U.S. Investigational Review Board, Inc.

TO: Deanne Robinson, MD, Principal Investigator
Modern Dermatology

SUBJECT: Approval of Final Protocol dated November 30, 2020; Investigator's Brochure dated October 10, 2019; Information and Consent Form and Authorization to Disclose Health Information dated December 15, 2020; Form FDA 1571 dated December 11, 2020; Form FDA 1572 dated December 8, 2020; IND Cover Letter dated December 14, 2020; Cross Reference Letter dated December 10, 2020 and the Investigator

IRB NUMBER: U.S.IRB2020MD/01

PROTOCOL NUMBER: DMRR-001

DATE OF MEETING: December 15, 2020

PROTOCOL TITLE: To assess the effectiveness of multiple dose, multiple concentrations of clostridium histolyticum-aases, Qwo, for the treatment of mild to moderate cellulite in adult females to the buttocks and thighs

The U.S. Investigational Review Board, Inc. is a review committee structured in compliance with the regulations of the Food and Drug Administration contained in the Code of Federal Regulations (21 CFR Parts 50 and 56), and is in compliance with the International Conference of Harmonization (ICH), Good Clinical Practice (GCP) guidelines for IRB/IEC and operates in accordance with GCP guidelines and applicable laws and regulations.

At the meeting date indicated above, the Committee reviewed and unanimously approved the Final Protocol dated November 30, 2020; Investigator's Brochure dated October 10, 2019; Information and Consent Form and Authorization to Disclose Health Information dated December 15, 2020; Form FDA 1571 dated December 11, 2020; Form FDA 1572 dated December 8, 2020; and the Investigator, for the above captioned research study. The Committee recommended that minor changes be made to the Informed Consent Forms. These changes have been incorporated into the approved Informed Consent Forms dated the day of this meeting and are attached. The approved Informed Consent Forms are stamped U.S.IRB "APPROVED" with the date of this meeting as indicated above and contains all regulatory required consent elements. All materials given to subjects are also stamped U.S.IRB "APPROVED" with the date of this meeting.

This research study has been approved for **one year valid to December 14, 2021**. At the end of this time, you are required to provide this IRB Committee a written status report of this research and obtain approval for the continued research. In the event that you complete the research within this time period, please notify this Committee, in writing, of your completion of this research study. Changes to the protocol or use of non-approved advertisement cannot be initiated without this IRB review and approval. Written notice to this IRB is required in the event of any serious adverse reactions, significant deviations from the protocol or any problems in the research. Please provide this reporting to the address noted below so that appropriate follow-up will be initiated.

Rosa M. Fraga, Chairperson
U.S. Investigational Review Board, Inc.

U.S.IRB
DEC 15 2020
"APPROVED"

6400 SW 72 COURT, MIAMI, FLORIDA 33143
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DMR Research, PLLC
1032 Post Road East
Westport, CT 06880

To assess the effectiveness of multiple dose, multiple concentrations of clostridium histolyticum-aases, Qwo, for the treatment of mild to moderate cellulite in adult females to the buttocks and thighs

Sponsor Name: DMR Research, PLLC

Sponsor Legal Registered Address: 1032 Post Road East Westport, CT 0688-Regulatory Agency Identifier Number: TBD

IND: 154245

Protocol Number: DMRR-001

Original Protocol: 30 November 2020

1 PROTOCOL SUMMARY

1.1 Synopsis

Name of Sponsor/Company: DMR Research, PLLC **Sponsor:** Endo Pharmaceuticals Inc.	
Name of Investigational Product: Qwo CCH	
Name of Active Ingredient: Collagenase clostridium histolyticum	
Title of Study: Treatment of 5 subjects to assess the effectiveness of multiple dose, multiple concentrations of clostridium histolyticum-aases, QWO, for the treatment of mild to moderate cellulite in adult females to the buttocks and thighs.	
Lead Principal Investigator: Deanne Mraz Robinson, MD	
Study period: Estimated date first subject enrolled: 15Feb2021 Estimated date last subject completed: 15May2021	**Phase of development:** 4

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To assess the effectiveness of multiple dose, multiple concentrations of clostridium histolyticum-aases for the treatment of mild to moderate cellulite in adult females to the buttocks and thighs	The proportion of subjects with improved (+1 or better) score on the Investigator Global Aesthetic Improvement Scale (I-GAIS) for buttock and thigh at Day 90.
Secondary	
To evaluate effectiveness of CCH-aaes in individuals when concomitantly treating the buttock and the thigh in one treatment session	The proportion of subjects with improved (+1 or better) score on I-GAIS for either buttock or either thigh on Days 22, 43, and 90.
To assess subject satisfaction with CCH treatment of buttock or thigh cellulite in adult females.	Mean change from baseline in Body-Q Appraisal of Cellulite[d] to Day 90.
To generate calculations to determine a matrix of buttock and thigh injections possible from a single 1.84 mg vial	Dilution matrix used in clinical settings.

Overall Design:

This is a single center, off-label, multiple dose, multiple injection areas, Phase 4 study to assess the safety and efficacy of multi-dilution CCH in adult women with mild or moderate edematous fibrosclerotic panniculopathy (EFP). 5 subjects will be screened and dosed in the buttock and thigh areas using a multi-dilution injection technique.

Qualified subjects (determined by investigator assessment) will receive a single vial of 0.84 mg of CCH to treatment areas (buttocks and thighs) for a total dose of 1.68 mg in both buttocks and both thighs per treatment session × 3 treatment sessions (Day 1, Day 22, and Day 43). Subjects will have follow-up visits at approximately 90 after Day 1.

Subjects will participate in the study for approximately 90 days (approximately 3 months). The duration of the study from first subject first visit to last subject last visit will be dependent upon the ability of sites to identify and enroll subjects. The entire study is expected to require approximately3 months to complete.

As little as one buttock dimple can be treated with the prepared buttock reconstitution.

Then the following table will be utilized to reconstitute to thigh concentration with sterile saline as follows:

Starting volume per 1.84 mg vial of Qwo after recon	Number of buttock sites	Number of thigh sites	Volume of saline to add after buttock injection*
8 ml	26	0	N/A
	25	1	2
	24	2	3.2
	23	3	4.4
	22	4	5.6
	21	5	6.8
	20	6	8
	19	7	9.2
	18	8	10.4
	17	9	11.6
	16	10	12.8
	15	11	14
	14	12	15.2
	13	13	16.4
	12	14	17.6
	11	15	18.8
	10	16	20
	9	17	21.2
	8	18	22.4
	7	19	23.6
	6	20	24.8
	5	21	26

	4	22	27.2
	3	23	28.4
	2	24	29.6
	1	25	30.8
40 ml	N/A	26	N/A

a. The proposed maximum number of injections sites per treatment area has been determined based on safety data of 0.84 mg/treatment area.

b. A maximum of up to 26 injections can be administered throughout the treatment sites

Disclosure Statement: This is an off-label efficacy study with multi-dilution and multi-treatment to 5 subjects.

Number of Subjects (planned):

5 subjects enrolled

Treatment Groups and Duration:

All subjects will receive 3 treatment sessions 21 to 35 days apart and consisting of 1.68 mg total dose mg of CCH in each treatment areas (buttocks and thighs). The total amount of CCH to be administered per subject over the course of the study will not exceed 5.04 mg (1.68 mg on 3 separate visits).

Data Monitoring Committee: No data monitoring committee will be used for this study.

1.2 Schedule of Activities

Table 1: Schedule of Activities

Activities	Screening (Day -14 to Day -1)	Day 1 (Treatment Session I)	Day 22 (+7 Days) (Treatment Session II)	Day 43 (+14 Days) (Treatment Session III)	Day 90 (+14 Days)
Informed consent[a]	X				
Inclusion/exclusion criteria review[b]	X	X			
Medical and Surgical history	X				
EFP history	X				
Prior medications (including all prior medications for cellulite)[b]	X	X			
Physical examination	X				X
Height	X				
Weight	X	X	X	X	X
Fitzpatrick Skin Type	X				
Hexsel CSS Subsection D[b]	X				
Urine pregnancy test	X	X	X	X	X
Body-Q Appraisal of Cellulite[d]	X				X

[a] Performed prior to any study-required assessments, unless exceptions granted for standard of care procedures.

[b] Should be reassessed and verified prior to dosing.

[c] Assessment should be completed independently of, and prior to, any investigator cellulite assessments (CR-PCSS, I-GAIS, Investigator Satisfaction with CCH).

[d] Before and after marking target dimples at treatment visits. No manipulation of the treatment area should be done prior to the "before" images.

[e] CR-PCSS-Buttock and CR-PCSS-Thigh will both be done at screening.

[f] I-GAIS will be completed after CR-PCSS when both are required at the same visit.

[g] AEs/SAEs will be captured from the time of informed consent signature until the Day 90/Early Termination Visit or until 28 days after last dose of study drug whichever is later. There is no time limit on collection of

SAEs felt to be related to study treatment.

Note: Unless otherwise stated above or outlined below (and with the exception of injection site reactions/local tolerability in the areas treated), all assessments
should be completed prior to dosing on treatment days (Days 1, 22, and 43).

2. INTRODUCTION

Qwo™ (CCH) is a parenteral lyophilized product comprised of 2 collagenases in an approximate 1:1 mass ratio, Collagenase I (Clostridial class I collagenase [AUX-I]) and Collagenase II (Clostridial class II collagenase [AUX-II]). Qwo is an FDA-approved injectable for moderate to severe cellulite in the buttocks of adult women. QWO targets a primary structural cause of cellulite – the fibrous septae.1,2

2.1 Study Rationale

The results from phase 3b EN3835-305 received FDA approval of Qwo for 3-aliquot injection technique in buttocks (up to 12 injections x 0.23 mg/mL x 0.3 mL/injection = 0.84 mg/buttock). Study EN3835-305 uses a 5-aliquot injection technique for treatment of thighs (up to 12 injections x 0.047 mg/mL x 1.5 mL/injection = 0.84 mg/thigh)(Palm ASDS 2020; Gold VCS2020) EN3835-305 administered subjects in either buttock (with 3-aliquot) technique or thigh (with 5-aliquot technique) using sterile saline. The purpose of this study is to determine the mechanics and effectiveness of treating cellulite subjects with both the 3-aliquot technique in the buttock and 5-aliquot technique in the thigh during the same treatment session without compromising effectiveness of treatment.

2.2 Background

Collagenase clostridium histolyticum-aaes is a combination of bacterial collagenases AUX-I and AUX-II, in an approximate 1:1 mass ratio, which are isolated and purified from the fermentation of Clostridium histolyticum bacteria. Collagenase AUX-I is a single polypeptide chain consisting of approximately 1000 amino acids. Collagenase AUX-II is a single polypeptide chain consisting of approximately 1000 amino acids.

QWO (collagenase clostridium histolyticum-aaes) for injection is supplied as a sterile, preservative-free, lyophilized powder (appearing as a white cake) in single-dose vials for subcutaneous use after reconstitution with the Diluent for QWO.

To investigate the effectiveness and feasibility of multiple dose, multiple concentrations of clostridium histolyticum-aases for the treatment of mild to moderate cellulite in adult females to the buttocks and thighs

More specifically, to evaluate effects of CCH-aaes in individuals when concomitantly treating the buttock and the thigh in one treatment session:

- with 3-aliquot injection technique (0.23 mg/mL x 0.3 mL/injection) in buttock using supplied diluent
- with 5-aliquot injection technique (0.047 mg/mL x 1.5 mL/injection) in thigh using sterile saline to dilute

2.3 Risk/Benefit Assessment

Current treatments for EFP have limited efficacy and undesirable side effects. There remains an unmet need for safe and effective nonsurgical therapies to improve the aesthetic outcome in women with cellulite.

The following AEs have been commonly observed in subjects treated with CCH for EFP: local injection site reactions including injection site bruising, injection site swelling, and injection site pain. These events are similar to events reported in the clinical trials of EN3835 for the approved indications. Postmarketing safety data are consistent with safety data reported in clinical trials.

More detailed information about the known and expected benefit, risks, and reasonably expected AEs associated with CCH can be found in the current version of the Investigators Brochure.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To assess the effectiveness of multiple dose, multiple concentrations of clostridium histolyticum-aases for the treatment of mild to moderate cellulite in adult females to the buttocks and thighs	The proportion of subjects with improved (+1 or better) score on the Investigator Global Aesthetic Improvement Scale. (I-GAIS) for buttock and thigh at Day 90.
Secondary	
To evaluate effectiveness of CCH-aaes in individuals when concomitantly treating the buttock and the thigh in one treatment session	The proportion of subjects with improved (+1 or better) score on I-GAIS for either buttock or either thigh on Days 22, 43, and 90.
To assess subject satisfaction with CCH treatment of buttock or thigh cellulite in adult females.	Mean change from baseline in Body-Q Appraisal of Cellulite[d] to Day 90.
To generate calculations to determine a matrix of buttock and thigh injections possible from a single 1.84 mg vial	Dilution matrix used in clinical settings.

4. STUDY DESIGN

4.1 Overall Design

Treatment of 5 subjects to assess the effectiveness of multiple dose, multiple concentrations of Qwo, clostridium histolyticum-aases for the treatment of mild to moderate cellulite in adult females to the buttocks and thighs.

The concept of this study would be to determine the effectiveness of treating multiple areas simultaneously by diluting with company provided diluent to buttock concentration, treating buttocks dimples appropriately with accepted injection technique and then diluting remaining CCH-ases with sterile saline to appropriate thigh concentration. Thigh dimples will then be treated with standard injection technique as in EN3835-305 Phase 3b.

Reconstitution prep and injection technique

Buttock – on label; importantly will be dosed first

- Reconstitution: 1.84 mg reconstitution with 8 mL of supplied diluent = 0.23mg/mL
- Use up to 3.6 mL for buttock injections dependent on number of dimples (injections) present

Thigh

- Reconstitution (EN3835-305 approved dilution technique); to the 0.047 mg/mL concentration with sterile saline
- Based on how many buttock injections to were performed, the remaining 0.23mg/mL solution will be diluted 5-fold with sufficient sterile saline to yield 0.047 mg/mL concentration necessary for thigh
- Based on the final volume generated from 5-fold dilution of the 0.23 mg/mL retain will determine the number of injections possible in thigh

Scientific Rationale for the Study Design

This is an off-label exploratory study to determine proper dilution techniques of CCH in EFP to be used in clinical practices.

4.2 Justification for Dose

The results from a Phase 2b study (EN3835-201) suggested that CCH 0.84 mg per treatment area (1 buttock or 1 thigh) is safe and effective. The Phase 3 studies (EN3835-302, EN3835-303 and EN3835-305) using the same dose in each buttock showed a similar safety profile with most AEs being mild to moderate in severity and transient. The immunogenicity profile of CCH has been consistent across all clinical studies to date. Therefore, the dose of 0.84 mg per treatment area (each buttock or each thigh – for a total dose of 1.68 mg of CCH for 2 buttocks and 2 thighs) will be used in this study.

4.3 End of Study Definition

A subject is considered to have completed the study if the subject has completed the Day 90 visit.

The end of the study is defined as the completion of the final assessment for the last subject enrolled in the trial.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Subject Inclusion Criteria

In order to be eligible to participate in the study, at the Screening Visit and on Study Day 1, subjects must:

1. Be female and 18-60 years of age at the time of consent.
2. Have both buttocks and both posterolateral thighs with:

a. A score of 2 or 3 (mild or moderate) as reported by the investigator using the Clinician-Reported Photonumeric Cellulite Severity Scale (CR-PCSS).

b. A Hexsel Cellulite Severity Scale (CSS) Subsection D "Grade of Laxity, Flaccidity, or Sagging Skin" score of 0 (absence of laxity, flaccidity, or sagging skin), or 1 (slightly draped appearance) at the Screening Visit only.

3. Have a body mass index (BMI) score between 18.0 kg/m^2 and 30.0 kg/m^2 and intends to maintain stable body weight (:S10% change from the Day 1 Visit weight) throughout the duration of the study (from the Screening Visit through the Day 180/Early Termination Visit).
4. Be willing to apply sunscreen to the treatment areas before each exposure to the sun for the duration of the study (from the Screening Visit through the Day 180/Early Termination Visit).
5. Be judged by the investigator to be in good health, based upon the results of a medical history and physical examination,.
6. Be of nonchildbearing potential (history of hysterectomy, bilateral oophorectomy, bilateral tubal ligation, or postmenopausal with no history of menstrual flow in the 12 months prior to the Screening Visit); or, if of childbearing potential, be nonpregnant, nonlactating, and agree to use effective contraception when with a male partner for the duration of the study. Acceptable forms of contraception include hormonal measures (oral contraceptive pills, contraceptive patch, contraceptive ring, injections, etc), intrauterine devices, double barrier method (condom plus diaphragm, condom or diaphragm plus spermicidal gel or foam), surgical sterilization of the male partner, and abstinence.
7. Have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test prior to dosing at each treatment session.
8. Be willing and able to comply with all protocol required visits and assessment Be able to read, understand, and independently complete patient reported outcome instruments in English.
9. Be able to read, understand, and independently complete patient reported outcome instruments in English.
10. Be adequately informed and understand the nature and risks of the study and be able to provide consent as outlined in Section 10.1.3.

5.2 Subject Exclusion Criteria

A subject is ineligible for study participation if, at the Screening Visit or on Day 1, the subject:

1. Is from a vulnerable population, as defined by the United States (US) Code of Federal Regulations (CFR) Title 45, Part 46, Section 46.111(b) and other local and national regulations, including but not limited to, employees (temporary, part-time, full-time, etc) or a family member of the research staff conducting the study, or of the sponsor, or of the contract research organization, or of the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

c. Has a history of sensitivity or allergy to collagenase or any other excipient of CCH.
d. Has any of the following systemic conditions:
1. Coagulation disorder.
2. Evidence or history of malignancy (other than excised basal-cell carcinoma) unless there had been no recurrence in at least 5 years.
3. History of keloidal scarring or abnormal wound healing.
4. 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 will be discussed with the Medical Monitor.
5. Evidence of clinically significant abnormalities on physical examination, vital signs, , or clinical laboratory values.
e. Has any of the following local conditions in the areas to be treated (both buttocks or both thighs):

1. History of lower extremity thrombosis or post-thrombosis syndrome.
2. Vascular disorder (eg, varicose veins, telangiectasia).
3. Inflammation or active infection.
4. Active cutaneous alteration including rash, eczema, or psoriasis.
5. A tattoo or other artificially inflicted body marker.
6. Has a mole located within 2 cm of any injection site.
f. Has skin laxity or linear undulations on the treatment region (both buttocks or both thighs) that can be effaced by lifting skin.
g. Has a Hexsel CSS Subsection D "Grade of laxity, flaccidity, or sagging skin" of 2 (moderate draped appearance) or 3 (severe draped appearance).
h. Requires anticoagulant or antiplatelet medication during the study or has received anticoagulant or antiplatelet medication (except for :S150 mg aspirin daily) within 7 days before injection of study treatment.
i. Has used any of the following for the treatment of EFP on either thigh and either buttock within the timelines identified below or intends to use any of the following at any time during the course of the study:
j. Liposuction during the 12-month period before dosing with study treatment.
k. Injections (eg, mesotherapy, dermal fillers, biostimulatory fillers); radiofrequency device treatments; laser treatment; buttock and thigh implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision) during the 12-month period before injection of study treatment.
l. Any investigational treatment for EFP on a buttock and thigh during the 12-month period before the injection of study treatment.
m. Endermologie or similar treatments during the 6 month period before injection of study treatment.

o. Massage therapy during the 3-month period before injection of study treatment. Creams (eg, Celluvera™, TriLastin®) and/or home therapies to prevent or mitigate EFP during the 2-week period before injection of study treatment.
p. Has received any collagenase treatments at any time prior to treatment in this study and/or has received previous treatment with EN3835 or CCH for cellulite.
q. Has received treatment with an investigational product within 30 days (or 5 half-lives, whichever is longer) of the Screening Visit.
r. Is pregnant and/or is providing breast milk or plans to become pregnant and/or to provide breast milk during the course of the study.
s. Intends to initiate an intensive sport or exercise program during the study.
t. Intends to initiate an intensive weight reduction program during the study.
u. Has any other condition(s) that, in the investigator's opinion, might indicate the subject to be unsuitable for the study.

6. Lifestyle Considerations

See Section 5.1 and Section 5.2.

6.1 Screen Failures

Screen failures are defined as subjects who consent to participate in this study but are not subsequently treated. Eligibility confirmation by the sponsor or designee is required for this study (see Section 8.1).

Subjects who do not meet all of the eligibility criteria at the Screening or Day 1 Visits will be deemed a screen failure and the following information must be recorded for all subjects who are screen failures:

- Demography (age, gender, race/ethnicity).
- Reason for screen failure.
- Which eligibility criterion was not met.

7. STUDY TREATMENT

Study treatment is defined as any investigational treatment, marketed product, placebo, or device intended to be administered to a study subject according to the study protocol.

7.1 Selecting and Marking Target Dimples for Treatment

For treatment, the investigator or qualified designee will select up to 12 dimples within each treatment area (each buttock or each thigh) that are well-defined, evident when the subject is standing, and suitable for treatment. These dimples will be designated as the target dimples and will be treated at each treatment session (Days 1, 22, and 43) as long as they remain visible. Dimples in the buttock will be treated first and will not exceed the maximum amount of 12 dimples. After the buttock treatment, the dilution matrix will be utilized to determine the dilution ratio for the thigh treatment area. The maximum dose per treatment area (each buttock or each thigh) will not exceed 0.84 mg.

For each target 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 target dimples selected for treatment.

7.2 Treatment Administration

CCH is a sterile lyophilized powder that is reconstituted with a sterile diluent made of 0.6% sodium chloride and 0.03% calcium chloride dihydrate in water. Subjects who qualify for the study will be given a maximum dose of 0.84 mg of CCH per treatment area buttock and thigh per treatment visit (total maximum dose of 1.68 mg per treatment session × 3 treatment sessions [Days 1, 22, and 43] for a maximum total dose of 5.04 mg.

In this study, the reconstitution volumes and angles of injection will be different for the buttocks and the posterolateral thighs. However, the total dose in each treatment area (buttocks and thighs) will be no more than 0.84 mg of CCH per treatment session.

Buttock cellulite dimple injections will consist of administration of 0.3 mL of reconstituted CCH, administered in 3 aliquots of 0.1 mL each. For thighs, cellulite dimple injections will consist of 1.5 mL of reconstituted CCH, administered in 5 aliquots of 0.3 mL each.

Specific instructions for CCH reconstitution and administration, including the injection techniques, will be provided in the Pharmacy Manual.

7.3 Table 2: Study Treatment

Starting volume per 1.84 mg vial of Qwo after recon	Number of buttock sites	Number of thigh sites	Volume of saline to add after buttock injection*
8 ml	26	0	N/A
	25	1	2
	24	2	3.2
	23	3	4.4
	22	4	5.6
	21	5	6.8
	20	6	8
	19	7	9.2
	18	8	10.4
	17	9	11.6
	16	10	12.8
	15	11	14
	14	12	15.2
	13	13	16.4
	12	14	17.6
	11	15	18.8
	10	16	20
	9	17	21.2
	8	18	22.4
	7	19	23.6
	6	20	24.8
	5	21	26
	4	22	27.2
	3	23	28.4
	2	24	29.6
	1	25	30.8
40 ml	N/A	26	N/A

a. The proposed maximum number of injections sites per treatment area has been determined based on safety data of 0.84 mg/treatment area.

b. A maximum of up to 26 injections can be administered throughout the treatment sites

NOTE: CCH is a foreign protein and investigators must be prepared to address and manage an allergic reaction should it occur. At the time of each injection, a 1:1,000 solution of epinephrine for injection, 50-mg diphenhydramine injection or a suitable equivalent, and oxygen must be available and the investigator and site staff must be familiar with their use. To evaluate the subject for possible immediate immunological AEs, the subject will remain in direct observation of medical personnel who are skilled in the management of an allergic reaction for 30 minutes after receiving the injections of study treatment 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.

After the completion of dosing at each treatment session, the investigator or qualified designee will apply a sterile dressing to the injection areas with hypoallergenic tape. The subject will be instructed to remove the dressing in the evening.

At the discretion of the investigator, compression at the treatment area may be recommended to the subject. If compression at the treatment area is used by the subject, the start and stop date and type of compression used will be recorded in the source documents and the eCRF.

7.4 Study Treatment Preparation/Handling/Storage/Accountability

Vials of 1.84 mg Qwo CCH will be supplied to the site. Each vial of Qwo will be labeled with contents, sponsor identification, storage, administration/use, and appropriate caution statements. CCH and the diluent must be stored in an appropriate, secure area. Study treatment must be kept in a temperature-monitored refrigerator (2°C to 8°C) with locked access until used or returned to Endo.

The investigator or designee will confirm that appropriate temperature control conditions have been maintained during transit for all study treatments received and that any discrepancies are reported and resolved prior to study treatment administration.

Only subjects enrolled in the study will receive study treatment and only authorized study staff will dispense study treatment.

In accordance with the International Council for Harmonisation (ICH) requirements, at all times the investigator will be able to account for all study treatment furnished to the study site. An accountability record will be maintained for this purpose. The investigator must maintain accurate records indicating dates and quantity of study treatment received, to whom it was administered (subject-by-subject accounting), and accounts of any study treatment accidentally or deliberately destroyed. All unused study treatment not involved in immediate subject treatment will be maintained under locked, temperature-controlled storage at the study site.

Please refer to the Pharmacy Manual for complete information regarding preparation, handling, storage, and accountability of study treatment.

7.5 Measures to Minimize Bias

This is an open label, nonrandomized study; measures to minimize bias using treatment blinding or randomization are not applicable to this study.

7.6 Study Treatment Compliance

All subjects will receive study treatment administered by the investigator at the study site. All dosing information will be recorded for each subject visit. Drug inventory will be maintained in the IRT system for each site, and all original containers of used and unused study treatment and diluent will be returned to the sponsor (or designee) at the end of the study.

Accidental or intentional overdoses should be reported to the sponsor/designee promptly (see Section 8.5).

7.7 Prior and Concomitant Medications and Procedures

The start and stop date, dose, unit, frequency, route of administration, and indication for all prior (taken within the 90 days prior to the Screening Visit) and concomitant (taken from the Screening Visit through the Day 90/Early Termination Visit) medications and nondrug therapies (eg, blood transfusions, oxygen supplementation, physical therapy, etc) received will be recorded.

In addition, all prior treatments for EFP will be recorded with start and stop date, dose, unit, frequency and route of administration.

The use of compression at the treatment areas is allowed during the study at the discretion of the investigator. Compression is considered a concomitant procedure and will be recorded appropriately, if used.

7.7.1 Prohibited Medications and Procedures

The following medications are prohibited for 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: S150 mg per day will be permitted during study.

The following procedures/treatments are not allowed in the selected treatment region (both buttocks or both thighs) during the course of the study (from the Screening Visit through the Day 180 End of Study/Early Termination Visit):

- Liposuction.
- Any injectable treatment (eg, KYBELLA) or any similar treatment that could destroy fat cells and/or remove fat deposits.
- Injections (eg, mesotherapy); radiofrequency device treatments; laser treatment; buttock implant treatment; cryolipolysis; or surgery (including subcision and/or powered subcision).
- Any investigational treatment for EFP (other than CCH as prescribed in this study).
- Endermologie or similar treatments.
- Massage therapy.
- Creams (eg, Celluvera, TriLastin) and/or home therapies to prevent or mitigate EFP.

If any prohibited medication or procedure is used during the study, all pertinent information will be recorded. The designated study medical monitor must be informed immediately so the sponsor may determine whether to continue the subject in the study.

8. DISCONTINUATION FROM STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

8.1 Discontinuation of Study Treatment

Subjects who discontinue from study treatment or withdraw from the study for any reason after the Day 1 dosing will be encouraged to complete the remaining study visits and evaluations and provide any additional follow-up information as required by the study, unless the subject specifically indicates that they will not participate in any further evaluations. The date of, and reason for, study treatment discontinuation will be recorded.

Permanent study treatment discontinuation is required for the following:

- The subject becomes pregnant during the active treatment phase of the study (Day 1 through Day 43).

Subjects who discontinue from study treatment at any time after the first dose of study drug will not be replaced.

8.2 Subject Withdrawal from the Study

Subjects may withdraw from the study at any time at their own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. The date of and reason for withdrawal from the study will be recorded.

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such withdrawal of consent. If a subject withdraws from the study, the subject may request destruction of any samples taken and not yet tested. The investigator must document this in the site study records.

A subject may be withdrawn from the study for the following medical or administrative reasons:

- Withdrawal by subject (reason must be specified).
- A protocol violation (reason must be specified, for example: lack of compliance, use of a prohibited concomitant medication, etc).
- 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 Early Termination procedures should be conducted as detailed in the Schedule of Activities. The date a subject discontinues and the reason for discontinuation will be recorded in the source documentation and the electronic case report form (eCRF). If, however, a subject withdraws consent, no additional procedures are required except the collection of AE information. This information should be recorded in the source documentation and the eCRF.

Subjects who have been withdrawn from the study at any time after the first dose of study drug will not be replaced.

8.3 Lost to Follow-up

A subject will be considered lost to follow-up if the subject repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and to ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls, and if necessary, a certified letter to the subject's last known mailing address; or local equivalent methods). These attempts will be documented.
- Should the subject continue to be unreachable, the subject will be considered to have withdrawn from the study.

Subjects who have been lost to follow-up at any time after the first dose of study drug will not be replaced.

9. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Activities (Section 1.2). Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct. Protocol waivers or exemptions are not allowed. The details of activities outlined in the Clinical Operations Manual must be followed or will result in a protocol deviation.

Urgent safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue study treatment and/or be withdrawn from the study.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screen failure, as applicable.

Procedures conducted as part of the subject's routine clinical management and obtained before signing of the informed consent form (ICF) may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities.

9.1 Eligibility Confirmation

All subjects deemed eligible for the study will be at the sole discretion of the Principal Investigator.

9.2 Efficacy Assessments

Efficacy assessments will be evaluated at times specified in the Schedule of Activities. Below is a general description of each of these assessments. Specific instructions and questionnaires/forms (where appropriate) will be provided in the Study Operations Manual.

9.2.1 Imaging for Outcome Assessments

Although digital photographs are not direct efficacy measurements, digital photography will be utilized in the assessment of certain efficacy measurements (ie, to assess certain cellulite severity parameters at specific intervals). At screening, the investigator or qualified designee will photograph each of the 2 treatment areas (both buttocks and both thighs) independently using a sponsor-supplied standardized digital camera in a standardized manner. For subsequent visits only the areas receiving treatment (both buttocks or both thighs) will be photographed. The subject will be standing in a consistent, relaxed standing pose (ie, standing position with relaxed gluteus muscles) for each photography session and will be wearing a standardized photographic garment as described in the Photography Manual. These photographs will be taken before and after marking of the treatment area for dosing at treatment visits.

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

9.2.2 Subject and Investigator Cellulite Assessments

Investigator cellulite assessments are independent of the subject assessments. Therefore, all subject cellulite assessments must be completed before the investigator's cellulite assessments are initiated. Subject assessments will occur while the subject is alone with no study site personnel in the room. Investigators will be instructed not to verbalize their ratings while in the presence of the subject and vice versa.

9.2.3 Body-Q Appraisal of Cellulite

The Body-Q Appraisal of Cellulite is a subset of questions from the Body-Q questionnaire that was developed to measure patient perceptions of weight loss and/or body contouring (Scott et al, 2012).

9.2.4 Clinician-reported Photonumeric Cellulite Severity Scale -Buttock

The CR-PCSS-Buttock will be used to assess the severity of cellulite of both treatment areas (each buttock, independently). The CR-PCSS-Buttock is a 5-level photonumeric scale developed specifically for clinicians and used by the investigator to assess the severity of the subject's cellulite in each buttock by live assessments. The ratings range from 0 (None) to 4 (Severe) with labels and descriptors to aid the investigator in the assessments. This assessment should be made while the subject is in the standing position with relaxed gluteus muscles.

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

9.2.5 Clinician-reported Photonumeric Cellulite Severity Scale- Thigh

The CR-PCSS-Thigh will be used to assess the severity of cellulite of both treatment areas (each thigh, independently). The CR-PCSS-Thigh is a 5-level photonumeric scale developed specifically for clinicians and used by the investigator to assess the severity of the subject's cellulite in each thigh by live assessments. The ratings range from 0 (None) to 4 (Severe) with labels and descriptors to aid the investigator in the assessments. This assessment should be made while the subject is in the standing position with relaxed gluteus muscles at Screening only to determine study eligibility.

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

9.2.6 Hexsel Cellulite Severity Scale

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 (Hexsel et al, 2009; Nürnberger and Müller, 1978). Each of these features is evaluated on a 4-point scale from a low of 0 to a high of 3.

Investigators who are physicians will independently use the Hexsel CSS Section D (laxity, flaccidity or sagging of skin) to assess the severity of laxity in each buttock or each thigh at the Screening Visit to determine subject eligibility. This assessment should be made while the subject is in the standing position with relaxed gluteus muscles.

9.2.7 Investigator Global Aesthetic Improvement Scale

Investigators who are physicians will use the I-GAIS to determine the degree of improvement of each buttock or thigh by comparing the cellulite from the Day 1 pretreatment (baseline) outcome image of each buttock or each thigh to the images taken at the subsequent visits specified in the Schedule of Activities. In visits where both I-GAIS and CR-PCSS are scheduled, I-GAIS assessment will occur after the CR-PCSS assessment to avoid introducing potential bias to the static CR-PCSS assessment by the investigator.

9.2.8 Target Dimple Count

As described in Section 6.2, up to 12 target dimples per treatment area (each buttock and each thigh) will be identified and treated at Study Day 1. At each subsequent visit, the number of target dimples that remain visible will be recorded. Site will relocate the original dimples using the Day 1 predose photographs taken after marking the dimples.

9.2.9 Ultrasound

Not applicable.

9.3 Safety Assessments

All safety assessments will be performed at the times outlined in the Schedule of Activities. Additional (unscheduled) safety assessments may be performed as needed.

9.3.1 Medical and Surgical History

Medical and surgical history will be obtained at the Screening Visit. Medical history will include a review of the following systems: general, dermatological, respiratory, cardiovascular, gastrointestinal, genitourinary, gynecological, endocrine, musculoskeletal, hematological, neuropsychological, immune (allergies), and head, eyes, ears, nose, and throat. Historical and current medical conditions including date of last menstrual period will be recorded. History of tobacco and alcohol use (never, current, former) will also be collected.

Surgical history will include a review of all surgical procedures completed in the prior 5 years and any surgery completed at any time in the treatment area.

EFP history will include the start date of the condition and any family history of EFP.

9.3.2 Physical Examination

The complete physical examination will follow the sites standard of care and may include evaluation of the head, eyes, ears, nose, throat, neck (including thyroid), cardiovascular system (including assessment of heart, peripheral pulses, presence or absence of edema), lungs, abdomen (including liver and spleen, bowel sounds), lymph nodes, musculoskeletal system (including spine, joints, muscles) neurological system (including cranial nerves, reflexes, sensation, strength), skin (excluding cellulite), extremities, and other conditions of note.

All examinations will be performed by a physician or health professional listed on the Form FDA 1572 and licensed to perform physical examinations. The investigator will review all physical exam findings for clinical significance. Any physical exam finding meeting the investigator's or sponsor's criteria for clinical significance will be recorded as an AE or SAE as appropriate.

9.3.3 Height and Weight

Height will be collected at screening only. Weight will be collected as outlined in the Schedule of Activities. Any change from the Screening Visit in subject weight that is considered by the investigator to be clinically significant will be recorded as an AE (or SAE, if appropriate).

9.3.4 Fitzpatrick Skin Scale

The Fitzpatrick Skin Scale is a 6-level scale (levels I-VI) for assessment of skin color and propensity for tanning. The skin types range from level I: Pale white skin, blue/hazel eyes, blond/red hair, always burns, does not tan to level VI: Dark brown or black skin, never burns, always tans darkly. The investigator (or designee) will determine the Fitzpatrick Skin Type for all subjects at screening.

9.3.5 Pregnancy Testing

All female subjects of childbearing potential will have serum and/or urine pregnancy tests at the time points outlined in the Schedule of Activities. Results must be available prior to protocol mandated study treatment. Subjects with positive results at the Screening Visit or on Day 1 will be ineligible for study entry. Any female subject that becomes pregnant during the study will be immediately withdrawn from treatment and will have the pregnancy reported as per Section 8.4.5.

For all female subjects of childbearing potential, the subject's agreement to use contraception throughout their study participation (Screening Visit through the Day 180/Early Termination

9.4 Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Section 10.3.

All AEs, including both observed or volunteered problems, complaints, signs or symptoms must be recorded, regardless of whether associated with the use of study treatment. 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.

9.4.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs and AEs will be collected by the investigator from the time of signing the informed consent through the Day 180/Early Termination Visit or for 28 days after the last study treatment for those who early terminate. This will include any AEs that are ongoing at the time of completion/termination of the study. All ongoing AEs must be followed until resolution or for 28 days after the subject's last study treatment, whichever comes first.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs and SAEs after conclusion of subject study participation. However, if the investigator learns of any SAE, including death, at any time after the subject has been discharged from the study, and the investigator considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and submitting SAE reports are provided in Section 10.3.

9.4.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

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 nonleading question such as, "How do you feel?" Study site personnel will then record all pertinent information. The study drug compliance record should also be reviewed to detect potential intentional or unintentional overdoses.

9.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed to resolution, stabilization, the event is

otherwise explained, or the subject is lost to follow-up. Further information on follow-up procedures is provided in Section 10.3.

9.4.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities regarding the safety of the study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of the study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements regarding safety reporting to regulatory authorities, IRBs/IECs, and investigators.

Investigator safety reports must be prepared for suspected, unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy, and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (ie, summary or listing of SAEs) from the sponsor will review and then file it with the Investigator's Brochure, and will notify the IRB/IEC, if appropriate according to local requirements.

9.4.5 Pregnancy

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 treatment 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. 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, or any other serious events) must additionally be reported as such using the Serious Adverse Event (SAE)/Reportable Event Form (see Section 10.3). Spontaneous miscarriages should also be reported and handled as SAEs.

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

A subject who becomes pregnant must immediately be discontinued from study treatment but may remain in the study if the investigator judges that the potential benefit to the subject outweighs any potential risk to the subject and/or the fetus, and the subject continues to give informed consent for further participation. The investigator should counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

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

9.4.6 AEs/SAEs Experienced by Nonsubjects Exposed to Study Treatment

Nonsubjects are persons who are not enrolled in the study but have been exposed to study treatment, including instances of diversion of study treatment. All such AEs/SAEs occurring in nonsubjects from such exposure will be reported to Endo (when the nonsubject agrees) on the Serious Adverse Event (SAE)/Reportable Event Form regardless of whether the event is serious or not. Instructions for completing the form for events experienced by nonsubjects will be provided. SAEs occurring in nonsubjects exposed to study medication will be processed within the same SAE reporting timelines as described in Section 10.3. Additionally, the drug accountability source documentation at the site should reflect this occurrence.

9.4.7 Adverse Events of Special Interest

AESIs for this study include:

9.4.7.1 Bruising, ecchymosis, hematomas, and contusions that occur remote to the site of drug administration.

9.4.7.2 Any hypersensitivity reactions.

9.4.7.3 Local AEs associated with the injection site, including bruising, pain, nodules/mass, ulceration, erythema, pruritus, swelling, and/or induration.

These events will be reported as AEs in the eCRF. All AEs will be evaluated for seriousness and severity. If any of these events meet the criteria for an SAE, they will also be reported as such using the procedure outlined in Section 10.3.

9.5 Treatment Overdose

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

Any treatment 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 10.3, 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 Serious Adverse Event (SAE)/Reportable Event Form and in an expedited manner, but should be noted as nonserious on the form and the Adverse Event eCRF.

9.6 Pharmacokinetics

Not applicable.

9.7 Pharmacodynamics

Not applicable.

9.8 Genetics

Not applicable.

9.9 Biomarkers

9.9.1 Immunogenicity Assessments

Not applicable.

9.10 Medical Resource Utilization and Health Economics

Not applicable.

10. STATISTICAL CONSIDERATIONS AND METHODS

10.1 Sample Size Determination

The proposed sample size is 5 subjects.

10.2 Populations for Analysis

For the purposes of analysis, the following populations are defined:

- The Safety Population will include all subjects who receive at least 1 injection of study treatment. All safety evaluations will be based on the Safety Population.
- The Evaluable Population will include all subjects who receive at least 1 injection of study treatment and have at least 1 I-GAIS evaluation. All efficacy evaluations will be based on the Evaluable Population.

10.3 Statistical Hypotheses and Analyses

This section provides a general summary of the statistical methods to be used in analyzing study data. A more detailed statistical analysis plan will be developed and finalized prior to the interim analysis.

10.3.1 Efficacy Analysis

The primary efficacy endpoint of the proportion of subjects with improved (+1 or better) score on I-GAIS for either buttock or either thigh at Day 90 will be summarized by cohort using appropriate summary statistics and its 95% confidence interval will be provided.

All secondary and exploratory efficacy endpoints will be summarized using appropriate descriptive statistics by time point and cohort.

10.3.2 Safety Analyses

All subjects who receive at least 1 dose of study drug will be included in the safety analyses.

10.3.3 Adverse Events

AEs will be coded using MedDRA by preferred term within system organ class. The number of AEs and the number of subjects reporting AEs will be listed and summarized descriptively by body system, preferred term, severity, and causality for each treatment group. Only TEAEs (events that are new in onset or aggravated in severity following treatment) will be included in all summaries. SAEs (including death) will be listed.

10.4 Interim Analysis

Because of the lower responder rate for thigh (60%) and an anticipated high drop-out rate (10%), an interim data analysis will be done when approximately the first 40 Cohort 1 (thigh) subjects complete their Day 90 assessments. The interim analysis will include the primary endpoint (the proportion of subjects with improved [+1 or better] score on I-GAIS for either thigh at Day 90) and mean change from baseline in Body-Q Appraisal of Cellulite at Day 90 for thigh treated subjects.

Depending on the outcome of the interim analysis for the primary endpoint, the study sample size may be revisited.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1 Appendix 1: Regulatory, Ethical and Study Oversight Considerations

11.1.1 Regulatory and Ethical Considerations

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 Food and Drug Administration (FDA) guidelines for Good Clinical Practices (GCP) and in accordance with the ethical principles that have their origins in the Declaration of Helsinki defined in 21 CFR, 312.120.

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/IEC members that demonstrates appropriate composition or other documentation of assurance of appropriate composition per local and national regulations (eg, a Department of Health and Human Services [DHHS] Assurance Number will satisfy this requirement for IRBs in the US).

The study protocol, the ICF, 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, 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 Investigator's Brochure, Package Insert, or Summary of Product Characteristics, 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. No protocol amendment may be implemented (with the exceptions noted below) before it has been approved by the IRB/IEC and the signature page, signed by the investigator, has been received by Endo. Where the protocol is amended to eliminate or reduce the risk to the subject, the amendment may be implemented before IRB/IEC review and approval. However, the IRB/IEC 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.

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

11.1.2 Financial Disclosure

Investigator will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after the completion of the study.

11.1.3 Informed Consent Process

The ICF must be approved by the sponsor and the IRB/IEC before any subject provides consent. The investigator will provide the sponsor with a copy of the IRB/IEC-approved ICF and a copy of the IRB/IEC's written approval before the start of the study.

The ICF must contain all applicable elements of informed consent and the mandatory statements as defined by national and local regulations, including confidentiality.

At the Screening Visit (and at other time as may be required by the study or when changes are made to the consent form), subjects will read the consent form(s) and any privacy authorization as required by local and national regulations (such as the Health Insurance Portability and Accountability Act [HIPAA] authorization form), after being given an explanation of the study. Before signing the consent form(s) and the privacy authorization form (if applicable), subjects will have an opportunity to ask questions about the study and discuss the contents of these forms with study site personnel. The consent/assent process shall be recorded in source documents.

Subjects must assent understanding of and voluntarily sign these forms in compliance with ICH GCP and all applicable national and international regulations, before participating in any study-related procedures. Subjects will be made aware that they may withdraw from the study at any time for any reason.

All versions of each subject's signed ICF must be kept on file by the site for possible inspection by regulatory authorities and the sponsor. Signed copies of the consent form(s) and the privacy authorization form, if applicable, will be given to the subject.

The subjects will be made aware of their right to see and copy their records related to the study for as long as the investigator has possession of this information. If the subject withdraws consent and/or HIPAA authorization, the investigator can no longer disclose health information, unless it is needed to preserve the scientific integrity of the study.

11.1.4 Data Protection

Study subjects will be assigned a unique identifier by the sponsor or designee. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure (in accordance with local and/or national law) must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

11.1.5 Committee Structure

No independent data and/or safety monitoring board will be used for this study.

11.1.6 Dissemination of Clinical Study Data

Aggregate results data will be provided to the sites that actively enrolled subjects into this study after the clinical study report is finalized.

Study results and de-identified individual subject data will be released as required by local and/or national regulation.

11.1.7 Data Quality Assurance

Steps to assure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the 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 noncompliance 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 in a timely fashion and will be 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, 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.

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 for inspection and copying, in keeping with national and local regulations.

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.

11.1.8 Source Documents

All subject information recorded in the eCRF will be attributable to source data from the investigational site unless otherwise outlined in this protocol.

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.

The investigator shall retain and preserve 1 copy of all data collected or databases generated in the course of the study, specifically including but not limited to those defined by GCP as essential. Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational medicinal product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. Prior to destruction of any study essential documents, the investigator must first obtain written approval from the sponsor.

11.1.9 Study and Site Closure

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

11.1.10Publication Policy

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.

Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

12.0 Definitions

An AE is any unfavorable or unintended change in body structure (signs), body function (symptoms), laboratory result (eg, chemistry, ECG, X-ray, etc), or worsening of a pre-existing condition associated temporally with the use of the study medication whether or not considered related to the study medication. AEs will be captured once a subject has signed the informed consent. AEs include:

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

A 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).

A 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 preplanned surgery, procedure, or drug therapy does not constitute an SAE)
- Results in permanent or substantial disability (permanent or substantial disruption of one's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect (in offspring of a subject using the study medication regardless of time to diagnosis)
- Is considered an important medical event

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

12.1 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.

12.2Intensity 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.

12.3Reporting Adverse Events and Serious Adverse Events

12.3.1 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 the Day 180/End of Study Visit or for 28 days after the last study treatment in subjects who terminate early. All ongoing AEs must be followed until resolution or until the Day 180/End of Study Visit or until 28 days after the last dose of study medication for subjects who terminate early, whichever comes first.

12.3.2 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 Serious Adverse Event (SAE)/Reportable Event Form 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 the Day180/End of Study Visit or until 28 days after the last dose of study treatment (in subjects who terminate early. SAE that occur within 28 days following study treatment discontinuation or within 28 days following premature study withdrawal 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.

All SAEs should be reported via email (research@moderndermct.com) or fax (203-635-0771).

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

12.3.3 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.

a. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

See Section 5 and Section 8.3.9.

b. Appendix 5: Genetics

Not applicable.

c. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Not applicable.

d. Appendix 7: Medical Device Incidents

Not applicable.

e. Appendix 8: Country-specific Requirements

Not applicable.

f. Appendix 9: Abbreviations

Abbreviation	Explanation
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AUX-I	Clostridial class I collagenase
AUX-II	Clostridial class II collagenase
BDDQ	Body Dysmorphic Disorder Questionnaire
BMI	Body mass index
CFR	Code of Federal Regulations
CR-PCSS	Clinician-reported Photonumeric Cellulite Severity Scale
CSS	Cellulite Severity Scale
DHHS	Department of Health and Human Services
ECG	Electrocardiogram
eCRF	Electronic case report form
EFP	Edematous fibrosclerotic panniculopathy
EGAL	Endo Global Aesthetics Limited
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed consent form
ICH	International Council for Harmonisation
ID	Identification
IEC	Independent Ethics Committee
I-GAIS	Investigator Global Aesthetic Improvement Scale
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
QTc	Corrected QT interval
SAE	Serious adverse event
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States

11. 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