Endo Pharmaceuticals Inc.
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EN3835

EN3835-205

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

IND 110077

Date:

August 31, 2017

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

[redacted]

2. SUMMARY OF CHANGES

Not applicable.

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]	Office: [redacted] Cell: [redacted]
[redacted]	[redacted]	[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 2 Open-label Study of EN3835 in the Treatment of Edematous Fibrosclerotic Panniculopathy	
Lead Principal Investigator: TBD	
Study Period: Estimated date first subject enrolled: Nov-2017 Estimated date last subject completed: Jul-2018	**Phase of Development**: 2

Objectives:

Primary Objective:

- To assess the safety of EN3835 in the treatment of edematous fibrosclerotic panniculopathy (EFP), commonly known as cellulite, in adult women

Secondary Objective*:*

- To assess effectiveness of EN3835 in the treatment of EFP

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

Subjects will receive an open-label treatment course which consists of up to 3 treatment visits (ie, Day1, Day 22, and Day 43). Each treatment visit will consist of 12 injections (0.3 mL per injection of EN3835 0.07 mg/injection) in each of the treatment areas of the region for a total volume of 7.2 mL (1.68 mg). Selection of dimples to be treated in the assigned treatment areas will be at the discretion of the Investigator. End-of-study will occur at study Day 180.

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

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

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

Number of Subjects (planned): Up to 150

Study Center(s): Approximately 10 sites in United States

Name of Sponsor/Company: Endo Pharmaceuticals Inc.

Name of Investigational Product: EN3835

Name of Active Ingredient: Collagenase clostridium histolyticum

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

***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 area to be treated:
   a. History of lower extremity thrombosis or post-thrombosis syndrome
   b. Vascular disorder (eg, varicose veins, telangiectasia) in area to be treated
   c. Inflammation or active infection
   d. Active cutaneous alteration including rash, eczema, psoriasis, or skin cancer
   e. Has a tattoo and/or a mole located within 2 cm of the site of injection
3. Requires the following concomitant medications before or during participation in the trial:
   a. Anticoagulant or antiplatelet medication or has received anticoagulant or antiplatelet medication (except for ≤150 mg aspirin daily) within 7 days before injection of study drug

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4. Has used any of the following for the treatment of EFP on the legs or buttocks within the timelines identified below or intends to use any of the following at any time during the course of the study: a. Liposuction in the areas of the body selected for treatment during the 12-month period before injection of study drug b. Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; buttock and/or thigh implant treatment, cryolipolysis, or surgery (including subcision and/or powered subcision) within the assigned treatment areas during the 12-month period before injection of study drug c. Endermologie or similar treatments within the assigned treatment areas during the 6-month period before injection of study drug d. Massage therapy within the assigned treatment areas during the 3-month period before injection of study drug e. Creams (eg, Celluvera™, TriLastin®) to prevent or mitigate EFP within the assigned treatment areas during the 2-week period before injection of study drug 5. Is presently nursing 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
Investigational Product, Dosage and Mode of Administration: EN3835, 1.68 mg, subcutaneous. A dose of 0.84 mg of EN3835 per treatment area will be administered as 12 subcutaneous injections (0.3-mL injection administered as three 0.1-mL aliquots per injection) in each of two treatment areas for a total dose of 1.68 mg and a total volume of 7.2 mL (3.6 mL per treatment area). Total number of injections will be 24 injections per treatment visit into the assigned region (left and right buttocks or left and right posterolateral thighs). There will be 3 treatment visits at 21-day intervals, ie, treatments on Days 1, 22, and 43 will be administered.
Duration of Study: Up to 194 days (includes screening phase) **Screening Phase**: Up to 14 days

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Criteria for Evaluation:

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 [redacted]
- 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, injection site reactions/local tolerability in the treated areas (through subject and Investigator reporting) will be assessed.

Effectiveness:

- 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, 90, and 180) for each treatment area
- Subject satisfaction with cellulite treatment assessment: 5-level scale ranging from 2 (very satisfied) to −2 (very dissatisfied) (Day 180)

Statistical Methods:

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

Analysis Populations:

- Safety population: The Safety population is defined as all subjects who receive at least 1 injection of EN3835
- Effectiveness population: The effectiveness population is defined as all subjects in safety population with a baseline and 1 post-injection evaluation of the CR-PCSS in at least one treatment area.

Analyses:

<u>Safety Endpoints</u>:

The following variables are safety endpoints:

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

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

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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 and Day 180 will be analyzed for anti-AUX-I and anti-AUX-II and a subset will be analyzed for neutralizing antibodies.

Effectiveness Endpoints:

- Proportion at each level of improvement in the CR-PCSS of each assigned treatment area (Days 22, 43, 90, and 180):
  - Proportion of responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS
  - Proportion of responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS
- Number of responses at each level of the subject satisfaction with cellulite treatment (Day 180)

All effectiveness endpoints will be summarized as numbers and percentages.

5. SCHEDULE OF EVENTS

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

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

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

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7. LIST OF ABBREVIATIONS

The following abbreviations and special 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
CRF	Case report form
CR-PCSS	Clinician-Reported Photonumeric Cellulite Severity Scale
CSS	Cellulite Severity Scale
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EFP	Edematous fibrosclerotic panniculopathy
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HREC	Human Research Ethics Committee
IB	Investigator brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
I-GAIS	Investigator-Global Aesthetic Improvement Scale
IRB	Institutional Review Board
IWRS	Interactive web response system
LOCF	Last Observation Carried Forward
PR-PCSS	Patient-Reported Photonumeric Cellulite Severity Scale
Qualified designee	Qualified by education and training to perform the study procedure (eg, sub-Investigator, nurse).
Region	Bilateral buttocks or bilateral thighs (each consisting of 2 treatment areas, ie, left/right buttock or left/right thigh). To be suitable for treatment, the region must have an Investigator CR-PCSS score of 2 or higher and a Hexsel CSS score of no greater than 13 at the Screening visit.
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.
Treatment area	Left buttock, right buttock, left thigh, or right thigh.

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. This creates an uneven surface with dimpling.(1) EFP is a medical condition resulting in a potentially cosmetically unacceptable alteration of the skin, and affects an estimated 85% to 98% of postpubertal women.(1,3)

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

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

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

8.1.2. 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 kiloDaltons (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 degrees 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 posterolateal thigh or a right posterolateral thigh) of cellulite with EN3835 0.84mg 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 the Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS), Patient Reported Photonumeric Cellulite Severity Scale (PR-PCSS), Investigator Global Aesthetic Improvement Scale (I-GAIS), Subject Global Aesthetic Improvement Scale (S-GAIS), 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 treated quadrant as assessed by the primary endpoint of 2-level composite responder analyses, the proportion of responders based on an improvement of ≥2 level 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 sixty-two percent (62.9%) of subjects in the EN3835 0.84mg 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 four 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 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 100% 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 0.84mg in 11 female subjects with EFP showed that there was no quantifiable levels of AUX-I or AUX-II at any timepoint after subcutaneous injection of EN3835 0.84mg into one quadrant. A second Phase 1, open-label, safety and pharmacokinetic study of a single dose of EN3835 0.84mg per treatment area in two treatment areas (buttock-buttock, thigh-thigh, or buttock-thigh) concurrently (total dose of 1.68mg) showed that there was no quantifiable levels of AUX-I or AUX-II at any timepoint post-dose attributable to the injection of EN3835 1.68mg.

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, and 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. Post-marketing safety data have been consistent with 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 alterations found in EFP are due largely to fibrosis of the connective tissues in the dermis and/or subcutaneous tissues.(2) Subcutaneous fat lobes are separated from one another by thin, usually rigid strands of connective tissues, which cross the fatty layers and connect the dermis to the underlying fascia. These collagen septae stabilize the subcutis and divide the fat. Shortening and thickening of the septae due to fibrosis provokes retraction at the insertion points of the trabeculae, causing the depressions that characterize EFP.(2)

The pharmacologic activity of EN3835 involves selective lysis of the triple-helical region of collagen under physiological conditions at the site of injection. EN3835 targets the collagenase structural matrix (eg, septae), which is the underlying cause of the skin dimpling, and does not require systemic exposure to be effective. The pharmacologic activity of EN3835 is local, rapid, and is essentially complete within 24 hours.

The data from the Phase 2a EFP dose-ranging study (AUX-CC-831) suggest that EN3835 0.84 mg was 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 sessions of EN3835 0.84 mg in the treatment of EFP (section 5.3.1.3). 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 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 this study.

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 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 a region (buttocks or posterolateral thighs) warranted further investigation in this study.

Treating two bilateral treatment areas of a region at each treatment visit will potentially provide a symmetrical-like improvement in appearance. Support for evaluation of the treatment of two treatment areas 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 (a region) concurrently.

9. OBJECTIVES

9.1. Primary Objective

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

9.2. Secondary Objective

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

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 10 study centers located in the United States. This clinical study will be conducted as a multicenter, open-label study of EN3835 in adult women with EFP. The study will consist of 3 treatment visits, 21 days apart. Subjects meeting the entry criteria for this study will receive EN3835 treatment within an investigational site and assigned region (ie, bilateral buttocks or bilateral thighs) on Day 1, Day 22, and Day 43, and will be followed for up to 180 days from the first day of treatment. Subjects will receive follow-up visits at 1, 3, 6, and 13 days after each treatment course (either by phone or, for subjects participating in the photographic sub-study, in the clinic), and 2 follow-up visits at Day 90 and Day 180 to assess treatment effectiveness. The study also includes a photographic sub-study (conducted at two sites) in which subjects will return to the clinic for photographs at 1, 3, 6, and 13 days after each treatment course to coincide with the follow up visits. Sites participating in the photographic sub-study will also follow subjects for the same 180-day period.

The complete schedule of events is provided in section 5.

Figure 1: Study Design

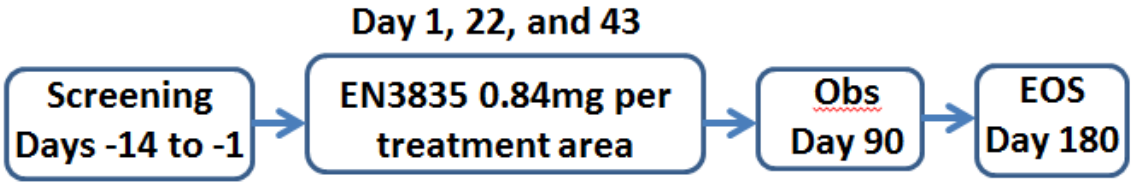


Table 3: Study Treatment Groups

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=up to 150	0.3 mL	12 per treatment area x 2 treatment areas = 24	0.84 mg per treatment area x 2 treatment areas = 1.68 mg (12 injections per treatment area x 0.07 mg/injection x 2 treatment areas)	3.6 mL per treatment area x 2 treatment area = 7.2 mL (24 injections × 0.3 mL)	5.04 mg (3 treatment visits × 0.84 mg per treatment area x 2 treatment areas)

[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 experience 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 a Phase 2b study (EN3835-201).

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.

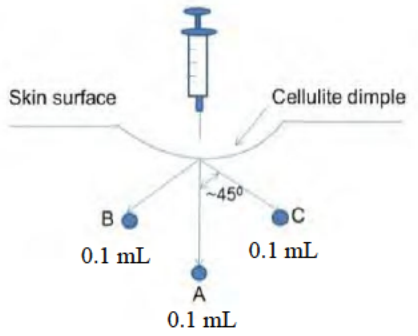
Based on the efficacy and safety findings from the Phase 2a and 2b EFP studies, the EN3835 0.84-mg dose per treatment area was carried forward to this study. The findings from previous studies that the majority of adverse events after EN3835 treatment are local to the injection site and that there is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

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 Figure 2. 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, eight (8) syringes (4 syringes per treatment area) 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 selected treatment areas 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 the treatment area (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 treatment areas 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 injection of study drug and until the subject exhibits no sign of an immunological or other clinically significant systemic or local AE. The subject's vital signs should be stable before the subject can leave direct observation (see section 14.9).

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 assess the safety of EN3835 0.84 mg per treatment area in the concurrent treatment (total dose of 1.68 mg) of EFP in a treatment region (bilateral buttocks or bilateral posterolateral thigh) in adult women. It is an open-label study.

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

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

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

If a subject discontinues from the study, all end-of-study procedures should be conducted as detailed in section 5, Schedule of Events. The date a subject discontinues and the reason for discontinuation will be recorded in the source documentation and Electronic Case Report Form (eCRF). If, however, a subject withdraws consent, no end-of-study procedures are required (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. 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 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 (sections 11.1 and 11.2)
3. The Investigator will conduct live assessments of subject's cellulite severity of the 4 treatment areas using the CR-PCSS (section 13.1.1); the subject is blinded to these ratings

4. After the Investigator has completed the CR-PCSS rating, the Investigator will conduct live cellulite evaluation of the 4 treatment areas using the Hexsel CSS. The ratings from the CR-PCSS and Hexsel CSS (section 13.1.3) will be used to assess initial eligibility of treatment areas for study entry.
5. If eligible based on CR-PCSS, and Hexsel CSS ratings, random assignment of a treatment region (two bilateral treatment areas) for treatment (section 12.1.2.3)
6. Medical history including EFP history (section 12.1.2.1)
7. Record prior and concomitant medications/procedures (section 12.9)
8. Physical examination including measurement of body weight, height, Fitzpatrick skin type (section 14.11)
9. Vital sign measurements (section 14.9)
10. 12-lead electrocardiogram (ECG) (section 14.10)
11. Collection of samples for:
    a. Clinical laboratory testing (section 14.7)
    b. Serum pregnancy testing (section 14.7)
12. Adverse events (section 14)

12.1.2.3. Assignment of Treatment Areas

Subjects must have at least 1 eligible treatment region (eg, 2 bilateral treatment areas) that meet the following criteria for inclusion into the study:

- CR-PCSS score of 2 or greater in each treatment area, and
- Hexsel CSS score no greater than 13 in either treatment area.

Assignment of the treatment region will be chosen randomly by the interactive web response system (IWRS) from the regions meeting the above inclusion criteria. If no two bilateral treatment areas meet the criteria, the IWRS will inform the site that the subject does not have treatment regions that qualify for the study.

12.2. Selecting and Marking Dimples during Treatment

Selection of dimples to be treated in the two assigned treatment areas 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 visits of study drug unless the treatment area is dimple-free (score of 0 on CR-PCSS as reported by the Investigator).

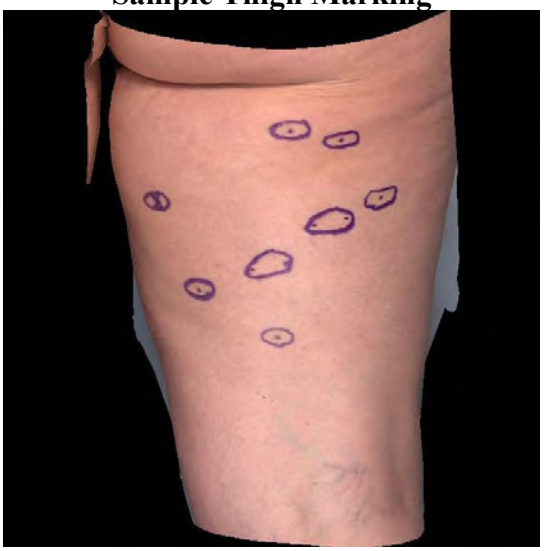
Treatment consists of 12 injections per treatment area (total 24 injections) per visit. Because the goal of treatment is to improve the aesthetic appearance of each entire treatment area, the Investigator will be instructed to select dimples that in his/her opinion would most improve the aesthetic appearance of each entire treatment area. The same dimples within a treatment area or different dimples within a treatment area may be treated at each visit but injections must all be within the assigned treatment area for all 3 visits. Each treatment area will receive all 3 treatment

visits unless the assigned treatment area has no treatable EFP dimples and the Investigator rates the treatment area a score of 0 on the CR-PCSS. If no injections in a particular treatment area are given at Treatment Visit 2, subjects will still be assessed for treatment in the contralateral treatment area at Treatment Visit 2, and will return for the Day 43 visit and the assigned treatment areas will again be evaluated by the Investigator (CR-PCSS). If the Investigator rates either or both of the assigned treatment areas greater than 0 on the CR-PCSS, injections at Treatment Visit 3 should be given.

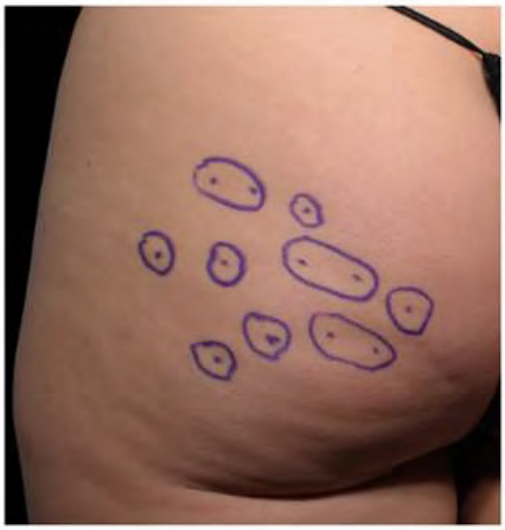
At each treatment visit, prior to selecting and marking dimples, sites participating in the photography sub-study should photograph the selected treatment areas. For each dimple selected for treatment, the Investigator or qualified designee will choose injection sites (injection sites within a dimple 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 assigned treatment area should not overlap (Figure 3). Sites participating in the photographic sub-study (section 12.12) will be instructed to obtain photographs of the subject's marked treatment areas prior to injection on the visit days that require treatment (section 5).

Figure 3: Examples of Subject Dimple and Injection Site Markings

Sample Thigh Marking



Sample Buttock Marking



12.3. Treatment Visit 1 (Day 1)

12.3.1. Treatment Visit 1: Pre-Injection

1. For eligible treatment areas, obtain kit numbers of study treatment and reconstitute drug product using aseptic technique
2. Record concomitant medications/procedures (section 12.9)
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 treatment area before marking dimples and injection sites (NOTE: This is ONLY for sites participating in the photographic sub-study.)
6. Select and mark dimples to be treated in each of the assigned treatment areas (section 12.2)
7. Digital photographs of each treatment area after marking dimples and injection sites (section 12.12)

12.3.2. 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 assigned treatment areas
3. Vital sign measurements (section 14.9)
4. Injection site reactions and local tolerability
5. Adverse events (section 14)

12.4. Follow-up Visits at 1, 3, 6, and 13 Days Following Each Treatment Visit

12.4.1. For Sites Participating in the Photographic Sub-study (section 12.12)

1. Any changes in concomitant medications or procedures
2. Injection site reactions and local tolerability
3. Adverse events (section 14)
4. Digital photographs of each treatment area

12.4.2. For Sites not Participating in the Photographic Sub-study

1. Any changes in concomitant medications or procedures
2. Injection site reactions and local tolerability
3. 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 12.9)
2. Body weight measurement

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 treatment area before marking dimples and injection sites (NOTE: This is ONLY for sites participating in the photographic sub-study.)
6. Investigator Cellulite Assessments of each of the assigned treatment areas prior to marking dimples and injection sites using:
    a. Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) live assessment of subject (section 13.1.1)
7. Select and mark dimples to be treated in each assigned treatment areas (section 12.2)
8. Digital photographs of each buttock after marking dimples and injection sites (section 12.12)

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

1. For eligible assigned treatment area(s), obtain kit number(s) of study treatment and reconstitute drug product using aseptic technique.
2. Administration of study drug in the prone position (section 10.3)
3. Record number of dimples treated and number of injections administered in each assigned treatment area
4. Vital sign measurements (section 14.9)
5. Injection site reactions and local tolerability
6. Adverse events (section 14)

12.6. Day 90 (±3 days)

The following procedures will be performed on Day 90:

1. Record concomitant medications/procedures (section 12.9)
2. Measurement of body weight
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. Investigator Cellulite Assessments of each of the assigned treatment areas using:
    a. Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) live assessment of subject (section 13.1.1)

6. Injection site reactions and local tolerability
7. Adverse events (section 14)

12.7. Day 180 (+7 days) End-of-Study / Early Termination

The following procedures will be performed on Day 180:

1. Measurement of body weight
2. Vital sign measurements (section 14.9)
3. Collection of samples for:
   a. Clinical laboratory testing (section 14.8)
   b. Anti-AUX-I and anti-AUX-II antibody testing (section 14.7)
   c. Serum pregnancy testing (section 14.7)
4. Subject Cellulite Assessment using:
   a. Subject Satisfaction with Cellulite Treatment Assessment (section 13.1.2)
5. Investigator Cellulite Assessments of each of the assigned treatment areas using:
   a. Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS) live assessment of subject (section 13.1.1)
6. Injection site reactions and local tolerability
7. Adverse events (section 14)

12.8. 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.

12.9. Prior and Concomitant Medications and Procedures

All prior medications taken within 90 days before Day 1 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.

12.9.1. 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 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.

12.10. Treatment Compliance

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).

12.11. Blinding and Randomization

This is an open-label study. Each subject will have one or two regions (bilateral buttocks and/or thighs) eligible for treatment. If two regions are eligible, the IWRS will randomly assign each subject a treatment region.

12.12. Photographic Sub-study

Two (2) or more sites will participate in a photographic sub-study designed to capture photographic records of subjects' progression through the study treatment. In the sub-study, the treatment areas will be photographed before and after dimple marking while the subject is standing in a consistent relaxed pose as described in the Photography Manual. Subjects will be instructed to return to the clinic for follow-up photographs at 1, 3, 6, and 13 days after each treatment visit.

12.13. Medical Status Follow-up

Subjects will be contacted (either by telephone, or in person for subjects participating in the Photographic Sub-study) at 1, 4, 8, and 14 days after each treatment visit to provide updates on their medical status following treatment. Specific updates to medical status will include:

1. Any changes in concomitant medications or procedures
2. Injection site reactions and local tolerability
3. Adverse events (section 14)

13. ASSESSMENT OF EFFECTIVENESS

13.1. Effectiveness Measurements

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

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

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 4 treatment areas by assessing subjects using the CR-PCSS for buttock (Appendix B) or thigh (Appendix C). Before injections on treatment visits Day 1, Day 22, and Day 43, and on visit Day 90 and Day 180, Investigators will evaluate each of the two assigned treatment areas via live assessment. If the buttocks are the treated region, the Investigator will use the CR-PCSS for the buttock to make his/her evaluation; if the thighs are the treated region, the Investigator will use the CR-PCSS for the thigh to make his/her evaluation.

13.1.2. Subject Satisfaction with Cellulite Treatment Assessment

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

For subjects that had buttocks treated:

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 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.

Or

For subjects that had thighs treated:

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

Table 6: Subject Satisfaction with Cellulite Treatment Assessment - Thighs

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

13.1.3. 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-level scale from a low of 0 to a high of 3 as described in Table 7 (Appendix D and Appendix E). The total score is the summation of all 5 features.

The Investigator or qualified designee will independently use the Hexsel CSS to assess the severity of EFP in each of the 4 treatment areas at the Screening visit and each of the two assigned treatment areas on Day 1. All cellulite assessments should be made while the subject is in the standing position with relaxed gluteus muscles. However, when evaluating the subject for Category E (classification scale by Nürnberger and Müller) (13) if the subject has no evident depressions, the subject should be asked to contract her gluteus muscles or the pinch test should be applied (by pinching the skin between the thumb and index finger) so the Investigator or qualified designee can differentiate between scores/grades of zero (0) or I.

Table 7: Hexsel Cellulite Severity Scale

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

Source: Hexsel DM, Dal'Forno T, Hexsel CL. A validated photonumeric cellulite severity scale. *J Eur Acad Dermatol Venereol.* 2009;23(5):523-8.

[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.

[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 AE (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 Institutional Review Board (IRB) per their IRB policy.

14.5.2.1. Follow-up Procedures for Serious Adverse Events

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

14.6. Special Reporting Situations

14.6.1. Adverse Events of Special Interest

Adverse events such as [redacted] 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 12.10) 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[a]
	Aspartate transaminase (AST)	
	Alanine transaminase (ALT)	
	Gamma-glutamyl transferase (GGT)	
	Total bilirubin (TBL) (direct bilirubin reflex if elevated)	
	Albumin	
	Alkaline phosphatase (ALP)	
	Uric acid	

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

For women of childbearing potential, a serum pregnancy test will be performed at Screening and Day 180/End of Study/Early Termination, and any Unscheduled Visits. Urine pregnancy tests will be performed at Day 1, Day 22, Day 43, and Day 90 (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 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 Day 1, Day 22, Day 43, and at the Day 90 and Day 180 visit. A subset [redacted] of subject samples will be tested for neutralizing antibodies from Day 1and Day 180 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. These parameters include pulse rate, respiratory rate, systolic and diastolic blood pressure, and body temperature. Pulse and blood pressure readings will be taken after the subject has been sitting for 5 minutes. Height should be recorded at Screening Visit only.

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 90 and Day 180 visits.

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

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

17.2. Subject Populations

The following populations are considered in the statistical analysis of the study: safety, effectiveness and per-protocol (PP).

17.2.1. Safety Population

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

17.2.2. Effectiveness Population

The effectiveness population is defined as all subjects in Safety Population with a baseline and at least 1 post-injection evaluation of the Investigator CR-PCSS in at least one treatment area. All evaluations of effectiveness will be based on the effectiveness population.

17.2.3. Per-Protocol (PP) Population

Not applicable in the current study.

17.3. Subject Disposition

The number of subjects included in each study population will be summarized by assigned region (buttock or thigh) and overall. Subjects excluded from the safety and effectiveness populations will be listed.

The number and percentage of subjects completed and prematurely discontinued during the treatment periods will be presented for each assigned region (buttock or thigh) and 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 assigned region and overall for all enrolled subjects.

17.4. Demographics and Other Baseline Characteristics

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

Demographic characteristics, including sex, age, age group, race, height, and weight, will be summarized by assigned region and overall, for Safety and Effectiveness Populations, using appropriate 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. Effectiveness Analyses

17.5.1. Effectiveness Variables

- Proportion at each level of improvement in the CR-PCSS of each assigned treatment area (Day 22, Day 43, Day 90, and Day 180):
  - Proportion of responders defined as subjects with an improvement in severity from baseline of at least 2 levels of severity in the CR-PCSS
  - Proportion of responders defined as subjects with an improvement in severity from baseline of at least 1 level of severity in the CR-PCSS
- Proportion of responses at each level of the subject satisfaction with cellulite treatment (Day 180)

All effectiveness variables will be summarized as the number and percentages.

Mean and standard deviation for changes in CR-PCSS from baseline will be summarized.

17.6. Safety Analyses

Safety variables include adverse events, laboratory parameters, vital signs, ECG (screening only), and physical examination. 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 area:

- Total number of treatment visits
- Number of subjects who had treatment visit done or treatment visit not done at each treatment day

- For subjects who had the treatment visit done, the number of subjects who got all 12 injections per treatment area
- 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 three treatment visits and who did not receive a total of 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 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.

Listings will be presented for all subjects. Additionally, 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. Vital signs listings for all subjects will be provided.

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 subjects values will be provided including the subject ID, study center, baseline and post-baseline 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 180 will be presented for each clinical laboratory parameter. Listings for clinical laboratory values for all subjects will be provided.

The number and percentage of subjects with potentially clinically important (PCI) post-baseline clinical laboratory values will be tabulated. 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, baseline and post-baseline 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, Day 90, and Day 180 as well as their change from baseline (Day 1) at those time points will be presented.

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 by [redacted] for Endo.

EN3835 is a sterile lyophilized powder containing 0.46 mg of collagenase clostridium histolyticum [redacted] in a 2 mL vial.

EN3835 sterile diluent for reconstitution is 0.6% sodium chloride and 0.03% calcium chloride dehydrate, 2 mL/vial.

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 2 vials of EN3835 and sufficient sterile diluent to reconstitute the EN3835 vials.

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. Drug product must be prepared using aseptic technique.

For each dose visit, the IWRS will dispense 2 kits, 1 kit for each treatment area to be treated. Two (2) 0.9-mL syringes will be prepared from each vial of EN3835, 4 syringes/kit, for a total of 8 syringes (4 syringes for each treatment area).

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 is stable at [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, allocation, and aseptic preparation 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 designated 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. At a minimum, all data required to be collected by the protocol should have supporting source documentation for entries in the eCRF, unless the protocol specifies that data can be recorded directly on/in the eCRF or other device.

19.2. Study Monitoring

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

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

19.3. Audits and Inspections

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

19.4. Institutional Review Board (IRB)

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

19.5. Data Recording and Documentation

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

20. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

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

21. ETHICS

21.1. Ethics Review

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

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

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

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

21.2. Ethical Conduct of the Study

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

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

21.3. Subject Information and Consent

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

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

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

24.2. Delegation of Responsibilities and Adequate Resources

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

24.3. Medical Care of Study Subjects

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

24.4. Use of Investigational Materials

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

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 Drug 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.
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4. Terranova F, Berardesca E, Maibach H. Cellulite: nature and aetiopathogenesis. *Int J Cosmetic Sci.* 2006;28(3):157-67.
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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.

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

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

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

Table 1 Current classification of cellulite, based on the data from medical literature

Grade or stage	Clinical characteristics
0 (zero)	There is no alteration of the skin surface.
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.
II	The orange skin or mattress appearance is evident when standing, without the use of any manipulation (skin pinching or muscle contraction).
III	The alterations described in grade or stage II, are present together with raised areas and nodules.

measures. Therefore, appropriate research to investigate treatment options is warranted.

With recent advances in surgical and medical treatments, such as Subcision®, liposuction,[6] non-invasive laser lypolisis,[7] radiofrequency, and the increasing marketing of topical or mechanical treatments for cellulite, research is needed and a comprehensive objective method of measuring cellulite can be potentially very useful.

With the purpose of creating an objective method to measure cellulite severity and the effects of different treatment modalities, a new cellulite severity scale (CSS) and classification was developed. Validation was carried out in order to test its efficacy and reproducibility in the diagnosis and classification of the condition. The proposed scale expands the current classification by adding four items, therefore allowing a comprehensive measurement of the intensity of the condition. It is an objective method that can facilitate patient follow-up and measure treatment outcomes.

Objective

To develop and validate a photonumeric scale for grading severity of cellulite, called the *Hexsel, Dal'Forno & Hexsel Cellulite Severity Scale* (CSS) and a new classification system for cellulite.

Materials and methods

A photonumeric scale that grades the severity of cellulite was developed based on extensive clinical and photographic evaluations of baseline pictures from a sample of 55 patients that participated in two cellulite clinical trials. These trials were approved by local Ethic Committee and were performed in conformance to the ethical guidelines of the 1975 Declaration of Helsinki. Informed consent for participation and release of photographs for scientific purposes was obtained from all participants. To be included, patients had to be healthy female individuals, 18–45 years of age (mean 33.8 ± 7.58), body mass index between 18.5 and 29.9 (mean 25 ± 3.01) with a clinical diagnosis of cellulite with grades I to III according to the classification that ranges from 0 to III[8] (Table 1), located on the thighs and/or buttocks.

The photographs were taken in a standardized manner: in the same room by the same investigator, with the same camera fixed at the same location. All patients stood at the same distance from the camera, in the standing position with relaxed gluteus muscles, as illustrated in Fig. 1. A one-piece black body suit was used as standard clothing by all patients.

Five key clinical morphologic features of cellulite were identified: (A) the number of evident depressions; (B) depth of depressions; (C) morphological appearance of skin surface alterations; (D) grade of laxity, flaccidity or sagging skin; and (E) the classification scale originally described by Nürnberger and Müller[8] (Fig. 1). After extensive analysis of the photographs of all the 55 patients, the photonumeric scale was constructed based on the most representative pictures of the sample of 55 patients. The final photonumeric scale consists of 20 pictures, which were derived from 18 of these 55 patients.

The severity of each item was graded from 0 to 3, allowing a final sum of scores that range numerically from 1 to 15. Based on the final numeric score, cellulite was further classified as mild, moderate, or severe. Since cellulite mainly affects the buttocks and thighs, other areas of the body such as the abdomen, arms, and back that are less frequently affected were not included in the validation of the scale. After the development of the photonumeric scale, the scale was validated.

Validation of the scale

As determined a priori by the statistician, for a significance level of $P < 0.05$, one of the authors of the scale, Dr T. Dal'Forno as the 'gold standard' or the 'evaluator author', applied the scale thrice to all the photographs of the sample of 55 patients. These was once during the study and twice again during the validation process with one week interval. As determined a priori by the statistician, for a significance level of $P < 0.05$, independent evaluation of the set of standardized photographs of the aforementioned 55 patients, was also obtained from two dermatologists that were unfamiliar with the scale. A copy of the CSS (Fig. 1) was provided to all three dermatologist evaluators. The two independent evaluators and the evaluator author applied the CSS to each photograph of each of the following areas: left buttock (LB), right buttock (RB), left posterior thigh (LT), and right posterior thigh (RT).

Statistical analysis

As determined a priori, statistical analysis for validation included four tests: intraclass correlation coefficient, item-total correlation, Cronbach's alpha, and factor analysis.

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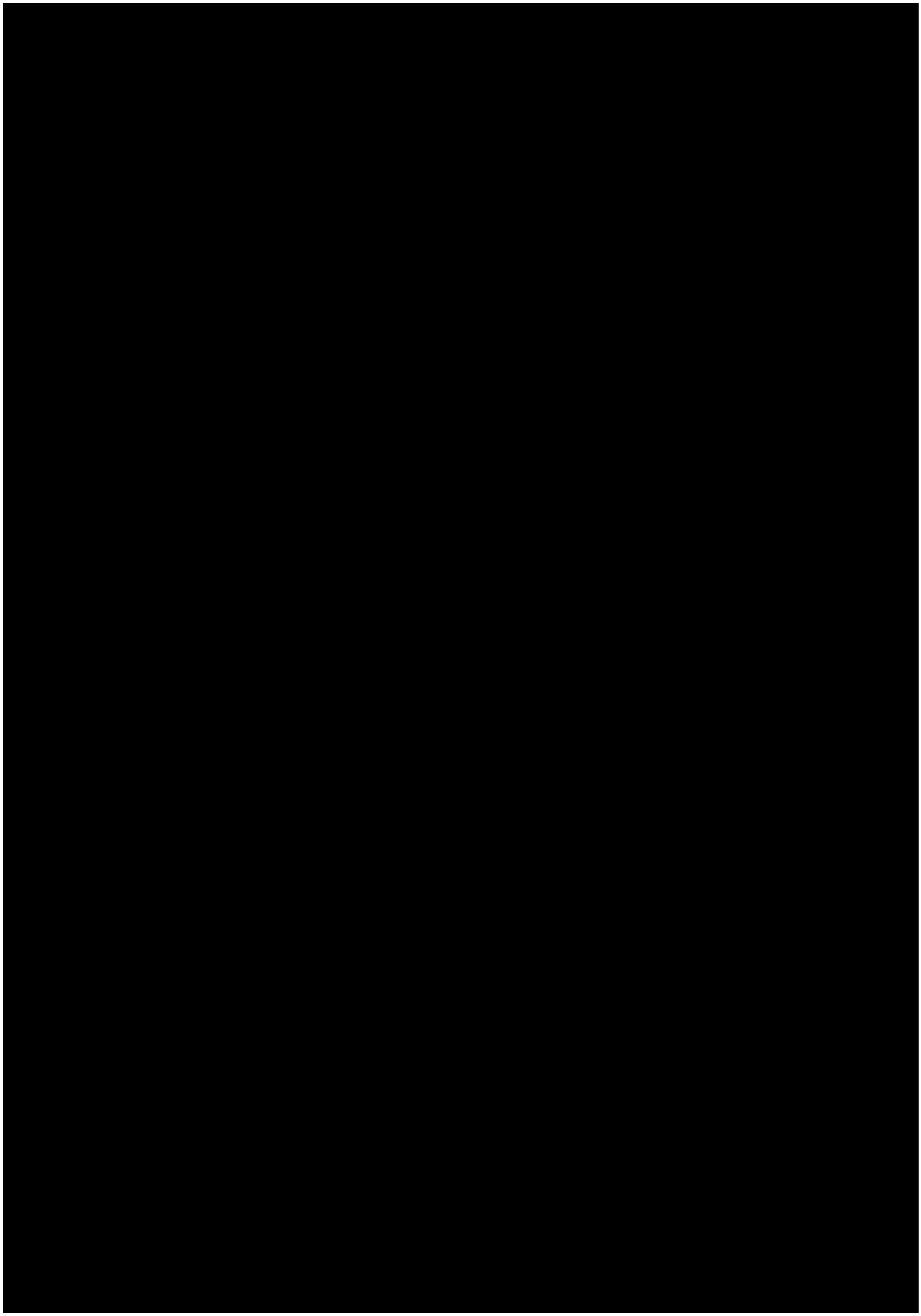

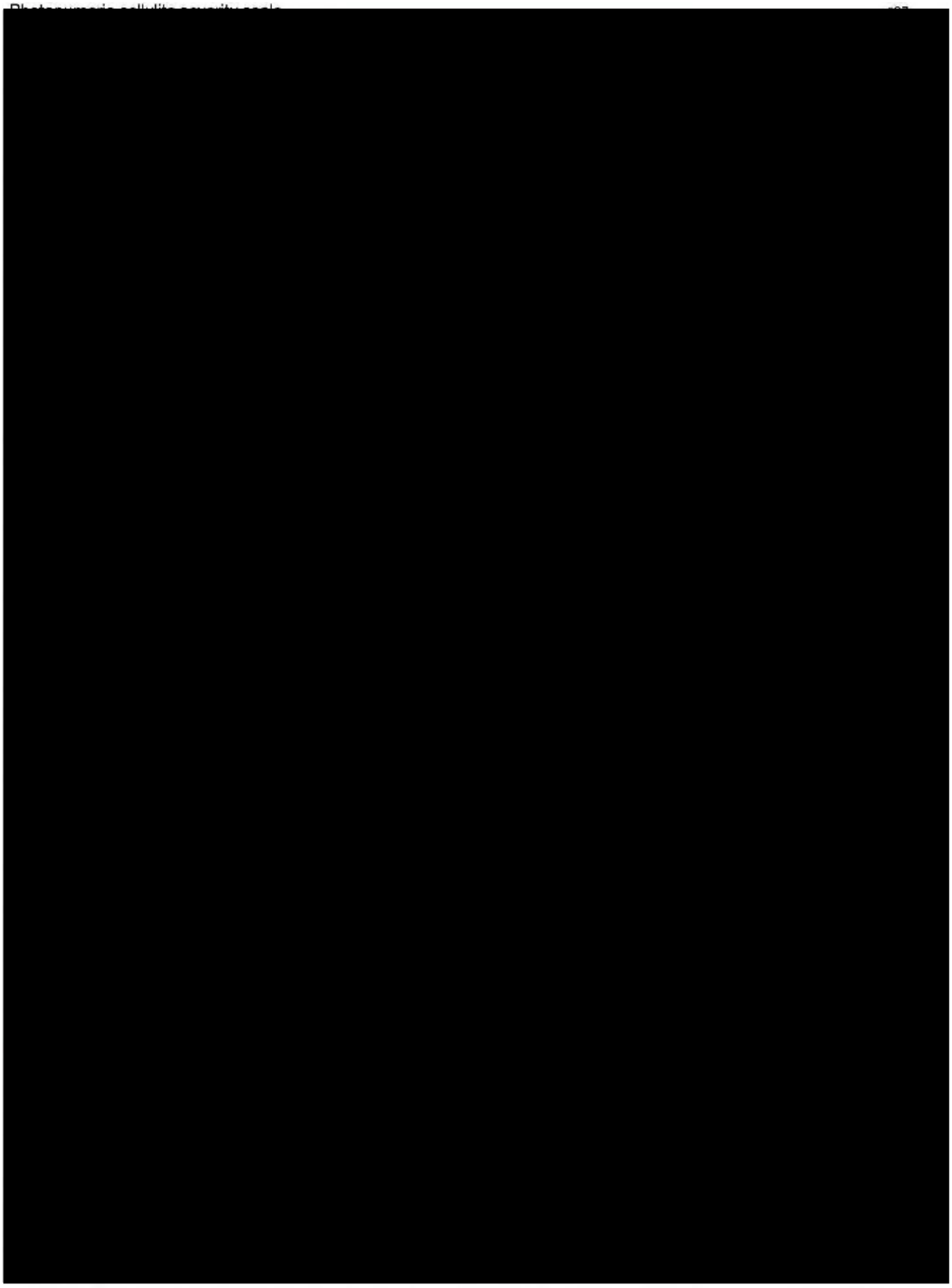

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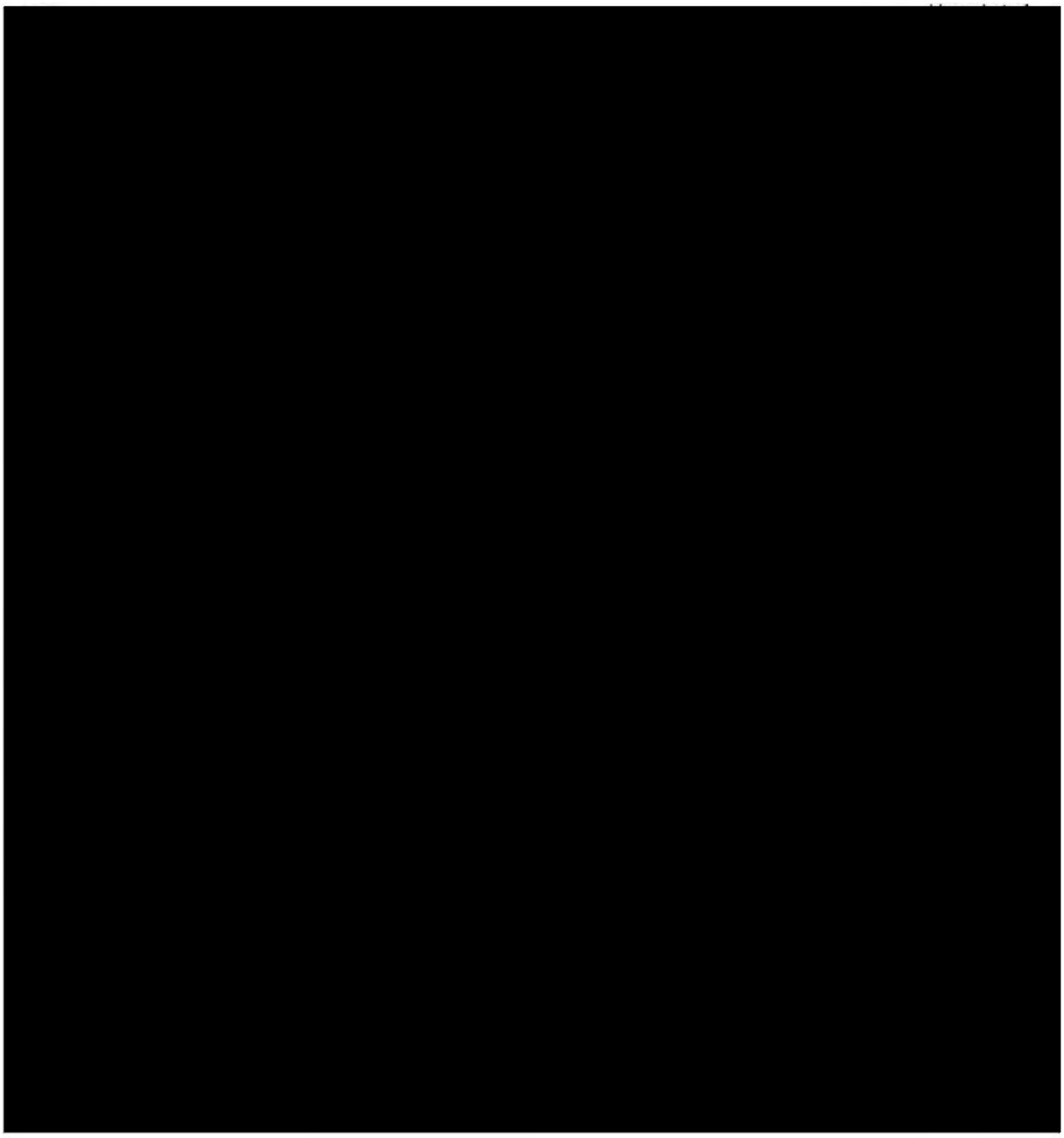

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APPENDIX E. REFERENCE IMAGES FOR HEXSEL SEVERITY RATINGS