OF SAFETY

14.1. Definitions

14.1.1. Adverse Events

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. Adverse events 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 Events

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 malignancy, 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 28 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 28 days after the last dose of study medication. SAEs that occur within 28 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 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.

14.6. Special Reporting Situations

14.6.1. Adverse Events of Special Interest

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

14.6.2.1. Overdose

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 12.9) 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

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

Any 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 28 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.

A subject who becomes pregnant must be withdrawn from the study. 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. AEs/SAEs 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 PVRM Department (when the non-subject agrees) on the departmental form for serious adverse experiences 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, Reporting Serious Adverse Events. Additionally, the drug accountability source documentation at the site should reflect this occurrence.

14.7. Clinical Laboratory 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 or qualified designee must acknowledge the review of laboratory results.

The Investigator will review all abnormal lab results for potentially clinically important. Any abnormal clinical laboratory test result meeting the Investigator's criteria for potentially clinically important (refer to central laboratory manual) 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).

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

Clinical laboratory parameters that will be measured in this study are listed in Table 8.

Table 8: Clinical Laboratory Tests

Hematology	**Biochemistry**	**Urinalysis**
Hemoglobin	Glucose	Glucose
Hematocrit	Sodium	Protein
Red blood cell	Potassium	Specific gravity
White blood cell (WBC)	Calcium	pH
Platelets	Chloride	Ketones
WBC Differential	CO_2	Bilirubin
	Inorganic phosphate	Urobilinogen
	Blood urea nitrogen	Nitrite
	Creatinine	Blood*
	Creatinine clearance (estimated)	Leukocytes*
	Aspartate transaminase (AST)	
	Alanine transaminase (ALT)	
	Gamma-glutamyl transferase (GGT)	
	Total bilirubin (TBL) (direct bilirubin reflex if elevated)	
	Albumin	
	Alkaline phosphatase (ALP)	
	Uric acid	

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

For women of childbearing potential, a serum pregnancy test will be performed at Screening and Day 71/End of Study/Early Termination, and urine pregnancy tests will be performed at Day 1, Day 22, and Day 43 (refer to section 5). Female subjects of childbearing potential must have a negative pregnancy test at the Screening Visit and at Day 1 (Baseline), Day 22, and Day 43 to be randomized and/or 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.

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

Serum samples will be collected and will be tested for binding anti-AUX-I and anti-AUX-II antibody testing before injection on Days 1, 22, and 43, and at the Day 71 visit. A subset [redacted] of subject samples will be tested for neutralizing antibodies from Day 1 and Day 71 visits; additional samples will be retained.

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.

14.9. Vital Signs

Vital sign measurements will be documented as described in the Schedule of Events (section 5). 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.

The Investigator will review all vital sign values for clinical significance prior to discharge. 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 9 after the subject has rested for at least 5 minutes.

Table 9: 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

14.10. Electrocardiogram

A 12-lead ECG recording will be conducted at the Screening Visit. The subject should be in a supine position for at least 5 minutes before the recording is conducted. Lead position will be that of a standard 12-lead ECG; no additional or special lead placements will be necessary.

A qualified physician will interpret, sign, and date the ECGs. ECG findings will be documented as normal; abnormal, clinically significant; or abnormal, not clinically significant. The Investigator or qualified designee must sign and date the ECG, thereby acknowledging review of ECG results. 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).

14.11. Physical Examination

A complete physical examination will be performed at the Screening Visit. All examinations will be performed by a physician or health professional listed on the Form FDA 1572 and licensed to perform physical examinations. Height and body weight will be measured and recorded at screening.

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).

At screening, the Investigator will also assess the subject's skin type using the Fitzpatrick scale (Table 10). Only the Fitzpatrick Scale shown below may be used during the study.

Table 10: Fitzpatrick Scale

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

Follow-up body weight will be measured before injection on Day 22 and Day 43 and at the Day 71 visit.

14.12. 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

The primary variable is the proportion of 2-level composite responders at Day 71 defined as subjects with at least one of two treated buttocks with:

- an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator, and
- an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS as assessed by the subject while viewing the digital image of the same buttock.

A subject will be considered a responder if these criteria are met in either the left buttock or right buttock or both buttocks in that subject. In other words, a subject will be considered a responder if she has an improvement of at least 2 levels on the PR-PCSS and an improvement of at least 2 levels on the CR-PCSS on that same buttock; that buttock could be the left buttock or right buttock or both buttocks.

The results of a prior Phase 2b study of this drug (Study EN3835-201) demonstrated the overall rate for treated buttocks of composite responders with an improvement of at least 2 levels on both the PR-PCSS and the CR-PCSS was 14.9% in the EN3835 treatment group versus 1.1% in the Placebo group. Given this result, the study is planned to randomize 420 subjects with a 1:1 ratio into either the EN3835 arm (0.84 mg/buttock, 1.68 mg total dose) or placebo arm.

The sample size calculation was based on the following assumptions: [redacted] 3) treatment effect of at least 12% of composite responders with an improvement of at least 2 levels on both the PR-PCSS and the CR-PCSS for at least one treated buttock; 4) Fisher exact test; 5) type I error of 0.05; 6) an power of at least 90%; and 7) dropout rate of approximate 10%.

This sample size will also provide >90% power with type 1 error of 0.025 to detect 1-level responder rate difference for buttocks using the PR-PCSS of 72% in the EN3835 group and 48% in the placebo group as well as 1-level responder rate difference using the S-GAIS of 75% in the EN3835 group and 39% in the placebo group, which were estimated from the EN3835-201 study.

17.2. Subject Populations

Four (4) populations are considered in the statistical analysis of the study: safety, intent-to-treat (ITT), modified ITT (mITT), and per-protocol (PP).

17.2.1. Safety Population

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

17.2.2. Intent-to-Treat (ITT) Population

The ITT population is defined as all randomized subjects who have received at least one injection of study medication. All demographic and baseline characteristic summaries will be based on this population. The primary and key secondary efficacy parameters will be summarized based on this population.

17.2.3. Modified Intent-to-Treat (mITT) Population

The mITT population is defined as all intent-to-treat subjects with a baseline and at least 1 post-injection evaluation of both the Investigator CR-PCSS and subject PR-PCSS for both left and right buttocks. All secondary and supportive efficacy evaluations will be based on the mITT population.

17.2.4. Per-Protocol (PP) Population

The per-protocol population is defined as the mITT subjects without any major protocol deviation that will impact the subject's efficacy and safety. This population may be used in the efficacy sensitivity analysis.

17.3. Subject Disposition

The number of subjects included in each study population will be summarized by treatment group. Subjects excluded from the safety and efficacy (eg, ITT) populations will be listed by treatment group.

The number and percentage of subjects completed and prematurely discontinued during the treatment period will be presented for each treatment group and pooled across treatment groups. Screen failures (ie, screened but not randomized subjects) and the associated failure reasons will be tabulated overall. Reasons for premature discontinuation from the treatment period as recorded on the termination page of the eCRF will be summarized (number and percentage) by treatment group for all randomized subjects. Percentage of premature discontinuations will be compared between treatment groups.

17.4. Demographics and Other Baseline Characteristics

The summarization of demographic variables (eg, age, sex, race, weight, height, and body mass index [BMI]), medical and surgical history, and other baseline characteristics relevant to the indication studied in the study will be described.

Demographic characteristics, including sex, age, age group, race, height, and weight, will be summarized by treatment group, for the ITT population, using descriptive statistics. All screening characteristics and medical information will also be summarized by treatment group using descriptive statistics. The descriptive summaries will include frequency tables for all categorical response variables and n, mean, standard deviation (SD), median, minimum and maximum for all continuous variables.

17.5. Efficacy Analyses

All efficacy endpoints including supportive efficacy analysis will be summarized as percentages. The dichotomous secondary endpoints (ie, responder endpoints) will be analyzed using a Cochran-Mantel-Haenszel test adjusted for Investigator. Changes in the PR-PCSS ratings and CR-PCSS ratings from baselines, S-GAIS scores, and I-GAIS scores will be analyzed using the Wilcoxon rank sum test. All the tests are two-sided.

The primary endpoint will be summarized as percentages and analyzed using a Cochran-Mantel-Haenszel test that compares the 2 treatment groups and adjusts for Investigator at a level of significance of 0.05 based on the ITT population. Any subject who does not have an evaluation of CR-PCSS and/or PR-PCSS at Day 71 will be classified as a non-responder.

The key secondary efficacy analyses will be analyzed in the same manner as the primary endpoint based on the ITT population. Any subject who does not have an evaluation at Day 71 will be classified as a non-responder for the analyses. The family #1 key secondary efficacy analyses will be performed only if the primary efficacy analysis is significant ($p \leq 0.05$; gatekeeping strategy). Similarly family #2 key secondary efficacy analyses will be performed only if at least one of the key secondary efficacy endpoints of family #1 is significant ($p \leq 0.025$; parallel gatekeeping strategy). Within a family of key secondary efficacy endpoints, Bonferroni method will be performed to relocate unused alpha for testing each endpoint to assure an overall error rate of $p \leq 0.05$. The details of the testing procedures will be provided in the statistical analysis plan for the study.

All supportive endpoints will be summarized as subject counts and percentages for categorical data or n, mean, SD, median, minimum, and maximum for continuous data. All the supportive analyses will be performed based on all observed data (ie, missing data not imputed) in the mITT population at all visits without multiplicity adjustment. This analysis will also be performed at Day 71 with missing data at Day 71 imputed by a last observation carried forward (LOCF) approach if subjects have at least one post-dose assessment. The dichotomous secondary endpoints (ie, responder endpoints) will be analyzed using a Cochran-Mantel-Haenszel test adjusted for Investigator. Changes in the PR-PCSS ratings and CR-PCSS ratings from baselines, S-GAIS scores, and I-GAIS scores will be analyzed using the Wilcoxon rank sum test. Changes in PR-CIS from baselines will be analyzed using an analysis of covariance (ANCOVA) adjusted for baseline values

17.5.1. Primary Efficacy Variable

The primary efficacy variable is the proportion of 2-level composite responders at Day 71 defined as subjects with at least one of two treated buttocks with:

- an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator, and
- an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS by the subject while viewing the digital image of the same buttock.

A subject will be considered a responder if these criteria are met in either the left buttock or right buttock or both buttocks in that subject. In other words, a subject will be considered a responder if she has an improvement of at least 2 levels on the PR-PCSS and an improvement of at least 2 levels on the CR-PCSS on that same buttock; that buttock could be the left buttock or right buttock or both buttocks.

Sensitivity analyses for the primary endpoint will include:

- ITT subjects with missing data handled by multiple imputation (MI) approach
- ITT subjects with missing data handled by an LOCF approach
- mITT subjects with missing data handled by an LOCF approach
- Observed data only (no missing data handling)
- Per-protocol (PP) subjects with missing data handled by an LOCF approach if 10% or more subjects are excluded in the PP population from mITT population

17.5.2. Secondary Efficacy Variables

17.5.2.1. Key Secondary Variables

There will be 4 key secondary endpoints grouped in two families of 2 endpoints per family analyzed in a hierarchical order.

- Family #1 – two endpoints:
  - Proportion of 1-level PR-PCSS responders defined as subjects with ≥1-level improvement in PR-PCSS severity rating of left buttock at Day 71 compared to Day 1
  - Proportion of 1-level PR-PCSS responders defined as subjects with ≥1-level improvement in PR-PCSS severity rating of right buttock at Day 71 compared to Day 1
- Family #2 – two endpoints:
  - Proportion of 1-level S-GAIS responders defined as subjects with ≥1-level improvement (improved, much improved or very much improved) in the S- GAIS assessment of left buttock at Day 71
  - Proportion of 1-level S-GAIS responders defined as subjects with ≥1-level improvement (improved, much improved or very much improved) in the S-GAIS assessment of right buttock at Day 71

17.5.3. Supportive Efficacy Variables

17.5.3.1. Supportive Variables

The supportive variables will evaluate assessments at various study time points and using various populations.

- Proportion of 2-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS of the left buttock (Days 22, 43, and 71)
- Proportion of 2-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS of the right buttock (Days 22, 43, and 71)
- Proportion of 1-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS of left buttock (Days 22, 43, and 71)
- Proportion of 1-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS of right buttock (Days 22, 43, and 71)
- Proportion of 2-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject.
- Proportion of 1-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject.
- Proportion of 2-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks.
- Proportion of 1-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks.
- Proportion of 2-level CR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the left buttock (Days 22, 43, and 71)
- Proportion of 2-level CR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the right buttock (Days 22, 43, and 71)
- Proportion of 1-level CR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the left buttock (Days 22, 43, and 71)

- Proportion of 1-level CR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the right buttock (Days 22, 43, and 71)
- Proportion of 2-level CR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject.
- Proportion of 1-level CR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject.
- Proportion of 2-level CR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks.
- Proportion of 1-level CR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks.
- Proportion of 1-level composite responders of the left buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the left buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same left buttock) (Days 22, 43, and 71)
- Proportion of 1-level composite responders of the right buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the right buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same right buttock) (Days 22, 43, and 71)
- Proportion of 1-level composite responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject.
- Proportion of 1-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks.
- Proportion of 2-level composite responders of the left buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the left buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same left buttock) (Days 22, 43, and 71)
- Proportion of 2-level composite responders of the right buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the right buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same right buttock) (Days 22, 43, and 71)

- Proportion of 2-level composite responders of at least one of two buttocks (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject.
- Proportion of 2-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks.
- Proportion of subjects at each level of the S-GAIS of the left buttock (Days 22, 43, and 71)
- Proportion of subjects at each level of the S-GAIS of the right buttock (Days 22, 43, and 71)
- Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S- GAIS of the left buttock (Days 22, 43, and 71)
- Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S- GAIS of the right buttock (Days 22, 43, and 71)
- Proportion 1-level S-GAIS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject.
- Proportion of 1-level S-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks.
- Proportion of subjects at each level of the I-GAIS of the left buttock (Days 22, 43, and 71)
- Proportion of subjects at each level of the I-GAIS of the right buttock (Days 22, 43, and 71)
- Proportion of 1-level I-GAIS responders (defined as subjects with a response of at least 1 (improved) in the Investigator GAIS assessment) of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject.
- Proportion of 1-level I-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks.
- Change from baseline (Day 1) of the PR-CIS total score at Day 71
- Change from baseline (Day 1) of the abbreviated PR-CIS score at Day 71
- Proportion of subjects with a change from baseline (Day 1) of the PR-CIS ≥ 12 at Day 71
- Proportion of subjects with a change from baseline (Day 1) of the abbreviated PR-CIS ≥ 10 at Day 71

- Proportion of subjects at each level of the subject satisfaction with cellulite treatment (Day 71)
- Proportion of satisfied responders (defined as subjects with a response of at least 1 (ie, 1-Satisfied or 2-Very Satisfied) in the subject satisfaction with cellulite treatment assessment (Day 71)

17.6. Safety Analyses

Safety variables include adverse events, laboratory parameters, vital signs, ECG parameters, and physical examinations. For each safety parameter, the last assessment made prior to the first dose of study drug will be used as the baseline for all analyses of that safety parameter.

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. Prior medication will be defined as any medication taken prior to the first dose of study drug. Concomitant medication is defined as any medication taken on or after the date of first dose of study drug.

Prior and concomitant medication use will be summarized descriptively by the number and percentage of subjects for each preferred term (generic name from WHO dictionary) by treatment. Multiple use of the same medication by a subject will be counted only once.

17.6.2. Study Drug Exposure

The following information regarding treatment will be summarized per each treated buttock by treatment group:

- Total number of treatment visits
- Number of subjects who had treatment session done or treatment session not done at each treatment visit
- For subjects who had the treatment session done, the number of subjects who got all 24 injections at the treatment visit or who received less than 24 injections
- Number of injections given at each treatment visit
- Number of dimples treated at each treatment visit
- Average number of injections per dimple at each treatment visit

Subjects who did not receive all 3 treatment visits and who did not receive 24 injections at a treatment visit will be listed.

17.6.3. Measurement of Treatment Compliance

Not applicable (the study drug is administered at the site by the study investigator).

17.6.4. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code AEs.

An AE (classified by preferred term) that started on or after the date of the first dose of the study drug 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.

The by-frequency summaries will also include incidence of the SAEs and non-SAEs by preferred term that at least 2% of the subjects in one treatment group. Duration of AEs will be tabulated by treatment group.

Fisher exact test will be used to compare EN3835 to placebo.

Listings will be presented for subjects with SAEs, subjects with AEs leading to discontinuation of study or study drug, 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 study will be presented by treatment group.

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 will be detailed in the Statistical Analysis Plan (SAP). The PCI percentages will be calculated relative to the number of subjects with baseline and at least one post-baseline assessment. A supportive listing of subject values will be provided including the subject ID, study center, treatment group, baseline and post-baseline values.

The change from baseline for vital signs parameters are compared between EN3835 and placebo using an analysis of variance (ANOVA) with a factor of drug (EN3835 or placebo) while Fisher exact test will be used for the incidence of PCI values.

17.6.6. Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values in International System of Units (SI units) and changes from baseline at Day 71 will be presented by treatment group for each clinical laboratory parameter.

The number and percentage of subjects with potentially clinically important (PCI) post-baseline clinical laboratory values will be tabulated by treatment group. The criteria for PCI laboratory values will be detailed in the Statistical Analysis Plan (SAP). The PCI percentages will be calculated relative to the number of subjects with at least one post-baseline assessment. A supportive listing of subjects with post-baseline PCI values will be provided, including the subject ID, study center, treatment group, baseline and post-baseline values.

The change from baseline for clinical laboratory parameters are compared between EN3835 and placebo using an ANOVA with a factor of drug (EN3835 or placebo) while Fisher exact test will be used for the incidence of PCI values.

17.6.7. Electrocardiogram

Not applicable (ECG is done only at screening for the subject's enrollment eligibility).

17.6.8. Physical Examination

Body weight and BMI at Day 22, Day 43, and Day 71 as well as their change from baseline (Day 1) at those time points will be presented by treatment group.

17.6.9. Other Safety Measurements

Not applicable.

17.7. Pharmacokinetic Analyses

Not applicable.

17.8. Pharmacodynamic Analyses

Not applicable.

17.9. Other Data (eg, Health Economics/QOL, Pharmacogenetic, etc.)

Not applicable.

17.10. Interim Analysis

No interim analysis is planned for this study.

17.11. Statistical Software

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

18. STUDY DRUG MATERIALS AND MANAGEMENT

18.1. Study Drug Identity

EN3835 is manufactured and supplied by Endo.

EN3835 is a sterile lyophilized powder consisting of 0.92 mg of collagenase clostridium histolyticum, 18.9 mg sucrose, 1.1 mg Tris, 37.7 mg mannitol, hydrochloric acid QS to pH 8.5, in a 5-mL vial.

Placebo for injection is a sterile lyophilized powder consisting of 18.9 mg sucrose, 1.1 mg Tris, 37.7 mg mannitol, hydrochloric acid QS to pH 8.5, in a 5-mL vial.

EN3835 sterile diluent for reconstitution is 0.6% sodium chloride and 0.03% calcium chloride dehydrate in water for injection filled into 5-mL vials.

18.2. Study Drug Packaging and Labeling

Each vial of study drug and diluent will minimally be labeled with contents, Sponsor identification, storage, administration/use, and appropriate cautions statements. Each kit will contain one vial of EN3835 or placebo and sufficient sterile diluent to perform reconstitution of the one product vial. Kits containing EN3835 or placebo will be indistinguishable and only identifiable by their unique kit number.

18.3. Study Drug Storage

All study drug will be provided by Endo. Study drug must be stored in an appropriate, secure area. Study drug must be kept in a temperature-monitored refrigerator (2°C-8°C) with locked access until used or returned to Endo.

18.4. Study Drug Preparation

Refer to the Reconstitution Instructions for detailed preparation instructions.

For each dose session, the IWRS will dispense 2 kits, 1 kit for each buttock to be treated. Four (4) 0.9-mL syringes will be prepared from each vial of EN3835 or placebo, 4 syringes/kit, for a total of 8 syringes (4 syringes for each buttock).

Used drug vials should be returned to the kit carton and stored in a secure location until reconciled and returned by the Clinical Research Associate (CRA). Dispose of used diluent vials, needles, and syringes per local regulations.

The reconstituted study drug solution should be administered as soon as possible after reconstitution. The study drug solution can be kept at room temperature [redacted] emove drug/prepared syringes from the refrigerator and allow it to stand at room temperature for 15 minutes prior to injection of study drug.

18.5. Study Drug Accountability

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/IEC, and regulatory agencies for routine inspection and accountability during monitoring visits. When instructed by Endo, the Investigator agrees to return all original used or unused study drug kits to Endo's return vendor.

18.5.1. Study Drug Handling and Disposal

The Investigator agrees not to supply study drug to any person except to those subjects enrolled in the study. The Investigator is responsible for recording the receipt and use of all drugs supplied and for ensuring the supervision of the storage and allocation of these supplies. All used and 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 and its use. At the end of the study, all used and unused drug supplies will be returned to Endo’s return vendor.

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:

- PR-PCSS
- CR-PCSS
- S-GAIS
- I-GAIS
- PR-CIS
- Subject Satisfaction with Cellulite Treatment Assessment

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/assent, the Investigator is responsible for obtaining any additional documentation to demonstrate compliance with local privacy laws applicable to activities performed.

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

A unique Subject identification number will be assigned according to section 12.1.2.2 at the time that the Subject signs the informed consent form.

22. DATA HANDLING AND RECORDKEEPING

22.1. Data Collection

Endo will provide an electronic data capture (EDC) system for this study. 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).

Data entries will be corrected by changing the entry in the EDC system. Any changes or corrections to eCRF data will be electronically tracked and will include the reason for correction, who made the correction, and the date/time stamp when the correction was made within the audit trail of the EDC system.

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 case report form (CRF) data for his/her files.

23. REPORTING AND PUBLICATION

All data generated in this study are the property of Endo Pharmaceuticals Inc. 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 Pharmaceuticals Inc.

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 FDA 1572. If during the course of the study any information reported on the Form FDA 1572 changes, a revised Form FDA 1572 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 FDA 1572 (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.

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 Pharmaceuticals Inc. 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)/Clinical Trial Authorization (CTA) or request for marketing approval (New Drew Application [NDA]/Marketing Authorization Application [MAA]).

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 Pharmaceuticals Inc. 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 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 STATEMENT

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):361-70.
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):175-90.
4. Terranova F, Berardesca E, Maibach H. Cellulite: nature and aetiopathogenesis. *Int J Cosmetic Sci.* 2006;28(3):157-67.
5. Avram MM. Cellulite: a review of its physiology and treatment. *J Cosmet Laser Ther.* 2004;6(4):181-5.
6. Khan MH, Victor F, Rao B, Sadick NS. Treatment of cellulite: Part II. Advances and controversies. *J Am Acad Dermatol* 2010;62(3):373-84.
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):1110-4.
8. Hexsel DM, Mazzuco R. Subcision: a treatment for cellulite. *Int J Dermatol.* 2000;39(7):539-44.
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;22:233-7.
10. DiBernardo BE. Treatment of cellulite using a 1440-nm pulsed laser with one-year follow-up. *Aesthet Surg J.* 2011;31(3):328-41.
11. Investigational Brochure: Collagenase Clostridium Histolyticum for Injection (AA4500/EN3835), Version 7.0. Endo Pharmaceuticals Inc.; May 2016.

[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. PATIENT-REPORTED PHOTONUMERIC CELLULITE SEVERITY SCALE (PR-PCSS) FOR THE BUTTOCK

APPENDIX C. CLINICIAN-REPORTED PHOTONUMERIC CELLULITE SEVERITY SCALE (CR-PCSS) FOR THE BUTTOCK

APPENDIX D. PATIENT REPORTED CELLULITE IMPACT SCALE (PR-CIS)

Please select the rating that best represents your answer on a scale of 0 to 10 with 0 representing "Not at all" and 10 representing "Extremely" while viewing digital images of your buttocks. Please answer each question.

1. Thinking about the areas selected for treatment, how happy are you with the appearance of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

2. Thinking about the areas selected for treatment, how bothered are you by the appearance of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

3. Thinking about the areas selected for treatment, how self-conscious are you about the appearance of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

4. Thinking about the areas selected for treatment, how embarrassed are you about the appearance of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

5. Thinking about the areas selected for treatment, how much older do you look because of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

6. Thinking about the areas selected for treatment, how overweight or out of shape do you look because of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

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

EN3835

EN3835-303

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF EN3835 IN THE TREATMENT OF EDEMATOUS FIBROSCLEROTIC PANNICULOPATHY

IND 110077

Date:

September 27, 2017

Auxilium Pharmaceuticals, Inc. (Auxilium) was acquired by Endo International plc. in January 2015. The sponsor of the application remains as Auxilium Pharmaceuticals, LLC, 1400 Atwater Drive, Malvern, PA; however, Endo Pharmaceuticals Inc. is authorized to act and to communicate on behalf of Auxilium.

Confidentiality Statement

2. SUMMARY OF CHANGES

Not applicable.

[redacted]

3. SPONSOR CONTACT INFORMATION

Table 1: Sponsor Contact Information

Role in Study	Name	Telephone and Email Address
Clinical Development Lead	[redacted]	[redacted]
Clinical Operations Lead	[redacted]	[redacted]
Medical Monitor	[redacted]	[redacted]
SAE Reporting Pathway	Not Applicable	[redacted]

A list of other key study personnel and vendors will be provided 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 3, Randomized, Double-Blind, Placebo-Controlled Study of EN3835 in the Treatment of Edematous Fibrosclerotic Panniculopathy

Lead Principal Investigator:

Study Period:		**Phase of Development**: 3
Estimated date first subject enrolled:	Jan-2018	
Estimated date last subject completed:	Sep-2018	

Objectives:

To assess the efficacy and safety of EN3835 in the treatment of edematous fibrosclerotic panniculopathy (EFP), commonly known as cellulite, in adult women

Study Design: This study is a Phase 3 randomized, double-blind, placebo-controlled study of the efficacy and safety of EN3835 in the treatment of EFP in adult women. Subjects will be screened for study eligibility within 14 days prior to enrolling in this study. Subjects with 2 treatment areas (bilateral buttocks) (also referred to as quadrants) with moderate or severe levels of cellulite as independently assessed by the subject using the Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) and by the Investigator using the Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) and a Hexsel Cellulite Severity Scale no greater than 13 will be eligible. The eligibility of the buttocks will be confirmed on Day 1.

Once the eligibility of the buttocks is confirmed, subjects will be randomly assigned to a treatment group (EN3835 0.84 mg per buttock or placebo) in a 1:1 ratio within an investigational site. Each subject will receive a treatment course which consists of up to 3 treatment visits (sessions), separated by 21 days (ie, Days 1, 22, and 43). Each treatment visit will consist of 12 injections (0.3 mL per injection of EN3835 0.07 mg/injection or placebo; 0.84 mg in 3.6 mL per buttock) in each of the two buttocks for a total volume of 7.2 mL (1.68 mg). Selection of dimples to be treated in the buttocks will be at the discretion of the Investigator. End of study will occur at study day 71.

At each treatment visit, each of the buttocks will be photographed before and after marking dimples and injection sites while the subject is in a consistent, standardized relaxed standing pose. The subject will assess the digital photographic image (pre-marking) of each of the buttocks using the PR-PCSS to determine the severity of EFP in each of the buttocks. In addition, the subject will evaluate each of the buttocks using a Subject Global Aesthetic Improvement Scale (S-GAIS). Subsequently, the Investigator will conduct live assessments of each buttock using the CR-PCSS. The subject assessments will always be completed prior to and independently of the Investigator assessments at each treatment visit. In addition, the Investigator will assess each of the buttocks using an Investigator Global Aesthetic Improvement Scale (I-GAIS). All of the assessments must be done before the dimple marking.

At Day 71 (End of Study/Early Termination), photographs of each of the buttocks will be taken and evaluated by subject using the PR-PCSS. The Investigator will conduct live assessments of each of the buttocks using the CR-PCSS. Global assessment evaluations will be completed by both the subject and the Investigator.

Number of Subjects (Planned): 420

[redacted]

Name of Sponsor/Company: Endo Pharmaceuticals Inc.

Name of Investigational Product: EN3835

Name of Active Ingredient: Collagenase clostridium histolyticum

Study Center(s): Approximately 25 sites in United States

Diagnosis and Inclusion/Exclusion Criteria:

Inclusion Criteria:

1. Voluntarily sign and date an informed consent agreement
2. Be a female ≥18 years of age
3. At Screening visit, have 2 bilateral buttocks with each buttock having:
   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
4. At Day 1 visit, have 2 bilateral buttocks with each buttock having:
   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 buttocks before each exposure to the sun while participating in the study (ie, Screening 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
7. Have a negative serum pregnancy test at Screening and a negative urine pregnancy test before injection of study drug and be using a stable and effective contraception method (eg, abstinence, intrauterine device [IUD], hormonal [estrogen/progestin] contraceptives, or double barrier method) for at least 1 menstrual cycle prior to study enrollment and for the duration of the study; or be menopausal defined as 12 months of amenorrhea in the absence of other biological or physiological causes, as determined by the Investigator; or post-menopausal for at least 1 year; or be surgically sterile
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:

A subject will be excluded from study participation if she:

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

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

2. Has any of the following local conditions in the areas to be treated:
   a. History of lower extremity thrombosis or post-thrombosis syndrome
   b. Vascular disorder (eg, varicose veins, telangiectasia) in area to be treated
   c. Inflammation or active infection
   d. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer
   e. Has a tattoo and/or a mole located within 2 cm of the site of injection
3. Requires the following concomitant medications before or during participation in the trial:
   a. Anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication (except for ≤150 mg aspirin daily) within 7 days before injection of study drug
4. Has used any of the following for the treatment of EFP on a buttock within the timelines identified below or intends to use any of the following at any time during the course of the study:
   a. Liposuction in a buttock during the 12-month period before injection of study drug
   b. Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; buttock implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision) within a buttock during the 12-month period before injection of study drug
   c. Any investigational treatment for EFP on a buttock during the 12-month period before injection of study drug
   d. Endermologie™ or similar treatments within a buttock during the 6-month period before injection of study drug
   e. Massage therapy within a buttock during the 3-month period before injection of study drug
   f. Creams (eg, Celluvera™, TriLastin®) and/or home therapies to prevent or mitigate EFP within a buttock during the 2-week period before injection of study drug
5. Is presently nursing or providing breast milk
6. Intends to become pregnant during the study
7. Intends to initiate an intensive sport or exercise program during the study
8. Intends to initiate a weight reduction program during the study
9. Intends to use tanning spray or tanning booths during the study
10. Has received an investigational drug or treatment within 30 days before injection of study drug
11. Has a known systemic allergy to collagenase or any other excipient of study drug
12. Has received any collagenase treatments at any time prior to treatment
13. Was a subject in a previous cellulite clinical trial of collagenase clostridium histolyticum (CCH): AUX-CC-830, AUX-CC-831, EN3835-102, EN3835-104, EN3835-201, and/or EN3835-202
14. Any other condition(s) that, in the Investigator's opinion, might indicate the subject to be unsuitable for the study

Name of Sponsor/Company: Endo Pharmaceuticals Inc.

Name of Investigational Product: EN3835

Name of Active Ingredient: Collagenase clostridium histolyticum

Investigational Product, Dosage and Mode of Administration: EN3835, 1.68 mg, subcutaneous. A dose of 0.84 mg of EN3835 per buttock will be administered as 12 subcutaneous injections (0.3-mL injection administered as three 0.1-mL aliquots per injection) in each of two buttocks for a total dose of 1.68 mg and a total volume of 7.2 mL (3.6 mL per buttock). Total number of injections will be 24 injections per treatment visit into the two buttocks. There will be 3 treatment visits at 21 days intervals, ie, treatments on Days 1, 22, and 43 will be administered.

Duration of Study: Approximately 84 days (includes screening phase)

Screening Phase: Up to 14 days

Criteria for Evaluation:

Efficacy:

- Subject using PR-PCSS while viewing digital image of the left buttock: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the left buttock
- Subject using PR-PCSS while viewing digital image of the right buttock: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the right buttock
- Investigator using the CR-PCSS by live assessment: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the left buttock
- Investigator using the CR-PCSS by live assessment: 5-level scale ranging from 0 (no cellulite) to 4 (severe cellulite) (Day 1 (Baseline) and Days 22, 43, and 71) for the right buttock
- Investigator Global Aesthetic Improvement Scale (I-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the left buttock
- Investigator Global Aesthetic Improvement Scale (I-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the right buttock
- Subject Global Aesthetic Improvement Scale (S-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the left buttock
- Subject Global Aesthetic Improvement Scale (S-GAIS): 7-level scale ranging from 3 (very much improved) to −3 (very much worse) (Days 22, 43, and 71) for the right buttock
- Subject satisfaction with cellulite treatment assessment: 5-level scale ranging from 2 (very satisfied) to −2 (very dissatisfied) (Day 71) for both left and right buttocks

Safety:

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

- Adverse events (AEs) (including those of special interest (AESI); which are adverse events such as bruising, ecchymosis, hematomas, and contusions that occur remote to the site of drug administration, or any hypersensitivity reactions, including anaphylaxis)
- Vital signs
- Clinical laboratory tests

Name of Sponsor/Company: Endo Pharmaceuticals Inc.

Name of Investigational Product: EN3835

Name of Active Ingredient: Collagenase clostridium histolyticum

- 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 study drug in this study, injection site reactions/local tolerability in the treated buttocks (through subject and Investigator reporting) will be assessed.

Statistical Methods:

The primary endpoint is the proportion of 2-level composite responders at Day 71 defined as subjects with at least one of two treated buttocks with:

- an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator, and
- an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS as assessed by the subject while viewing the digital image of the same buttock.

A subject will be considered a responder if these criteria are met in either the left buttock or right buttock or both buttocks in that subject.

Sample Size Consideration: The results of a prior Phase 2b study of this drug (Study EN3835-201) demonstrated the overall rate for treated buttocks of composite responders with an improvement of at least 2 levels on both the PR-PCSS and the CR-PCSS was 14.9% in the EN3835 treatment group versus 1.1% in the Placebo group. Given this result, the study is planned to randomize 420 subjects with a 1:1 ratio into either the EN3835 arm (0.84 mg/buttock, 1.68 mg total dose) or placebo arm.

The sample size calculation was based on the following assumptions: [redacted]; 3) treatment effect of at least 12% of composite responders with an improvement of at least 2 levels on both the PR-PCSS and the CR-PCSS for at least one treated buttock; 4) Fisher exact test; 5) type I error of 0.05; 6) a power of at least 90%; and 7) dropout rate of approximately 10%.

This sample size will also provide >90% power with type 1 error of 0.025 to detect 1-level responder rate difference for buttocks using the PR-PCSS of 72% in the EN3835 group and 48% in the placebo group as well as 1-level responder rate difference using the S-GAIS of 75% in the EN3835 group and 39% in the placebo group, which were estimated from the EN3835-201 study.

Analysis Populations:

- The intent-to-treat (ITT) population: The ITT population is defined as all randomized subjects who have received at least 1 injection of study medication.
- Modified intent-to-treat (mITT) population: The mITT population is defined as all intent-to-treat subjects with a baseline and 1 post-injection evaluation of both the CR-PCSS and PR-PCSS for each buttock.
- Safety population: The Safety population is defined as all subjects who have received at least 1 injection of study medication.
- Per-Protocol population: The Per-Protocol population is defined as those mITT subjects who do not have any major protocol deviations.

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Analyses:

Analyses of Primary Endpoint:

The primary endpoint is the proportion of 2-level composite responders at Day 71 defined as subjects with at least one of two treated buttocks with:

- an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator, and
- an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS as assessed by the subject while viewing the digital image of the same buttock.

A subject will be considered a responder if these criteria are met in the left buttock or right buttock or both buttocks in that subject.

The primary endpoint will be summarized as percentages and analyzed using a Cochran-Mantel-Haenszel test that compares the 2 treatment groups and adjusts for Investigator at a level of significance of 0.05. The ITT population will be evaluated for the primary endpoint with any subject not having an evaluation of CR-PCSS and/or PR-PCSS at Day 71 classified as a non-responder.

Sensitivity analyses for the primary endpoint will include:

- ITT subjects with missing data handled by multiple imputation (MI) approach
- ITT subjects with missing data handled by a last observation carried forward (LOCF) approach
- mITT subjects with missing data handled by an LOCF approach
- Observed data only (no missing data imputed)
- Per-protocol (PP) subjects with missing data handled by an LOCF approach if 10% or more subjects are excluded in the PP population from mITT population.

Analyses of Key Secondary Endpoints:

There will be 4 key secondary endpoints grouped as two families of 2 endpoints per family analyzed in a hierarchical order.

- Family #1 – two endpoints:
  - Proportion of 1-level PR-PCSS responders defined as subjects with ≥1-level improvement in PR-PCSS severity rating of left buttock at Day 71 compared to Day 1
  - Proportion of 1-level PR-PCSS responders defined as subjects with ≥1-level improvement in PR-PCSS severity rating of right buttock at Day 71 compared to Day 1
- Family #2 – two endpoints:
  - Proportion of 1-level S-GAIS responders defined as subjects with ≥1-level improvement (improved, much improved or very much improved) in the S-GAIS assessment of left buttock at Day 71
  - Proportion of 1-level S-GAIS responders defined as subjects with ≥1-level improvement (improved, much improved or very much improved) in the S-GAIS assessment of right buttock at Day 71

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The key secondary efficacy analyses will be analyzed in the same manner as the primary endpoint based on the ITT population. The family #1 key secondary efficacy analyses will be performed only if the primary efficacy analysis is significant at a significance level of $p \leq 0.05$ (gatekeeping strategy). Similarly, family #2 key secondary efficacy analyses will be performed only if at least one of the key secondary efficacy endpoints of family #1 is significant at a significance level of $p \leq 0.025$ (parallel gatekeeping strategy). Within a family of key secondary efficacy endpoints, Bonferroni method will be performed to relocate unused alpha for testing each endpoint to assure an overall error rate of $p \leq 0.05$. The details of the testing procedures will be provided in the statistical analysis plan for the study.

Supportive Endpoints:

The supportive variables will evaluate assessments at various study time points and using various populations.

- Proportion of 2-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS) of the left buttock (Days 22, 43, and 71)
- Proportion of 2-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS) of the right buttock (Days 22, 43, and 71)
- Proportion of 1-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS) of the left buttock (Days 22, 43, and 71)
- Proportion of 1-level PR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS) of the right buttock (Days 22, 43, and 71)
- Proportion of 2-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject.
- Proportion of 1-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject.
- Proportion of 2-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks.
- Proportion of 1-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks.
- Proportion of 2-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS) of the left buttock (Days 22, 43, and 71)
- Proportion of 2-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS) of the right buttock (Days 22, 43, and 71)

[redacted]

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• Proportion of 1-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS) of the left buttock (Days 22, 43, and 71) • Proportion of 1-level CR-PCSS responders (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS) of the right buttock (Days 22, 43, and 71) • Proportion of 2-level CR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject • Proportion of 1-level CR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject • Proportion of 2-level CR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks • Proportion of 1-level CR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks • Proportion of 1-level composite responders of the left buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the left buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same left buttock) (Days 22, 43, and 71) • Proportion of 1-level composite responders of the right buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the right buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same right buttock) (Days 22, 43, and 71) • Proportion of 1-level composite responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject. • Proportion of 1-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks. • Proportion of 2-level composite responders of the left buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the left buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same left buttock) (Days 22, 43, and 71)

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- Proportion of 2-level composite responders of the right buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the right buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same right buttock) (Days 22, 43, and 71)
- Proportion of 2-level composite responders of at least one of two buttocks (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject.
- Proportion of 2-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks.
- Proportion of subjects at each level of the S-GAIS of the left buttock (Days 22, 43, and 71)
- Proportion of subjects at each level of the S-GAIS of the right buttock (Days 22, 43, and 71)
- Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S- GAIS of the left buttock (Days 22, 43, and 71)
- Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S- GAIS of the right buttock (Days 22, 43, and 71)
- Proportion 1-level S-GAIS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject.
- Proportion of 1-level S-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks.
- Proportion of subjects at each level of the I-GAIS of the left buttock (Days 22, 43, and 71)
- Proportion of subjects at each level of the I-GAIS of the right buttock (Days 22, 43, and 71)
- Proportion of 1-level I-GAIS responders (defined as subjects with a response of at least 1 (improved) in the Investigator GAIS assessment) of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject.
- Proportion of 1-level I-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks.
- Proportion of subjects at each level of the subject satisfaction with cellulite treatment (Day 71)
- Proportion of satisfied responders (defined as subjects with a response of at least 1 (ie, 1-Satisfied or 2-Very Satisfied) in the subject satisfaction with cellulite treatment assessment (Day 71)

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All supportive endpoints will be summarized as percentages. The dichotomous secondary endpoints (ie, responder endpoints) will be analyzed using a Cochran-Mantel-Haenszel test adjusted for Investigator. Changes in the PR-PCSS ratings and CR-PCSS ratings from baselines, S-GAIS scores, and I-GAIS scores will be analyzed using the Mann-Whitney test. 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. Fisher exact test will be used to compare EN3835 to placebo. Descriptive statistics will be presented for actual and change from baseline at each visit for vital signs and for each clinical laboratory test parameter. The comparison between treatment groups will be based on the change from baseline for clinical laboratory tests and vital signs using an analysis of variance (ANOVA) with a factor of drug (EN3835 or placebo). Immunogenicity: Anti-AUX-I and anti-AUX-II antibody levels will be summarized using descriptive statistics for the actual value at the visit. Samples from Day 1, Day 22, Day 43, and Day 71 visits will be analyzed for anti-AUX-I and anti-AUX-II antibodies and a subset of Day 1 and Day 71 samples will be analyzed for neutralizing antibodies.

5. SCHEDULE OF EVENTS

Procedures	Day -14 to -1 Screening	Day 1 Treatment Visit 1	Day 22 (± 3 d) Treatment Visit 2	Day 43 (± 3 d) Treatment Visit 3	Day 71 (+ 5 d) / End of Study / Early Termination	Unscheduled Clinic Visit[a]
Informed consent	X					
Inclusion/exclusion	X					
Digital photography	X	X[b]	X[b]	X[b]	X	X
Medical history/EFP history including previous treatments	X					
Prior/concomitant medications/procedures	X	X	X	X	X	X
Physical examination:	X				X	
• Body weight	X		X[c]	X[c]	X	X
• Height	X					
• Fitzpatrick skin type	X					
Vital signs	X	X[d]	X[d]	X[d]	X	X
12-lead ECG	X					
Collection of samples:						
• Clinical laboratory	X				X	X
• Anti-AUX-I/anti-AUX-II antibody level		X[c]	X[c]	X[c]	X	
• Pregnancy testing	X[e]	X[c,e]	X[c,e]	X[c,e]	X[e]	X
Subject cellulite assessments[f]:						
• Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS)	X[g,h]	X[c,g,h]	X[c,g,h]	X[c,g,h]	X[g,h]	
• Subject Global Aesthetic Improvement (S-GAIS)			X[c,g,h]	X[c,g,h]	X[g,h]	
• Subject Satisfaction With Cellulite Treatment Assessment					X[g]	

Procedures	Day -14 to -1 Screening	Day 1 Treatment Visit 1	Day 22 (± 3 d) Treatment Visit 2	Day 43 (± 3 d) Treatment Visit 3	Day 71 (+ 5 d) / End of Study / Early Termination	Unscheduled Clinic Visit[a]
Investigator cellulite assessments:						
• Selection of dimples to be treated within the two buttocks		X[c]	X[c]	X[c]		
• Marking the dimples and injection sites to be treated within the buttocks		X[c]	X[c]	X[c]		
• Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)	X	X[c,h]	X[c,h]	X[c,h]	X[h]	
• Hexsel Cellulite Severity Scale (CSS)	X[h,i]	X[c,h,i]				
• Investigator Global Aesthetic Improvement (I-GAIS)			X[c,h]	X[c,h]	X[c,h]	
Confirm eligibility		X[c]				
Randomize to treatment		X[c,j]				
Study drug administration		X	X	X		
Injection site reactions/local tolerability in the buttocks		X	X	X	X	X
Adverse events	Monitored Throughout Study					

[a] During unscheduled visits, the Investigator or designee may perform any study procedure that they deem clinically necessary (eg, vital signs, clinical lab assessments, and pregnancy test).
[b] Before and after marking the dimples and injection sites.
[c] Before injection.
[d] Up to 4 hours before injection; approximately 15 and 30 minutes after injection. Vital signs must be stable before the subject is discharged.
[e] Serum pregnancy test on Screening visit and Day 71/EOS visit; urine pregnancy test on Day 1, Day 22, and Day 43 visits.
[f] Subject assessments should be completed independently and prior to Investigator assessments at each visit.
[g] Assessment made via photographs (if treatment visit, use photographs taken before marking dimples and injection sites).
[h] Assessment of each of the 2 buttocks independently.
[i] Initial Hexsel CSS at Screening must be ≤13 on each of 2 bilateral buttocks and the buttocks must again be ≤13 at Day 1 visit
[j] Before randomization, each of the subject's buttocks must have ratings of 3 or 4 (moderate or severe) in both the CR-PCSS and PR-PCSS, and Hexsel CSS score ≤13.
NOTE: Subject cellulite assessments must be completed before the Investigator cellulite assessments are conducted at each visit.
d=Days; ECG=Electrocardiogram; EFP=Edematous fibrosclerotic panniculopathy; EOS=End of study

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7. LIST OF ABBREVIATIONS

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

Table 2: Abbreviations and Special Terms

Abbreviation	Definition
AE	Adverse event
AUX-I	Clostridial class I collagenase
AUX-II	Clostridial class II collagenase
BMI	Body mass index
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
ePRO	Electronic patient reported outcome
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HREC	Human Research Ethics Committee
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
I-GAIS	Investigator-Global Aesthetic Improvement Scale
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive web response system
LOCF	Last observation carried forward
mITT	Modified intent-to-treat
PR-PCSS	Patient Reported Photonumeric Cellulite Severity Scale
Quadrant	A quadrant is a treatment area
Qualified designee	Qualified by education and training to perform the study procedure (eg, sub-Investigator, nurse).
SAE	Serious adverse event
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. Background

8.1.1. 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 a contour abnormality of the skin.(1) The condition manifests as dimpled skin, particularly in the gluteal-femoral region.(2,3) EFP is caused by herniation of subcutaneous fat lobules through the dermohypodermal junction and/or shortening of the collagen septa that cross the hypodermal layer and connects the dermis to the underlying fascia. This creates an uneven surface with dimpling.(1,2) 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.

8.1.2. Current EFP Treatments

There are therapies that have been utilized in an attempt to treat cellulite; however, there are no approved pharmacologic treatments. 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,(6) topical agents,(5) massage,(7) liposuction,(5,6) mesotherapy,(6) radiofrequency,(6) subcision and powered subcision,(8) and laser therapies;(9,10) some of these treatments may pose an increased risk for adverse effects.(5)

There remains an unmet medical need for safe and effective therapies to improve the aesthetic 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 that is bothersome to many women.

8.1.3. 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 (brand name is XIAFLEX®) 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° at the start of therapy.

A recent Phase 2b, randomized, double-blind, placebo-controlled study (EN3835-201) of 375 women randomized to treatment of one treatment area (quadrant) (quadrant was defined in study EN3835-201 as a left buttock, a right buttock, a left posterolateral thigh or a right posterolateral thigh) of cellulite with EN3835 0.84 mg or placebo in a 1:1 ratio assessed the effectiveness and safety of EN3835. Efficacy in this study was evaluated based on cellulite assessments using Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS), Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS), Investigator Global Aesthetic Improvement Scale (GAIS-I), Subject Global Aesthetic Improvement Scale (GAIS-S), and Subject Satisfaction with Cellulite Treatment.

Results from the Phase 2b study demonstrated that treatment (3 visits approximately 21 days apart) improved the cellulite severity of the treatment area as assessed by the primary endpoint of 2-level composite responder analyses, the proportion of responders based on an improvement of ≥2 levels in the appearance of cellulite in both the patient PR-PCSS and the clinician CR-PCSS of buttocks and thighs was statistically significantly greater in subjects who received EN3835 0.84 mg (10.6%; $p<0.001$) compared to subjects who received placebo (1.6%); 1-level (or greater) responders in the PR-PCSS of EN3835-treated subjects (72.3%) was significantly

greater than 1-level responders in the placebo group (51.6%) ($p<0.001$); statistically significant ($p\leq0.001$) improvement in the appearance of cellulite based on the subject S-GAIS were observed in EN3835 0.84-mg group (73.1%) compared to the placebo group (44.0%); and 62.9% of subjects in the EN3835 0.84 mg group were satisfied or very satisfied with the results of their cellulite treatment compared with only 35.9% of subjects in the placebo group ($p<0.001$). In subjects treated in buttocks (n=187), the proportion of 2-level composite responders was statistically significantly greater in subjects who received EN3835 0.84 mg (14.9%; $p<0.001$) compared to subjects who received placebo (1.1%); 1-level (or greater) responders in the PR-PCSS of EN3835-treated subjects (72.7%) was significantly greater than 1-level responders in the placebo group (47.8%) ($p<0.001$).

The study also demonstrated EN3835 to be well tolerated with no serious adverse events (SAEs) related to EN3835. Safety results from a total of 4 studies (1 pilot, 2 Phase 1, and 2 Phase 2 studies) in which 435 adult females received subcutaneous injections of EN3835 indicate that the majority of treatment-emergent adverse events (TEAEs) are transient, non-serious, mild or moderate in intensity, and related to the local administration of EN3835. The immunogenicity profile after 3 treatment visits of EN3835 indicate that greater than 90% of EN3835-treated subjects were seropositive for AUX-I and/or AUX-II antibodies; this profile of EN3835 is similar to that observed in the Dupuytren's contracture and Peyronie's disease programs.

A Phase 1, open-label safety and pharmacokinetic study of a single dose of EN3835 0.84 mg in 11 female subjects with EFP showed that there was no quantifiable levels of AUX-I or AUX-II at any time point after subcutaneous injection of EN3835 0.84 mg into one quadrant. A second Phase 1, open-label safety and pharmacokinetic study of a single dose of EN3835 0.84 mg per treatment area in two treatment areas (buttock-buttock, thigh-thigh, or buttock-thigh) concurrently (total dose of 1.68 mg) showed that there was no quantifiable levels of AUX-I or AUX-II at any time point post-dose attributable to the injection of EN3835 1.68 mg.

The results from these studies suggest that subcutaneous injections of EN3835 in the area of cellulite may be a well-tolerated and effective medical treatment for adults with EFP.

8.2. Summary of Nonclinical Studies

Non-clinical studies necessary to support clinical studies have been performed and are summarized in the Investigator Brochure (IB).(11) Non-clinical studies in the following areas were performed: toxicology, reprotoxicity, genotoxicity, and hypersensitivity.

8.3. Summary of Known Risks and Benefits

A summary of safety risks is provided in the IB.(11) The following events have been commonly observed: local injection site reactions (injection site bruising, injection site swelling, injection site pain) for the various approved indications as well as those being investigated. In the phase 2b study of EN3835 in women with EFP, the following treatment related adverse events ≥2% of 189 EN3835-treated women were reported: injection site bruising (75.1%), injection site pain (59.3%), injection site nodule (14.3%), injection site pruritus (11.1%), injection site swelling (7.4%), injection site induration (5.8%), injection site mass (5.3%), injection site discolouration (3.2%), and injection site erythema (2.1%). These events are similar to events reported in the clinical trials of EN3835 for the approved indications. Postmarketing safety data are consistent with safety data reported in clinical trials.

Although a thorough benefit of EN3835 has not been fully evaluated in the treatment of EFP, the efficacy results from the Phase 2b study and previous EFP studies warranted further development.

8.4. Rationale

The results from the Phase 2b EFP study (EN3835-201) further suggested that EN3835 0.84 mg per treatment area (quadrant) is an effective treatment of EFP based on improvement in the severity of cellulite as determined by the Investigator and the subject. There were no safety concerns following 0.84 mg per treatment area in the treatment of EFP (section 8.1.3). Safety findings from the Phase 2b EFP study are similar to that observed in previous clinical studies with EN3835 in the treatment of EFP and XIAFLEX in the treatment of Dupuytren's contracture and Peyronie's disease, in that that the majority of AEs occurred at the site of injection and resolved before the next scheduled treatment. The immunogenicity profile of EN3835 in the Phase 2b EFP study is similar in previous studies and programs.

Based on the efficacy and safety findings from the Phase 2a and 2b EFP studies, the EN3835 0.84-mg dose per treatment area in two treatment areas (buttocks) warranted further investigation in this study.

Treating two buttocks at each treatment visit will potentially provide a symmetrical-like improvement in appearance. Support for evaluation of the treatment of two buttocks concurrently is based on: 1) the safety findings from the previous EFP studies are local to the injection site, 2) the pharmacological activity of EN3835 is local and does not require systemic exposure, and 3) no significant quantifiable systemic concentration has been attributable to injection of two buttocks concurrently.

The integration of dose and use justification supports this study of evaluation of EN3835 0.84 mg per treatment area in two treatment areas (buttocks) concurrently.

9. OBJECTIVES

9.1. Primary Objective

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

9.2. Secondary Objectives

There are no secondary objectives of this study.

9.3. Exploratory Objectives

There are no exploratory objectives of this study.

10. INVESTIGATIONAL PLAN

10.1. Study Design

This study will be performed at approximately 25 study centers located in the United States. This clinical study will be conducted as a multicenter, randomized, double-blind, placebo-controlled study comparing EN3835 to placebo in adult women with EFP. The study will consist of 71 days of double-blind treatment. Subjects meeting the entry criteria for this study will be randomized to EN3835 treatment or placebo treatment in a 1:1 ratio within an investigational site.

The complete Schedule of Events is provided in section 5.

Figure 1: Study Design

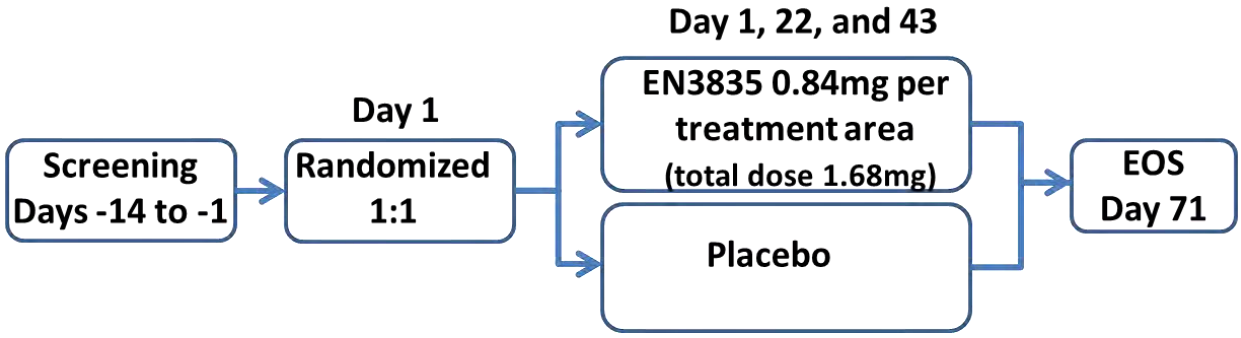


Table 3: Study Treatment Groups

Dose per Each Injection[a] / Number of Subjects	Injection Volume per Each Injection	Number of Injections at Each Treatment Visit	Dose (mg) at Each Treatment Visit	Injection Volume (mL) per Each Treatment Visit	Cumulative EFP Dose
EN3835 0.07 mg / N=210	0.3 mL	12 per buttock × 2 buttocks = 24 injections	0.84 mg per buttock × 2 buttocks = 1.68 mg (12 injections per buttock × 0.07 mg/injection × 2 buttocks)	3.6 mL per buttock × 2 buttocks = 7.2 mL (24 injections × 0.3 mL)	5.04 mg (3 treatment visits × 0.84 mg per buttock × 2 buttocks)
Placebo / N=210	0.3 mL	12 per buttock × 2 buttocks = 24 injections	-	3.6 mL per buttock × 2 buttocks = 7.2 mL (24 injections × 0.3 mL)	-

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

10.2. Selection of Doses

The dose of EN3835 chosen for this study was based on the results from earlier studies.

The data from the Phase 2a EFP dose-ranging study (AUX-CC-831) suggest that EN3835 0.84 mg is most effective in the treatment of EFP based on improvement in the severity of

cellulite as determined by both the Investigator and the subject, although the EN3835 0.48-mg group did show improvement in some of the efficacy parameters.

- There were no safety concerns following administration of up to 3 treatment visits of EN3835 0.84 mg in the treatment of EFP (AUX-CC-831 CSR). The safety profile of EN3835 0.84 mg in the treatment of EFP was similar to that observed in the EN3835 0.06-mg group and the EN3835 0.48-mg group. No notable differences were observed across the 3 treatment groups.
- Safety findings from the Phase 2a EFP dose-ranging study are similar to that observed in previous clinical studies with XIAFLEX in the treatment of Dupuytren's contracture and Peyronie's disease, in that the majority of AEs occurred at the site of injection and resolved before the next scheduled treatment.
- The immunogenicity profile of EN3835 in the Phase 2a EFP dose-ranging study is similar to that observed in the Dupuytren's contracture and Peyronie's disease programs.
- Based on the efficacy and safety findings from the Phase 2a EFP dose-ranging study, the EN3835 0.84-mg dose was carried forward to the Phase 2b study.

The results from the Phase 2b EFP study (EN3835-201) further suggested that EN3835 0.84 mg is an effective treatment of EFP based on improvement in the severity of cellulite as determined by the Investigator and the subject. There were no safety concerns following EN3835 0.84 mg in the treatment of EFP (section 8.4). Safety findings from the Phase 2b EFP study are similar to that observed in previous clinical studies with XIAFLEX in the treatment of Dupuytren's contracture and Peyronie's disease, in that that the majority of AEs occurred at the site of injection and resolved before the next scheduled treatment. The immunogenicity profile of EN3835 in the Phase 2b EFP study is similar to that observed in the Dupuytren's contracture and Peyronie's disease programs.

Based on the efficacy and safety findings from the Phase 2a and 2b EFP studies, the EN3835 0.84-mg dose per treatment area was carried forward to this study. The findings from previous studies that the majority of adverse events after EN3835 treatment are local to the injection site and that there is no quantifiable systemic exposure observed after concurrent treatment of two buttocks (total dose of 1.68 mg) supports the proposed study to evaluate EN3835 treatment of two buttocks.

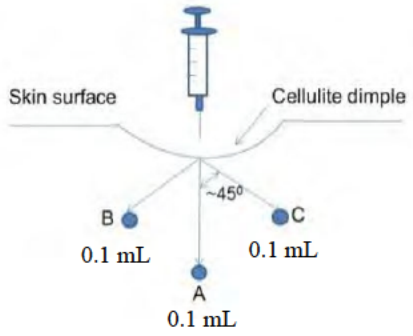
10.3. Study Drug Administration

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 visit, 8 syringes (4 syringes per buttock) will be prepared for dosing. Each syringe will contain 0.9 mL of study drug (ie, 3 injections in each syringe). Twelve (12) skin

injections of 0.3 mL per injection will be administered within each of the two buttocks during each treatment visit.

Figure 2: Study Drug Administration at Each Injection Site



- **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 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 each buttock (three 0.3-mL injections per syringe, each injection administered as three 0.1-mL aliquots). Twelve (12) skin injections of 0.3 mL will be administered within each of the two treated buttocks during each treatment visit.
- The plane containing injection deposition points A, B, and C should be perpendicular to the skin and perpendicular to the long axis of a dimple if the dimple is an elongated trough-like dimple.
- 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 Visits 1, 2, and 3.

NOTE: EN3835 is a foreign protein and Investigators should 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 must be available with the Investigator and site staff must be familiar with their use.

10.4. 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 injections 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 14.9).

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

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

The design of this study was based on the primary objective to evaluate the efficacy and safety of EN3835 0.84 mg per buttock in the concurrent treatment (total dose of 1.68 mg) of 2 bilateral buttocks with EFP in adult women compared with placebo treatment. The study design, a multi-center, double-blind, placebo-controlled study is in accordance with regulatory guidelines of adequate and well-controlled clinical studies (Food and Drug Administration [FDA] Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, 1998.; ICH E8 and E10).

11. SELECTION AND WITHDRAWAL OF SUBJECTS

11.1. Subject Inclusion Criteria

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

1. Voluntarily sign and date an informed consent agreement
2. Be a female ≥18 years of age
3. At Screening visit, have 2 bilateral buttocks with each buttock having:
   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
4. At Day 1 visit, have 2 bilateral buttocks with each buttock having:
   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 buttocks before each exposure to the sun while participating in the study (ie, Screening 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
7. Have a negative serum pregnancy test at Screening and a negative urine pregnancy test before injection of study drug and be using a stable and effective contraception method (eg, abstinence, intrauterine device [IUD], hormonal [estrogen/progestin] contraceptives, or double barrier method) for at least 1 menstrual cycle prior to study enrollment and for the duration of the study; or be menopausal defined as 12 months of amenorrhea in the absence of other biological or physiological causes, as determined by the Investigator; or post-menopausal for at least 1 year; or be surgically sterile
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. Subject Exclusion Criteria

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

1. Has any of the following systemic conditions:
   a. Coagulation disorder
   b. Evidence or history of malignancy (other than excised basal-cell carcinoma) unless there has been no recurrence in at least 5 years
   c. History of keloidal scarring or abnormal wound healing

   d. Concurrent diseases or conditions that might interfere with the conduct of the study, confound the interpretation of the study results, or endanger the subject's well-being. Any questions about concurrent diseases should be discussed with the Medical Monitor
   e. Evidence of clinically significant abnormalities on physical examination, vital signs, electrocardiogram (ECG), or clinical laboratory values

2. Has any of the following local conditions in the areas to be treated:
   a. History of lower extremity thrombosis or post-thrombosis syndrome
   b. Vascular disorder (eg, varicose veins, telangiectasia) in area to be treated
   c. Inflammation or active infection
   d. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer
   e. Has a tattoo and/or a mole located within 2 cm of the site of injection
3. Requires the following concomitant medications before or during participation in the trial:
   a. Anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication (except for ≤150 mg aspirin daily) within 7 days before injection of study drug
4. Has used any of the following for the treatment of EFP on a buttock within the timelines identified below or intends to use any of the following at any time during the course of the study:
   a. Liposuction in a buttock during the 12-month period before injection of study drug
   b. Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; buttock implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision) within a buttock during the 12-month period before injection of study drug
   c. Any investigational treatment for EFP on a buttock during the 12-month period before the injection of study drug
   d. Endermologie or similar treatments within a buttock during the 6-month period before injection of study drug
   e. Massage therapy within a buttock during the 3-month period before injection of study drug
   f. Creams (eg, Celluvera™, TriLastin®) and/or home therapies to prevent or mitigate EFP within a buttock during the 2-week period before injection of study drug
5. Is presently nursing or providing breast milk
6. Intends to become pregnant during the study
7. Intends to initiate an intensive sport or exercise program during the study
8. Intends to initiate a weight reduction program during the study
9. Intends to use tanning spray or tanning booths during the study

10. Has received an investigational drug or treatment within 30 days before injection of study drug
11. Has a known systemic allergy to collagenase or any other excipient of study drug
12. Has received any collagenase treatments at any time prior to treatment
13. Was a subject in a previous cellulite clinical trial of CCH: AUX-CC-830, AUX-CC-831, EN3835-102, EN3835-104, EN3835-201, and/or EN3835-202
14. Any other condition(s) that, in the Investigator's opinion, might indicate the subject to be unsuitable for the study

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
- Lack of efficacy
- 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 including safety and efficacy assessments should be conducted as detailed in the Schedule of Events (section 5). 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 and assessments are required (but are encouraged to reduce missing information) except the collection of adverse event (AE) information. This information should be recorded in the source documentation and the eCRF.

11.3.1. Replacement Procedures

Subjects who discontinue from the study will not be replaced.

12. TREATMENT OF SUBJECTS

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. Informed Consent

Signed and dated informed consent will be obtained from each subject before any study procedures are undertaken, or before any changes to the subject's medication regimen are made. Details about how the informed consent will be obtained and documented are provided in section 21.3, Subject Information and Consent.

12.1.2. Subject Screening

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. The screening log will be captured directly by the electronic data capture (EDC) system.

12.1.2.1. Medical History

During the screening period, the Investigator or qualified designee will obtain a medical history from each subject that includes relevant diagnoses and/or procedures/therapies with onset/resolutions dates. Medical histories should also include history of EFP (start date and family history), and history of tobacco and alcohol use (never, current, former).

12.1.2.2. Screening Period (Day -14 to Day -1)

Subjects meeting the relevant eligibility criteria listed in section 11 may be enrolled in the study after the nature and purpose of the protocol have been explained and written informed consent to participate has been voluntarily provided by the subject or their legally authorized representative.

The subject identification number will consist of 8 digits. The first 4 digits represent the study site number followed by a 4-digit subject number.

The following procedures will be performed and documented during the screening period:

1. Obtain written informed consent (section 12.1.1)
2. Evaluate eligibility based on inclusion/exclusion criteria (section 11.1 and section 11.2)
3. Subject will have digital photographs taken of her two buttocks (section 13.1.1)
4. Subjects will get instruction on the use of the PR-PCSS (section 13.1.2.1)

5. Prior to Investigator CR-PCSS or Hexsel CSS assessment, subjects will rate each of their two buttocks using the PR-PCSS while viewing their digital images (section 13.1.2.1); the Investigator is blinded to these scores
6. After the subject has completed the PR-PCSS ratings, the Investigator will conduct live assessments of subject's cellulite severity of each of the two buttocks using the CR-PCSS (section 13.1.2.4); the subject is blinded to these ratings
7. After the Investigator has completed the CR-PCSS ratings, the Investigator will conduct live evaluation of each of the two buttocks using the Hexsel CSS; the subject is blinded to these ratings. The ratings from the PR-PCSS, CR-PCSS, and Hexsel CSS (section 13.1.2.6) will be used to assess initial eligibility of the buttocks for study entry
8. Medical history including EFP history (section 12.1.2.1)
9. Record prior and concomitant medications/procedures (section 12.8)
10. Physical examination including measurement of body weight, height, Fitzpatrick skin type (section 14.11)
11. Vital sign measurements (section 14.9)
12. 12-lead ECG (section 14.10)
13. Collection of samples for:
    a. Clinical laboratory testing (section 14.7)
    b. Serum pregnancy testing (section 14.7)
14. Adverse events (section 14)

12.2. Selecting and Marking Dimples during Treatment Visits

Selection of dimples to be treated in the two buttocks is at the discretion of the Investigator. Dimples must be well-defined and evident when the subject is standing in a consistent, standardized relaxed pose (without the use of any manipulation such as skin pinching or muscle contraction). Each subject will receive 3 treatment visits of study drug according to randomization unless the buttock is dimple-free (score of 0 on CR-PCSS as reported by the Investigator) at Treatment Visit 2 and/or Treatment Visit 3 (a dimple -free buttock at Treatment Visit 1 is precluded by the eligibility criteria); a dimple-free buttock at Treatment Visit 2 and/or Treatment Visit 3 does not preclude treatment of the contralateral buttock unless it is dimple-free also. During each treatment visit, each of the buttocks will be photographed before and after marking dimples and injection sites while the subject is standing in a consistent, standardized relaxed pose as described in the Photography Manual. The cellulite severity assessments using the PR-PCSS, CR-PCSS, and Hexsel CSS (note that the Hexsel CSS assessment is performed at Screening visit and Day 1 visit only) will be completed prior to marking dimples and injection sites.

The Investigator or qualified designee will select dimples within each buttock that are well-defined, evident when the subject is standing, and suitable for treatment; treatment consists of 12 injections per buttock (24 injections total in two buttocks) per treatment visit. Because the goal of treatment is to improve the aesthetic appearance of each entire buttock, the Investigator

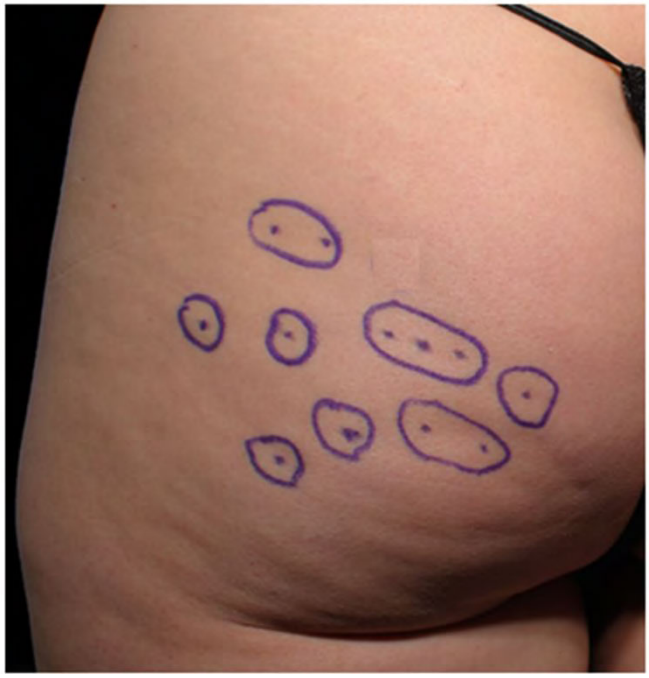
will be instructed to select dimples that in his or her opinion would most improve the aesthetic appearance of each entire buttock. The same dimples within a buttock or different dimples within a buttock may be treated at each treatment visit but injections must all be within the buttocks (12 injections per buttock) for all 3 visits. Each buttock will receive all 3 treatment visits unless the buttock has no treatable EFP dimples and the Investigator rates the buttock a score of 0 on the CR-PCSS. If no injections in a particular buttock (right or left) are given at Treatment Visit 2, subjects will still be assessed for treatment in the contralateral buttock at Treatment Visit 2, and will return for the Day 43 visit and each of the buttocks will again be evaluated by the subject (PR-PCSS) and Investigator (CR-PCSS). If the Investigator rates either or both of the buttocks greater than 0 on the CR-PCSS, injections at Treatment Visit 3 should be given.

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; locating at least one injection site at the nadir, if present, of the dimple). 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 buttock should not overlap.

Each of the buttocks will be photographed before and after marking dimples and injection sites while the subject is standing in a consistent, standardized relaxed pose as described in the Photography Manual.

Examples of subject dimple and injection site markings are shown as follows:

Sample Buttock Marking



12.3. Digital Photography during Treatment Visits 1, 2, and 3

During each treatment visit, each of the two buttocks will be photographed before and after marking dimples and injections sites while the subject is standing in a consistent, standardized relaxed pose as described in section 13.1.1.

12.4. Treatment Visit 1 (Day 1)

12.4.1. Treatment Visit 1: Pre-Injection

1. Confirm eligibility criteria
2. Take digital photography of each of the buttocks before marking dimples and injection sites (section 13.1.1)
3. Subjects will get instruction on the use of the PR-PCSS (Patient Instructions for Use of PR-PCSS)
4. Subjects will rate each of their buttocks using the PR-PCSS (section 13.1.2.1); the Investigator is blinded to these scores
5. The Investigator will conduct live assessments of subject's cellulite severity of each of the buttocks using the CR-PCSS (section 13.1.2.4); the subject is blinded to these ratings
6. The Investigator will conduct live cellulite evaluation of each of the buttocks using the Hexsel CSS. The ratings from the PR-PCSS, CR-PCSS and Hexsel CSS (section 13.1.2.6) will be used to assess eligibility for randomization
7. Subjects with PR-PCSS or CR-PCSS ratings in either of the buttocks <3 or a Hexsel CSS total score in either of the buttocks greater than 13 (section 13.1.2.6) will be excluded from participation
8. Randomization of subjects with two buttocks eligible for treatment (eligible criteria being each buttock have PR-PCSS and CR-PCSS scores of 3 or 4 and a Hexsel CSS total score not greater than 13) to treatment (section 12.10); obtain kit numbers of study treatment
9. Record concomitant medications/procedures (section 12.8)
10. Vital sign measurements (section 14.9)
11. Collection of samples for:
    a. Anti-AUX-I and anti-AUX-II antibody testing (section 14.8)
    b. Urine pregnancy testing (section 14.7)
12. Select and mark dimples to be treated in each of the buttocks (section 12.2)
13. Take digital photograph of each of the buttocks after marking dimples and injection sites (section 13.1.1)

12.4.2. Treatment Visit 1: Injection and Post-injection

1. Administration of study drug in the prone position (section 10.3)

2. Record number of dimples treated and number of injections administered in each of the two buttocks
3. Vital sign measurements (section 14.9)
4. Injection site reactions and local tolerability
5. Adverse events (section 14)

12.5. Treatment Visit 2 (Day 22 [±3 days]) and Treatment Visit 3 (Day 43 [±3 days])

12.5.1. Treatment Visits 2 and 3: Pre-injection

1. Record concomitant medications/procedures (section 12.8)
2. Body weight measurements
3. Vital sign measurements (section 14.9)
4. Collection of samples for:
   a. Anti-AUX-I and anti-AUX-II antibody testing (section 14.8)
   b. Urine pregnancy testing (section 14.7)
5. Digital photographs of each of the two buttocks before marking dimples and injection sites (section 13.1.1)
6. Subject Cellulite Assessments of each of the buttocks using the photographic image of each buttock before marking dimples and injection sites (NOTE: complete subject cellulite assessments before Investigator cellulite assessments) in the following sequential order using:
   a. Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) assessment (section 13.1.2.1); complete this prior to conducting S-GAIS
   b. Subject Global Aesthetic Improvement Scale (S-GAIS) (section 13.1.2.2)
7. Investigator Cellulite Assessments live of each of the buttocks in the following sequential order prior to marking dimples and injection sites using:
   a. Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) live assessment of subject (section 13.1.2.4)
   b. Investigator Global Aesthetic Improvement Scale (I-GAIS) (section 13.1.2.5)
8. Select and mark dimples to be treated in each buttock (section 12.2)
9. Digital photographs of each buttock after marking dimples and injection sites (section 13.1.1)
10. For eligible buttock(s), obtain kit number(s) of study treatment

12.5.2. Treatment Visits 2 and 3: Injection and Post-injection

1. Administration of study drug in the prone position (section 10.3)
2. Record number of dimples treated and number of injections administered in each buttock

3. Vital sign measurements (section 14.9)
4. Injection site reactions and local tolerability
5. Adverse events (section 14)

12.6. Day 71 (+5 days) End of Study / Early Termination

The following procedures will be performed on Day 71:

1. Record concomitant medications/procedures (section 12.8)
2. Measurement of body weight
3. Vital sign measurements (section 14.9)
4. Collection of samples for:
   a. Clinical laboratory testing (section 14.7)
   b. Serum pregnancy test (section 14.7)
   c. Anti-AUX-I and anti-AUX-II antibody testing (section 14.8)
5. Digital photographs of each of the buttocks
6. Subject Cellulite Assessment of each of the two buttocks using the photographic image before marking dimples and injection sites (NOTE: complete subject cellulite assessments before Investigator cellulite assessments) using:
   a. Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) assessment (section 13.1.2.1)
   b. Subject Global Aesthetic Improvement Scale (S-GAIS) (section 13.1.2.2)
   c. Subject Satisfaction with Cellulite Treatment Assessment (section 13.1.2.3); note this assessment is of both left and right buttocks rather than each individual buttock
7. Investigator Cellulite Assessments of each of the buttocks live using:
   a. Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) live assessment of subject (section 13.1.2.4)
   b. Investigator Global Aesthetic Improvement Scale (I-GAIS) (section 13.1.2.5)
8. Injection site reactions and local tolerability
9. Adverse events (section 14)

12.7. Unscheduled Visits

If any subject needs to return to the site prior to her next scheduled visit, site staff should follow the Unscheduled Visit procedures outlined in section 5. Site staff may conduct additional study procedures if required.

12.8. Prior and Concomitant Medications and Procedures

All prior medications taken within 90 days before randomization will be recorded. All medications (including over-the-counter medications) taken by the subject on Day 1 through the

end of the study must be recorded. Any prior treatments (medications or procedures) for EFP through the end of the study must be recorded on the appropriate eCRF page.

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.

12.8.1. Prohibited Medications or Procedures

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

Procedures listed in exclusion criterion #4 (section 11.2, Exclusion Criterion #4) are prohibited for randomized subjects during the study.

Table 4: Concomitant Medication Restrictions for Subjects during the Treatment Phase of Study

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

12.9. Treatment Compliance

Randomized subjects will receive study drug administered by an Investigator at the Investigator's site.

Accidental or intentional overdoses should be reported to the Sponsor/designee promptly (see section 14.6.2.1, Overdose).

12.10. Blinding and Randomization

On Day 1, if each of the buttocks again meet the criteria (3 or 4 on the PR-PCSS and CR-PCSS and no greater than 13 on Hexsel CSS) the subject will be randomized to a treatment group. The interactive web response system (IWRS) will randomly assign each subject to a treatment group (EN3835 0.84 mg per buttock × two buttocks or placebo) in a 1:1 ratio within an investigational site. The treatment group will remain blinded to the Investigator, subjects, all site personnel, and the sponsor. The IWRS will assign the subject study drug kit numbers associated with the randomized treatment. At Day 22 and 43 visits, the IWRS will again assign the subject study drug kit numbers associated with the randomized treatment assigned at Day 1.

All precautions will be taken to ensure that the blinding of EN3835 and placebo is maintained throughout the study period. Unblinding will not be permitted by the study site unless it is deemed necessary for treatment of a medical emergency. Before breaking the blind, the Investigator should make every attempt to contact the Medical Monitor to discuss the necessity of breaking the blind. The study site will have the ability to immediately determine treatment identification in the event of an emergency by using the unblinding function within the IWRS, however, the Medical Monitor must be notified immediately. The Investigator will be required to

make a full written explanation of the reason for unblinding the subject and the date. In the event that a subject is unblinded prior to contacting the Medical Monitor, the Investigator must provide this information in writing to the Medical Monitor as soon as possible. Breaking the blind at the investigative site will immediately disqualify the subject from further participation in the study. In addition, the event(s) leading to emergency unblinding must be reported as an SAE according to instructions in section 14.5.2, Reporting Serious Adverse Events.

In addition, it may be necessary for the Investigator or qualified designee to unblind a subject as a result of a clinically significant finding noted during safety review by the Investigator, Safety Monitor, Medical Monitor and/or qualified designee that might jeopardize subject safety.

13. ASSESSMENT OF EFFICACY

13.1. Efficacy Measurements

13.1.1. Digital Photography

Although digital photographs are not direct efficacy measurements, digital photography will be utilized in the assessment of certain efficacy measurements ie to assess certain cellulite severity parameters at specific intervals (see section 5, Schedule of Events). At the Screening visit, the Investigator or qualified designee will photograph each buttock using a Sponsor-supplied standardized digital camera in a standardized manner. 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 each of the two buttocks while the subject is standing in a consistent, standardized relaxed standing pose, ie, standing position with relaxed gluteus muscles, at the following time points:

- Screening (no markings of dimples or injection site) - each of the two buttocks
- Before and after marking dimples and injection sites (prior to injections) on Days 1, 22, and 43 - each of the two buttocks
- During the Day 71 visit (end of study/early termination) (no dimple or injection site markings) - each of the two buttocks

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.

13.1.2. Subject and Investigator Cellulite Assessments

Investigator cellulite assessments are independent of the subject assessments. Therefore, all subject cellulite assessments must be completed before the Investigator's cellulite assessments are initiated. The subject assessments will be done using a subject-assigned password protected electronic patient reported outcome (ePRO) system and the Investigator and study site personnel will not have access to the subject's assessments or password; the clinician assessment will be recorded in an investigator-assigned password protected system and the subject will not have access to the Investigator's assessments or password. Subject assessments will be done alone with no study site personnel in the room. Investigators will be instructed not to verbalize their ratings while in the presence of the subject.

13.1.2.1. 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. The scale is a 5-level photonumeric scale developed specifically for patients and used by the subject to assess the severity of their cellulite in the buttocks by viewing digital images of each of their buttocks 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.

At Screening and at the beginning of their visits on Day 1, Day 22, Day 43, and Day 71, subjects will have digital photographs taken of each of their two buttocks. Subjects will be given instructions in the proper use (Patient Instructions for Use of PR-PCSS) of the PR-PCSS and then perform the PR-PCSS for each of the buttocks (Appendix B). While viewing the digital images of each of their buttocks on a standardized computer monitor and using PR-PCSS for buttock, subjects will be instructed to answer the following question for each buttock: *Today, how would you rate the severity of your cellulite in the area displayed using the PR-PCSS?* The subject will be given the following explanations*: Please try to match the severity of your cellulite, as seen in this digital image, with one of the cellulite levels on the PR-PCSS. Please look at the image of your cellulite and the pictures, labels, and descriptions on the PR-PCSS carefully before selecting your answer. If you feel that your cellulite level is between 2 of the levels, please select the level that is closest to your image. If you feel that your cellulite is exactly halfway between two PR-PCSS levels of cellulite severity, please select the more severe response.*

The subject will enter their rating electronically into an ePRO system; the Investigator and other site personnel will be blinded to the rating entered by the subject. This variable will 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.

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

Subjects will complete the S-GAIS for each of the buttocks as described below at the Day 22, Day 43, and Day 71 study visits using the pre-treatment Day 1 digital image (Baseline) of each of the buttocks for comparison.

All treated subjects will be instructed to answer the following question for each buttock:

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. The subject will view each of their pre-treatment Day 1 digital images alongside their Day 22, Day 43 or Day 71/End of study visit digital images of each of their buttocks to aid in the assessment (Table 5). Subjects will provide a rating from those below that best represents their answer for each treated buttock.

This variable will 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 5: 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.

Table 5: Subject Global Aesthetic Improvement Scale (S-GAIS) (Continued)

Rating	Response Option	Description
−1	Worse	My treated cellulite looks worse than it did originally.
−2	Much worse	My treated cellulite looks much worse than it did originally.
−3	Very much worse	My treated cellulite looks very much worse than it did originally.

13.1.2.3. Subject Satisfaction with Cellulite Treatment Assessment

At the Day 71 visit, subjects will be instructed to answer a question related to their treated buttocks. Subjects will be given a list of responses and they will provide a rating from those below that best represents their answer (Table 6).

Today, how satisfied are you with the results of the cellulite treatment you received on the specific area or areas on your buttocks that were treated?

Table 6: Subject Satisfaction with Cellulite Treatment Assessment - Buttocks

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

13.1.2.4. 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. The scale is a 5-level photonumeric scale developed specifically for clinicians and used by the Investigator to assess the severity of the subject's cellulite in each buttock by live assessments; the ratings range from 0 (None) to 4 (Severe) with labels and descriptors to aid the Investigator in the assessments.

Investigators will be trained and qualified on the use of the CR-PCSS prior to assessing any subjects.

At the Screening visit, the Investigator will determine severity of cellulite of each of the two buttocks via live assessment of the subject using the CR-PCSS for buttock (Appendix C) after the subject has completed her self-assessment using the PR-PCSS. Before injections on treatment visits Day 1, Day 22, and Day 43, and on visit Day 71; Investigators will evaluate each of the two buttocks by live assessments using the CR-PCSS for the buttock to make his/her evaluation. At each visit, the Investigator will make his/her assessment independently and after the subject has conducted her self-assessment using the PR-PCSS.

This variable will 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.

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

On the Day 22, Day 43, and Day 71 study visits, the Investigator will determine the degree of improvement of each buttock by comparing the cellulite from the Day 1 pre-treatment (Baseline) digital image of each buttock to the cellulite seen in a live assessment (Table 7). The I-GAIS assessment will occur after the CR-PCSS assessment (section 13.1.2.4) to avoid introducing potential bias to the static CR-PCSS assessment by the Investigator. For each buttock, the Investigator will provide the rating from those below that best represents his/her answer.

This variable will 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 7: 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

13.1.2.6. 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 8. The total score is the summation of all 5 features (Appendix D).

The Investigator or qualified designee will independently use the Hexsel CSS to assess the severity of EFP in each of the two buttocks at the Screening visit and each of the two buttocks on Day 1 (Note: In this study, the Hexsel CSS is used exclusively for assessment of subject eligibility; it is not used as an efficacy assessment). 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 will 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: 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.

[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.

Source: Hexsel DM, Dal'Forno T, Hexsel CL. A validated photonumeric cellulite severity scale. *J Eur Acad Dermatol Venereol.* 2009;23(5):523-8.

[redacted]

14. ASSESSMENT OF SAFETY

14.1. Definitions

14.1.1. Adverse Events

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. Adverse events 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 Events

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 malignancy, 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 28 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 28 days after the last dose of study medication. SAEs that occur within 28 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 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.

14.6. Special Reporting Situations

14.6.1. Adverse Events of Special Interest

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

14.6.2.1. Overdose

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 12.9) 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

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

Any 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 28 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.

A subject who becomes pregnant must be withdrawn from the study. 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. AEs/SAEs 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 PVRM Department (when the non-subject agrees) on the departmental form for serious adverse experiences 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, Reporting Serious Adverse Events. Additionally, the drug accountability source documentation at the site should reflect this occurrence.

14.7. Clinical Laboratory 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 or qualified designee must acknowledge the review of laboratory results.

The Investigator will review all abnormal lab results for potentially clinically important. Any abnormal clinical laboratory test result meeting the Investigator's criteria for potentially clinically important (refer to central laboratory manual) 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).

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

Clinical laboratory parameters that will be measured in this study are listed in Table 9.

Table 9: Clinical Laboratory Tests

Hematology	**Biochemistry**	**Urinalysis**
Hemoglobin	Glucose	Glucose
Hematocrit	Sodium	Protein
Red blood cell	Potassium	Specific gravity
White blood cell (WBC)	Calcium	pH
Platelets	Chloride	Ketones
WBC Differential	CO_2	Bilirubin
	Inorganic phosphate	Urobilinogen
	Blood urea nitrogen	Nitrite
	Creatinine	Blood*
	Creatinine clearance (estimated)	Leukocytes*
	Aspartate transaminase (AST)	
	Alanine transaminase (ALT)	
	Gamma-glutamyl transferase (GGT)	
	Total bilirubin (TBL) (direct bilirubin reflex if elevated)	
	Albumin	
	Alkaline phosphatase (ALP)	
	Uric acid	

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

For women of childbearing potential, a serum pregnancy test will be performed at Screening and Day 71/End of Study/Early Termination, and urine pregnancy tests will be performed at Day 1, Day 22, and Day 43 (refer to section 5). Female subjects of childbearing potential must have a negative pregnancy test at the Screening Visit and at Day 1 (Baseline), Day 22, and Day 43 to be randomized and/or 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.

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

Serum samples will be collected and will be tested for binding anti-AUX-I and anti-AUX-II antibody testing before injection on Days 1, 22, and 43, and at the Day 71 visit. A subset [redacted] of subject samples will be tested for neutralizing antibodies from Day 1 and Day 71 visits; additional samples will be retained.

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.

14.9. Vital Signs

Vital sign measurements will be documented as described in the Schedule of Events (section 5). 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.

The Investigator will review all vital sign values for clinical significance prior to discharge. 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 10 after the subject has rested for at least 5 minutes.

Table 10: 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

14.10. Electrocardiogram

A 12-lead ECG recording will be conducted at the Screening Visit. The subject should be in a supine position for at least 5 minutes before the recording is conducted. Lead position will be that of a standard 12-lead ECG; no additional or special lead placements will be necessary.

A qualified physician will interpret, sign, and date the ECGs. ECG findings will be documented as normal; abnormal, clinically significant; or abnormal, not clinically significant. The Investigator or qualified designee must sign and date the ECG, thereby acknowledging review of ECG results. 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).

14.11. Physical Examination

A complete physical examination will be performed at the Screening Visit. All examinations will be performed by a physician or health professional listed on the Form FDA 1572 and licensed to perform physical examinations. Height and body weight will be measured and recorded at screening.

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).

At screening, the Investigator will also assess the subject's skin type using the Fitzpatrick scale (Table 11). Only the Fitzpatrick Scale shown below may be used during the study.

Table 11: Fitzpatrick Scale

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

Follow-up body weight will be measured before injection on Day 22 and Day 43 and at the Day 71 visit.

14.12. 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

The primary variable is the proportion of 2-level composite responders at Day 71 defined as subjects with at least one of two treated buttocks with:

- an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator, and
- an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS as assessed by the subject while viewing the digital image of the same buttock.

A subject will be considered a responder if these criteria are met in either the left buttock or right buttock or both buttocks in that subject. In other words, a subject will be considered a responder if she has an improvement of at least 2 levels on the PR-PCSS and an improvement of at least 2 levels on the CR-PCSS on that same buttock; that buttock could be the left buttock or right buttock or both buttocks.

The results of a prior Phase 2b study of this drug (Study EN3835-201) demonstrated the overall rate for treated buttocks of composite responders with an improvement of at least 2 levels on both the PR-PCSS and the CR-PCSS was 14.9% in the EN3835 treatment group versus 1.1% in the Placebo group. Given this result, the study is planned to randomize 420 subjects with a 1:1 ratio into either the EN3835 arm (0.84 mg/buttock, 1.68 mg total dose) or placebo arm.

The sample size calculation was based on the following assumptions: [redacted] 3) treatment effect of at least 12% of composite responders with an improvement of at least 2 levels on both the PR-PCSS and the CR-PCSS for at least one treated buttock; 4) Fisher exact test; 5) type I error of 0.05; 6) an power of at least 90%; and 7) dropout rate of approximate 10%.

This sample size will also provide >90% power with type 1 error of 0.025 to detect 1-level responder rate difference for buttocks using the PR-PCSS of 72% in the EN3835 group and 48% in the placebo group as well as 1-level responder rate difference using the S-GAIS of 75% in the EN3835 group and 39% in the placebo group, which were estimated from the EN3835-201 study.

17.2. Subject Populations

Four (4) populations are considered in the statistical analysis of the study: safety, intent-to-treat (ITT), modified ITT (mITT), and per-protocol (PP).

17.2.1. Safety Population

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

17.2.2. Intent-to-Treat (ITT) Population

The ITT population is defined as all randomized subjects who have received at least one injection of study medication. All demographic and baseline characteristic summaries will be based on this population. The primary and key secondary efficacy parameters will be summarized based on this population.

17.2.3. Modified Intent-to-Treat (mITT) Population

The mITT population is defined as all intent-to-treat subjects with a baseline and at least 1 post-injection evaluation of both the Investigator CR-PCSS and subject PR-PCSS for both left and right buttocks. All secondary and supportive efficacy evaluations will be based on the mITT population.

17.2.4. Per-Protocol (PP) Population

The per-protocol population is defined as the mITT subjects without any major protocol deviation that will impact the subject's efficacy and safety. This population may be used in the efficacy sensitivity analysis.

17.3. Subject Disposition

The number of subjects included in each study population will be summarized by treatment group. Subjects excluded from the safety and efficacy (eg, ITT) populations will be listed by treatment group.

The number and percentage of subjects completed and prematurely discontinued during the treatment period will be presented for each treatment group and pooled across treatment groups. Screen failures (ie, screened but not randomized subjects) and the associated failure reasons will be tabulated overall. Reasons for premature discontinuation from the treatment period as recorded on the termination page of the eCRF will be summarized (number and percentage) by treatment group for all randomized subjects. Percentage of premature discontinuations will be compared between treatment groups.

17.4. Demographics and Other Baseline Characteristics

The summarization of demographic variables (eg, age, sex, race, weight, height, and body mass index [BMI]), medical and surgical history, and other baseline characteristics relevant to the indication studied in the study will be described.

Demographic characteristics, including sex, age, age group, race, height, and weight, will be summarized by treatment group, for the ITT population, using descriptive statistics. All screening characteristics and medical information will also be summarized by treatment group using descriptive statistics. The descriptive summaries will include frequency tables for all categorical response variables and n, mean, standard deviation (SD), median, minimum and maximum for all continuous variables.

17.5. Efficacy Analyses

All efficacy endpoints including supportive efficacy analysis will be summarized as percentages. The dichotomous secondary endpoints (ie, responder endpoints) will be analyzed using a Cochran-Mantel-Haenszel test adjusted for Investigator. Changes in the PR-PCSS ratings and CR-PCSS ratings from baselines, S-GAIS scores, and I-GAIS scores will be analyzed using the Wilcoxon rank sum test. All the tests are two-sided.

The primary endpoint will be summarized as percentages and analyzed using a Cochran-Mantel-Haenszel test that compares the 2 treatment groups and adjusts for Investigator at a level of significance of 0.05 based on the ITT population. Any subject who does not have an evaluation of CR-PCSS and/or PR-PCSS at Day 71 will be classified as a non-responder.

The key secondary efficacy analyses will be analyzed in the same manner as the primary endpoint based on the ITT population. Any subject who does not have an evaluation at Day 71 will be classified as a non-responder for the analyses. The family #1 key secondary efficacy analyses will be performed only if the primary efficacy analysis is significant ($p \leq 0.05$; gatekeeping strategy). Similarly family #2 key secondary efficacy analyses will be performed only if at least one of the key secondary efficacy endpoints of family #1 is significant ($p \leq 0.025$; parallel gatekeeping strategy). Within a family of key secondary efficacy endpoints, Bonferroni method will be performed to relocate unused alpha for testing each endpoint to assure an overall error rate of $p \leq 0.05$. The details of the testing procedures will be provided in the statistical analysis plan for the study.

All supportive endpoints will be summarized as percentages. All the supportive analyses will be performed based on all observed data (ie, missing data not imputed) in the mITT population at all visits without multiplicity adjustment. This analysis will also be performed at Day 71 with missing data at Day 71 imputed by a last observation carried forward (LOCF) approach if subjects have at least one post-dose assessment. The dichotomous secondary endpoints (ie, responder endpoints) will be analyzed using a Cochran-Mantel-Haenszel test adjusted for Investigator. Changes in the PR-PCSS ratings and CR-PCSS ratings from baselines, S-GAIS scores, and I-GAIS scores will be analyzed using the Wilcoxon rank sum test.

17.5.1. Primary Efficacy Variable

The primary efficacy variable is the proportion of 2-level composite responders at Day 71 defined as subjects with at least one of two treated buttocks with:

- an improvement in severity from baseline (Day 1 visit) of at least 2 levels of severity in the CR-PCSS as assessed live by the Investigator, and
- an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS by the subject while viewing the digital image of the same buttock.

A subject will be considered a responder if these criteria are met in either the left buttock or right buttock or both buttocks in that subject. In other words, a subject will be considered a responder if she has an improvement of at least 2 levels on the PR-PCSS and an improvement of at least 2 levels on the CR-PCSS on that same buttock; that buttock could be the left buttock or right buttock or both buttocks.

Sensitivity analyses for the primary endpoint will include:

- ITT subjects with missing data handled by multiple imputation (MI) approach
- ITT subjects with missing data handled by an LOCF approach
- mITT subjects with missing data handled by an LOCF approach
- Observed data only (no missing data handling)
- Per-protocol (PP) subjects with missing data handled by an LOCF approach if 10% or more subjects are excluded in the PP population from mITT population

17.5.2. Secondary Efficacy Variables

17.5.2.1. Key Secondary Variables

There will be 4 key secondary endpoints grouped in two families of 2 endpoints per family analyzed in a hierarchical order.

- Family #1 – two endpoints:
  - Proportion of 1-level PR-PCSS responders defined as subjects with ≥1-level improvement in PR-PCSS severity rating of left buttock at Day 71 compared to Day 1
  - Proportion of 1-level PR-PCSS responders defined as subjects with ≥1-level improvement in PR-PCSS severity rating of right buttock at Day 71 compared to Day 1
- Family #2 – two endpoints:
  - Proportion of 1-level S-GAIS responders defined as subjects with ≥1-level improvement (improved, much improved or very much improved) in the S- GAIS assessment of left buttock at Day 71
  - Proportion of 1-level S-GAIS responders defined as subjects with ≥1-level improvement (improved, much improved or very much improved) in the S-GAIS assessment of right buttock at Day 71

17.5.3. Supportive Efficacy Variables

17.5.3.1. Supportive Variables

The supportive variables will evaluate assessments at various study time points and using various populations.

- Proportion of 2-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS of the left buttock (Days 22, 43, and 71)
- Proportion of 2-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the PR-PCSS of the right buttock (Days 22, 43, and 71)

- Proportion of 1-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS of left buttock (Days 22, 43, and 71)
- Proportion of 1-level PR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the PR-PCSS of right buttock (Days 22, 43, and 71)
- Proportion of 2-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject.
- Proportion of 1-level PR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject.
- Proportion of 2-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks.
- Proportion of 1-level PR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks.
- Proportion of 2-level CR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the left buttock (Days 22, 43, and 71)
- Proportion of 2-level CR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the right buttock (Days 22, 43, and 71)
- Proportion of 1-level CR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the left buttock (Days 22, 43, and 71)
- Proportion of 1-level CR-PCSS responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the right buttock (Days 22, 43, and 71)
- Proportion of 2-level CR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject.
- Proportion of 1-level CR-PCSS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject.
- Proportion of 2-level CR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks.

- Proportion of 1-level CR-PCSS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks.
- Proportion of 1-level composite responders of the left buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the left buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same left buttock) (Days 22, 43, and 71)
- Proportion of 1-level composite responders of the right buttock (defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS of the right buttock assessed live by the Investigator and an improvement of severity from baseline of at least 1 level of severity in the PR-PCSS of that same right buttock) (Days 22, 43, and 71)
- Proportion of 1-level composite responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject.
- Proportion of 1-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks.
- Proportion of 2-level composite responders of the left buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the left buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same left buttock) (Days 22, 43, and 71)
- Proportion of 2-level composite responders of the right buttock (defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS of the right buttock assessed live by the Investigator and an improvement of severity from baseline of at least 2 levels of severity in the PR-PCSS of that same right buttock) (Days 22, 43, and 71)
- Proportion of 2-level composite responders of at least one of two buttocks (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject.
- Proportion of 2-level composite responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks.
- Proportion of subjects at each level of the S-GAIS of the left buttock (Days 22, 43, and 71)
- Proportion of subjects at each level of the S-GAIS of the right buttock (Days 22, 43, and 71)
- Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S- GAIS of the left buttock (Days 22, 43, and 71)

- Proportion of 1-level S-GAIS responders defined as subjects with a response of at least 1 (improved) in the S- GAIS of the right buttock (Days 22, 43, and 71)
- Proportion 1-level S-GAIS responders of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject.
- Proportion of 1-level S-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks.
- Proportion of subjects at each level of the I-GAIS of the left buttock (Days 22, 43, and 71)
- Proportion of subjects at each level of the I-GAIS of the right buttock (Days 22, 43, and 71)
- Proportion of 1-level I-GAIS responders (defined as subjects with a response of at least 1 (improved) in the Investigator GAIS assessment) of at least one buttock (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in the left buttock or right buttock or both buttocks in that subject.
- Proportion of 1-level I-GAIS responders of two buttocks in the same individual (Days 22, 43, and 71). A subject will be considered a responder if this criterion is met in both left and right buttocks.
- Proportion of subjects at each level of the subject satisfaction with cellulite treatment (Day 71)
- Proportion of satisfied responders (defined as subjects with a response of at least 1 (ie, 1-Satisfied or 2-Very Satisfied) in the subject satisfaction with cellulite treatment assessment (Day 71)

17.6. Safety Analyses

Safety variables include adverse events, laboratory parameters, vital signs, ECG parameters, and physical examinations. For each safety parameter, the last assessment made prior to the first dose of study drug will be used as the baseline for all analyses of that safety parameter.

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. Prior medication will be defined as any medication taken prior to the first dose of study drug. Concomitant medication is defined as any medication taken on or after the date of first dose of study drug.

Prior and concomitant medication use will be summarized descriptively by the number and percentage of subjects for each preferred term (generic name from WHO dictionary) by treatment. Multiple use of the same medication by a subject will be counted only once.

17.6.2. Study Drug Exposure

The following information regarding treatment will be summarized per each treated buttock by treatment group:

- Total number of treatment visits
- Number of subjects who had treatment session done or treatment session not done at each treatment visit
- For subjects who had the treatment session done, the number of subjects who got all 24 injections at the treatment visit or who received less than 24 injections
- Number of injections given at each treatment visit
- Number of dimples treated at each treatment visit
- Average number of injections per dimple at each treatment visit

Subjects who did not receive all 3 treatment visits and who did not receive 24 injections at a treatment visit will be listed.

17.6.3. Measurement of Treatment Compliance

Not applicable (the study drug is administered at the site by the study investigator).

17.6.4. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code AEs.

An AE (classified by preferred term) that started on or after the date of the first dose of the study drug 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.

The by-frequency summaries will also include incidence of the SAEs and non-SAEs by preferred term that at least 2% of the subjects in one treatment group. Duration of AEs will be tabulated by treatment group.

Fisher exact test will be used to compare EN3835 to placebo.

Listings will be presented for subjects with SAEs, subjects with AEs leading to discontinuation of study or study drug, 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 study will be presented by treatment group.

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 will be detailed in the Statistical Analysis Plan (SAP). The PCI percentages will be calculated relative to the number of subjects with baseline and at least one post-baseline assessment. A supportive listing of subject values will be provided including the subject ID, study center, treatment group, baseline and post-baseline values.

The change from baseline for vital signs parameters are compared between EN3835 and placebo using an analysis of variance (ANOVA) with a factor of drug (EN3835 or placebo) while Fisher exact test will be used for the incidence of PCI values.

17.6.6. Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values in International System of Units (SI units) and changes from baseline at Day 71 will be presented by treatment group for each clinical laboratory parameter.

The number and percentage of subjects with potentially clinically important (PCI) post-baseline clinical laboratory values will be tabulated by treatment group. The criteria for PCI laboratory values will be detailed in the Statistical Analysis Plan (SAP). The PCI percentages will be calculated relative to the number of subjects with at least one post-baseline assessment. A supportive listing of subjects with post-baseline PCI values will be provided, including the subject ID, study center, treatment group, baseline and post-baseline values.

The change from baseline for clinical laboratory parameters are compared between EN3835 and placebo using an ANOVA with a factor of drug (EN3835 or placebo) while Fisher exact test will be used for the incidence of PCI values.

17.6.7. Electrocardiogram

Not applicable (ECG is done only at screening for the subject's enrollment eligibility).

17.6.8. Physical Examination

Body weight and BMI at Day 22, Day 43, and Day 71 as well as their change from baseline (Day 1) at those time points will be presented by treatment group.

17.6.9. Other Safety Measurements

Not applicable.

17.7. Pharmacokinetic Analyses

Not applicable.

17.8. Pharmacodynamic Analyses

Not applicable.

17.9. Other Data (eg, Health Economics/QOL, Pharmacogenetic, etc)

Not applicable.

17.10. Interim Analysis

No interim analysis is planned for this study.

17.11. Statistical Software

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

18. STUDY DRUG MATERIALS AND MANAGEMENT

18.1. Study Drug Identity

EN3835 is manufactured and supplied by Endo.

EN3835 is a sterile lyophilized powder consisting of 0.92 mg of collagenase clostridium histolyticum, 18.9 mg sucrose, 1.1 mg Tris, 37.7 mg mannitol, hydrochloric acid QS to pH 8.5, in a 5-mL vial.

Placebo for injection is a sterile lyophilized powder consisting of 18.9 mg sucrose, 1.1 mg Tris, 37.7 mg mannitol, hydrochloric acid QS to pH 8.5, in a 5-mL vial.

EN3835 sterile diluent for reconstitution is 0.6% sodium chloride and 0.03% calcium chloride dehydrate in water for injection filled into 5-mL vials.

18.2. Study Drug Packaging and Labeling

Each vial of study drug and diluent will minimally be labeled with contents, Sponsor identification, storage, administration/use, and appropriate cautions statements. Each kit will contain one vial of EN3835 or placebo and sufficient sterile diluent to perform reconstitution of the one product vial. Kits containing EN3835 or placebo will be indistinguishable and only identifiable by their unique kit number.

18.3. Study Drug Storage

All study drug will be provided by Endo. Study drug must be stored in an appropriate, secure area. Study drug must be kept in a temperature-monitored refrigerator (2°C-8°C) with locked access until used or returned to Endo.

18.4. Study Drug Preparation

Refer to the Reconstitution Instructions for detailed preparation instructions.

For each dose session, the IWRS will dispense 2 kits, 1 kit for each buttock to be treated. Four (4) 0.9-mL syringes will be prepared from each vial of EN3835 or placebo, 4 syringes/kit, for a total of 8 syringes (4 syringes for each buttock).

Used drug vials should be returned to the kit carton and stored in a secure location until reconciled and returned by the Clinical Research Associate (CRA). Dispose of used diluent vials, needles, and syringes per local regulations.

The reconstituted study drug solution should be administered as soon as possible after reconstitution. The study drug solution can be kept at room temperature [redacted] Remove drug/prepared syringes from the refrigerator and allow it to stand at room temperature for 15 minutes prior to injection of study drug.

18.5. Study Drug Accountability

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/IEC, and regulatory agencies for routine inspection and accountability during monitoring visits. When instructed by Endo, the Investigator agrees to return all original used or unused study drug kits to Endo's return vendor.

18.5.1. Study Drug Handling and Disposal

The Investigator agrees not to supply study drug to any person except to those subjects enrolled in the study. The Investigator is responsible for recording the receipt and use of all drugs supplied and for ensuring the supervision of the storage and allocation of these supplies. All used and 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 and its use. At the end of the study, all used and unused drug supplies will be returned to Endo’s return vendor.

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:

- PR-PCSS
- CR-PCSS
- Hexsel CSS
- S-GAIS
- I-GAIS
- Subject Satisfaction with Cellulite Treatment Assessment

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/assent, the Investigator is responsible for obtaining any additional documentation to demonstrate compliance with local privacy laws applicable to activities performed.

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

A unique Subject identification number will be assigned according to section 12.1.2.2 at the time that the Subject signs the informed consent form.

22. DATA HANDLING AND RECORDKEEPING

22.1. Data Collection

Endo will provide an electronic data capture (EDC) system for this study. 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).

Data entries will be corrected by changing the entry in the EDC system. Any changes or corrections to eCRF data will be electronically tracked and will include the reason for correction, who made the correction, and the date/time stamp when the correction was made within the audit trail of the EDC system.

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 case report form (CRF) data for his/her files.

23. REPORTING AND PUBLICATION

All data generated in this study are the property of Endo Pharmaceuticals Inc. 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 Pharmaceuticals Inc.

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 FDA 1572. If during the course of the study any information reported on the Form FDA 1572 changes, a revised Form FDA 1572 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 FDA 1572 (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.

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 Pharmaceuticals Inc. 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)/Clinical Trial Authorization (CTA) or request for marketing approval (New Drew Application [NDA]/Marketing Authorization Application [MAA]).

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 Pharmaceuticals Inc. 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 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 STATEMENT

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):361-70.
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):175-90.
4. Terranova F, Berardesca E, Maibach H. Cellulite: nature and aetiopathogenesis. *Int J Cosmetic Sci.* 2006;28(3):157-67.
5. Avram MM. Cellulite: a review of its physiology and treatment. *J Cosmet Laser Ther.* 2004;6(4):181-5.
6. Khan MH, Victor F, Rao B, Sadick NS. Treatment of cellulite: Part II. Advances and controversies. *J Am Acad Dermatol* 2010;62(3):373-84.
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):1110-4.
8. Hexsel DM, Mazzuco R. Subcision: a treatment for cellulite. *Int J Dermatol.* 2000;39(7):539-44.
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;22:233-7.
10. DiBernardo BE. Treatment of cellulite using a 1440-nm pulsed laser with one-year follow-up. *Aesthet Surg J.* 2011;31(3):328-41.
11. Investigational Brochure: Collagenase Clostridium Histolyticum for Injection (AA4500/EN3835), Version 7.0. Endo Pharmaceuticals Inc.; May 2016.
12. Hexsel DM, Dal'Forno T, Hexsel CL. A validated photonumeric cellulite severity scale. *J Eur Acad Dermatol Venereol.* 2009;23(5):523-8.
13. Nürnberger F, Müller G. So-called cellulite: an invented disease. *J Dermatol Surg Oncol.* 1978;4(3):221-9.

[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]).

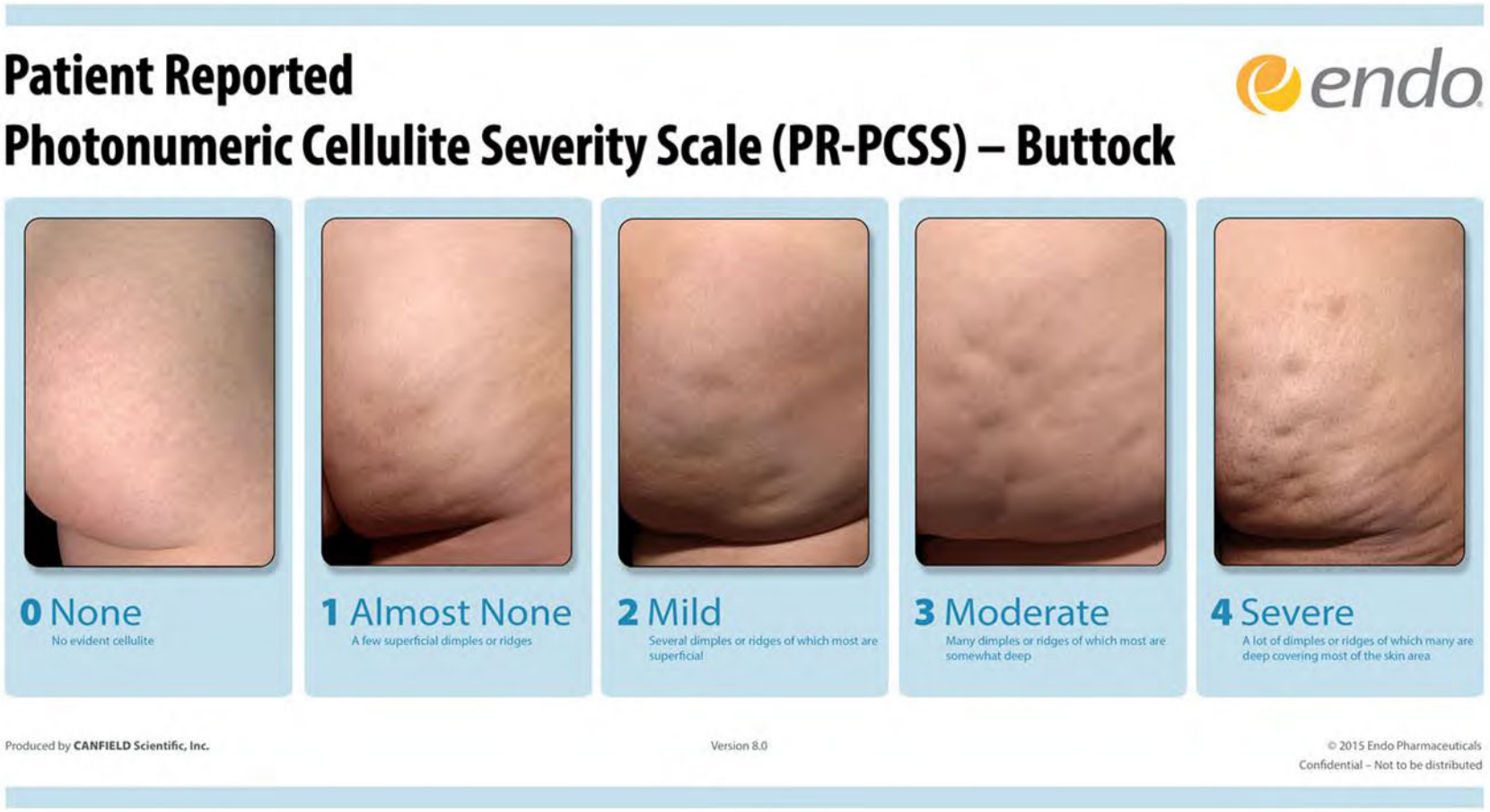
8. Financial Disclosure Certification or Certification of Non-Disclosure (for studies to be submitted for a US New Drug Application/Biologics License Application [NDA/BLA]).

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. PATIENT-REPORTED PHOTONUMERIC CELLULITE SEVERITY SCALE (PR-PCSS) FOR THE BUTTOCK

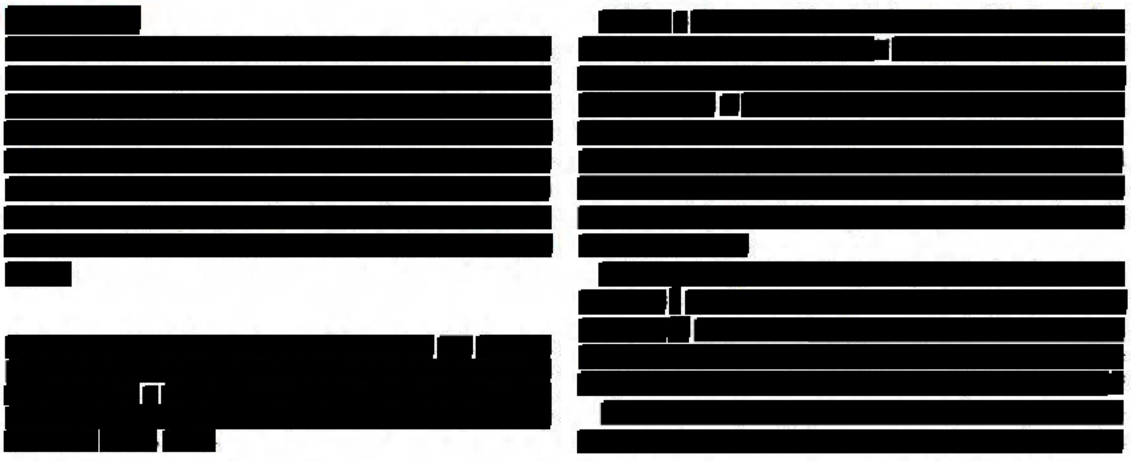


APPENDIX C. CLINICIAN-REPORTED PHOTONUMERIC CELLULITE SEVERITY SCALE (CR-PCSS) FOR THE BUTTOCK

APPENDIX D. HEXSEL DM, DAL'FORNO T, HEXSEL CL. A VALIDATED PHOTONUMERIC CELLULITE SEVERITY SCALE. *J EUR ACAD DERMATOL VENEREOL*. 2009;23(5):523-8

DOI: 10.1111/j.1468-3083.2009.03101.x JEADV

[redacted]



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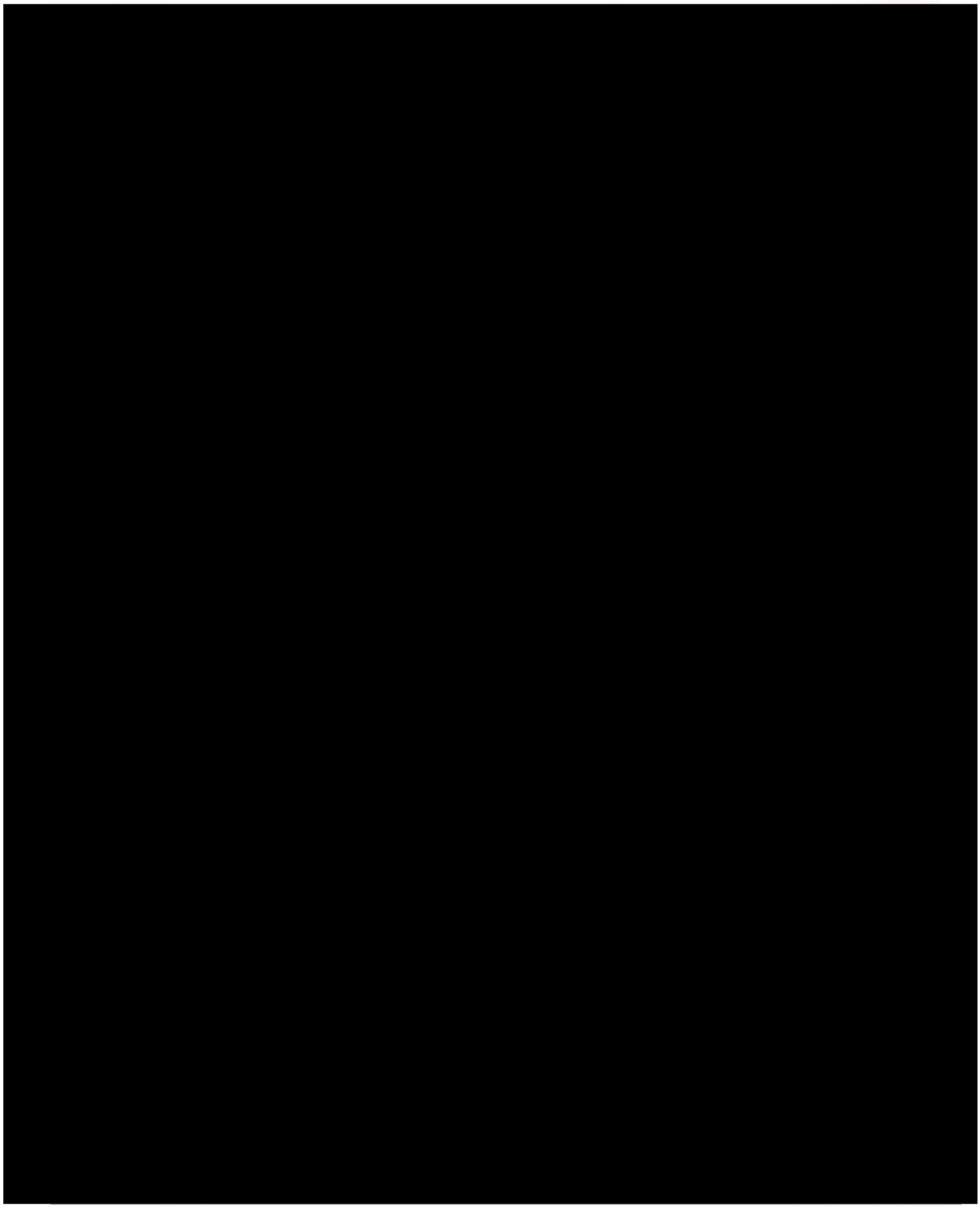

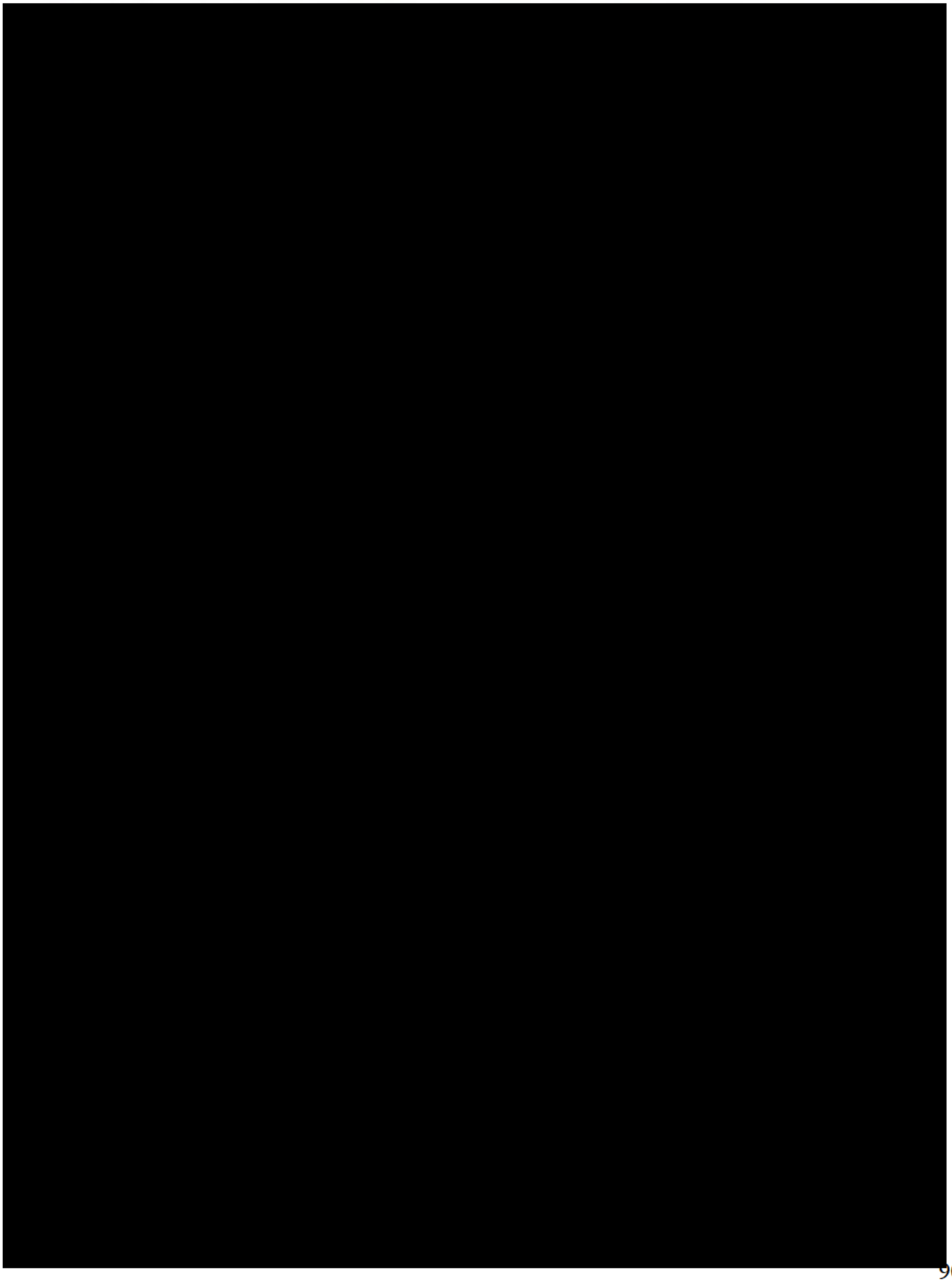

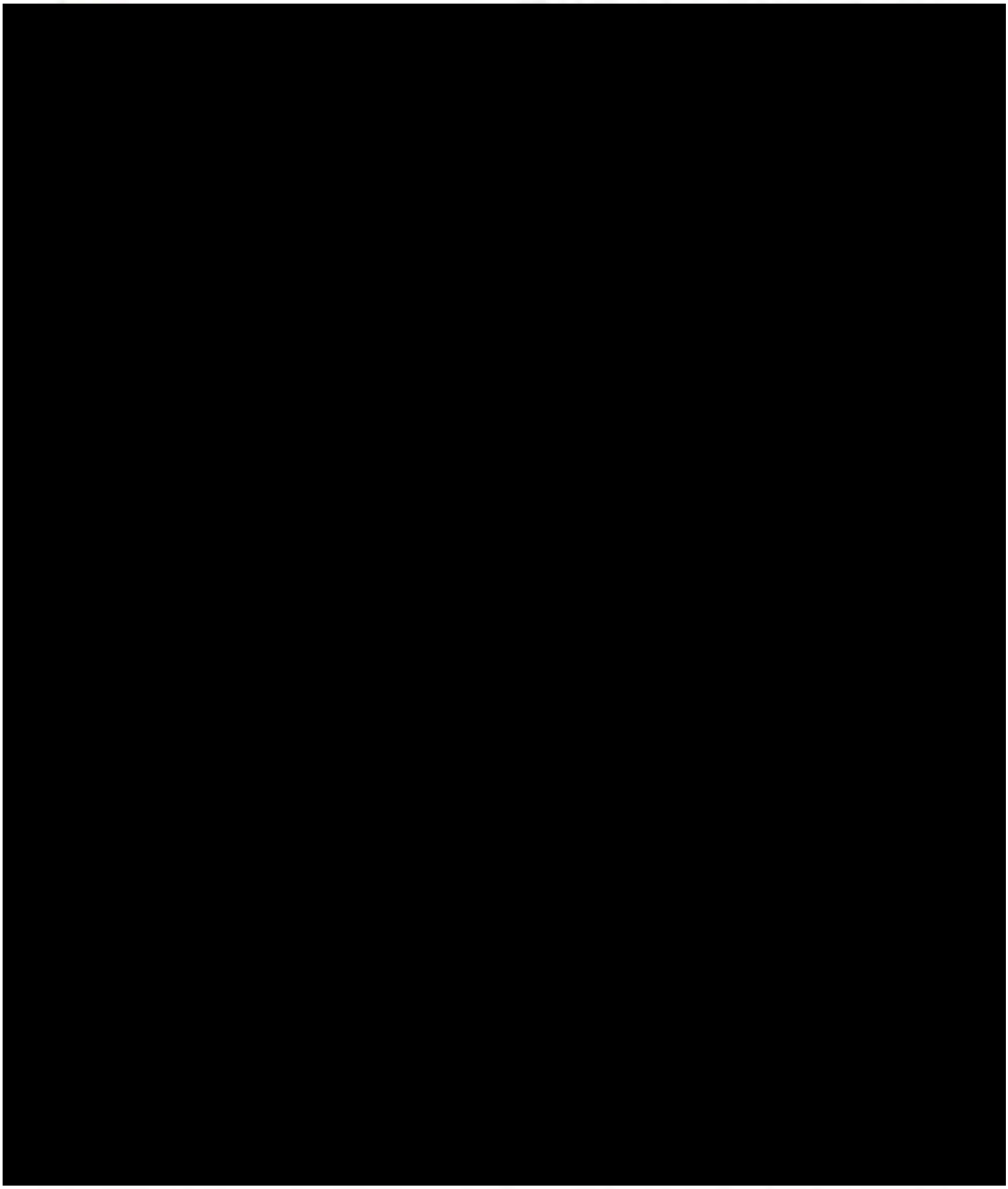

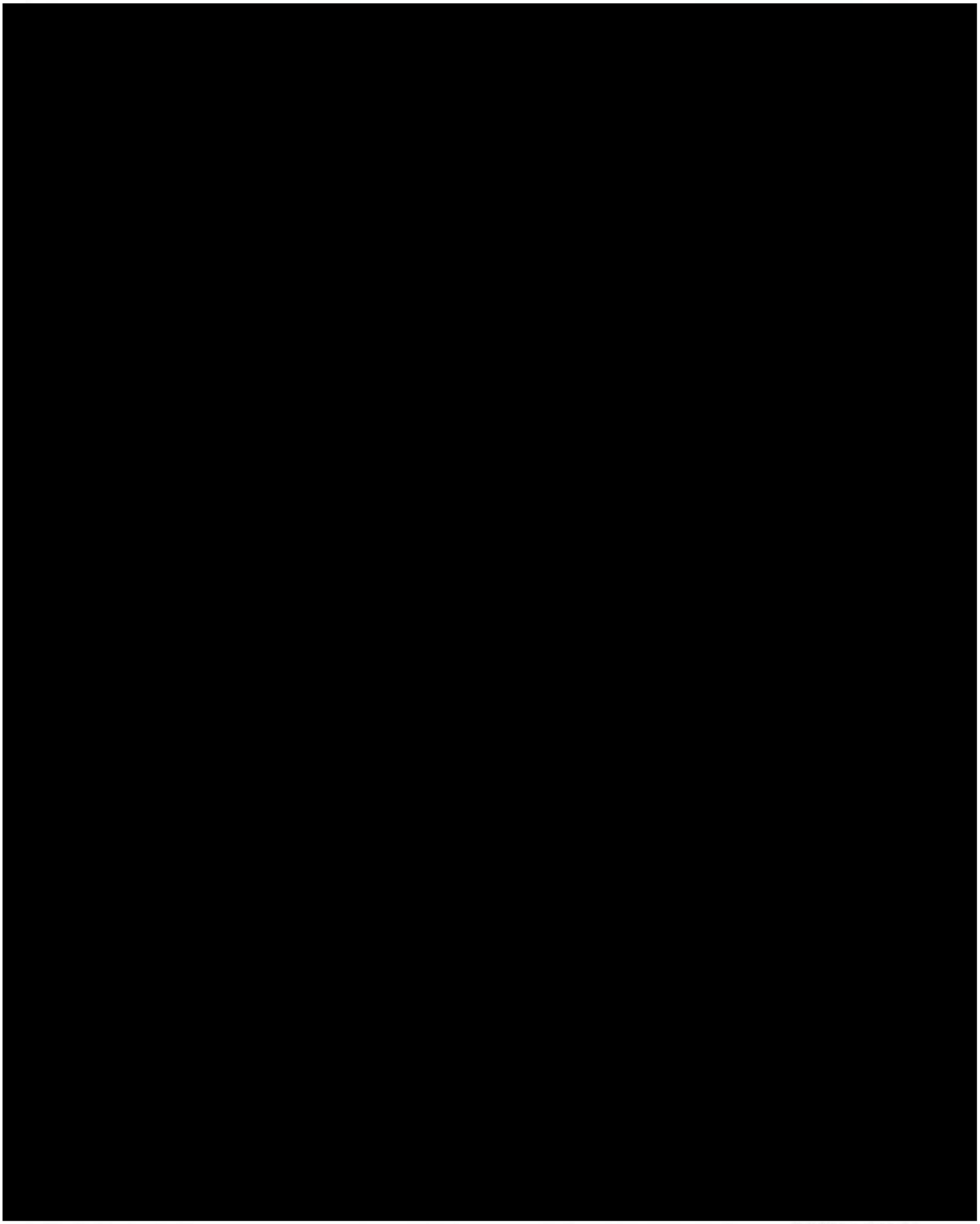

JEADV 2009, 23, 523–528

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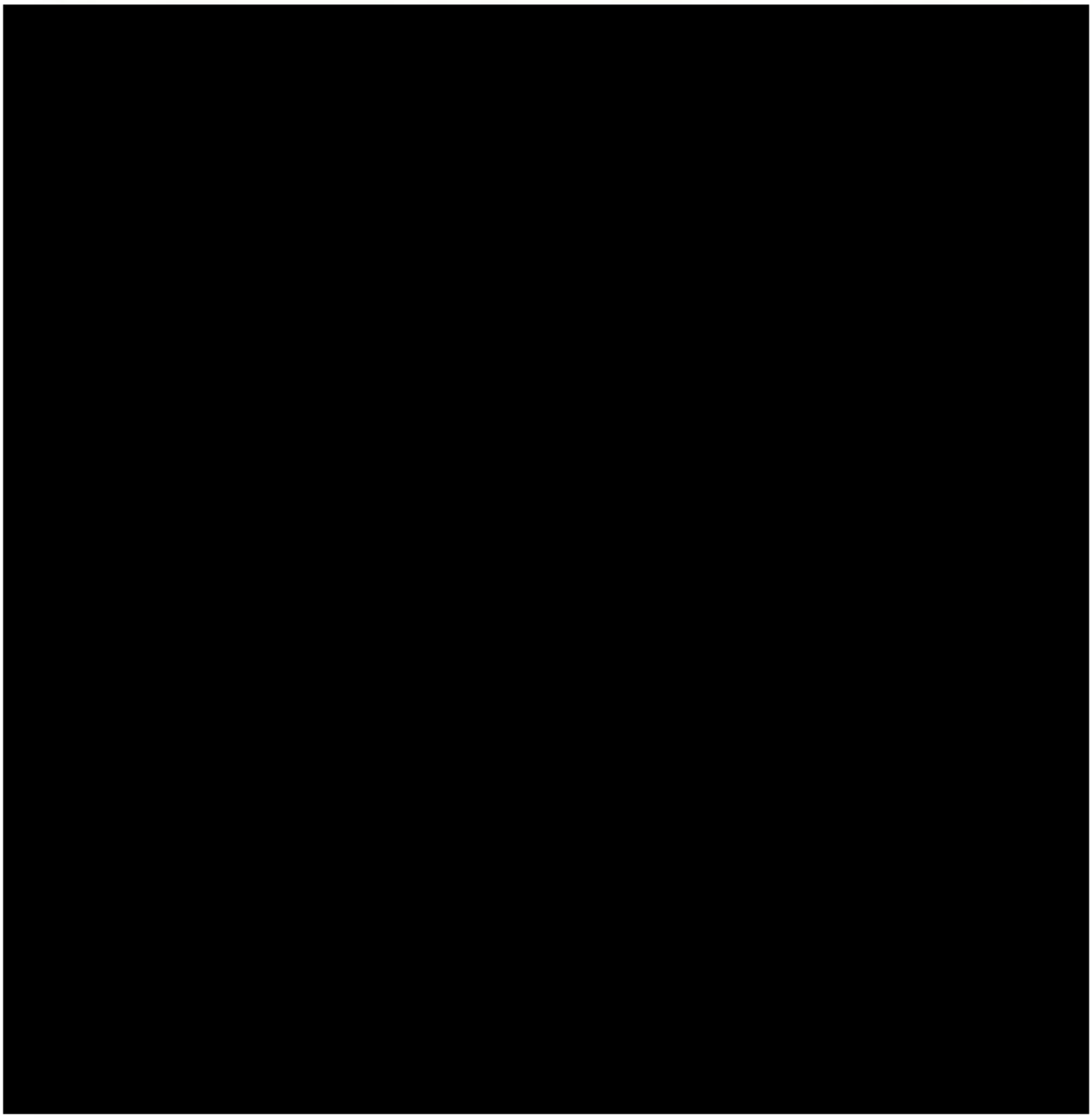

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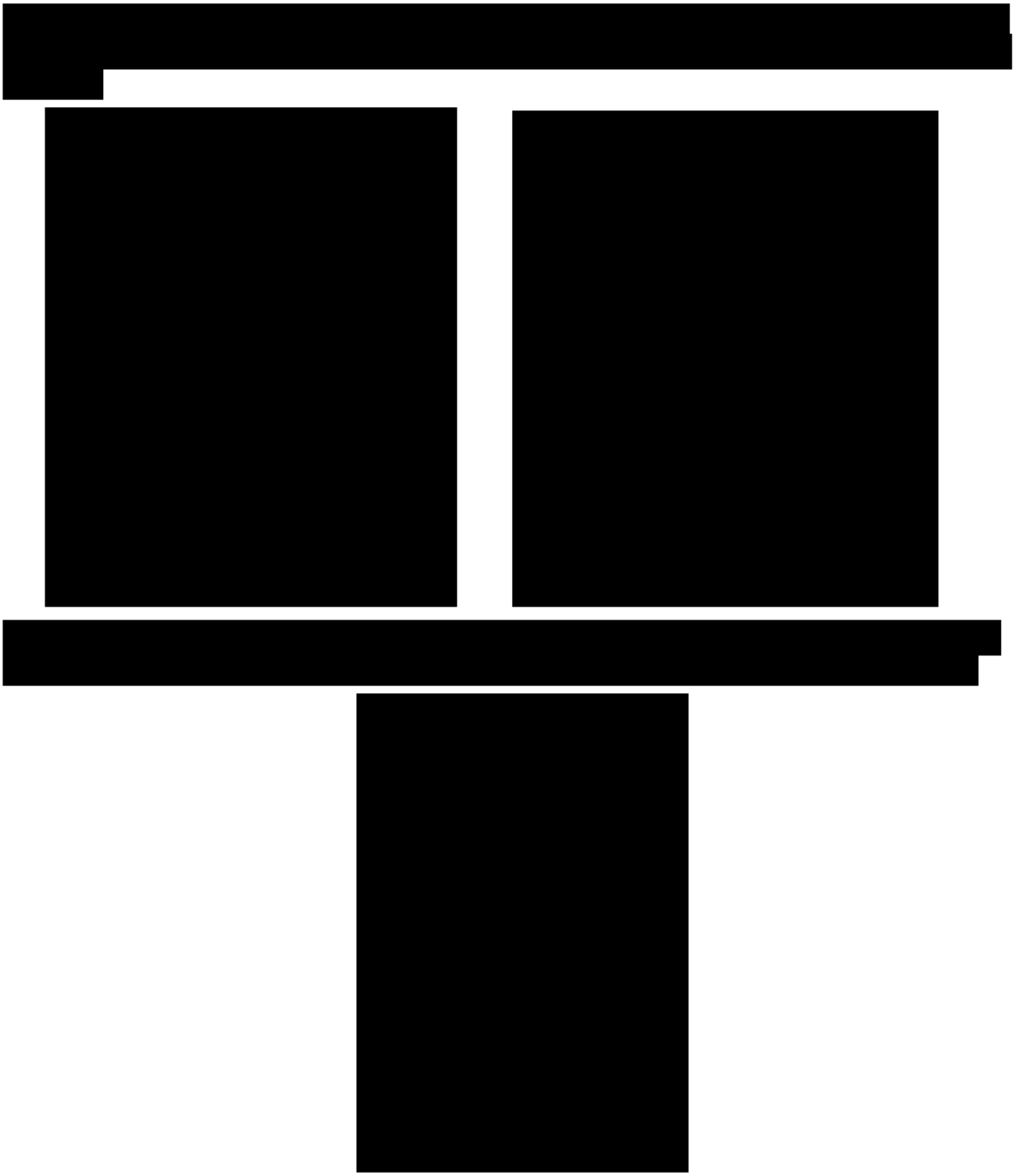
APPENDIX E. REFERENCE IMAGES FOR HEXSEL SEVERITY RATINGS



SAP MODULE 1 – DETAILED STATISTICAL METHODOLOGY

STUDY EN3835-303

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF EN3835 IN THE TREATMENT OF EDEMATOUS FIBROSCLEROTIC PANNICULOPATHY

Version 3.0

August 30, 2018

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

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[redacted]

LIST OF TABLES

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
AE	Adverse event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AUX-I	Clostridial Class I Collagenase
AUX-II	Clostridial Class II Collagenase
BMI	Body mass index
CMH	Cochran Mantel Haenszel
CR-PCSS	Clinician Reported Photonumeric Cellulite Severity Scale
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EFP	Edematous fibrosclerotic panniculopathy
EN3835	Purified lyophilized clostridial collagenase
GAIS	Global Aesthetic Improvement Scale
I-GAIS	Investigator Global Aesthetic Improvement Scale
ISE	Integrated summary of efficacy
ITT	Intent to treat
IWRS	Interactive web response system
LOCF	Last observation carried forward
LSMEAN	Least square mean
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
mITT	Modified intent to treat
MNAR	Missing not at random
PCI	Potentially clinically important
PP	Per protocol
PR-CIS	Patient Reported Cellulite Impact Scale
PR-PCSS	Patient Reported Photonumeric Cellulite Severity Scale
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SE	Standard error
S-GAIS	Subject Global Aesthetic Improvement Scale
SSRS	Subject Self-rating Scale
TEAE	Treatment-emergent adverse event
TP	Tipping point
WHO	World Health Organization

1. STUDY OBJECTIVE

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

2. STUDY DESIGN AND MEASURES

This study is a Phase 3 randomized, double-blind, placebo-controlled study of the efficacy and safety of EN3835 in the treatment of EFP in adult women. Subjects will be screened for study eligibility within 14 days prior to enrolling in this study. Subjects with 2 treatment areas (bilateral buttocks) (also referred to as quadrants) with moderate or severe levels of cellulite as independently assessed by the subject using the Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS) and by the investigator using the Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS).

Once the eligibility of the buttocks is confirmed again on Day 1, subjects will be randomly assigned to 1 of 2 treatment groups, EN3835 1.68 mg total dose (0.84 mg per buttock) or placebo, in a 1:1 ratio within an investigational site. A treatment course will consist of 3 treatment sessions (ie, Days 1, 22, and 43). Each treatment session will consist of 12 injections (0.3 mL per injection of EN3835 0.07 mg/injection or placebo) in each of the buttocks for a total volume of 7.2 mL. Selection of dimples to be treated in each buttock will be at the discretion of the investigator. End of study will occur at study Day 71. Of the two assigned eligible buttocks, one buttock will be randomly selected as the target buttock on Day 1 for the primary efficacy endpoint. The other (remaining) buttock will be considered the non-target buttock. Subjects, investigators, site personnel, and Endo personnel will be blinded to the identification of the target and non-target buttocks.

At each treatment session, each of the buttocks will be photographed before and after marking dimples and injection sites while the subject is in a consistent, standardized relaxed standing pose. The subject will assess the digital photographic image (pre-marking) of each of the buttocks using the PR-PCSS to determine the severity of EFP in each of the buttocks. The subject will also evaluate each of the buttocks using a Subject Global Aesthetic Improvement Scale (S-GAIS). Subsequently, the investigator will conduct live assessments of each of the buttocks using the CR-PCSS. At Day 1, the subject will complete a Patient Reported Cellulite Impact Scale (PR-CIS) assessment and a Subject Self-rating Scale (SSRS) assessment. The subject assessments will always be completed prior to and independently of the investigator assessments at each treatment visit. The investigator will assess each of the buttocks using an Investigator Global Aesthetic Improvement Scale (I-GAIS). All the assessments must be done before the dimple marking.

At Day 71 (End of Study/Early Termination), photographs of each of the buttocks will be taken and evaluated by the subject using the PR-PCSS. The investigator will conduct live assessments of each of the buttocks using the CR-PCSS. Global assessment evaluations will be completed by both the subject and the investigator.

Table 1 contains the schedule of assessments.

Table 1: Study EN3835-303 Assessments

Procedures	Day -14 to -1 Screening	Day 1 Treatment Visit 1	Day 22 (± 3 d) Treatment Visit 2	Day 43 (± 3 d) Treatment Visit 3	Day 71 (+ 5 d) / End of Study / Early Termination	Unscheduled Clinic Visit [a]
Informed consent	X					
Inclusion/exclusion	X					
Digital photography	X	X [b]	X [b]	X [b]	X	X
Medical history/EFP history including previous treatments	X					
Prior/concomitant medications/procedures	X	X	X	X	X	X
Physical examination:	X					
• Body weight	X		X [c]	X [c]	X	X
• Height	X					
• Fitzpatrick skin type	X					
Vital signs	X	X [d]	X [d]	X [d]	X	X
12-lead ECG	X					
Collection of samples:						
• Clinical laboratory	X				X	X
• Anti-AUX-I/anti-AUX-II antibody level		X [c]	X [c]	X [c]	X	
• Pregnancy testing	X [e]	X [c,e]	X [c,e]	X [c,e]	X [e]	X
Subject cellulite assessments [f]:						
• Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS)	X [g,h]	X [c,g,h]	X [c,g,h]	X [c,g,h]	X [g,h]	
• Patient Reported Cellulite Impact Scale (PR-CIS)		X [c,g]			X [g]	
• Subject Global Aesthetic Improvement (S-GAIS)			X [c,g,h]	X [c,g,h]	X [g,h]	
• Subject Satisfaction With Cellulite Treatment Assessment					X [g]	
• Subject Self-rating Scale (SSRS)		X [c]			X	

Table 1: Study EN3835-303 Assessments (Continued)

Procedures	Day -14 to -1 Screening	Day 1 Treatment Visit 1	Day 22 (± 3 d) Treatment Visit 2	Day 43 (± 3 d) Treatment Visit 3	Day 71 (+ 5 d) / End of Study / Early Termination	Unscheduled Clinic Visit [a]
Investigator cellulite assessments:						
• Selection of dimples to be treated within the two buttocks		X [c]	X [c]	X [c]		
• Marking the dimples and injection sites to be treated within the buttocks		X [c]	X [c]	X [c]		
• Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)	X	X [c,h]	X [c,h]	X [c,h]	X [h]	
• Investigator Global Aesthetic Improvement (I-GAIS)			X [c,h]	X [c,h]	X [c,h]	
Confirm eligibility		X [c]				
Randomize to treatment		X [c,i]				
Study drug administration		X	X	X		
Injection site reactions/local tolerability in the buttocks		X	X	X	X	X
Adverse events	Monitored Throughout Study					

[a] During unscheduled visits, the Investigator or designee may perform any study procedure that they deem clinically necessary (eg, vital signs, clinical lab assessments, and pregnancy test).
[b] Before and after marking the dimples and injection sites.
[c] Before injection.
[d] Up to 4 hours before injection; approximately 15 and 30 minutes after injection. Vital signs must be stable before the subject is discharged.
[e] Serum pregnancy test on Screening visit and Day 71/EOS visit; urine pregnancy test on Day 1, Day 22, and Day 43 visits.
[f] Subject assessments should be completed independently and prior to Investigator assessments at each visit.
[g] Assessment made via photographs (if treatment visit, use photographs taken before marking dimples and injection sites).
[h] Assessment of each of the 2 buttocks independently.
[i] Before randomization, each of the subject's buttocks must have ratings of 3 or 4 (moderate or severe) in both the CR-PCSS and PR-PCSS.
NOTE: Subject cellulite assessments must be completed before the Investigator cellulite assessments are conducted at each visit.
d=Days; ECG=Electrocardiogram; EFP=Edematous fibrosclerotic panniculopathy; EOS=End of study

2.1. Inclusion Criteria

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

1. Voluntarily sign and date an informed consent agreement
2. Be a female ≥18 years of age
3. At Screening visit, have 2 bilateral buttocks with each buttock having:
   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)
4. At Day 1 visit, have 2 bilateral buttocks with each buttock having:
   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)
5. Be willing to apply sunscreen to the buttocks before each exposure to the sun while participating in the study (ie, Screening 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
7. Have a negative serum pregnancy test at Screening and a negative urine pregnancy test before injection of study drug and be using a stable and effective contraception method (eg, abstinence, intrauterine device [IUD], hormonal [estrogen/progestin] contraceptives, or double barrier method) for at least 1 menstrual cycle prior to study enrollment and for the duration of the study; or be menopausal defined as 12 months of amenorrhea in the absence of other biological or physiological causes, as determined by the Investigator; or post-menopausal for at least 1 year; or be surgically sterile
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

2.2. Exclusion Criteria

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

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

2. Has any of the following local conditions in the areas to be treated:
    a. History of lower extremity thrombosis or post-thrombosis syndrome
    b. Vascular disorder (eg, varicose veins, telangiectasia) in area to be treated
    c. Inflammation or active infection
    d. Severe skin laxity, flaccidity, and/or sagging
    e. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer
    f. Has a tattoo and/or a mole located within 2 cm of the site of injection
3. Requires the following concomitant medications before or during participation in the trial:
    a. Anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication (except for ≤150 mg aspirin daily) within 7 days before injection of study drug
4. Has used any of the following for the treatment of EFP on a buttock within the timelines identified below or intends to use any of the following at any time during the course of the study:
    a. Liposuction in a buttock during the 12-month period before injection of study drug
    b. Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; buttock implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision) within a buttock during the 12-month period before injection of study drug
    c. Any investigational treatment for EFP on the buttock during the 12-month period before the injection of study drug
    d. Endermologie or similar treatments within a buttock during the 6-month period before injection of study drug
    e. Massage therapy within a buttock during the 3-month period before injection of study drug
    f. Creams (eg, Celluvera™, TriLastin®) and/or home therapies to prevent or mitigate EFP within a buttock during the 2-week period before injection of study drug
5. Is presently nursing or providing breast milk
6. Intends to become pregnant during the study
7. Intends to initiate an intensive sport or exercise program during the study
8. Intends to initiate a weight reduction program during the study
9. Intends to use tanning spray or tanning booths during the study
10. Has received an investigational drug or treatment within 30 days before injection of study drug
11. Has a known systemic allergy to collagenase or any other excipient of study drug
12. Has received any collagenase treatments at any time prior to treatment

13. Was a subject in a previous cellulite clinical trial of CCH: AUX-CC-830, AUX-CC-831, EN3835-102, EN3835-104, EN3835-201, EN3835-202, and/or EN3835-205
14. Any other condition(s) that, in the Investigator's opinion, might indicate the subject to be unsuitable for the study

2.3. Selection of Target Buttock

Upon confirmation of the two buttocks that are eligible for treatment (eligible criteria being each buttock have PR-PCSS and CR-PCSS scores of 3 or 4) on Day 1 prior to treatment randomization, the IWRS system will randomly assign one buttock as the target buttock in the background. The other (remaining) buttock will be considered the non-target buttock. The target buttock will be used for the primary efficacy endpoint. Subjects, investigators, site personnel and Endo personnel will be blinded to the target buttock assignment and will remain blinded until the clinical study database has been cleaned and locked.

2.4. Selection of Dimples and Injection Sites During Treatment Visits

2.4.1. Selecting and Marking the Dimples

Selection of dimples to be treated in the two buttocks is at the discretion of the Investigator. 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 three visits, ie, Day 1, Day 22, and Day 43, according to randomization unless the buttock is dimple-free (score of 0 on CR-PCSS as reported by the Investigator); a dimple-free buttock does not preclude treatment of the contralateral buttock unless it is dimple-free also. During each treatment session, each of the buttocks will be photographed before and after marking dimples and injection sites 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 marking dimples and injection sites.

The Investigator or qualified designee will select dimples within each buttock that are well-defined, evident when the subject is standing, and suitable for treatment; treatment consists of 12 injections per buttock (24 injections total in two buttocks) per session. Because the goal of treatment is to improve the aesthetic appearance of each entire buttock, the Investigator will be instructed to select dimples that in his or her opinion would most improve the aesthetic appearance of each entire buttock. The same dimples within a buttock or different dimples within a buttock may be treated at each session but injections must all be within the buttocks (12 injections per buttock) for all 3 sessions. Each buttock will receive all 3 treatment sessions unless the buttock has no treatable EFP dimples and the Investigator rates the buttock a score of 0 on the CR-PCSS. If no injections in a particular buttock (right or left) are given at Treatment Session 2, subjects will still be assessed for treatment in the contralateral buttock at Treatment Session 2, and will return for the Day 43 visit and each of the buttocks will again be evaluated by the subject (PR-PCSS) and Investigator (CR-PCSS). If the Investigator rates either or both of the buttocks greater than 0 on the CR-PCSS, injections at Treatment Session 3 should be given.

2.4.2. Selecting Injection Sites

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; locating at least one injection site at the nadir, if present, of the dimple). 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 buttock should not overlap.

2.5. Randomization and Study Drug Administration

2.5.1. Randomization

If the 2 buttocks continue to meet eligibility criteria at Day 1, the subject will be eligible for randomization to study medication. Subjects will be randomized to EN3835 1.68 mg total dose (0.84 mg per buttock) or placebo in a 1:1 ratio. There will be approximately 210 subjects assigned to the EN3835 treatment group and 210 subjects assigned to the placebo group. Randomization of assigned treatment will be stratified by site using the interactive web response system (IWRS).

2.5.2. Blinding and Unblinding

This will be a double-blind study in which the investigator, study subject, and other study personnel involved in the evaluation of the subject efficacy and safety are blinded to the study drug treatment. The data vendor personnel in charge of the IWRS and the Endo personnel in charge of drug supply will be unblinded to study drug assignment, but will have no interaction with the subjects, investigators, clinical personnel, or study data.

Unblinding of study treatment assignments will occur after all subjects have completed the study and the clinical study database has been cleaned and locked. Unblinding will occur by matching the kit numbers reported in the electronic case report form (eCRF) to the master list of kits in the IWRS. Any mistreatments will be reported as major protocol violations. In the case of a medical emergency, sites have the ability to determine treatment identification. If this occurs, the medical monitor will be notified immediately.

2.5.3. Study Drug Administration

At each treatment session, the site will request study drug kit numbers from the IWRS used for injections. For each of the two buttocks, the site personnel in charge of drug preparation will then reconstitute the study medication and prepare 4 syringes for study drug administration per buttock. The kit number, the number of injections given, and the number of dimples treated for each buttock will be recorded in the eCRF. The investigator will also indicate whether the subject received the injections per buttock as described in the protocol. If less than 12 injections are given for any buttock at any treatment session, the investigator is to indicate on the eCRF the number of injections and state the reason why fewer than 12 injections were given for that buttock.

2.6. Digital Photographs

The investigator or qualified designee will photograph each buttock using a Sponsor-supplied standardized digital camera (Vectra, Canfield Scientific, Inc.) in a standardized manner. The subject will be standing for each photography session and will be wearing a standardized photographic garment as described in the Photography Manual. Each buttock will be photographed while the subject is standing in a consistent, relaxed standing pose, ie standing position with relaxed gluteus muscles, at the following time points:

- Screening (no markings of dimples or injection site) - each of the two buttocks
- Before and after marking dimples and injection sites (prior to injections) on Day 1, Day 22, and Day 43 - each of the two buttocks
- During the Day 71 visit (end of study/early termination) (no dimple or injection site markings) - each of the two buttocks

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

Subjects will rate the severity of their cellulite of each of their two buttocks at Screening and on Day 1, Day 22, Day 43, and Day 71 using the PR-PCSS. The PR-PCSS is a photonumeric scale ranging from 0 to 4. The following labels and descriptions are associated with each level of severity on the PR-PCSS:

0: None: No evident cellulite

1: Almost None: A few superficial dimples or ridges

2: Mild: Several dimples or ridges of which most are superficial

3: Moderate: Many dimples or ridges of which most are somewhat deep

4: Severe: A lot of dimples or ridges of which many are deep covering most of the skin area

Subjects will be instructed to sequentially look at each buttock under evaluation on a standardized 22” computer monitor and decide which of the images, labels, and descriptions on the PR-PCSS (mounted on a 10”×18” foam board) best match the severity of the cellulite in the scale. Subjects will be instructed that rating responses must be given in whole numbers; no half numbers are allowed. Subjects will be instructed to choose a PR-PCSS rating that is closest to their cellulite severity in the buttock being evaluated. Subjects will be instructed that if they consider the severity of the cellulite in the buttock is exactly halfway between 2 levels, to choose the more severe level. Subjects will enter their responses directly into an electronic data capture (EDC) system using a handheld tablet; the investigator and site personnel will be blinded to the rating entered by the subject. Each subject will have their own username and password to gain entry into the EDC system. The investigator and the investigator’s personnel will not have access to subject’s password. Once subjects have completed their evaluations for the visit, they will log out from the EDC system.

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

Investigators will rate the severity of the cellulite of each of the two buttocks at Screening and on Day 1, Day 22, Day 43, and Day 71 using the CR-PCSS. The CR-PCSS mirrors the PR-PCSS in every manner except the descriptions.

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

0: None: No dimples or evident cellulite

1: Almost None: Few dimples that are mostly superficial in depth

2: Mild: Several dimples of which most are shallow in depth

3: Moderate: Many dimples of which most are moderate in depth

4: Severe: A lot of dimples with some of more severe depth

Investigators will be instructed to look at each buttock under evaluation 'live' with the subject standing in front of him/her. The investigator is to decide which of the images, labels and descriptions on the CR-PCSS (mounted on a 10"×18" foam board) best match the severity of the cellulite in the buttock. Investigators will be trained that responses must be given in whole numbers; no half numbers are allowed. Investigators will be trained that if they observe the cellulite in the buttock is exactly halfway between 2 levels, to choose the more severe level. Investigators will enter their responses directly into an EDC system using a handheld tablet. They will enter their username and password to gain access to the EDC system; the subject will not have access to view the investigator ratings. Investigators will be instructed not to verbalize their rating(s) or any opinion of the subject's cellulite severity in order not to influence the subject. At each visit, the Investigator will make his/her assessment using the CR-PCSS independently and after the subject has conducted her self-assessment using the PR-PCSS

Investigators will go through a training process and will need to pass a qualifying exercise prior to using the CR-PCSS.

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

The Patient Reported Cellulite Impact Scale is a 6-item static questionnaire; each item is answered by a subject on an 11-level numerical rating scale from 0 (equating to no impact but with wording specifically based on the question) to 10 (equating to extreme impact but with wording specifically based on the question) while viewing digital images of their buttocks at that visit. The PR-CIS items and their response options are listed below:

Please select the rating that best represents your answer on a scale of 0 to 10 with 0 representing "Not at all" and 10 representing "Extremely". Please answer each question.

1. Thinking about the areas selected for treatment, how happy are you with the appearance of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

2. Thinking about the areas selected for treatment, how bothered are you by the appearance of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

3. Thinking about the areas selected for treatment, how self-conscious are you about the appearance of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

4. Thinking about the areas selected for treatment, how embarrassed are you about the appearance of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

5. Thinking about the areas selected for treatment, how much older do you look because of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

6. Thinking about the areas selected for treatment, how overweight or out of shape do you look because of your cellulite?

Not at all										Extremely
0	1	2	3	4	5	6	7	8	9	10

Subjects will be asked to answer the PR-CIS at Day 1 and Day 71 after they rate their cellulite severity on buttocks. Subjects will enter their responses to each of the 6 items directly into an EDC system using a handheld tablet.

2.10. Subject Self-rating Scale (SSRS)

The SSRS is a measure that assesses subject satisfaction with appearance in association with cellulite on the buttocks using whole numbers on a 7-level scale that ranges from 0 (extremely dissatisfied) to 6 (extremely satisfied). The patient will be asked to respond to the question related to the satisfaction with appearance of the cellulite on their buttocks on Day 1 and Day 71. No photographs or reference to previous ratings or evaluations will be used. Subjects will be given a list of responses and they will provide a rating from those below that best represents their answer (Table 2).

Subjects will enter their responses directly into an EDC system using a handheld tablet.

Table 2: Subject Self-rating Scale (SSRS)

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

2.11. Global Assessment Ratings

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

Subjects will complete the S-GAIS for each of the buttocks on Day 22, Day 43, and Day 71 using the pre-treatment Day 1 image (Baseline) of the same buttock for comparison. Subjects will be asked to determine the degree of change seen in each buttock compared with how it looked before treatment on the following scale (Table 3). The subject will conduct the S-GAIS assessment after she completes her PR-CSS assessment to avoid introducing potential bias to the static PR-PCSS assessment.

Table 3: Subject Global Aesthetic Improvement Scale (S-GAIS)

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

Subjects will enter their responses directly into an EDC system using a handheld tablet. Subjects will be instructed not to reveal their responses to the investigators or site personnel and the investigators or site personnel will not have access to view subjects' responses.

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

On Day 22, Day 43, and Day 71, the investigator will determine the degree of improvement of each of the buttocks by comparing the cellulite by live assessment on Day 22, Day 43, and Day 71 to the Day 1 pre-treatment (Baseline) image of that buttock (Table 4). The I-GAIS assessment will occur after the CR-PCSS assessment to avoid introducing potential bias to the static CR-PCSS assessment by the investigator at the site. The I-GAIS assessment will be conducted after the subject completes her assessments (PR-PCSS and/or S-GAIS).

Table 4: 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

Investigators will enter their responses directly into an EDC system using a handheld tablet. The investigators will be instructed not to reveal their responses to the subjects and subjects will not have access to view the investigator ratings.

2.11.3. Subject Satisfaction with Cellulite Treatment Assessment

At the Day 71 visit, subjects will be asked to rate their overall satisfaction with the cellulite treatment on the two buttocks on the following scale (Table 5).

Table 5: Subject Satisfaction with Cellulite Treatment Assessment - Buttocks

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

Subjects will enter their responses directly into an EDC system using a handheld tablet.

2.12. Skin Assessment (Fitzpatrick Scale)

At the Screening visit, subject skin type will be evaluated by the Investigator using the Fitzpatrick Scale, shown in Table 6.

Table 6: Fitzpatrick Scale

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

2.13. Weight, Height, and BMI

At the Screening visit, height and weight measurements will be taken. Baseline body mass index (BMI) will be computed from these measurements as the weight in kilograms (kg) divided by height in meters squared (m^2). Body weight will also be measured at the Day 22, Day 43, and Day 71 visits; BMI will be computed from each of these measurements using the height at screening.

2.14. Adverse Events

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

The following information will be collected for all AEs:

- Verbatim description
- Date of Onset
- Date of Resolution/or Ongoing
- Severity (Mild, Moderate, Severe)
- Relationship to Study Drug (Not Related, Unlikely Related, Possibly Related, Probably Related)
- Action taken with study drug (None, Drug Interrupted, Drug Withdrawn)
- Outcome (Recovered/Resolved, Recovered/Resolved w/Sequelae, Recovering/ Resolving, Not Recovered/Not Resolved, Fatal, Unknown)
- Whether the AE led to study discontinuation
- Whether or not a concomitant medication or procedure was required
- Classified as a serious adverse event (SAE) or not
- SAE Code (Death, Life-threatening, Inpatient or prolonged hospitalization, Persistent or significant disability/incapacity, Congenital anomaly or birth defect, Other medically important event)
- Designation of an AE of Special Interest: AEs including bruising, ecchymosis, hematomas, and contusions that occur **remote** to the site of drug administration, or any hypersensitivity reactions, including anaphylaxis, will be recorded as an AE of special interest and reported as an AE or SAE as appropriate. In addition, local adverse events associated with the injection site, including bruising, pain, nodules/mass, ulceration, erythema, pruritus, swelling, and/or induration, will be recorded and evaluated for seriousness and severity

2.15. Medical History

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

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

For reproductive history, subjects are to indicate the date of their last menstrual period and the number of pregnancies they have had.

2.16. Edematous Fibrosclerotic Panniculopathy Disease History

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

2.17. Physical Examination

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

2.18. Vital Signs

Blood pressure (systolic/diastolic), respiratory rate, pulse rate, and body temperature will be assessed at each study visit. On injection days, blood pressure, respiratory rate, and pulse rate will be measured prior to the injections (up to 4 hours prior to the injection), and at 15 and 30 minutes after the injection. If at the 30-minute measurement, the vital signs are not stable, subjects will be required to remain at the site until all the vital signs are stable. The investigator will record only the last vital sign measurement prior to discharge. On injection days, body temperature will be taken only prior to the injection, at the 30-minute post-dose measurement, and, if necessary, at the prior to discharge measurement. On injection days, the time the vital signs are taken will also be recorded.

2.19. 12-Lead Electrocardiogram

During the screening period, subjects will have a resting 12-lead ECG. A qualified physician will assess the ECG as normal, abnormal not clinically significant, or abnormal clinically significant. The investigator or qualified designee must sign and date the ECG, thereby acknowledging review of the ECG results. The investigator will be able to record any comments regarding the ECG, including explaining any abnormal findings or providing details if the ECG was not done per protocol.

2.20. Clinical Laboratory

Blood (15 mL) and urine samples will be collected for testing the following clinical laboratory parameters during the screening period and at the Day 71 visit. The analytes listed in Table 7 will be obtained. A certified central laboratory will process specimens and provide results for each subject.

Table 7: Clinical Laboratory Parameters

Hematology	Biochemistry	Urinalysis
Hemoglobin Hematocrit Red blood cell White blood cell (WBC) Platelets WBC Differential	Glucose Sodium Potassium Calcium Chloride Carbon dioxide (CO_2) Inorganic phosphate Blood urea nitrogen (BUN) Creatinine Creatinine clearance (estimated) Aspartate transaminase (AST) Alanine transaminase (ALT) Gamma-glutamyl transferase (GGT) Total bilirubin (TBL) (direct bilirubin reflex if elevated) Albumin Alkaline phosphatase (ALP) Uric acid	Glucose Protein Specific gravity pH Ketones Bilirubin Urobilinogen Nitrite Blood [a] Leukocytes [a]

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

2.21. Pregnancy Test

For all subjects, serum pregnancy tests will be done at Screening and Day 71/End of Study/Early Termination and urine pregnancy tests will be performed at Day 1, Day 22, and Day 43 prior to the study drug administration to assess subject's eligibility for entry into the study and eligibility for administration of study drug.

A certified laboratory will process specimens and provide results for each subject at Screening and Day 71. Urine dipsticks will be done on site at the Day 1, Day 22, and Day 43 visits.

2.22. Immunogenicity Samples

Serum samples to be analyzed for anti-AUX-I and anti-AUX-II antibodies will be drawn before the injection on the Day 1, Day 22, and Day 43 visits, and at the Day 71 visit. Serum samples will be tested for binding anti-AUX- and anti-AUX-II antibodies at those visits. A subset [redacted] of subject samples will be tested for neutralizing antibodies from the Day 1 and Day 71 visits; additional samples will be retained.

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

2.23. Concomitant Medications

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

- Verbatim name of medication
- Medication start date
- Medication end date or ongoing
- Dose, units, frequency, and route of medication
- Reason for medication (medical history, AE, prophylaxis, health maintenance, EFP/cellulite, birth control, or other)

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

2.24. Concomitant Procedures/Therapies

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

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

Additional space is available for comments regarding reason for procedure.

3. STUDY PARAMETERS

3.1. Subject Disposition

Subjects will be considered as completing the study (ie, completers) if they complete the Day 71 visit. Subjects who do not complete the study will report their reason for early discontinuation. Time in the study (days) will be computed as the date of last visit minus the date of Day 1 + 1, where the date of the last visit is determined as the following:

- The date of Day 71 if the subject completes the study
- The date of early termination visit if the subject is terminated early from study at a non-scheduled visit
- The date of the latest scheduled visit if the subject is terminated early from study at a scheduled visit or lost to follow-up

3.2. Number of Treatment Sessions

A treatment session will be counted as given overall if at that treatment session a subject receives at least 1 injection of study drug in either or both of the buttocks. Total number of treatment sessions overall received will be calculated.

For each of the buttocks (target or non-target buttock), subjects who receive at least 1 injection of study medication on Day 1, Day 22, or Day 43 will be counted as having a treatment session. Subjects will be classified into cohorts by buttock based on the number of treatment sessions they have. The reason why a treatment session was not done will be obtained and classified into one of the following:

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

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

- 12 injections per buttock given
- Less than 12 injections per buttock given due to not enough evident dimples
- Less than 12 injections per buttock given due to AE
- Less than 12 injections per buttock given due to other reasons

3.3. Early Termination Visit Assessments

Subjects who discontinue early will have all Day 71 procedures and assessments completed at an early termination visit. Those assessments and measurements will not be used for the observed data analysis at Day 71 but for the Day 71 (last observation carried forward [LOCF]) analysis.

3.4. Treatment Groups

Subjects will be divided into 1 of 2 treatment groups based on their randomization. The 2 treatment groups will be referred to as:

- EN3835 1.68 mg total dose (0.84 mg per buttock)
- Placebo

These group assignments will remain regardless of the actual dose or type of study medication received. Subjects who receive a different dose or different study medication at any of the treatment sessions (due, for example, to a pharmacy error) from the treatment to which they were randomized will be summarized within their randomized group unless explicitly specified. These subjects will also be reported as a protocol deviation.

3.5. Efficacy Parameters

3.5.1. PR-PCSS

3.5.1.1. Baseline PR-PCSS Rating

For each buttock (target or non-target), the baseline PR-PCSS rating will be based on the subject's PR-PCSS evaluation done at Day 1. If no evaluation is done for a buttock on Day 1 (eg, done using an incorrect digital image), the rating of the subject's PR-PCSS for that buttock at Screening will be used for the baseline.

3.5.1.2. Change from Baseline PR-PCSS Rating

For each buttock (target or non-target), the change from baseline PR-PCSS rating will be the visit rating minus the baseline rating. A more negative change in rating indicates a greater improvement of cellulite severity in that buttock.

3.5.1.3. Subject PR-PCSS Responders for Target Buttock

A 2-level PR-PCSS responder for the target buttock is defined as a subject with an improvement in the PR-PCSS rating of at least 2 levels from baseline (ie, change from baseline PR-PCSS rating of -2, -3, or -4) on the target buttock.

A 1-level PR-PCSS responder for the target buttock is defined as a subject with an improvement in the PR-PCSS rating of at least 1 level from baseline (ie, change from baseline PR-PCSS rating of -1, -2, -3, or -4) on the target buttock at an evaluation time point.

3.5.1.4. Subject PR-PCSS Responders for Non-target Buttock

A 2-level PR-PCSS responder for the non-target buttock is defined as a subject with an improvement in the PR-PCSS rating of at least 2 levels from baseline (ie, change from baseline PR-PCSS rating of -2, -3, or -4) on the non-target buttock.

A 1-level PR-PCSS responder for the non-target buttock is defined as a subject with an improvement in the PR-PCSS rating of at least 1 level from baseline (ie, change from baseline PR-PCSS rating of -1, -2, -3, or -4) on the non-target buttock at an evaluation time point.

3.5.1.5. PR-PCSS Responders for at Least One Buttock

A 1-level PR-PCSS responder for at least one buttock is defined as a subject who is a 1-level PR-PCSS responder (as defined previously, this is a subject with at least a 1-level improvement in PR-PCSS from baseline rating) for either the target buttock or the non-target buttock or both buttocks at an evaluation time point.

A 2-level PR-PCSS responder for at least one buttock is defined as a subject who is a 2-level PR-PCSS responder for either the target buttock or the non-target buttock or both buttocks at an evaluation time point.

3.5.1.6. PR-PCSS Responders for Two Buttocks

A 1-level PR-PCSS responder for the two buttocks in the same individual subject is defined as a subject who is a 1-level PR-PCSS responder for both buttocks at an evaluation time point.

A 2-level PR-PCSS responder for the two buttocks in the same individual subject is defined as a subject who is a 2-level PR-PCSS responder for both buttocks at an evaluation time point.

3.5.2. S-GAIS

3.5.2.1. S-GAIS Rating

The S-GAIS rating is directly obtained from the subject's assessments of each buttock (target or non-target) at an evaluation visit.

3.5.2.2. S-GAIS Responders for Target Buttock

A 1-level S-GAIS responder for the target buttock is defined as a subject with S-GAIS rating of at least 1 (ie, 1, 2 or 3) on the target buttock at an evaluation time point.

A 2-level S-GAIS responder for the target buttock is defined as a subject with S-GAIS rating of at least 2 (ie, 2 or 3) on the target buttock at an evaluation time point.

3.5.2.3. S-GAIS Responders for Non-target Buttock

A 1-level S-GAIS responder for the non-target buttock is defined as a subject with S-GAIS rating of at least 1 (ie, 1, 2 or 3) on the non-target buttock at an evaluation time point.

A 2-level S-GAIS responder for the non-target buttock is defined as a subject with S-GAIS rating of at least 2 (ie, 2 or 3) on the non-target buttock at an evaluation time point.

3.5.2.4. S-GAIS Responders for at Least One Buttock

A 1-level S-GAIS responder for at least one buttock is defined as a subject who is a 1-level S-GAIS responder for either the target buttock or the non-target buttock or both buttocks at an evaluation time point.

3.5.2.5. S-GAIS Responders for Two Buttocks

A 1-level S-GAIS responder for the two buttocks in the same individual subject is defined as a subject who is a 1-level S-GAIS responder for both buttocks at an evaluation time point.

3.5.3. PR-CIS

The PR-CIS total score will be the sum of the six items on the scales. Item #1 on the PR-CIS asking how happy the subject is about their appearance of cellulite will be reversed by subtracting the subject's reported assessment from 10 (ie, for purposes of the composite, scoring for the "happy" question was reversed (reflected) to make it directionally consistent with the other questions). In this manner, a higher number on six of the PR-CIS questions will reflect a more negative impact. The PR-CIS total score can range from 0 to 60 with higher numbers reflecting more negative impact from the cellulite. If scores on two or less of the 6 items are missing, the PR-CIS total score will be computed as the mean of the answered items times 6. If scores on three or more of the six items are missing, then the PR-CIS total score will be set to missing.

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

3.5.3.1. Baseline PR-CIS Item Scores

Baseline PR-CIS score for each individual item will be based on the subject's response to the item at Day 1.

3.5.3.2. Change from Baseline PR-CIS Item Scores

The change from baseline PR-CIS item score will be the visit score minus the baseline score. For Item #1, a more positive change in score indicates a greater improvement of impact of the cellulite on subject's happiness while for other items a more negative change in score indicates a greater reduction of impact of the cellulite on subject's life.

3.5.3.3. Responders Based on PR-CIS Item Scores

A PR-CIS responder for each item is defined as a subject with a reduction in the PR-CIS total score of at least 2 from baseline at an evaluation time point.

3.5.3.4. Baseline PR-CIS Total Scores

Baseline PR-CIS total score will be based on the subject's PR-CIS total score at Day 1.

3.5.3.5. Change from Baseline PR-CIS Total Scores

The change from baseline PR-CIS total score will be the visit total score minus the baseline total score. A more negative change in score indicates a greater reduction of impact of the cellulite on subject's life.

3.5.3.6. Responders Based on PR-CIS Total Score

For PR-CIS total score, a PR-CIS responder is defined as a subject with a reduction in the PR-CIS total score of at least 12 from baseline (ie, average of at least 2 for each item) at an evaluation time point.

3.5.3.7. Baseline PR-CIS Abbreviated Total Scores

Baseline PR-CIS abbreviated total score will be based on the subject's PR-CIS abbreviated total score at Day 1.

3.5.3.8. Change from Baseline PR-CIS Abbreviated Total Scores

The change from baseline PR-CIS abbreviated total score will be the visit abbreviated total score minus the baseline abbreviated total score. A more negative change in score indicates a greater reduction of impact of the cellulite on subject's life.

3.5.3.9. Responders Based on PR-CIS Abbreviated Total Scores

For PR-CIS abbreviated total score, a PR-CIS responder is defined as a subject with a reduction in the PR-CIS total score of at least 10 from baseline (ie, average of at least 2 for each item) at an evaluation time point.

3.5.4. SSRS

3.5.4.1. SSRS Rating Scores

The subject SSRS rating score is directly obtained from the subject's assessments of a region, ie, two buttocks, at baseline (Day 1) and the Day 71/early termination visit.

3.5.4.2. Subject 1-Level SSRS Responders

A 1-Level SSRS responder is defined as a subject with at least slightly satisfied (ie, slightly satisfied [4], very satisfied [5] or extremely satisfied [6]) with her appearance of the cellulite on her buttocks at Day 71/early termination visit.

3.5.5. Subject Global Satisfaction With Cellulite Treatment

3.5.5.1. Subject Global Satisfaction With Cellulite Treatment Rating

The subject global satisfaction with cellulite treatment rating is directly obtained from the subject's assessments of a region, ie, two buttocks, at the Day 71/early termination visit.

3.5.5.2. Subject-satisfied Responders

Subject-satisfied responder is defined as subjects with a response of "Satisfied" or "Very Satisfied" in the subject satisfaction with cellulite treatment assessment at Day 71/early termination visit.

3.5.6. CR-PCSS

3.5.6.1. Investigator Baseline CR-PCSS Rating

For each buttock (target or non-target), investigator baseline CR-PCSS rating will be based on the investigator's CR-PCSS evaluation done at Day 1.

3.5.6.2. Investigator Change from Baseline CR-PCSS Rating

For each buttock (target or non-target), the investigator change from baseline CR-PCSS rating will be the investigator visit rating minus the investigator baseline rating at an evaluation time point. A more negative change from baseline indicates a greater improvement of cellulite severity in that buttock.

3.5.6.3. CR-PCSS Responders for Target Buttock

A 2-level CR-PCSS responder for the target buttock is defined as a subject with an improvement in the CR-PCSS rating of at least 2 levels from baseline (ie, change from baseline CR-PCSS rating of -2, -3, or -4) on the target buttock at an evaluation time point.

A 1-level CR-PCSS responder for the target buttock is defined as a subject with an improvement in the CR-PCSS rating of at least 1 level from baseline (ie, change from baseline CR-PCSS rating of -1, -2, -3, or -4) on the target buttock at an evaluation time point.

3.5.6.4. CR-PCSS Responders for Non-target Buttock

A 2-level CR-PCSS responder for the non-target buttock is defined as a subject with an improvement in the CR-PCSS rating of at least 2 levels from baseline (ie, change from baseline CR-PCSS rating of -2, -3, or -4) on the non-target buttock at an evaluation time point.

A 1-level CR-PCSS responder for the non-target buttock is defined as a subject with an improvement in the CR-PCSS rating of at least 1 level from baseline (ie, change from baseline CR-PCSS rating of -1, -2, -3, or -4) on the non-target buttock at an evaluation time point.

3.5.6.5. CR-PCSS Responders for at Least One Buttock

A 1-level CR-PCSS responder for at least one buttock is defined as a subject who is a 1-level CR-PCSS responder for either the target buttock or the non-target buttock or both buttocks at an evaluation time point.

A 2-level CR-PCSS responder for at least one buttock is defined as a subject who is a 2-level CR-PCSS responder for either the target buttock or the non-target buttock or both buttocks at an evaluation time point.

3.5.6.6. CR-PCSS Responders for Two Buttocks

A 1-level CR-PCSS responder for the two buttocks in the same individual subject is defined as a subject who is a 1-level CR-PCSS responder for both the target and non-target buttocks at an evaluation time point.

A 2-level CR-PCSS responder for the two buttocks in the same individual subject is defined as a subject who is a 2-level CR-PCSS responder for both the target and non-target buttocks at an evaluation time point.

3.5.7. I-GAIS

3.5.7.1. I-GAIS Rating

The I-GAIS rating is directly obtained from the investigator's assessments at an evaluation visit.

3.5.7.2. I-GAIS Responders for Target Buttock

A 1-level I-GAIS responder for the target buttock is defined as a subject with I-GAIS rating of at least 1 (ie, 1, 2, or 3) on the target buttock at an evaluation time point.

3.5.7.3. I-GAIS Responders for Non-target Buttock

A 1-level I-GAIS responder for the non-target buttock is defined as a subject with I-GAIS rating of at least 1 (ie, 1, 2, or 3) on the non-target buttock at an evaluation time point.

3.5.7.4. I-GAIS Responders for at Least One Buttock

A 1-level I-GAIS responder for at least one buttock is defined as a subject who is a 1-level I-GAIS responder for either the target buttock or the non-target buttock or both buttocks at an evaluation time point.

3.5.7.5. I-GAIS Responders for Two Buttocks

A 1-level I-GAIS responder for the two buttocks in the same individual subject is defined as a subject who is a 1-level I-GAIS responder for both the target and non-target buttocks at an evaluation time point.

3.5.8. Subject (PR-PCSS)/Investigator (CR-PCSS) Composite Responders

3.5.8.1. Composite Responders for Target Buttock

For each visit (Day 22, Day 43, and Day 71), the subject PR-PCSS responder classification and investigator CR-PCSS responder classification for the target buttock will be used to compute the composite responder classification for that buttock. If the classification is missing for 1 or both components (ie, the PR-PCSS component or the CR-PCSS component), then the composite responder classification is missing for that visit.

A 2-level composite responder for the target buttock is defined as any subject who is both a 2-level PR-PCSS responder and a 2-level CR-PCSS responder for the target buttock. If the subject is a 2-level responder on 1 component but not on the other or on neither component for the target buttock, then the subject will be classified as a 2-level non-composite responder for the target buttock.

A 1-level composite responder for the target buttock is defined as any subject who is both a 1-level PR-PCSS responder and a 1-level CR-PCSS responder for the target buttock. If the subject is a 1-level responder on 1 component but not on the other or on neither component for the target buttock, then the subject will be classified as a 1-level non-composite responder for the target buttock.

3.5.8.2. Composite Responders for Non-target Buttock

For each visit (Day 22, Day 43, and Day 71), the subject PR-PCSS responder classification and investigator CR-PCSS responder classification for the non-target buttock will be used to compute the composite responder classification for that buttock. If the classification is missing for 1 or both components, then the composite responder classification is missing for that visit.

A 2-level composite responder for the non-target buttock is defined as any subject who is both a 2-level PR-PCSS responder and a 2-level CR-PCSS responder for the non-target buttock. If the subject is a 2-level responder on 1 component but not on the other or on neither component for the non-target buttock, then the subject will be classified as not a “2-level composite responder for the non-target buttock”.

A 1-level composite responder for the non-target buttock is defined as any subject who is both a 1-level PR-PCSS responder and a 1-level CR-PCSS responder for the non-target buttock. If the subject is a 1-level responder on 1 component but not on the other or on neither component for the non-target buttock, then the subject will be classified as not a "1-level composite responder for the non-target buttock".

3.5.8.3. Composite Responders for at Least One Buttock

A 2-level composite responder for at least one buttock is defined as any subject who is a 2-level composite responder for the target buttock or the non-target buttock or both buttocks; otherwise the subject will be defined as not a "2-level composite responder for at least one buttock".

A 1-level composite responder for at least one buttock is defined as any subject who is a 1-level composite responder for the target buttock or the non-target buttock or both buttocks; otherwise the subject will be defined as not a "1-level composite responder for at least one buttock".

3.5.8.4. Composite Responders for Two Buttocks

A 2-level composite responder for the two buttocks in the same individual subject is defined as any subject who is a 2-level composite responder for both the target buttock and the non-target buttock; otherwise the subject will be defined as not a "2-level composite responder for the two buttocks".

A 1-level composite responder for the two buttocks in the same individual subject is defined as any subject who is a 1-level composite responder for both the target buttock and the non-target buttock; otherwise the subject will be defined as not a "1-level composite responder for the two buttocks".

3.6. Safety Parameters

3.6.1. Adverse Events

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

3.6.1.1. Adverse Event Treatment Session

An AE's association with a treatment session will be based on the start date of the AE compared to the date of the injection. Adverse events with a start date between the Day 1 visit date and the day prior to the next dose or, if no further dose, the last visit date in the study will be associated with Treatment Session 1. If study drug is administered at the Day 22 visit, AEs with a start date between the Day 22 visit date and the day prior to the next dose or, if no further dose, the last visit date in the study will be associated with Treatment Session 2. If study drug is administered at the Day 43 visit, AEs with a start date between the Day 43 visit date and the Day 71 visit date will be associated with Treatment Session 3.

3.6.1.2. Adverse Event Duration

Duration of an AE will be the AE end date minus the AE start date + 1. If AEs are still ongoing at the end of the study or AEs have partial start or stop dates, durations of those AEs are not determined.

The duration of AEs will be used to determine the categories of AE durations (1-4 days, 5-7 days, 8-14 days, 15-21 days, and >21 days). For ongoing AEs, the category of AE duration will be missing unless those events have an onset date 21 days prior to the subject's last visit in the study. In this case, the category of the AE duration will be classified as ">21 days".

3.6.2. Vital Signs and Clinical Laboratories

3.6.2.1. Baseline Values and Change from Baseline Values

The baseline values for vital signs (study baseline) and clinical laboratories will be the last available measurement prior to the first dose of study medication. For clinical laboratories this could be the screening value or it could be an unscheduled lab, if the unscheduled lab is the closest value preceding the first injection. For vital signs, baseline will be those taken at Day 1 predose for the by-visit analyses.

Vital signs will additionally be analyzed on each injection day. For each injection day, baseline (injection day baseline) will be a predose value taken on that day.

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

3.6.2.2. Sponsor-defined Potentially Clinically Important Laboratory Values

Table 8 presents the criteria for determining potentially clinically important (PCI) laboratory values.

Table 8: Sponsor-defined Potentially Clinically Important Laboratory Criteria

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

ALT=Alanine aminotransferase; AST=Aspartate aminotransferase; BUN=Blood urea nitrogen; PCI=Potentially clinically important; ULN=Upper limit of normal

3.6.2.3. Sponsor-defined Potentially Clinically Important Vital Sign Values

Table 9 presents the criteria (using study baseline) for determining PCI vital sign values.

Table 9: Sponsor-defined Potentially Clinically Important Vital Sign Criteria

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

bpm=Beats per minutes; brpm=Breaths per minute; PCI=Potentially clinically important

3.7. Other Parameters

3.7.1. Immunogenicity

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

Samples to be assayed for neutralizing antibodies for AUX-I and AUX-II will be obtained from a subset of seropositive binding antibodies samples on Day 1 and Day 71 (see section 2.22). Samples will be classified as positive or negative for neutralizing antibodies based on the results of these assays.

3.7.2. Medical History

Medical history will be mapped to preferred term using MedDRA. Subjects with medical histories of Dupuytren's disease, Ledderhose's disease, knuckle pads, diabetes, and epilepsy will be summarized. Subjects will be coded as having these disorders based on the preferred term of their reported medical histories. Knuckle pads will also include the preferred term of 'Garrod pads'. Ledderhose's disease will also include the preferred term of 'fibromatosis'. Epilepsy will also include the preferred term of 'convulsion'. Diabetes will include the preferred terms of 'diabetes mellitus', 'type 1 diabetes mellitus', or 'type 2 diabetes mellitus'. Diabetes will not include subjects who report 'glucose tolerance impaired' (borderline diabetes or pre-diabetes), 'diabetic vascular disorder' or 'blood glucose increased'. All medical history terms will be reviewed by the study medical monitor to determine if any other terms should be included in the summary.

Age at EFP symptoms onset will be computed as the date of the EFP symptoms reported on the medical history eCRF minus the date of birth divided by 365.25. If the date of EFP symptom onset is incomplete, the date will be imputed according to the rules set up in section 6.2.2.

3.7.3. Prior/Concomitant Medications

All medications will be coded with the World Health Organization (WHO) drug dictionary. A concomitant medication is any medication with a stop date on or after the date of the first injection or the medication is reported as ongoing. A prior medication is any medication with a stop date prior to the date of the first injection.

3.7.4. Prior EFP Treatment

Prior EFP treatment will be obtained from the prior/concomitant medication and prior/ concomitant procedure pages of the eCRF. If on either of these pages a medication or treatment is reported with the indication 'EFP/cellulite' with a start date prior to the first dose of study medication, then the medication or procedure will be considered a prior EFP treatment. All medications will be classified as EFP drug. All procedures will be classified into one of the following groups:

- Liposuction
- Laser treatments
- Surgery (subcision or powered subcision)
- Massage
- Radiofrequency
- Mesotherapy (including injections)
- Cryolipolysis
- Buttock implant treatment
- Cream
- Other

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

Time since the last EFP treatment will be computed as the date of the most recent EFP treatment minus the date the informed consent was signed divided by 365.25. If the date of any EFP treatments is incomplete, the date will be imputed according to the rules set up in section 6.2.2.

4. ANALYSIS POPULATIONS

4.1. Safety Population

The safety population is defined as all enrolled subjects who have at least 1 injection of study medication. All safety parameters will be summarized based on this population.

4.2. Intent-to-Treat (ITT) Population

The ITT population is defined as all randomized subjects who have at least 1 injection of study medication. All demographic and baseline characteristic summaries will be based on this population. The primary and key secondary efficacy parameters will be summarized based on this population.

4.3. Modified Intent-to-Treat (mITT) Population

The mITT population is defined as all ITT subjects with a baseline and at least 1 post-injection evaluation of both the investigator CR-PCSS and subject PR-PCSS for both the target and non-target buttocks. All efficacy evaluations will be analyzed based on the mITT population.

4.4. Per-Protocol (PP) Population

The PP population is defined as a subset of the mITT population who are considered compliant with the protocol to ensure the efficacy analysis most closely reflects the scientific model underlying the protocol.(1)

Study subjects will be excluded from the PP population if they meet any of the following criteria:

- Placebo randomized subject who receives EN3835 treatment
- EN3835 randomized subject who receives placebo treatment only throughout study
- Any subject who receives protocol-prohibited medications
- Subject missing PR-PCSS and/or CR-PCSS assessment at Day 71
- Subject with a buttock not receiving all three treatment sessions without medical reasons (eg, adverse events or CR-PCSS rated as zero (0))
- Subject who did not meet all inclusion and exclusion criteria

If more than 10% of the mITT population subjects are excluded from the PP population, then all efficacy summaries will be repeated for the PP population. All protocol violations, major and minor, will be listed.

5. STATISTICAL METHODS

5.1. Overview

The primary efficacy endpoint will be summarized as percentages and analyzed using a CMH test that compares the 2 treatment groups and adjusts for analysis center at a level of significance of 0.05 based on the ITT population. Any subject who does not have an evaluation of either CR-PCSS or PR-PCSS at Day 71 will be classified as a non-responder.

The key secondary efficacy endpoints except for change from baseline in the PR-CIS total score at Day 71 will be summarized as percentages and analyzed using a CMH test that compares the 2 treatment groups and adjusts for analysis center based on the ITT population. Any subject who does not have an evaluation or assessment at Day 71 will be classified as a non-responder. The change from baseline in the PR-CIS total score at Day 71 will be summarized using descriptive

statistics (n, mean, standard deviation (SD), median, minimum and maximum) and analyzed by ANCOVA with a factor of treatment group and analysis center adjusting for baseline value. The key secondary efficacy Family #1 analyses will be performed only if the primary efficacy analysis is significant at a significance level of $p \leq 0.05$. Similarly key secondary efficacy Family #2 analyses will be performed only if at least one of four key secondary efficacy Family #1 endpoints is significant at a significance level of $p \leq 0.0125$ and key secondary efficacy Family #3 analyses will be performed only if at least one of two key secondary efficacy Family #2 endpoints is significant at a significance level of unused alpha from Family #1 divided by 2. Any subject who does not have a PR-CIS evaluation or assessment at Day 71 will be imputed as baseline value for the analysis. Within a family of key secondary efficacy endpoints a Bonferroni procedure will be performed to assure an overall type I error rate of no more than 0.05.

All supportive efficacy endpoints will be summarized as percentages. All the supportive analyses are performed based on the observed data only at all the visits in the mITT population without multiplicity adjustment. An additional analysis will be performed at Day 71 with missing data at Day 71 handled by an LOCF approach if subjects have at least one post-dose evaluation. If a subject does not have any post-dose evaluation, analysis value will be missing (not imputed). The dichotomous secondary endpoints (ie, responder endpoints) will be analyzed using a CMH test adjusted for analysis center. Changes in the PR-PCSS ratings and CR-PCSS ratings from baselines, S-GAIS ratings, and I-GAIS ratings will be analyzed using the Wilcoxon rank sum test. Changes from baselines in PR-CIS individual items, total scores or abbreviated total scores will be analyzed using the analysis of covariance (ANCOVA) adjusted for baseline values.

The AE endpoints will be summarized as count and percentages by preferred term and by treatment group and *p* values will be obtained from the Fisher exact test to test treatment difference of incidence. The change from baseline for vital signs and clinical laboratory parameters are compared between EN3835 and placebo using an analysis of variance (ANOVA) with a factor of drug (EN3835 or placebo) while the Fisher exact test will be used for the incidence of PCI values.

The following SAS code will be used for CMH test:

```
Proc Freq data=<dataset>;
   Table CENTER*DRUG*OCCUR/CMH;
Run;
```

Where CENTER is the analysis center, DRUG is the randomized treatment group (EN3835 1.68 mg total dose or placebo) and OCCUR is the incidence of the event variable.

The following SAS code will be used for Wilcoxon rank sum test:

```
Proc NPAR1WAY data=<dataset> Wilcoxon;
   Class DRUG;
   Var DEPVAR;
Run;
```

Where DRUG is the randomized treatment group (EN3835 1.68 mg total dose or placebo) and DEPVAR is the dependent variable.

[redacted]

The following SAS code will be used for the Fisher exact test:

```
Proc Freq data=<dataset>;
   Table DRUG*DEPVAR/Fisher;
Run;
```

Where DRUG is the randomized treatment group (EN3835 1.68 mg total dose or placebo) and OCCUR is the incidence of the event variable.

The following SAS code will be used for ANCOVA with a factor of treatment group adjusted for baseline:

```
Proc GLM data=<dataset>;
   Class DRUG;
   Model DEPVAR = DRUG CENTER BASE / ss3;
Run;
```

Where DRUG is the randomized treatment group (EN3835 1.68 mg total dose or placebo), CENTER is the analysis center, DEPVAR is the dependent variable, and BASE is the value of the dependent variable at baseline.

The following SAS code will be used for ANOVA with a factor of treatment group:

```
Proc GLM data=<dataset>;
   Class DRUG;
   Model DEPVAR = DRUG / ss3;
Run;
```

Where DRUG is the randomized treatment group (EN3835 1.68 mg total dose or placebo) and DEPVAR is the dependent variable.

5.2. Analysis Centers

Small centers will be combined into analysis centers for the CMH analyses. Any site with at least 8 subjects per treatment arm will stand alone as an analysis center. The smallest sites are to be pooled together until the analysis center has at least 8 subjects per treatment arm. The next larger centers will be then pooled together to reach at least 8 subjects per treatment arm, etc., until all analysis centers have at least 8 subjects per treatment arm. If the last pooled analysis center does not have at least 8 subjects per treatment arm, it will be pooled into the previously pooled center. If two or more small sites enrolled the same number of subjects in the study, the smaller number of subjects of either of the two treatment groups within a site or site ID number will be used to break the tie:

- The site with the lowest number of subjects in either treatment group will be pooled first.
- In the event the sites have the same lowest number of subjects in either treatment group, then the site with the lower site ID will be pooled first.

Consistency of treatment response across analysis centers for the primary endpoint will be assessed by plotting the proportion of responders on the EN3835 arm versus the proportion of responders on the placebo arm by center. Additionally, site to site variability as well as analysis center to center variability will be assessed by the Breslow-Day test.

5.3. Missing Data Handling

Missing efficacy data will be imputed or handled prior to each pre-specified statistical analysis by one of the following:

- Missing data points are imputed as baseline values. For responder analysis, missing data are considered as non-responders
- Last observation (post-dose) carried forward (LOCF) for the visit
- Multiple imputation (MI)
- Missing data points are not used in the analysis

See individual sections for details.

5.4. Subjects Given Incorrect Treatment

All the efficacy analyses will be performed based on the randomized (ITT) treatment group regardless of actual treatments. All safety analyses will be based on actual treatment received by subjects and for overall summary any subjects who received EN3835 in at least 1 treatment session will be included in the EN3835 group and subjects who only received placebo during the study will be included in the placebo group.

5.5. Subject Disposition

The disposition summary will be summarized by treatment group and total (ie, 2 treatments combined) and will include:

- Subjects screened
- Subjects randomized/enrolled
- Subjects in the ITT population
- Subjects in the mITT population
- Subjects in the safety population
- Subjects in the PP population
- Subjects who complete the study
- Subjects who early terminated from the study
- Subjects who early terminated from the study by termination reason
- Time in the study
- Subjects at each investigational site

5.6. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group and total and will include:

- Age
- Age category (<25, 25-34, 35-44, and 45 years of age or greater)
- Gender
- Race
- Ethnicity
- Weight (in kg)
- Height (in cm)
- BMI (in kg/m^2)
- BMI group (underweight [<18.5 kg/m^2], normal weight [18.5-<25 kg/m^2], overweight [25.0-<30 kg/m^2], obese [≥30 kg/m^2])
- Skin category based on Fitzpatrick scale rating
- Alcohol use
- Tobacco use

5.7. EFP Risk Factors and EFP History

EFP risk factors and EFP history characteristics variables will be summarized by treatment group and total and will include:

- Family history of cellulite
- Medical history of Dupuytren's disease, knuckle pads, Ledderhose's disease, diabetes, epilepsy (see section 3.7.2)
- Age at EFP symptom onset (in years)
- Prior treatments for EFP including liposuction, laser, massage, radiofrequency, surgery (subcision and powered subcision), drug, cryolipolysis, buttock implants, mesotherapy, cream, other, or none. Subjects can report more than 1 prior EFP treatment.
- Number of prior EFP treatments (0, 1, 2, or ≥3)
- Time since most recent EFP treatment (in years)

5.8. Cellulite Baseline Severity

5.8.1. Cellulite Severity at Screening

For each buttock (target or non-target), EFP severity at Screening will be summarized by treatment group and total and will include:

- Subject PR-PCSS rating at Screening
- Investigator CR-PCSS rating at Screening
- PR-PCSS ratings versus CR-PCSS ratings at Screening

5.8.2. Cellulite Baseline Severity

For each buttock (target or non-target), EFP baseline severity will be summarized by treatment group and total and will include:

- Subject PR-PCSS rating at Day 1
- Investigator CR-PCSS rating at Day 1
- PR-PCSS ratings versus CR-PCSS ratings at Day 1

5.8.3. Cellulite Severity at Screening Versus Day 1

For each buttock (target or non-target), cross tabulation of EFP severity at Screening versus at Day 1 will be summarized by treatment group and total and will include:

- Subject PR-PCSS ratings
- Investigator CR-PCSS ratings

5.9. Efficacy Evaluation

The integrated summary and statistical inference (*p* values and 95% confidence intervals) of the primary and key secondary endpoints based on two design-identical, double-blind, placebo-controlled, phase 3 studies, EN3835-302 and EN3835-303, will be performed in the Integrated Summary of Efficacy (ISE) to provide more accurate and substantial evidence of efficacy of EN3835 in the treatment of EFP on the buttocks in adult women.

5.9.1. Overview of Treatment

The following information regarding treatment sessions for the target buttock will be summarized by treatment group:

- Number of treatment sessions per subject
- Number of subjects who had treatment done or treatment not done at each treatment visit
- For subjects who had the treatment done, the number of subjects who got all 12 injections in the target buttock at the treatment visit or who received less than 12 injections in the target buttock and the reason why (see section 3.2)

- For subjects who did not have the treatment done, the reason why the treatment was not done (see section 3.2)
- Number of injections given at each treatment visit
- Number of dimples treated at each treatment visit
- Number of injections per dimple at each treatment visit (calculated)

The following information regarding treatment sessions for the non-target buttock will be summarized by treatment group:

- Number of treatment sessions per subject
- Number of subjects who had treatment done or treatment not done at each treatment visit
- For subjects who had the treatment done, the number of subjects who got all 12 injections in the non-target buttock at the treatment visit or who received less than 12 injections in the non-target buttock and the reason why (see section 3.2)
- For subjects who did not have the treatment done, the reason why the treatment was not done (see section 3.2)
- Number of injections given at each treatment visit
- Number of dimples treated at each treatment visit
- Number of injections per dimple at each treatment visit (calculated)

For the two buttocks overall, the following information regarding treatment sessions will be summarized by treatment group:

- Number of treatment sessions given overall per subject
- Total number of treatment sessions given overall
- Number of injections given at each treatment visit
- Number of dimples treated at each treatment visit
- Number of injections per dimple at each treatment visit (calculated)

Subjects who did not receive all 3 treatment sessions will be listed. The listing will include the treatment group, subject ID, treatment area, treatment not done, and the reason why no treatment was done.

Subjects who did not receive 12 injections at a treatment visit for any treated buttock will be listed. The listing will include the treatment group, subject ID, treatment area, treatment visit, number of injections given, and the reason why 12 injections were not given.

5.9.2. Multiple Comparisons for Efficacy Endpoints

Individual *p* values obtained in section 5.9.3 through section 5.9.6 (also called raw *p* values) form a basis for multiple comparisons with type 1 error controlled for the study efficacy endpoints. The overall type 1 error rate is 0.05 for the study. A hierarchical gatekeeping procedure is used to control the family-wise error rate between families of efficacy endpoints

(primary and key secondary endpoints). Table 10 lists the multiplicity tests for efficacy endpoints.

The multiple comparison results will be used for a claim of EN3835 treatment effect against placebo.

Table 10: Multiplicity Tests for Efficacy Endpoints

Order	Group	Endpoint	Raw *P* Value [a]	Significance at 0.05 [b]
1	Primary	Two-level composite responders of the target buttock at Day 71	x.xxx	*
2	Secondary Family #1	One-level PR-PCSS responders of the target buttock at Day 71	x.xxx	*
2	Secondary Family #1	Two-level PR-PCSS responders of the target buttock at Day 71	x.xxx	*
2	Secondary Family #1	One-level composite responders of the target buttock at Day 71	x.xxx	*
2	Secondary Family #1	Two-level composite responders of the non-target buttock at Day 71	x.xxx	*
3	Secondary Family #2	One-level SSRS responders at Day 71	x.xxx	*
3	Secondary Family #2	Change from baseline (Day 1) of the PR-CIS total score at Day 71	x.xxx	
4	Secondary Family #3	One-level S-GAIS responders of the target buttock at Day 71	x.xxx	
4	Secondary Family #3	Two-level S-GAIS responders of the target buttock at Day 71	x.xxx	

[a] *P* value from pre-defined analysis without multiplicity adjustment.
[b] Asterisk (*) represents statistical significance at significant level of 0.05, see sections 5.9.3 - 5.9.6.
PR-CIS=Patient Reported Cellulite Impact Scale; PR-PCSS=Patient Reported Photonumeric Cellulite Severity Scale; S-GAIS=Subject Global Aesthetic Improvement Scale; SSRS=Subject Self-rating Scale

5.9.3. Primary Endpoint

The rate of subjects who are 2-level composite responders (see section 3.5.8.3) for the target buttock will be summarized by treatment group with counts and percentages based on the ITT population. *P* value (raw *p* value for the multiplicity test) will be computed using CMH test adjusted for analysis center (see section 5.1). A cross-tabulation summary of subject 2-level responders versus investigator 2-level responders for the target buttock will be presented by treatment group.

If the 2-level composite responder status of the target buttock cannot be determined at Day 71, ie, the target buttock is missing a CR-PCSS rating, a PR-PCSS rating, or both, then the subject will be classified as a non-responder of the target buttock.

5.9.4. Key Secondary Endpoints – Family #1

The 1-level PR-PCSS responders for the target buttock (see section 3.5.1.3), the 2-level PR-PCSS responders for the target buttock (see section 3.5.1.3), the 1-level composite responders for the target buttock (see section 3.5.8.1), and the 2-level composite responders for the non-target buttock (see section 3.5.8.2) at Day 71 will be summarized by treatment group

with counts and percentages based on the ITT population. Any missing value at Day 71 will be imputed as a non-responder in the analysis. *P* values (raw *p* values for the multiplicity test) will be computed using CMH test adjusted for analysis center (see section 5.1).

The inference for each of 4 key secondary Family #1 endpoints is primarily based on the results at the Day 71 using the Bonferroni method if and only if the primary endpoint is claimed statistically significant (raw *p* value<0.05).

5.9.5. Key Secondary Endpoints – Family #2

The 1-level SSRS responders (see section 3.5.4.2) and the change from baseline in the PR-CIS total score (see section 3.5.3.9) at Day 71 will be summarized by treatment group with counts and percentages based on the ITT population. Any missing value at Day 71 will be imputed as a non-responder or a baseline value in the analysis. *P* values (raw *p* values for the multiplicity test) will be computed using CMH test adjusted for analysis center (see section 5.1).

The inference for each of 2 key secondary Family #2 endpoints is conducted if and only if at least one of 4 key secondary endpoints in the first family is claimed statistically significant (raw *p* value<0.0125). Unused alpha (0.05, 0.0375, 0.025, 0.0125 corresponding to 4, 3, 2, or 1 of the key secondary endpoints in the first Family being statistically significant, respectively) from the Family #1 tests will be carried over to the inference of 2 key secondary endpoints in the second Family. The inference for each of 2 key secondary Family #2 endpoints will be based on the raw *p* value, unused alpha and the Bonferroni method for alpha spending.

5.9.6. Key Secondary Endpoints – Family #3

The 1-level S-GAIS responders for the target buttock and the 2-level S-GAIS responders for the target buttock (see section 3.5.2.2) at Day 71 will be summarized by treatment group with counts and percentages based on the ITT population. Any missing value at Day 71 will be imputed as a non-responder in the analysis. *P* values (raw *p* values for the multiplicity test) will be computed using CMH test adjusted for analysis center (see section 5.1).

The inference for each of 2 key secondary Family #3 endpoints is conducted if and only if at least one of 2 key secondary endpoints in the second family is claimed statistically significant (raw *p* value<half of the unused alpha from the Family #1). Unused alpha from Family #2 tests, ie, half of unused alpha from the Family #1 tests multiplied by number of endpoints in the Family #2 that are deemed statistically significant from the multiple tests, will be carried over to the inference of 2 key secondary endpoints in the 3rd Family. The inference for each of 2 key secondary Family #3 endpoints will be based on the raw *p* value, unused alpha and the Bonferroni method for alpha spending.

5.9.7. Sensitivity Analyses

The following sensitivity analyses will be conducted for the primary efficacy endpoint. Selected sensitivity analyses will be conducted for key secondary efficacy endpoints, as indicated below. The ITT population will be used for sensitivity analyses unless otherwise noted.

5.9.7.1. Multiple Imputation (MI) for Missing Data

Primary Endpoint: 2-level composite responders for the target buttock,
Key Secondary endpoints: 1-level composite responders for the target buttock and 2-level composite responders for the non-target buttock

A sensitivity analysis examining the potential impact of missing data on the result of the primary efficacy analysis will be performed using multiple imputation. The individual components (PR-PCSS and CR-PCSS) of the primary endpoint (two-level composite responders of the target buttock at Day 71) will be imputed separately on the original 5-point ordinal scales (rating 0-4) within each treatment group with missing values. Multiple datasets (100 datasets) will be generated using the logistic regression method in SAS PROC MI. The logistic models for Day 71 PR-PCSS and Day 71 CR-PCSS will include the 'core' variables, baseline value, and value at a previous visit. The core variables include age, baseline BMI, Fitzpatrick skin type (I-III versus IV-VI), and number of treatments received. A pre-specified seed will be used in SAS procedure PROC MI which is listed in Table 11. The imputed primary composite endpoint will be derived based on the imputed individual components (Day 71 PR-PCSS and Day 71 CR-PCSS). Each imputed dataset will be analyzed via the CMH test, adjusting for analysis center. The values of the general association test statistic from the CMH analysis will be transformed using the Wilson-Hilferty transformation (2) to create a more normally distributed statistic:

$$z = \frac{\sqrt[3]{\text{CMH}} - \left(\frac{7}{9}\right)}{\sqrt{\frac{2}{9}}}$$

The resulting transformed values will be pooled using PROC MIANALYZE in SAS to yield the corresponding pooled *p* value.

Table 11: Initial Seeds for Multiple Imputations

Order	Variable	Initial Seed
1	CR-PCSS rating score	1315377
2	PR-PCSS rating score	4586501
3	S-GAIS rating score	6788473
4	SSRS rating score	9346929
5	PR-CIS total score	5194632

CR-PCSS=Clinician Reported Photonumeric Cellulite Severity Scale; PR-PCSS=Patient Reported Photonumeric Cellulite Severity Scale; S-GAIS=Subject Global Aesthetic Improvement Scale; SSRS=Subject Self-rating Scale; PR-CIS=Patient Reported Cellulite Impact Scale

Key Secondary Endpoints – Binary Responder Endpoints sections 5.9.4, 5.9.5, and 5.9.6:
1-level PR-PCSS responders for the target buttock,
2-level PR-PCSS responders for the target buttock,
1-level SSRS responders,
1-level S-GAIS responders for the target buttock and
2-level S-GAIS responders for the target buttock

A similar approach that was used for composite binary responder sensitivity analysis will be used for this group of binary responder endpoints. Multiple imputation (MI) will be performed only

on the raw reported scales and then the responder variables will be derived based on the imputed raw reported scales.

Key Secondary Endpoints – Continuous Endpoint section 5.9.5
Change from baseline in PR-CIS total score

For this variable, the imputation will be performed on the endpoint directly by using the linear regression method in SAS PROC MI within each treatment group with missing data. The regression model will include the 'core' variables and corresponding baseline value.

Once all the missing data are imputed, each set of imputed data will be analyzed and the resulting statistics from 100 sets will be combined using PROC MIANALYZE for the statistical inference from the ANCOVA with factor variables: treatment group and analysis center, and covariate variable: baseline PR-CIS total score. The resulting least square means (LSMEANs) and standard errors (SEs) of the LSMEANs will be pooled using PROC MIANALYZE to yield the corresponding p value.

5.9.7.2. Tipping Point Analysis

A sensitivity analysis examining the robustness of the results of the primary efficacy analysis to assumptions about missing data will be performed using a Tipping Point (TP) analysis. More specifically, the TP analysis will examine under what conditions the conclusion of the study remains unchanged, even if the missing data mechanism depends on the unobservable missing values and the data are Missing Not At Random (MNAR).

In the TP analysis, missing values of the composite primary efficacy endpoint (2-point composite responder for target buttock at Day 71) will be assigned based on treatment group and analysis center.

Define the following values based on the observed data:

m_p = the number of subjects in the placebo group with missing primary efficacy endpoint

m_t = the number of subjects in the EN3835 group with missing primary efficacy endpoint

The basis of the TP analysis will be an m_p -by- m_t grid with m_t values along the x-axis and m_p values along the y-axis. Each grid point (i,j) will contain a summary statistic s_{ij} corresponding to the result of the primary analysis with random responder assignment of missing data such that there are i additional responders in the EN3835 group and j additional responders in the placebo group.

First, the data is analyzed under the "worst case" conditions. In this step, all subjects in the placebo group with missing primary efficacy endpoint are assumed to be responders and all subjects in the EN3835 group are assumed to be non-responders. This is a distinct condition from that of the data from the main analysis in which all subjects with missing outcome are assumed to be non-responders, regardless of treatment group. The "worst case" dataset is analyzed using the same methodology as that for the primary endpoint defined in section 5.9.3 (ie, using CMH test adjusted for analysis center). If the result of the analysis of the "worst case" dataset supports the conclusion of the main study analysis (ie, both analyses provide statistically significant evidence for a positive treatment effect), then there is no need to implement the full TP analysis and the result of the main study analysis is robust to assumptions about the missing efficacy data.

If the analysis of the "worst case" dataset reverses the conclusion of the main study analysis, then the TP analysis will be performed by performing responder assignment based on treatment group and analysis center, and calculating summary statistics s_{ij} for additional grid points (i,j). Starting at the at grid location corresponding to the "worst case" condition (0, m_p) an incremental step in both directions will be taken to grid location (1, m_p -1). For the responder assignment, the number of datasets D_{ijz} will be generated, taking analysis center into account, depending on the number of patients with missing data at specific analysis centers.

Each dataset D_{ijz} is analyzed using the same methodology as that for the primary endpoint defined in section 5.9.3 (ie, using CMH test adjusted for analysis center). The results of the analysis over all D_{ijz} are summarized using a pooled *p* value from the v_{ij} datasets, based on the method of Wilson-Hilferty transformation. The pooled *p* value from this set of datasets will be the summary statistic s_{ij} for grid location (i,j). If at any point summary statistic s_{ij} is not less than the critical *p* value defined in section 5.9.3, and therefore reverses the conclusion of the primary analysis of the study, then that point represents one condition of the Tipping Point.

The TP analysis will continue at grid locations (2, m_p -2), (3, m_p -3), etc., by repeating the process of random responder assignment, analyzing the data, then calculating the pooled *p* value until the first location of the Tipping Point is reached. Once one grid location of the Tipping Point is found, all eight adjacent grid locations will be searched to reveal additional Tipping Point grid locations. The process will be repeated until all Tipping Point grid locations are found. A summary table and a figure will be presented for the TP analysis which will display the collection of points identified as the Tipping Points.

5.9.7.3. Missing Data Handled by a Last Observation (Post-dose) Carried Forward (LOCF)

Missing data at Day 71 will be imputed as follows:

- If the subject has at least one post-dose classification then the last classification will be carried forward for Day 71 for the analysis
- If the subject has no post-dose classification then the baseline value will be carried forward for Day 71 for the analysis

5.9.7.4. Other Sensitivity Analyses

The primary efficacy endpoint and all the key secondary efficacy endpoints will be summarized by treatment group with descriptive statistics based on the PP population if the number of subjects in the PP population is 90% or less than those in the mITT population, ie, if more than 10% of subjects are excluded in the PP population compared to those in the mITT population. *P* value will be computed using ANCOVA with factors of treatment group and analysis center adjusting for baseline value for change from baseline in the PR-CIS score or CMH test adjusted for analysis center for other efficacy endpoints (see section 5.1). In addition, similar summary and statistical analysis will be performed based on the observed data at Day 71, ie, using observed data without missing data imputed, for the mITT population as well as the PP population if more than 10% of subjects are excluded in the PP population compared to those in the mITT population.

5.9.8. Supportive Efficacy Endpoints

All the supportive efficacy endpoints for the target buttock or the non-target buttock or two buttocks (see section 3.5) will be analyzed based on the mITT population at all the visits where missing values will not be imputed (observed data only). In addition, all the supportive efficacy endpoints with missing data handled using the LOCF approach will be performed at Day 71. If no classification post the initial treatment is available then the subject will be excluded in the analyses.

Analysis summaries will be performed by either the target buttock, the non-target buttock, at least one buttock, or both buttocks in the same individual subject.

If the number of subjects in the PP population is 90% or more than those in the mITT population, all the supportive efficacy endpoint analyses will also be analyzed based on the PP population.

5.9.8.1. Endpoints Based on Subject PR-PCSS Rating

The subject PR-PCSS ratings for the target buttock will be summarized by treatment group at baseline (Day 1), Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts and percentages at each severity rating and with means and standard deviations, respectively.

The subject PR-PCSS ratings for the non-target buttock will be summarized by treatment group at baseline (Day 1), Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts and percentages at each severity rating and with means and standard deviations, respectively.

The change from baseline rating of PR-PCSS rating for the target buttock will be summarized by treatment group at Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts at each rating change and with means and standard deviations, respectively. The change from baseline rating can vary from -4 (change from severe [rating = 4] to none [0]) to +1 (change from moderate [3] to severe [4]). *P* values will be computed for change from baseline rating at each visit with Wilcoxon rank sum test.

The change from baseline rating of PR-PCSS rating for the non-target buttock will be summarized by treatment group at Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts at each rating change and with means and standard deviations, respectively. The change from baseline rating can vary from -4 (change from severe [rating = 4] to none [0]) to +1 (change from moderate [3] to severe [4]). *P* values will be computed for change from baseline rating at each visit with Wilcoxon rank sum test.

The subject 2-level PR-PCSS responder and 1-level PR-PCSS responder for the target buttock will be summarized by treatment group at Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts and percentages, respectively. *P* values will be computed at each visit using a CMH test adjusted for analysis center.

The subject 2-level PR-PCSS responder and 1-level PR-PCSS responder for the non-target buttock will be summarized by treatment group at Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts and percentages, respectively. *P* values will be computed at each visit using a CMH test adjusted for analysis center.

The subject 2-level PR-PCSS responder and 1-level PR-PCSS responders for at least one buttock will be summarized by treatment group at Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts and percentages, respectively. *P* values will be computed at each visit using a CMH test adjusted for analysis center.

The subject 2-level PR-PCSS responder and 1-level PR-PCSS responders for the two buttocks in the same individual subject will be summarized by treatment group at Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts and percentages, respectively. *P* values will be computed at each visit using a CMH test adjusted for analysis center.

5.9.8.2. Endpoints Based on Subject S-GAIS Rating

The subject S-GAIS ratings (-3 to +3) for the target buttock will be summarized by treatment group at Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts and percentages at each rating and with means and standard deviations, respectively. *P* values will be computed for change from baseline ratings at each visit with Wilcoxon rank sum test.

The subject S-GAIS ratings (-3 to +3) for the non-target buttock will be summarized by treatment group at Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts and percentages at each rating and with means and standard deviations, respectively. *P* values will be computed for change from baseline ratings at each visit with Wilcoxon rank sum test.

The subject 1-level S-GAIS responder for the target buttock will be summarized by treatment group at Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts and percentages, respectively. *P* values will be computed at each visit using a CMH test adjusted for analysis center.

The subject 1-level S-GAIS responder for the non-target buttock will be summarized by treatment group at Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts and percentages, respectively. *P* values will be computed at each visit using a CMH test adjusted for analysis center.

The subject 1-level S-GAIS responder for at least one buttock will be summarized by treatment group at Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts and percentages, respectively. *P* values will be computed at each visit using a CMH test adjusted for analysis center.

The subject 1-level S-GAIS responders for the two buttocks in the same individual subject will be summarized by treatment group at Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts and percentages, respectively. *P* values will be computed at each visit using a CMH test adjusted for analysis center.

5.9.8.3. Endpoints Based on Subject PR-CIS Ratings

The subject PR-CIS score of each individual item, total score or abbreviated total score will be summarized by treatment group at baseline (Day 1), Day 71 and Day 71 (LOCF) with n, mean, SD, median, minimum and maximum.

The change from baseline in subject PR-CIS score of each individual item, total score or abbreviated total score will be summarized by treatment group at Day 71 and Day 71 (LOCF) with n, mean, SD, median, minimum and maximum. P values will be computed for change from baseline in subject PR-CIS score of each individual item, total score or abbreviated total score at Day 71 and Day 71 (LOCF) with ANCOVA with factors of treatment group and analysis center adjusted for baseline values.

The subject PR-CIS responder for each individual item will be summarized by treatment group at Day 71 and Day 71 (LOCF) with counts and percentages, respectively. *P* values will be computed at each visit using a CMH test adjusted for analysis center.

The subject PR-CIS responder for total score will be summarized by treatment group at Day 71 and Day 71 (LOCF) with counts and percentages, respectively. *P* values will be computed at each visit using a CMH test adjusted for analysis center.

The subject PR-CIS responder for abbreviated total score will be summarized by treatment group at Day 71 and Day 71 (LOCF) with counts and percentages, respectively. *P* values will be computed at each visit using a CMH test adjusted for analysis center.

5.9.8.4. Endpoints Based on SSRS Ratings

The subject SSRS ratings (0 to 6) will be summarized by treatment group at Baseline, Day 71 and Day 71 (LOCF), ie, Day 71/Early Termination, with counts and percentages at each rating and with means and standard deviations. *P* values will be computed using Wilcoxon rank sum test.

The subject 1-level SSRS responders will be summarized by treatment group at Day 71, and Day 71 (LOCF) with counts and percentages, respectively. *P* values will be computed using a CMH test adjusted for analysis center.

5.9.8.5. Endpoints Based on Subject Satisfaction With Cellulite Treatment

The subject satisfaction ratings with cellulite treatment (-2 to +2) will be summarized by treatment group at Day 71 and Day 71 (LOCF), ie, Day 71/Early Termination, with counts and percentages at each rating and with means and standard deviations. *P* values will be computed using Wilcoxon rank sum test.

The subject satisfied responders will be summarized by treatment group at Day 71, and Day 71 (LOCF) with counts and percentages, respectively. *P* values will be computed using a CMH test adjusted for analysis center.

5.9.8.6. Endpoints Based on Investigator CR-PCSS Rating

The investigator CR-PCSS ratings for the target buttock will be summarized by treatment group at baseline (Day 1), Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts and percentages at each severity rating and with means and standard deviations, respectively.

The investigator CR-PCSS ratings for the non-target buttock will be summarized by treatment group at baseline (Day 1), Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts and percentages at each severity rating and with means and standard deviations, respectively.

The change from baseline investigator CR-PCSS rating for the target buttock will be summarized by treatment group at Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts at each rating change and with means and standard deviations, respectively. The change from baseline rating can vary from -4 (change from severe to none) to +1 (change from moderate to severe). *P* values will be computed for change from baseline ratings at each visit with Wilcoxon rank sum test.

The change from baseline investigator CR-PCSS rating for the non-target buttock will be summarized by treatment group at Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts at each rating change and with means and standard deviations, respectively. The change from baseline rating can vary from -4 (change from severe to none) to +1 (change from moderate to severe). *P* values will be computed for change from baseline ratings at each visit with Wilcoxon rank sum test.

The investigator 2-level CR-PCSS responder and 1-level CR-PCSS responder for the target buttock will be summarized by treatment group at Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts and percentages, respectively. *P* values will be computed at each visit using a CMH test adjusted for analysis center.

The investigator 2-level CR-PCSS responder and 1-level CR-PCSS responder for the non-target buttock will be summarized by treatment group at Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts and percentages, respectively. *P* values will be computed at each visit using a CMH test adjusted for analysis center.

The investigator 2-level CR-PCSS responder and 1-level CR-PCSS responders for at least one buttock will be summarized by treatment group at Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts and percentages, respectively. *P* values will be computed at each visit using a CMH test adjusted for analysis center.

The investigator 2-level CR-PCSS responder and 1-level CR-PCSS responders for the two buttocks in the same individual subject will be summarized by treatment group at Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts and percentages, respectively. *P* values will be computed at each visit using a CMH test adjusted for analysis center.

5.9.8.7. Endpoints Based on Investigator I-GAIS Rating

The investigator I-GAIS ratings (-3 to +3) for the target buttock will be summarized by treatment group at Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts and percentages at each rating and with means and standard deviations, respectively. *P* values will be computed for change from baseline ratings at each visit with Wilcoxon rank sum test.

The investigator I-GAIS ratings (-3 to +3) for the non-target buttock will be summarized by treatment group at Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts and percentages at each rating and with means and standard deviations, respectively. *P* values will be computed for change from baseline ratings at each visit with Wilcoxon rank sum test.

The investigator 1-level I-GAIS responder for the target buttock will be summarized by treatment group at Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts and percentages, respectively. *P* values will be computed at each visit using a CMH test adjusted for analysis center.

The investigator 1-level I-GAIS responder for the non-target buttock will be summarized by treatment group at Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts and percentages, respectively. *P* values will be computed at each visit using a CMH test adjusted for analysis center.

The investigator 1-level I-GAIS responder for at least one buttock will be summarized by treatment group at Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts and percentages, respectively. *P* values will be computed at each visit using a CMH test adjusted for analysis center.

The investigator 1-level I-GAIS responder for the two buttocks in the same individual subject will be summarized by treatment group at Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts and percentages, respectively. *P* values will be computed at each visit using a CMH test adjusted for analysis center.

5.9.8.8. Endpoints Based on Subject PR-PCSS Rating and Investigator CR-PCSS Rating

The subject/investigator 2-level composite responder and 1-level composite responder for the target buttock will be summarized by treatment group at Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts and percentages, respectively. *P* values will be computed at each visit using a CMH test adjusted for analysis center.

The subject/investigator 2-level composite responder and 1-level composite responder for the non-target buttock will be summarized by treatment group at Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts and percentages, respectively. *P* values will be computed at each visit using a CMH test adjusted for analysis center.

The subject/investigator 2-level composite responder and 1-level composite responder for at least one buttock will be summarized by treatment group at Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts and percentages, respectively. *P* values will be computed at each visit using a CMH test adjusted for analysis center.

The subject/investigator 2-level composite responder and 1-level composite responder for the two buttocks in the same individual subject will be summarized by treatment group at Day 22, Day 43, Day 71, and Day 71 (LOCF) with counts and percentages, respectively. *P* values will be computed at each visit using a CMH test adjusted for analysis center.

5.9.8.9. Change from Baseline in PR-PCSS by S-GAIS Rating at Day 71

The change from baseline (or severity improvement) in PR-PCSS at Day 71 will be summarized by S-GAIS rating grouped by:

- Treatment group and buttock
- Treatment group and two buttocks combined
- Buttock and two treatments combined
- Overall

5.9.8.10. By-center Exploratory Analyses

By-center summaries will be based on the mITT population.

The following treatment related variables will be summarized by analysis center and treatment group and by each of the two buttocks:

- Percentage of subjects given full treatment exposure for that buttock (12 injections) at each treatment session
- Average number of injections given, average numbers of dimples treatment, and average number of injections per dimple

The following efficacy variables will be summarized by analysis center and treatment group:

- Subject PR-PCSS rating at baseline, Day 71 (LOCF), and change from baseline for the target buttock
- Subject PR-PCSS rating at baseline, Day 71 (LOCF), and change from baseline for the non-target buttock
- Subject PR-PCSS responder analysis of 2-level responders and 1-level responders at Day 71 (LOCF) for the target buttock
- Subject PR-PCSS responder analysis of 2-level responders and 1--level responders at Day 71 (LOCF) for the non-target buttock
- Subject PR-PCSS responder analysis of 2-level responders and 1-level responders at Day 71 (LOCF) for at least one buttock
- Subject PR-PCSS responder analysis of 2-level responders and 1-level responders at Day 71 (LOCF) for the two buttocks in the same individual subject
- Investigator CR-PCSS rating at baseline, Day 71 (LOCF), and change from baseline for the target buttock
- Investigator CR-PCSS rating at baseline, Day 71 (LOCF), and change from baseline for the non-target buttock
- Investigator CR-PCSS responder analysis of 2-level responders and 1-level responders at Day 71 (LOCF) for the target buttock
- Investigator CR-PCSS responder analysis of 2-level responders and 1-level responders at Day 71 (LOCF) for the non-target buttock
- Investigator CR-PCSS responder analysis of 2-level responders and 1-level responders at Day 71 (LOCF) for at least one buttock
- Investigator CR-PCSS responder analysis of 2-level responders and 1-level responders at Day 71 (LOCF) for the two buttocks in the same individual subject
- Two-level composite responder and 1-level composite responder at Day 71 (LOCF) for the target buttock
- Two-level composite responder and 1-level composite responder at Day 71 (LOCF) for the non-target buttock

- Two-level composite responder and 1-level composite responder at Day 71 (LOCF) for at least one buttock
- Two-level composite responder and 1-level composite responder at Day 71 (LOCF) for the two buttocks in the same individual subject
- Subject 1-level S-GAIS responders at Day 71 (LOCF) for the target buttock
- Subject 1-level S-GAIS responders at Day 71 (LOCF) for the non-target buttock
- Subject 1-level S-GAIS responders at Day 71 (LOCF) for at least one buttock
- Subject 1-level S-GAIS responders at Day 71 (LOCF) for the two buttocks in the same individual subject
- Investigator 1-level I-GAIS responders at Day 71 (LOCF) for the target buttock
- Investigator 1-level I-GAIS responders at Day 71 (LOCF) for the non-target buttock
- Investigator 1-level I-GAIS responders at Day 71 (LOCF) for at least one buttock
- Investigator 1-level I-GAIS responders at Day 71 (LOCF) for the two buttocks in the same individual subject
- PR-CIS total score at baseline, Day 71 (LOCF), and change from baseline
- PR-CIS abbreviated total score at baseline, Day 71 (LOCF), and change from baseline
- SSRS rating score at baseline and Day 71 (LOCF)
- One-level SSRS Responders at Day 71 (LOCF)
- Mean subject global satisfaction with cellulite treatment and percentage of subjects with ratings of satisfied and very satisfied

5.10. Safety Evaluation

5.10.1. Adverse Events

The following listings will be provided based on **all AEs**:

- Listing of deaths
- Listing of non-fatal SAEs
- Listing of non-serious AEs leading to discontinuation from study
- Listing of non-serious AEs leading to interruption or discontinuation of study drug

The following summary tables of AEs will be presented by treatment group:

- TEAEs
  - Overall summary
  - By preferred term (overall, ≥5% and ≥2%, respectively)
  - By preferred term and severity

  - By frequency of SAEs
  - By frequency of most common non-SAE
- Treatment-related AEs
  - Overall summary
  - By preferred term (overall, ≥5% and ≥2%, respectively)
  - By preferred term and severity
  - By preferred term and treatment session
  - Duration of AEs
- AEs of special interest
  - By preferred term

The overall summary will consist of the following items:

- Total number of AEs
  - All AEs
  - Mild AEs
  - Moderate AEs
  - Severe AEs
- Total number of subjects with
  - At least 1 AE
  - At least 1 SAE
  - At least 1 severe AE
  - No severe AEs but at least 1 moderate AE
  - No severe/moderate AEs but at least 1 mild AE
  - At least 1 AE leading to discontinuation from study
  - At least 1 AE leading to interruption or discontinuation of study drug
- Total number of subjects who died (treatment-emergent only)

Percentages for the total number of mild, moderate, and severe AEs will be based on the total number of all AEs in the treatment group.

The by frequency summaries will also include the total number of occurrences the AE preferred term was reported as well the number of subjects with at least 1 report of the AE. Most common non-SAEs are any preferred term AE that at least 5% of the subjects in 1 treatment group report at least once. Adverse events that are classified as most common in at least 1 treatment group will be reported in all treatment groups.

5.10.1.1. Adverse Event Conventions

The following conventions will be followed:

- Table by preferred term - If an AE preferred term occurred multiple times within a body system for the same subject, the preferred term will only be counted once for the subject for the summary of preferred terms. If an AE body system occurred multiple times for the same subject, the body system will only be counted once for the subject for the summary of body systems. If a subject has any AE, the subject will be counted once in the summary of subjects with at least 1 AE.
- Table by preferred term and severity - If an AE preferred term occurred multiple times within a body system for the same subject, only the most severe one will be used. If the most severe preferred term of an AE occurred multiple times within a body system for the same subject, only 1 will be counted. In addition, this summary will also contain the total number of subjects with at least 1 mild, 1 moderate, or 1 severe. If a subject has at least 1 severe AE, then the subject will be counted in the severe category. If the subject has no severe AEs, but at least 1 moderate AE, then the subject will be counted in the moderate category, and if the subject has no severe and no moderate AEs, but has at least 1 mild AE, then the subject will be counted in the mild category.
- Table by preferred term and treatment session – If an AE preferred term occurred multiple times within a body system for the same subject within a treatment session, the preferred term will only be counted once for the subject in the treatment session for the summary of preferred terms. If an AE preferred term occurred multiple times within a body system for the same subject in different treatment sessions, the preferred term will be counted at each treatment session. If an AE body system occurred multiple times for the same subject within a treatment session, the body system will only be counted once for the subject in the treatment session for the summary of body systems. If an AE body system occurred multiple times for the same subject in different treatment sessions, the body system will be counted at each treatment session for the summary of body systems. If a subject has any AE within a treatment session, the subject will be counted once in the treatment session in the summary of subjects with at least 1 AE. If a subject has any AE in different treatment sessions, the subject will be counted in each treatment session in the summary of subjects with at least 1 AE.
- Table of treatment-related AEs by duration category – This summary will be based on individual events rather than subjects. Each related AE will be classified into one of duration categories (1-4 days, 5-7 days, 8-14 days, 14-21 days, or >21 days) based on its duration. If an AE preferred term occurred within a body system multiple times for the same subject, each occurrence will be counted in the summary. In addition, all related AEs by treatment will also be included in this summary. If the AE is reported as ongoing or the AE stop date is missing or incomplete, the AE duration will not be computed and the AE will not be included in the duration analysis.

- Table of frequency of preferred terms – Preferred terms will be ordered by their descending frequency within the EN3835 treatment group. If 2 or more preferred terms are tied in their frequency, then the preferred terms will be ordered alphabetically.

5.10.2. Weight and BMI

Weight and BMI at baseline, visit (Day 22, Day 43, and Day 71) and change from baseline will be summarized by treatment group.

5.10.3. Vital Signs

Vital signs at baseline (Day 1 pre-injection), all study visits (Day 22 pre-injection, Day 43 pre-injection, and Day 71) and change from baseline (study baseline) will be summarized by treatment group. *P* values for change from baseline will be based on the ANOVA with a factor of treatment group.

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

The incidence of subjects with sponsor-defined PCI vital sign values (see Table 9) at any time during the study (including post-30-minute measurements) will be presented by treatment group. *P* values for the incidence of subjects with sponsor-defined PCI vital sign values will be based on the Fisher exact test.

Any subject with at least 1 PCI vital sign will have all vital sign values listed.

5.10.4. Clinical Laboratory

Clinical laboratory results (hematology and chemistry only) at baseline, Day 71, and change from baseline will be summarized by treatment group. Routine urinalysis results will not be summarized. Any hematology or chemistry lab result not reported as a continuous value will not be included in the summaries. *P* values for change at Day 71 from baseline will be based on the ANOVA with a factor of treatment group.

All post-injection laboratory values (Day 71 and unscheduled labs taken on Day 1 or later) will be used to determine the incidence of PCI laboratory values. The incidence of subjects with sponsor-defined PCI laboratory values (see Table 8) will be presented. *P* values for the incidence of subjects with sponsor-defined PCI laboratory values will be based on the Fisher exact test.

Any subject with at least 1 PCI laboratory value will have all the values for that analyte listed.

5.10.5. Immunogenicity

Anti-AUX-I and anti-AUX-II antibody titer levels will be analyzed at Day 1, Day 22, Day 43, and Day 71 by treatment group. The immunogenicity analysis will summarize the number of subjects with an immunogenicity sample tested, the percent of subjects with a positive sample, and the average titer level of the positive samples. The titer levels will be log 10 transformed prior to being summarized.

The Day 71 LOCF anti-AUX-I and anti-AUX-II antibody titer levels will be summarized by treatment session cohorts (subjects with 1, 2, or 3 treatment cycles) and treatment group.

The number and percentage of assayed serum samples that will detect the presence or absence of neutralizing antibodies (positive/negative) to AUX-I and AUX-II will be summarized by anti-drug antibody quartiles for the EN3835-treated subjects with descriptive statistics (number and percentage) at Day 1 and Day 71.

5.10.6. Concomitant Medications

Concomitant medications will be summarized for preferred term (generic name from WHO dictionary) by treatment group. If 2 medications are coded to the same preferred term, it will be counted only once for a subject. Medications will be ordered alphabetically by drug class and preferred term within drug class.

6. DERIVED VARIABLES

6.1. Subject Level Variables

The following variables will be determined for each subject (see Table 12).

Table 12: Subject Level Derived Dataset Variables

Variable	Definition
Age Group	<35 years 35 – <45 years 45 – <65 years ≥65 years
Height (cm)	If height unit is inches, then height is equal to the recorded value multiplied by 2.54 and then rounded to 1 decimal point.
Weight (kg)	If weight unit is pounds, then weight is equal to the recorded value multiplied by 0.454 and then rounded to 1 decimal point.
BMI (kg/m^2)	$Weight/(Height/100)^2$
BMI Group	Underweight (<18.5 kg/m^2) Normal Weight (18.5 – <25.0 kg/m^2) Overweight (25.0 – <30.0 kg/m^2) Obese (≥30.0 kg/m^2)
Date of First Injection	Day 1 visit date
Last Date in Study	Date of last visit where subject was seen by the investigator. If subject was lost to follow-up, then last date of contact. If the subject had contact with the site after the final visit (eg, to follow-up on an AE), the last visit date will still be used as last date in the study.
Time in Study	Last Date in Study – Date of First Injection + 1
Age at EFP Symptom Onset	Start Date of EFP Symptom Onset (from medical history) – Date of Birth/365.25, truncated to integer value. See section 6.2.2 for handling of partial or unknown EFP symptom onset dates.

AE=Adverse event; BMI=Body mass index; EFP=Edematous fibrosclerotic panniculopathy

6.2. Safety Variables

6.2.1. Adverse Events

Adverse events will be organized in 2 different ways: by event and by subject. The by event dataset will include all the characteristics of the event obtained on the eCRF plus the derived variables presented in Table 13. A second by event dataset will be created for the AE duration analysis. This duration dataset will contain only the subject number, treatment session, body system classification, preferred term, and duration.

Table 13: Adverse Event Variables by Event

Variable	Values/Definition
Treatment-Emergent	AE with a start date after the first dose of study medication
Treatment-Related	If relationship to study medication is reported as possible, probable or missing; 'unlikely related' AE will be classified as not a treatment-related AE.
Onset Day	AE Start Date - Date of First Injection + 1
Duration	AE Stop Date - AE Start Date + 1
Treatment Session	The number of the treatment session immediately preceding the AE onset date

AE=Adverse event

The by-subject dataset will summarize all the AE events for a subject and will include the variables presented in Table 14. The same variables will be computed for TEAEs and treatment-related AEs.

Table 14: Adverse Event Variables by Subject

Variable	Values/Definition
Total AEs	Sum of number of AEs the subject reported
Total Mild AEs	Sum of number of mild AEs the subject reported
Total Moderate AEs	Sum of number of moderate AEs the subject reported
Total Severe AEs	Sum of number of severe AEs the subject reported
Had AE	Flag (Y/N) to indicate subject had at least 1 AE
Had Severe AE	Flag (Y/N) to indicate subject had at least 1 AE of moderate or severe severity
Had SAE	Flag (Y/N) to indicate subject had at least 1 serious AE
Had AE Leading to Discontinuation	Flag (Y/N) to indicate subject had at least 1 AE that lead to discontinuation from the study

AE=Adverse event; SAE=Serious adverse event; Y/N=Yes/No

6.2.2. Laboratory Variables

Laboratory variable, Creatinine clearance (eCrCl), will be derived by Endo using the Cockcroft-Gault formula (3) as follows:

$$\text{eCrCl (mL/min)} = \{[(140\text{-age}) \times \text{weight}]/[72 \times \text{Scr}]\} \times 0.85 \text{ for female,}$$

where age is expressed in years (y), weight is expressed in kilograms (kg), and serum creatinine concentration (Scr) is expressed in milligrams per deciliter (mg/dL).

6.3. Imputation of Partial Dates

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

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

6.4. Relative Study Day/Treatment Session Study Day

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

Adverse events will have a treatment session study day, computed as the date of event minus the date of preceding injection + 1.

6.5. Conventions and Algorithms

6.5.1. Summary Tables/Subject Listings Conventions

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

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

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

The summary tables will clearly indicate the effective sample size per treatment group. All summary tables involving percentages will round the percentages off to 1 decimal place. All summary tables involving descriptive statistics of continuous variables will round the mean and median to 1 decimal place more than the variable's standard form and round the standard

deviation to 2 decimal places more than the variable's standard form. The standard form of a percent change variable is zero decimal places.

When calculating percentages, the denominator will be based on the number of non-missing responses. The number of missing responses will be presented as a count only. If the denominator is expected to change over time, then the denominator used to calculate the percentage should be presented on the table. Any subject removed from an analysis will be noted at the bottom of the table along with the reason the subject was removed. These subjects will also be listed.

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

By-subject listings for AEs, vital signs, laboratory test values, immunogenicity results will be provided. Other by-subject listings will be provided as support for summary tables and serve as a data source substitute when a summary table is deemed either inappropriate or unnecessary. All subject listings will be organized by investigational site and treatment group, sorted by subject number. When applicable, the subject listings will include the visit date, and days relative to the start of first treatment and start of treatment session.

7. INTERIM ANALYSES

No interim analysis is planned in this study. Blinded tables will be produced prior to database lock. A dummy randomization will be done to classify subjects as receiving EN3835 or placebo. Changes in the tables, figures, and listings may occur as a result of the review of the blinded tables.

8. SAMPLE SIZE CALCULATION

The primary variable will be the overall rate of composite responders with an improvement of at least 2 levels on both the PR-PCSS and the CR-PCSS in at least one of two treated buttocks. The results of the EN3835-201 study demonstrated the overall rate for treated buttocks of composite responders with an improvement of at least 2 levels on both the PR-PCSS and the CR-PCSS was 14.9% in the EN3835 treatment group versus 1.1% in the placebo group. Given this result, the study is planned to randomize 420 subjects with a 1:1 ratio into either the EN3835 arm (0.84 mg/buttock, 1.68 mg total dose) or the placebo arm.

The sample size calculation was based on the following assumptions [redacted] 2) Fisher exact test; 3) Type I error of 0.05; 4) power of at least 90%; and 5) dropout rate of approximate 10%.

This sample size will also provide >90% power with Type 1 error of 0.05 to detect the treatment difference for all the key secondary endpoints based on the following results, majority of which were estimated from previous EN3835 study results.

Table 15: Previous Results as Bases for Sample Size

Efficacy Endpoint	EN3835	Placebo	Power
1-level PR-PCSS responders of the target buttock	[redacted]	[redacted]	[redacted]
2-level PR-PCSS responders of the target buttock	[redacted]	[redacted]	[redacted]
1-level composite responders of the target buttock	[redacted]	[redacted]	[redacted]
2-level composite responders of the non-target buttock	[redacted]	[redacted]	[redacted]
Proportion of subjects with SSRS rating ≥4	[redacted]	[redacted]	[redacted]
Change in PR-CIS Score (Mean (SD)	[redacted]	[redacted]	[redacted]
1-level S-GAIS responders of the target buttock	[redacted]	[redacted]	[redacted]
2-level S-GAIS responders of the target buttock	[redacted]	[redacted]	[redacted]

* Rates are estimated based on the reported results from the pooled pivotal studies of a drug approved for an aesthetic indication.
PR-CIS=Patient Reported Cellulite Impact Scale; PR-PCSS=Patient Reported Photonumeric Cellulite Severity Scale; SD=Standard deviation; S-GAIS=Subject Global Aesthetic Improvement Scale; SSRS=Subject Self-rating Scale

9. TABLES, LISTINGS, AND GRAPH SHELLS

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

10. CHANGE FROM PROTOCOL

Table 16 lists any significant changes in the SAP from what is proposed in the protocol.

Table 16: Changes from Protocol

Text in Protocol	Change in SAP	Justification

11. REVISION HISTORY

Non-editorial changes made to any of the sections of this SAP will be recorded in Table 17. All significant changes require a new signature page be completed.

Table 17: Revision History

Description of Change/Reason for Change	Document Version Number Before Change	Date of Change
Original	N/A	N/A
Section 4.4, Per-protocol (PP) population: Modified the exclusion criteria from the mITT population to the per-protocol population so that the per-protocol population is unambiguously defined	1	05-Jun-2018
Section 5.2, Analysis Center: Modified the pooling procedure so that the analysis centers are uniquely formed. In addition, add the Breslow-Day test to assess site to site variability and analysis center to center variability.	1	05-Jun-2018
Section 5.9.7, Sensitivity Analyses: Added tipping point analysis for the primary and key secondary endpoints	1	05-Jun-2018
Section 6.1, Subject Level Variables: modified the definition of age groups in Table 12	1	05-Jun-2018
Section 5.9.7.1, Multiple Imputation (MI) for Missing Data: Re-organize primary endpoint and key secondary endpoints into different groups in which how multiple imputations for missing data are implemented.	2	20-Aug-2018
Section 5.9.7.2, Tipping Point Analysis: Original tipping point paragraph in Section 5.9.7.1 is extended to a new section. More detailed methodology and implementation as well terminology are given in the section.	2	20-Aug-2018
Section 5.9, Efficacy Evaluation: Pre-specified analyses of the primary and key secondary endpoints have been added based on integrated data from two design-identical, double-blind, placebo-controlled, phase 3 studies, EN3835-302 and EN3835-303.	2.1	30-Aug-2018

N/A=Not applicable

12. REFERENCES

1. US Food and Drug Administration. Guidance for Industry, *E9 Statistical Principles for Clinical Studies* (ICH E9); 1998:30.
2. Wilson EB, Hilferty MM. The Distribution of Chi-Square. *Proc Natl Acad Sci U S A*. 1931. 17(12):684-8.
3. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976; 16(1):31-41.